



Emilie C. Holland

Jesus College

Supervisor

Prof. Yiannis Ventikos

COMPUTATIONAL MODELLING OF
TRANSPORT PHENOMENA IN
CEREBRAL ANEURYSMS

**A thesis submitted for the degree of
Doctor of Philosophy**

Trinity 2012

To FD - your timing is impeccable.
(Your patience isn't that bad either)

Abstract

An estimated 85% of haemorrhagic strokes are secondary to the rupture of an intracranial aneurysm (IA), a localised, blood-filled dilation of the artery wall. The clinically observed rupture of occluded IAs has led to hypothesise that the presence of thrombus may restrict the transport of nutrients, most notably oxygen, to the aneurysmal wall, thus heightening the risk of rupture through the deleterious effects of hypoxia on cellular functionality. The limited research into O_2 transport within IAs demonstrate the need for further exploration into the possible detrimental hypoxic conditions as a result of intrasaccular haemodynamics and thrombus formation in untreated, treated and evolving IAs, with the ultimate goal of further understanding disease evolution and developing prognostic decision support models for clinical intervention.

Preliminary computational fluid dynamic simulations conducted on a 2D-axisymmetric model of a thrombosed artery highlighted the relative importance of wall-side versus the fluid-side mass transport of oxygen. A sensitivity analysis demonstrated that variations in thrombus thickness, and arterial wall cellular respiration rates have the greatest influence on the oxygen distribution to the portion of wall in direct contact with the thrombus.

The results of the coupled flow-mass transport computational fluid dynamic simulations within patient-specific IA show that a reduction in intrasaccular flow as a consequence of stent deployment affects the rate at which oxygenated blood reaches the entirety of the dome. Nonetheless, the distribution of O_2 to the aneurysmal wall itself does not differ from the observed oxygen distribution across the wall when the same IA is left untreated. Conversely, the low velocity recirculations observed in an IA presenting with a very high aspect ratio (i.e a narrow neck and high sack height) limited the transport of oxygen to such an extent as to completely deprive the delivery of oxygen to the fundus. The presence of thrombus within the IA dome results in a dramatic reduction in oxygen delivery to the wall, the extent of which is dependent on the local thrombus thickness.

Finally, a novel fluid-solid-growth-mass transport (FSGT) mathematical model is conceived to explore the biochemical role of thrombus on the evolution of an IA. The shear-regulate propagation of a thrombus layer during membrane expansion leads to the gradual decrease in oxygen tension within the wall. Moreover, as a consequence of coupling this oxygen deficiency to fibroblast functionality, the col-

lagen fibre mass density was shown to increase at an insufficient rate to compensate for the transfer in load from the degrading elastinous constituents to the collagenous constituents, thus resulting in the increased stretch of collagen fibres in order to maintain mechanical equilibrium. Moreover this over-expansion results in the gradual unstable evolution of the IA.

The observed obstruction to oxygen delivery as a result of intrasaccular haemodynamics and thrombosis compounds the need for further development of more comprehensive chemo-mechano-biological models of IAs so as to better ascertain the level of rupture risk posed by a hypoxic environment. Refinement to the models proposed within this work would prove invaluable to creating a fully integrated multi-physics, multi-scale *in silico* framework in aid to patient diagnostics and individual treatment planning of IAs.

Statement of Originality

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the University of Oxford or any other educational institution, except where due acknowledgment is made in the thesis.

Any contribution made to the research by others, with whom I have worked at the University of Oxford or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Emilie C. Holland.

5th October 2012.

Acknowledgements

Foremost, I would like to express my gratitude to my supervisor Prof. Yiannis Ventikos for giving me the opportunity to conduct this work and for his continuous support in my research.

My sincere thanks also go to Dr. Paul Watton ('Postdoc Paul') for his insight and guidance with regard to the understanding of modelling aneurysm evolution, and his supervision of the research presented in Chapter 7. His continual encouragement and infectious enthusiasm were invaluable in the completion of this thesis.

I would also like to thank fellow students of the FBG group: Dr. Basel Rifai, Dr. Brett Tully, Dr. Nick Hawker, Dr. Tim Bowker, Alisa Selimovic and Malebogo Ngoepe, for willingly imparting their knowledge whenever I needed their help, but mostly for their unwavering friendship. I am particularly indebted to Dr. Tim Bowker for mentoring me in all matters CFD during my first year and his collaboration in the work presented in Chapter 5.

A special thank you to Penny Hill, whose counsel and guidance during my time at Oxford I shall cherish for a life time.

I would like to thank Mum and Dad, my stepparents Ross and Stella and my brother James for their continual support and encouragement.

To my fiancé Florian. Thank you for your unconditional love, confidence and support in everything I do. You have brought meaning to it all.

I would like to express my gratitude for the financial support provided by EPSRC.

Dissemination

Peer-Reviewed Journal Papers

Ventikos, Y., **Holland, E.C.**, Bowker, T.J., Watton, P.N., Kakalis, N.P.M., Megahed, M., Zhu, F., Summers, P.E., Byrne, J.V. *Computational modelling for cerebral aneurysms: risk evaluation and interventional planning*. British Journal of Radiology. 82:S62-S71, January 2009.

Holland, E.C., Chen,D., Luo, X., Watton, P.N., Ventikos, Y. *Computational modelling of blood flow for cardiovascular diseases and interventions*. International Journal for Numerical Methods in Biomedical Engineering. 2012 (in review).

Book Chapter

Holland, E.C., Watton, P.N., Ventikos, Y. *Biological Fluid Mechanics: Integrative and Multiscale Computational Modelling* in Comprehensive Biotechnology. Young, M.M. et al Ed., Comprehensive Biotechnology 2nd edition, Elsevier, 2011.

Conferences

Holland, E.C., Bowker, T.J., Megahed, M., Ventikos, Y. *Stent evaluation for cerebrovascular disease: haemodynamic assessment for cerebral aneurysms*. Bioengineering'09, Oxford, UK, 24-25th September 2009.

Kamran, M., Rane, N., **Holland, E.C.**, Ventikos, Y., Byrne, J.V. *Correlation of posterior communicating artery aneurysm growth patterns, arterial environment, and symptoms*. British Society of Neuroradiologists Annual Conference, Nottingham, 8-9th October 2009.

Holland, E.C., Ventikos, Y. *Modelling the effect of intraluminal thrombus on oxygen mass transfer within cerebral aneurysms*. Welmec Annual Networking Meeting, York racecourse, 25-26th May 2011.

Holland, E.C., Watton, P.N., Ventikos, Y. *Modelling the effect of intraluminal thrombus on cerebral aneurysm evolution*. IUTAM 2011: Symposium on Computer Models in Biomechanics. San Francisco, CA, USA, 29th August - 2nd September 2011.

Baptista, T., Watton, P.N., **Holland, E.C.**, Byrne, J., Reis, J., *Dinâmica de Flúidos Computacional aplicada a dois aneurismas intra-cranianos tratados com sistemas de derivação de fluxo*. SILAN 2011, Lisbon, Portugal, 10-14th October, 2011.

Holland E.C., Peach T.W. , Selimovic A., Tully B.J., Watton P.N., Ventikos Y., *Transport Phenomena, Fluid Mechanics and Multiscale Modelling Techniques for Clinical Decision Support*. Eight International Conference on Fluid Dynamics, Sendai, Miyagi, Japan, November 9-11th, 2011

Baptista, T; Watton, P.N., **Holland, E.C.**, Penrose, J.M.T., Chiarini, A., Byrne, J., Reis, J. *Computational Fluid Dynamics in patients treated with flow-diverter devices*. European Congress of Radiology, Vienna, Austria, March 1st-5th, 2012.

Zajarias-Fainsod, D., Spranger, K., **Holland, E.C.** , Selimovic, A., Chen, H., Ngoepe, M., Peach, T., Baptista, T., Chiarini, A., Penrose, J., Byrne, J., Watton, P.N., Ventikos, Y. *Modelling intracranial aneurysms treated with flow diverters: correlation of intra-aneurysm sac flow dynamics with thrombus evolution*. 8th European Solid Mechanics Conference, Graz, Austria, July 9th-13th, 2012.

CONTENTS

Contents	ix
List of Figures	xiii
List of Tables	xviii
1 Motivation: Intracranial aneurysm pathophysiology and unmet clinical needs	1
1.1 Arterial Wall Histology	5
1.1.1 Intima	6
1.1.2 Media	8
1.1.3 Adventitia	12
1.2 Intracranial aneurysm pathophysiology	14
1.2.1 Initiation	14
1.2.2 Progression	17
1.2.3 Rupture	19
1.3 Current treatment options for IAs	25
1.4 The uncertainties of thrombus occlusion	29
1.4.1 Thrombus pathogenesis	29
1.4.2 Importance of thrombus organisation	34
1.4.3 Beneficial mechanical properties of thrombus	35
1.4.4 Detrimental effects of thrombus	36
1.5 Hypoxia: an unfavourable environment	38
1.5.1 Adaptive responses to hypoxic environments	39
1.5.2 Oxidative damage to arterial cells	41
1.5.3 Detrimental effects to cellular functionality	43
2 Modelling of IAs: History and Observation	46
2.1 Oxygen mass transport in arteries	46
2.1.1 Atherosclerosis: a motivation	46
2.1.2 Mass transport of oxygen in large arteries	48
2.1.3 Mass transfer in ‘healthy’ aneurysms	55
2.1.4 Mass transport of oxygen in thrombosed aneurysms	56
2.2 Modelling of Endovascular Treatment	58
2.3 Modelling IA evolution	60

2.4	Aims of the Thesis	65
3	Theory and Methodologies	67
3.1	Governing conservation equations	67
3.1.1	Navier-Stokes Equations	67
3.1.2	Conservation of scalars	68
3.2	Discretisation: the finite volume method	69
3.2.1	Generalised transport equation	70
3.2.2	Spatial differencing schemes	71
3.2.3	Temporal discretisation	73
3.2.4	Pressure Correction	74
3.2.5	Algebraic multigrid	76
4	2D model of oxygen mass transport in a thrombosed artery	77
4.1	2D Model Description	77
4.1.1	Artery Geometry	77
4.1.2	Oxygen mass transport properties	78
4.1.3	Simulation input parameters	82
4.1.4	Boundary Conditions	85
4.1.5	Spatial differencing and solver settings	86
4.1.6	Grid generation	86
4.2	Results	87
4.2.1	Oxygen transport within the lumen	87
4.2.2	Oxygen distribution through the thrombus and wall	88
4.3	Discussion and Concluding remarks	99
5	Optimisation of mesh generation for 3D patient-specific geometries	102
5.1	Model Description	104
5.1.1	Aneurysm Geometry	104
5.1.2	Grid Generation	105
5.1.3	Simulation Inputs	108
5.1.4	Inflow velocity calculations	108
5.2	Results	109
5.2.1	Velocity field	109
5.2.2	Wall Shear Stress	113
5.3	Concluding remarks	114
6	Mass Transport of Oxygen in Intracranial Aneurysms	116
6.1	3D Patient-generated aneurysm geometries.	116

6.2	Geometry Preparation	119
6.2.1	Generation of IA surface geometry from patient scans	119
6.2.2	Generation of arterial wall layer	121
6.2.3	Creation of thrombus layer	123
6.3	Mesh generation	129
6.4	Simulation input parameters	130
6.4.1	Volume conditions	130
6.4.2	Boundary conditions	132
6.4.3	Spatial differencing and solver settings	132
6.5	Results and Discussion	133
6.5.1	Impact of aneurysm geometry on oxygen delivery	133
6.5.2	Oxygen tension at the lumen/wall interface	152
6.5.3	Oxygen distribution through the aneurysmal wall	160
6.6	Concluding Remarks	164
7	A novel chemo-mechano-biological mathematical model of intracranial aneurysm evolution	166
7.1	Model Formulation	166
7.1.1	Continuum basis for IA evolution	167
7.1.2	Thrombus propagation	174
7.1.3	Steady state oxygen diffusion through two layers	175
7.1.4	Influence of oxygen levels on fibroblast functionality	179
7.1.5	Summary of the coupled FSGT numerical model	180
7.2	Arterial geometry, physiological data and material properties	182
7.3	Results	185
7.4	Discussion and future considerations	195
7.5	Concluding remarks	202
8	Conclusions and considerations for model development	204
	References	211
A	Governing equations	235
A.1	2D axisymmetric conservation equations	235
A.1.1	Navier-Stokes equations for a fluid domain	235
A.1.2	Navier-stokes equations for a porous medium	236
A.2	3D Cartesian conservation equations	236
A.2.1	Navier-Stokes equations	236
A.2.2	Convection-diffusion equations	237

B	Solution to simultaneous equations of 1D diffusion equations	239
----------	---	------------

LIST OF FIGURES

1.1	Two major types of strokes: ischaemic versus haemorrhagic.	2
1.2	Saccular intracranial aneurysm on the internal carotid artery which supplies blood to the brain.	3
1.3	Artery composition	6
1.4	Scanning electron microscopy of organised collagen.	11
1.5	The Circle of Willis.	16
1.6	Altered EC permeability in ruptured intracranial aneurysms.	24
1.7	Schematic of the composition of blood	31
1.8	Schematic of the coagulation and plasmin-mediated fibrinolysis cascades involved in the building and degradation of clots.	32
1.9	Colourised scanning electron micrograph of a coronary artery thrombus.	33
1.10	Spontaneous thrombus.	33
1.11	Reactive oxygen species: sequential reduction of oxygen in four single-electron steps.	41
3.1	Finite volume of centre node P in a 2D Cartesian structured grid (<i>a</i>) and a 3D tetrahedral grid (<i>b</i>)	72
4.1	2D axisymmetric model of anterior communicating artery.	77
4.2	Oxyhaemoglobin dissociation curve in arterial blood flow (as defined by Kelman (1966)).	80
4.3	2D axisymmetric model flow and scalar boundary conditions	85
4.4	Convection and diffusion of oxygen within the lumen.	87
4.5	Convection and diffusion of oxyhaemoglobin within the lumen.	87
4.6	Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_1 = 1e-2$ mol/m ³ /s ($t=60s$).	89
4.7	Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_2 = 1e-3$ mol/m ³ /s ($t=120s$).	89
4.8	Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_3 = 1e-4$ mol/m ³ /s ($t=300s$).	90

4.9	Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_4 = 1e-5$ mol/m ³ /s ($t=300$ s).	90
4.10	Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Not thrombus layer.	91
4.11	Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.025$ mm.	91
4.12	Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.05$ mm.	92
4.13	Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.1$ mm.	92
4.14	Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.15$ mm.	93
4.15	Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.2$ mm.	93
4.16	Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.025$ mm.	96
4.17	Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.05$ mm.	96
4.18	Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.1$ mm.	97
4.19	Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.15$ mm.	97
4.20	Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.2$ mm.	98
5.1	STL of unstented anatomical model of a side wall aneurysm located on the internal carotid artery.	105
5.2	STL surfaces of deployed stents.	105
5.3	Example of grid generation on an imperfect surface using the adaptive unstructured grid method implemented by CFD-VisCART. Adapted from Wang and Srinivasan (2002).	106

5.4	Cut through aneurysm neck showing the grid refinement at the arterial wall and around the cross section of a stent struts for case S3: (a) ~ 5 million cells and (b) ~ 30 million cells.	107
5.5	Cutting plane P across the aneurysm neck resulting in a cross-sectional area of A_{neck}	108
5.6	Aneurysm sac inlet flow for cases U, S1, S2 and S3 meshed with CFD-VisCART: isovelocity surface $v = 0.1\text{m/s}$	113
5.7	Velocity magnitude contours for for cases U, S1, S2 and S3 meshed with CFD-VisCART. The line divides the inlet and outlet flow regions.	113
5.8	WSS distribution across the wall for cases U, S1, S2 and S3 meshed with CFD-VisCART . In both cases white demarcations demonstrates WSS = 1.5Pa threshold in the aneurysm dome.	114
6.1	OX12: Isosurface extracted from MRA scan of a 44-year-old female patient presenting with an IA at the bifurcation between the right internal carotid, the right middle cerebral and the right anterior cerebral arteries. (View inset taken from Borden (2007).)	117
6.2	Four model case scenarios	118
6.3	Segmentation procedure for OX12 aneurysm geometry	120
6.4	Creation of wall layer	123
6.5	Inlet flow rate and outlet pressure waveform for the left ICA, extracted from the Aneufuse database.	125
6.6	Flow streamlines showing regions of recirculating flow in the aneurysm dome at (a) peak systole and at (b) end diastole.	126
6.7	WSS distribution across the dome at (a) peak systole and at (b) end diastole.	127
6.8	OSI and RRT distribution across the aneurysm dome.	128
6.9	Artificial thrombus layer creation.	128
6.10	Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case A.	134
6.11	Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case B.	134
6.12	Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case C.	134
6.13	Case A Cross-sectional distribution of velocity and oxygen in the x - y plane for Case A.	135
6.14	Case A Cross-sectional distribution of velocity and oxygen in the z - x plane for Case A.	136
6.15	Case B Cross-sectional distribution of velocity and oxygen in the x - y plane for Case B.	137

6.16	Case B Cross-sectional distribution of velocity and oxygen in the z - x plane for Case B.	138
6.17	Case C Cross-sectional distribution of velocity and oxygen in the x - y plane for Case C.	139
6.18	Case C Cross-sectional distribution of velocity and oxygen in the z - x plane for Case C.	140
6.19	Plot of oxyhaemoglobin saturation and normalised oxygen concentration with time at points P1 and P2 for Case A.	143
6.20	Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case D.	144
6.21	Case D Cross-sectional distribution of velocity and oxygen in the x - y plane 1 for Case D.	146
6.22	Case D Cross-sectional distribution of velocity and oxygen in the x - y plane 2 for Case D.	147
6.23	Case D Cross-sectional distribution of velocity and oxygen in the x - y plane 3 for Case D.	148
6.24	Case D Cross-sectional distribution of velocity and oxygen in the z - x plane for Case D.	149
6.25	Case D Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 10s and (d) 20s	153
6.26	Case A Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 5s and (d) 20s	154
6.27	Case B Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 10s and (d) 28s	155
6.28	Case C Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 10s and (d) 20s	156
6.29	Case A Oxyhaemoglobin saturation level, C_{HbO_2} , at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 5s and (d) 20s	157
6.30	Normalised oxygen concentration at the thrombus/wall interface plotted against thrombus thickness δ_{th}	159
6.31	Normalised oxygen concentration versus radial distance for the untreated (A), stented (B) and thrombosed (C) VISC cases.	161
7.1	Relationship between the unloaded configuration Ω_0 , the recruitment configuration Ω^R and the loaded configuration Ω^t	169
7.2	The unloaded, loaded and recruitment configurations of the membranous cylinder. Adapted from Watton et al. (2009b)	171
7.3	Plot demonstrating the prescribed exponential degradation of elastin over the first five years and the complete loss over the following 25 years.	173

7.4	1D oxygen mass transfer across two layers in the r-direction.	176
7.5	Flow chart of the coupled growth and remodelling and oxygen mass transport model	181
7.6	Shear rate at the inner radius (i.e. the lumen/thrombus interface r_{th}) over 30 years for each growth function. Inset A within the graph allows a closer look at the variation in shear rate after the first 5 years.	186
7.7	Thrombus propagation velocity (V_{th}) over 30 years for each growth function.	186
7.8	The thickness of the wall layer, h , with time for each GE	187
7.9	The thickness of the thrombus layer, h_{th} , with time for each GE	187
7.10	Normalised average oxygen concentration across the thrombus and wall layers with time for each growth function case.	190
7.11	Oxygen consumption rate with time for each growth function case	190
7.12	Collagen growth rate β with time for each growth function case	191
7.13	Comparison of collagen mass density evolution with time for the uncoupled G&R and coupled GRM models.	192
7.14	Stretch in the collagen fibres for the uncoupled G&R and coupled GRM models.	192
7.15	Circumferential stretch of the cylinder with time for the uncoupled G&R and coupled GRM models.	193
7.16	Endothelium, adventitia and thrombus radii versus time for uncoupled G&R model and coupled GRM model with varying growth functions. . . .	194
8.1	Coupled flow, mass transfer and GR modelling cycle.	207

LIST OF TABLES

4.1	Experimental values of arterial wall oxygen consumption rates	83
4.2	Simulation input parameters for coupled flow and mass transfer model .	84
4.3	Number of grid cells for each section of the three layer 2D axisymmetric model of an artery without and with thrombus thickness δ_{th}	86
4.4	Normalised oxygen concentration values at the lumen/thrombus (l/t) and thrombus/wall (t/w) interfaces for varying consumption rates and thrombus thicknesses.	94
4.5	Percentage difference between oxygen concentration values when thrombus transport is modelled through diffusion only and when it is modelled as a porous medium at the lumen/thrombus (l/t) and thrombus/wall (t/w) interfaces for varying consumption rates and thrombus thicknesses.	95
4.6	Percentage reduction in oxygen concentration at the wall interface when comparing each thrombus case to the ‘healthy’ artery case with no thrombus layer.	99
5.1	Grid independence studies: inflow rate for cross-sectional area A_{neck} . . .	110
5.2	Inflow rate change for each stent compared to the unstented case for the greater mesh sizes for each case. Other results from the VISC07 challenge are also reported here for comparison (Radaelli et al. (2008); Cavazzuti et al. (2011)).	112
6.1	Simulation input parameters for coupled flow and mass transfer model .	131
7.1	Simulation input parameters for coupled G&R and mass transfer model of a cylindrical membrane	183

MOTIVATION: INTRACRANIAL ANEURYSM PATHOPHYSIOLOGY AND UNMET CLINICAL NEEDS

The rupture of an intracranial aneurysm (IA) has been identified as the direct cause of 85% of subarachnoid haemorrhagic strokes. A close inspection of IA pathophysiology draws attention to the complexity of the biochemical, mechanobiological and haemodynamic factors involved in their initiation, progression and possible rupture. The uniqueness of each IA highlights the difficulties clinicians are faced with in determining not only if an aneurysm will remain asymptomatic or is at risk of rupture, but also which treatment option has the greatest chances of success. Advancements in clinical treatment have brought to light the efficacy of embolisation (spontaneous or that induced by the implantation of endovascular device) for the occlusion of an IA from blood circulation. Nevertheless, various clinical observations have demonstrated that these occluded aneurysms may still rupture. Although the formation of a stable thrombus within the aneurysm sac is universally deemed beneficial there is speculation that thrombus may in some instances impair the diffusion of oxygen through to the arterial wall. An investigation into the deleterious effects of a hypoxic environment on cellular functionality leads to the hypothesis that the presence of thrombus could lead to ultimate yielding of the wall.

Cerebrovascular disease is the second most common cause of death worldwide and is considered one of the main causes of long-term disability (Murray and Lopez (1997b,a)). Strokes account for 10-12% of deaths in industrialised countries with 88% of these being in people over the age of 65 (Bonita (1992)). In the United Kingdom alone, approximately 134,000 people suffer a new or recurrent stroke every year (Carroll et al. (2001)) and without intervention, the number of global deaths is projected to rise to 6.5 million in 2015 and to 7.8 million in 2030 (Strong et al. (2007)). In terms of worldwide healthcare costs, cerebrovascular disease represents 2-4% (Donnan et al. (2008)).

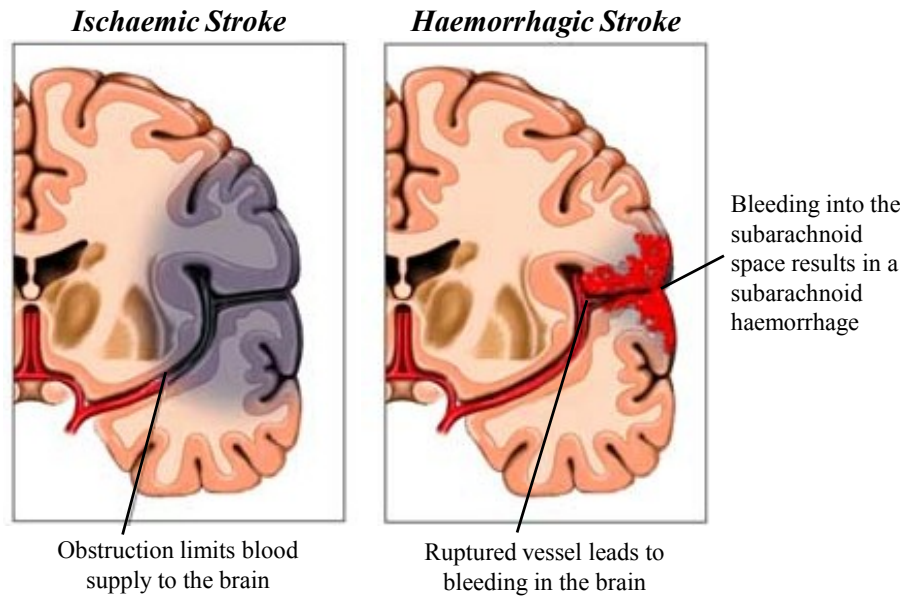


Figure 1.1: Two major types of strokes: ischaemic versus haemorrhagic. Images ©Nucleus Medical Media, Inc.

Strokes can be classified into two major categories: ischaemic, whereby there is an interruption to blood flow (e.g. a stenosis or an embolism) which account for 87% of all strokes (Rosamond et al. (2008)), and haemorrhagic as a result of rupture of a blood vessel or abnormal vasculature (Figure 1.1). Haemorrhagic strokes are clinically defined in terms of the location of the primary haemorrhage. The central nervous system, i.e. the brain and spinal chord, are envelopped by a system of membranes known as the meninges. The three meninges are the dura mater, the arachnoid mater and the pia mater. The most superficial haemorrhage is epidural, which occurs in the space between the skull and the dura mater. This is followed by subdural haemorrhage, occuring inbetween the dura and archnoid maters, and then subarachnoid, occuring between the arachnoid and pia maters. Intracerebral haemorrhages indicate bleeding within the brain itself and finally the rarest location of haemorrhages being intravascular, whereby bleeding occurs within the ventricular system which contain cerebrovascular spinal fluid. The most predominant

haemorrhagic strokes are generally intracerebral haemorrhages or subarachnoid haemorrhages (SAH), which account for 10% and 5% of first strokes respectively (Bamford et al. (1990)). Moreover, an estimated 85% of SAH are secondary to the rupture of intracranial aneurysms (IAs) (Van Gijn and Van Dongen (1980); Kassell et al. (1990b); Velthuis et al. (1998)) with the remaining 15% of SAHs attributable to either non-aneurysmal perimesencephalic haemorrhages (confined to the basal cisterns around the midbrain which account for 10% or to rarer conditions such as arterial dissection (the separation of layers within the arterial wall), cerebral arteriovenous malformation (the abnormal connection between arteries) and cavernous angioma (large clusters of abnormal blood filled vessels with little or no intervening brain matter) which together account for 5% (Van Gijn and Rinkel (2001); Arauz et al. (2007)).

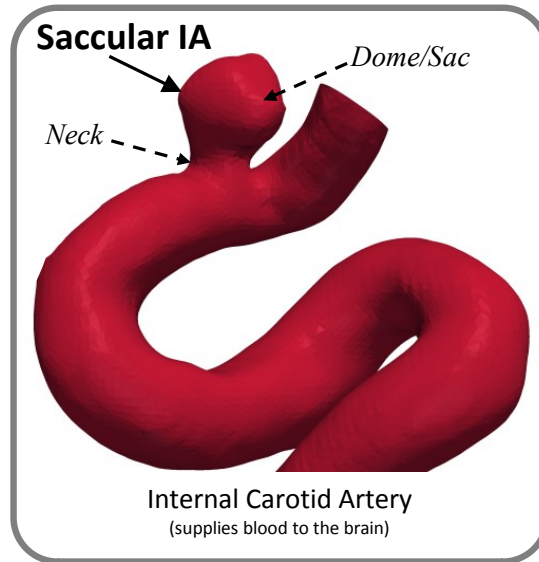


Figure 1.2: Saccular intracranial aneurysm on the internal carotid artery which supplies blood to the brain.

IAs can be: saccular, whereby the artery exhibits a unilateral pouch-like bulge; fusiform, whereby the artery expands around the entirety of its circumference resulting in a spindle like bulge; dissecting, whereby the the outpouching of the vessel

is a consequence of the haemorrhagic separation of one of the wall layers; mycotic, whereby the bulge in the vessel is a consequence of an infectious process within the arterial wall; traumatic, as a result of traumatic injury to the arterial wall; and neoplastic, also referred to as oncotic or metastatic, which occurs as a result of a tumorous invasion within the wall. Saccular IAs, as depicted in Figure 1.2, represent 80-90% of intracranial aneurysms (Wiebers et al. (2006)) and hence are the leading cause of aneurysmal SAHs.

Ruptured aneurysmal SAHs have a 30-day mortality rate of 45%, with an estimated 50% of survivors sustaining irreversible brain damage (Graves (1999)). It is also reported that within the first 24 hours after an aneurysmal SAH, 2-4% haemorrhage again and a further 15-20% bleed again within the first two weeks (Greenberg (2000)). The exact prognosis for anyone suffering from a ruptured aneurysm will depend on the age and general health of the individual, any pre-existing neurological conditions and the medical attention received. The principle complications after the occurrence of aneurysmal SAHs are cerebral vasospasms (a sudden and prolonged narrowing of the vessel) and rebleeding (Hijdra et al. (1988); Kassell et al. (1990a); Leipzig et al. (1997); Roos and Vermeulen (2003)), the former leading to a possible cerebrovascular event as half of patients with symptomatic vasospasm will develop an ischaemic infarct (Mayberg et al. (1994)). The overall healthcare cost of aneurysmal SAH in the United Kingdom is an estimated £510 million annually (Rivero-Arias et al. (2010)).

Although, as discussed above, the prognosis of an aneurysmal SAH is poor, IAs usually go undetected until rupture. However, with the increasing use of noninvasive intracranial imaging, an increasing number of unruptured incidental IAs (found

during investigation into another disease) and asymptomatic IAs (found in patients already suffering from a symptomatic aneurysm) are being incidentally discovered: the prevalence of incidental intracranial aneurysms among adults undergoing cerebral angiography is between 0.5 and 1% (Schievink (1997b)). Estimates of the incidence of aneurismal SAH range from 9 to 20 per 100 000 per year (van Munster et al. (2008)) which is far lower than the 3.6% prevalence and 6% prevalence observed in prospective autopsy and angiographic studies respectively (Rinkel et al. (1998)), suggesting that the majority of IAs do not rupture. .

If treatment is not imperative then this heightens the need to establish key guidelines on the stability of an aneurysm and its potential to lead to a SAH. A greater understanding of the biomechanical behaviour at the initiation and growth stages of an IA is required in order to confidently ascertain which course of treatment, if any is required at all, is optimum for a particular patient case. The following section will assess the pathophysiological factors that have been identified in the initiation, progression and potential rupture of intracranial aneurysms.

1.1 ARTERIAL WALL HISTOLOGY

Within the cardiovascular system there are two types of arteries: elastic and muscular. The elastic arteries are larger vessels which are generally in proximity to the heart, such as the aorta and the pulmonary artery. Muscular arteries distribute blood to the organs and muscles, such as the coronary arteries around the heart and the cerebral arteries within the brain. Both elastic and muscular arteries are composed of three concentric layers: the intima, the media and the adventitia which are uniquely structured depending on the type of artery. The greatest distinction

is down to the particular distribution of elastin, collagen and smooth muscle cells. The elastic arteries have a higher elastic and collagen content within the media to accommodate for the amount of stretch and recoil required during each cardiac pulse. In comparison muscular arteries require a higher density of smooth muscle cells to enable the dilation and contraction of the vessel in order to regulate the blood supply.

The following sections are aimed at understanding the basic composition of a healthy cerebral artery, in order to achieve a greater appreciation of the key elements that play a role in the aetiology, progression and potential rupture of an IA.

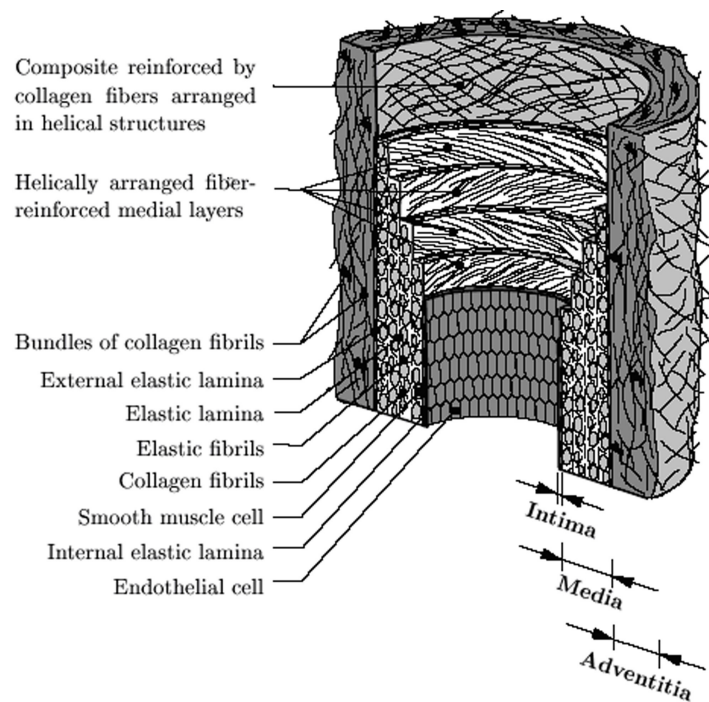


Figure 1.3: The artery is composed of three distinct layers: the intima, media and adventitia (Holzapfel et al. (2000))

1.1.1 Intima

The intima is the innermost layer of the arterial wall. It is composed of a single layer of vascular endothelial cells (ECs) and a subendothelial basal membrane.

1.1.1.1 Basal membrane

The basal membrane mainly consists of Type IV collagen, laminin and proteoglycans; although the basal membrane provides a minimal amount of tensile strength to the arterial wall, its primary function is to act as a support for the ECs (Stanley et al. (1982)).

1.1.1.2 Endothelial cells

The layer of endothelial cells that line the entire lumen carry out many functions such as blood pressure control, blood clotting and the formation of new blood vessels. These spindle shaped cells respond to both stretch and wall shear stress (WSS), by means of mechanotransduction, whereby the mechanical force induces a cellular biomolecular response through to the arterial medial layer (Davies (1995)). Changes in WSS due to a variation in blood pressure will be sensed by ECs, triggering a cascade of signalling pathways, resulting in the release of vasoconstrictors, such as nitric oxide (NO), or vasodilators, such as Endothelin-1 (ET-1), which regulate the constriction of smooth muscle cells present in the media. Endothelial cells are highly responsive to shear stress and arrange themselves in the direction of flow. Whereas, physiologic arterial WSS ($\sim 1.5\text{Pa}$) induces tightly aligned, quiescent ECs that align in the direction of flow (Moore et al. (1994); Topper et al. (1996); Malek et al. (1999)), low arterial WSS ($> 0.4\text{Pa}$) results in increased EC proliferation (Malek et al. (1999); Li et al. (2005); Chien (2008)) and increased EC permeability (Phelps and DePaola (2000); Tarbell (2010)). The role of high and low WSS are intrinsically linked to the growth and rupture of aneurysms, implying that endothelial mechanotransduction plays a vital role in the pathophysiology of the disease. ECs also act as a selective barrier between the lumen and the artery wall. There are four types of

junctions between endothelial cells: gap junctions, tight junctions, adherens junctions and syndesmos. These junctions each carry out specific functions, such as the regulation of endothelium permeability and the communication between adjacent cells and between ECs and neighbouring cells in the medial layer. In particular, EC permeability is regulated by intracellular junctions, controlling the passage of macromolecules and cells.

Dysfunction of the intima is linked to many arterial diseases. For instance, a decrease in the endothelium's permeability (i.e. intracellular junctions may become less impermeable during cell proliferation or cell apoptosis) lead to an accumulation of undesirable macromolecules within the intima; for example, in the case of atherosclerosis the artery wall thickens and hardens with the increase of low-density-lipoproteins (LDL) within the intima, or in the event of thrombosis the intracellular gaps allow for adherence of circulating platelets.

1.1.2 Media

The media is composed of numerous layers of concentrically arranged smooth muscle cells (SMCs) and of an extracellular matrix (ECM). In addition to this, an internal elastic lamina separates the intima from the media. This fenestrated elastin sheet, whilst allowing for the passage of water and nutrients, creates an added barrier to undesirable macromolecules (Penn et al. (1994)). However, unlike other systemic arteries, cerebral arteries do not have an external elastic lamina separating the media from the adventitia.

1.1.2.1 Smooth muscle cells

Cerebral arteries are categorised as muscular arteries as the SMCs occupy approximately 70% of the tunica media (Walmsley (1983)). Their predominant role is arterial contraction: each cell is individually composed of thin actin and thick myosin filaments which slide over each other causing contraction. As mentioned in the previous section, various mechanochemical signals initiate SMC contraction, such as the production of NO and ET-1. Local levels of O_2 and CO_2 , and most importantly the concentration of intracellular free calcium (Ca^{2+}), are also associated with muscle contractility (Murtada et al. (2010)). Under normal physiological conditions the SMCs are partially contracted and form the basal muscular tone.

SMCs also carry out various other functions during vascular development and vascular repair following injury. SMCs convert between two phenotypes: contractile and synthetic. Mature, fully differentiated SMCs express only a small amount of contractile proteins and have very slow proliferation rates (Owens (1995)). However, the sessile contractile phenotype can dedifferentiate to a synthetic phenotype during arterial disease or injury in order to migrate, proliferate, and subsequently differentiate back to their contractile state. Furthermore the dedifferentiated SMCs can upregulate the production of ECM (Owens (1995)): e.g. during vasculogenesis SMCs synthesise extracellular matrix proteins, most notably elastin, collagen and proteoglycans for the *de novo* formation of vessel walls.

Similarly to endothelial cells, SMCs are also tightly interconnected via junctions: gap junctions to facilitate intracellular communication and the propagation of electrical stimuli for contraction, and tight junctions providing mechanical coupling during contraction (Sanchrawala and Keaney (1997)).

1.1.2.2 Extracellular matrix

The extracellular matrix is essentially a mesh of fibrous proteins (e.g. collagen and elastin), adhesive glycoproteins (e.g. fibrillin, fibronectin and laminin) and ground substance (e.g. glycosaminoglycans and proteoglycans).

Adhesive glycoproteins, secreted into the ECM by fibroblasts present in the adventitia, fundamentally act as scaffolds for the deposition of elastin and collagen. Whereas the ground substance, made up of glycosaminoglycan and proteoglycan molecules, is an amorphous gel-like solution in which the fibrous proteins are embedded. Furthermore this aqueous medium plays an important role in the diffusion of nutrient through the media.

Predominant fibrous proteins forming the ECM are elastin and collagen. Elastin provides arteries with their resilience, allowing for stretch and recoil of the arterial wall. Elastin molecules, secreted into the extracellular space by the fibroblasts present in the adventitia and the SMCs present in the media (Ross (1971)), become tightly cross-linked to form elastic fibres, which in turn cross-link to form elastic sheets. Elastin has a long half-life of approximately 70 years (Shapiro et al. (1991)).

Within the medial ECM the fibrillar collagen molecules are 30% Type I and 70% Type III (von der Mark (1981); Shekhonin et al. (1985)). Collagen molecules are secreted by SMCs and fibroblasts into the extracellular space, assemble into collagen fibrils, which aggregate together to form bundles of fibrils known as collagen fibres. Type I collagen creates thin reticulous fibres, whereas Type III collagen assembles into thicker bundles, each adding particular mechanical properties to the media (Kroon (2010)). When cross-linked into the matrix these collagen fibres are

unloaded (histology shows their appearance to be 'crinkled', shown in Figure 1.4) and have a low modulus at low strains (Canham et al. (1991)); they effectively only become load bearing when straightened under high stress. When the collagen is loaded however, it can only undergo a 3-5% extension in length before rupturing (Kroon (2010)). Compared to elastin, collagen has a very high turnover rate, with a half-life ranging between 15 to 90 days depending on the type (Nissen et al. (1978); Humphrey and Rajagopal (2002)); notably, Type III has a shorter half-life than Type I (Rucklidge et al. (1992)).

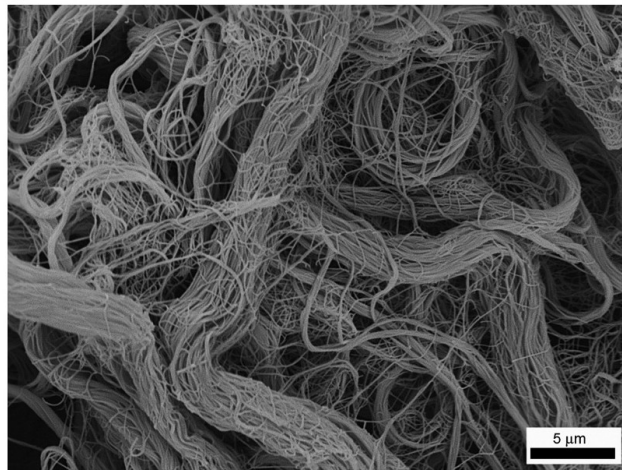


Figure 1.4: Scanning electron microscopy of organised collagen. (Flynn (2010)).

In terms of biomechanics, elastin and collagen together exhibit a highly nonlinear stress-strain relationship, hence prescribing the arterial wall with strength and resilience. Elastic fibres, accommodating for the pulsatile nature of blood flow, are active at low stresses giving rise to the compliance of arteries. Whereas collagen fibres resist stretch at high pressures, hence prescribing the anisotropic property of arteries (Roach and Burton (1957)). The composition of the media provides the greatest strength properties to the artery: the interconnection of the smooth muscle cells, elastin and collagen, form a continuous fibrous helix allowing the media to resist high loads in the circumferential direction (Holzapfel (2008)).

1.1.3 Adventitia

The outer-most layer of the wall, the adventitia, is essentially composed of an extracellular matrix with scattered fibroblasts, macrophages and nerves.

1.1.3.1 Adventitial extracellular matrix

Type I collagen, together with a small amount of elastin, present within the adventitial ECM provide further strength and compliance to the arterial wall. Collagen fibres come into play in response to high pressure conditions in order to prevent over-distention of smooth muscle cells within the media (Schulze-Bauer et al. (2002)). Differing from the circumferentially arranged collagen in the media, the collagen direction in the outer layer may vary from longitudinal to circumferential (Finlay et al. (1995)).

1.1.3.2 Fibroblasts

Fibroblasts are connective-tissue cells that secrete, synthesise and organise the extracellular matrix. Not only do fibroblasts synthesise collagen molecules but they also regulate the orientation, shape and size of developing collagen fibres (Birk et al. (1990)). The integrins (cell surface receptors) that physically attach the fibroblast to the ECM allow the fibroblasts to adapt the attachment of collagen in response to sensing local strains and stresses (Chiquet et al. (2003)). Moreover, the fibroblasts attach and configure the fibres in a state of stretch (Alberts et al. (2008)). Hence, arterial wall remodelling occurs in response to fluctuations in blood pressure, axial stretch and blood flow (Gibbons and Dzau (1994); Langille (1996); Jackson et al. (2002)). Fibroblasts are fundamental to vascular remodelling by maintaining homeostasis: in response to changes in mechanical strains they adjust the expression of

ECM components or matrix degrading proteases (Gupta and Grande-Allen (2006)).

Fibroblasts also play an important role in arterial wall repair. In response to lesions, a sequence of events is triggered starting with cell apoptosis (programmed cell death), followed by fibroblast proliferation and migration resulting in the release of plasma and proteins into the wound site. Fibroblasts are versatile connective-tissue cells and in certain cases will differentiate (e.g. into myofibroblasts (Scott et al. (1996); Siow et al. (2003))) before migrating to the site of injury to reconstruct the damaged ECM.

1.1.3.3 The lack of *vasa vasorum*

The predominant role of arteries is the supply of oxygenated blood to tissues and organs, however it is important to appreciate that the artery itself is a living tissue comprising of cells which require oxygen to function effectively. In most muscular arteries, a network of vessels, the *vasa vasorum*, supply blood flow to the outer layers of arteries, supplementing the provision of nutrients and oxygen diffused from the lumen. Development of *vasa vasorum* in the adventitia (which for some arteries may sometimes grow into the media) depends on arterial wall thickness and oxygen partial pressure within the lumen (Williams and Heistad (1996)): hence the presence of *vasa vasorum* is not ubiquitous within the systemic circulation. Histological studies have shown that most major intracranial arteries lack *vasa vasorum* under normal physiological conditions (Aydin (1998); Takaba et al. (1998)). There are two theories as to why cerebral aneurysms do not require increased blood supply to the outer layer of the wall. In muscular intracranial arteries, the width of each layer is thinner in relation to the diameter of the lumen than compared with any other systemic artery (Walmsley and Canham (1979)), in particular, cerebral arter-

ies have a very thin adventitial layer. For this reason, the first thought is that the nutritional needs of each arterial layer are entirely met by the diffusion of oxygen from the lumen. Secondly, the Circle of Willis is partially embedded in brain tissue and partially surrounded by cerebral spinal fluid (CSF) found in the ventricles and subarachnoid space and so it is hypothesised that for certain arteries the external layers of the wall may acquire oxygen by passive diffusion from cerebral spinal fluid (CFS) (Aydin (1998)).

1.2 INTRACRANIAL ANEURYSM PATHOPHYSIOLOGY

1.2.1 Initiation

Although not all research is in agreement with the specific pathogenesis of IAs, there is a general understanding that initiation is a complex interplay between cellular response to defects within the wall (i.e. due to intimal injury or congenital deficiencies in the media) and shear-mediated responses to haemodynamic forces.

A multitude of factors are thought to predispose the inception of an IA such as genetics, smoking, obesity, diabetes, hypertension, age and gender (Lasheras (2007)). Genetic risk factors include hereditary connective tissue diseases, such as Marfan's syndrome and Ehlers-Danlos Type IV syndromes (Schievink (1997a); van den Berg et al. (1999)). Marfan's syndrome causes abnormal fibrillin, a glycoprotein that is secreted by fibroblasts to be incorporated into the microfibrils composing the scaffold for the deposition of elastin, whilst Type IV Ehlers-Danlos syndrome causes a defect in Type III collagen. Another correlation is found in autosomal dominant polycystic kidney disease (ADPKD), the most common inherited renal disease. Approximately 10% of ADPKD patients present with an IA (Huston

et al. (1993); Ruggieri et al. (1994)). ADPKD is caused by the mutation of polycystin glycoproteins expressed in SMCs which are believed to interfere with their intracellular junctions causing arterial weakening (Arnaout (2000)). Overall these genetic deficiencies alone provoke irregular wall remodelling, which can be all the more aggravated by the increase in cyclic stress, due to certain 'lifestyle' risk factors (e.g. hypertension, smoking). This increase is thought to lead to fatigue remodelling of the ECM which could cause the arterial wall to slowly distend (Lasheras (2007)). In itself, cigarette smoking has been linked to accumulation of elastase, thought to induce injury to elastin within the media and trigger the initial dilation (Weitz et al. (1987); Bergoeing et al. (2007)).

The supply of blood to the brain is achieved through two circulations: whilst the anterior circulation supplies the forebrain, the posterior circulation supplies the posterior cortex, the midbrain and the brainstem. These two circulations are interconnected by an arterial ring at the base of the brain called the circle of Willis (Figure 1.5). The built-in redundancy of this 'circular' communication between the forebrain and hindbrain aids in maintaining a certain level of cerebral perfusion should an artery occlude or haemorrhage. Approximately 85% of saccular IAs are located in the anterior circulation: ~ 30-35% on the anterior communicating artery (AComA), ~ 30-35% at the bifurcation between the internal carotid artery (ICA) and the posterior communicating artery (PComA) and ~ 20% on the middle cerebral artery (MCA) (Kassell et al. (1990a); Brisman et al. (2006); Vlak et al. (2011b)). The remaining ~ 15% of saccular IAs are located at the basilar artery bifurcation and on other posterior arteries.

The circle of Willis is a tortuous circuit with many bends and bifurcations. In

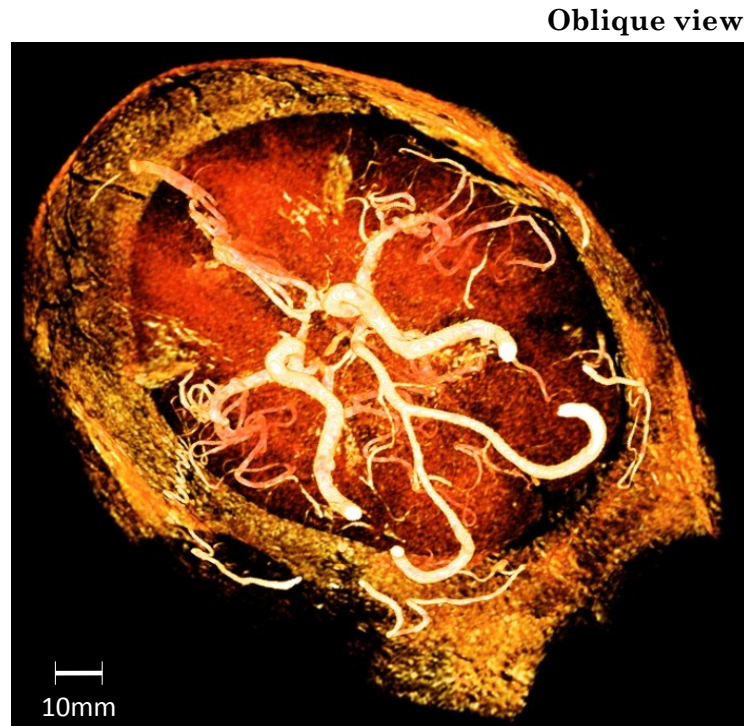


Figure 1.5: Voxel intensity volume extracted from patient MRA scan, highlighting the arterial network which makes up the Circle of Willis.

terms of haemodynamics, these geometrical characteristics prescribe the complexity of the blood flow, and together with the pulsatile, non-uniform nature of blood, dictate WSS variability at certain locations. The consistent formation of IAs at bifurcations has brought into question the effect of haemodynamic characteristics such as WSS, and wall shear stress gradient (WSSG) on aneurysm genesis. The wall subjected to accelerated flow away from the impingement point at the bifurcation apex experiences high WSS and high WSSG which can lead the loss of the IEL, ECs and SMCs (DePaola et al. (1992); Meng et al. (2007); Szymanski et al. (2008)). The pathological remodelling of the wall in these instances is postulated to disrupt wall homeostasis and initiate the formation of an IA. There is some debate as to whether the loss of SMCs is a prenatal congenital deficiency (Fujimoto (1996)) or a postnatal defect as a result (and not the cause) of an IA (Stehbens (1975)). Conversely,

saccular IAs also occur at non-branching sites (Takemura et al. (2010)). Kondo et al. (1997) were able to induce intracranial saccular aneurysms in rats at non-branching sites by stimulating increased haemodynamic stresses and hypertension, suggesting haemodynamics alone may play a vital role in aneurysm aetiology. It is important to note at this point that whereas animal models, such as the aforementioned study conducted by Kondo et al. (1997), can contribute to the overall general understanding of a disease, the data collected may not necessarily reflect the exact pathophysiology of aneurysm development in humans. This is to be kept in mind with regard to any other references made to animal models in the following sections.

1.2.2 Progression

Once the focal weakening of the artery wall is instigated, various pathophysiological processes promote the continual enlargement of IAs: chronic inflammatory response, apoptosis and loss of smooth muscle cells, fragmentation of the internal elastic lamina, breakage and decay of elastin and most importantly, increased and continual turn-over of collagen fabric. Similarly to its aetiology, IA expansion is the interconnection of biological reactions and mechanical responses.

Histological studies of developing IAs show thinning of the aneurysm wall, consisting primarily of an endothelial lining and a markedly thin adventitial (Asari and Ohmoto (1994)). As in vascular repair, SMCs are thought to participate in aneurysmal wall remodelling by changing phenotype, proliferating and migrating (Nakajima et al. (2000)). However there is also an elevated rate of SMC apoptosis during IA growth (Sakaki et al. (1997); Kondo et al. (1998)). Furthermore, cysteine cathepsin proteases (such as Cathepsin K, B and S) expressed by SMCs and macrophages have

deleterious effects on elastin and heightened expression of these elastases within the arterial wall promotes aneurysm growth (Aoki et al. (2008)). The combination of loss of SMCs, which synthesise elastin, and the slow turn-over rate of elastin (which also decreases with age (Hornebeck et al. (1978))) may further explain the limitation of elastin renewal following the degradation by proteases. Elastin deterioration results in a moderate dilatation of the wall (approximately 6-10% (Dobrin and Mrkvicka (1994))), which is preserved because collagen fibres are in a continual state of degradation and deposition in order to maintain wall homeostasis.

Proteolysis is a leading process in aneurysm progression; over-expression of matrix degrading proteases by ECs, SMCs and fibroblasts disrupt wall homeostasis. Matrix metalloproteinases (MMPs) serve many purposes, most notably: degradation of ECM structural elements, ECM organisation, creating paths for cell migration (SMC migration during myointimal hyperplasia, for example) and directly or indirectly adapting signalling molecules within the wall (Page-McCaw et al. (2007)). Various MMPs participate in maintaining homeostasis during vascular remodelling. The most widely reported are the collagen Type IV gelatinases MMP-2 and MMP-9, which also cleave partially degraded Type I and Type III collagens (Watanabe et al. (1993); Aimes and Quigley (1995)). MMP-1, an interstitial collagenase of Type I and Type III, and MMP-8, a neutrophil collagenase of Type I and III collagen and glycoproteins, are also critically involved in the breakdown of the ECM. Proteolytic activity of MMPs is controlled by expression of inhibitors, the most potent of which are tissue inhibitors of metalloproteinases (TIMPs). Immunohistological studies have revealed an increased activity of MMPs (Bruno et al. (1998); Wilson et al. (2005); Caird et al. (2006); Aoki et al. (2007a); Takemura et al. (2010)), and a decrease in the

expression of TIMPs (Aoki et al. (2007b)) during IA growth. Collagenolytic imbalances occur as a simultaneous consequence of down-regulation of collagen synthesis and TIMPs and an over expression of MMPs, which, in conjunction with impaired elasticity due to loss of elastin and increased haemodynamic stresses, sustains aneurysm expansion.

Structural proteins are not the only elements of the ECM that are affected. For example, increased expression of plasmin, a serine protease that cleaves the fibronectin and tenascin glycoproteins within the ECM, will further weaken the ECM scaffold itself (Bruno et al. (1998)). In addition, plasmin also activates diverse MMPs, further aggravating the degradation of the matrix structural constituents.

Haemodynamics also plays an important role in IA progression. Pulsatile flow induces rapid changes in flow directions into the aneurysm sac during the accelerating and subsequent decelerating of the systolic and diastolic phases respectively, producing distinct areas of varying WSS (Gonzalez et al. (1992)). Low WSS increases ECs turn-over, by affecting their function, shape and rate of apoptosis (Dewey et al. (1981); Dimmeler et al. (1996); Pentimalli et al. (2004)), promotes SMC migration (Sakamoto et al. (2006)) and activates MMPs and TIMPs (Sakamoto et al. (2006); Kang et al. (2008)). Whereas focal points of high WSSG are postulated to lead to degenerative remodelling (DePaola et al. (1992); Meng et al. (2007)).

1.2.3 Rupture

Risk factors for aneurysmal SAHs include gender (they are twice as likely to occur in women (Rinkel et al. (1998))), age, hypertension and various population-attributed ‘triggers’ (Vlak et al. (2011a)). Such triggers were identified as coffee con-

sumption (10.6%), the undertaking of vigorous exercise (7.9%), and other seemingly benign events such as nose-blowing (5.4%) and startling (2.7%). The underlying cause for rupture in these cases is the ultimate mechanical failure of the wall under increased loading: essentially the increase in blood pressure overcomes the wall tensile strength. However, as previously mentioned, only a small percentage of aneurysms rupture, and so there must be some underlying cause as to why some aneurysms are prone to rupture and some remain stable.

For each individual case, the initiation and progression is a distinct amalgamation of one or all mechanical stimuli and subsequent cellular responses described in the previous two sections. These dictate a perpetually evolving IA architecture due to changes in haemodynamic environment hence the potential for rupture is just as unique and misunderstood as the aetiology and pathology. In the aim of distinguishing a trend, many clinical studies have correlated various geometrical attributes with aneurysm rupture potential. Due to the nature of diagnostics, whereby clinical assessment is limited to image acquisition during patient scans, aneurysm diameter is widely used as a rupture index in interventional treatment planning. Reports state varying critical maximum diameters, ranging from 5 to 10mm (Kassell and Torner (1983); Wiebers et al. (1987); International Study of Unruptured Intracranial Aneurysms Investigators (1998); Weir et al. (2002); Beck et al. (2006); Imai et al. (2010)); although a small percentage of aneurysms smaller than 5mm have shown to rupture (Schievink et al. (1992)). To date, this criterion alone is widely used by clinicians as an indicator for intervention. However, advancements in imaging and 3D image processing techniques, such as 3D-rotational angiography, have highlighted many other morphological traits. Ujiie et al. (2001) measured aneurysm aspect ra-

tio (sac height over neck diameter) from angiographic data and found that 80% of ruptured aneurysms had an aspect ratio greater than 1.6. Other observed geometrical features include volume, surface area, undulation index, ellipticity index, non-sphericity index, size ratio and aneurysm angle (Gonzalez et al. (1992); Raghavan et al. (2005); Dhar et al. (2008); Chien et al. (2011); Xiang et al. (2011)). Dhar et al. (2008) state that aneurysms presenting with a aneurysm-to-vessel size ratio greater than 2.05 and an aneurysm angle (that is the angle of inclination between the IA and the plane of the neck) greater than 112 degrees have a 83% and 80% chance of rupture respectively. Furthermore the location within the Circle of Willis may also have an impact on incidence: a majority of small ruptured aneurysms are located within the anterior circulation (Beck et al. (2006)).

Aneurysm shape also dictates intrasaccular flow behaviour. The angle at which an IA rests in comparison to flow entry, or its proximity to turbulent flows out of bends and bifurcations, imposes the manner in which an aneurysm fills and determines impingement location and diameter. Exact locations of rupture within the fundus have been correlated with complex unstable flow patterns, secondary inflows, impingement jets, flow stasis, focal points of low WSS and high average WSS (Cebal and Löhner (2005); Hassan et al. (2005)).

From a mechanics perspective it is believed that IA shape (i.e. asymmetry, asphericity) and wall thickness have a greater influence on wall tensile stress distributions than overall size (Kyriacou and Humphrey (1996); Humphrey (1998); Ma et al. (2004)). Comparative clinical studies have demonstrated that in over 80% of cases the rupture of an aneurysm occurs at the fundus rather than at the neck (Sekhar and Heros (1981); Kataoka et al. (1999); Frösen et al. (2004)), suggesting that wall strength

is more compromised in certain portions of the dome. Histological observations of IA apex regions show fragmented internal elastic lamina and medial thinning (Crawford (1959); Abruzzo et al. (1998)). As the elastin degrades over time, the vessel distensibility decreases as load is transposed to the stiffer collagen fibres. With a debate as to whether Type III synthesis ceases during expansion (Neil-Dwyer et al. (1983); Ostergaard and Oxlund (1987); Leblanc et al. (1989); Kuivaniemi et al. (1993)) it is possible to hypothesise that the only (albeit stronger) load-bearing component remaining is the collagen Type I. Moreover, lysyl oxidase (LOX), a protein that plays a pivotal role in covalent crosslinking of ECM fibrous proteins, is also downregulated during aneurysm progression (Aoki et al. (2009)), and in ruptured cases the number of crosslinks is significantly reduced (Gaetani et al. (1997)). Furthermore, research has shown highly elevated levels of MMPs at the site of rupture (Todor et al. (1998); Wilson et al. (2006)); although it is ambiguous whether global proteolysis (i.e. a steady increase in MMP as the aneurysm expands) or local proteolysis (i.e. an accelerated response to local medial hemorrhaging) leads to rupture. Together with increased turn-over of collagen due to collagenolytic imbalances, these findings suggest continual deposition of unstable, immature collagen fibres. Taking all these mechanical discrepancies into consideration, the wall structure is no longer an organised helical mesh of SMCs and fibrous proteins suggesting its resistance to high loads is greatly compromised, which over the course of time could lead to focal weakness and subsequent failure of the wall.

As no two IAs are the same, the rate at which the wall yields may vary greatly. Aneurysms that display a rapid growth over a short period of time, classified as '*de novo*' aneurysms, are thought to have increased chances of rupture (Mitchell and

Jakubowski (2000); Yasuhara et al. (2002); Yoneoka et al. (2004)). One particular case study showed an aneurysm on the basilar artery which developed and ruptured within 44 days (Schebesch et al. (2008)). As these timescales can be approximated to collagen half-life, it has been suggested that these particular instances are structurally unstable and therefore more prone to rupture (Humphrey and Taylor (2008)).

Aneurysm enlargement does not necessarily imply wall thinning. Frösen et al. (2004) performed histological studies of 24 unruptured and 42 ruptured saccular IAs and classified four types of wall compositions: (i) thin wall comprising solely of ECs and organised SMCs, (ii) thick wall with disorganised SMCs, (iii) thick hypocellular (less than the normal number of cells) wall with myointimal hyperplasia or organised thrombus, and (iv) hypocellular wall with an extremely thin thrombus lining. All four types of aneurysms are likely to rupture: focal weakening is not only attributed to degenerative alterations to the ECM, it is also attributed to cellular dysfunction and local inflammation. The proliferation of SMCs following an inflammatory response often leads to myointimal hyperplasia

Wall thickening in this manner is believed to be an adaptive response to haemodynamic stresses (Intengan and Schiffrin (2001)). However the migration of SMCs to the luminal surface is only possible through the degradation of the matrix by MMPs (Zempo et al. (1994)) and Frösen et al. (2004) go on to speculate that IAs lined with myointimal hyperplasia rupture due to the excessive proteolytic activities. Furthermore immunohistochemical studies of ruptured aneurysms show a significant amount of degenerated SMCs that seem to have lost any particular phenotype characteristic (Nakajima et al. (2000)). It has also been shown that, under

altered flow conditions, dysfunctional ECs will continually trigger proinflammatory and proliferative signalling pathways (Chien (2008)). Histological observations in human IAs reveal that inflammatory cells, in particular macrophages, B- and T-lymphocytes, increase at the site of rupture (Chyatte et al. (1999); Kataoka et al. (1999); Frösen et al. (2004)). Inflammation is the initial biological response to invading pathogens, and the presence of proinflammatory cytokines released by lymphocytes and macrophages is indicative of cellular degradation and death. From the cohort of IAs studied by Kataoka et al. (1999) 50% of unruptured and 100% of the ruptured IAs presented with these inflammatory cells. Furthermore, as the aneurysm expands the inner lining of the aneurysm sac is composed of organised, uniformly shaped endothelial cells (Frösen et al. (2004)) which are understood to preserve a degree of response to hemodynamic stresses, whereas in ruptured cases the ECs are disorganised and the intracellular junctions may become less impermeable allowing for the adhesion or passage of unwanted cells and detrimental macromolecules (Figure 1.6).

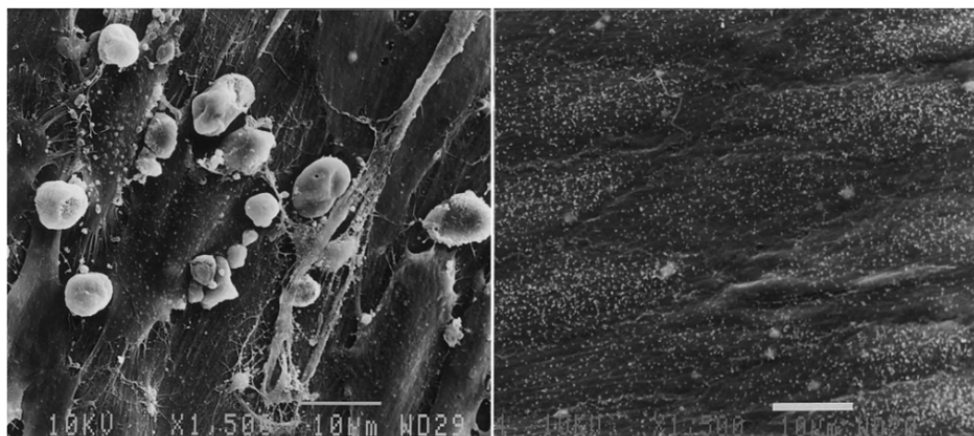


Figure 1.6: Scanning electron microscopy (SEM) of endothelial cells in intracranial aneurysms. Left, ruptured middle cerebral artery aneurysm: the arrangement of ECs is disrupted, and blood cells adhere to intracellular spaces. Right, incidentally discovered middle cerebral artery aneurysm, note the normal shape of the longitudinal EC layer. Bar=10 μ m. Taken from Kataoka et al. (1999).

Thus, the culmination of certain pathological responses such as disruption to the IEL, loss of ECs and SMCs, the gradual decay in elastin, the chronic inflammatory invasion of cells and the unstable deposition of the collagen matrix results in a mechanically fragile wall over time which will become weak enough to rupture.

1.3 CURRENT TREATMENT OPTIONS FOR IAS

Once the aneurysm has been detected, and a decision to intervene has been made the question remains as to which treatment would be the most successful given a particular IA architecture. Furthermore ruptured and unruptured aneurysms constitute distinctly different clinical entities and need to be treated as such. Imaging modalities offer the first step in diagnosis, and from these clinicians must assess which treatment is most suitable for a specific aneurysm type. The main objectives of treatment are to prevent haemorrhaging, obtain complete isolation of the aneurysm whilst still preserving the patency of the parent artery, and limit thromboembolic complications.

Interventional treatment of IAs focuses on the removal of the aneurysm from circulation, be it by neurosurgical or endovascular intervention. The more radical solutions involve neurosurgical procedures. Surgical clipping is a well established technique whereby a metal clip is placed across the base or the neck of the aneurysm in order to isolate it from normal circulation. The risk of recurrence or incomplete occlusion is in the order of 1.5% and 5.2% respectively (David et al. (1999); Thornton et al. (2000)). In rare cases where the artery itself is damaged, parent artery occlusion is performed, sometimes accompanied by a bypass, to reroute the flow of blood away from the afflicted artery. However these interventions are very invasive,

which over the years has led to the emergence of various endovascular therapies.

The endovascular implantation of mechanical devices aims to reduce intrasaccular flow and eventually trigger the formation of stable thrombus within the sac. Balloon embolisation is the oldest form of endovascular treatment. Pioneered by Serbinen (1974), this method of parent artery occlusion uses two balloons, one distal and one proximal to the opening of the aneurysms, into which a coagulating agent is injected through a catheter. It has been reported that this deconstructive procedure is particularly effective for giant intracranial aneurysms that are too large to clip or too large to achieve complete occlusion by coils or stents (Lubicz et al. (2004); Parkinson et al. (2008)). The real breakthrough in endovascular treatment was the inception of Guglielmi detachable coils (GDC, Boston Scientific/Target Therapeutics, CA, USA) in 1991 (Guglielmi et al. (1991)). The original procedure involves threading platinum (biologically inactive) coils through a catheter and inducing electrothrombosis by passing an electrical current through the coils before deployment. The process may be repeated with several coils until the aneurysm sac is deemed sufficiently packed. Although, electrothrombosis is not always necessary to induce the formation of the clot: the presence of coils alone is enough to obstruct the flow from circulating within the sac. Whilst the risk of complications is reported to be in the range of 3.7%, the rate of incomplete occlusion is reported to be 46% (Brilstra et al. (1999)). The leading cause for incomplete occlusions is coil migration and compaction which may lead to re-growth or even the formation of a secondary aneurysm (both of which would require re-treatment). Other risks are primarily arterial dissection, parent-artery occlusion and thromboembolic phenomena (Friedman et al. (2003)) whereas minor complications are comparable to those of diag-

nostic catheter angiography (Murayama et al. (2003)). When comparing with microsurgical clipping, the lower rates of complete occlusion and the higher rates of rebleeding and recurrence (Raftopoulos (2005)) question the long-term efficacy of coiling.

In particular, the low rates of occlusion found in wide-necked aneurysms led to the emergence of conjunctive endovascular strategies, such as balloon remodelling or intravascular stent placement as an aid to coiling (e.g. Higashida et al. (1997); Tong et al. (2000)). The first successful stent-assisted coil embolization of a ruptured IA was reported by Higashida et al. (1997), whereby a stainless steel coronary balloon-expandable stent was deployed before guiding GDC through the interstices of the stent. Thus, the stent was originally used to act as a scaffold across the aneurysm neck, trapping the microcatheter into place and stabilising the coil deployment. Nonetheless, the initial types of coronary intravascular stent used were fairly rigid (i.e inflexible) which limited navigation within the tortuous circuit that is the Circle of Willis. They also required high radial forces during balloon-catheter expansion to prevent recoil after deployment (Aziz et al. (2007)) which could lead to vessel injury or even rupture (Gross and Frerichs (2013)) due to the difference between the elastic coronary arteries and the muscular cerebral arteries. These inadequacies led to the development of flexible, higher porosity self-expandable stents that were designed out of shape memory alloys, such as the nitinol Neuroform (Boston Scientific Corporation, Natick, MA, USA) and nitinol Enterprise (Codman Neurovascular, Miami, FL, USA) stents, and their increasing implementation in stent-assisted coiling of IAs (Mericle et al. (1998); Lylyk et al. (2001); Fiorella et al. (2004); Howington et al. (2004); Lee et al. (2005); Higashida et al. (2005); Fiorella

et al. (2005, 2006); Weber et al. (2007)). With this technique Fiorella et al. (2005) observed high rates of progressive thrombosis of small aneurysms with wide necks (65%), with very low rates of recanalisation (5%). Following this study, Fiorella et al. (2006) observed that the presence of stent struts across the neck sufficiently altered the haemodynamics into the aneurysm sac. Ohta et al. (2005) speculated that intracranial stents reduce the shear stress on the aneurysmal wall and increase viscosity within the aneurysm sac, both of which are believed to induce a prothrombotic environment. From these early observations came the development of using these self-expandable stents as stand-alone devices (Vanninen et al. (2003); Wanke et al. (2003); Lylyk et al. (2005); Szikora et al. (2006a); Wanke and Forsting (2008)). These initial reports suggest that although these highly porous stents do affect the inflow into the aneurysm, a much lower porosity would further encourage embolisation and thus research was also conducted into the overlapping of multiple self-expanding stents (Benndorf et al. (2001a,b); Doerfler et al. (2004)). The success of these preliminary studies has led to the introduction of flow diverters, which are effectively self expandable stents of high metal surface area density and low porosity specifically designed for the embolization of intracranial aneurysms. The Silk Flow Diverter (Balt Extrusion, Montmorency, France) and the Pipeline Embolization Device (ev3 Endovascular Inc, MN, USA) are current the two commercially available designs. These devices have proved successful in the treatment of wide-necked, giant and thin-walled aneurysms, i.e. types which are deemed unfavourable for other embolisation techniques (Kallmes et al. (2007); Fiorella et al. (2009); Lylyk et al. (2009); Fiorella et al. (2010); Szikora et al. (2010); Byrne et al. (2010); Szikora et al. (2010); Nelson et al. (2011); Fischer et al. (2012)). Nelson et al. (2011) reported complete occlusion in 93.3% of IAs treated with a Pipeline flow-diverter. Nonetheless

there are some concerns with this technique also, the most significant being stenosis of the parent artery due to endothelialisation and neointimal growth over the stented segment (Fiorella et al. (2009)).

The rapid advances in endovascular device design have progressed to the point where surgical intervention is a rarity, resorted to only in particularly complex situations. However, the choice between devices, or between different designs and implementations of the same type of device, is a complicated and still unresolved problem. Randomised clinical trials, such as that conducted by the International Study of Unruptured Intracranial Aneurysms Investigators (1998) and the International Subarachnoid Aneurysm Trial (Molyneux et al. (2005)), give some insight into the benefits and risks of available treatment plans and their application to different classes of aneurysms (e.g. wide neck, giant). However, findings from clinical trials cannot necessarily be extrapolated to fit a different cohort of IAs, which is not surprising considering there are still some uncertainties as to why one aneurysm grows, stabilises and remains asymptomatic and another continues to expand to the point of yielding. Even with high occlusion rates, there are still some complications which will lead to initial or further haemorrhaging: any additional information that can be provided to clinicians can only ensure greater success rates in the treatment of IAs.

1.4 THE UNCERTAINTIES OF THROMBUS OCCLUSION

1.4.1 Thrombus pathogenesis

The formation of a stable thrombus is the whole basis behind endovascular treatment. Interestingly, thrombus can also occur spontaneously. It has been observed that thrombus is present in 55% of cases of giant intracranial aneurysms

(Peerless and Drake (1982); Whittle et al. (1982); Gerber et al. (1994)). Giant IAs (i.e. where the largest dimension is more than 2.5cm) constitute approximately 14% of IAs (Sharma et al. (2008)). A small percentage of saccular IAs (9-14%) also present with spontaneous thrombus (Brownlee et al. (1995)). Regardless of whether thrombus is a consequence of endovascular intervention or a spontaneous event, the mechanisms for initiation of this auto-healing process are the same. Three key factors are thought to predispose the initiation of thrombosis, known as Virchow's triad:

- i. Dysfunction or injury of the endothelium: whereas a functional, intact endothelium will prevent platelet activation and adhesion, a dysfunctional endothelium (as observed in Figure 1.6) will expose collagen to platelets which will then bind directly, or indirectly via the binding of a von Willebrand factor (vWF) (a subendothelium protein), to glycoproteins (Freedman (2008)).
- ii. Altered haemodynamics: slow and recirculating flows promote the accumulation and adhesion of pro-thrombogenic proteins. The slower the flow, the longer the particle residence times, which further encourages the development of a thrombus.
- iii. Blood hypercoagulability (or thrombophilia): deficiencies in blood anticoagulant factors and proteins lead to increased thrombus production.

In the instance of IAs, dysfunctional ECs and areas of slow recirculating flow within the sac are deemed to be particularly pro-thrombogenic. In essence, these antecedents allow for the adherence and activation of circulating platelets: tiny fragments of cells found in the blood. Blood is composed of a fluid portion, known as

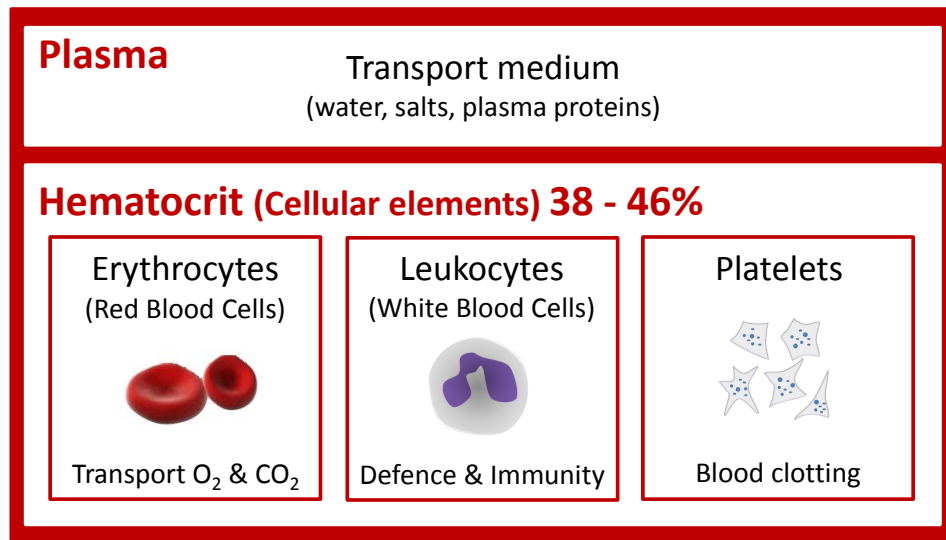


Figure 1.7: Schematic of the composition of blood

plasma, and a cellular portion, known as hematocrit (Figure 1.7). Erythrocytes (red blood cells) account for 99% of the hematocrit and their primary function is the transport of O_2 and CO_2 . The remaining 1% is composed of leukocytes (white blood cells) which are involved in defense and immunity, and platelets which have an important role in blood clotting; it is the aforementioned adherence of platelets that is the primary step in the coagulation cascade (Figure 1.8). It is widely discussed that two parallel pathways trigger coagulation: (i) intrinsic platelet activation by contact with exposed collagen, and (ii) extrinsic platelet activation by tissue factor (also known as Factor III or thrombokinase) present in the blood and/or the arterial wall. It is particularly believed that both occur simultaneously (Hoffman (2004); Furie and Furie (2007, 2008); Smith (2009)). Both pathways involve a series of enzymatic reactions of various coagulation factors (each factor is denoted as a roman numeral, e.g. Factor XII) which activate prothrombinase (Factor X). Following this, prothrombinase subsequently catalyzes the conversion of prothrombin (Factor II), a protein found in plasma, into thrombin (Factor IIa), a serine protease. Thrombin cleaves

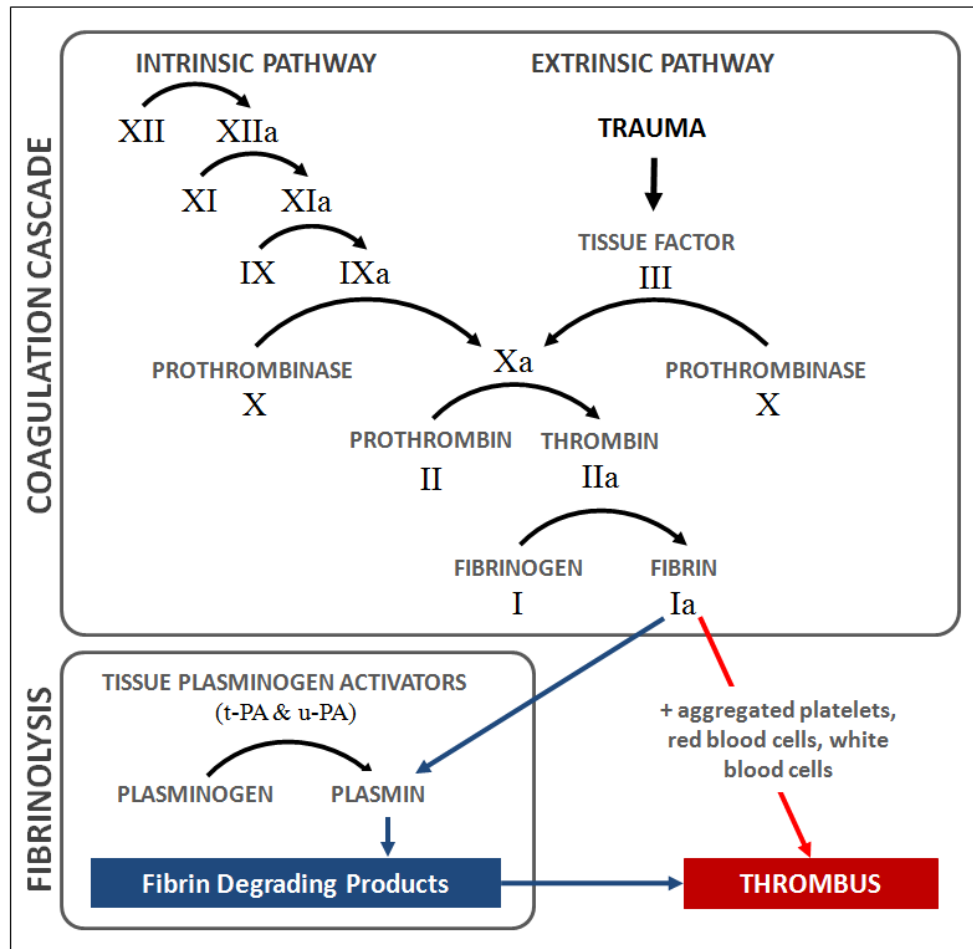


Figure 1.8: Schematic of the coagulation and plasmin-mediated fibrinolysis cascades involved in the building and degradation of clots.

the soluble plasma protein, fibrinogen (Factor I), into insoluble fibrin (Factor Ia) forming a dense network that captures red blood cells (erythrocytes), white blood cells (leukocytes) and platelets, i.e. a clot (Figure 1.9).

Clotting is the first part of the healing process, creating a seal over the wound site, the size of which is regulated by the plasmin-mediated fibrinolysis cascade (also shown in Figure 1.8). The enzymatic production of plasmin from its inactive form (plasminogen) breaks up the fibrous network through fibrin degrading products. Ineffective fibrinolysis due to limited antithrombogenic activities turns the

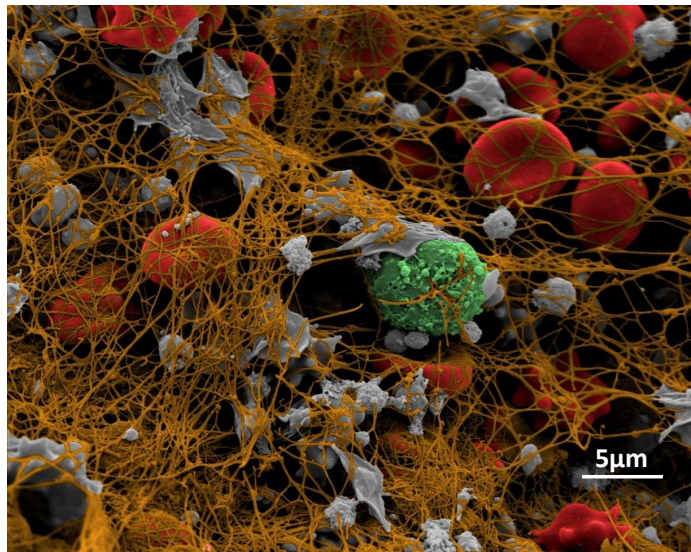


Figure 1.9: Colourized scanning electron micrograph of a coronary artery thrombus. Fibrin fibres are brown; platelet aggregates are grey; red blood cells are red; leukocytes are green (Weisel (2009)).

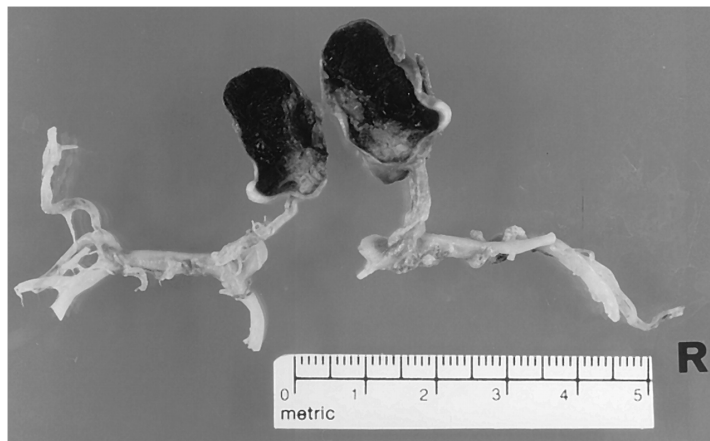


Figure 1.10: Spontaneous thrombus: gross photograph of IA and associated arteries. Aneurysm was cut in half, revealing the thrombus within its lumen (Brownlee et al. (1995)).

process pathogenic, causing the thrombus to continually expand, potentially leading to stenosis of the parent-artery. Figure 1.10 shows the presence of spontaneous unorganised thrombus completely filling the aneurysm sac; this patient succumbed to an ischemic attack due to the resulting block in blood flow as the thrombus progressed into the parent-artery. The balance between coagulation and fibrinolysis is a vital component to the formation of a stable clot.

1.4.2 Importance of thrombus organisation

The whole basis behind the implantation of flow-diverters is to disrupt the flow of blood to such an extent as to induce the formation of a stable (organised) thrombus, without affecting the patency of the parent artery (as shown in Figure 1.10). The ultimate goal of using flow-diverters as endovascular devices is that the thrombus becomes organised and retracts (D’Urso et al. (2011); Berge et al. (2012)). Nonetheless there have been reports of delayed rupture of IAs treated with flow-diverts due to the rapid formation of unstable thrombosis (Kulcsár et al. (2011); Turowski et al. (2011); Byrne and Szikora (2012)). Moreover, histologic assessment of coiled aneurysms demonstrate chronic compaction of disorganised thrombi around the coils (Kallmes et al. (1999); Szikora et al. (2006b)). These studies highlight the fact that thrombus formation alone is not sufficient for permanent occlusion: successful healing relies entirely on the fibrotic alteration of thrombus into granulated tissue. Mature granulated tissue no longer contains thrombus and is primarily composed of leukocytes, collagen, ECs, SMCs and myofibroblasts (Leu et al. (1988); Szikora et al. (2006a); Lee et al. (2007)). In the aim of promoting organisation research has been conducted into creating biologically active devices: modified with collagen (Szikora et al. (1997); Murayama et al. (1999)) or controlled release of a basic fibroblast growth factor (bFGF) (Kim et al. (2010)) to promote organised thrombus. Similarly, patients receiving endovascular treatment also require prophylactic antiplatelet therapy.

1.4.3 Beneficial mechanical properties of thrombus

The primary benefit is of course the successful occlusion of the aneurysm from the flow, hopefully halting its growth and reducing the risk of rupture. For the latter, one of the main hypotheses is that this added layer of organised thrombus partially relieves stress within the aneurysmal wall, reducing the risk of it yielding (Mower et al. (1997); Wang et al. (2001, 2002); Di Martino and Vorp (2003); Thubrikar et al. (2003); Bluestein et al. (2009)). *In silico* stress analysis of patient-specific abdominal aortic aneurysms (AAA) has demonstrated that thrombus affects the magnitude and distribution of wall stress (Wang et al. (2002); Di Martino and Vorp (2003); Bluestein et al. (2009)). *In vivo* pressure measurements of AAAs conducted by Thubrikar et al. (2003) found that, although thrombus allows for the transmission of luminal pressure to the aneurysm wall, the strains in the circumferential and longitudinal directions were significantly reduced to help prevent aneurysm rupture. Analysis of idealised AAA models carried out by Speelman et al. (2010) demonstrate that a decrease in WSS due to the presence of thrombus highly depends on the shear modulus and volume of the thrombus. As intra-luminal thrombus in abdominal aortic aneurysms is much more common (observed in 75% of cases (Harter et al. (1982))), there has been more research in this area. Although AAA and IAs are slightly different clinical entities they share many histopathological and biomechanical characteristics (Lasheras (2007); Humphrey and Taylor (2008)), and so it is possible to speculate that the effect of thrombus would be the same for IAs.

1.4.4 Detrimental effects of thrombus

1.4.4.1 Contribution to medial inflammation and degradation

It is speculated that thrombus may have deleterious effects on the portion of aneurysmal wall in which it is in direct contact. Kazi (2003) compared electron-micrographs of aneurysmal tissue not covered by thrombus and tissue covered by thrombus, and observed SMC apoptosis, accumulation of inflammatory T-cells, and fragmentation elastin fibres in the latter group. Fontaine et al. (2002) conducted *ex-vivo* immunohistochemistry studies and concluded that thrombus trapped circulating leukocytes and absorbed plasma components which secrete proteases into the aneurysm wall, whereas the aneurysm wall itself contained mainly tissue proteases, including MMPs. Platelets within thrombus also express several MMPs, including MMP-2 and MMP-9 (Sawicki et al. (1998); Fernandez-Patron et al. (1999)), which could further alter the homeostatic balance within an already vulnerable IA wall. Furthermore the portion of the wall in contact with thrombus has been reported to contain higher levels of plasmin which may further degrade the ECM scaffold (Jean-Claude et al. (1994)). The degrading qualities of thrombus is all the more prominent in cases where thrombus remains unorganised whereby the proteolytic environment is most unbalanced. Satta et al. (1996) speculates that thrombus thickness correlates to the level of fibrinolysis within the wall and measurement may be used as a indicator for potential rupture.

1.4.4.2 Risks of hypoxia

The effect of intraluminal thrombus on oxygen transport has been extensively researched for abdominal aortic aneurysms (for similar reasons as stated above).

Crompton (1966) speculates that mural thrombus impairs the diffusion of oxygen and metabolites into the aneurysm wall. Vorp et al. (2001) measured a reduction in oxygen partial pressure of up to 80% in the wall of AAAs coated with a thick layer of thrombus. In this same study it was demonstrated that these cases also presented with greater neovascularisation, that is the development of new blood vessels throughout the thrombus. The possible hypoxic conditions could therefore trigger the creation of new vessels in order to supply freshly oxygenated blood to the deprived areas. Giant IAs which have been completely occluded by endovascular treatment have been reported to continue growing and remain symptomatic (Schubiger et al. (1987); Hirasawa et al. (1992); Maruishi et al. (1994); Iihara et al. (2003); Dehdashti et al. (2009)). Furthermore it is observed that rupture occurs at the periphery of the thrombus (Teng et al. (2003); Krings et al. (2007)). These particular manifestations form a sub-category of giant IAs, termed partially thrombosed intracranial aneurysms (PTIAs), whereby the continual expansion is down to neovascularisation and recurring intramural haemorrhaging. Arterial occlusion by thrombus is a potent stimulus for the formation of intra- and extravascular neovascularisation in intracranial aneurysms (Aydin (1998)). Iihara et al. (2003) observed *vasa vasorum* on the parent artery proximal to the IA and on the neck itself. Yasargil (1984) and Schubiger et al. (1987) found an external network of *vasa vasorum* around the fundus of PTIAs. Dehdashti et al. (2009) observed vessels in the mural part adjacent to the thrombus layer but no pathological evidence of neovascularisation in the thrombus itself. Whereas, Nagahiro et al. (1995) observed intramural vessels through the remaining intima and adventitia that constituted the wall, as well as a network of intrathrombotic channels which interconnect the parent lumen to the wall. Rupture of either type of vessel is believed to result in intra-

mural haematomas. Nagahiro et al. (1995) speculate that the difference in pressure caused by blood flow from the parent artery into the small patent channels within the thrombus may cause large intramural haemorrhaging, separating the old organised thrombus from the wall. Each new haemorrhage incites the formation of a new clot, creating layers of thrombus of varying age and organisation giving the thrombus a laminated, ‘onion-skin-like’ appearance.

Given the above evidence, the following section investigates the possible deleterious environment created under hypoxic conditions to assess whether the presence of thrombus poses a great enough risk to aneurysmal wall functionality.

1.5 HYPOXIA: AN UNFAVOURABLE ENVIRONMENT

The systemic circulation plays a pivotal role in the body: it transports nutrients and oxygen to trillions of cells and carries away metabolic products. This task is achieved by the network of arteries that bifurcate and taper all the way to minute capillary vessels, where diffusion-based exchange can take place within tissues and organs. As oxygen plays such a critical role within the cardiovascular system, arterial cells are particularly sensitive to fluctuations in O_2 availability and have a multitude of mechanisms set in place to maintain homeostasis until normoxic conditions are restored. Should the hypoxic environment persist, it could ultimately lead to cell death, either due to energy depletion as the cellular respiration gradually comes to a halt or due to oxidative injury whereby the build up of reactive oxygen species (ROS), lactic acid and NO compromises cell viability.

This section will take a look at the adaptive responses to oxygen deprivation, and moreover, the resulting oxidative damage should these responses be ineffective.

1.5.1 Adaptive responses to hypoxic environments

1.5.1.1 Cellular respiration

All physiological mechanisms require energy in order to function and the basis behind this energy is the adenosine triphosphate (ATP) molecule. The conversion of biochemical energy from nutrients into ATP is achieved through aerobic and anaerobic metabolic reactions. Effectively each process involves the release of energy from the breakdown of glucose obtained from food. When the oxygen supply is plentiful, ATP is generated through aerobic glycolysis, whereby glucose is broken down in the presence of oxygen through cellular respiration, of which the waste products are CO_2 and H_2O . As the levels of O_2 decrease to a minimum, the ATP generation pathway switches to anaerobic glycolysis, whereby glucose is metabolised through fermentation in the absence of molecular oxygen (this switch in pathways is known as the Pasteur effect). In this instance however the by-products are CO_2 with ethanol or lactic acid. Fermentation only produces 2 molecules of ATP from each molecule of glucose oxidised, compared to the 36 molecules of ATP produced through cellular respiration (Purves et al. (2001)).

The mitochondrion only synthesises ATP in response to cellular demand, with respiratory control regulating the quantity of energy needed to meet required cellular activities; for instance, during muscle contraction replacement of energy consumed is achieved by increased cell oxidation of glucose for ATP synthesis. In instances of intermittent hypoxia, cells will adapt metabolic respiration in order to undergo oxygen conformance: a decrease in mitochondrial oxygen consumption within cells. In other terms, cellular energy demand is adjusted to the minimum

requirement for aerobic energy production through adaptive responses to hypoxia, including gene expression, membrane transport and metabolism suppression (Rissanen et al. (2006)). Should the hypoxic environment become chronic, then these adaptive respiratory responses are insufficient, and over time the cells will become completely energy depleted and will ultimately die.

1.5.1.2 Growth Factors

Oxygen conformance is not the only protective activity for adaptation to lower oxygen levels. In response to hypoxia, ECs will express the hypoxia inducible factor-1 (HIF-1). HIF-1 responds to variance in oxygen and mediates the transcription of genes involved in cellular respiration pathways in order to maintain oxygen homeostasis (Semenza (2007a)). HIF-1 also regulates the adaptive mechanisms responsible for increasing oxygen availability such as erythropoiesis: the production of red blood cells (effectively increasing the number of oxygen-carrying haemoglobin), and angiogenesis: the growth of new blood vessels from pre-existing ones (Wang et al. (1995)).

For angiogenesis, the presence of HIF-1 induces the expression of various growth factors. For example, expression of platelet-derived growth factor (PDGF) by granulated platelets, vascular endothelial growth factor (VEGF) by macrophages, and fibroblast growth factor (FBG) by injured ECs (Schultz and Grant (1991); Burke et al. (2003)). These growth factors stimulate ECs to secrete MMPs which degrade the underlying basal membrane, allowing for the proliferation, differentiation and infiltration of endothelial cells and the construction of new vessels. This is the process which leads to the neovascularisation observed in PTIAs. However, in certain instances the dome is completely denuded of ECs and this raises the question as to

whether this form of adaptation is always achieved or not, leading to hypoxia of the arterial wall.

1.5.2 Oxidative damage to arterial cells

1.5.2.1 Reactive Oxygen Species

Should the adaptive responses be inadequate there is a potential that arterial cells will be subjected to increased oxidative stress. During aerobic respiration, the oxidation of substrates yields two ‘waste’ products: carbon dioxide (CO₂) and water (H₂O). Molecular oxygen (O₂) is an ultimate electron acceptor, which can be reduced by four electrons. For instance, water molecules are produced when an oxygen molecule accepts four electrons, accompanied by two hydrogen atoms (i.e. protons) for each oxygen atom from the solution. In a few instances, oxygen accepts less than four electrons which yields certain reactive oxygen species (ROS): a one-electron reduction generates superoxide anion radical (O₂^{•-}), a two-electron reduction generates hydrogen peroxide (H₂O₂) and a three-electron reduction generates hydroxyl radical (OH[•]) (Figure 1.11).

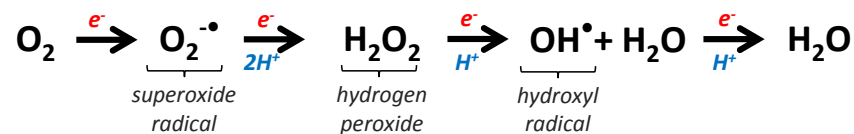


Figure 1.11: Reactive oxygen species: sequential reduction of oxygen in four single-electron steps.

Free radicals are effectively atoms with an unbalanced electrical charge, which attempt to cleave electrons from other molecules. So although oxygen by itself is fairly innocuous, its highly reactive forms can have serious deleterious effects. OH[•] in particular is extremely reactive and highly toxic. Being highly charged it cleaves

an electron from whichever molecule it comes into contact with, including DNA, proteins, carbohydrates and lipids (Kehrer (1993)).

In normal physiological conditions, approximately 5% of molecular oxygen is converted into ROS, however the simultaneous expression of antioxidants forms an adequate defense mechanism. Antioxidants scavenge ROS by giving up their electrons to these free radicals and rendering them harmless. Decreased oxygen levels during hypoxia results in a reduction in the rate of electron transfer to O_2 culminating in the excessive formation of ROS. Should the cellular antioxidant capacity be unable to detoxify the higher concentrations of ROS this leads to oxidative stress which compromises cellular functions; the chronic oxidation of lipids, nucleic acids and proteins by free radicals may result in cell dysfunction or death (Semenza (2007b)).

1.5.2.2 The toxicity of nitric oxide

Within the cerebral circulation, the primary response to low oxygen levels is the dilation of the arteries in order to increase blood circulation, i.e. the quantity of oxygen rich haemoglobin, through to the arterioles in order to maintain brain tissue perfusion. As discussed previously (section 1.1.2.1), NO is a potent vasodilator, the expression of which modulates SMC contractility. Actually, NO also regulates SMC migration and proliferation, EC stimulation, inhibits platelet activation and adherence, and prevents thrombosis (Cooke et al. (1990); Shultz and Raji (1992)). It is in higher doses that NO becomes highly toxic. Whereas low concentrations of NO will act as an antioxidant, whereby it scavenges electrons from ROS, higher levels will render it pro-oxidative (Joshi et al. (1999)); high levels of NO will not only induce further formation of ROS (Ide et al. (2001)) but also the formation of harmful

reactive nitrogen species (RNS) (Berg et al. (2004)). Excessive amounts of NO also affect the membrane potential of mitochondria, which in itself is instrumental to ATP production (Kaim and Dimroth (1999)). Extremely low levels of O₂ equate to reduced mitochondrial activity and as the last remaining ATP is absorbed, all that is left from anaerobic glycolysis is the overproduction of lactic acid and NO.

1.5.3 Detrimental effects to cellular functionality

‘Reduction-oxidation’ (Redox) imbalances have been shown to contribute to the pathogenesis of various cardiovascular diseases (Halliwell (1994)). In terms of arterial viability, a redox imbalance is speculated to degrade proteoglycans and collagens within the ECM (Henrotin et al. (2003)). Moreover, mitochondrial oxidative damage has been linked to endothelial dysfunction (Rubanyi and Vanhoutte (1986); Doughan et al. (2008); Schulz et al. (2008)) and the resulting modified phenotypes have been reported to promote SMC proliferation, adhere to circulating leukocytes and promote thrombosis (Loscalzo (2002)). In addition to the latter, oxidants are believed to enhance the formation of thrombin by stimulating the expression of tissue factor and inhibiting fibrinolytic pathways (Ambrosio et al. (1997)). ROS are also believed to modify IA structures to become proinflammatory (Tulamo et al. (2010)), specifically with the upregulation of proinflammatory cytokines such as Interleukin(IL)-2, IL-4 and interferon- γ (Losso and Bawadi (2005)).

The migration of macrophages within the thrombus and the damaged wall accentuates all the more the inflammatory responses to hypoxia. Macrophages, differentiated from a type of white blood cell (monocytes), are phagocytes whose function is to ingest cellular debris. Together with fibroblasts, macrophages are crit-

ical cellular components in wound repair and immune defence, and neither cell type undergoes necrosis during transient hypoxia: their proliferative capacity is significantly regulated by this stimulus (Agocha et al. (1997); Stenmark et al. (2002); Sakamoto and Seiki (2010)). Effectively these two cell types work together to regain homeostasis through the production of cytokines, growth factors, and ROS by macrophages and the secretion of matrix and matrix-degrading proteases by fibroblasts. Paradoxically, the overexpression of these proteases could have deleterious effects on the integrity of the arterial wall.

Diminished O_2 levels directly affect SMCs functionality. Ray et al. (2008) studied rat aortic SMCs in hypoxia and found that continued exposure to 1% O_2 increased rates of SMC proliferation and apoptosis. Furthermore altered steady-state Ca_2^+ levels within SMC as a consequence of hypoxia have been reported to impair contractility (Aalkjaer and Lombard (1995); Taggart and Wray (1998)). Hypoxia also affects their ability to synthesise collagen (Pietilä and Jaakkola (1984); Stavenow and Berg (1987)). Rabbit aortic SMCs in culture were subjected to hypoxia by Pietilä and Jaakkola (1984) and it was observed that the SMC collagen synthesis rate decreased to approximately half of that of the control subjected to normoxia. Furthermore collagen production by fibroblasts was shown to precipitously downregulate after a 48h exposure to 2% O_2 (Steinbrech et al. (1999)).

Lee et al. (2002) examined the effect of NO on fibroblast cell survival under normoxia (21% O_2) and hypoxia (1.5% O_2), and found that under hypoxic conditions NO inhibited the generation of mitochondrial ATP and, under prolonged exposure, activated mitochondrial-dependant apoptosis of fibroblasts. Furthermore fibroblasts, macrophages, ECs and SMCs all depend on glycolysis for ATP production and

are rendered non-functional and energy depleted when subjected to chronic hypoxia. Under these severe conditions, the renewal of ECM proteins could cease altogether leading to further structural imbalances.

Thus, it is hypothesised that chronic hypoxia could lead to the culmination of endothelial dysfunction, SMCs and fibroblast apoptosis, excessive production of proteases, reduced collagen deposition and the accumulation of inflammatory cells causing the ultimate rupture of an aneurysmal wall.

MODELLING OF INTRACRANIAL ANEURYSMS: HISTORY AND OBSERVATION

Extensive exploration of solute transport in atherosclerosis has led to an array of studies of oxygen distribution in large arteries. Whilst earlier analytical models shed a little light onto the influence of both ‘fluid-side’ and ‘wall-side’ oxygen transport properties, this is all the more emphasised with the emergence of coupled flow-mass transport (FM) computational modelling of idealised and patient-generated arterial models. Nonetheless, the limited investigations into oxygen mass transport within IAs demonstrate the need for further exploration into the potential deleterious hypoxic conditions as a result of intrasaccular haemodynamics in untreated, treated (i.e. thrombus formation, endovascular devices) and evolving aneurysms.

2.1 OXYGEN MASS TRANSPORT IN ARTERIES

2.1.1 Atherosclerosis: a motivation

Atherosclerosis, as the single leading cause of morbidity and mortality in the Western world (NIHLB (2009)), has led to great advancements in modelling of arterial disease. Thus, a brief comment is made on the aetiology and pathophysiology of atherosclerosis in order to provide an insight into the initial motivation behind the development of solute mass transport modelling in arteries.

The specific underlying cellular and molecular mechanisms that contribute to atherosclerosis are not fully understood. It is commonly believed that low density lipoprotein (LDL), a molecule that carries cholesterol from the liver to the tissues of the body, penetrates the arterial wall through the endothelium and into the intima. Oxidization of the LDL triggers the recruitment of monocytes, which differentiate into macrophages, ingest oxidized LDL, and form foam cells (in early development

of the disease, these foam cells are characterized as fatty streaks) (Ross (1999); Libby (2002)). As the disease progresses, the fatty streaks become fibrous plaques, expanding due to lipid accumulation, SMC migration and proliferation, and platelet aggregation (Guyton and Klemp (1989)). In the advanced stages of the disease, a layer composed primarily of vascular smooth muscle cells and collagen forms between the plaque and the lumen, often defining a necrotic lipid core. Rupture of this cap can lead to local thrombogenesis or distal embolisation, whilst plaque growth results in wall remodelling and the chronic stenosis of the lumen, potentially leading to a myocardial infarction or an ischemic stroke (Ross (1999); Libby (2002)).

Atherosclerosis appears to occur at bifurcations and in areas of marked curvature, locations that are believed prone to adaptive thickening of the intima in response to haemodynamic WSS (Irace et al. (2004); Cunningham and Gotlieb (2005)). A leading hypothesis is that the observed locations of low WSS relate to regions of wall hypoxia, which could result in increased endothelium permeability (due to adaptive responses such as the expression of VEGF), thus allowing for the passage of damaging macromolecules (Himburg et al. (2004)). This hypothesis has led to the extensive development of mass-transport modelling of various molecules in larger arteries, such as LDL (Packham et al. (1967); Somer and Schwartz (1972); Deng et al. (1993, 1995); Wada and Karino (1999, 2002); Ueda et al. (2004); Koshiha et al. (2007); Sun et al. (2007)); albumin (another macromolecule thought to play a key role in atherosclerosis) (Tarbell et al. (1988); Rappitsch and Perktold (1996b); Karner et al. (2001)); and oxygen (Back (1976); Buerk and Goldstick (1982); Rappitsch and Perktold (1996a); Rappitsch et al. (1997); Ma et al. (1997); Moore and Ethier (1997); Qiu and Tarbell (2000); Stangeby and Ethier (2002b,a); Kaazempur-Mofrad and Ethier (2001); Kaazempur-Mofrad et al. (2005)).

The following section will give a historical outline of the fundamental principles that have emerged from the analytical and numerical modelling of oxygen mass transport within large arteries.

2.1.2 Mass transport of oxygen in large arteries

2.1.2.1 Pioneering analytical models

The earliest investigations into mass transport of oxygen in larger arteries were conducted in single layer 2D geometries (Back (1975); Friedman and Ehrlich (1975); Ehrlich and Friedman (1977)). These ‘wall-free’ models comprise of analytically solve the axial and radial Navier-Stokes flow equations across the mass transport boundary layer at the lumen-wall interface. Trans-mural oxygen transport is not taken into account and the radial passage of oxygen at the lumen-wall interface is hypothesised to be limited by the cell-free plasma layer adjacent to the endothelium, represented by the introduction of a resistance coefficient within the oxygen diffusive flux calculations at the boundary.

Back (1976) went on to consider a 2D straight artery with a single layer wall. Steady state Navier-Stokes and radial convection-diffusion equations were analytically solved across an estimated mass transport boundary layer within the lumen for both Newtonian steady and pulsatile flow. Here again, the flux at the wall was limited by a transfer coefficient which accounts for the postulated barrier created by the plasma layer. The filtration velocities of oxygen were measured to be 2-3 orders of magnitude lower than oxygen diffusion velocities, thus convective flux was deemed negligible and trans-mural transport was limited to diffusion only. Furthermore a source term is introduced into the wall-side oxygen diffusion equation to take into consideration the cell ‘*utilisation*’. This term is assumed uniform, independent of local O_2 concentration, and through lack of experimental data, is evaluated using trans-capillary exchange kinetics. Results demonstrated that whilst flow pulsatility had small effects on the oxygen concentration in the near-wall regions, the overall distribution across the wall is mostly affected by the prescribed resistance of the endothelium and the ‘enzymatic utilisation’ of oxygen. Comparison with *in vivo* trans-mural oxygen partial pressure (PO_2) measurements conducted in rabbits (Ninikoski et al. (1973)) showed a reasonable correlation between measured and pre-

dicted oxygen tensions, thus demonstrating the importance of including ‘wall-side’ mass transport in simulations.

In a series of studies, Schneiderman, Goldstick and co-workers (Schneiderman et al. (1974); Schneiderman (1975); Goldstick et al. (1977); Schneiderman and Goldstick (1978a,b); Schneiderman et al. (1982)) developed a more comprehensive 2D axisymmetric model which took into consideration the transport of oxygen through both the ‘blood-side’(fluid-phase) and ‘wall-side’. The unique characteristics of this model are four-fold:

→ *Blood-side*:

(i) The fluid-phase accounts for both the free dissolved oxygen in the plasma and the oxygen that becomes unbound from oxyhaemoglobin in the hematocrit. The non-linearity of oxygen dissociation from oxyhaemoglobin is prescribed by the equilibrium curve defined by Hill (1910).

(ii) Both the axial and radial convection-diffusion equations are numerically solved across the mass transport boundary layer at the lumen/wall interface.

→ *Wall-side*:

(iii) The wall is represented by a multi-layered composite of homogeneous layers : intima, avascular media, vascularised media and vascularised adventitia (as large arteries present with *vasa vasorum*). Steady state 1D diffusivity is numerically solved in the radial direction only. Each layer is prescribed a specific oxygen diffusivity and consumption term found in the literature. The diffusive flux across each tissue layer interface is considered continuous.

(iv) The constant supply of fresh oxygen by the *vasa vasorum* is represented by constant influx of oxygen at the media-adventitia interface.

Incremental improvements are made to the model as the observed radial oxygen profiles through the wall layers are consistently validated against physiological data ((e.g. Schneiderman et al. (1974); Schneiderman (1975); Schneiderman and Goldstick (1978b))). One of the most notable observations brings into question the hypothesis that oxygen is limited by the presence of the plasma layer adjacent to the

endothelium. Schneiderman and Goldstick (1978b) showed an insignificant difference in trans-mural oxygen profiles when varying the plasma layer thickness. However, a variation in diffusivity coefficients (originating from conflicting experimental data) led to substantial alterations to the oxygen distribution through the fluid and wall layers. Furthermore, in agreement with findings by Back (1976), a series of evaluations ascertained the relatively small difference between steady and pulsatile flow on convective oxygen transport in both rigid and distensible walls (Schneiderman (1975); Goldstick et al. (1977); Schneiderman et al. (1982)). In particular, Schneiderman et al. (1982) postulated the wall consumption term had a dampening effect on pulsatility. In essence, this exhaustive sequence of studies lead to the same conclusion: oxygen transport is limited by wall-side properties.

Buerk and Goldstick (1982) compared experimental data of transmural PO_2 profiles of a dog thoracic aorta measured *in vivo* to analytical calculations of radial diffusion through the artery wall. Curve fitting led to the speculation that the spatial distribution of vascular wall properties (e.g. consumption rate, diffusion coefficient) varies radially across the intima, media and adventitia layers.

2.1.2.2 Computational modelling of oxygen mass transport

Advancements in computational methods for numerically solving governing conservation equations of mass, momentum and species (e.g finite-element (Donea and Huerta (2003)) and finite-volume methodologies (Patankar (1980); Ferziger and Peric (2002))) led to the emergence of coupled flow-mass transport (FM) computational models of oxygen transport in arteries.

One of the earliest numerical simulations of coupled FM, was applied to an idealised 2D axi-symmetric representation of a stenosed artery (Rappitsch and Perktold (1996a)) and an idealised 3D representation of a curved artery (Rappitsch et al. (1997)). The computational domain was of the fluid-phase only, and the wall-side effects were characterised by a simple boundary condition. The pulsatile flow was assumed incompressible Newtonian with a no-slip boundary condition at the outer

wall (i.e. the lumen/wall interface). Two particular solutes were modelled, LDL and oxygen, and both were assumed to be transported by convective and diffusive flux. The flux at the lumen-wall interface was explored for two cases: a constant permeability and a linear shear-dependent permeability (as the WSS reduces, so does the arterial permeability). The transient simulations of the coupled velocity field and convection-diffusion of oxygen were computed using a finite element approach: the streamline upwind/Petrov-Galerkin (SUPG) technique (Brooks and Hughes (1982)) was used as the flow was considered convection dominated.

For both geometries (2D and 3D) the results of shear-dependent permeability resulted in a greater spatial variation of wall flux than when the wall permeability is maintained constant. Whereas wall shear stress is believed to affect the endothelial transport barrier to the permeation of large macromolecules such as LDL and albumin (Jo et al. (1991); Tarbell (1993)), this is not believed to be the case for oxygen. Experiments conducted on human endothelial cells demonstrate very high permeability of the endothelium to oxygen (Liu et al. (1992)), and may be neglected completely (Qiu and Tarbell (2000)). Tarbell (2003) classifies the type of transport mechanisms with regard to the kinetics of the particular solute:

- (i) For a reactive species, such as ATP, the endothelium is modelled as a reactive surface across which enzyme catalysation occurs;
- (ii) Large macromolecules, such as LDL and albumin, permeate through EC intracellular junctions but do not interact with the intima, thus the endothelium may be modelled as a shear-dependant permeable membrane;
- (iii) The permeation of gases, such as O_2 , is not limited by the endothelium, hence the passage across the entire length of the endothelium is simply driven by the consumption of O_2 by the underlying layers (e.g SMC respiration within the media).

Thus, the aforementioned models that take into account endothelium permeability of oxygen may be considered too restrictive. Nonetheless, the results from both

studies highlight the strong correlation between flow field (i.e. velocity gradient, WSS) and the resulting spatial distribution of solute concentration. The 2D axisymmetric model of a stenosis (Rappitsch and Perktold (1996a)) demonstrated a reduction in oxygen concentration downstream of the stenosis, where it is speculated that the slower recirculating flow in the separation region limits the oxygen transport to diffusion only. Results from the 3D curved artery simulations (Rappitsch et al. (1997)) demonstrate a strong correlation between areas of low wall shear stress and low solute transport at the lumen-wall interface of the inner curvature.

Ma et al. (1997) computed the coupled FM in a 2D planar representation of a carotid bifurcation with the aid of computational fluid dynamics (CFD). The steady-state incompressible, Newtonian flow and convection-diffusion equations within the lumen were solved using finite volume methods; the pressure-velocity coupling was achieved using the Semi-Implicit Method for Pressure-Linked Equations (SIMPLE) algorithm (Patankar (1980); Ferziger and Peric (2002)). This ‘wall-free’ model implements a no-slip condition for the flow and a constant oxygen concentration at the wall boundary. Once again a strong correlation was found between the regions flow separation, vortical and secondary flows, and low WSS and the zones of spatial variation in oxygen levels within the lumen. The geometrical attributes of the 2D planar model are based on biplanar measurements of patient angiograms (Bharadvaj et al. (1982a,b)). Comparisons made between this experimental data and the computed solute transport demonstrate a link between oxygen deficiency and measured arterial wall thickening.

Moore and Ethier (1997) carried out a coupled FM CFD simulation in an idealised 2D axisymmetric stenosed artery. This two layered model takes into consideration:

- (i) Fluid-phase mass transport: the convection and diffusion of free oxygen and oxhaemoglobin were computed across the whole lumen. Similarly to Schneiderman and Goldstick (1978b) the non-linear dissociation of oxygen from oxy-

haemoglobin was based on the Hill equation (Hill (1910));

- (ii) Wall-side mass transport: based on the findings by Back (1976) the convective flux was assumed to be negligible, hence the transport of oxygen was reduced to the diffusive flux and the consumption of oxygen by cells. The diffusivity and consumption terms were both maintained constant across the homogeneous wall.

The flow field and mass transport equations were solved using with a finite volume power law spatial differencing scheme (Patankar (1980); Ferziger and Peric (2002)). A comparison is made between a fluid-phase only model, with a constant oxygen tension at the wall boundary, and a coupled fluid-wall model which takes into account diffusion and consumption in the wall. The fluid-phase results demonstrate a reduction in tension as oxygen is convected away from the wall at the flow separation point and a diffusion dominated flux within the recirculation zone (similar to observations by Rappitsch and Perktold (1996a)). However the results of the coupled fluid-wall model suggest that wall-side oxygen mass transfer resistance is much larger than blood-side resistance. The haemodynamic features downstream of the stenosis seem to have a negligible effect and the local oxygen convective flux is maintained by the wall-side oxygen demand due to the prescribed consumption term. This work brings back to the fore the importance of taking into consideration the wall-side oxygen transport (as originally highlighted by the earlier analytical studies of Back (1976) and Schneiderman and Goldstick (1978b)). Two other important observations were made within this work: (i) exclusion of oxygen transport by oxyhaemoglobin leads to large difference in oxygen tension, thus cannot be neglected; (ii) a variation in wall thickness affects the oxygen distribution through the wall, however has no effect on ‘blood-side’ oxygen delivery to the wall due to the dominance of the consumption term.

Numerous numerical studies were carried out on 3D realistic and idealised models of arteries to consider the effect of arterial curvature (Qiu and Tarbell (2000);

Kaazempur-Mofrad and Ethier (2001); Coppola and Caro (2008)), arterial bifurcations (Tada and Tarbell (2006)), and stenosis (Kaazempur-Mofrad et al. (2005)) on oxygen mass transport. All these model fluid-phase effects only with the implementation of a constant oxygen tension at the wall boundary. The results continue to provide resounding evidence that secondary and recirculation flows, flow separation, low WSS, low oscillating WSS have a large impact on local concentrations of oxygen. Arguably, the assertions regarding the importance of fluid-phase oxygen transport are not physically relevant as they do not account for oxygen respiration in the wall. All previous fluid-wall studies have demonstrated that oxygen transport is wall-limited and not fluid-limited (Back (1976); Schneiderman and Goldstick (1978b); Moore and Ethier (1997)). This notion is substantiated by the results of comparative finite-volume simulations carried out by Tada and Tarbell (2006) and Tada (2010). The coupled FM of oxygen is simulated in a 3D idealised geometry of a carotid artery bifurcation. Both studies are identical in that the governing transient equations were solved for pulsatile flow and oxygen convection-diffusion within the lumen domain. However, they differ in wall representations: the wall-free model (Tada and Tarbell (2006)) implements a constant oxygen tension of 0mmHg at the fluid/wall interface (i.e it is assumed that the oxygen is instantaneously consumed as it reaches the wall inner boundary), whilst the coupled fluid-wall model (Tada (2010)) models the oxygen diffusion and consumption through the wall boundary, with a continuous flux boundary at the lumen/wall interface and a constant supply of oxygen from the *vasa vasorum* at the outer wall boundary. The earlier wall-free model demonstrates a notable limitation to oxygen distribution in the region of flow separation in the internal carotid artery sinus. The results from the latter fluid-wall model revealed an almost uniform distribution of oxygen within the fluid-region regardless of local haemodynamic phenomena. The latter case also highlights the transport behaviour within the wall: a thin boundary layer forms at the lumen/wall interface as a consequence of slower transport through the wall, the thickness of which is affected by the slow reversed flow at the sinus, resulting in a lower oxygen

tension within the wall itself. Hence, although fluid-side transport is dominated by the wall consumption term, the wall-side transport is also limited by the flow features of the blood-side. Furthermore, Tada (2010) computed both steady and pulsatile flow and results demonstrated qualitatively similar mass transport distribution patterns in both flow conditions.

2.1.3 Mass transfer in ‘healthy’ aneurysms

To the author’s knowledge, the coupled FM CFD analysis conducted by Imai et al. (2010) is the only study that explores solute transport in IAs. The wall-free simulations were carried out in 24 idealised 3D geometries of saccular IAs to explore the effect of parent vessel curvature, aneurysm angle (relative to the parent vessel) and aneurysm geometry (depth and height of sac) on ATP transport. Flow and convection-diffusion in the fluid domain were solved by a finite-volume method, with the SIMPLE algorithm for pressure-velocity coupling (Patankar (1980); Ferziger and Peric (2002)). The free flux at the wall interface is limited by the hydrolysis of ATP to adenosine diphosphate (ADP) (i.e. the endothelium is modelled as a reactive surface (Tarbell (2003))). The results revealed a strong correlation between ATP concentration and distribution across the wall interface of the aneurysm dome and the magnitude and direction of flow from the parent artery into the aneurysm sac prescribed by variations in arterial curvature (particularly due to the influence of secondary flows) and aneurysm angle. Furthermore, low velocity recirculation within the aneurysm dome itself created areas of low ATP concentration, consistent with areas of low WSS. This work makes a particular note within the discussion regarding the similarity between ATP and O_2 (both low molecular weight molecules are believed to be limited in the same way by fluid-phase transport (Tarbell (2003))) and speculates that oxygen distribution in an IA would not be dissimilar to that of ATP. However this assertion neglects the dominance of wall-side transport on oxygen distribution through the lumen and wall that has been elucidated by Moore and Ethier (1997) and Tada (2010). This highlights the need for a more comprehensive model

that models fluid-wall mass transport of oxygen in IAs.

2.1.4 Mass transport of oxygen in thrombosed aneurysms

Wolf et al. (1994) measured AAA diameter, area and volume and corresponding thrombus area and volume of 80 aneurysms in a series of follow-up CT scans over the course of 8 years, and found a strong correlation between thrombus load and aneurysm evolution. These findings led Vorp et al. (1996) to make the initial hypothesis that thrombus served as a barrier to diffusion of oxygen from the lumen to the arterial wall, thus inciting accelerated degradation to the wall. A simple analytical calculation of radial oxygen flowrate across a thrombus layer in an idealised geometry of a AAA demonstrated a 20-fold difference between the oxygen levels at the thrombus/wall interface and the required oxygen levels required for SMC respiration. Following this preliminary investigation, Vorp et al. (1998) extended this to a 3D idealised mass transport model of an axisymmetric AAA to investigate the effect of thrombus thickness and bulge diameter (i.e. the maximum radius of the fusiform geometry) on oxygen distribution. This single layer model only takes into account the steady state diffusion of oxygen through the thrombus layer. The lumen/thrombus boundary is set to a constant blood-side constant, whereas the continuous flux through the thrombus/wall boundary is driven by a consumption term representative of oxygen consumption by SMCs in the wall. It was concluded that thrombus thickness has the greatest effect on oxygen delivery to the thrombus/wall interface: with a thrombus thickness of 1.5cm the normalised (relative to luminal value) oxygen partial pressure decreases to $\approx 10\%$ at the lumen/wall interface. Nonetheless this model has several limitations, most notably that it does not take into account blood-side or wall-side oxygen transport.

Sun et al. (2009) conducted finite-element modelling of coupled FM in a patient-specific model of AAA presenting with intraluminal thrombus. The arterial geometry reconstructed from patient CT is defined as the thrombus/wall interface, whilst a uniform wall thickness is artificially created. The inhomogeneous thrombus ge-

ometry is also segmented from patient scans thus the effect of varying thickness distribution on wall oxygenation is inherently investigated in this study. The fluid-wall model is an extension of a previous 2D model of a 'healthy' artery (Sun et al. (2006)) which neglects convective flux and thus only solves a diffusive-consumption for oxygen transport in the wall. Flow through the thrombus is deemed insignificant, therefore mass transport is limited to diffusion-only flux through this layer. Although the variation in WSS at the lumen/thrombus interface is significant (0 to 1Pa), the normalised oxygen concentration only varies from 90 to 100% which suggests the oxygen distribution to the thrombus is not greatly limited by local WSS. However, observations of oxygen distribution at the thrombus-wall interface demonstrate significant impairment. The extent of oxygen depletion appears to be a factor of thrombus thickness: in regions where the thrombus is 1mm thick the oxygen concentration is approximately 26% of the prescribed inlet concentration, whilst in regions of thickness <5mm the normalised concentration is $\approx 5\%$.

The salient haemodynamic features of a saccular IA are intrinsically different to that of a fusiform AAA. Studies have shown that the accelerating and decelerating flow during the cardiac pulse through a fusiform AAA results in the separation of flow from the wall, effectively creating a vortical structure within the enlarged circumference of the spindle shaped aneurysms (e.g. Finol and Amon (2003); Stam-topoulos et al. (2010); Arzani and Shadden (2012)). Conversely, saccular IAs are often observed within arterial bends and at the apex of bifurcations, effectively regions whereby the flow entering the sac results in more complex three-dimensional vortical structures, as well as the geometry of the sac itself inducing recirculation and stagnation areas during the cardiac cycle (Steinman et al. (2003); Valencia et al. (2006); Yagi et al. (2013) to give an example of the multiple studies conducted). This brings into question whether the inflow patterns, recirculating flow and low WSS in saccular IAs would compound the effect of oxygen mass transport to the thrombus within the dome.

2.2 MODELLING OF ENDOVASCULAR TREATMENT

Patient-specific 3D IA models can be extracted from angiography, CT or MRI scans by means of segmentation algorithms and various studies have been undertaken using these methods to explore aneurysm haemodynamics (Steinman et al. (2003); Castro et al. (2006)). The outcomes of such image-based models have demonstrated the importance of such factors as aneurysm geometry (Hoi et al. (2004); Jou et al. (2005)), flow patterns (Szikora et al. (2008)) and WSS (Tateshima et al. (2003); Shojima et al. (2004); Tremmel et al. (2009)) on the initiation, growth and rupture of aneurysms. Since haemodynamics play a predominant role in the way aneurysms fill, gaining insight on how such flow patterns develop for each case has the potential to increase the chances of successful intervention. For this reason, minimally invasive interventional planning of IAs with the aid of CFD is becoming more frequent.

Various computational studies have shown the influence of embedded coils on the flow patterns in both the aneurysm sac and the parent artery lumen. Haemodynamic studies show a reduction in inflow region and lower shear stress, both of which are believed to promote thrombus embolisation (Byun and Rhee (2004)). The greatest concern when selecting coiling as the method of embolisation is the effective occlusion of the aneurysm and for this reason most computational investigations have evaluated the effect of coil density on complete occlusion of aneurysms. Groden et al. (2001) studied the haemodynamics of a coiled aneurysm on a 3D computer model based on *in vivo* data and predicted that 20% of the aneurysm needs to be packed with platinum coils in order prevent coil migration due to the formation of thrombolysis on the fresh clotting. Kakalis et al. (2008) simulated embolised coils as a porous medium and demonstrated the potential to establish the level of coiling required to achieve full embolisation of the aneurysm sac.

Initially, basic idealised 3D models of stented basilar wall aneurysms were used to carry out haemodynamic computations (Aenis et al. (1997); Stuhne and Stein-

man (2004)). In 2005, Cebal and Lohner (Cebal and Löhner (2005)) advanced this research to anatomical models by implementing an adaptive embedded mesh technique to patient-specific geometries with the virtual deployment of idealised stents. Such studies demonstrated that the deployment of a stent across the aneurysm neck leads to a reduction in intrasaccular flow velocities, therefore favouring the embolisation of the aneurysm dome. The demand for pre-treatment simulations in aid to treatment decisions has led to a series of studies into the virtual deployment of stents (Appanaboyina et al. (2008); Kim et al. (2008); Larrabide et al. (2008); Valencia et al. (2009); Larrabide et al. (2010)). In terms of the haemodynamic benefits of one stent over another the comparison of stent design in patient-specific aneurysms is particularly at the forefront of pre-treatment CFD evaluations. Kim et al. (2008) conducted a study to ascertain the haemodynamic differences between two commercially available stents, of varying porosity and design, by running CFD analyses on both idealised 3D straight, and curved aneurysm models as well as on an anatomical model. The investigation led by Radaelli et al. (2008) utilises the virtual stent deployment technique developed by Appanaboyina et al. (2008) to map three commercially available stents to the same patient-specific aneurysm. The results not only demonstrated the reproducibility of pre-treatment CFD analyses but also the ability to assess the benefits of one stent design over another for a specific patient geometry. Kim et al. (2008) and Radaelli et al. (2008) both noted the influence of stent design and porosity on the inflow region across the neck, inflow velocity into the aneurysm sac and the increase in low WSS distribution across the aneurysm dome. The emergence of flow-diverters has resulted in haemodynamic evaluation of device efficacy. Studies have demonstrated a correlation between low porosity and design of the flow-diverter and the subsequent alterations to intra-saccular flow (Lieber et al. (1997); Augsburger et al. (2009)).

The actual positioning of the stent struts across the aneurysm ostium will vary depending on the particular anatomy of the parent vessel and aneurysm (Clarençon et al. (2012)) and various CFD have analysed whether this may have an influ-

ence on the haemodynamic benefits of the flow diverter (Liou et al. (2008); Appanaboyina et al. (2009); Bernardini et al. (2010, 2011)). In particular Bernardini et al. (2010, 2011) compared the effect of different finite-element deployment approaches, whereby stent release is described by means of partial differential equations which take into consideration wall deformability and stent material properties, versus the fast virtual stenting (FSV) method proposed by Larrabide et al. (2010), on intrasaccular flow dynamics within an idealised saccular IA. It was concluded that although small differences in average flow and WSS fields were observed between each stent position, all scenarios resulted in an important reduction in intrasaccular flow thus demonstrating the relatively small influence of strut positioning, whilst also highlighting the adequateness of implementing the simple, time-efficient FSV method for modelling patient-specific stent deployment.

Since haemodynamics play a predominant role in the way aneurysms fill gaining insight on how such flow patterns develop for each case has the potential to increase the chances of successful intervention. Although the alterations to the haemodynamic environment have been extensively assessed, none have taken into consideration the possible resulting change in biochemical environment.

2.3 MODELLING IA EVOLUTION

Modelling aneurysm evolution is a complex, challenging area of research. A realistic model of a healthy artery is required before this can be adapted to capture the stress-mediated mechanobiological responses that are involved in the initiation and progression of an aneurysm. Leading research within arterial biomechanics has concentrated on formulating continuum-based constitutive models (i.e. mathematical descriptions of the way in which materials respond to loading) of arteries with various forms of strain-energy functions (SEFs) (e.g Fung et al. (1979); Chuong and Fung (1983); Deng et al. (1994); Humphrey (1995); Delfino et al. (1997); Holzapfel and Weizsäcker (1998); Holzapfel et al. (2000) to name but a few). These SEFs define the energy stored within the strained fibres under elastic deformation.

The passive mechanical response of the arterial wall is primarily provided by the elastin and collagen fibres within the ECM (as discussed in Section 1.1.2.2). Together these fibres exhibit a highly nonlinear stress-strain relationship which prescribes the artery with both strength and resilience. Thus, in recent years, constitutive models of the arterial wall have implemented two-termed SEFs to capture both the pseudoelastic isotropic and anisotropic behaviour of the elastinous and collagenous constituents respectively (Holzapfel et al. (2000); Schulze-Bauer et al. (2003); Gasser et al. (2006)). Phenomenological-based, whereby material parameters are defined by curve fitting to experimental data, and invariant-based structural constitutive models (for an extensive review of both types the reader is referred to both Humphrey and Rajagopal (2002) and Holzapfel and Ogden (2010)) have provided the general framework on which to build more sophisticated models of healthy and diseased arteries. In particular, the last decade has shown an increase in structural-based constitutive mathematical models of arterial growth and remodelling (G&R). Humphrey and Rajagopal (2002) defines these terms as:

- *Growth* - ‘an increase in mass that is achieved locally via an increase in the number or size of cells and/or via a synthesis of extracellular matrix that exceeds removal.’
- *Remodelling* - ‘a change in structure that is achieved by reorganising existing constituents or by synthesising new constituents that have a different organisation.’

Humphrey and Rajagopal (2002) introduce the concept that growth and remodelling of soft tissues in general may be characterised by a constrained mixture theory, whereby constitutive equations are postulated for each constituent (i.e. collagen, elastin, muscle fibers) by taking into consideration individual rates of synthesis and degradation, material properties and stress-free configurations.

Histological observations of aneurysms show apoptosis of smooth muscle cells, fragmentation of the internal elastic lamina, breakage and decay of elastin and most

importantly, increased and continual turn-over of collagen fabric (all discussed in greater detail in Section 1.2.2). This last point has led to the emergence of mathematical modelling of aneurysm evolution governed by the constant growth and remodelling of collagenous material as an adaptation to redistributions in load as other components degrade. On this basis, Watton et al. (2004) proposed the first mathematical G&R model of aneurysm evolution, in application to AAA development in particular. Similarly to Humphrey and Rajagopal (2002) the overall growth of the arterial wall is postulated to be a combination of the individual constitutive relations for the elastin and collagenous constituents, whilst disregarding the contribution of smooth muscle cells. The rule-of-mixtures is followed by assuming that the total stress of the artery wall is a sum of the constitutive stresses. However, the G&R model proposed by Watton et al. (2004) not only takes into consideration the biological synthesis and degradation of constituents due to normal turnover rate, but also takes into consideration the pathological growth and remodelling of collagen as a consequence of elastin degradation observed during aneurysm progression. The 3D representation of an abdominal aorta is modelled as a cylindrical non-linearity membrane subjected to an axial prestretch and a constant internal systolic pressure. The fundamental constitutive equations for this model were taken from the realistic two-layer (i.e. media, adventitia) structural arterial wall model proposed by Holzapfel et al. (2000), taking into account collagen direction in each layer. The two-termed SEF is adapted to take into account:

- (i) Degradation of elastin - through lack of experimental data the decay of elastin is prescribed by an exponential decline in elastin fibre density over time.
- (ii) Growth and remodelling of collagen fabric - this is based on two key hypotheses: firstly, the relatively short half-life of collagen fibres (ranging between 15 to 90 days depending on the type (Nissen et al. (1978); Humphrey and Rajagopal (2002))) suggest a continual state of deposition and degradation. And secondly, fibroblasts attach and configure the collagen fibres to the ECM in a state of stretch (cf. Section 1.1.3.2). Humphrey (1999) postulates that this ‘attachment

stretch' remains constant regardless of the altered configuration of an artery. It is assumed that as the elastin degrades, the load is transferred over to the collagen which results in the stretch in collagen fibers to exceed their attachment stretch. Thus, Watton et al. (2004) assumes that fibroblasts attempt to reduce the stretch as which collagen is recruited to bear load (i.e. remodels), as well as increase or decrease the mass density of collagen fibers (i.e. grows) in order to maintain mechanical equilibrium. This material equilibrium is achieved when collagen fibres are restored to the attachment stretch.

Following validation of this G&R model against clinical observations (Watton and Hill (2009)), this computational framework was adapted demonstrate the evolution and possible stabilisation of conceptual cylindrical and spherical representations of IAs (Watton et al. (2009b)) and of cylindrical model of a saccular IA on the internal carotid artery (Watton and Hill (2009)).

Baek et al. (2005, 2006) developed a mathematical framework to simulate the expansion of fusiform cerebral aneurysms, by adopting the G&R theory proposed by Humphrey and Rajagopal (2002). This constitutive framework takes into account the hypotheses that the attachment stretch of newly deposited collagen fibres remains constant. Furthermore it is postulated that the stress in the new constituents may not be equal to the stress in the neighbouring fibres thus a new natural (i.e. stress-free) configuration for the newly deposited collagen is defined at every time step. The turnover of collagen rate itself is governed by the current stresses in the wall. The initial dilatation is triggered by imposing a 20% decrease in mass. The orientation of the newly deposited collagen fibres are dependent on principal stresses and stretches with the aim of exploring the effect of collagen alignment on producing a stable enlargement.

Kroon and Holzapfel (2007, 2008) proposed the first structural model of saccular IAs. The aneurysm wall is represented by a hyperelastic membrane characterised by the G&R theory proposed by Holzapfel et al. (2000). The membrane itself is char-

acterised as multiple superimposed layers of collagen fibres. Initiation of enlargement is caused by defining a ‘damage zone’ where there is complete loss of media. Collagen deposition (in a state of stretch) for each layer is governed by stretches within the wall, whilst continuous collagen turnover induces aneurysm growth. Refinement to this model include the incorporation of axial pre-stretch (Eriksson et al. (2009)) and cyclic stretch (Kroon and Holzapfel (2009)).

At this point in time, none of the aforementioned biomechanical models have taken into consideration the contribution of blood flow to the progression of an aneurysm. However histological studies have shown a correlation between WSS and the degradation of the wall components (cf. Section 1.2.1). The development of coupled Fluid-Solid-Growth (FSG) modelling allowed for the indispensable linking of local haemodynamic stimuli to stress-mediated aneurysm G&R. Feng et al. (2008) simulated the first FSG model of an aneurysm in a straight and curved cylindrical representation of an artery. For the straight artery the initial deterioration of the wall is prescribed. CFD was used to simulate blood flow and a finite-element-method (FEM)-based method was used to solve the pseudo-elastic deformation. It is hypothesised that wall deterioration can be modelled by linking critically higher levels of WSS with a decrescence in wall Young’s modulus. Although aneurysm evolution is simulated, the artery wall is simply represented as an isotropic linear elastic membrane without taking into consideration G&R of elastinous and collagenous constituents. Conversely Watton and co-workers carried out a series of FSG simulations which explicitly link a critical WSS to the initial and subsequent degradation of the elastinous constituents in an idealised cylindrical 3D tube (Watton et al. (2009a)) and subsequently for 3D patient-specific geometries (Watton et al. (2011a,b)). The general theoretical framework for these models is that presented in (Watton and Hill (2009)).

Whilst these models do take into account the haemodynamic environment, none link the biochemical environment to the mechanobiological one. Clinical measurements from CT scans demonstrated a correlation between thrombus

loading and aneurysm expansion (Wolf et al. (1994)). *In silico* stress analysis on patient-specific AAAs presenting with various thrombus thicknesses and the depth of thrombus thickness was found to correspond with higher AAA growth rates observed in follow up clinical assessments of AAA geometry (Speelman et al. (2010)). This leads to the speculation that, although the thrombus may alleviate the wall of stress (refer to Section 1.4.3), the increased proteolytic and hypoxic environment within both the thrombus and the wall may lead to further distention of the wall. It has been discussed that the depletion of oxygen can have deleterious effects on arterial cellular functionality (see Section 1.5.3). In particular the levels of O_2 may alter the synthesis and degradation of collagenous material: Steinbrech et al. (1999) observed that collagen production by fibroblasts precipitously downregulated to $\sim 4\%$ from the baseline after a 48h exposure to 2% O_2 .

These findings highlight the need for a coupled flow-solid-growth-transport (FSGT) model which would link the biochemical environment created by the presence of a thrombus and the possible effect on oxygen levels within the wall to the G&R modelling of IAs.

2.4 AIMS OF THE THESIS

Not all research is in agreement with a specific pathogenesis, nonetheless there is a general understanding that the initiation of an IA is a complex interplay between cellular response to defects within the media and haemodynamic factors. Computational modelling has greatly helped in assessing the relative impact of the parameters suspected to play a key role, as well as aiding in the implementation and assessment of preventative treatment so as to reduce the risk of fatal rupture.

Observations from the clinic suggest that the formation of a stable thrombus not only occlude the aneurysm from flow but also reduce the pressure exerted on the aneurysmal wall. Conversely, the rupture of occluded IAs has brought into question the possible deleterious effects of thrombus on wall viability, in particular the

limitation of oxygen supply to the aneurysmal wall. Thus, although the widely reported haemodynamic and mechanical benefits of thrombus formation have been the basis for choosing endovascular therapy, a broader understanding of the possibly detrimental biochemical impact of thrombus is vital to ensure optimum patient care. On this basis, the work presented within this thesis aims to investigate:

- (i) whether wall side was is more or less important than fluid side mass transport of O_2 in a simple 2D model of an artery
- (ii) whether variation in IA geometry, introduction of a stent or thrombus development had the greatest impact on O_2 levels at locations important for IA failure in 3D patient-specific models
- (iii) the relative importance of cellular respiration and thrombus thickness on IA growth in a 1D coupled chemo-mechanobiological growth and remodelling simulation.

Within this thesis the mass transfer of oxygen transport within arteries is simulated for three different scenarios: *(i)* 2D axisymmetric model of an artery in Chapter 4; *(ii)* 3D patient specific models of IAs in Chapter 6; *(iii)* coupled to the growth and remodelling of a 1D cylindrical representation of an artery in Chapter 7. Section 3.1 of this Chapter details the governing conservation equations for fluid and mass transport phenomena on which these three different frameworks are built. Section 3.2 details the finite volume discretisation methods for numerically solving these equations with the aid of computational fluid dynamics for scenarios *(i)* and *(ii)*.

3.1 GOVERNING CONSERVATION EQUATIONS

3.1.1 Navier-Stokes Equations

The mathematical formulation of fluid phenomena is expressed via a series of conservation laws - more specifically the conservation of mass, momentum and energy. The former two are often referred to as the Navier-Stokes equations, a system of coupled partial differential equations (PDEs). Since most blood flow situations do not involve substantial variations in temperature, the term ‘governing equations’ pertaining to blood flow almost invariably implies conservation of mass and momentum. The full derivations will not be demonstrated here, however primary equations shall be stated in vector form.

The conservation of mass (also known as the continuity equation) and conservation of momentum equations are derived by evaluating the fluxes and forces across a control volume (CV). The continuity equation dictates a balance of masses entering and exiting the control volume per unit time with the rate of change of the fluid density ρ . For a flow velocity vector $U(u_1, u_2, u_3)$, the continuity equation in vector

form can be written as:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho U) = 0. \quad (3.1)$$

The rate of change of momentum equals the sum of the forces acting on the control volume surface, such as pressure and surface friction, together with body forces, such as gravity, which act on the mass (this is known as Newton's second law). For an incompressible Newtonian fluid the momentum equation is:

$$\frac{\partial}{\partial t}(\rho U) + \nabla \cdot (\rho U U) = -\nabla P + \mu \nabla^2 U + f, \quad (3.2)$$

where μ is the dynamic viscosity of the fluid, P is the pressure acting on the fluid and f encompasses the other body forces.

Navier-Stokes equations for porous media

In the instance that thrombus is modelled as a porous medium (Chapter 4), the domain is defined as a fluid with porosity ε and permeability κ . The filtration velocities through the porous medium are solved using the following adapted mass conservation and continuity equations (ESI-CFD (2010)):

$$\frac{\partial \varepsilon \rho}{\partial t} + \nabla \cdot (\varepsilon \rho U) = 0, \quad (3.3)$$

$$\frac{\partial}{\partial t}(\varepsilon \rho U) + \nabla \cdot (\varepsilon \rho U U) = -\varepsilon \nabla P + \frac{\varepsilon^2 \mu}{\kappa} \nabla^2 U + f. \quad (3.4)$$

As $\varepsilon \rightarrow 1$ and $\kappa \rightarrow \infty$ the Navier-Stokes equations for purely fluid regions are recovered.

3.1.2 Conservation of scalars

The convection-diffusion equation is derived from the continuity equation: conservation of mass of a scalar quantity dictates that the rate of change of solute concentration C equates to the flux of scalar quantity J through the control volume, with the addition of consumption or generation of solute (sink/source term S). The convection-diffusion equation of a scalar in two or more directions can hence be

written in the following vector form:

$$\frac{\partial C}{\partial t} + \nabla \cdot J = S. \quad (3.5)$$

The flux J is a summation of the diffusive flux (also known as Fick's first law of diffusion) and the convective flux,

$$J = -D \cdot \nabla C + UC. \quad (3.6)$$

The convective term defines the transport of a species by means of fluid motion (and hence is a factor of flow velocity magnitude U). The diffusive term accounts for the transport of the solute through random motion; the rate at which this occurs is defined by the diffusion coefficient, D . The source/sink term, S , accounts for increase/decreases in solute concentration due to chemical reactions or consumption rates. Substituting equation (3.6) into equation (3.5), and rearranging (assuming a constant diffusivity) yields the following equation:

$$\frac{\partial C}{\partial t} - D \nabla^2 C + U \cdot \nabla C = S. \quad (3.7)$$

3.2 DISCRETISATION: THE FINITE VOLUME METHOD

Since the governing PDEs for blood flow can rarely be treated analytically, their numerical solution is often the only option. The first step for such a procedure is the subdivision of the domain of interest into smaller, discrete, elements. This process, referred to as discretisation, involves the construction of a mesh, or grid, that spans the domain. Dividing the fluid domain into such a grid allows the application of suitable numerical analysis techniques for the solution of the above-mentioned PDEs.

For the models in this thesis the governing equations are solved in the computational fluid dynamics suite **CFD-ACE+** (ESI Software, Paris, FR) which employs an implicit finite volume (or control volume) method. The domain is divided into control volumes with a node assigned either to each centre or each corner. The algebraic equations at each node are obtained from surface and volume approximation

integrals of each variable over the control volume. Various differencing methods are utilized to define the value of the variables for each control volume, in relation to values at neighboring nodes. The most appealing features of the finite volume methods are that they are relatively simple to implement, that they satisfy the conservation laws identically (in all but the crudest approximations), and that the transparent physical meaning of the fluxes they are based on allows for the easy implementation of additional physics in the fluids models. It is probably for these reasons that finite volume methods have dominated the fluid mechanics solvers market.

3.2.1 Generalised transport equation

The conservation of any quantity (e.g. mass, momentum, species concentration...) can in fact be expressed as a more convenient generalised transport equation:

$$\underbrace{\frac{\partial}{\partial t}(\rho\Phi)}_{\text{transient}} + \underbrace{\nabla \cdot (\rho U\Phi)}_{\text{convection}} - \underbrace{\nabla \cdot (\Gamma_\Phi \nabla \Phi)}_{\text{diffusion}} = \underbrace{S_\Phi}_{\text{source/sink}}, \quad (3.8)$$

whereby Φ is the conserved quantity of interest, Γ_Φ is the diffusivity coefficient of this conserved quantity and S_Φ is the source/sink term. For example, the continuity equation is recovered by setting $\Phi = 1$, $\Gamma_\Phi = 0$ and $S_\Phi = 0$, whilst the convection-diffusion equation is recovered by setting $\Phi = C$, $\Gamma_\Phi = D$ and $S_\Phi = S$.

Integrating the generalised transport equation (Equation 3.8) over a control volume $\mathcal{V}$ yields the following expression:

$$\int_{\mathcal{V}} \left[\frac{\partial}{\partial t}(\rho\Phi) + \nabla \cdot (\rho U\Phi) - \nabla \cdot (\Gamma_\Phi \nabla \Phi) \right] d\mathcal{V} = \int_{\mathcal{V}} S_\Phi d\mathcal{V}. \quad (3.9)$$

The convective and diffusive terms are determined by evaluating the net flux through the whole control volume by converting the above equation into a surface integral using the Gauss (or divergence) theorem:

$$\int_{\mathcal{V}} \frac{\partial}{\partial t}(\rho\Phi) d\mathcal{V} + \sum_{\text{faces}}^{\text{surface}} \int_l [\nabla \cdot \rho U\Phi - \Gamma_\Phi \nabla \Phi] \cdot \vec{n}_l d\mathcal{S} = \int_{\mathcal{V}} S_\Phi d\mathcal{V}. \quad (3.10)$$

ι represents any of the faces on the control volume and $\vec{n}_\iota$ is the unit vector normal to that surface $\mathcal{S}$.

3.2.2 Spatial differencing schemes

CFD-ACE+ employs a co-located cell-centered variable arrangement: the average value of any quantity within a control volume is given by its value at the cell centre P . Various spatial differencing schemes are implemented in the finite volume method in order to define the algebraic equations at each centre node. The most widely used schemes, particularly in vascular flows where the prevailing Reynolds number indicates laminar flow in most cases, are the central differencing scheme (CDS) and upwind differencing scheme (UDS).

3.2.2.1 Central differencing scheme

CDS is a linear interpolation between the two nearest neighbours of a control volume's central node. Put simply, if we take face e of a 2-D structured Cartesian grid (Figure 3.1) we can make an approximation of the central node value by the linear interpolation between the two nearest nodes of the control volume.

$$\int_e [\rho U \Phi - \Gamma_\Phi \nabla \Phi] \cdot \vec{n}_e d\mathcal{S} = \left(\rho u_1 \Phi - \Gamma \frac{\partial \Phi}{\partial x_1} \right)_e A_e. \quad (3.11)$$

The conserved quantity at cell face e is simply calculated using the following expressions:

$$\Phi_e = \frac{\Phi_P + \Phi_E}{2} \quad (3.12)$$

$$\left(\frac{\partial \Phi}{\partial x_1} \right)_e = \frac{\Phi_E - \Phi_P}{\delta x_1} \quad (3.13)$$

The above expressions are then substituted back into the finite volume expression. The same discretisation approach is applied to all surfaces of a control volume in all three coordinate directions resulting in the general expression:

$$a_P \Phi_P = \sum_{\iota}^{\text{neighbour nodes}} a_\iota \Phi_\iota + S_P, \quad (3.14)$$

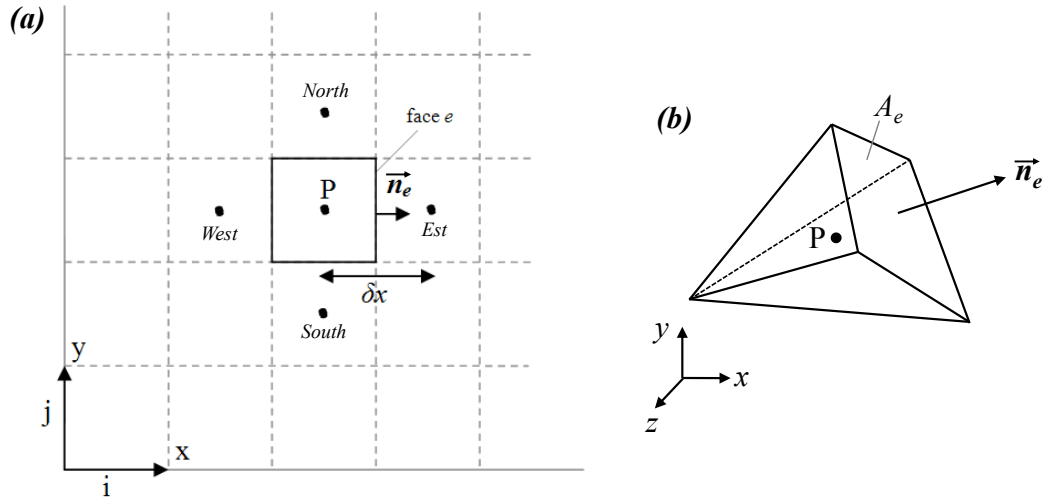


Figure 3.1: Finite volume of centre node P in a 2D Cartesian structured grid (a) and a 3D tetrahedral grid (b). The normal to each cell face of area A_i is denoted $\vec{n}_i$, whereby the index i corresponds to the adjoining faces to neighbouring control volumes (of cell centres North, West, South, Est).

here S_P represents the discretised source term and the coefficients a_P and a_i are related to the summation of terms from equations (3.12) and (3.13) for all faces of the control volume. The velocity component U and neighbouring values of the conserved quantity Φ_P in these coefficients are mostly unknown quantities so an iterative process is adopted whereby the equations are solved repeatedly over the entire mesh.

With this scheme, the nodal value of a variable will be equally influenced by the upstream and downstream values, implying that it does not take into account flow direction. It can be shown that central differencing is second order accurate but it may lead to unbounded and thus unstable solutions, when the local strength of normalised convection exceeds that of normalised diffusion.

3.2.2.2 First-order upwind differencing scheme

First-order UDS is an interpolation between the two (locally) upstream cells, whereby the value at the cell face of a control volume is considered to be that of the upstream node, which takes into account the convective influence of the flow

domain (known as transportiveness):

$$\Phi_e = \begin{cases} \Phi_P & \text{if } U > 0, \\ \Phi_E & \text{if } U < 0. \end{cases} \quad (3.15)$$

Although this method will present physically plausible results, false diffusion is often observed rendering the results numerically inaccurate. In order to achieve a more stable result it is possible to combine the central and first-order upwind differencing schemes:

$$\Phi_e = \vartheta \Phi_e^{UDS} + (1 - \vartheta) \Phi_e^{CDS}, \quad (3.16)$$

whereby ϑ is the blending factor: $\vartheta = 0$ yields the CDS scheme and $\vartheta = 1$ yields the UPS scheme. This factor allows some damping needed for stability, whilst limiting non-physical oscillations in the numerical solution.

3.2.3 Temporal discretisation

As time accuracy is of importance when simulating transient coupled flow and mass transport the implicit second-order Crank-Nicolson discretisation scheme is implemented. As a demonstration, in 1D x -direction the differencing is performed in the following manner:

$$\frac{\Phi_j^{k+1} - \Phi_j^k}{\Delta t} = \left(\eta \frac{\Phi_{j+1}^{k+1} - 2\Phi_j^{k+1} + \Phi_{j-1}^{k+1}}{\Delta x^2} + (1 - \eta) \frac{\Phi_{j+1}^k - 2\Phi_j^k + \Phi_{j-1}^k}{\Delta x^2} \right), \quad (3.17)$$

whereby Δt is the timestep, k is the current time and j is the current cell in which the computation is being performed for the variable Φ . The first part of the right hand side is an implicit scheme which provides stability, whilst the second is an explicit scheme which provides accuracy. Second order accuracy is achieved when the blending factor is equal to $\eta = 0.5$. The **CFD-ACE+** recommended value of 0.6 is used for all transient computations in this thesis.

3.2.4 Pressure Correction

Whereas some solution methodologies cast a single system for all conservation equations, it is commonplace to solve each equation separately (since their non-linearity implies an iterative approach anyways). This approach however carries the inherent problem that the continuity equation does not involve pressure. In other words, a method is required to ensure that the calculated velocity field satisfies the continuity equation. For this, the pressure correction method is often used in incompressible flows, where an algebraic pressure correction equation is derived from the continuity equation. This approximate pressure equation is solved in sequence with the other discretized equations and the pressure field is modified to ensure that the computed velocity field satisfies continuity at convergence. **CFD-ACE+** implements the semi-implicit for pressure-linked equations consistent (SIMPLEC) solver (ESI-CFD (2010); Van Doormaal and Raithby (1984)), an adaptation of the SIMPLE pressure correction method. As an example of the methodology, take the finite difference form of the momentum equation in the x -direction (shown in the generalised form in equation (3.14)):

$$a_P (u_1)_P = \left(\sum_i a_i (u_1)_i + S_P \right) - \left(\sum_e p_e A_e \vec{n}_e \right). \quad (3.18)$$

Taking note that P is the centre node, whilst lower case p is the pressure. In the first iteration, the velocity field is initially solved using a guessed value for pressure p^* :

$$a_P (u_1)_P^* = \left(\sum_i a_i (u_1)_i^* + S_P \right) - \left(\sum_e p_e^* A_e \vec{n}_e \right). \quad (3.19)$$

This first solution for velocity will not satisfy continuity and so corrections u_1' and p' are added to obtain an improved solution,

$$u_1 = u_1^* + u_1' \quad (3.20)$$

$$p = p^* + p' \quad (3.21)$$

An expression for $(u_1)_P^*$ is obtained by assuming that $(u_1)_i'$ can be approximated by $(u_1)_P'$ and subtracting equation (3.18) from equation (3.19):

$$a_P (u_1)_P' = \frac{-1}{a_P - \sum_i a_i} \left(\sum_e p_e' A_e \vec{n}_e \right). \quad (3.22)$$

The velocity correction at face e is found by averaging the cell-centre values,

$$(u_1)'_e = \Upsilon_e (u_1)'_P + (1 - \Upsilon_e) (u_1)'_E \quad (3.23)$$

Matching correction equations are established for flow velocities in the y - and z -directions. Integrating the mass conservation equation (3.1) over the cell volume $\mathcal{V}$ yields the following

$$\frac{\rho_P^k \mathcal{V}^k - \rho_P^{k-1} \mathcal{V}^{k-1}}{\Delta t} + \sum_e \rho_e U_e^n A_e = \dot{m} \mathcal{V}^k \quad (3.24)$$

whereby $\dot{m}$ is the mass flow rate through the volume should the continuity equation not be satisfied. The face-normal component of the velocity of face e is $U_e^n = (u_1)_e \vec{n}_x + (u_2)_e \vec{n}_y + (u_3)_e \vec{n}_z$. If the mass flux through the cell face e $C_e = \rho_e U_e^n A_e$ is evaluated with values u_1^* , u_2^* , u_3^* and p^* this would not satisfy the continuity equation and so a correction may be applied:

$$C_e = C_e^* + C'_e. \quad (3.25)$$

Substituting this back into equation (3.24) yields

$$\frac{\rho'_P \mathcal{V}}{\Delta t} + \sum_e C'_e = S_m. \quad (3.26)$$

S_m represents the mass correction in the control volume:

$$S_m = \frac{\rho_P^{k-1} \mathcal{V}^{k-1} - \rho_P^* \mathcal{V}^*}{\Delta t} + \dot{m} \mathcal{V} - \sum_e C_e^*. \quad (3.27)$$

By expressing the face-normal velocity and density corrections in terms of the pressure correction, the pressure correction equation can be recast as:

$$a_P p'_P = \sum_i a_i p'_i + S_m \quad (3.28)$$

This updated pressure correction is used to solve the discretised velocity momentum equations and hence the pressure and velocities fields are then updated at each node. This whole loop is iterated until satisfactory convergence is achieved.

3.2.5 Algebraic multigrid

Various techniques are used to accelerate convergence when solving the set of algebraic equations. **CFD-ACE+** uses a multigrid technique that constructs a hierarchy of grids, from fine (original volume mesh) to coarse. The original fine grid is used to acquire residuals for the first iterations. These residuals are then used as source terms when solving the equations on the algebraically coarsened grid during the following iterations. The corrections obtained from the coarsened grid are then interpolated back onto the finer grid to update the solution. Algebraic multigrid (AGM) requires less memory than direct solvers and, for fully unstructured meshes, provides significantly faster solution convergence by eliminating residuals of multiple wavelengths simultaneously (ESI-CFD (2010)).

2D MODEL OF OXYGEN MASS TRANSPORT IN A THROMBOSED ARTERY

This chapter presents the preliminary feasibility studies of a couple fluid-mass transport of oxygen in a 2D axisymmetric model of a thrombosed artery without the presence of an aneurysm, in the aim of setting up simulation parameters for the 3D modelling of patient-specific IAs. Parametric simulations involving the variation in thrombus thickness, thrombus filtration velocities, and arterial wall cellular respiration rates demonstrate their combined influence on oxygen distribution to the portion of wall in direct contact with the clot.

4.1 2D MODEL DESCRIPTION

4.1.1 Artery Geometry

The 2D axisymmetric model consists of three layers: (i) a fluid lumen, (ii) a thrombus layer of constant thickness that spans the length of the wall and (iii) a homogeneous single layer wall. The geometric attributes were modelled on the anterior communicating artery (Figure 4.1), where an estimated 30% of IAs are formed (Brisman et al. (2006)).

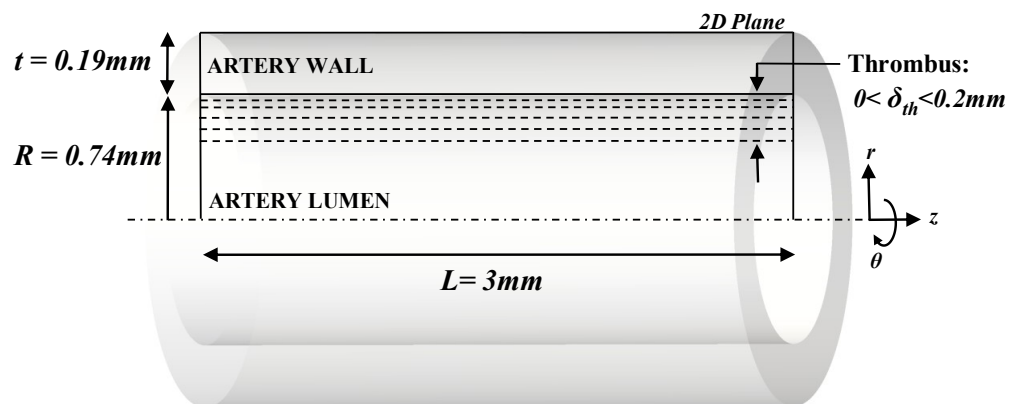


Figure 4.1: 2D axisymmetric model of anterior communicating artery. Physiological dimensions taken from Krayenbuehl and Yasargil (1982) and Moore et al. (2006).

The physiological dimensions of the vessel were obtained from the literature (Krayenbuehl and Yasargil (1982); Moore et al. (2006)). A total of five thickness values are modelled to establish whether there is a correlation between the thrombus depth and the level of hypoxia within the wall: $\delta_{th} = 0.025, 0.05, 0.1, 0.15$ and 0.2mm . As a baseline the thrombus layer was omitted completely so as to assess the oxygen transport within a ‘healthy’ artery.

4.1.2 Oxygen mass transport properties

The oxygen mass transport properties of the lumen and wall are adapted from the 2D axisymmetric coupled fluid-mass transfer model proposed by Moore and Ethier (1997).

4.1.2.1 Free and facilitated diffusion of oxygen in the blood

In a healthy artery 97% percent of oxygen transported in the blood is bound to haemoglobin, the iron-containing protein present in red blood cells, with the remaining 3% of oxygen present as dissolved free state in the plasma (cf. Figure 1.7). The concentration of bound oxygen in blood depends on the quantity of haemoglobin within the hematocrit (the fraction of erythrocytes in blood) and on how many of these are carrying oxygen; each haemoglobin molecule has the capacity to carry four oxygen molecules. As oxygen is present in the blood in two forms, that dissolved in plasma and that bound to haemoglobin, both quantities are taken into account when modelling O_2 mass transport through the lumen. The expression for the convective and diffusive transport of free oxygen for a 2D axisymmetric domain may be written:

$$\begin{aligned} \frac{\partial C_{O_2}}{\partial t} - D_b \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{O_2}}{\partial r} \right) + \frac{\partial^2 C_{O_2}}{\partial z^2} \right] \\ + \left[\frac{u_r}{r} \frac{\partial (r C_{O_2})}{\partial r} + u_z \frac{\partial C_{O_2}}{\partial z} \right] = R_{Hb}. \end{aligned} \quad (4.1)$$

and that of oxyhaemoglobin saturation may be written:

$$\begin{aligned}
 [Hb] \frac{\partial C_{HbO_2}}{\partial t} - [Hb] D_{Hb} \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{HbO_2}}{\partial r} \right) + \frac{\partial^2 C_{HbO_2}}{\partial z^2} \right] \\
 + [Hb] \left[\frac{u_r}{r} \frac{\partial (r C_{HbO_2})}{\partial r} + u_z \frac{\partial C_{HbO_2}}{\partial z} \right] = -R_{Hb}. \quad (4.2)
 \end{aligned}$$

The conserved quantities are the concentration of oxygen (C_{O_2}), and the oxyhaemoglobin saturation (C_{HbO_2}). D_b and D_{Hb} are the diffusivity coefficients for free oxygen and oxyhaemoglobin respectively. $[Hb]$ is the oxygen carrying capacity of haemoglobin.

The reaction term R_{Hb} is the source and sink term for each expression, which links the local concentration of free oxygen with the dissociation of oxygen from haemoglobin. In this work the reaction term is computed using the following expression (Clark et al. (1985)):

$$R_{Hb} = [Hb] K_{Hb} \frac{(C_{HbO_2} - S)}{(1 - S)}, \quad (4.3)$$

where K_{Hb} is the backward reaction rate for the oxyhaemoglobin reaction. The fractional haemoglobin saturation (S) is a function of oxygen partial pressure of oxygen (PO_2), shown by the oxyhaemoglobin dissociation curve in Figure 4.2.

From this curve the following equations for fractional saturation were determined (Kelman (1966)):

$$S = f(PO_2) = 0.003683 PO_2 + 0.000584 PO_2^2 \quad PO_2 < 12 \text{ mmHg} \quad (4.4)$$

$$S = f(PO_2) = \frac{a_1 PO_2 + a_2 PO_2^2 + a_3 PO_2^3 + PO_2^4}{a_4 + a_5 PO_2 + a_6 PO_2^2 + a_7 PO_2^3 + PO_2^4} \quad PO_2 \geq 12 \text{ mmHg} \quad (4.5)$$

The constants in equation (4.5) are as follows:

$$\begin{aligned}
 a_1 &= -8.5322289 \times 10^3; & a_2 &= 2.1214010 \times 10^3; & a_3 &= -6.7073989 \times 10; \\
 a_4 &= 9.3596087 \times 10^5; & a_5 &= -3.1346258 \times 10^4; & a_6 &= 2.3961674 \times 10^3; \\
 a_7 &= -6.7104406 \times 10.
 \end{aligned}$$

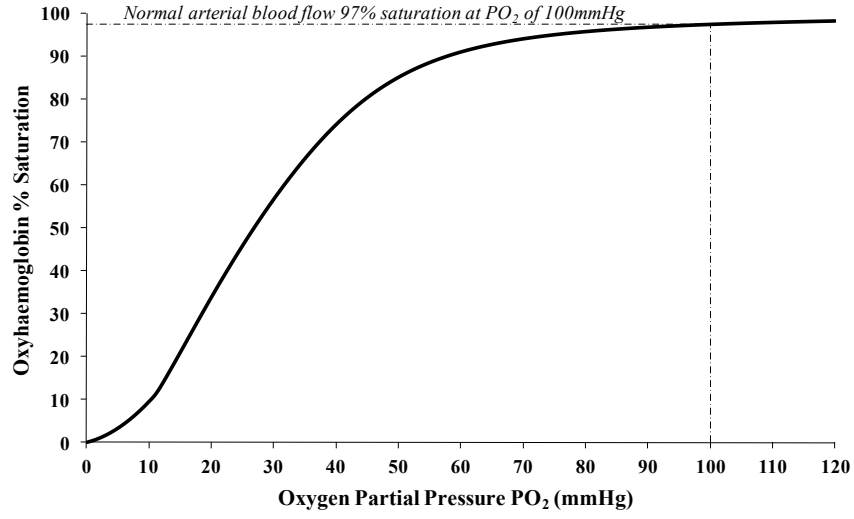


Figure 4.2: Oxyhaemoglobin dissociation curve in arterial blood flow (as defined by Kelman (1966)).

The value of partial oxygen pressure is obtained by converting the concentration of free oxygen (C_{O_2}) at each cell center using the following expression for Henry's gas law:

$$C_{O_2} = \alpha PO_2. \quad (4.6)$$

O_2 are uncharged molecules, which not only permits them to easily dissolve in water but also in hydrophobic environments, therefore allowing the diffusion from extra-cellular fluid into the plasma membrane and subsequently the cytoplasm of cells (Bolsover et al. (2004)). The extent to which the oxygen may dissolve is defined by its solubility: α (mol/m³/mmHg).

4.1.2.2 Oxygen transport through the arterial wall

The transport resistance of the endothelium is assumed negligible as the endothelial permeability to oxygen is considered very high (Tarbell and Qiu (2000)). Experimental measurements of filtration velocities through the arterial wall are in the range of $1e^{-5}$ mm/s (Back (1976); Tedgui and Lever (1984)). Whereas the measured values of oxygen diffusion coefficients are in the range of $D_w \sim 1e^{-9}$ m²/s. Moore and Ethier (1997) made a simple approximation of O_2 diffusion velocities

through the wall by using the following expression:

$$V_D = \frac{D_w}{h_w}, \quad (4.7)$$

whereby h_w is the wall thickness. For this particular geometry $h_w = 0.19\text{mm}$ which equates to a diffusion velocity of $V_D \sim 5e^{-3}\text{mm/s}$. Given that the filtration velocity is ~ 2 orders of magnitude smaller than the diffusion rate the convective transport of O_2 across the wall is not taken into account. The diffusion-only transport of free oxygen across the wall can hence be written:

$$\frac{\partial C_{\text{O}_2}}{\partial t} - D_w \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{\text{O}_2}}{\partial r} \right) + \frac{\partial^2 C_{\text{O}_2}}{\partial z^2} \right] = -r \dot{q}, \quad (4.8)$$

whereby the consumption rate $\dot{q}$ accounts for cellular respiration.

4.1.2.3 Diffusion of oxygen through the thrombus layer

The cellular content of thrombus is mostly circulating cells such as macrophages, T-cells and erythrocytes (Adolph et al. (1997)). It is speculated that the respiration rate by these cells is comparatively low and is not taken into account in this work. It is believed that thrombus is more permeable than the arterial wall (Adolph et al. (1997); Diamond (1999)). Furthermore measurements of structural properties have revealed a correlation between clot permeability and thrombus compactness (Diamond (1999)). To explore the influence of possible convective flux of oxygen through the thrombus, the oxygen mass transport through this domain was modelled (i) as simple diffusion and (ii) as both convection and diffusion through a porous medium. The convection-diffusion of oxygen through thrombus may be written:

$$\begin{aligned} \frac{\partial C_{\text{O}_2}}{\partial t} - D_{th} \left[\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{\text{O}_2}}{\partial r} \right) + \frac{\partial^2 C_{\text{O}_2}}{\partial z^2} \right] \\ + \left[\frac{u_r}{r} \frac{\partial (r C_{\text{O}_2})}{\partial r} + u_z \frac{\partial C_{\text{O}_2}}{\partial z} \right] = 0, \end{aligned} \quad (4.9)$$

whereby D_{th} is the diffusivity coefficient of oxygen within thrombus. When only modelling the diffusive transport of O_2 the convective term in the above equation is simply removed.

4.1.3 Simulation input parameters

The artery lumen is modelled as a steady incompressible Newtonian fluid with a no-slip velocity at the arterial wall interface (or at the thrombus interface if present). The flow magnitudes within the lumen and porous thrombus layers was solved using the conservation of mass and momentum equations in 2D axisymmetric polar coordinates, as detailed in Appendix A.

4.1.3.1 Consumption rate

The consumption rate of oxygen within the walls of human cerebral arteries specifically is scarcely found within the literature as this value is not widely monitored. The variation between respiration rates is not only a factor of species type, but also specific arteries; the aorta is an elastic artery that has a distinctly different cellular wall composition than the muscular cerebral arteries, which leads to the supposition that the metabolic respiration requirements may depend on arterial wall composition. One of the most important findings is that the consumption rate within the wall is not constant and varies radially throughout the wall (Buerk and Goldstick (1982); Kirk and Laursen (1955); Whereat (1961)). In particular a slightly greater consumption rate is observed within the medial layer. This may be due to the levels of energy required by SMCs (that occupy 70% of the medial layer in muscular arteries(Walmsley (1983))) in order to maintain vascular tone. Table 4.1 summarises some of the values of oxygen consumption rates found using *ex vivo*, *in vivo* and *in vitro* measurement techniques.

In this case study, the wall is modelled as one simple homogeneous layer, hence the radial variation in consumption rate is not taken into account. Unable to identify a specific value for human cerebral arteries (and unable to ascertain the suitability of animal observations), a total of four consumption rates were chosen: $\dot{q}_1 = 1e^{-2}$, $\dot{q}_2 = 1e^{-3}$, $\dot{q}_3 = 1e^{-4}$ and $\dot{q}_4 = 1e^{-5}$ mol/m³/s. The first three values cover the range found in the experimental studies outlined in Table 4.1. All four values also allow the possibility of analysing the effect of oxygen conformance as a regu-

relative response to a hypoxic environment: a 10% and more drastic 1% reduction in respiration from normoxic consumption rate of $\dot{q}_1$ equates to $\dot{q}_2$ and $\dot{q}_3$ respectively. Similarly 10% of $\dot{q}_2$ equates to $\dot{q}_3$ and 1% of $\dot{q}_2$ equates to $\dot{q}_4$.

Artery	$\dot{q}$ (mol/m ³ /s)	Method and source
Human aorta	$9.3e^{-4}$	<i>ex vivo</i> : Kirk et al. (1954)
Rabbit aorta <i>Intima</i>	$1.6e^{-4}$	<i>ex vivo</i> : Whereat (1961)
Dog aorta		<i>in vivo</i> : Buerk and Goldstick (1982)
<i>Intima</i>	$3.1e^{-4}$	
<i>Media</i>	$6.9e^{-3}$	
Dog femoral artery	$5.8e^{-3}$	<i>in vivo</i> : Crawford et al. (1983)
Pig carotid artery <i>SMCs only</i>	$2.8e^{-4}$	<i>in vitro</i> : Barron et al. (1996)
Pig carotid artery <i>SMCs only</i>	$1.0e^{-3}$	<i>in vitro</i> : Pittman and Duling (1973)
Pig carotid artery <i>SMCs only</i>	$1.8e^{-4}$	<i>in vitro</i> : Krisanda and Paul (1984)

Table 4.1: Experimental values of arterial wall oxygen consumption rates

4.1.3.2 Flow and mass transfer volume conditions

Since the variability of oxygen within the wall is assumed to occur over a long time period (and not simply over a couple of cardiac cycles) steady flow conditions are applied.

Mass transport properties for the lumen, thrombus and wall domains were obtained from the literature. For oxygen the ratio between free and effective (that inherently take into account the tortuous diffusivity around cellular components) diffusivity of oxygen is one (Stangeby and Ethier (2002b)). Thus, the diffusivity coefficient remains the same when modelling thrombus as a porous medium.

Diamond (1999) measured the structural properties of fibrin and blood clots and established that the overall porosity of a compacted fibrin clot to be within the region of 0.75-0.9, and the permeability to be $1e^{-12}\text{m}^2$ for coarse fibrin and in the range of $1e^{-14}$ - $1e^{-17}\text{m}^2$ for compacted thrombus. Table 4.2 summarises the volume conditions for each domain.

Parameter Name	Variable	Value
Artery Lumen		
<i>Flow parameters:</i>		
Blood density	ρ_b	1060 kg/m ³
Blood viscosity	μ_b	4e ⁻³ kg/ms
<i>Mass transport properties of free oxygen:</i>		
Diffusivity coefficient ^a	D_b	1.2e ⁻⁹ m ² /s
Solubility ^a	α	1.114e ⁻³ mol/m ³ /mmHg
<i>Mass transport properties of oxygen bound to haemoglobin:</i>		
Diffusivity coefficient ^a	D_{HbO_2}	1.5e ⁻¹¹ m ² /s
Oxygen carrying capacity of haemoglobin ^a	$[Hb]$	9.1 mol/m ³
Backward reaction rate of oxyhaemoglobin ^b	K_{Hb}	40 s ⁻¹
Artery Wall		
Diffusivity coefficient of oxygen ^a	D_w	0.9e ⁻⁹ m ² /s
Consumption rate	$\dot{q}$	1e ⁻² -1e ⁻⁵ mol/m ³ /s
Thrombus		
<i>Porous media properties</i>		
Thrombus density	ρ_{th}	1060 kg/m ³
Porosity	ε	0.75, 0.99
Permeability	κ	1e ⁻¹² -1e ⁻¹⁷ m ²
<i>Mass transport properties</i>		
Thrombus thickness	δ_{th}	0.025-0.20 mm
Diffusivity coefficient of oxygen ^c	D_{th}	2.4e ⁻⁹ m ² /s

^a Schneiderman and Goldstick (1978a)^b Vorp et al. (1996)^c Murray (1971)**Table 4.2:** Simulation input parameters for coupled flow and mass transfer model

To assess the influence of cellular respiration, thrombus thickness and thrombus permeability on oxygen transport to the wall three different parametric studies were conducted:

- I *Healthy artery*: thrombus thickness $\delta_{th} = 0$; consumption rates $\dot{q}_1 = 1e^{-2}$, $\dot{q}_2 = 1e^{-3}$, $\dot{q}_3 = 1e^{-4}$ and $\dot{q}_4 = 1e^{-5}$ mol/m³/s.
- II *Diffusion-only transport through thrombus*: thrombus thickness $\delta_{th} = 0.025$ -0.2mm; consumption rates: $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$.

III *Diffusion-convection transport through thrombus as a porous medium*: thrombus thickness: $\delta_{th} = 0.025\text{-}0.2\text{mm}$; consumption rates: $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$; porosity: $\varepsilon_1 = 0.75$ and $\varepsilon_2 = 0.99$; permeability: $\kappa_1 = 1e^{-12}\text{m}^2$, $\kappa_2 = 1e^{-14}\text{m}^2$ and $\kappa_3 = 1e^{-17}\text{m}^2$.

4.1.4 Boundary Conditions

In **CFD-ACE+** the boundary conditions for scalar quantities are set using the following equation:

$$a \left(D \frac{\partial \Phi}{\partial n} \right) + b \Phi = c. \quad (4.10)$$

D is the diffusivity coefficient of the scalar concentration Φ and n is the normal to the boundary. The values of the coefficients a , b and c dictate the type of boundary condition. A fixed value (also known as Dirichlet) boundary condition is set when $a = 0$ and $b \neq 0$ so that $\Phi = c/b$. A fixed flux (also known as Neumann) boundary condition is achieved by setting $a \neq c \neq 0$ and $b = 0$, giving $(\partial \Phi / \partial n) = c/a$. When both $a \neq 0$ and $b \neq 0$, this dictates a flux as a function of value boundary condition.

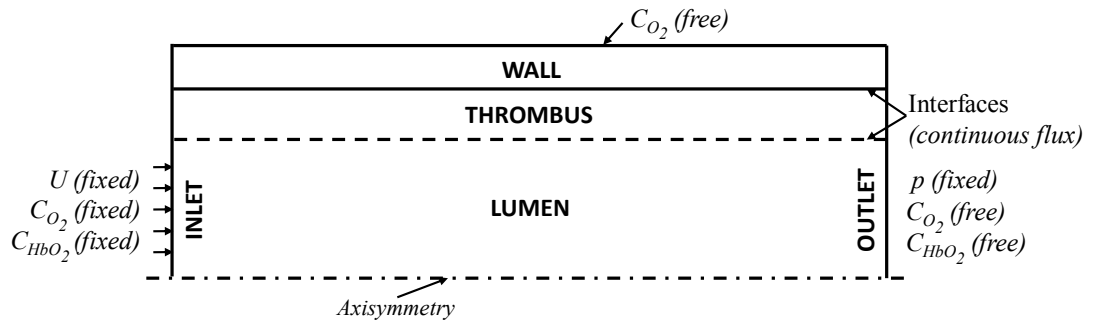


Figure 4.3: 2D axisymmetric model flow and scalar boundary conditions

Figure 4.3 shows the boundary conditions applied to the 2D axisymmetric model. The inlet velocity is set to $U_i = 0.01\text{m/s}$ in order to mimic the slower flow which could induce thrombus in an aneurysm, whilst a fixed pressure outlet enforces flow through the lumen. Normal arterial blood flow has an arterial partial pressure of $PO_2 = 100\text{mmHg}$ and an oxyhaemoglobin saturation level of 97%. Thus the inlet concentration of free oxygen is calculated to be a fixed value of $(C_{O_2})_i = 0.1114\text{mol/m}^3$ (from equation (4.6)) and the inlet concentration of oxyhaemoglobin sat-

uration was simply set to a fixed value of $(C_{HbO_2})_i = 0.97$. So as to allow free flux at the outlet, the axial gradients $(\partial C_{O_2} / \partial n)_z$ and $(\partial C_{HbO_2} / \partial n)_z$ were set to zero for the outlet boundary condition (i.e. $a = 1$ and $b = c = 0$). Oxygen flux through the adventitial boundary was also set as $(\partial C_{O_2} / \partial n)_{adv} = 0$ permitting free flux out of the wall into the surrounding environment. The diffusion flux normal to each layer interface is conserved through the following set of equations:

$$\left(D \frac{\partial \Phi}{\partial n}\right)_{lumen} = \left(D \frac{\partial \Phi}{\partial n}\right)_{wall} \quad (4.11a)$$

$$\left(D \frac{\partial \Phi}{\partial n}\right)_{lumen} = \left(D \frac{\partial \Phi}{\partial n}\right)_{thrombus} \quad (4.11b)$$

$$\left(D \frac{\partial \Phi}{\partial n}\right)_{thrombus} = \left(D \frac{\partial \Phi}{\partial n}\right)_{wall} \quad (4.11c)$$

4.1.5 Spatial differencing and solver settings

Velocity, oxygen and oxyhaemoglobin scalars were solved using a combined CDS and UPS differencing scheme (see Equation (3.16)). For velocity the blending factor was set to $\vartheta=0.1$, whilst for C_{O_2} and C_{HbO_2} it was set to $\vartheta=0.5$, offering a greater stability in numerical solutions when solving convection-diffusion of both scalars.

4.1.6 Grid generation

The grid for this model is a simple Cartesian structured mesh: the number of cells for the three layers for each thrombus thickness value are detailed in Table 4.3.

	Lumen	Wall	Thrombus
$\delta_{th} = 0\text{mm}$	13535	5771	-
$\delta_{th} = 0.025\text{mm}$	13134	5771	1791
$\delta_{th} = 0.05\text{mm}$	12736	5771	2786
$\delta_{th} = 0.10\text{mm}$	11741	5771	3781
$\delta_{th} = 0.15\text{mm}$	10945	5771	4776
$\delta_{th} = 0.20\text{mm}$	9950	5771	5771

Table 4.3: Number of grid cells for each section of the three layer 2D axisymmetric model of an artery without and with thrombus thickness δ_{th} .

All simulations were run under transient time conditions; for the grids used, satisfactory convergence of scalars was achieved when computing in timesteps of $dt = 1e^{-4}s$.

4.2 RESULTS

4.2.1 Oxygen transport within the lumen

Regardless of the thrombus thickness, or the consumption rate, the distribution of oxygen and oxyhaemoglobin within the lumen domain does not vary from case to case. As an example, Figures 4.4 and 4.5 demonstrate the normalised oxygen concentration and oxyhaemoglobin saturation levels at $t = 0.1s$, $0.2s$, $1s$ and $10s$ for the case of no thrombus layer with a wall respiration rate of $\dot{q}_2 = 1e-3 \text{ mol/m}^3/\text{s}$.

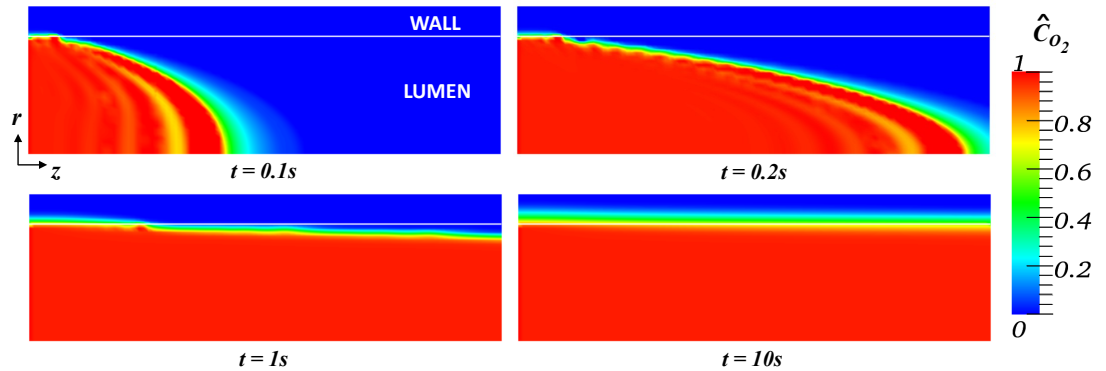


Figure 4.4: Convection and diffusion of oxygen within the lumen.

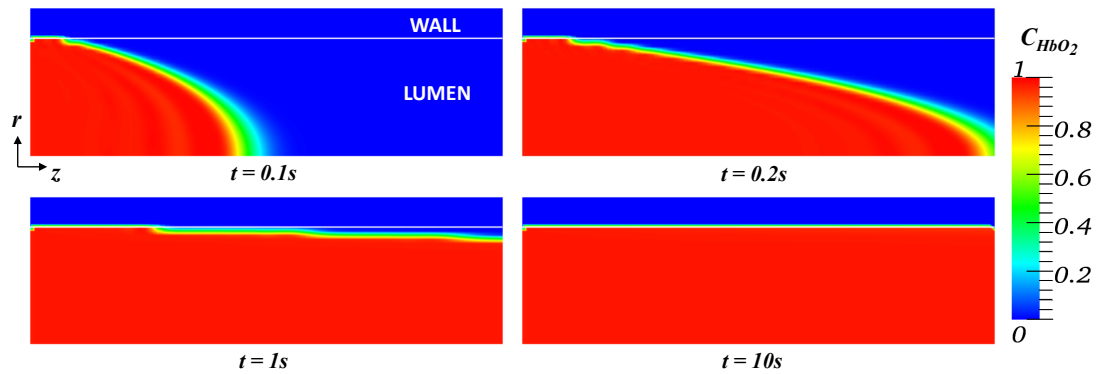


Figure 4.5: Convection and diffusion of oxyhaemoglobin within the lumen.

The normalised oxygen concentration is determined by dividing the oxygen concentration value at each cell centre by the inlet concentration: $\hat{C}_{O_2} = C_{O_2} / (C_{O_2})_i$. Throughout the rest of this thesis, any statement regarding to oxygen concentration refers to the normalised oxygen concentration $\hat{C}_{O_2}$, unless explicitly stated otherwise. The oxyhaemoglobin saturation is not normalised as this value is defined as a percentage.

The transport through the lumen domain happens very succinctly over the first 1s of computation for both quantities. For the oxygen distribution a constant value of $\hat{C}_{O_2} = 96\%$ is reached for the whole of the lumen up to a distance 0.1mm away from the lumen/wall or lumen/thrombus interface, at which point the thrombus and wall transport properties have an influence on radial concentrations. Similarly to the oxygen, once the whole lumen is filled, the oxyheamoglobin saturation maintains the inlet value of 97% saturation as the supply of fresh flow is never ceased through the lumen. At a distance 0.01mm away from the lumen/wall or lumen/thrombus interface C_{HbO_2} linearly decreases to naught as oxyhaemoglobin does not permeate through the thrombus or wall.

4.2.2 Oxygen distribution through the thrombus and wall

4.2.2.1 Diffusion-only transport through the thrombus

The radial values of $\hat{C}_{O_2}$ across the thrombus and wall layers reach steady state at different time points for each respiration rate: for $\dot{q}_1 = 1e^{-2} \text{ mol/m}^3/\text{s}$ steady state was reached at 60s, for $\dot{q}_2 = 1e^{-3} \text{ mol/m}^3/\text{s}$ it was reached at 120s, and for $\dot{q}_3 = 1e^{-4} \text{ mol/m}^3/\text{s}$ and $\dot{q}_4 = 1e^{-5} \text{ mol/m}^3/\text{s}$ it was reached at 300s. Furthermore at these time points, approximately $z = 1.1 \text{ cm}$ downstream from the inlet there was little variation (less than 1%) in longitudinal values. With this in mind, only a small segment of the model is shown in Figures 4.6, 4.7, 4.8 and 4.9: 0.15mm either side of the central axis $z_M = L/2 = 1.5 \text{ mm}$ as a representative of the distribution of oxygen in the entire domain. This allows for a better visualisation of the effect of each consumption rate by comparing the oxygen distribution for each thrombus thickness side by side.

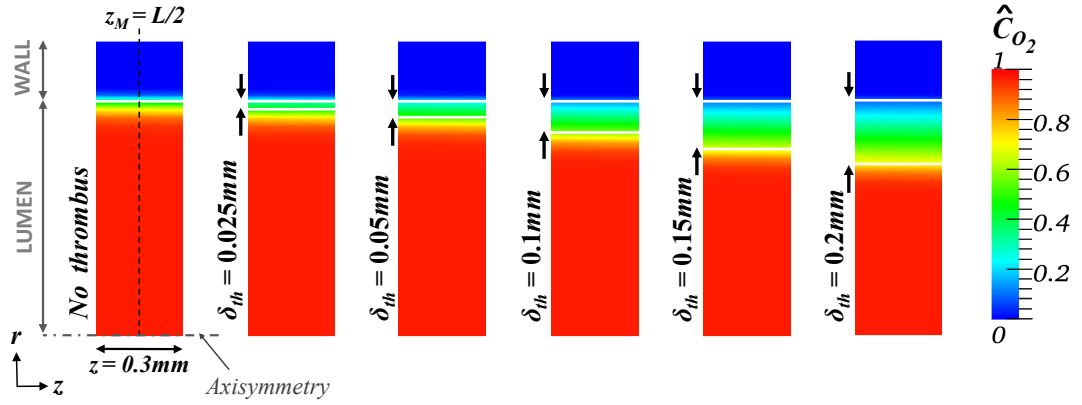


Figure 4.6: Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_1 = 1e-2 \text{ mol/m}^3/\text{s}$ ($t=60\text{s}$).

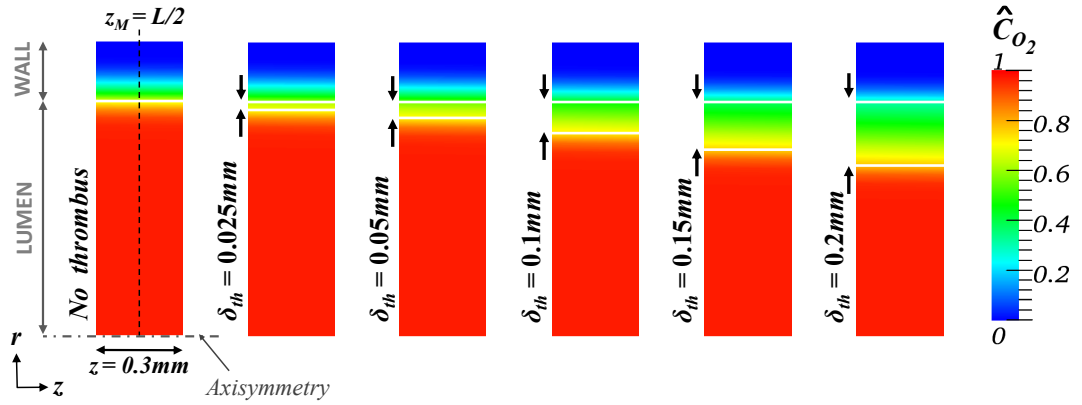


Figure 4.7: Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_2 = 1e-3 \text{ mol/m}^3/\text{s}$ ($t=120\text{s}$).

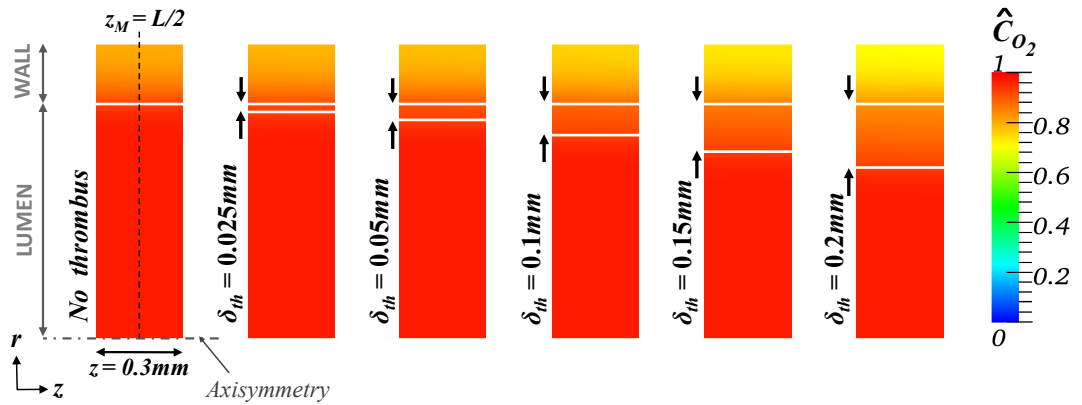


Figure 4.8: Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_3 = 1e-4 \text{ mol/m}^3/\text{s}$ ($t=300\text{s}$).

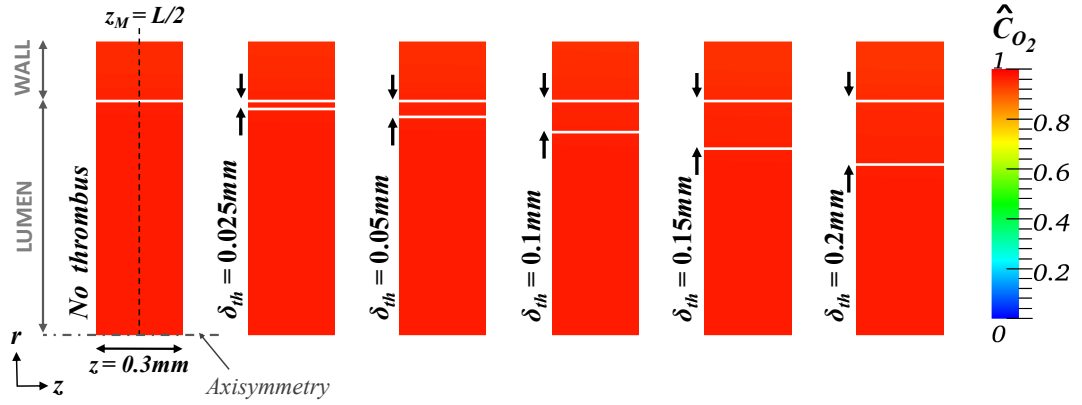


Figure 4.9: Normalised oxygen concentration through the lumen, thrombus and wall layers as the thrombus propagates from 0 to 0.2mm: $\dot{q}_4 = 1e-5 \text{ mol/m}^3/\text{s}$ ($t=300\text{s}$).

The respiration rate seems to have the greatest effect on transmural oxygen levels. The highest consumption rate ($\dot{q}_1$) appears to restrict the diffusion of oxygen into the wall within a very short distance of the endothelium regardless of the presence or thickness of thrombus. Conversely, consumption rate $\dot{q}_4$ is low enough that given enough time (300s in this case) the oxygen continues to diffuse through both the thrombus and the wall until each domain is completely ‘filled’. Both $\dot{q}_2$ and $\dot{q}_3$ permit oxygen diffusion into the wall, the latter in greater degrees. In these two cases there is an obvious reduction in diffusion distance and transmural oxygen levels as the thrombus thickens.

Figures 4.10 to 4.15 show the radial oxygen concentration levels across the $z_M = L/2$ axis for a healthy artery and for $\delta_{th} = 0.025 - 0.2\text{mm}$. These show in greater detail the effect of each consumption rate on thrombus and wall O_2 distributions. The radial oxygen plots for $\dot{q}_4$ confirm that such a low respiration rate allows for the slow diffusion of O_2 through both the thrombus and wall layers irrespective of the thrombus thickness; for each case the oxygen concentration throughout all domains stabilises at 96%. For consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$ the oxygen values decrease linearly through the thrombus layer. This is to be expected as simple diffusion-only equation of transport with no consumption term is prescribed to this domain. Overall the greater the cellular respiration, the greater the drop in oxygen across the thrombus. Moreover, for each consumption rate, the slope increases

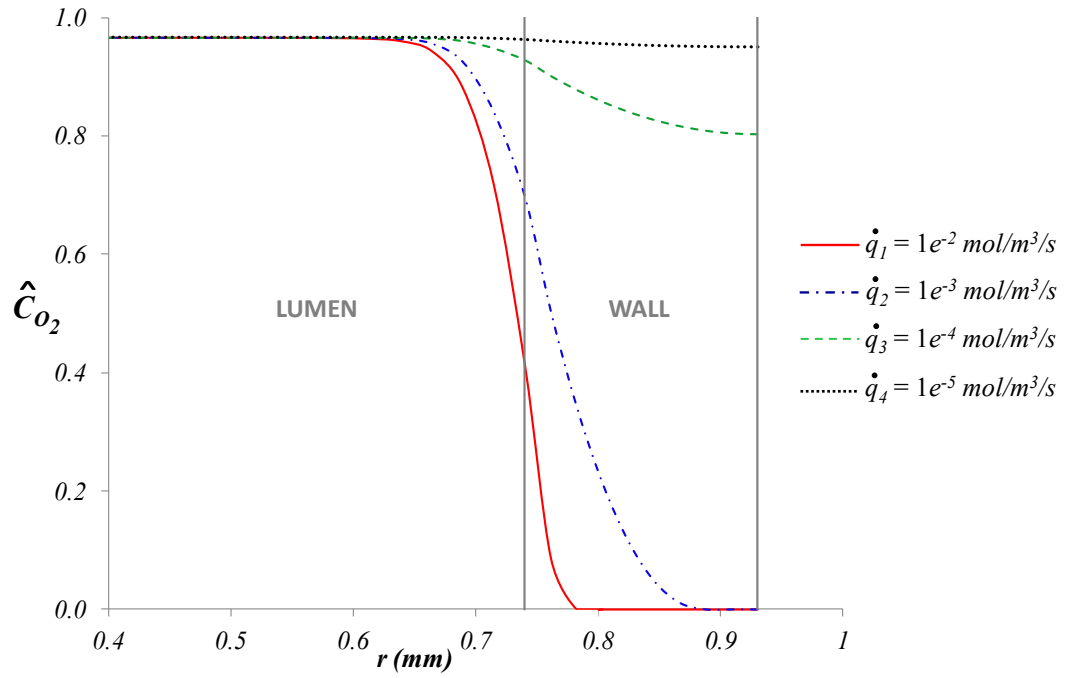


Figure 4.10: Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Not thrombus layer.

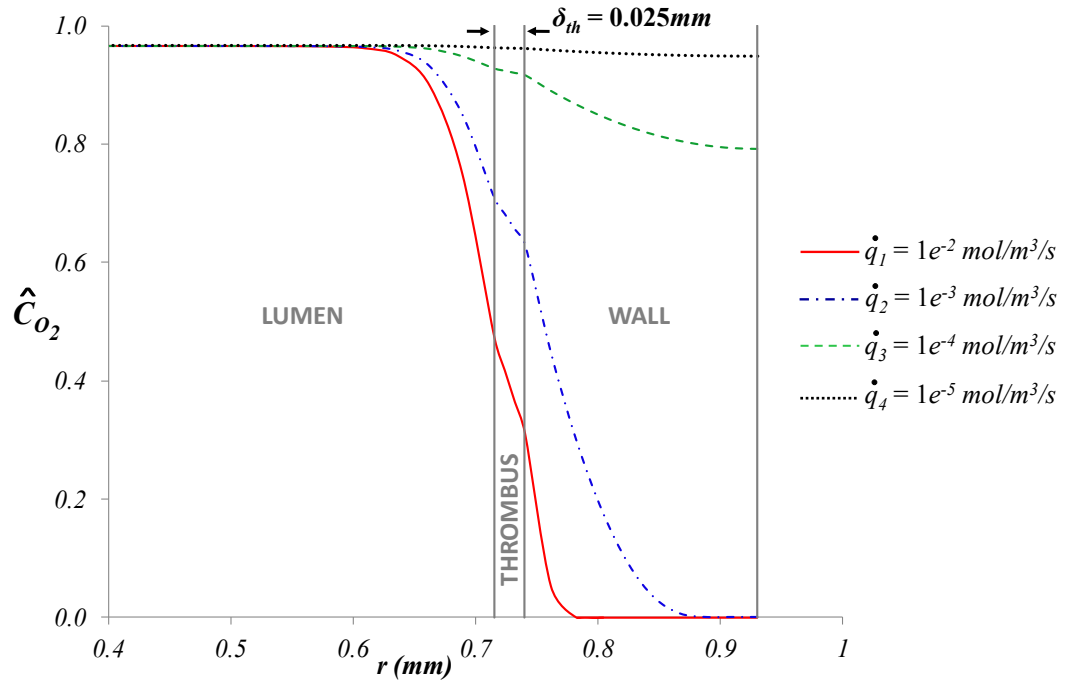


Figure 4.11: Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.025$ mm.

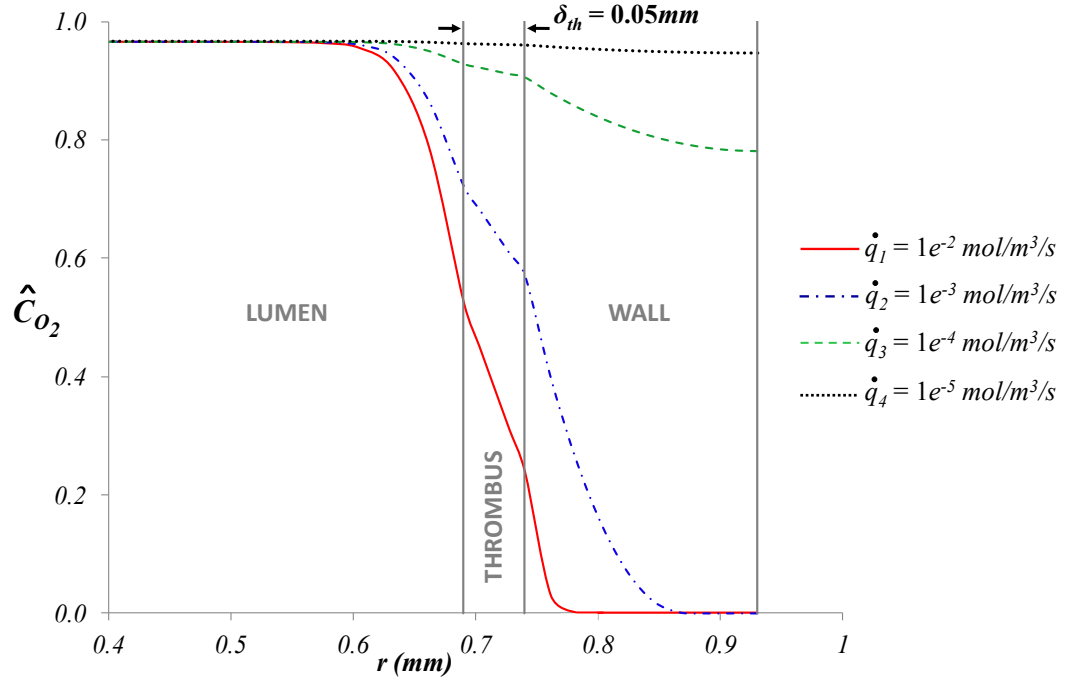


Figure 4.12: Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1, \dot{q}_2, \dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.05 \text{ mm}$.

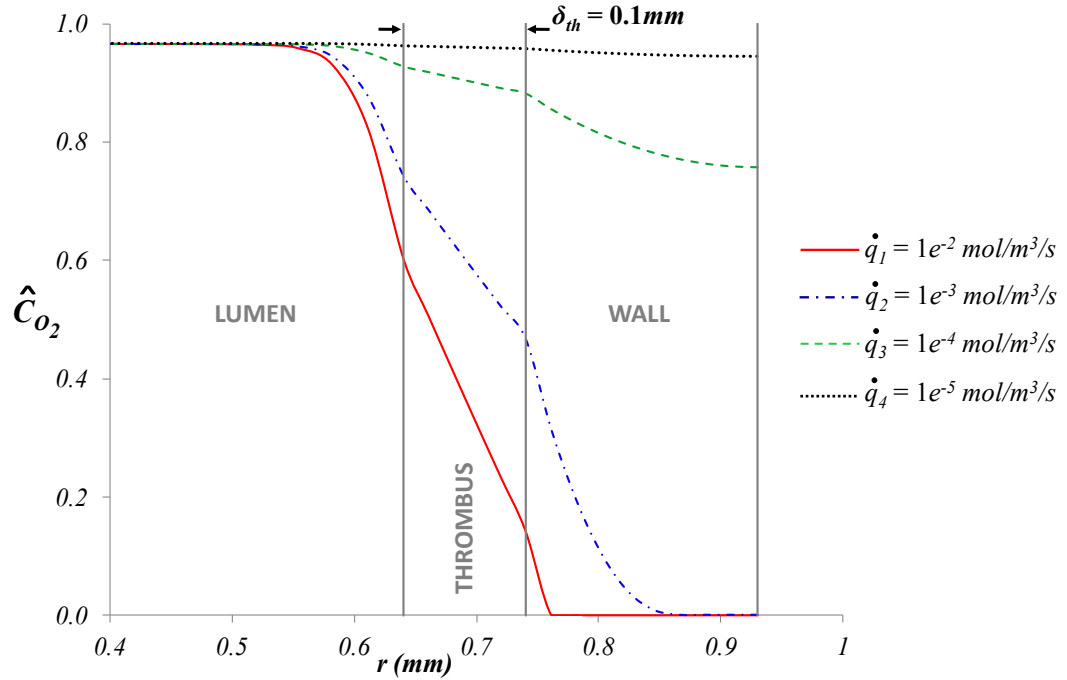


Figure 4.13: Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1, \dot{q}_2, \dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.1 \text{ mm}$.

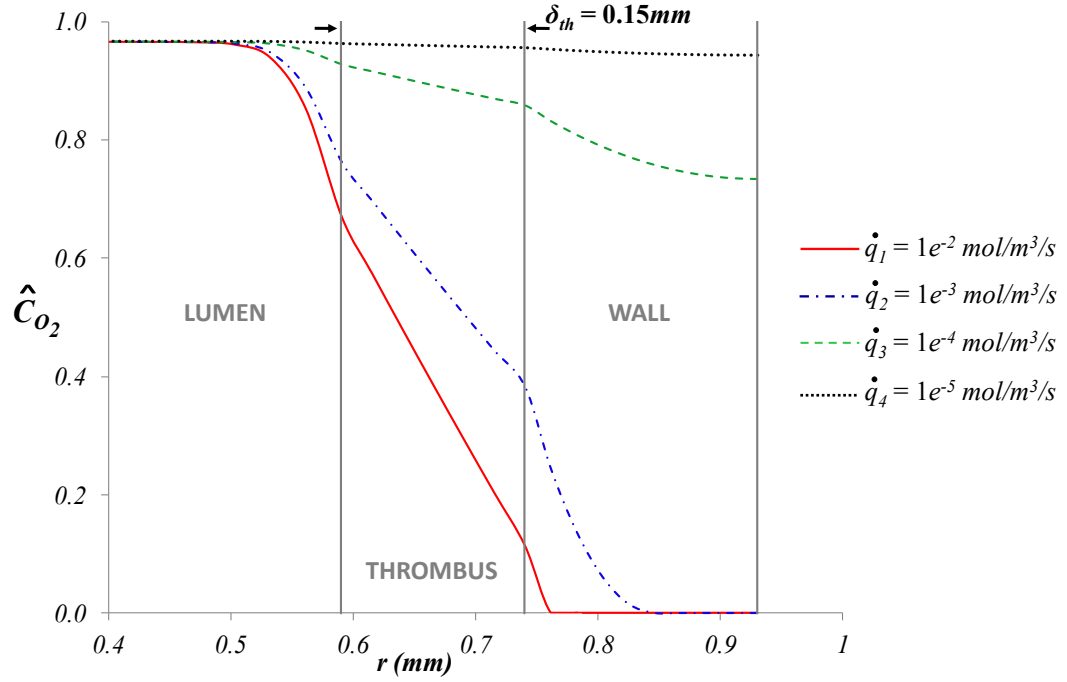


Figure 4.14: Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.15\text{mm}$.

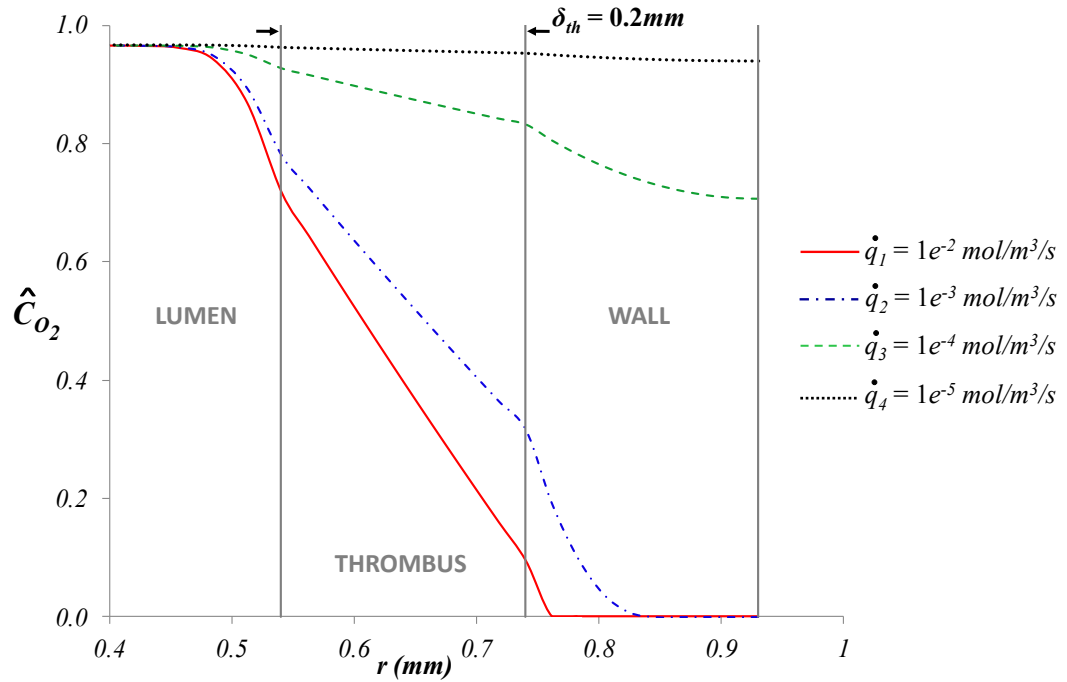


Figure 4.15: Radial profiles of normalised oxygen concentration across the $z_M = L/2$ axis for $\dot{q}_1$, $\dot{q}_2$, $\dot{q}_3$ and $\dot{q}_4$. Thrombus thickness $\delta_{th} = 0.2\text{mm}$.

across the domain as the thrombus thickness increases.

Table 4.4 details the oxygen concentration values at the lumen/wall (l/w), lumen/thrombus (l/t) and thrombus/wall (t/w) interfaces for each case.

	$\dot{q}_1$		$\dot{q}_2$		$\dot{q}_3$		$\dot{q}_4$	
δ_{th}	l/t	t/w	l/t	t/w	l/t	t/w	l/t	t/w
0	41%		70%		93%		96%	
0.025	47%	31%	71%	63%	93%	92%	96%	96%
0.05	52%	24%	72%	57%	93%	91%	96%	96%
0.1	60%	14%	74%	47%	93%	88%	96%	96%
0.15	67%	11%	76%	38%	93%	86%	96%	96%
0.2	72%	09%	78%	32%	93%	83%	96%	96%

Table 4.4: Normalised oxygen concentration values at the lumen/thrombus (l/t) and thrombus/wall (t/w) interfaces for varying consumption rates and thrombus thicknesses. For the healthy artery the single value is at the lumen/wall interface.

At the lumen/thrombus interface the oxygen concentration values increase from 41% when $\delta_{th}=0\text{mm}$ to 72% when $\delta_{th}=0.2\text{mm}$ for $\dot{q}_1$ and from 70% when $\delta_{th}=0\text{mm}$ to 78% when $\delta_{th}=0.2\text{mm}$ for $\dot{q}_2$. This increase may be down to the greater thickness of thrombus reducing the influence of the higher wall consumption of O_2 . Whilst for $\dot{q}_3$, the value at the lumen/thrombus interface does not vary as the thrombus grows and remains at a constant 93%. At the thrombus/lumen interface the concentration values decrease for each consumption rate: from 41% when $\delta_{th}=0\text{mm}$ to 9% when $\delta_{th}=0.2\text{mm}$ for $\dot{q}_1$, from 70% when $\delta_{th}=0\text{mm}$ to 32% when $\delta_{th}=0.2\text{mm}$ for $\dot{q}_2$, and from 93% when $\delta_{th}=0\text{mm}$ to 83% when $\delta_{th}=0.2\text{mm}$ for $\dot{q}_3$.

The concentration of oxygen across the wall itself is highly dependent on the respiration parameter. In the healthy artery model, the oxygen content of the wall for both $\dot{q}_1$ and $\dot{q}_2$ cases reduce to naught within 21% and 79% of the wall thickness respectively. As the thrombus thickness increases, this depletion of oxygen occurs within a shorter distance. When $\delta_{th}=0.2\text{mm}$ the oxygen reduces to naught within 10% of the wall thickness for $\dot{q}_1$ and within 56% of the wall thickness for $\dot{q}_2$. As for $\dot{q}_3$, the oxygen concentration reduces to 80% at the adventitial boundary when $\delta_{th}=0\text{mm}$, and reduces to a minimum of 71% when $\delta_{th}=0.2\text{mm}$.

4.2.2.2 Convection-Diffusion through thrombus as a porous medium

The difference between results for permeability values κ_1 , κ_2 and κ_3 were less than 0.01% whether the corresponding porosity value is ε_1 or ε_2 . Whereas the oxygen concentration results between porosity values (say cases $[\varepsilon_1, \kappa_1]$ versus $[\varepsilon_2, \kappa_1]$) were no greater than 1%. Hence, Figures 4.16 to 4.20 show only the radial oxygen concentration profiles across the $z_M = L/2$ axis for a thrombus of porosity $\varepsilon=0.9$ and permeability $\kappa_2=1e^{-14}m^2$ as a representation of the difference observed between diffusion-only and convection-diffusion transport. As there were no differences for results of the $\dot{q}_4$ cases these results are not shown here.

The concentration of oxygen and oxyhaemoglobin maintain stable levels of 96% and 97% respectively throughout the lumen. The percentage difference between $\hat{C}_{O_2}$ values when there is no flow and when there is a filtration velocity through the thrombus at the lumen/thrombus (l/t) and thrombus/wall (t/w) interfaces are detailed in Table 4.5.

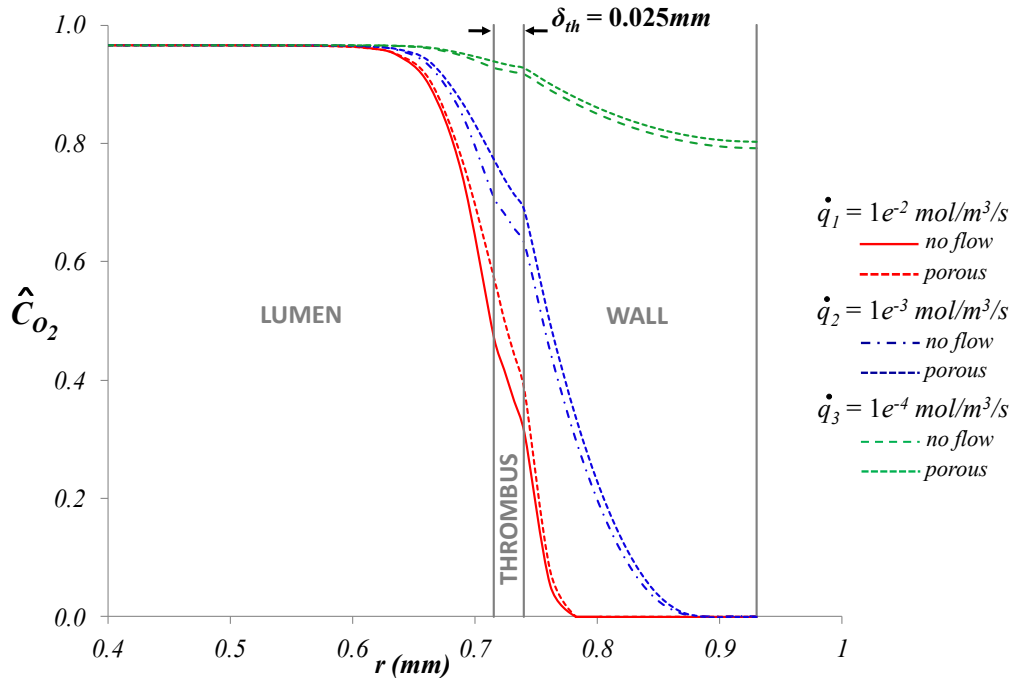


Figure 4.16: Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.025\text{mm}$.

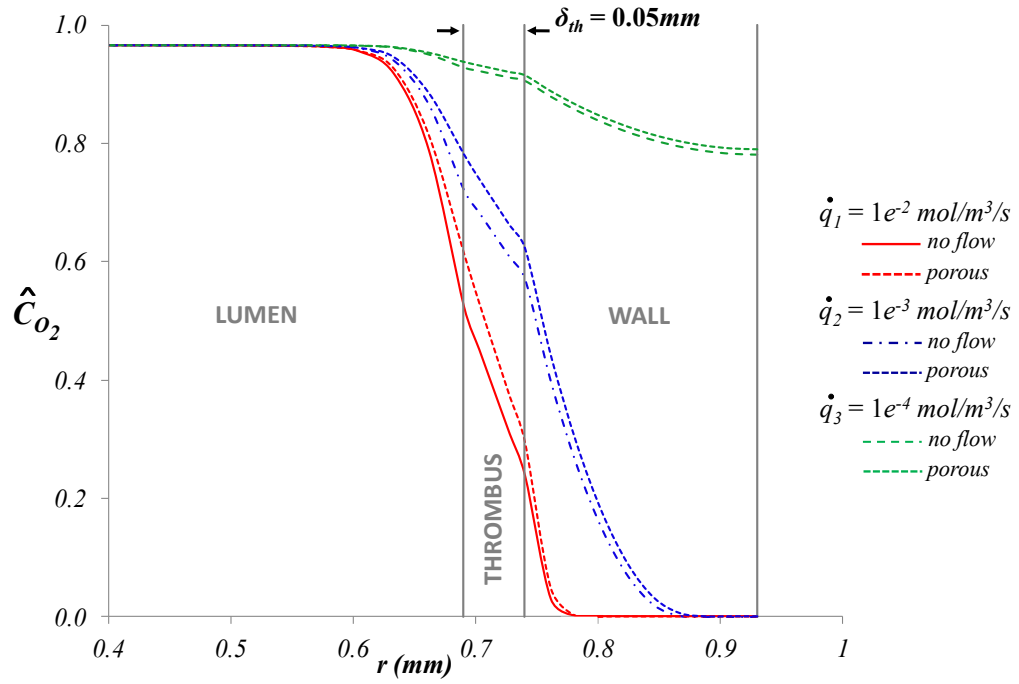


Figure 4.17: Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.05\text{mm}$.

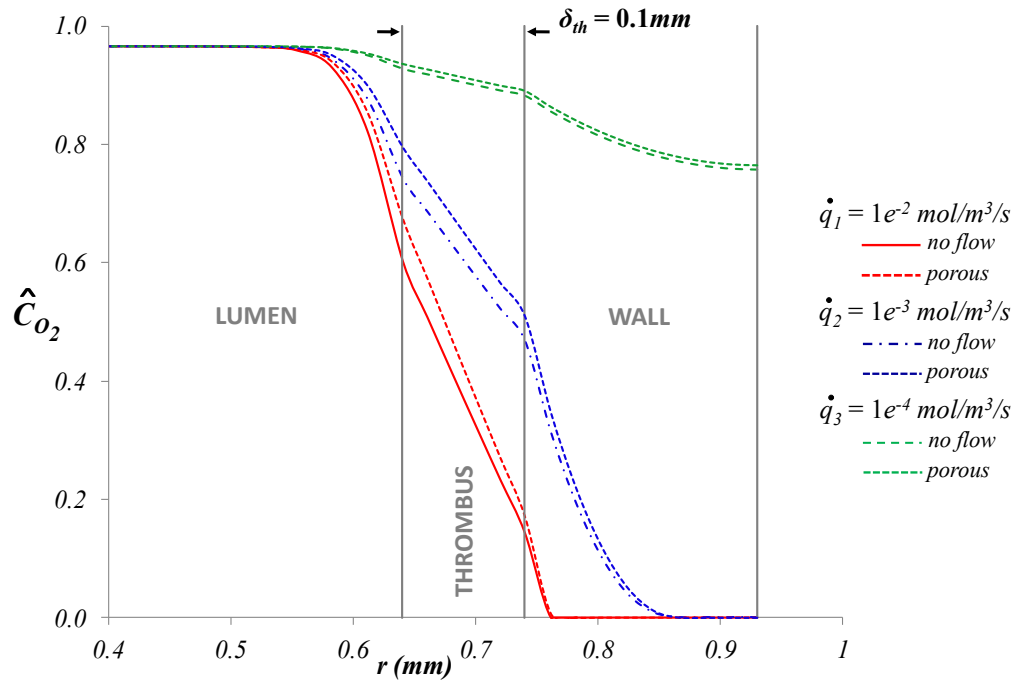


Figure 4.18: Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.1\text{mm}$.

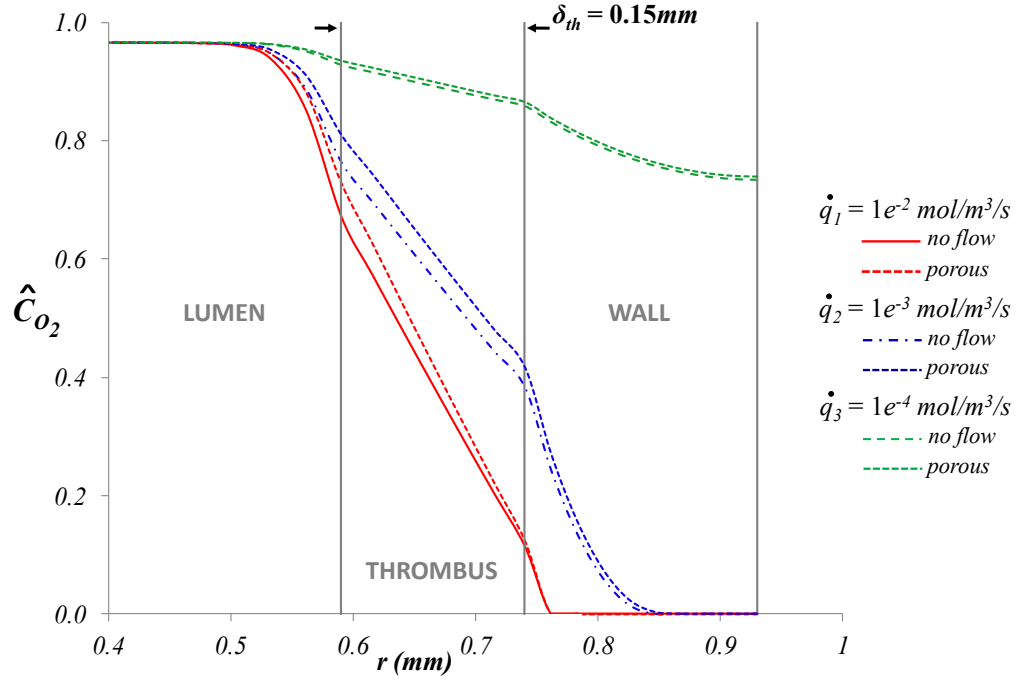


Figure 4.19: Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.15\text{mm}$.

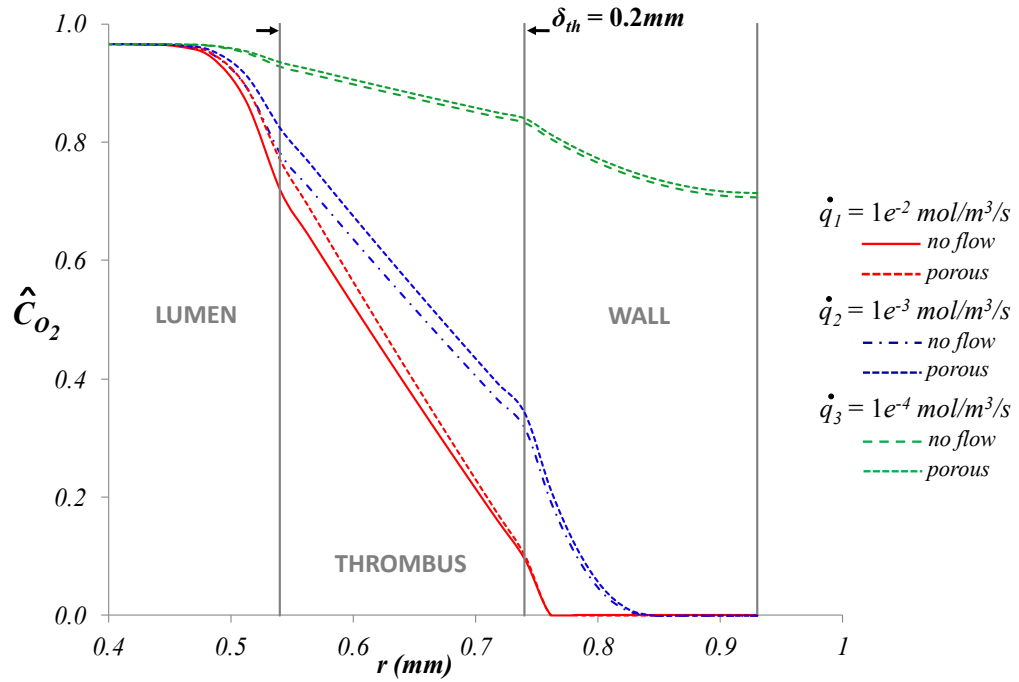


Figure 4.20: Comparison between diffusion-only and convection-diffusion of oxygen through the thrombus layer for consumption rates $\dot{q}_1$, $\dot{q}_2$ and $\dot{q}_3$. Thrombus thickness $\delta_{th} = 0.2\text{mm}$.

δ_{th}	$\dot{q}_1$		$\dot{q}_2$		$\dot{q}_3$	
	l/t	t/w	l/t	t/w	l/t	t/w
0.025	17.6%	18.8%	7.7%	8.4%	1.0%	1.0%
0.05	14.7%	19.7%	8.3%	7.7%	1.1%	1.1%
0.1	10.7%	16.4%	8.3%	7.2%	1.0%	1.1%
0.15	7.9%	8.6%	8.2%	5.7%	0.9%	1.0%
0.2	6.8%	7.1%	7.6%	5.1%	1.0%	1.1%

Table 4.5: Percentage difference between oxygen concentration values when thrombus transport is modelled through diffusion only and when it is modelled as a porous medium at the lumen/thrombus (l/t) and thrombus/wall (t/w) interfaces for varying consumption rates and thrombus thicknesses.

For each thrombus thickness and each consumption rate the oxygen concentration values are universally higher when thrombus is modelled as a porous medium. The greatest difference in interface values is observed for $\dot{q}_1$ with an increase in oxygen concentration of 17.6% at the lumen/thrombus interface and an increase of 18.6% at the thrombus/wall interface when $\delta_{th} = 0.025\text{mm}$. This difference becomes less prominent when the thrombus thickness is 0.15 and 0.1mm: both interface values show an increase of around 7-8% when modelled as a porous medium. The increase in $\hat{C}_{O_2}$ when the wall consumption rate is $\dot{q}_2$ at the lumen/thrombus interface is in the range of 7-8% for each thickness. This is also the case for the thrombus/wall interface for $\delta_{th} = 0.025, 0.05$ and 0.1mm , however the increase is slightly lower at 5-6% for $\delta_{th} = 0.15$ and 0.2mm . At the higher respiration rate of $\dot{q}_3$, the increase is approximately 1% across the entirety of the thrombus and wall layers.

This observed increase through the thrombus layer is speculated to be a consequence of the added convection term in the transport equation when modelling thrombus as a porous model. The maximum filtration velocities through the thrombus layer vary between $1e^{-4}\text{mm/s}$ ($\delta_{th} = 0.025\text{mm}$) and $1.55e^{-4}\text{mm/s}$ ($\delta_{th} = 0.025\text{mm}$) for a medium of porosity $\varepsilon_2 = 0.9$ (approximately an order of magnitude greater than the experimentally measured velocities through arterial walls). These velocities are $\sim 15\%$ lower for each thickness when modelling a medium of porosity $\varepsilon_1 = 0.75$. However it appears that this drop only accounts for a 1% differ-

ence in oxygen concentration distributions between ε_1 and ε_2 cases. Furthermore, at the higher consumption rates of $\dot{q}_1 = 1e-2$ mol/m³/s and $\dot{q}_2 = 1e-3$ mol/m³/s, the smaller differences observed at the wall interface for thrombus thicknesses 0.15mm and 0.20mm suggest that the greater distances may reduce the benefits of convective flux on oxygen transport through a porous medium.

The concentration across the wall layer is still under the influence of cellular respiration and any increase noted for the porous cases at the wall interface is succinctly reduced to a 1-2% difference within a short distance into the wall.

4.3 DISCUSSION AND CONCLUDING REMARKS

Table 4.6 summarises the percentage reduction in oxygen concentration at the wall interface when comparing the results for a healthy artery (i.e. the wall interface values in Figure 4.10), and all other thrombus cases explored in sections 4.2.2.1 and 4.2.2.2.

	$\dot{q}_1$		$\dot{q}_2$		$\dot{q}_3$	
δ_{th}	<i>No flow</i>	<i>Porous</i>	<i>No flow</i>	<i>Porous</i>	<i>No flow</i>	<i>Porous</i>
0.025	24.2%	4.1%	9.5%	0.1%	1.2%	0.1%
0.05	42.1%	26.7%	18.0%	9.6%	2.4%	1.2%
0.1	65.3%	57.7%	32.8%	26.3%	4.9%	3.9%
0.15	72.5%	69.7%	45.0%	39.8%	7.5%	6.6%
0.2	77.2%	75.3%	54.6%	50.7%	10.3%	9.4%

Table 4.6: Percentage reduction in oxygen concentration at the wall interface when comparing each thrombus case to the ‘healthy’ artery case with no thrombus layer.

The parametric studies conducted in this chapter demonstrate that the filtration velocities through a porous thrombus do have an evident influence on the transport of oxygen through the layer. However, the contribution of convective oxygen flux is less significant as the transport distance increases (a difference from diffusion-only $\hat{C}_{O_2}$ of $\sim 7 - 1\%$ for a thrombus of 0.2mm). Given that the computed filtration velocities through the thrombus are an order of magnitude higher than the experimentally measured values for arterial wall found in the literature (Back (1976); Tedgui

and Lever (1984)) and that the wall thickness is similar to the thickest of thrombus, this reinforces the assumption made that diffusive flux of oxygen is the dominant transport mechanism through the thrombus layer. Moreover the additional computational time incurred when solving flow conservation equations through a porous medium is notable; the average CPU times to reach steady state for the porous cases were 250% longer than when only calculating the scalar conservation equation over the same mesh.

Regardless of the clot formation, the radial O_2 profiles are prescribed by cellular respiration. The greater the consumption rate, the greater the impedance of the thrombus on the oxygen delivery to the wall interface. A very low respiration rate of $1e^{-5}$ mol/m³/s allows the slow distribution of oxygen through all domains regardless of the added obstruction created by the presence of a clot, whilst a propagating thrombus does not deliver enough oxygen to satisfy the high cellular demands imposed by a consumption rate of $1e^{-2}$ mol/m³/s. *In vivo* trans-arterial measurements of oxygen partial pressure in healthy dog carotid arteries (Santilli et al. (1995)) and rabbit aortas (Niinikoski et al. (1973); Santilli et al. (2000)) demonstrate that the lowest transmural oxygen tension is in the range of 20-40% of the luminal value. These particular arteries do have *vasa vasorum* and so the decrease from luminal partial pressure to the lowest level occurs approximately two-thirds of the way through the media. The tension levels then steadily increase through the rest of the media to the adventitia, which has a partial pressure provided by the *vasa vasorum*. Nonetheless, these findings suggests that in a ‘healthy’ artery there is always a base level of oxygen available after normoxic respiration by cells, allowing for a rapid response should cells require increased oxygenation. The computed levels of oxygen concentration when the thrombus layer is absent (Figure 4.10) emphasise that the use of a single uniform cellular respiration rate is not physiologically accurate. Whilst the consumption rate of $1e^{-3}$ mol/m³/s does not provide full oxygenation of the wall, the consumption rate of $1e^{-4}$ mol/m³/s does with a remaining base tension of 80%. The radial variation is most certainly an array of values between these two

phenomenologically measured values, and is dependent on the local cellular composition of the wall layer.

Looking at the results from the point of view of oxygen conformance, these simulations demonstrate that an adaptive reduction in respiration could offer temporary relief from ‘hypoxic’ conditions. Should the initial consumption rate for a healthy artery be in the range of $1e^{-2}$ mol/m³/s, then a 90% reduction in respiration (ie. $1e^{-3}$ mol/m³/s) would reduce the obstruction in oxygen supply to the wall from $\sim 75\%$ to $\sim 50\%$, whilst a 99% (ie. $1e^{-4}$ mol/m³/s) decrease in respiration would result in a $\sim 10\%$ reduction from normoxic values.

This simplified model of the wall does not allow for physiologically accurate interpretation of oxygen concentrations. However this is a model development exercise for the implementation into the first coupled flow-mass transport model of 3D patient-generated IAs with homogeneous a wall layer. And so, without being able to declare if any of these thrombus induced conditions are considered hypoxic enough to lead to cell death, these results nonetheless demonstrate the ability to simulate the overall impact of a propagating thrombus on the impairment of oxygen delivery to the arterial wall by the means of coupled flow-mass transport CFD analysis.

OPTIMISATION OF MESH GENERATION FOR 3D PATIENT-SPECIFIC GEOMETRIES

The case study outlined in the Virtual Intracranial Stenting Challenge (VISC) 2007 (Radaelli et al. (2008)) is reproduced to demonstrate the potential of CFD-VisCART (ESI GROUP, Paris, France), an adaptive unstructured Cartesian mesh generation tool, to minimise both pre- and post- processing when meshing patient specific geometries of an unstented and stented aneurysm.

Various comparative studies have been undertaken regarding rigid versus deformable walls (e.g. Kim et al. (2008)), steady versus pulsatile flow (e.g. Hoi et al. (2004); Cavazzuti et al. (2011)), and non-Newtonian versus Newtonian rheology (e.g. Fisher and Rossmann (2009)), noting the relative importance of each factor on certain hemodynamic variables. However, it appears that the accuracy of patient generated morphology (i.e., the image-generated definition of the computational domain) lead to far greater uncertainties in computed results. The sensitivity and specificity of imaging modalities, such as 3D rotational angiography (3DRA), computed tomography (CT), and magnetic resonance imaging (MRI), are ever increasing, thus allowing for detailed visualization of arterial morphology. Used as diagnostic tools originally, advancements in segmentation techniques have made it possible to extract patient-derived geometries from scans for use in CFD simulations. The output surface extracted from 3DRA/MRI/CT data is generally in stereolithography (STL) format. STL is essentially a surface grid composed of interconnecting triangles of varying sizes, depending on the level of curvature of the domain. Inaccuracies in geometry occur from segmentation artifacts (e.g., insufficient resolution, inadequate contrast dye in the case of angiographic imagery, or vessel motion over the course of the scan) and subsequent volume mesh generation. As software

and hardware evolves, the limiting factor seems to be obtaining (rapidly and with minimum user intervention) an accurate surface from imaging modalities, as the ever-increasing capabilities of CFD solvers to operate in parallel allow for the rapid computation of very fine meshes.

Although modern computational analysis allows for a variety of discretization and grid generation options (structured, unstructured, conforming, nonconforming, single block, multiblock, etc.), in most cases the complexity of the domain to be simulated implies that maximum flexibility in meshing is required. Finite volume discretisation is suitable for both structured and unstructured meshes. For a regular geometry a Cartesian or polar-cylindrical structured grid is the simplest option. The grid lines simply follow Cartesian coordinate directions and no further integrations are required to solve the general transport equation at each cell node. When constructing a grid in a complex geometry, such as a patient IA geometry with the presence of a stent (a flow-diverter when referred to as stand alone devices), it is vital that surface geometric fidelity is conserved, more importantly, that the mesh is fine enough to capture all important flow characteristics. Unstructured meshes, with tetrahedral elements and possibly prisms for near-wall resolution, offer the most flexibility for complex geometry and have extensively been used when conducting haemodynamic simulation of patient-generated aneurysm geometries (e.g. Geers et al. (2010); Lu et al. (2011); Luo et al. (2011)). Moreover the level of flexibility that such meshes allow, offers the further option to explore the interaction of virtually implanted medical devices (Radaelli et al. (2008); Morales et al. (2011)). Nonetheless unstructured meshes have their disadvantages. Firstly, there is often a need for time-consuming pre-processing: most commercially available mesh packages require the STL surface to be ‘watertight’, without gaps or overlaps, and perfect node-to-node matching of the triangles. Secondly, post-processing may be required to eliminate ‘bad’ cells that may arise from attempting to mesh regardless of surface mesh inconsistencies. Thirdly, unstructured meshes require a significant amount of CPU time as further integrations are required in order to solve the generalised

transport equation over each cell. Lastly, the amount of data from the integration, differentiation and interpolation approximations is stored at each cell node which also incurs on computational costs.

If CFD is to be implemented as an aid to diagnosing aneurysms and interventional planning of aneurysm treatment then the computational intensity needs to be kept to a minimum. The optimal clinical tool would be a quick and reliable integrated system which could provide computational fluid dynamic analysis from patient scans in a few simple steps (i.e. a few clicks of a mouse). One step towards this could be the reduction of user interaction at the grid generation level and thus, the aim of this chapter is to demonstrate the potential of CFD-VisCART (ESI GROUP, Paris, France), an adaptive unstructured Cartesian mesh generation tool that is part of the **CFD-ACE+** suite, to minimise both pre- and post-processing when meshing patient specific geometries of an unstented and stented aneurysms, such are explored in the case study outlined in the Virtual Intracranial Stenting Challenge (VISC) 2007 (Radaelli et al. (2008)).

5.1 MODEL DESCRIPTION

5.1.1 Aneurysm Geometry

The VISC07 project (Radaelli et al. (2008)) provided the STL of the unstented anatomical model of the aneurysm as well as the STLs of three different stents. The side-wall saccular IA is located on the internal carotid artery, between the ophthalmic and posterior communicating arteries. The STL was generated by segmentation of 3DRA data (Figure 5.1). The geometry was modified so there is only one inlet and outlet, therefore disregarding outflow from the side branching arteries. Three different commercially available stents are to be analysed: the first is a self-expandable Neuroform stent (Boston Scientific Corp., Natick, MA, USA), the second is self-expandable COOK Z-like stent (William Cook Corp Europe, Bjaeverskov, Denmark) and the third is a balloon expandable Pharos stent (Biotronik AG,

Bülach, Switzerland). The stent STLs were already in the deployed state using the virtual stent deployment technique developed by Appanaboyina et al. (2008): the end product can be seen in Figure 5.2.

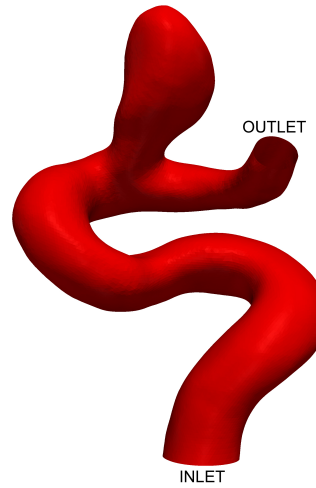


Figure 5.1: STL of unstented anatomical model of a side wall aneurysm located on the internal carotid artery.

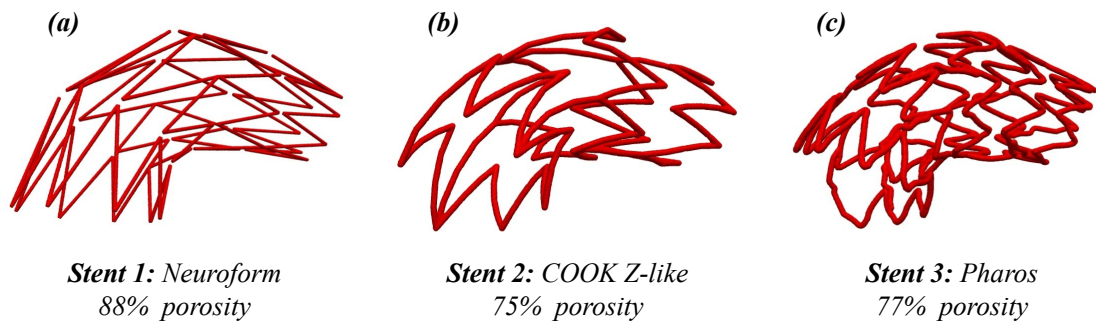


Figure 5.2: STL surfaces of deployed stents: (a) Neuroform; (b) COOK Z-like; (c) Pharos.

5.1.2 Grid Generation

5.1.2.1 The benefits of an adaptive unstructured Cartesian mesh

CFD-VisCART creates an adaptive unstructured Cartesian (AUC) mesh by first generating the interior volume of the domain with structured Cartesian hexahedral cells and the boundary is then connected through projections to assure surface geometric fidelity. The mesh is generated regardless of the disconnected outer surface thus avoiding the requirement of ‘watertightness’ (as shown in Figure 5.3). Any holes

in the surface that are smaller than the minimum cell size are simply ignored (Wada and Karino (2002))). The adaptive unstructured Cartesian mesh thus reduces the need for both pre-processing (closing) of the surface STL and post-processing as this method reduces the chances of ‘bad’ cells occurring from attempting to mesh discrepancies in the surface. Whilst this method offers less flexibility than a tetrahedral mesh, CFD-VisCART rapidly creates a body-fitted mesh with very limited user interaction (as outlined in the following section).

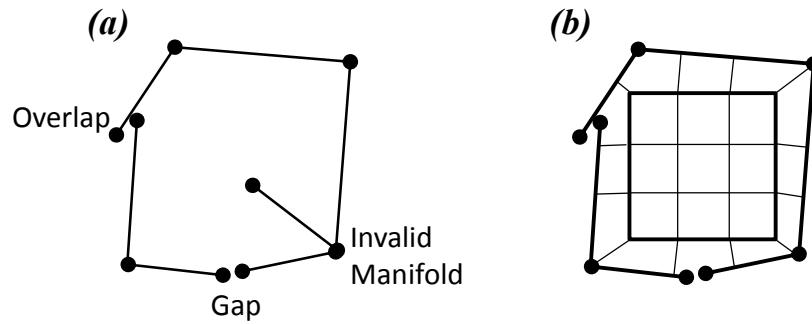


Figure 5.3: Example of grid generation on an imperfect surface using the adaptive unstructured grid method implemented by CFD-VisCART. (a) Example of surface imperfections in an STL surface. (b) Creation of an adaptive unstructured Cartesian mesh in imperfect STL.

5.1.2.2 Methodology of a projected AUC

Creation of the Cartesian grid is achieved through cell subdivision. The minimum cell size of the domain is allocated selecting a maximum division level and is defined by the following expression:

$$\text{cell size} = \frac{\text{bounding box}}{2^n} \quad (5.1)$$

whereby n is the maximum division level, which can be specified in the x , y and z directions. The bounding box of the domain is essentially considered the first cell, regardless of intersection with the boundary. For a maximum division level of 2 in all directions, the cell (bounding box) will be divided into 4. The way in which the cell is divided is defined by the Cartesian tree structure. CFD-VisCART offers two options: (i) Octree methods splits cells equally in the x , y and z directions; (ii) Omnitree allows the option of splitting along one, two or three directions. Any cells that

intersect with the boundary (or are too close to the boundary) are automatically removed, leaving exposed Cartesian faces which need to be connected to the surface through projection. CFD-VisCART allows this boundary refinement to be achieved in two ways: (i) '*Refine with normal and tangential size*' will split the boundary cell based on how it intersects with the boundary surface; (ii) '*Refine with specific cell size*' defines a consistent cell size for all intersecting cells. Furthermore the boundary refinement may be layered, the higher the number of layers, the slower the transition between coarse and fine mesh. Refinement may also be specified at surface sources, such as the surface of the stent struts. The type of refinement at this surface boundary is limited to '*Refine with normal and tangential size*'.

5.1.2.3 Grid Independence Studies

Grid independence studies were carried out for the unstented aneurysm case (U), and stented aneurysm cases (S1, S2 and S3), specifically looking at velocity and WSS. Haemodynamic simulations were run for mesh sizes of 1M, 5M, 10M, 20M and 30M. In order to achieve such a refinement three different grid variables were varied: the maximum division level, the boundary refinement at the wall, and the boundary refinement at the stent surface. For all mesh sizes cell division was achieved using

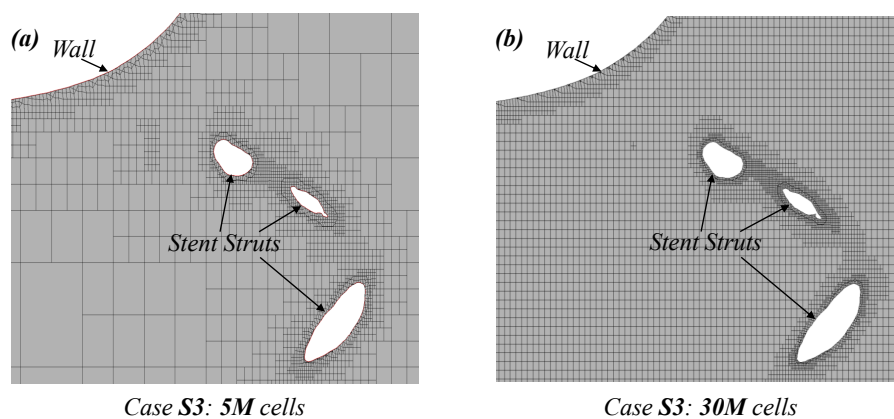


Figure 5.4: Cut through aneurysm neck showing the grid refinement at the arterial wall and around the cross section of a stent struts for case S3: (a) ~ 5 million cells and (b) ~ 30 million cells.

the Octree method and all boundary refinements were defined with respect to the cell normal and tangential size. Figure 5.4 demonstrates the difference in mesh density for case S3 with $\sim 5\text{M}$ cells and $\sim 30\text{M}$ cells.

5.1.3 Simulation Inputs

All simulations were run in **CFD-ACE+**. Blood was modeled as a Newtonian fluid with no-slip at the walls, of density $\rho_b = 1060 \text{ kg/m}^3$ and viscosity $\mu_b = 4e^{-3} \text{ kg/ms}$. A uniform velocity profile of $U = 0.1865 \text{ m/s}$ was set at the inlet, with a zero pressure condition at the outlet boundary. The velocity field was solved using the combined CDS and UPS scheme (see Equation (3.16)) with a blending factor of $\theta=0.1$. Simulations for meshes of size 10M, 20M and 30M were run in parallel on the in-house cluster. A work-load balance was adopted for mesh decomposition so that approximately 1M cells were allocated to 1 processor (i.e. for a 20M cell mesh, the domain was decomposed into 20 zones of approximately 1M cells each).

5.1.4 Inflow velocity calculations

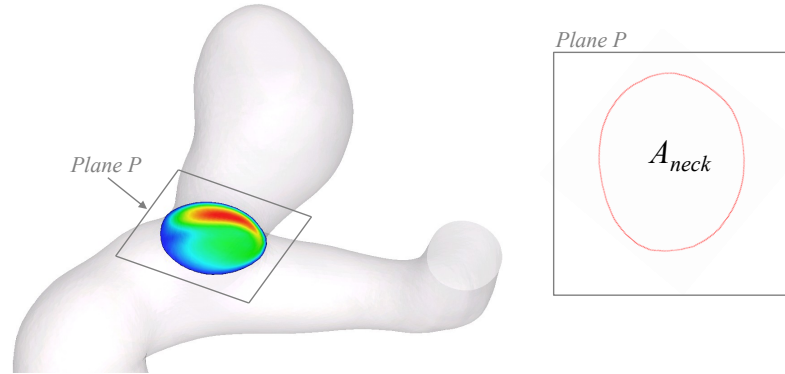


Figure 5.5: Cutting plane P across the aneurysm neck resulting in a cross-sectional area of A_{neck} .

Radaelli et al. (2008) suggest that the ability of a stent to promote thrombosis within the aneurysm sac is related to the reduction in inflow velocity across the neck. Figure 5.5 shows the cut-plane P and the resulting cross-sectional area A_{neck} . The exact coordinates of the plane are not explicitly detailed in the article and so an

approximation is made. The inflow rate $\dot{Q}$ is calculated with the following expression:

$$\dot{Q} = \int_{A_{neck}} v_{\perp}^+ dA. \quad (5.2)$$

whereby $v_{\perp}^+$ is the influx velocity perpendicular to the plane P .

5.2 RESULTS

5.2.1 Velocity field

Table 5.1 displays the inflow rate for the varying density grids generated with CFD-VisCART. To demonstrate the benefits of this technique comparisons were made between this approach and work carried out by Bowker (2010)) with similar sized unstructured tetrahedral meshes generated using the ICEM meshing software (ANSYS ICEM CFD, ANSYS Inc, PA, USA). Bowker (2010)) created the unstructured tetrahedral meshes using an Octree method (defined above) and a maximum size refinement at the stent surface, whilst also using a boolean intersection method between the artery/aneurysm surface and the stent struts. The percentage difference in inflow rate values for each mesh is calculated with respect to the largest mesh.

The finest grid independence (a difference of 1% between mesh density) is acquired from approximately 5M cells for the unstented case, whilst all three stent cases require a minimum of 20M cells. This accentuates the need for higher density meshes in order to capture the haemodynamic alterations as a result of stent placement.

The last column of Table 5.1 shows the percentage difference between the inflow rates across the neck when meshed with CFD-VisCART and when meshed with ICEM. In the unstented case the difference in inflow rates between both meshing techniques is no greater than 1.69% for the coarser grids, and becomes insignificant for the finer grids. For Stent 1 the greatest difference is found when comparing the 5M cell grids with a percentage of 10.29%. Looking at the flow rate values, the 5M

CFD-VisCART		ICEM		(Bowker (2010))		Comparison
Number of cells	Inflow rate ($\times 10^{-6}$ m ³ /s)	Difference to largest mesh (%)	Number of cells	Inflow rate ($\times 10^{-6}$ m ³ /s)	Difference to largest mesh (%)	CFD-VisCART vs. ICEM (%)
<i>No Stent</i>						
961777	0.354	-2.21	1669016	0.348	-3.88	<i>No Stent</i> -1.69
5061745	0.360	-0.55	4908433	0.355	-1.93	-1.39
10042661	0.364	+0.55	9992801	0.359	-0.83	-1.37
20228506	0.361	-0.28	19730495	0.361	-0.28	0.00
31767721	0.362	0.00	39984470	0.362	0.00	0.00
<i>Stent 1</i>						
786424	0.309	-6.36	1058904	0.309	-4.63	<i>Stent 1</i> 0.00
506838	0.311	-5.76	5027307	0.279	-13.83	-10.29
10084326	0.312	-5.45	9904179	0.306	-5.56	-1.92
20738147	0.329	-0.30	19368196	0.320	-1.23	-2.74
29937295	0.330	0.00	39501226	0.324	0.00	-1.82
<i>Stent 2</i>						
1047267	0.304	-4.95	1013703	0.304	-5.27	<i>Stent 2</i> 0.00
4977116	0.310	-3.02	4961652	0.310	-3.43	0.00
10079773	0.312	-2.36	10021894	0.308	-4.05	-1.28
19393980	0.319	-0.31	19948806	0.319	-0.62	0.00
29141462	0.320	0.00	40408135	0.321	0.00	+0.31
<i>Stent 3</i>						
1014969	0.241	-6.81	1001901	0.235	-6.97	<i>Stent 3</i> -2.49
5096456	0.242	-6.67	5005811	0.232	-8.06	-4.13
10076527	0.244	-5.80	10010625	0.236	-6.34	-3.28
20245050	0.256	-1.24	19010560	0.248	-1.95	-3.13
29877507	0.259	0.00	40068115	0.252	0.00	-2.70

Table 5.1: Grid independence studies; inflow rate for cross-sectional area A_{neck} .

ICEM case is significantly lower than the others in this set; although the grid and model setup were reinvestigated, no anomalies were found (Bowker (2010)). Otherwise the difference between grid generators for Stent 1 does not exceed 2.74%. For Stent 2, a maximum difference of 1.28% is found for a mesh density of 10M, otherwise the percentage difference is no greater than 0.30%. The difference in inflow rate between mesh generators varies from 4.13% to 2.43% for Stent 3. This reflects the greater differences observed between mesh densities for this particular stent. Although stent 3 is not the least porous, the stent structure itself leads to a greater strut density across the neck, and in consequence may lead to a greater variation in near-wall meshing around the struts. Overall, in all four cases (unstented and 3 stents) mesh density has a much greater impact on inflow rates through the aneurysm neck, than the grid generator employed to create the mesh.

A total of 6 groups produced simulations of cases U, S1, S2 and S3 in the original study (Radaelli et al. (2008)). For simplicity they are referred to by their group acronyms: DR-TMH, GMU-UPF, IBITECH, LABS-PM, USFD and EPFL-HUG (all accreditations are listed within the article). Furthermore Cavazzuti et al. (2011) also conducted further work on the VISC challenge by exploring the effects of non-Newtonian flow and pulsatile flow in all four cases (U, S1, S2 and S3). All groups produced unstructured grids composed of tetrahedral elements (ranging from 0.5M to 9M cells) and used several different solvers for calculating the velocity field. Nonetheless, the aim of the challenge was to demonstrate that various techniques will provide consistent predictions. In order to evaluate the reproducibility of simulating stent performance the percentage difference in aneurysmal inflow rate between the stented cases and the unstented case were calculated. These results are reproduced in Table 5.2, with the addition of the finer grid results for both CFD-VisCART and ICEM cases.

The change in inflow rate for each stent case meshed with both CFD-VisCART and ICEM are comparable to that reported by the 6 simulation teams in the study conducted by Radaelli et al. (2008) and the simulations carried out by Cavazzuti

	$\dot{Q}$ ($\times 10^{-6}$ m ³ /s)	Inflow rate change		
	Unstented	Stent 1	Stent 2	Stent 3
<i>Radaelli et al. (2008)</i>				
DR-TMH	0.368	n/a	-16%	-25%
GMU-UPF	0.389	-13%	-12%	-26%
IBITECH	0.379	-10%	-6%	n/a
LABS-PM	0.350	-13%	-11%	n/a
USFD	0.391	-6%	-3%	-20%
EPFL-HUG	0.355	-11%	-11%	-22%
<i>Cavazzuti et al. (2011)</i>				
Newtonian steady state	0.359	-11%	-10%	-28%
non-Newtonian steady state	0.359	-14%	-13%	-27%
time-averaged pulsatile	0.319	-10%	-9%	-15%
ICEM	0.362	-10.5%	-11.3%	-30.5%
CFD-VisCART	0.365	-9%	-11.7%	-28.5%

Table 5.2: Inflow rate change for each stent compared to the unstented case for the greater mesh sizes for each case. Other results from the VISC07 challenge are also reported here for comparison (Radaelli et al. (2008); Cavazzuti et al. (2011)).

et al. (2011). Although the effect of Stents 1 and 2 equate to a reduction in inflow of around 10 and 11% respectively, stent 3 is the most beneficial for this particular aneurysm as it offers a reduction in flow of around 25%. However, it is of note that the work conducted by Cavazzuti et al. (2011) demonstrates that the non-Newtonian characteristic of blood does have a small effect on the efficacy of Stents 1 and 2 when comparing directly with the Newtonian simulations conducted by the same study, however these values are within range of the results of some of the other simulations (e.g. those of GMU-UPF say). Moreover, Cavazzuti et al. (2011) demonstrate in their study that the inflow rate for Stent 3 actually increases at some points of the cardiac cycle, hence the difference in time-averaged inflow rate noted in Table 5.2, which suggests that blood pulsatility may not be disregarded but that this comes at a great computational cost. Pulsatility is not in the scope of the work presented in this thesis and so is not taken into account.

Figure 5.6 depicts the inflow region by means of an isovelocity surface ($v = 0.1\text{m/s}$) for the cases U, S1, S2 and S3 for the 30M cell CFD-VisCART meshes.

Whilst Figure 5.7 shows the velocity magnitude contour plots across the cut-plane P at the aneurysm neck for the same simulations. These images qualitatively confirm that the greatest reduction in inflow is achieved with Stent 3. Although the porosity of Stent 3 is not much greater than Stent 2 (75% versus 77%) the greater strut density across the neck impedes on intrasaccular flow. These figures correlate closely with the same images depicted in the work by Radaelli et al. (2008).

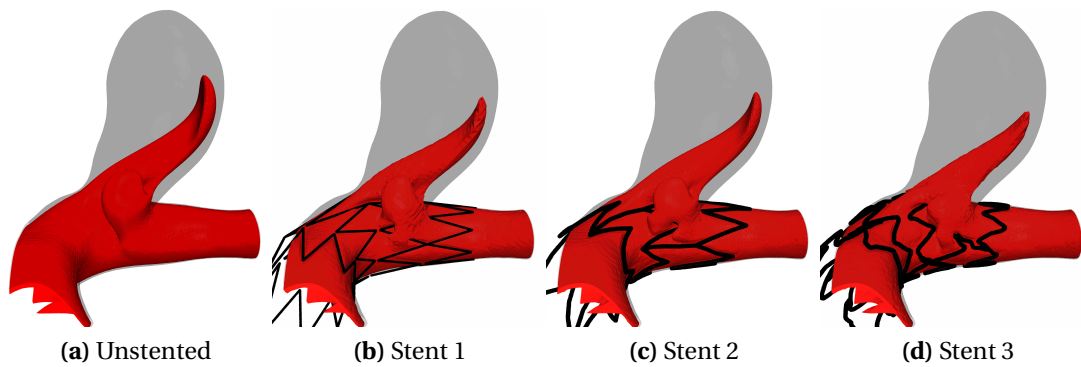


Figure 5.6: Aneurysm sac inlet flow for cases U, S1, S2 and S3 meshed with CFD-VisCART: isovelocity surface $v = 0.1\text{m/s}$

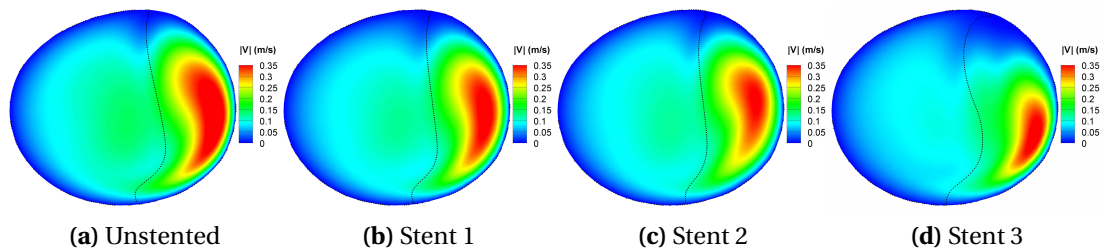


Figure 5.7: Velocity magnitude contours for for cases U, S1, S2 and S3 meshed with CFD-VisCART. The line divides the inlet and outlet flow regions.

5.2.2 Wall Shear Stress

Wall shear stress (WSS) distribution across the wall of the aneurysm were evaluated for the unstented case as well as with the three different stents. WSS contour maps for CFD-VisCART 30M mesh models of U, S1, S2 and S3 are displayed in Figure 5.8. The areas defined by the white lines indicate the threshold of $\text{WSS} = 1.5\text{Pa}$, a the typical physiological WSS level in a human artery Malek et al. (1999). All three stents show a reduction in WSS around the neck of the aneurysm due to stent deployment.

Similarly, the area of high WSS in the dome of the aneurysm is significantly reduced for all three stents. In particular Stent 3 shows to be the most effective in reducing the high region of WSS in the aneurysm. Not only is the lower WSS favorable for embolisation but also smaller high-WSS regions are less likely to rupture and so, in correlation with the findings by Radaelli et al. (2008), the third stent is found to be the most effective when modeled with CFD.

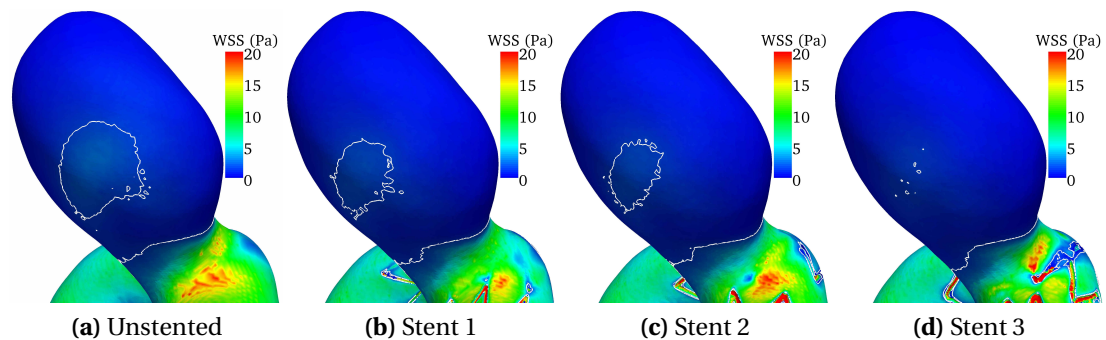


Figure 5.8: WSS distribution across the wall for cases U, S1, S2 and S3 meshed with CFD-VisCART. In both cases white demarcations demonstrates WSS = 1.5Pa threshold in the aneurysm dome.

5.3 CONCLUDING REMARKS

By conducting CFD of stented aneurysms it is possible to ascertain the patient-specific efficacy of various stent designs. With the particular anatomical aneurysm model investigated by the VISC 2007 project (Radaelli et al. (2008)) the greatest changes to velocity and WSS when conducting CFD simulations of steady state Newtonian blood flow were induced by the deployment of Stent 3, thus being the most likely design to create the intra-saccular haemodynamic environment that may lead to successful embolisation. These results were successfully reproduced within this Chapter using adaptive unstructured Cartesian grids created using CFD-VisCART. The extensive grid independence studies comparing CFD-VisCART to ICEM suggest that mesh density has a greater influence than the type of mesh technique used. The reproducibility of results confirms the validity of employing CFD-VisCART for meshing not only patient-specific aneurysms but also the more intri-

cate stented aneurysms. Whereas traditional tetrahedral meshing offers flexibility for complex geometries, the often unavoidable pre-processing to achieve ‘water-tightness’ requires both know-how (i.e. training) and time. CFD-VisCART requires limited user interactivity without compromise to simulation accuracy, thus enhancing the potential for cost-effective systematic CFD prediction as part of diagnostic and pre-intervential planning in a clinical setting.

Given the considerable changes observed with Stent 3 for a steady state Newtonian flow, this case is used as a comparison to the unstented IA case when investigating the impact of the haemodynamic environment on the transport of oxygen in Chapter 6.

MASS TRANSPORT OF OXYGEN IN INTRACRANIAL ANEURYSMS

This work presents simulations of coupled flow and mass transport of oxygen within patient-specific saccular IAs, the first of this type to the author's knowledge, in order to assess whether alterations to the intrasaccular haemodynamic environment would result in a change in the biochemical environment. The oxygen tension levels within the aneurysm dome and wall are evaluated for three particular scenarios: (i) the effect of aspect ratio on the delivery of O_2 to the dome; (ii) the effect of treatment on oxygen transport within the aneurysmal sac (iii) the effect of thrombus within an IA on the delivery of oxygen to the aneurysmal wall.

6.1 3D PATIENT-GENERATED ANEURYSM GEOMETRIES.

Two different anatomical aneurysm geometries were utilised in this study. The first geometry is that presented in the VISC 2007 project (Radaelli et al. (2008)): this side-wall saccular IA is located on the internal carotid artery, between the ophthalmic and posterior communicating arteries. The STL surface provided by the aforementioned project was generated by segmentation of 3DRA data. The geometry was modified so as to have a single inlet and a single outlet, therefore disregarding any outflow from the side branching arteries. The haemodynamic characteristics of this particular aneurysm were previously discussed in Chapter 5.

The second aneurysm case is that of a 44-year-old female patient with a ruptured IA at the bifurcation between the right internal carotid, the right middle cerebral and the right anterior cerebral arteries, as shown in Figure 6.1. This particular aneurysm geometry shall be referred to as OX12. The STL surface was created through segmentation of patient magnetic resonance angiography (MRA) scan data. The segmentation methodology is outlined in Section 6.2.1.

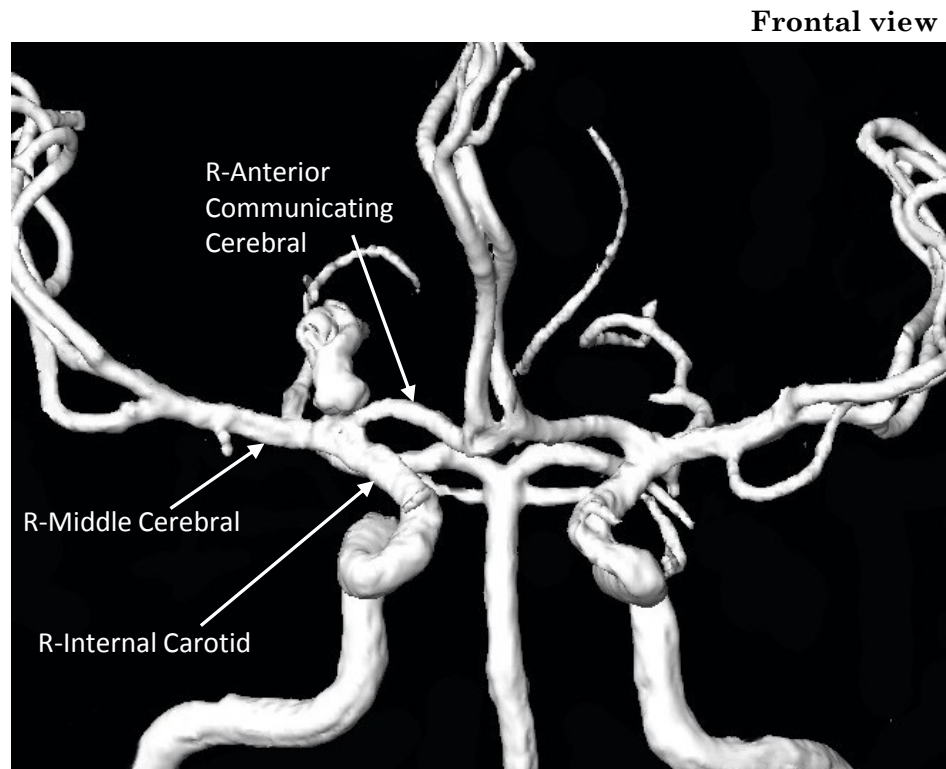


Figure 6.1: OX12: Isosurface extracted from MRA scan of a 44-year-old female patient presenting with an IA at the bifurcation between the right internal carotid, the right middle cerebral and the right anterior cerebral arteries. (View inset taken from Borden (2007).)

Coupled flow-mass transport (FM) computations were carried out on both the VISC and OX12 patient-specific geometries to explore the following four case scenarios, all depicted in Figure 6.2:

- (i) *Case A:* Untreated VISC aneurysm model.
- (ii) *Case B:* VISC aneurysm treated with Stent 3 (as considered in Chapter 5).
- (iii) *Case C:* VISC aneurysm presenting with a layer of thrombus within the dome.
- (iv) *Case D:* Untreated OX12 aneurysm.

A comparison of Cases A and D allows for the observation of varying IA geometry on O_2 delivery to the aneurysmal dome. A comparison between Cases A and B, i.e. the same aneurysm left untreated versus treated with a stent, demonstrates the

effect of the change in intra-saccular flow during treatment on the way oxygen fills the dome and the consequent oxygen tension within the wall. Lastly, analysis of Case D, that of an aneurysm presenting with a layer of thrombus within the dome, in contrast to the untreated Case A provides insight into the effect on O_2 levels within the portion of wall in direct contact with the thrombus.

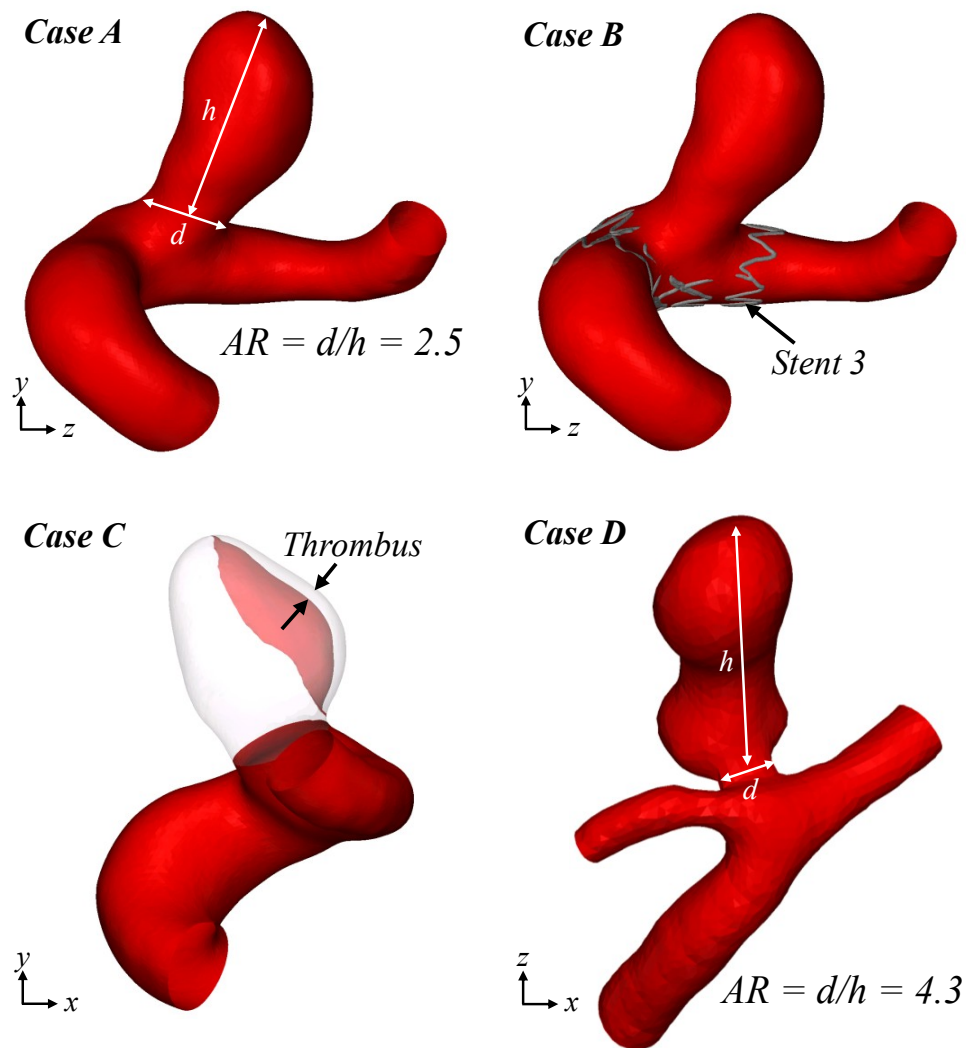


Figure 6.2: Four model case scenarios. *Case A:* unstented VISC aneurysm of aspect ratio 2.5 (Radaelli et al. (2008)). *Case B:* stented VISC aneurysm with Pharos stent of porosity 77% (Radaelli et al. (2008)). *Case C:* VISC aneurysm with a layer of thrombus within the dome. *Case D:* unstented OX12 aneurysm of aspect ratio 4.3.

6.2 GEOMETRY PREPARATION

6.2.1 Generation of IA surface geometry from patient scans

6.2.1.1 Diagnostic imaging modalities

Diagnostic evaluation of IAs is accomplished by the means of angiography. The benchmark being conventional catheter angiography, whereby images are acquired using X-ray based techniques to visualise radio-opaque contrast agent injected directly into the Circle of Willis by means of a catheter. The gold standard is digital subtraction angiography (DSA), which produces high-resolution 2D projectional images of the arterial network (the name inferring to the digital subtraction of ‘*pre-contrast*’ planar image from the ‘*post-contrast*’ image). Advancements in data acquisition and processing has led to the development of 3D rotational DSA (3DRA), thus eliminating some of the pitfalls of traditional 2D DSA (e.g. the need for multiple acquisitions to differentiate between overlapping vessels). Although these traditional methods offer high spatial resolution, catheter related neurological complications (1-2% (Willinsky et al. (2003))) has led to the emergence of less invasive imaging techniques such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA). CTA provides a computed 3D view of brain arteries and tissue through the digital reconstruction of 2D x-ray images taken around a single axis of rotation. Although this modality is less invasive, there are similar risks to DSA related to ionising radiation (Brenner and Hall (2007)). MRA uses a powerful magnetic field to align the nuclear magnetisation of hydrogen atoms within the tissues and blood flow (Stark et al. (1999)). By varying the radio frequency fields, the hydrogen nuclei produce a rotating magnetic field detectable by the scanner. The difference in atom concentration throughout the body will produce a variation in resonance, resulting in a clear distinction between similar adjoining tissues, and between brain matter and the blood flow through the arterial network.

Used as diagnostic tools originally, increases in image resolution and advance-

ments in segmentation techniques have made it possible to extract patient-derived geometries from scans for use in CFD simulations.

6.2.1.2 Segmentation of OX12

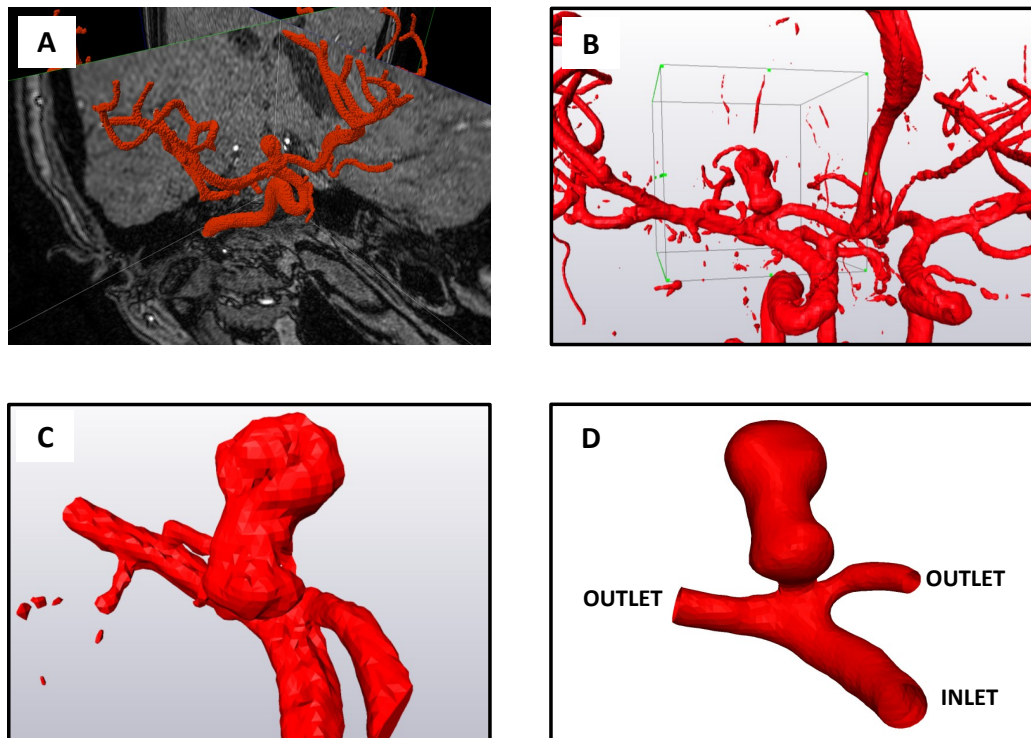


Figure 6.3: Segmentation procedure of OX12 aneurysm geometry. **A** Identification of arterial network by means of an intensity threshold. **B** Identification and cropping region of interest (i.e. the aneurysm). **C** Fully automated segmentation results in surface inconsistencies. **D** Final STL surface following manual editing.

The data acquired during the ‘time of flight’ (TOF) MRA scan of patient OX12 consisted of 140 transversal images of the head, each taken at interval distances of 0.5mm. TOF is a non-contrast enhanced method of MRA which relies on the motion of blood: ‘the difference in longitudinal magnetisation between the stationary saturated background tissue and unsaturated incoming blood generates high intensity within vessels’ (Clifton (2000)). This difference in intensity between the tissue and the blood flow through the Circle of Willis allowed for the automated rendering of arterial surfaces with the use of the segmentation software Amira (Visage Imaging GmbH, Berlin, Germany). An intensity threshold was set in order to extract

the whole arterial network from the gray matter (see Fig. 6.3 A). When setting this threshold, it is possible to select '*subvoxel accuracy*' (Stalling and Zockler (2001)): the weights calculated with this algorithm indicate the degree of confidence in the assignment of a voxel to a particular region which is subsequently implemented when applying smoothing during automatic surface generation. Once initial segmentation has been conducted, the data can be cropped to the region of interest, i.e. the aneurysm (see Fig. 6.3 B). Although the automated segmentation allows for an approximation of the arterial surface boundary there are often inconsistencies such as gaps, single voxel 'islands' and interrupted arterial branches due to segmentation artefacts (Fig. 6.3 C), which may be a consequence of insufficient resolution or vessel motion over the course of the scan for example. Hence manual slice-by-slice editing was required. Although this renders a more subjective interpretation of arterial geometry, these refinements insure an uninterrupted smooth surface of quality fine enough to mesh. The smaller arterial side-branches were completely removed, whilst one inlet (internal carotid artery) and two outlets (middle cerebral and anterior communicating cerebral arteries) were created by truncating across a plane normal to the arterial skeleton using an in-house cutting tool (tcut.tcl). The final STL surface is depicted in Figure 6.3 D.

6.2.2 Generation of arterial wall layer

The aim of this work is to create the first coupled fluid-wall flow mass transport (FMT) model of patient specific IAs. Thus, a second surface is required to represent the outer boundary of the arterial wall. However, the current clinical imaging modalities do not have the accuracy to enable the differentiation of the arterial wall from the surrounding matter. The single surface extracted from patient scans is inherently the interface between the high contrasting blood filled lumen and the arterial wall, in particular for TOF-MRA whereby vascular resolution is dependent on blood flow rate.

In order to implement the homogeneous wall model to the 3D aneurysm ge-

ometry, the STL file needs to be manipulated to establish a wall thickness. This can be achieved by offsetting the STL surface by the desired distance. One method of achieving this is the 3D offset of STL vertices in Blender (Blender Foundation, www.blender.org). Blender is an open source 3D content creation software originally developed for animation purposes, and is very proficient in vertex manipulation. The STL surface was imported into Blender and any ‘double’ vertices were deleted so as to insure that each adjoining triangle is interconnected by a single vertex. A simple ‘scale’ function projects the vertices along the surface normals whilst maintaining triangle connectivity. Physiological dimensions of the ICA, MCA and AComA show the wall thickness to be between 20-25% of the vessel radii (Monson et al. (2005); Alastruey et al. (2007)). Nonetheless blender does not offer the capability of detecting the arterial skeleton, thus wall thickness as a function of local arterial radius is not a possibility. As the ICA accounts for the greatest proportion of the domain a uniform thickness of 25% of the ICA inlet radius was chosen. For both cases this equates to a thickness of approximately 0.5mm. Furthermore, in most cases the aneurysm dome may be thinner as the IA evolves: i.e. SMCs apoptosis, elimination of IEL and degradation of elastin leaves only a thin layer of adapting collagen fibres (cf Section 1.2.2), however this was not implemented in this study.

Due to the particular curvature of the VISC geometry, the ‘scale up’ of the STL surface did not incur any overlapping surfaces, therefore no further editing was required. However, the particularly sharp variation within the neck region of the OX12 surface, led to a considerable amount of intersecting triangles in this region. Hence manual deletion and creation of vertices was required in order to maintain the neck curvature in the outer wall. Figure 6.4 shows the original STL representative of the lumen/wall interface extracted from the patient data (in red) and the resulting offset STL representative of the outer wall layer (transparent overlay).

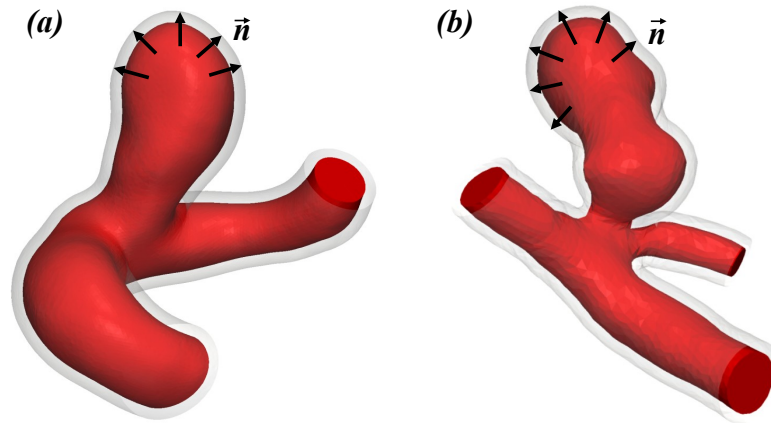


Figure 6.4: Creation of wall layer for (a) the VISC geometry and (b) the OX12 geometry. The offset STL was created by projecting the wall interface vertices along the normals to the surface ($\vec{n}$).

6.2.3 Creation of thrombus layer

Case C (See Figure 6.2) explores the effect of a layer of thrombus on oxygen transport within the aneurysm dome. Lacking a dependable patient case geometry presenting with thrombus, the VISC geometry was adapted by the means of an artificial layer created within the domain.

Several key haemodynamic factors are thought to predispose the formation of thrombus, most notably slow recirculating flow and shear related wall dysfunction. Pulsatile flow induces rapid changes in flow magnitude and direction within the aneurysm sac during the accelerating and subsequent decelerating stages of the systolic and diastolic phases respectively, producing distinct areas of varying WSS. High WSS conditions ($> 5\text{Pa}$) activate platelets (Huang and Hellums (1993); Kroll et al. (1996); Holme et al. (1997)) and promote von Willebrand factor (vFW)-mediated platelet adhesion to exposed endothelium (Ruggeri (2001); Shankaran et al. (2003); Ruggeri (2007)). Moreover, *in vitro* studies carried out by Sheriff et al. (2010) demonstrate that platelets that are exposed to very high WSS for a very short period of time (in the order of s) become highly ‘sensitive’, i.e. platelets are 20 times more likely to be activated when subsequently exposed to low WSS. Whereas, physiologic arterial WSS ($\sim 1.5\text{Pa}$) induces tightly aligned, quiescent ECs that secrete pro-

protective antithrombotic molecules (Moore et al. (1994); Topper et al. (1996); Malek et al. (1999)), low arterial WSS ($> 0.4\text{Pa}$) results in increased EC proliferation (Malek et al. (1999); Li et al. (2005); Chien (2008)), increased EC permeability (Phelps and DePaola (2000); Tarbell (2010)) and the upregulation of pro-thrombotic molecules which promote platelet aggregation (Brown et al. (1975); Malek et al. (1999)). Furthermore, focalised oscillatory shear stress also has detrimental effects to endothelial function (Ziegler et al. (1998)), in particular increased mitochondrial oxidative damage (Vita and Mitchell (2003); Doughan et al. (2008); Schulz et al. (2008)). The combination of endothelium dysfunction under local WSS conditions and flow stasis trigger the cascade of coagulation proteins and the subsequent formation of thrombus (a full description of which is defined in Section 1.4.1). *In vitro* studies demonstrate a strong correlation between flow residence time and the promotion of fibrin formation (Moake et al. (1988); Reininger et al. (1994); Friedrich and Reininger (1995)). The longer the particle residence times of pro-thrombogenic proteins, the more they will be susceptible to remaining in the same position, thus sustaining the thrombus.

It must be noted at this point that in order to establish such a layer in a more vigorous way, a full thrombosis model in 3D geometry is needed. To the best of the Author's knowledge such a model does not exist and falls outside the scope of this work. Thus, as a guideline for creating an artificial thrombus layer within the aneurysm dome, a transient simulation of the unstented VISC geometry (Case A) was carried out with a Newtonian pulsatile flow in order to observe flow and WSS behaviour within the aneurysm dome. The pulsatile inlet velocity and outlet pressure profiles were both extracted from the Aneufuse (Aneurist European Project, www.aneurist.org) for a left ICA and left MCA respectively (shown in Figure 6.5). Aneufuse is a medical image-based computational haemodynamic simulation suite developed as a clinical aid to intracranial aneurysm diagnosis and treatment in which a one-dimensional model of the human systemic tree (Reymond et al. (2009, 2011)) is integrated. This 1D model numerically calculates the pressure and flow

waveforms throughout the cerebral arterial network by solving the 1D form of the Navier-Stokes (momentum and continuity) equations whilst also taking into account ventricular-vascular interaction and wall viscoelasticity.

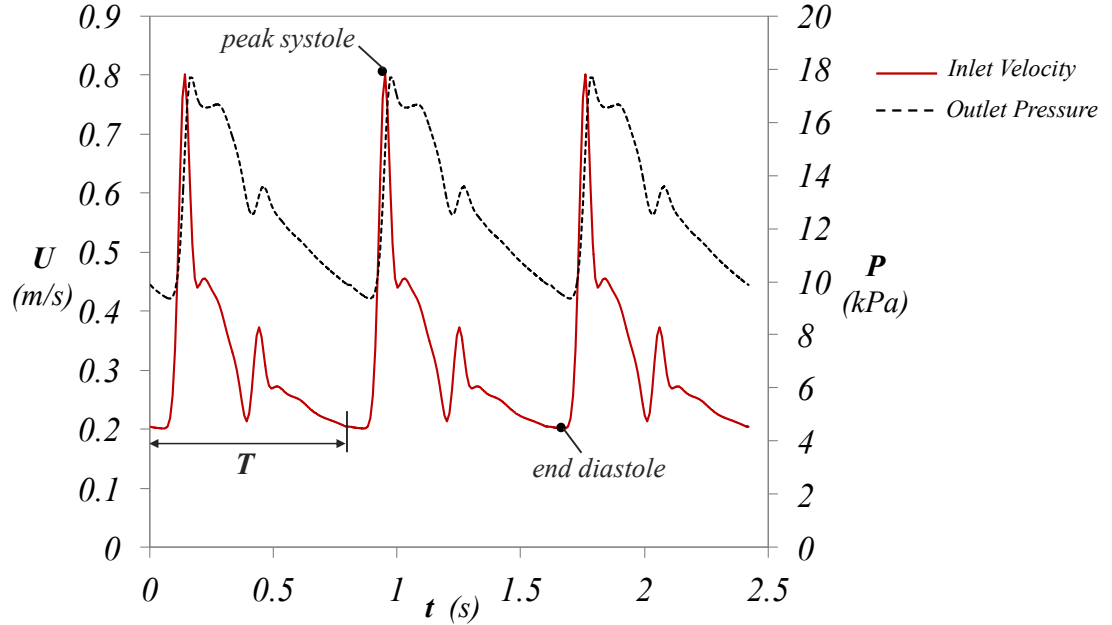


Figure 6.5: Inlet flow rate and outlet pressure waveform for the left ICA, extracted from the Aneufuse database.

Velocity was solved using a combined CDS and UPS differencing scheme (see Equation (3.16)) with blending factor set to $\vartheta=0.1$. The timestep was set to $dt = 0.01s$ and there were 84 time increments in one cardiac cycle. The simulation was run for a total time of three full cardiac cycles, achieving a stationary state by the third cycle. The 5M cell grid detailed in Chapter 5 showed grid independence.

Several *in silico* studies have suggested oscillatory shear index (OSI) and relative residence time (RRT) as haemodynamic indicators of thrombus location (Ku et al. (1985); Rayz et al. (2008, 2010); Basciano et al. (2011); Jou and Mawad (2011); Suh et al. (2011)). Ku et al. (1985) first introduced the notion of oscillatory shear index (OSI) in the CFD simulations of pulsatile flows. This parameter is used to map the temporal directionality of the WSS (τ) over the time of a cardiac cycle (T). The OSI varies between 0 and 0.5, whereby 0.5 indicates the maximum change in WSS direc-

tion.

$$OSI = \frac{1}{2} \left(1 - \frac{\left| \int_0^T \tau dt \right|}{\int_0^T |\tau| dt} \right) \quad (6.1)$$

The approximate relative residence time (RRT) of a particle within the flow domain was proposed by Himburg et al. (2004) in order to establish possible regions of stagnation. RRT is dependent on the time averaged WSS $\bar{\tau}$ and the OSI:

$$RRT = [(1 - 2 \cdot OSI) \bar{\tau}]^{-1} \quad (6.2)$$

Whereby, the time averaged WSS over a cardiac cycle of length T ,

$$\bar{\tau} = \frac{1}{T} \int_0^T |\tau| dt \quad (6.3)$$

Figure 6.6 shows the flow streamlines within the aneurysm dome at (a) peak systole and at (b) end diastole. The velocity entering the sac accelerates to a maximum of ~ 1 m/s at peak systole and decelerates to ~ 0.4 m/s at end diastole. Throughout the cardiac cycle the flow enters proximally at the neck with the jet impinging on the distal wall of the sac, which recirculates towards the proximal wall and exits distally at the neck. This recirculation creates a vortical structure within the centre of the aneurysm sac, resulting in near-stagnation areas in the flow near the wall.

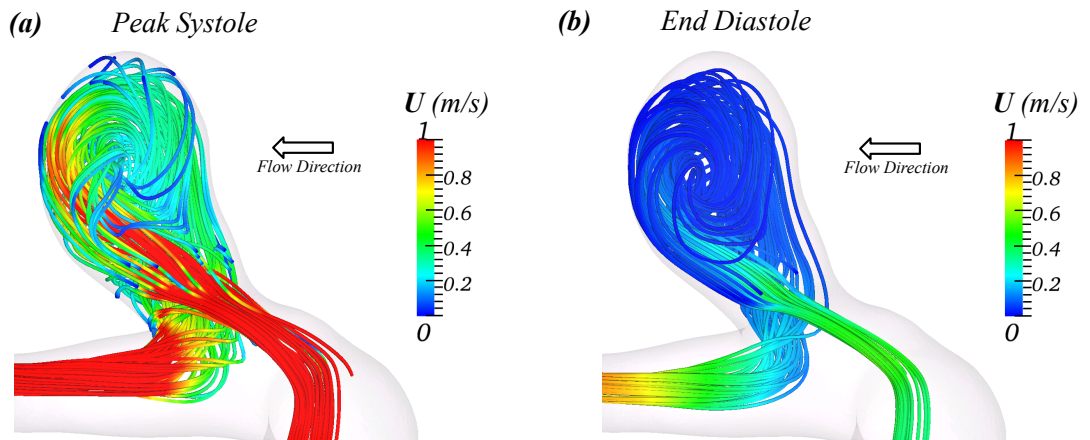


Figure 6.6: Flow streamlines showing regions of recirculating flow in the aneurysm dome at (a) peak systole and at (b) end diastole.

The WSS distribution across the dome at (a) peak systole and at (b) end diastole are shown in Figure 6.7. The WSS values at each cell centre were extracted for the entire cardiac cycle in order to calculate the OSI and RRT values with the aid of MATLAB. OSI and RRT were subsequently set as initial scalar values at each cell centre to be read in during a new steady state simulation in order to produce the distribution maps in Figure 6.8. At peak systole the area of lowest WSS ($> 1.5\text{Pa}$) is restricted to a small area on the aneurysm wall, with a minimum of 0.6Pa . This same area is subsequently exposed to a low WSS ($> 0.4\text{Pa}$) when the flow decelerates to its minimum at end diastole. Within the boundary outlined by the physiological WSS level of 1.5Pa at systole, the mapping outlines three distinct points whereby the WSS changes direction completely over the time of the cardiac cycle ($\text{OSI} = 0.5$). Furthermore the area that is continuously exposed to shear stress > 0.6 correlates with areas of most significant particle residence time ($\text{RRT} = 26\text{s}$). It is *hypothesised* that repetitive exposure to higher WSS ($\sim 5\text{Pa}$) followed by exposure to low WSS ($< 0.4\text{Pa}$) to the same area, may lead to EC dysfunction and platelet activation. Furthermore the specific points of high OSI and high RRT highlighted within this same region, which also correlate with the areas of flow stasis created by the moving vortex as the flow accelerates and decelerates, may allow for the subsequent aggregation of pro-thrombotic proteins.

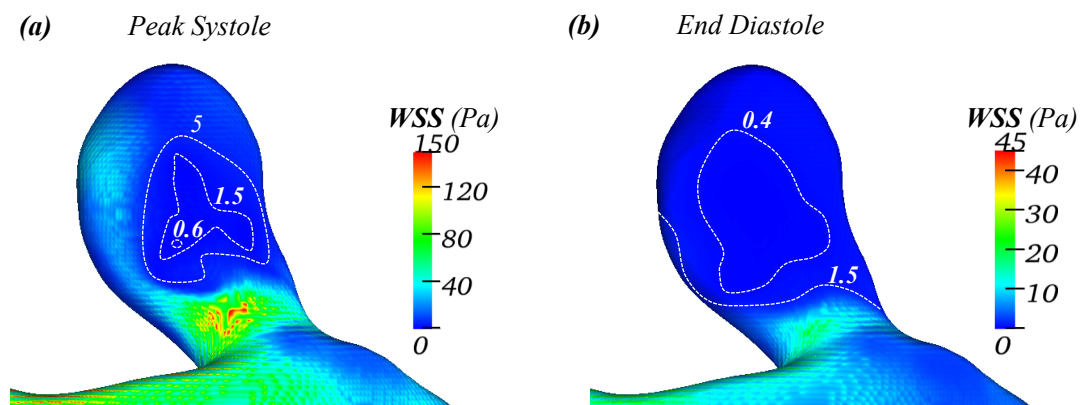


Figure 6.7: WSS distribution across the dome at (a) peak systole and at (b) end diastole. The white demarcations indicate the threshold for physiologic arterial WSS (1.5Pa), for low WSS (0.4Pa) and for high WSS (5Pa).

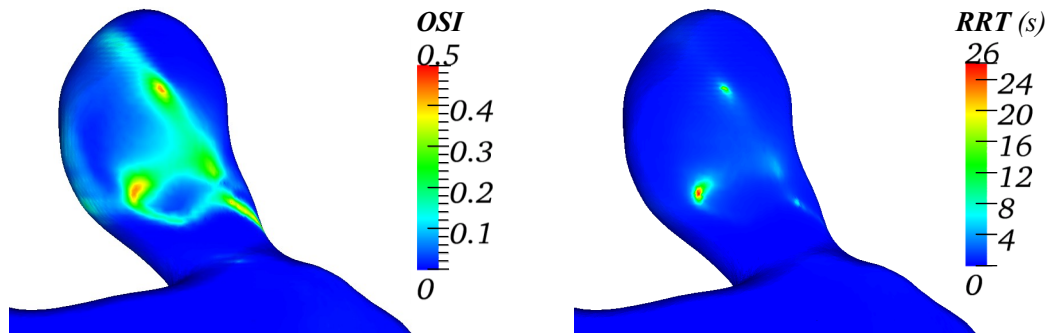


Figure 6.8: OSI and RRT distribution across the aneurysm dome.

With this hypothesis in mind, the ‘artificial’ thrombus layer was thus positioned adjacent to the portion of dome which has been identified to be most at risk of thrombosis. Once again the modification of the STL VISC surface was achieved by means of the Blender software. Vertices in the zone of interest were concentrically scaled along their normals to create a varied depth of thrombus (Figure 6.9). The greatest depth was set to 0.4mm and encompassed the entire region of interest highlighted by the WSS, OSI and RRT distributions across the dome. Smoothing was applied to ensure a seamless transition between the larger centre uniform depth and the two outer concentric layers (0.3mm and 0.2mm). However, the gradient between the outer concentric thrombus depth of 0.2mm and the attachment point to the lumen/wall interface was kept abrupt so as to facilitate meshing and maintain grid quality (e.g. avoiding very skewed cells).

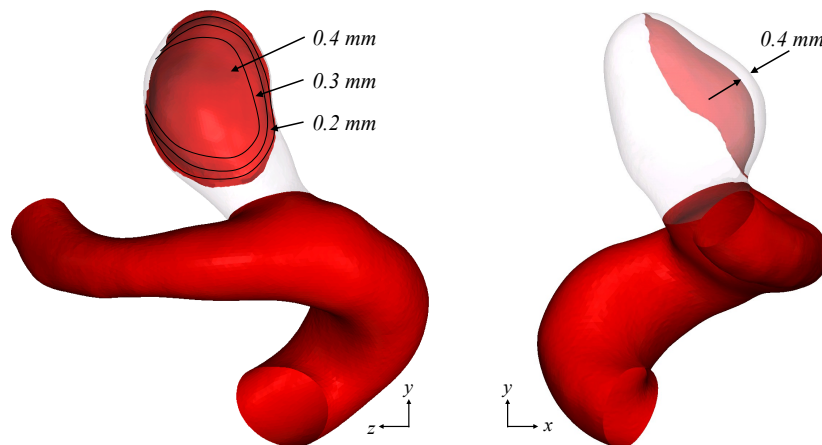


Figure 6.9: Artificial thrombus creation. Vertices in the zone of interest were concentrically scaled along their normals to create a varied depth of thrombus ranging from 0.4mm to 0.

6.3 MESH GENERATION

Preliminary simulations brought to attention the very high computational costs of computing transient coupled flow and mass transport through the VISC geometry as supplied by the VISC challenge (Radaelli et al. (2008)). For this reason, the upstream portion of the parent artery was reduced by half using the in-house cutting tool (tcut.tcl), resulting in the new domain shown in Figure 6.2.

All four cases (A to D) were meshed using the adaptive structured Cartesian mesh generation software CFD-ViSCART (ESI GROUP, Paris, France). The reader is referred to Chapter 5 for the methodology and benefits of this technique. The difference in this Chapter is that there are multiple regions in the computational domain: the lumen, the wall and, in Case C, the thrombus layer. This is overcome by simply manually specifying a domain marker in each of the zones. Similarly to the outer wall of a single domain, the cells are split at the interface in order to assure boundary refinement.

The overall number of computational elements for Case A, C and D exceeded 2M, whilst the number of mesh elements for Case B exceeded 2.5M due to the added refinement around the stent volume. The overall number of elements within the wall exceeded 4M in all cases. Preliminary mesh convergence tests confirmed these grids offered acceptable mesh independence for the computation of free and bound oxygen concentration.

All four cases were run in parallel on the in-house cluster. A work-load balance was adopted for mesh decomposition. The division over 8, 16, 32 and 64 cores demonstrated maximum time efficiency is achieved when each case was decomposed into 32 zones (i.e mapped on 32 cores). The average output of results is 10s/-month: e.g. the results for Case A reached steady state by 20s of transient simulations (as discussed in the results section) which took a total of 2 months to compute.

6.4 SIMULATION INPUT PARAMETERS

6.4.1 Volume conditions

The reader is referred to Chapter 4 (section 4.1.2 regarding the mass transport properties of oxygen within the lumen, the wall and the thrombus).

Comparative simulations carried out by Back (1976) and Tada (2010) demonstrate qualitatively similar mass transport distribution patterns in both steady and pulsatile flow conditions over the course of multiple cardiac cycles. Thus, the simulations carried out here are assuming a steady flow in order to keep computational costs to a minimum. The flow is modelled as a steady incompressible Newtonian fluid with a no-slip velocity at the arterial wall interface (or thrombus interface if present). The governing equations for flow and oxygen mass transport were solved using the conservation of mass and momentum equations in 3D Cartesian coordinates (Appendix A).

Preliminary studies conducted in Chapter 4 demonstrated the influence of thrombus thickness on the distribution of oxygen to the arterial wall. When modelling thrombus as a porous medium the computed filtration velocities were found to be an order of magnitude higher than the experimentally measured velocities through arterial wall ($1e^{-4}$ versus $\sim 1e^{-5}$ mm/s (Bolsover et al. (2004))) and accounted for a $\sim 7\%$ difference in $\hat{C}_{O_2}$ when the consumption rate is set to $\dot{q}_2$ (see Table 4.5). However on average, the additional solving of porous fluid conservation equations within the thrombus layer (that has a more refined grid than the lumen) generated an increase in CPU time of approximately 250%. Considering the computational costs incurred it was decided that the oxygen transport through the thrombus and wall layers would be limited to diffusion-only modelling.

The parametric studies in Chapter 4 highlighted the wall-side effect on oxygen transport caused by the cellular respiration rate $\dot{q}$. The composition of the arterial wall dictates varying respiration requirements dependent on the cellular composi-

tion of the intima, media and adventitia, as observed in experimental studies (the reader is referred to Section 4.1.3.1). The findings in Chapter 4 conclude that the radial variation is between the physiologically measured values of $1e^{-3}\text{mol/m}^3/\text{s}$ and $1e^{-4}\text{mol/m}^3/\text{s}$. This difference is believed to be a factor of the local cellular requirements, e.g. it is presumed that the continually contracting SMCs require a higher level of energy (i.e. ATP and therefore O_2) for optimum functionality. With this in mind, a uniform value of $1e^{-3}\text{mol/m}^3/\text{s}$ is implemented in Cases A to D in order to take into account the higher demands of certain layers within the wall.

The flow and mass transfer volume conditions are summarised in Table 6.1.

Parameter Name	Variable	Value
Artery Lumen		
<i>Flow parameters:</i>		
Blood density	ρ_b	1060 kg/m^3
Blood viscosity	μ_b	$4e^{-3} \text{ kg/ms}$
<i>Mass transport properties of free oxygen:</i>		
Diffusivity coefficient ^a	D_b	$1.2e^{-9} \text{ m}^2/\text{s}$
Solubility ^a	α	$1.114e^{-3} \text{ mol/m}^3/\text{mmHg}$
<i>Mass transport properties of oxygen bound to haemoglobin:</i>		
Diffusivity coefficient ^a	D_{HbO_2}	$1.5e^{-11} \text{ m}^2/\text{s}$
Oxygen carrying capacity of haemoglobin ^a	$[Hb]$	9.1 mol/m^3
Backward reaction rate of oxyhaemoglobin ^b	K_{Hb}	40 s^{-1}
Artery Wall		
Diffusivity coefficient of oxygen ^a	D_w	$0.9e^{-9} \text{ m}^2/\text{s}$
Consumption rate	$\dot{q}$	$1e^{-3} \text{ mol/m}^3/\text{s}$
Thrombus		
Diffusivity coefficient of oxygen ^c	D_{th}	$2.4e^{-9} \text{ m}^2/\text{s}$

^a Schneiderman and Goldstick (1978a)

^b Vorp et al. (1996)

^c Murray (1971)

Table 6.1: Simulation input parameters for coupled flow and mass transfer model

6.4.2 Boundary conditions

The inlet velocity originally supplied with the VISC challenge was of 0.1865 m/s. As the geometry has been adjusted for this work, this velocity needs to be adjusted so as to simulate the same extracellular flow characteristics as those defined in Chapter 5. An increased inlet velocity of $U_i = 0.2275$ m/s to account for the tapering of the omitted vasculature provided the same intrasaccular flow characteristics within 1%. This value was also used for the OX12 geometry. A fixed pressure outlet enforces flow through the lumen.

Normal arterial blood flow has an arterial partial pressure of $PO_2 = 100$ mmHg and an oxyhaemoglobin saturation level of 97%. Thus the inlet concentration of free oxygen is calculated to be a fixed value of $(C_{O_2})_i = 0.1114$ mol/m³ (from equation (4.6)) and the inlet concentration of oxyhaemoglobin saturation was simply set to a fixed value of $(C_{HbO_2})_i = 0.97$. So as to allow free flux at the outlet, the axial gradients $(\partial C_{O_2} / \partial n)_z$ and $(\partial C_{HbO_2} / \partial n)_z$ were set to zero for the outlet boundary condition. Oxygen flux through the adventitial boundary was also set as $(\partial C_{O_2} / \partial n)_{adv} = 0$ permitting free flux out of the wall into the surrounding environment. The diffusion flux normal to each layer interface is conserved (Equations 3.16).

6.4.3 Spatial differencing and solver settings

Velocity, oxygen and oxyhaemoglobin scalars were solved using a combined CDS and UPS differencing scheme (see Equation (3.16)). For velocity the blending factor was set to $\vartheta = 0.1$, whilst for C_{O_2} and C_{HbO_2} it was set to $\vartheta = 0.5$, offering a greater stability in numerical solutions when solving convection-diffusion of both scalars.

6.5 RESULTS AND DISCUSSION

6.5.1 Impact of aneurysm geometry on oxygen delivery

6.5.1.1 VISC geometry

Figures 6.10, 6.11, 6.12 show the velocity streamlines within the aneurysm dome for cases A, B, and C respectively. The flow characteristics for the VISC geometry are similar regardless of being untreated (A), treated with a stent (B) and when presenting with a layer of thrombus (C). The jet of flow branching away from the main parent artery enters the dome distally at the neck at its maximum velocity of approximately 0.35m/s and impinges on the distal wall of the sac. The flow stream subsequently decelerates as the flow circulates upwards to the apex, down the proximal side before exiting proximally at the neck. This recirculation creates a single central vortex within the dome. The intersection of the x - y and z - x planes in Figures 6.10, 6.11 and 6.12 mark the point at which the central vortex hits the arterial wall (right hand view) for cases A to C. Chapter 5 demonstrates that the implementation of the ‘Stent 3’ design results in a reduction in inflow velocity of $\sim 28\%$ compared to the untreated case. By carrying out the same inflow calculation across the neck for the thrombus case it was found that the reduction in sac volume caused by this added layer reduces the inflow area by $\sim 10\%$ compared to the untreated case. These differences also appear to impact on the recirculation within the dome itself, as the location of the stagnation area caused by the vortex centre in the near-wall region also differs slightly between cases.

The cross-sectional distributions of velocity, oxyhaemoglobin saturation and oxygen levels in the x - y and z - x planes are depicted in Figures 6.13 and 6.14 for case A, in Figures 6.15 and 6.16 for case B and finally in Figures 6.17 and 6.18 for case C. Normalised oxygen distribution plots within the dome at $t = 0.5$ s are shown in insets (a). These demonstrate the location of the x - y and z - x planes (which intersect the vortex centre at the proximal wall) and their directionality within the dome.

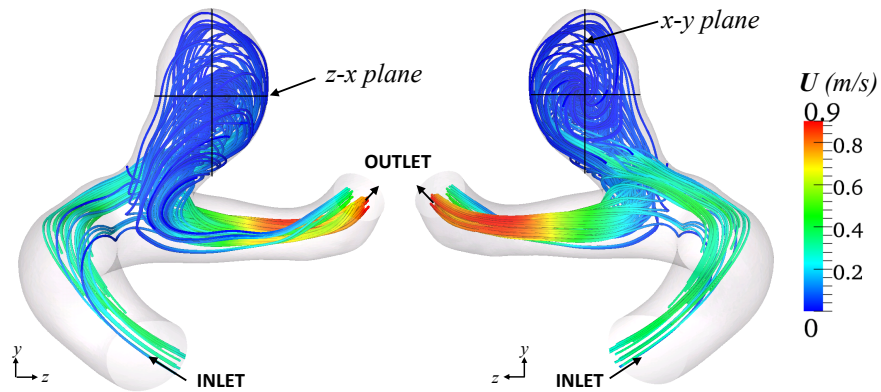


Figure 6.10: Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case A.

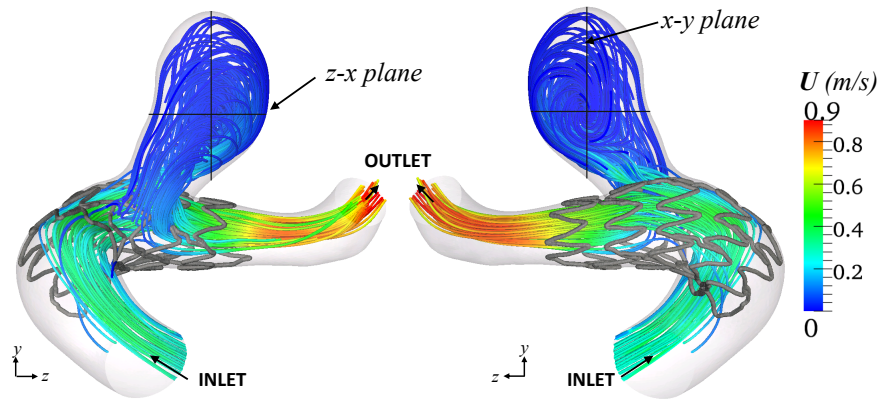


Figure 6.11: Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case B.

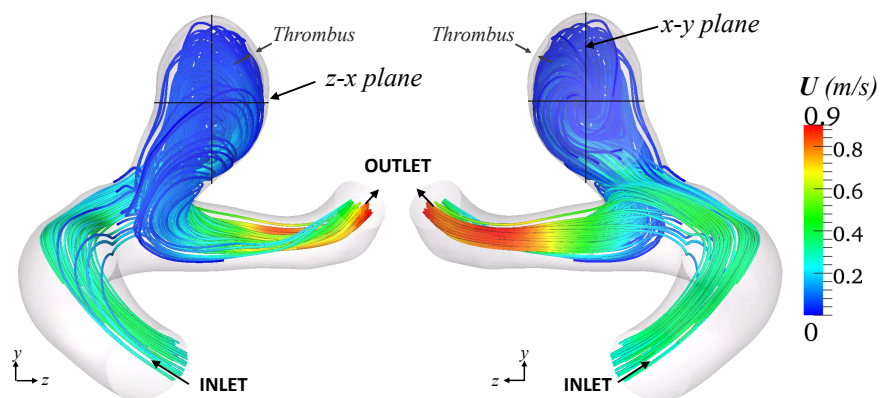


Figure 6.12: Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case C.

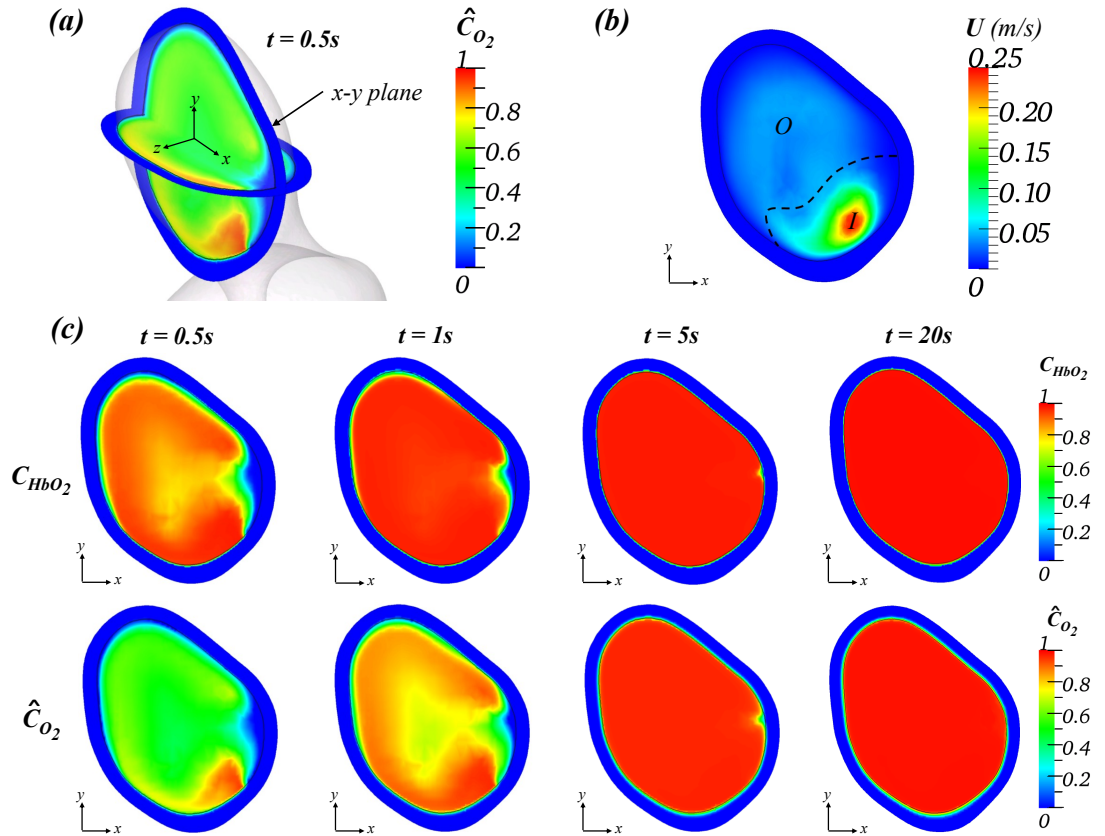


Figure 6.13: Case A Cross-sectional distribution of velocity and oxygen in the $x-y$ plane for Case A. (a) Oxygen concentration within the dome at $t = 0.5s$ across the $x-y$ and $z-x$ plane that intersect at the location of near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 0.5, 1, 5$ and $20s$.

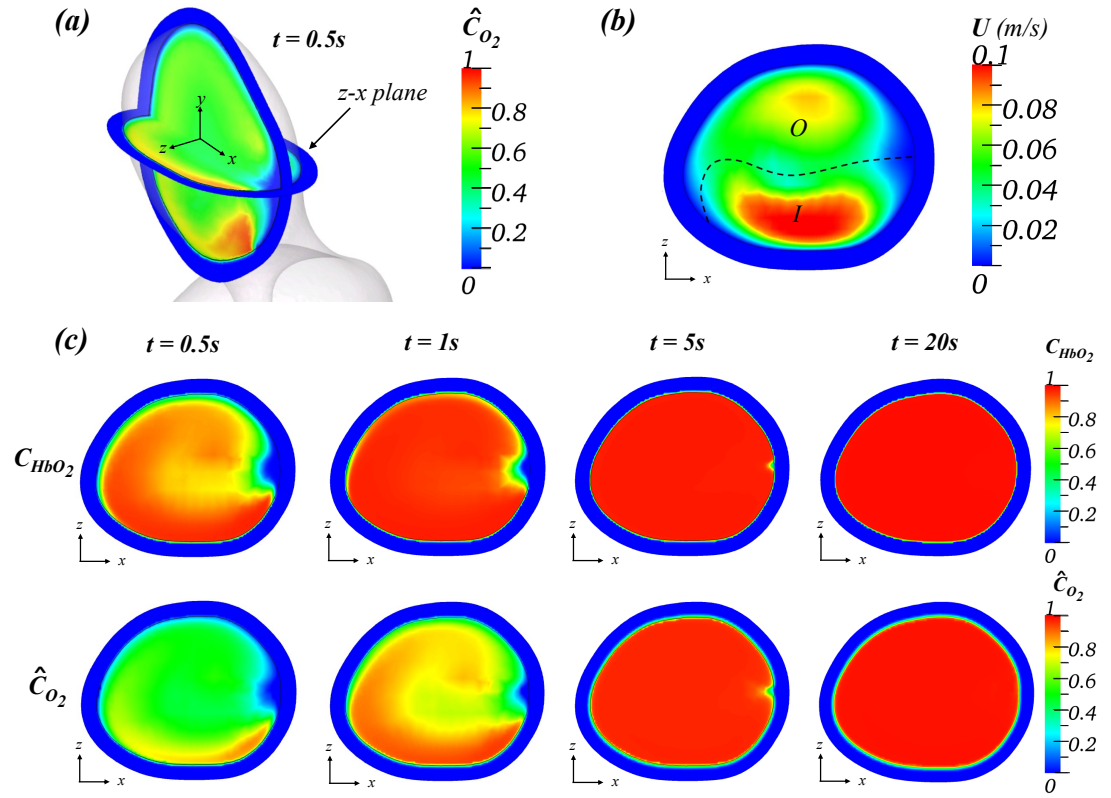


Figure 6.14: Case A Cross-sectional distribution of velocity and oxygen in the z - x plane for Case A. (a) Oxygen concentration within the dome at $t = 0.5s$ across the x - y and z - x plane that intersect at the location of near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 0.5, 1, 5$ and $20s$.

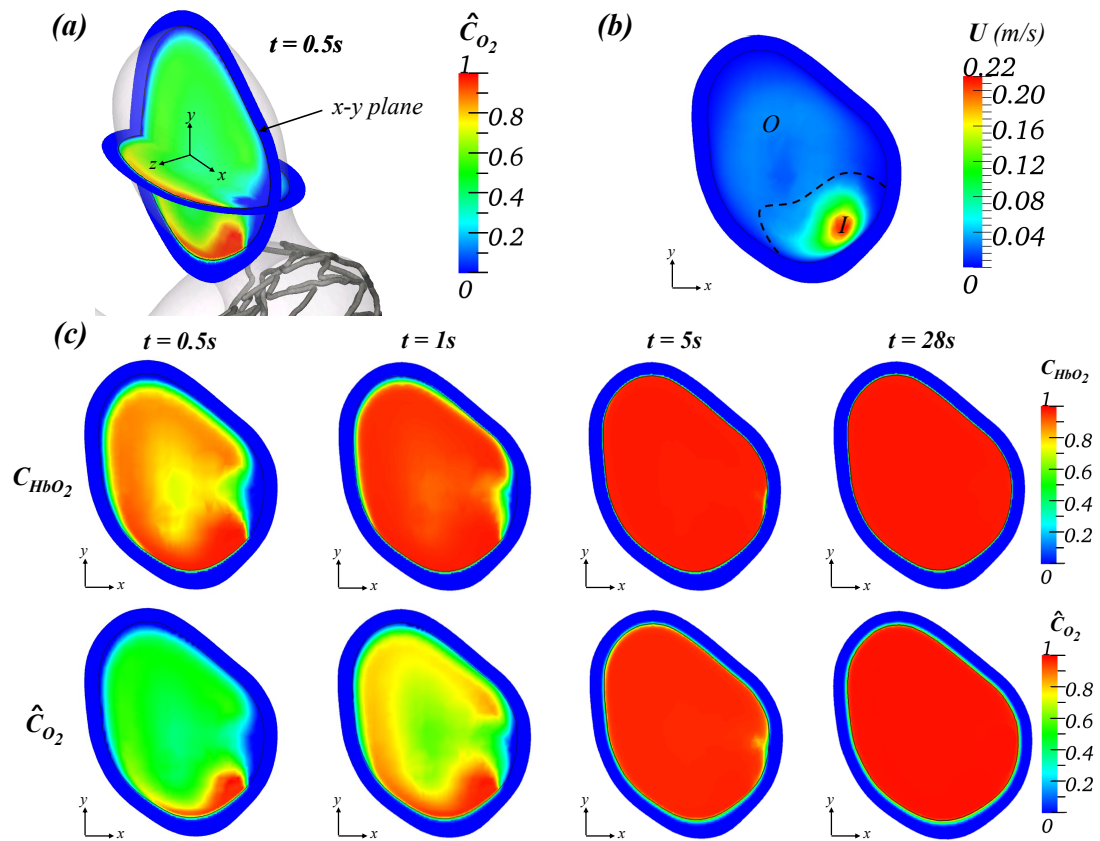


Figure 6.15: Case B Cross-sectional distribution of velocity and oxygen in the x - y plane for Case B. (a) Oxygen concentration within the dome at $t = 0.5s$ across the x - y and z - x plane that intersect at the location of near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 0.5, 1, 5$ and $28s$.

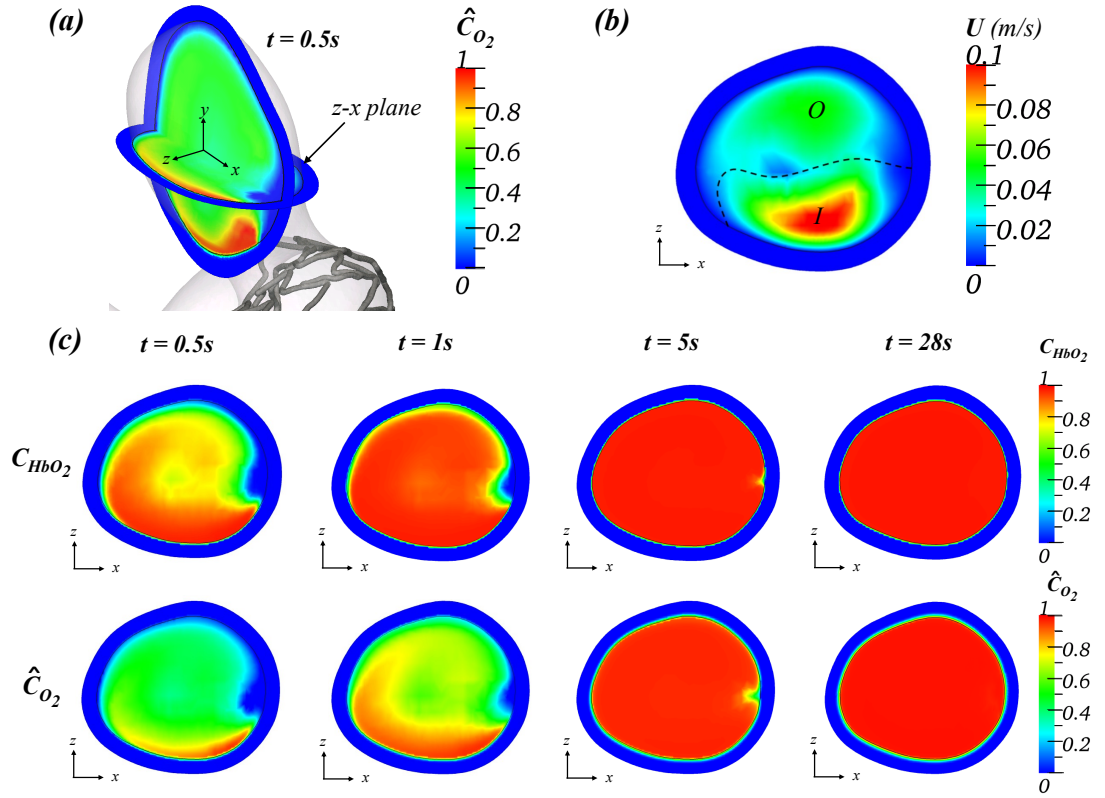


Figure 6.16: Case B Cross-sectional distribution of velocity and oxygen in the z - x plane for Case B. (a) Oxygen concentration within the dome at $t = 0.5s$ across the x - y and z - x plane that intersect at the location of near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 0.5, 1, 5$ and $28s$.

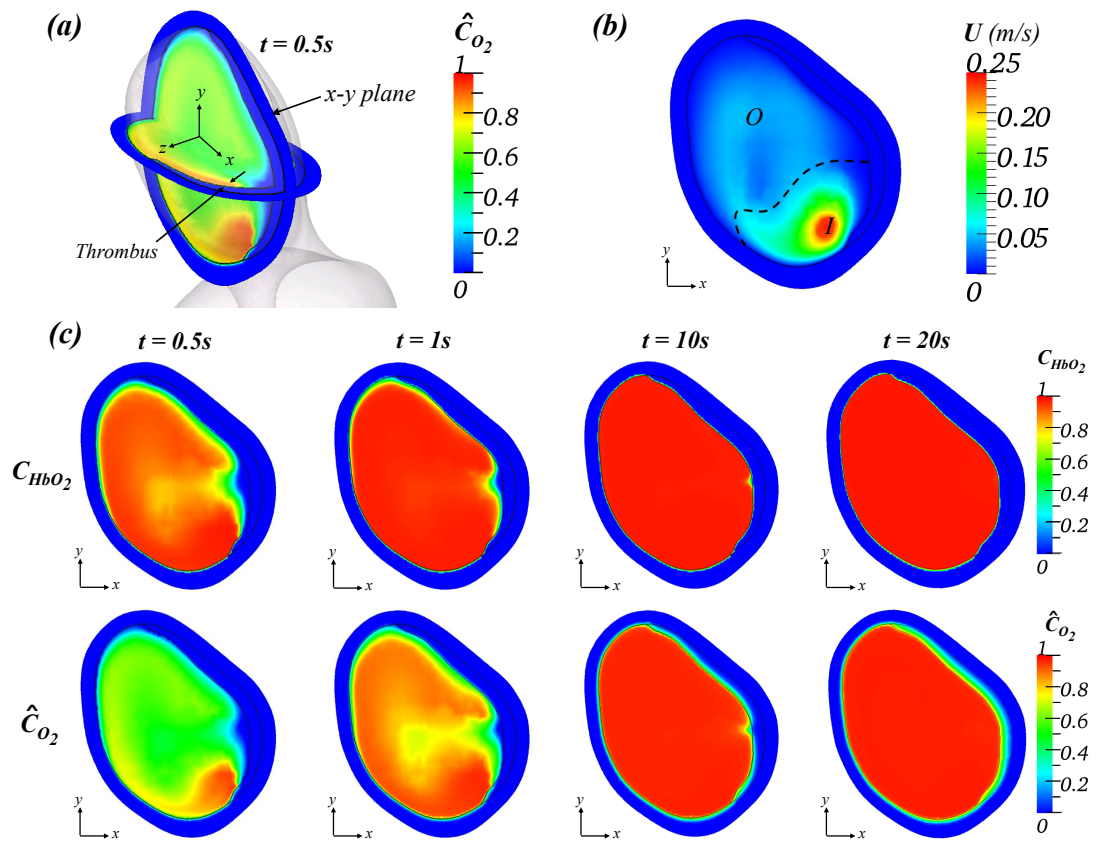


Figure 6.17: Case C Cross-sectional distribution of velocity and oxygen in the x - y plane for Case C. (a) Oxygen concentration within the dome at $t = 0.5s$ across the x - y and z - x plane that intersect at the location of near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 0.5, 1, 5$ and $20s$.

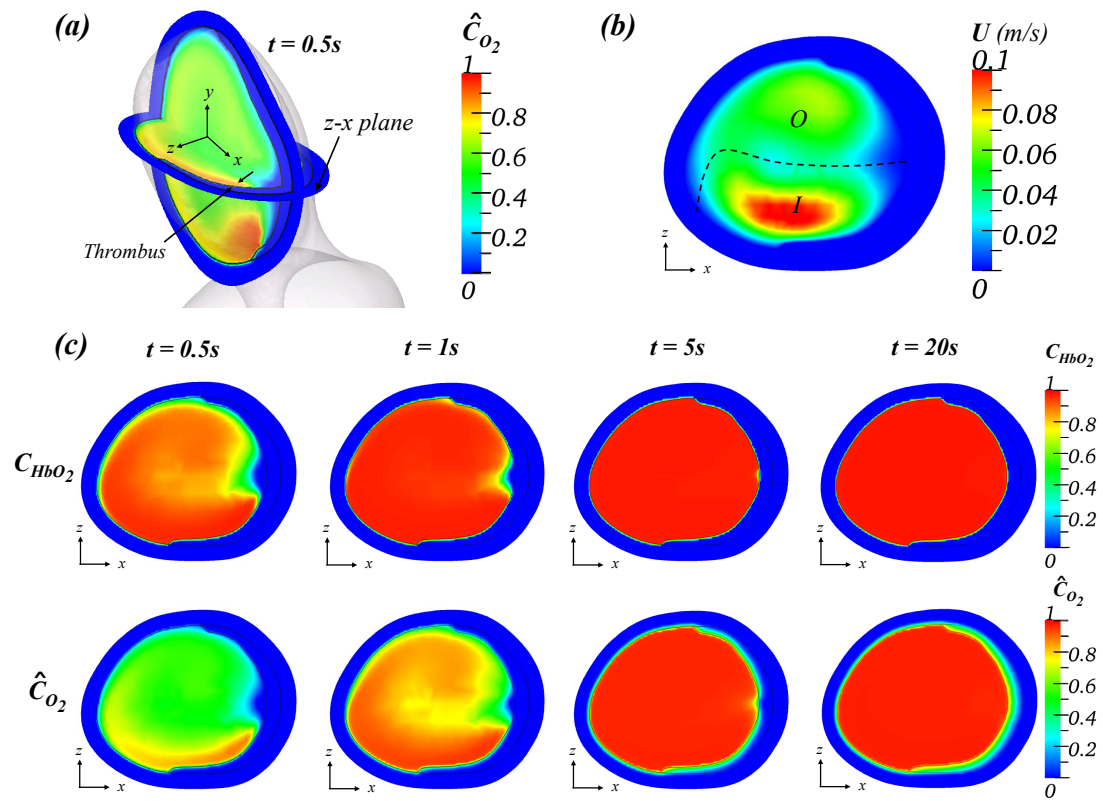


Figure 6.18: Case C Cross-sectional distribution of velocity and oxygen in the z - x plane for Case C. (a) Oxygen concentration within the dome at $t = 0.5s$ across the x - y and z - x plane that intersect at the location of near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 0.5, 1, 5$ and $20s$.

The velocity plots of each of these planes are shown in insets (*b*) of each Figure. The velocity scale is adjusted to the maximum for each plane, whilst the dashed line divides the inflow (*I*) and outflow (*O*) areas. Oxyhaemoglobin saturation and oxygen concentration levels with time for each plane are displayed in inset (*c*).

The velocity plots for each plane demonstrate the slight differences in inflow velocity for each case. In particular, the velocity in the unstented case (B) reaches a maximum of 0.22m/s in the x - y plane, whilst it reaches a maximum of 0.25m/s for the untreated (A) and thrombus (C) cases. In the respective z - x planes for each Case the maximal inflow velocity is of 0.1m/s, however the area of maximal flow is smaller for the stented (B) and thrombus (C) cases in comparison to the untreated case (A). Furthermore the outlet velocity of the z - x planes reaches a maximum of 0.08m/s for case A, 0.06m/s for case B and 0.07m/s for case C. The geometry of the aneurysm dome, as well as its position and angle in comparison to the parent artery dictates the directionality of the flow, thus the three VISC cases display the roughly similar inflow and outflow patterns within the dome. However these planar cuts demonstrate how the obstructions caused by the placement of a stent and the formation of a thrombus layer affect the velocity magnitude.

At $t = 0.5$ s the distribution of free oxygen across the planes does not vary greatly between cases. The high velocity field in proximity to the distal wall leads to the rapid transport of oxygen in the near-wall region. However, the volume and magnitude of the inflow region is significantly smaller when the aneurysm is treated with a stent (case B), resulting in a significantly lower distribution of $\hat{C}_{O_2}$ within the dome at $t = 1$ s. Although the flow is slightly altered with the presence of the thrombus layer the oxygen distribution is not dissimilar to the untreated case (A). The oxygen distribution throughout the majority of the aneurysm lumen reaches a constant value of $\hat{C}_{O_2} = 96\%$ by $t = 5$ s for all three cases, with the exception of a low concentration spot consistent with the vortex centre, where the velocity magnitude reaches a minimum of 5×10^{-3} m/s in the near wall region. Notably, this region of decelerated flow is greater for the unstented case (B). For this particular zone to be

fully oxygenated it takes a further 15s ($t=20$ s) for cases A and C, and a further 23s ($t=28$ s) for case B. These sequential images demonstrate the impact of local velocity fields on the rate at which oxygen is transported. Calculation of the Peclet number (Pe) gives a ratio of solute transport by convection versus diffusion. Pe is a product of the Reynolds and Schmidt numbers: $Pe = LU/D$, whereby the characteristic length L in this instance is the cell area, U is the local velocity at the cell centre and D is the diffusion coefficient of free oxygen. In slow velocity areas such as the centre of the vortex, where the velocity does not exceed 5×10^{-3} m/s, $Pe \rightarrow 0.1$, whereas in the higher flow region of velocity 0.1 m/s the $Pe = 2$. Thus, within the faster bulk flow, the convective flux plays a greater role, with faster velocities providing a faster delivery of fresh oxygenated blood. Whereas in regions of near-stagnant flow, such as at the vortex centre, the transport is mostly diffusion driven, thus the renewal of fresh oxygen in this area takes significantly longer.

The distribution plots of oxyhaemoglobin across the x - y and z - x planes in Figures 6.14c to 6.17c demonstrate the same directional characteristics imposed by the local flow field within the dome, however this occurs more succinctly. Although the convective flux would have the same influence on both solutes, the diffusion of HbO_2 is notably slower than that of O_2 due to the imposed diffusion coefficients ($1.5e^{-11}$ m²/s versus $0.9e^{-9}$ m²/s) connected with the difference in molecular weights and above all on the exclusively RBC-contained nature of haemoglobin. Nonetheless, the oxyhaemoglobin appears to be transported at a much faster rate than the free oxygen. At $t = 0.5$ s the average saturation level within the dome is $C_{HbO_2} \sim 80\%$ whilst the average oxygen concentration is only $\hat{C}_{O_2} \sim 50\%$. It is believed that this difference is due to the high O_2 demands of the arterial wall. As shown previously in Chapter 4, the oxygen profiles are prescribed by the cellular requirements of the wall. The initial condition imposed zero oxygen and zero oxyhaemoglobin within the whole domain apart from a set value at the inlet. As the oxygen travels upstream towards the neck of the aneurysm, the first influx of oxygen is absorbed by the unsaturated parent artery wall, thus significantly reducing the

concentration of oxygen available within the bulk flow. Furthermore, as the fresh oxygen enters the sac, the entire wall area of the dome is also completely unsaturated and so instantaneously absorbs available oxygen, thus further reducing the local oxygen concentration. As the oxyhaemoglobin does not permeate through the wall or thrombus the distribution is only limited by the local flow conditions and not the cellular requirements, therefore the bulk flow entering the aneurysm is already at a saturation level of 97%.

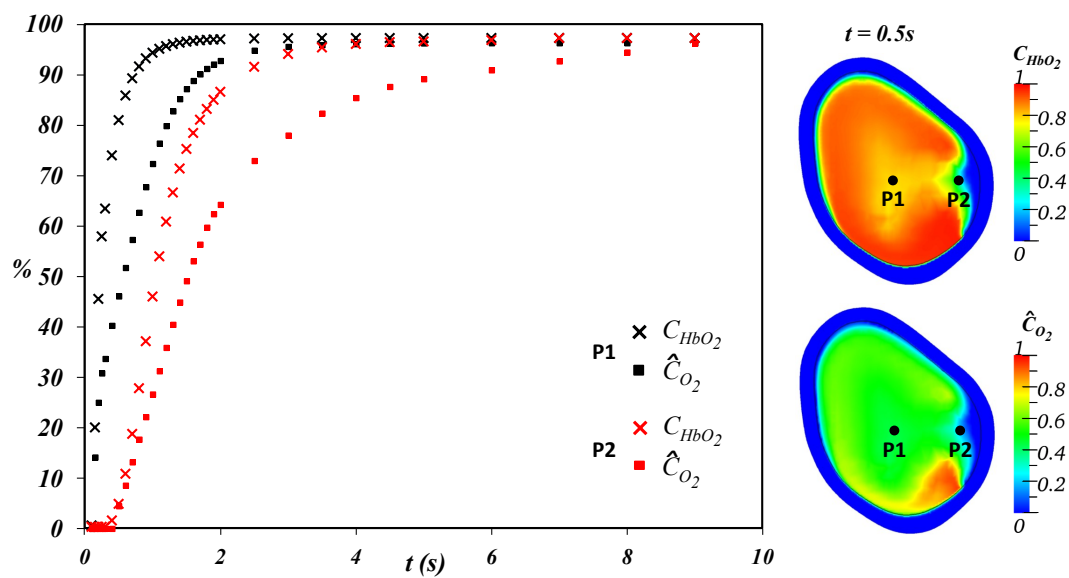


Figure 6.19: Plot of oxyhaemoglobin saturation and normalised oxygen concentration with time at points P1 and P2 for Case A.

Figure 6.19 shows the oxyhaemoglobin and normalised oxygen concentration with time at two distinct points for the untreated case (A). P1 is placed at a point within the centre of the recirculation zone where the velocity is 0.01m/s. P2 is located on the border of the vortex centre, where the velocity is of 0.004m/s. At point P1, the concentrations C_{HbO_2} and $\hat{C}_{O_2}$ linearly increase to approximately 85% within 0.5s and 1s respectively. The rate of increase subsequently decreases considerably as both values reach their maximum of $C_{HbO_2} = 97\%$ and $\hat{C}_{O_2} = 96\%$ at $t = 2s$ and $t = 5s$ respectively. At point P2, the concentrations linearly increase to $C_{HbO_2} \sim 80\%$ and $\hat{C}_{O_2} \sim 65\%$ within the first 2s. Similarly to P1, The rate of increase subsequently

decreases considerably as both values reach their maximum of $C_{HbO_2} = 97\%$ and $\hat{C}_{O_2} = 96\%$ at $t = 6s$ and $t = 7.5s$ respectively. It is speculated that the rapid increases in C_{HbO_2} and $\hat{C}_{O_2}$ levels (the linear portion of each curve) relates to a mostly convective transport, whereby the greater velocity at P1 leads to a faster accumulation molecules. The cellular respiration of the wall has a greater effect on the point P2 (as opposed to P1 which is located in the centre), which could explain the greater difference seen between the oxygen and oxyhaemoglobin concentration at $t = 2s$. At no point does the oxyhaemoglobin saturation level halt or decrease, suggesting that any dissociation of free oxygen that does occur in response to the lower oxygen tension is compensated for by the influx of fresh blood.

6.5.1.2 OX12 Geometry

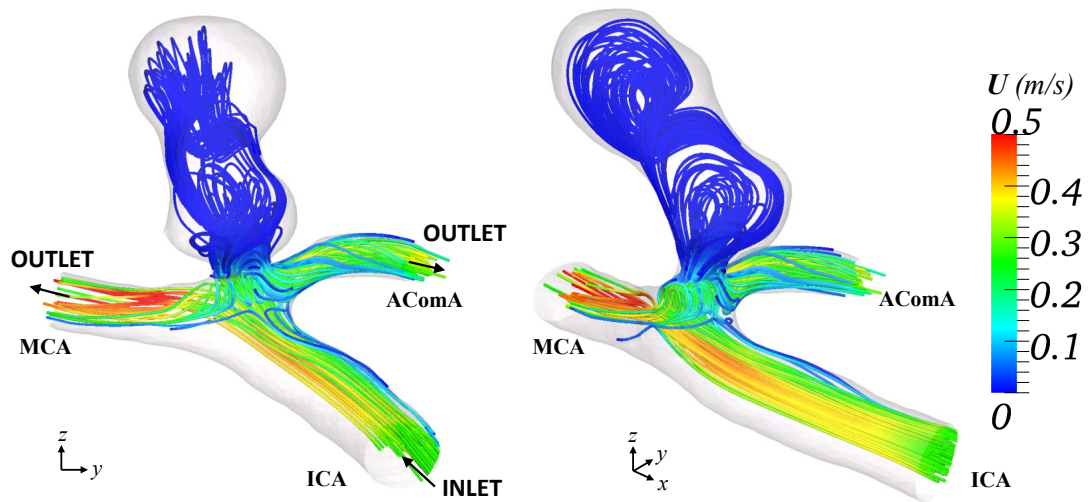


Figure 6.20: Flow streamlines showing regions of recirculating flow in the aneurysm dome for Case D.

Figure 6.20 shows the velocity streamlines within the aneurysm dome of geometry OX12 (Case D): the left-hand image shows the frontal view. The aneurysm is located at the bifurcation of the MCA and ACoMA with the ICA. The neck of the aneurysm is elliptical in shape, whereby the major radius is approximately $2/3$ of the ICA radius, whilst the minor radius is half of the major. The elliptical neck volume is 0.5mm in height. The aneurysm dome itself consists of two distinct volumes, not

dissimilar in shape to two adjoining spheres. Thus the maximal diameter varies from 4mm for the first ‘spherical’ volume (nearest to the neck region) to 3mm at the joint of both volumes, and increases to a further maximal diameter of 6mm for the second ‘spherical’ volume (the apex of the aneurysm). This particular shape creates a distinctive intrasaccular flow pattern. The majority of the flow from the ICA creates a vortex within the bifurcation region and subsequently redirects the flow towards both the MCA and AComA outlets. Due to the relatively small volume only a portion of the flow enters at the ‘back’ of the aneurysm neck (assuming the left-side image shows the ‘front’ of the aneurysm) at a reduced velocity of approximately 0.1m/s. The majority of that flow recirculates within the first ‘spherical’ compartment. A small percentage of that flow enters the second ‘spherical’ volume and circulates in the opposite direction forming a figure of eight flow pattern (as can be seen in the right-hand image of Figure 6.20). The flow exits the aneurysm at the ‘front’ of the neck region and is distributed towards either outlet.

Figures 6.21, 6.22, 6.23 and 6.24 show the velocity (insets *(b)*), oxyhaemoglobin saturation and oxygen (insets *(c)*) distributions across four different planes that intersect the aneurysm. Three *x-y* planes show the cross-sectional distributions at three distinct points within the aneurysm dome. A single *z-x* plane intersects the parent artery and the entire length of the aneurysm dome (Fig. 6.24). Once again the velocity plots show the maximum values across each plane, with exception to the singular *z-x* plane, whereby a lower scale is used to demonstrate the flow progression within the dome. The dotted lines in each case divide the inflow (*I*) from outflow regions (*O*).

The first *x-y* plane intersects the first ‘spherical’ volume of the aneurysm (Fig. 6.21*a*). The maximum velocity across this plane reaches a maximum of 7×10^{-3} m/s in a centralised region towards the ‘back’ of the aneurysm. This area shows the area in which most of the flow recirculation occurs before exiting the aneurysm. The flow velocity quickly decelerates to 5×10^{-4} m/s at the outer bounds of the recirculation zone, and decelerates further to 1×10^{-4} m/s in the near-wall region. The initial

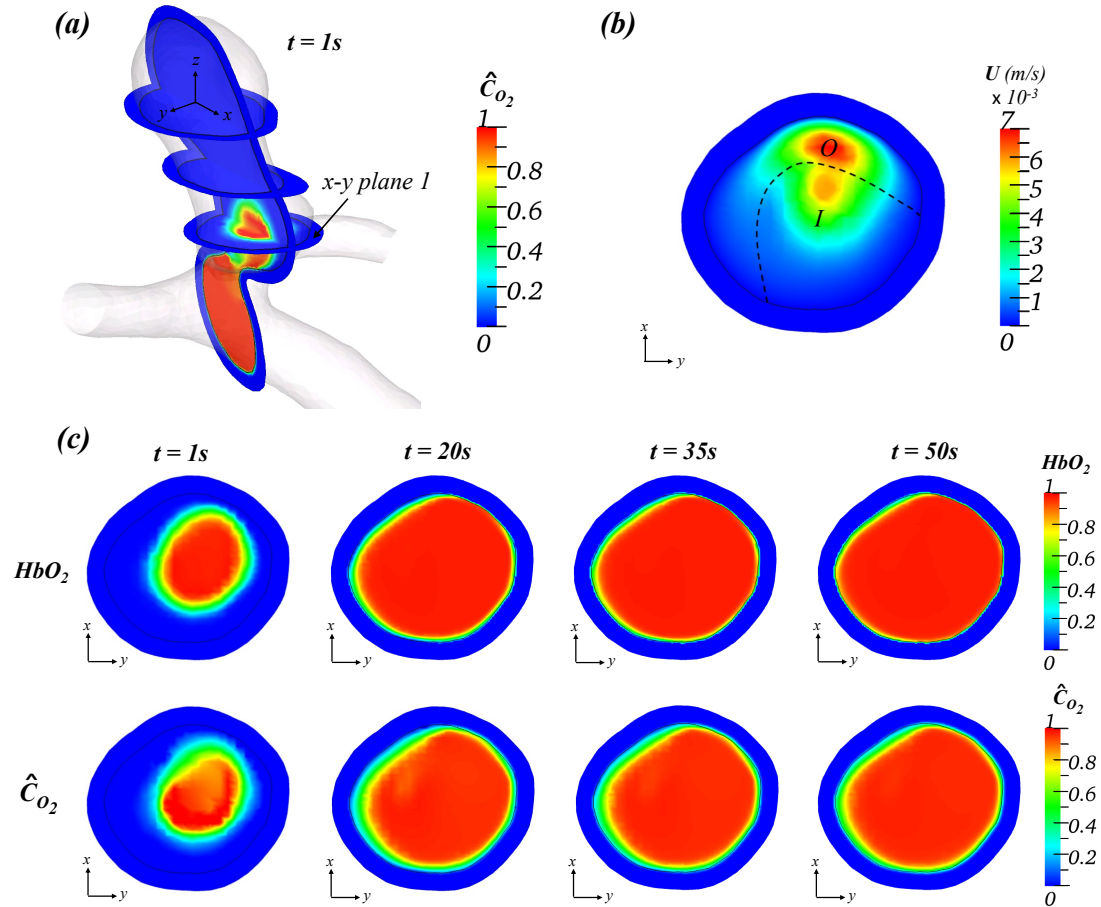


Figure 6.21: Case D Cross-sectional distribution of velocity and oxygen in the x - y plane 1 for Case D. (a) Oxygen concentration within the dome at $t = 1s$ across the x - y and z - x plane that intersect at the location near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 1, 20, 35$ and $50s$.

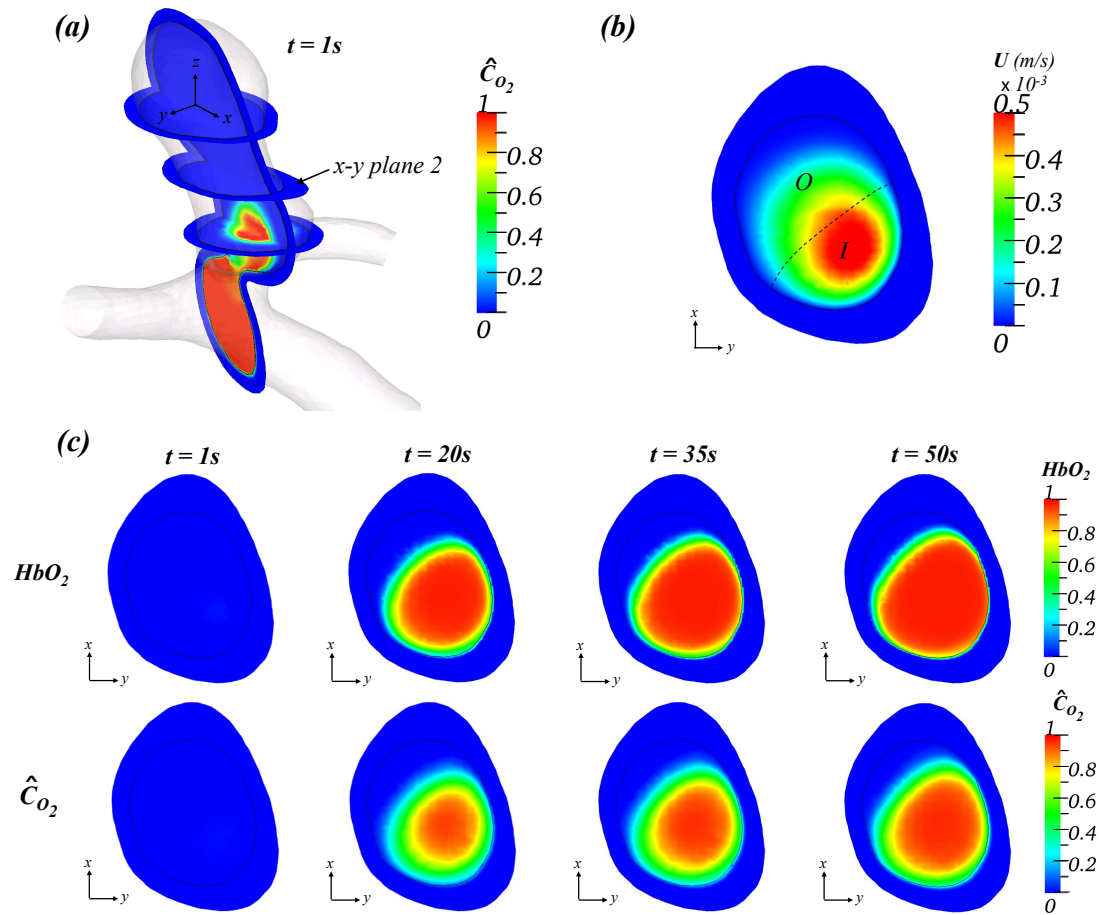


Figure 6.22: Case D Cross-sectional distribution of velocity and oxygen in the $x-y$ plane 2 for Case D. (a) Oxygen concentration within the dome at $t = 1s$ across the $x-y$ and $z-x$ plane that intersect at the location near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxyhaemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 1, 20, 35$ and $50s$.

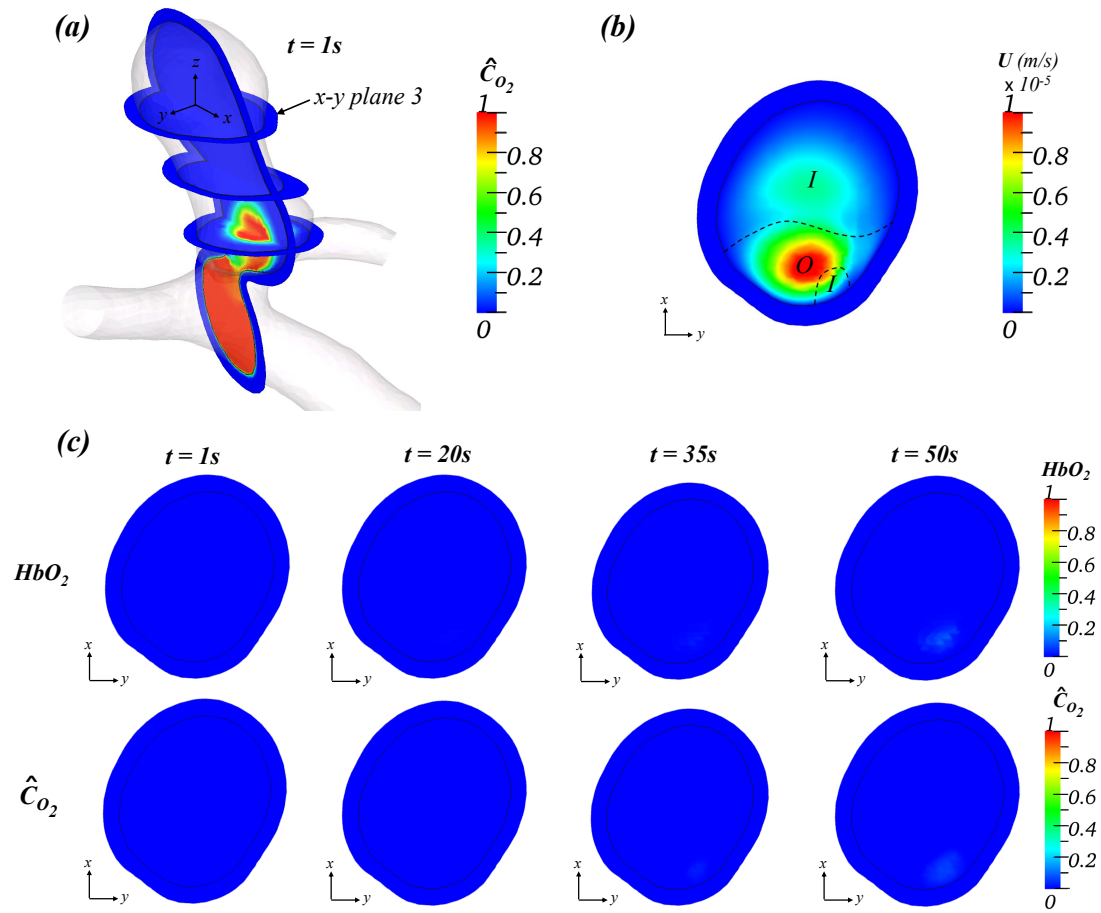


Figure 6.23: Case D Cross-sectional distribution of velocity and oxygen in the $x-y$ plane 3 for Case D. (a) Oxygen concentration within the dome at $t = 1s$ across the $x-y$ and $z-x$ plane that intersect at the location near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxyhaemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 1, 20, 35$ and $50s$.

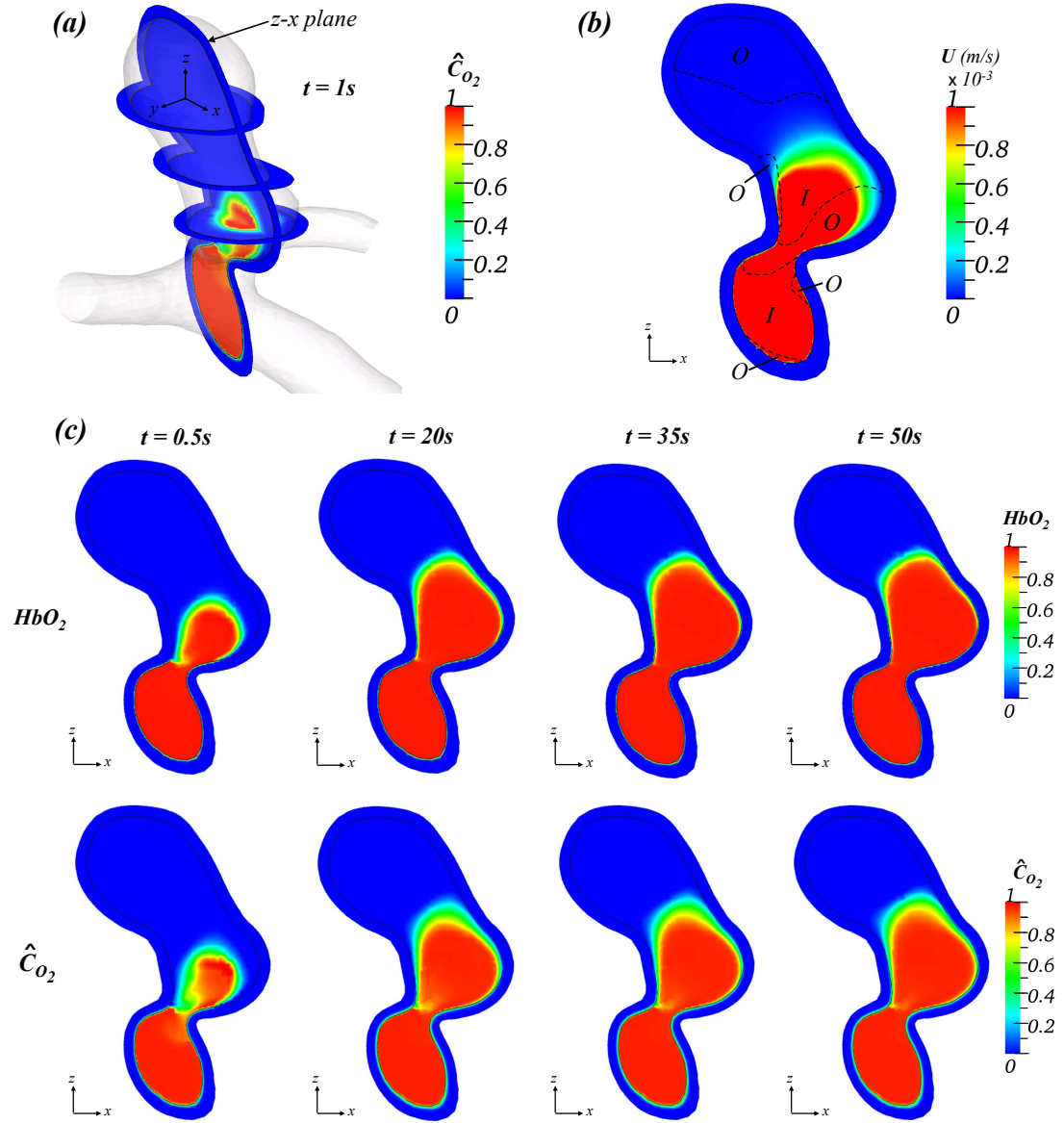


Figure 6.24: Case D Cross-sectional distribution of velocity and oxygen in the z - x plane 1 for Case D. (a) Oxygen concentration within the dome at $t = 1s$ across the x - y and z - x plane that intersect at the location near-stagnant flow. (b) Velocity magnitude contour plot; the dashed line divides the inlet (I) and outlet (O) flow regions. (c) Oxy-haemoglobin saturation plots (top row) and normalised oxygen concentration plots (bottom row) for $t = 1, 20, 35$ and $50s$.

transport of oxygen and oxyhaemoglobin occurs within the higher velocity recirculation zone, as can be seen at $t = 1s$ of inset (c). By $t = 20s$ the majority of the area has reached the constant values of $C_{HbO_2} = 96\%$ and $\hat{C}_{O_2} = 97\%$, with the exception of the near-wall region, in particular a crescent shaped zone on the left-hand side of the image. Over time the availability of free and bound oxygen remains limited in this region as can be seen at timesteps $t = 35s$ and $t = 50s$.

The second x - y plane intersects the dome within the interconnecting region of both ‘spherical’ volumes (Fig.6.22a). The maximum velocity across this plane reaches a maximum of $5 \times 10^{-4}m/s$ and outlines the outer recirculation region of the first ‘spherical’ volume. The velocity at the ‘back’ of the dome decreases rapidly to $1 \times 10^{-4}m/s$, and down to $1 \times 10^{-6}m/s$ in the near-wall region. It takes approximately 20s for the oxygen and oxyhaemoglobin saturation levels to reach a maximum in the region of highest velocity. The presence of both oxygen and oxyhaemoglobin saturation remains in one central region as time evolves. Whereas the area of maximum concentration ($C_{HbO_2} = 967\%$ and $\hat{C}_{O_2} = 96\%$) appears to expand concentrically at timesteps $t=35s$ and $t=50s$, the outer limits of both quantities does not extend throughout the whole domain. The area of stagnant flow at the ‘back’ of the dome remains completely unsaturated.

The third x - y plane intersects the second ‘spherical’ volume (Fig. 6.23a). The maximum velocity across this cross-section reaches a maximum of $1 \times 10^{-5}m/s$. Although a limited amount of flow does slowly recirculate within this secondary volume, it remains completely unsaturated of oxygen, either bound or unsaturated, over the 50s timeframe.

The final plane intersects the parent artery and the entire length of the aneurysm dome (Fig. 6.24a). The dotted lines superimposed on the velocity plot in inset (b) show the complex recirculation areas within the parent artery and dome. In particular, a split in outflow and inflow zones within the neck region limits the entrance of fresh oxygenated blood into the aneurysm dome. The scale of the velocity plot

demonstrates a correlation between the progression of oxygen and oxyhaemoglobin within aneurysm. By $t=20s$ both solutes reach a constant level of $C_{HbO_2} = 97\%$ and $\hat{C}_{O_2} = 96\%$ within the first ‘spherical’ volume of the dome. Two areas of recirculation result in reduced scalar values where the outflow and inflow regions intersect at the ‘front’ and ‘back’ of the dome. Over the next 30s both solutes slowly diffuse within these regions. Due to the limited flow within the secondary volume the oxygen and oxyhaemoglobin stagnate at the intersection juncture of both volumes.

In instances where the flow is slower than $1 \times 10^{-4}m/s$, $Pe < 0.1$, indicating the transport of oxygen is predominantly diffusion limited. Nonetheless, the consumption rate by wall cellular components is too great to compensate, thus portions of the wall will not be fully oxygenated. The velocity within the upper volume of the aneurysm is even slower ($1 \times 10^{-5}m/s$) and together with the distance between the recirculated oxygen and the aneurysmal wall at the apex, the oxygen consumption is not great enough to influence the diffusion of oxygen.

The OX12 geometry has a high aspect ratio of 4.3, whilst the VISC geometry has an aspect ratio of 2.5. Both of these cases are deemed a higher risk as they exceed the clinically accepted rupture risk index of 1.6 (Ujiie et al. (2001)). Nonetheless the way in which the VISC aneurysm fills does not limit the delivery of fresh oxygenated blood to the entirety of the aneurysmal wall. The velocity magnitude within the dome ranges from 0.2 to $1 \times 10^{-3}m/s$ which results in a longer transport time within the slower regions. Nonetheless the full dome is supplied of fresh oxygen within 20s for the untreated and thrombosed VISC cases (A and C) and within 28s for the stented VISC case (B). In terms of the latter, the presence of a stent (i.e. flow-diverter) effectively reduces the intrasaccular flow, but this only delays the rate at which the aneurysm is oxygenated without affecting the distribution through the wall. The markedly small neck region of the OX12 geometry results in limited advection within the whole dome with the velocity magnitude ranging from 0.1m/s at the neck, to $1 \times 10^{-3}m/s$ within the first compartment of the dome and lower than $1 \times 10^{-6}m/s$ at the apex. The near-stagnant flow within the upper volume of

the aneurysm limits the convective transport of O_2 resulting in prolonged hypoxia of the upper part of the aneurysmal dome. Thus, the geometrical attributes of the aneurysm dome may affect the intrasaccular flow to such an extent as to limit oxygenation of the wall.

6.5.2 Oxygen tension at the lumen/wall interface

6.5.2.1 OX12 case

Figure 6.25 presents the spatial distribution of normalised oxygen concentration with time at the wall interface for the OX12 case (D). The ICA and MCA arterial walls reach the steady state value of $\hat{C}_{O_2} = 80\%$ within the first few seconds. A delay is observed across the AcomA due to the mixing of outflow from the aneurysm. In correlation with reduced concentration observed in Figures 6.21 to 6.24, the increase in oxygen tension at the lumen/wall interface is limited due to the near-stagnant flow within the dome; the O_2 consumption within the wall is dominating in this instance. The small area adjacent to the entering flow through the neck does reach the maximal interface value of $\hat{C}_{O_2} = 80\%$. Otherwise the majority of the first ‘spherical’ volume does not exceed 40%, with exception to the region of very slow flow at the front of the aneurysm. As expected, the very limited distribution of oxygen in the upper portion of the dome results in an almost zero oxygen tension at the lumen/wall interface for the rest of the domain.

6.5.2.2 VISC cases

Figures 6.26, 6.27 and Figure 6.28 present the spatial distribution of normalised oxygen concentration with time at the wall interface for cases A, B and C respectively. These sequential images demonstrate a spatial variation in the rate at which the oxygen concentration at the wall reaches the steady state value of $\hat{C}_{O_2} = 80\%$. In each case the parent artery is the first to reach this maximal value, albeit a slight delay downstream of the aneurysm caused by the outgoing flow from the sac. For the aneurysm dome, the increase in oxygen tension occurs more rapidly in regions adjacent to the higher velocity field on the distal side, than regions adjacent to the

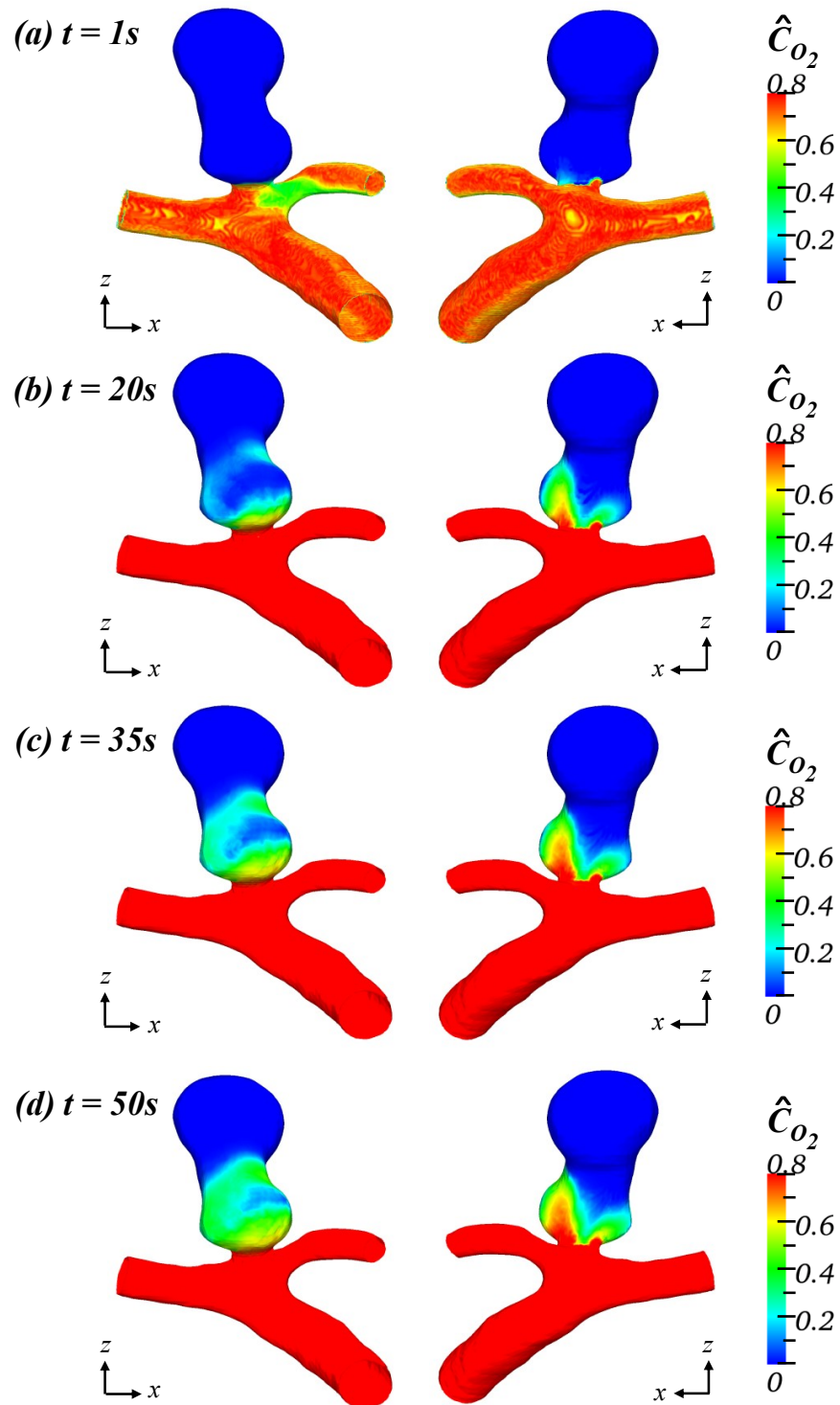


Figure 6.25: Case D Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 10s and (d) 20s

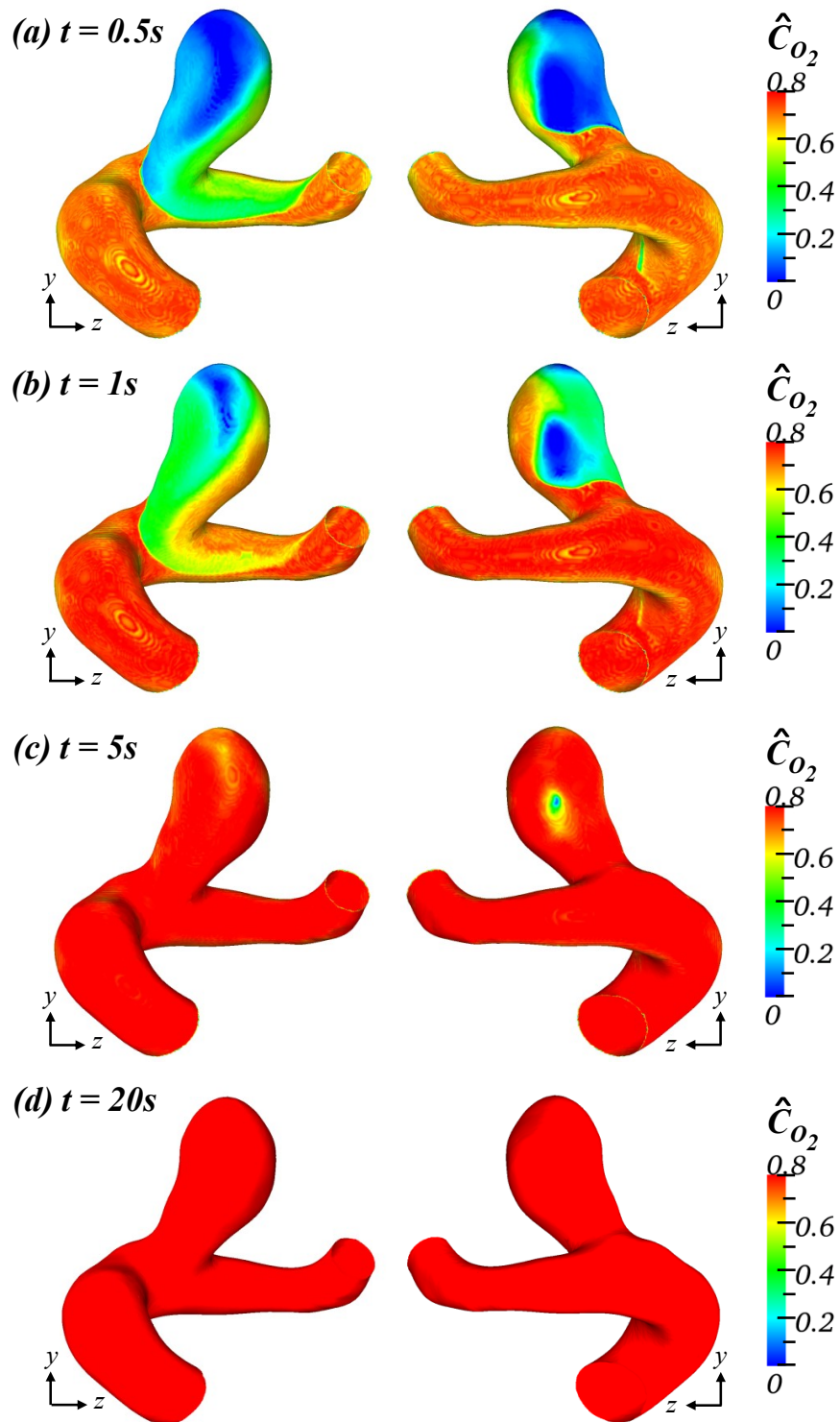


Figure 6.26: Case A Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 5s and (d) 20s

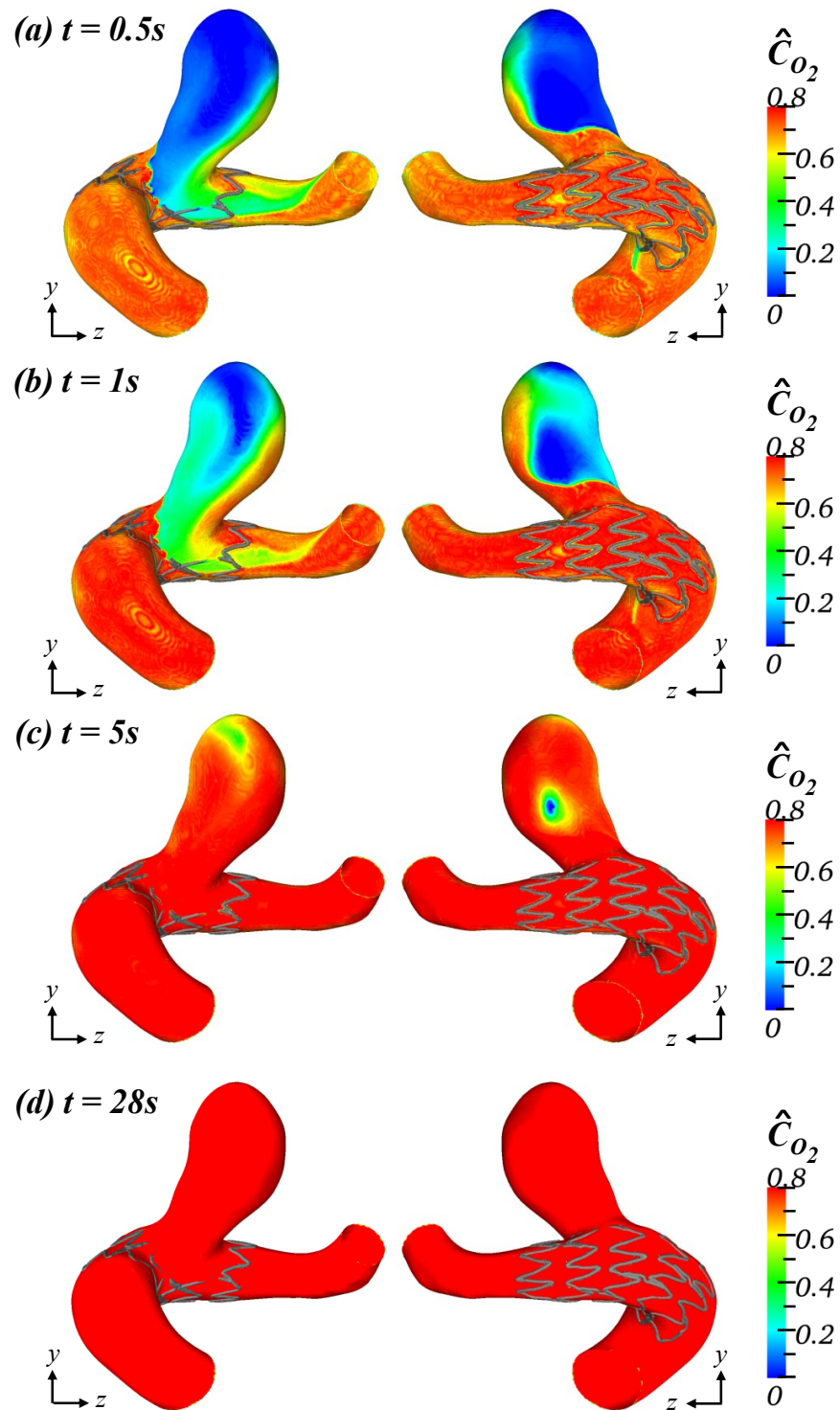


Figure 6.27: Case B Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 10s and (d) 28s

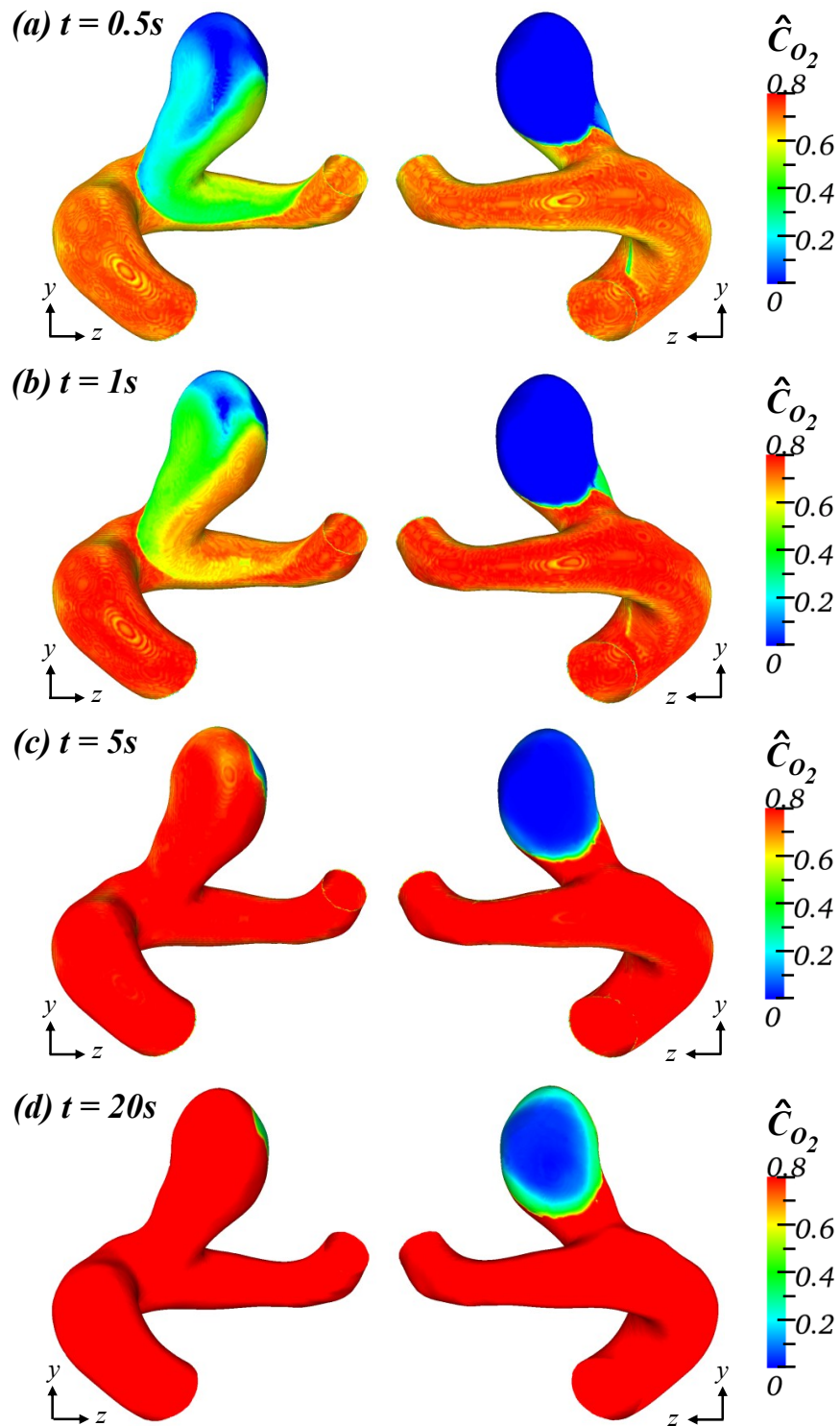


Figure 6.28: Case C Normalised oxygen concentration at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 10s and (d) 20s

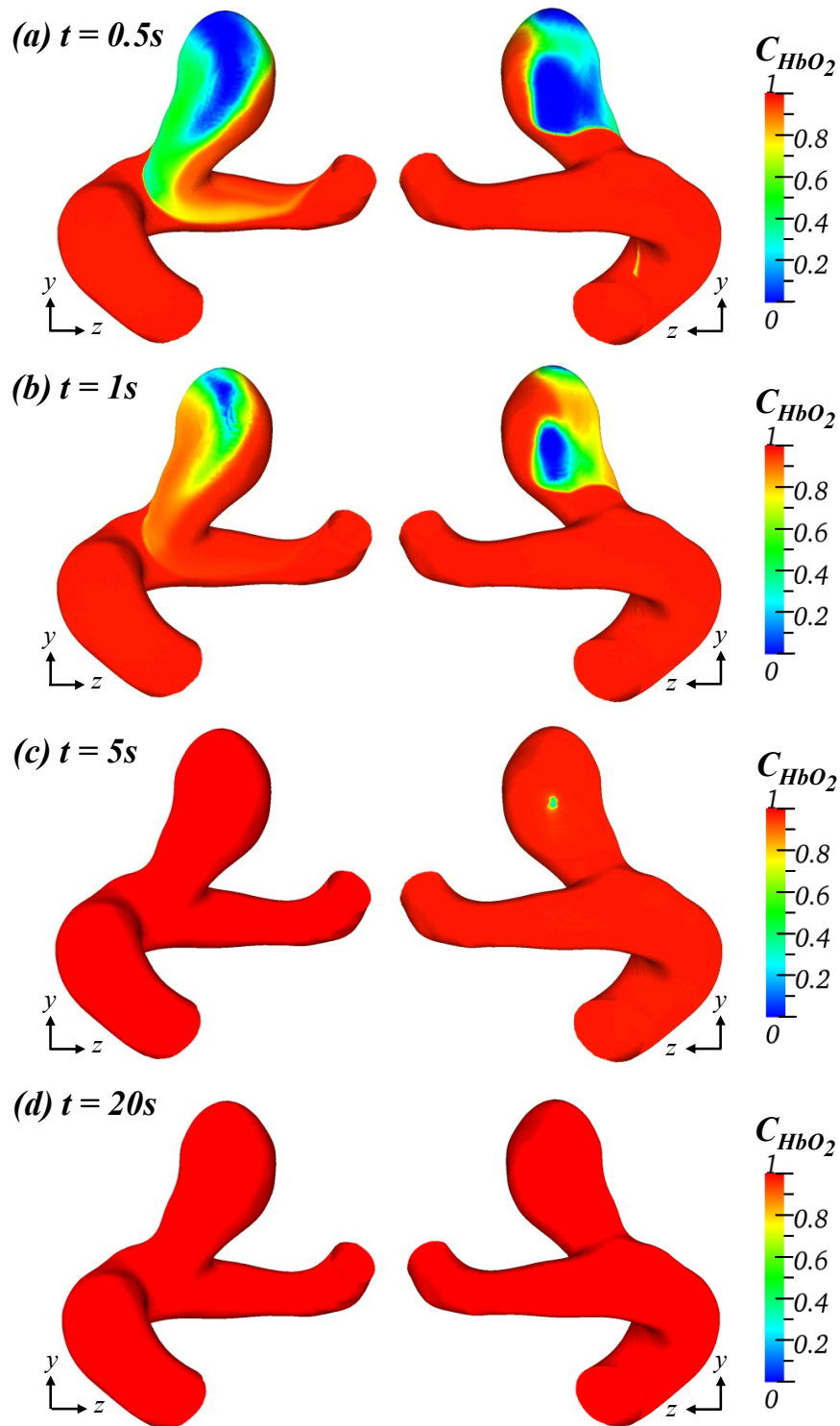


Figure 6.29: Case A Oxyhaemoglobin saturation level, C_{HbO_2} , at the lumen/wall interface at timesteps (a) 0.5s, (b) 1s, (c) 5s and (d) 20s

lower velocity fields at the apex and proximal side as expected due to convection. This correlates with the observations made regarding the rate at which oxygen fills the dome. The area of low concentration at the vortex centre is very apparent at timestep $t = 5s$ for the untreated (A) and treated (B) cases. This same area occurs at the lumen/thrombus interface for Case C and is not visible in these images. A crescent shaped area at the apex of the aneurysm highlights another area of low circulation that is not so apparent in the x - y and z - x planes shown in Figures 6.14 to 6.17. Notably these areas of reduced oxygen concentration is larger for the stented case (B) than for the untreated aneurysm (A) at $t = 5s$, thus reinforcing the limiting effect of a slower intrasaccular flow on the supply of oxygen to the entirety of the aneurysm dome.

To the Author's knowledge the only published study into solute transport in IAs is that conducted by Imai et al. (2010), whereby the transport of ATP within 24 idealised wall-free models of IAs which vary in arterial curvature and aneurysm angle (as discussed in further detail in Section 2.1.3). A high correlation was found between velocity circulation within the dome and low areas of ATP. Imai et al. (2010) also speculates that the distribution of the similarly low molecular weight O_2 molecule would result in similar distribution patterns at the lumen/wall interface of the IA. When comparing with the three VISC cases, the spatial distribution across the dome within the first 0.5-1s are effectively not dissimilar to those presented by Imai et al. (2010). However, the presence of 'wall-side' effects in the simulations presented here result in the full oxygenation of the lumen/wall (and lumen/thrombus if thrombus is present) over the course of time. Together with the work presented in Chapter 4, this confirms the dominance of wall-side transport on oxygen distribution through both the lumen and wall, a conclusion also drawn in the work by Moore and Ethier (1997) and Tada (2010). Thus, compounding the need to model both 'fluid-side' and 'wall-side' effects when simulating coupled FM of oxygen transport in patient-specific IAs.

As an example, Figure 6.29 presents the spatial distribution of oxyhaemoglobin

saturation with time for Case A. The rate at which the lumen/wall interface reaches the maximum steady state value of $C_{HbO_2} = 97\%$ correlates with the aforementioned flow distribution patterns through the dome. The distribution of oxyhaemoglobin occurs at a more successive rate than oxygen as a consequence of the faster diffusion throughout the aneurysm dome, as is discussed for Figures 6.13 and 6.14. Similar observations are found for the B and C VISC cases.

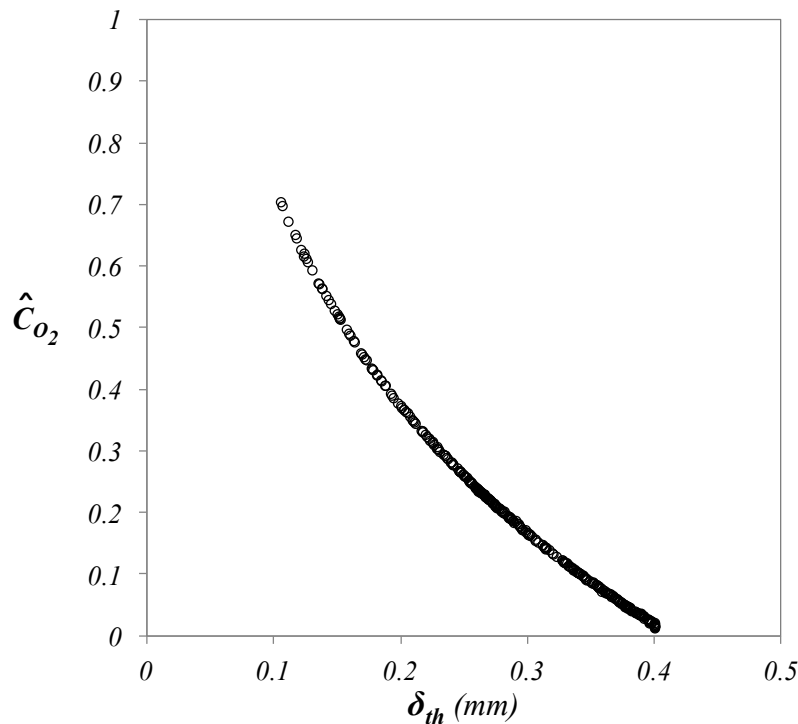


Figure 6.30: Normalised oxygen concentration at the thrombus/wall interface plotted against thrombus thickness δ_{th} .

For the thrombosed case (C), a total of 430 random points at the thrombus/wall interface were selected in order to observe the effect of thrombus thickness on oxygen delivery to the wall when the results have reached steady state (i.e. $t = 20s$). The normalised oxygen concentration at each point is plotted versus thrombus thickness in Figure 6.30. The minimal thrombus thickness measured was of $d_{th} = 0.1mm$ due to the abrupt transition between the thrombus layer and the portion of wall not affected. The ‘concentric’ decrease in oxygen across the portion of dome affected by thrombus is visible in Figure 6.28. When the thickness is of $0.1mm$ the oxygen value at the thrombus/wall interface decreases from $\hat{C}_{O_2} = 80\%$ to 70% . As the thrombus

thickens towards to the centre of the domain the oxygen concentration continually decreases: $\hat{C}_{O_2} = 38\%$ when $d_{th} = 0.2\text{mm}$ and $\hat{C}_{O_2} = 27\%$ when $d_{th} = 0.3\text{mm}$. The majority of the thrombus layer has a thickness of 0.4mm (as shown in Figure 6.30), the periphery of this thicker layer reaches a concentration of $\hat{C}_{O_2} = 2\%$, whilst the central area only reaches a concentration of 1.5% .

6.5.3 Oxygen distribution through the aneurysmal wall

A cross-sectional cut in the z - x plane was created at exactly the same height of the dome so as to compare the oxygen distribution across the lumen and wall for all three VISC cases (A,B and C). The plot in Figure 6.31 shows the normalised oxygen concentration across the z -axis at timesteps $t = 20\text{s}$ for cases A and C and $t = 28\text{s}$ for case B. This axis cuts across the aneurysm lumen and the two sections of wall either side. For case C it also intersects across a small portion of the thrombus, where the radial thickness of the thrombus is $d_{th} = 0.2\text{mm}$. The oxygen concentration through the aneurysm lumen for each case is $\hat{C}_{O_2} = 96\%$. Furthermore the distribution through both wall sections is also identical for all three cases, with exception to the portion of wall that is in direct contact with the thrombus layer in case C. When there is no thrombus present the concentration at the lumen/wall interface is of $\hat{C}_{O_2} = 80\%$, in correlation with the observations made from the distribution plots presented in Figures 6.26 to 6.25. The high respiration rate prescribed to the wall results in complete absorption of the oxygen within 50% of the wall thickness, resulting in hypoxia of the outer portion of the medial layer and of the adventitia.

The oxygen tension at the lumen/thrombus interface $\hat{C}_{O_2} = 82\%$, which is higher than that of the unaffected wall. Similar observations were made with regard to the 2D axisymmetric model in Chapter 4 and it is believed that the distance created by the thrombus thickness reduces the influence of wall respiration rate on diffusion through the layer. The tension at the thrombus/wall interface decreases to $\hat{C}_{O_2} = 38\%$ for this thrombus thickness of 0.2mm . Once again, due to the higher respiration rate of $1e^{-3}\text{mol/m}^3/\text{s}$, all oxygen is quickly absorbed within 35% of the wall

thickness. In the instance that $d_{th} = 0.4\text{mm}$, whereby the majority of the layer has a limited concentration at the thrombus/wall of $\hat{C}_{O_2} = 1.5\%$, only the first 1% of the wall is oxygenated. Moreover, this hypoxic environment is deemed chronic (i.e. will not improve with time) and thus it is possible to speculate that the portion of wall in direct contact with the thrombus may culminate in endothelial dysfunction, SMCs and fibroblast apoptosis, excessive production of proteases, reduced collagen deposition and the accumulation of inflammatory cells causing the ultimate rupture of the wall.

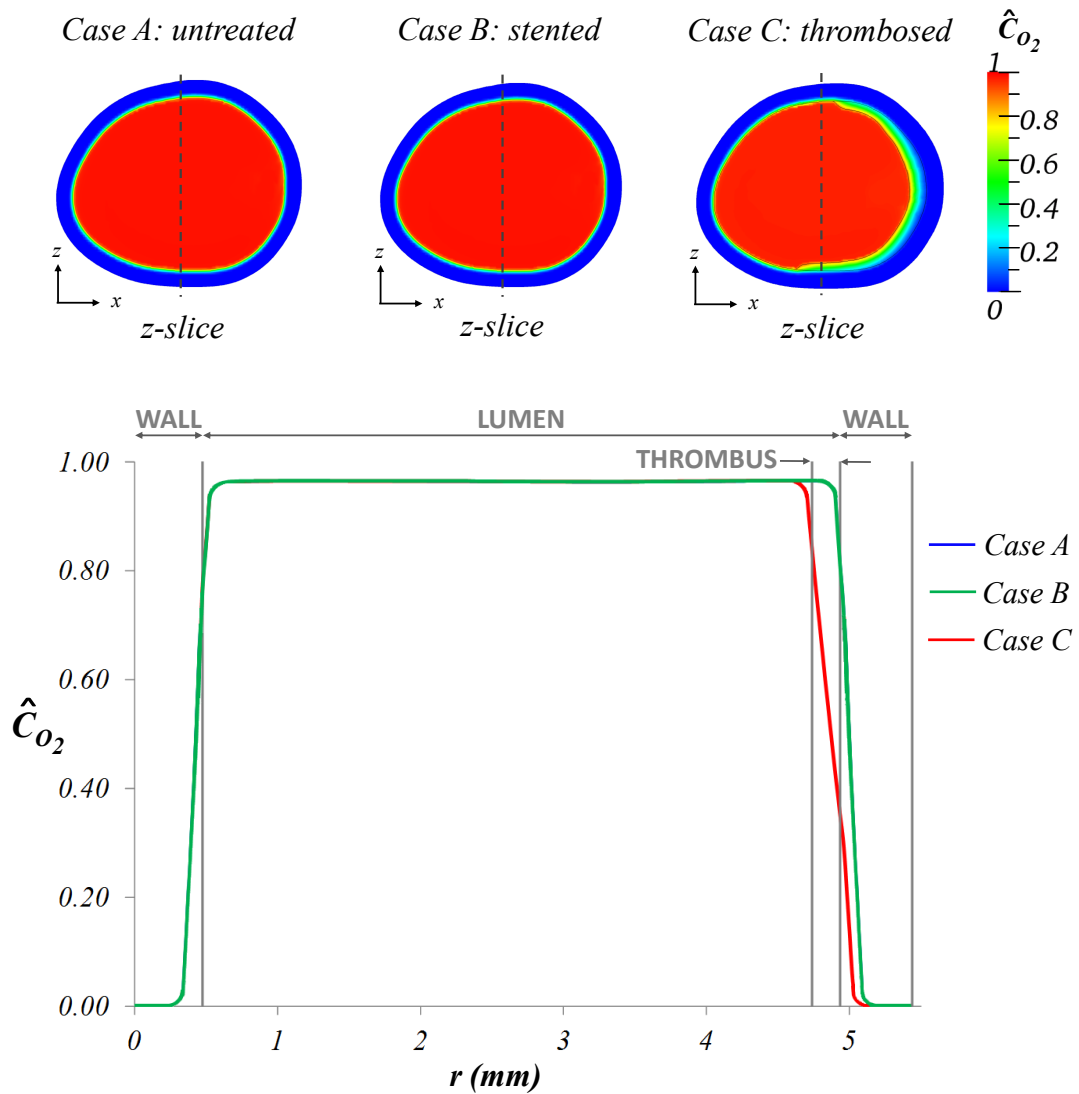


Figure 6.31: Normalised oxygen concentration versus radial distance for the untreated (A), stented (B) and thrombosed (C) VISC cases.

For portions of the OX12 aneurysmal wall that are fully oxygenated (i.e. the lumen/wall interface has reached the maximum value of $\hat{C}_{O_2} = 80\%$) the oxygen is also completely absorbed within 50% of the wall thickness. The rest of the aneurysmal wall within the dome does not exceed 40% resulting in very limited oxygen delivery to the wall, whereby any oxygen diffused through is consumed within the first 35% of the wall thickness. As a consequence of the very limited flow within the upper portion of the dome, the wall within the apex of the dome is completely deficient of oxygen. This case compounds the idea that in extreme situations the particular geometry of an aneurysm (neck size, aspect ratio) may limit the flow within the aneurysm sac to such an extent as to also limit the delivery of oxygen to portions of the dome. The clinical observations of this case affirm that this particular aneurysm ruptured precisely within the apex region, thus circumstantiating the possibility that the aneurysmal wall cells may have been subjected to chronic hypoxia, leading to wall dysfunction and subsequent rupture. It is also speculated that thrombus may have been present within the secondary volume of the dome. As the transport of oxygen within thrombus is believed to take place mainly through diffusion, the outcome is not thought to be any different as the initial convection of oxygen to this part is limited.

It is of note that for all four cases (A,B,C and D) the oxygen distribution through the wall within the healthy parent arteries for which the lumen/wall tension reaches the maximum value of $\hat{C}_{O_2} = 80\%$ is also fully depleted within 50% of the wall thickness.

The physiologically measured value of $1e^{-3} \text{ mol/m}^3/\text{s}$ was implemented in this work to represent the possible higher respiration of SMCs, which compose 70% of muscular arteries such as the ICA, MCA and AcomA (Walmsley (1983)). Nonetheless these results reinforce the hypothesis that the wall layer should not be treated as a single uniform wall layer. The intima, media and adventitia have distinct cellular compositions (e.g. ECs in the intima, SMCs in the media and fibroblasts in the adventitia) with specific oxygen requirements for functionality which would af-

fect the local rate of respiration. Moreover the wall thickness created for both the VISC and OX12 cases was set to a uniform thickness of 0.5mm. This results in the same distribution through the wall at any radial point within the dome and parent arteries. The thickness was selected as 25% of the ICA inlet radius based on physiological measurements (Monson et al. (2005); Alastruey et al. (2007)). However, the ICA narrows as it joins the Circle of Willis (CoW) resulting in a proportional decrease in wall thickness. This is all the more accentuated for the MCA and AcomA in the OX12 case: the 2D axisymmetric model in Chapter 4 is based on the AcomA which has a wall thickness of 0.19mm. Furthermore the aneurysm dome itself was also set to have a constant thickness of 0.5mm. However, this is not phenomenologically accurate. On the one hand the expansion of some aneurysms results in medial thinning as SMCs migrate and the elastin degrades (Crawford (1959); Abruzzo et al. (1998)), whilst on the other some aneurysms evolve with medial thickening due to myointimal hyperplasia (Frösen et al. (2004)).

It is taken into account that the arteries within the CoW lack *vasa vasorum* (as is discussed in Section 1.1.3.3). The belief is that the nutritional needs of these thinner arteries (in comparison to the aorta for example) is entirely met by the diffusion of oxygen from the lumen. However, there are some observations of a few *vasa vasorum* in the proximal portion of ICAs that present with unusually large radii (Aydin (1998)). Furthermore another hypothesis suggests that the cerebral arteries that are partially surrounded by cerebrospinal fluid (CSF) may acquire oxygen to the outer layers through passive diffusion (Aydin (1998)). These two factors therefore need to be taken into account in future modelling of oxygen diffusion within cerebral walls.

Relative to the total volume of the dome, the layer of thrombus is relatively small, and thus should the thrombus continue to grow it is possible to speculate that the hypoxia may worsen to anoxia. However, this is assuming that the thrombus layer continue to be modelled as a single homogeneous layer. Nonetheless, thrombus is a growing organism, which is continually evolving due to the fibrotic alteration into mature ‘organised’ granulated tissue composed notably of SMCs, fibroblasts

and collagen. The cellular respiration requirements of these cells may no longer be negligible. Furthermore, clinical observations (cf. Figure ??) have shown the development of vessels through both the thrombus and the wall of IAs as neovascularisation is activated in response to hypoxic conditions. Thus, modelling the thrombus and wall layers as porous mediums may allow for the modulation of permeability as new vessels form. To give FM modelling of IAs a greater physiological meaning, the volume and transport properties of oxygen for the thrombus layer merit further development.

6.6 CONCLUDING REMARKS

The aim of this work was to explore the effect of *(i)* aneurysm geometry, *(ii)* treatment and *(iii)* the presence of thrombus on oxygen delivery to the aneurysmal wall in patient-specific IAs.

It was observed that the particular geometry of an aneurysm (i.e. its aspect ratio and the shape of the sac) may limit the flow within the aneurysm to such an extent as to completely limit the delivery of oxygen to portions of the dome, bringing into question whether O_2 transport should be taken into consideration alongside other geometrical attributes which clinicians rely on to determine risk of rupture.

Although a reduction in intrasaccular flow as a consequence of stent deployment across the neck resulted in a difference in the rate at which ‘fresh’ oxygenated blood reaches the lumen/wall interface within the sac, the aneurysmal wall itself was not deprived of more oxygen than when the IA is left untreated.

It was shown that the presence of thrombus results in a dramatic reduction in oxygen delivery to the wall as $d_{th} \rightarrow 0.4\text{mm}$: the levels observed may be considered hypoxic as $\hat{C}_{O_2} \rightarrow 1\%$. Moreover, this hypoxic environment is deemed chronic (i.e. will not improve with time) and thus it is possible to speculate that the portion of wall in direct contact with the thrombus may culminate in endothelial dysfunction, SMCs and fibroblast apoptosis, excessive production of proteases, reduced colla-

gen deposition and the accumulation of inflammatory cells causing the ultimate rupture of the wall.

Overall, the results presented highlight the importance of modelling both ‘fluid-side’ and ‘wall-side’ effects on the transport of oxygen from the blood flow to the wall. However, the main limitation of these models is the simplistic representations of the thrombus and arterial wall. Whilst the former may still be defined as a single layer, the latter is made up of three distinct layers that have unique cellular compositions. A multi-layered approach (i.e. one thrombus layer and three wall layers) may allow for a greater phenomenological representation by taking into account local thickness (i.e. volume of consuming cells), the possible variability of consuming cells (i.e SMCs vs fibroblasts) and the radial cellular distribution (i.e. local respiration rate and diffusion coefficients of each layer). Moreover, all of these parameters may also vary between the parent artery and the aneurysmal wall itself as a consequence of the particular progression of the IA. The detrimental effect of thrombus on oxygen availability to the wall observed in the above results may then be confirmed by sophisticating the FM model to take these physiological variables into account.

A NOVEL CHEMO-MECHANO-BIOLOGICAL MATHEMATICAL MODEL OF INTRACRANIAL ANEURYSM EVOLUTION

Presented herein is the first coupled flow-solid-growth-transport (FSGT) mathematical model of IA evolution. The aim of this model is to establish the effect of thrombus on the delivery of oxygen to an arterial wall and the consequential influence on the growth and remodelling of the collagenous constituents therein. In this aim, a conceptual cylindrical model of IA evolution is extended to additionally (i) model dynamic thrombus formation; (ii) mass transport of oxygen through a propagating thrombus and thinning wall; (iii) link growth and remodelling (G&R) to local oxygen levels. In this conceptual model, we observe that impedance to wall oxygenation may arise as a result of thrombus propagation. Furthermore, the coupling of oxygen deficiency to fibroblast functionality made the difference between a stable and an enlarging aneurysm. This model demonstrates a starting point for multi-scale, multi-physics modelling of IA evolution which accounts for the biochemical, mechanobiological and haemodynamic processes involved in aneurysm pathophysiology.

7.1 MODEL FORMULATION

The structure of this section is as follows. The first section (7.1.1) details the general theoretical framework to describe the growth and remodelling of a conceptual elastinous and collagenous cylindrical membrane as proposed by Watton et al. (2009b). The ensuing sections outline the theoretical development conducted by the Author. Section 7.1.2 defines the prescribed propagation of thrombus within the artery based on local shear rates at the lumen/wall (or lumen/thrombus) interface. Section 7.1.3 details the steady state diffusion equations of oxygen transport through the thrombus and arterial wall layers. Furthermore, the oxygen consumption rate is defined in terms of mass density and respiration adaptation of cellular

components within the wall. Section 7.1.4 proposes several growth functions relating the local average oxygen levels the arterial wall to the rate at which fibroblasts synthesise or degrade collagen in response to variations in stretch. Lastly, Section 7.1.5 gives a summary of the coupled FSGT model.

7.1.1 Continuum basis for IA evolution

The conceptual cylindrical membrane model presented within this work is an adaptation of that proposed by Watton et al. (2009b). A geometric non-linear membrane theory is used to model the membranous cylindrical structure (refer to Wempner (1973); Heil (1996)). This is based on the assumption that this is a thin-walled aneurysm: i.e. SMCs apoptosis, elimination of IEL and degradation of elastin leaves only a thin layer of adapting collagen fibres.

7.1.1.1 Strain energy functions for heterogeneous aneurysmal wall

In this thesis, the mechanical response of the arterial membrane is expressed by the decoupled representation of a SEF suggested by Holzapfel and Weizsäcker (1998), whereby the overall elastic potential, Ψ , is an additive split of the elastinous (i.e. ground substance, elastin fibres and passive SMCs) and collagen contributions, Ψ^E and Ψ^C respectively:

$$\Psi = \Psi_{(iso)}^E + \Psi_{(aniso)}^C, \quad (7.1)$$

Elastin

The SEF for the elastinous constituents may be expressed in terms of the potential energy of elastin per unit volume, denoted $\hat{\Psi}^E$, and the elastin concentration m^E , i.e.

$$\Psi^E = m^E \hat{\Psi}^E. \quad (7.2)$$

The elastin concentration defines the ratio of mass density at time t to the mass density at time $t = 0$. Thus, $m^E = m^E(t)$, whereby $m^E|_{t=0} = 1$ and $m^E(t) \leq 1, \forall t \geq 0$. The isotropic behaviour of elastin may be characterised as a neo-Hookean material

(Holzapfel and Weizsäcker (1998)):

$$\hat{\Psi}^E = \frac{K_E}{2} (I_1 - 3), \quad (7.3)$$

whereby the constant K_E is the material parameter for elastin.

Collagen

•*Collagen fibre direction and stretch.* Whilst elastin fibres are concentrically aligned, collagen fibres are orientated in a range of directions depending on the type of artery and the location within the arterial layers (Finlay et al. (1995); Schriefl et al. (2012)). Furthermore collagen fibres are inactive under low loads (histology shows their appearance to be ‘crinkled’, as shown in Figure 1.4) and only become load bearing once straightened under higher strains. Thus, in the unloaded reference configuration, Ω_0 , the collagen fibres of orientation ϕ relative to the azimuthal axis, are crimped and unloaded. Whereas the stretch in elastin is defined relative to this unloaded configuration, the stretch in collagen fibres, denoted λ_ϕ^C , is defined relative to the recruitment configuration, Ω^R , i.e. the configuration at which the fibres are ‘recruited’ to become load bearing.

Figure 7.1 demonstrates the relationship between the unloaded configuration Ω_0 , the recruitment configuration Ω^R and the loaded configuration Ω^t . The stretch in elastin resolved in the direction of the collagen fibres is denoted λ_ϕ . The elastin and collagen stretches are related via the recruitment stretch (the stretch in the elastin in the direction of the collagen fibre as it becomes load bearing):

$$\lambda_\phi^C = \frac{\lambda_\phi}{\lambda_\phi^R} \quad (7.4)$$

Both the elastin and recruitment stretches can be defined in terms of the axial stretch (λ_z) and circumferential stretches in the loaded (λ) and recruitment (λ^R) configurations respectively:

$$\lambda_\phi = [\lambda_z^2 \sin^2 \phi + \lambda^2 \cos^2 \phi]^{0.5} \quad \text{in } \Omega^t, \quad (7.5)$$

$$\lambda_\phi^R = [\lambda_z^2 \sin^2 \phi + (\lambda^R)^2 \cos^2 \phi]^{0.5} \quad \text{in } \Omega^R. \quad (7.6)$$

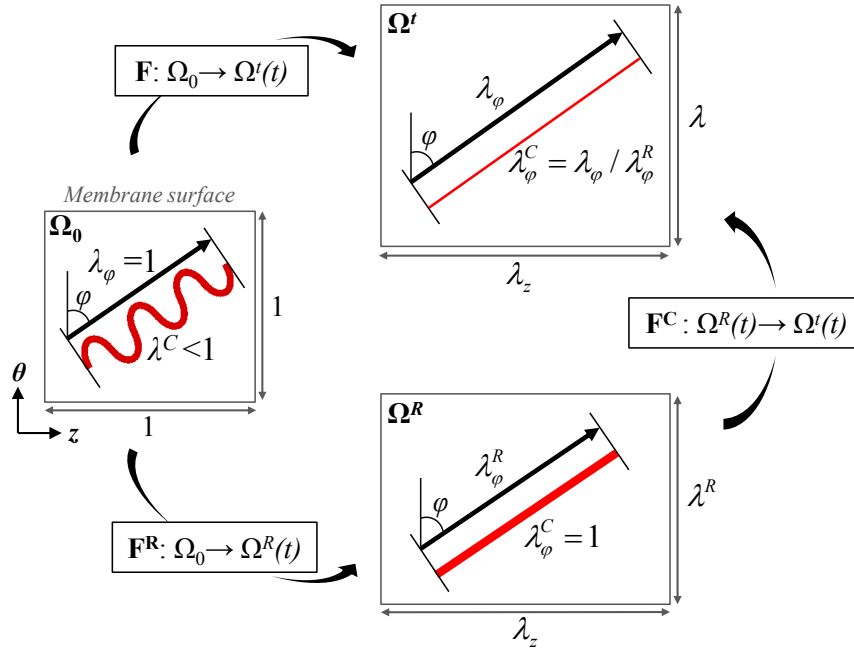


Figure 7.1: Relationship between the unloaded configuration Ω_0 , the recruitment configuration Ω^R and the loaded configuration Ω^t . In the reference configuration Ω_0 the collagen fibres do not contribute to load bearing and so $\lambda^C < 1$, whilst the stretch in elastin $\lambda_\phi = 1$. In the recruitment configuration Ω^R the collagen fibres are recruited to bear load when $\lambda^C = 1$. In the loaded configuration Ω^t collagen stretch is a factor of both stretch in the elastin fibres and the recruitment stretch in the direction ϕ : $\lambda_\phi^C = \lambda_\phi / \lambda_\phi^R$.

• **Attachment stretch.** Fibroblasts attach and configure the collagen fibres to the ECM in a state of stretch (Alberts et al. (2008)). Humphrey (1999) postulated that this ‘attachment stretch’ remains constant regardless of the altered configuration of an artery when modelling a 1D uniaxial model of collagen remodelling under strain. Taking this hypothesis into consideration the attachment stretch is set to remain constant regardless of the altered configuration and is defined as the stretch in the collagen fibres at systole ($t = 0$):

$$\lambda_{AT}^C = \lambda_\phi^C|_{(t=0)} = \frac{\lambda_\phi|_{(t=0)}}{\lambda_\phi^R|_{(t=0)}} = \frac{[\lambda_z^2 \sin^2 \phi + \lambda_0^2 \cos^2 \phi]^{0.5}}{[\lambda_z^2 \sin^2 \phi + (\lambda_0 / \lambda_D^S)^2 \cos^2 \phi]^{0.5}}. \quad (7.7)$$

It is assumed that the collagen fibres are recruited to load bearing at diastole. The artery is subject to a cyclic stretch of $\lambda_D^S = 1.1$ (an estimated 10% pulsation is representative for males/females aged 30 years (Hansen et al. (1995))). Hence, the diastolic circumferential stretch is initially $\lambda^R = \lambda_0 / \lambda_D^S$, whereby λ_0 is the circumferen-

tial stretch at systole.

• **SEF for collagenous constituents.** The SEF for collagen may be expressed in terms of the collagen concentration m^C and the strain-energy per unit volume of collagen, $\hat{\Psi}^C$:

$$\Psi^C = m^C \hat{\Psi}^C. \quad (7.8)$$

The collagen fibre concentration $m^C \in [0, \infty)$ denotes the ratio of mass density of fibres at time t to the mass density at $t = 0$, whereby $m^C|_{t=0} = 1$. For this case study, $\hat{\Psi}^C$ is set to a simple nonlinear polynomial function:

$$\hat{\Psi}^C = \frac{E_{AT}^C K_C}{6} \left(\frac{E_\phi^C}{E_{AT}^C} \right)^6, \quad E_\phi^C \geq 0. \quad (7.9)$$

$\hat{\Psi}^C = 0$ when the collagen fibres do not contribute to load bearing ($E_\phi^C < 0$). Here, the material parameter for collagen is denoted K_C . Whilst E_ϕ^C and E_{AT}^C are Green Lagrange strains in terms of the stretch of collagen λ_ϕ^C and the attachment stretch of collagen λ_{AT}^C , i.e.:

$$E_\phi^C = \frac{1}{2} \left[\left(\lambda_\phi^C \right)^2 - 1 \right], \quad E_{AT}^C = \frac{1}{2} \left[\left(\lambda_{AT}^C \right)^2 - 1 \right]. \quad (7.10)$$

7.1.1.2 Deformation and remodelling of a cylindrical membrane

An elastinous and collagenous cylindrical membrane is subjected to a constant axial stretch λ_z and a circumferential stretch λ due to the inflation by a constant internal pressure P acting normal to the membrane.

In the unloaded configuration (Ω_0) the incompressible cylindrical membrane has a radius R , length L and thickness H . In the loaded configuration (Ω_t), the cylinder has a radius λR , length $\lambda_z L$ and thickness $h = H/\lambda_z \lambda$ (Figure 7.2). The steady deformation of the arterial wall is governed by the principle of stationary potential energy, which requires that the first variation of the total potential energy vanishes (Holzapfel et al. (2000)). Hence:

$$\delta \Pi_{int} - \delta \Pi_{ext} = 0. \quad (7.11)$$

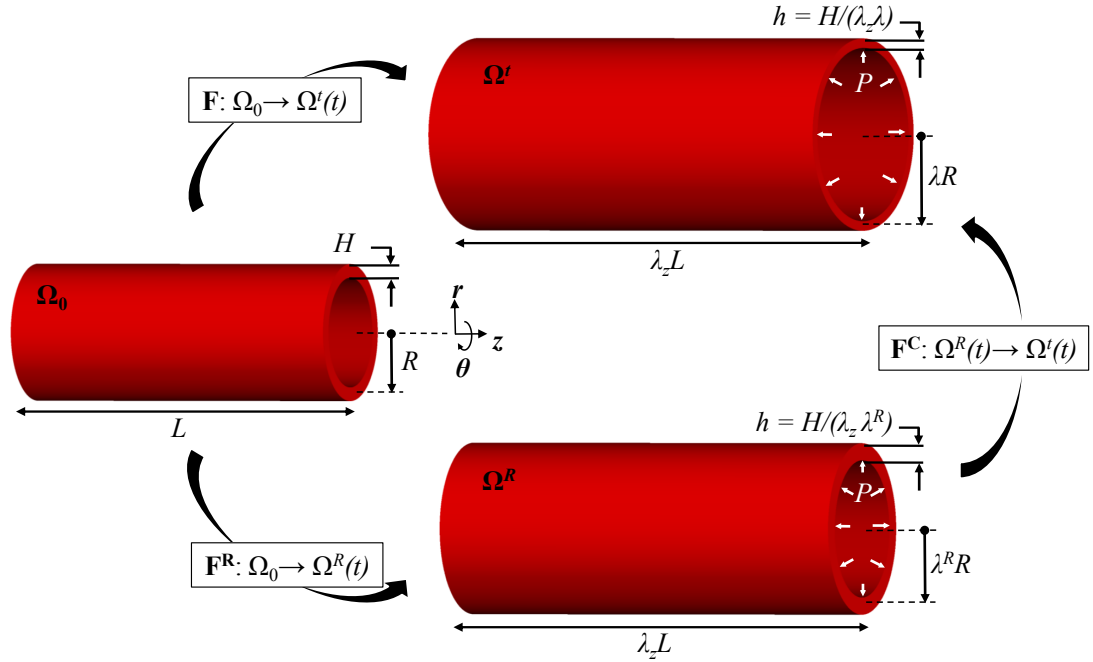


Figure 7.2: The unloaded, loaded and recruitment configurations of the membranous cylinder. The stretch of elastin is defined relative to the unloaded configuration (Ω_0), and the stretch of collagen is defined relative to the recruitment configuration (Ω^R).

Whereby $\delta\Pi_{int}$ is the variation of strain energy within the deformed arterial wall and $\delta\Pi_{ext}$ is the variation of external potential energy due to the pressure acting onto the wall. Given that the circumferential Cauchy stress in a thin-walled cylindrical membrane subjected to fixed axial stretch and radial inflation (i.e in the loaded configuration Ω^t) is

$$\sigma_\theta = P(\lambda R) \left(\frac{\lambda_z \lambda}{H} \right), \quad (7.12)$$

the force balance equation may be written:

$$P = \frac{1}{\lambda_z} \frac{H}{R} \left(m^E \frac{\hat{\sigma}^E}{\lambda^2} + m^C \frac{\hat{\sigma}^C}{\lambda_\phi^2} \right). \quad (7.13)$$

Whereby $\hat{\sigma}^E$ and $\hat{\sigma}^C$ are the azimuthal Cauchy stresses due to the elastinous and collagenous components respectively:

$$\hat{\sigma}^E \equiv \lambda^2 \frac{\partial \hat{\Psi}^E}{\partial E_{22}}, \quad \hat{\sigma}^C \equiv \left(\lambda_\phi^C \right)^2 \frac{\partial \hat{\Psi}^C}{\partial E_\phi^C} \cos^2 \phi. \quad (7.14)$$

E_{22} is the azimuthal Green Lagrange strain, i.e.

$$E_{22} = \frac{1}{2} [\lambda^2 - 1]. \quad (7.15)$$

The first invariant of the Cauchy-Green deformation tensor for an incompressible material is $I_1 = \lambda^2 + \lambda_z^2 + \frac{1}{\lambda_z^2 \lambda^2}$. Hence, differentiating the SEF for the elastinous constituents (eq. 7.3) with respect to E_{22} gives the following expression for $\hat{\sigma}^E$:

$$\hat{\sigma}^E = K_E \left(1 - \frac{1}{\lambda_z^2 \lambda^4} \right). \quad (7.16)$$

Differentiating the SEF for collagenous constituents (eq. 7.9) with respect to E_ϕ^C yields the following expression for the azimuthal Cauchy stress due to the collagen constituent:

$$\hat{\sigma}^C = K_C \left(\lambda_\phi^C \right)^2 \left(\frac{E_\phi^C}{E_{AT}^C} \right)^5 \cos^2 \phi, \quad E_\phi^C \geq 0. \quad (7.17)$$

Substituting these two equations for Cauchy stress into the force balance equation (eq. 7.13) yields the following equation for the mechanical equilibrium of the cylindrical membrane,

$$P = \frac{1}{\lambda_z} \frac{H}{R} \left(m^E K_E \left(1 - \frac{1}{\lambda_z^2 \lambda^4} \right) + m^C K_C \left(\frac{\lambda_\phi^C}{\lambda_\phi} \right)^2 \left(\frac{E_\phi^C}{E_{AT}^C} \right)^5 \cos^2 \phi \right), \quad E_\phi^C \geq 0 \quad (7.18)$$

$$P = \frac{1}{\lambda_z} \frac{H}{R} \left(m^E K_E \left(1 - \frac{1}{\lambda_z^2 \lambda^4} \right) \right), \quad E_\phi^C < 0 \quad (7.19)$$

7.1.1.3 Growth and Remodelling

Elastin degradation

As discussed within the introduction (Section 1.2) the exact pathophysiology of an IA is unknown. However certain histological observations have suggested that the elastin component slowly degrades over time, sometimes resulting in a markedly thick layer or even complete loss. To mimic this phenomena, such as proposed by Watton et al. (2009b), the concentration of elastin is assumed to exponentially degrade down to 1% of its original concentration over the first 5 years of evolution, after which time the elastin is instantaneously assumed completely degraded. This is achieved by setting the following:

$$m^E(t) = 0.01^{t/5}, \quad 0 \leq t \leq 5 \quad (7.20)$$

$$m^E(t) = 0, \quad \forall t > 5. \quad (7.21)$$

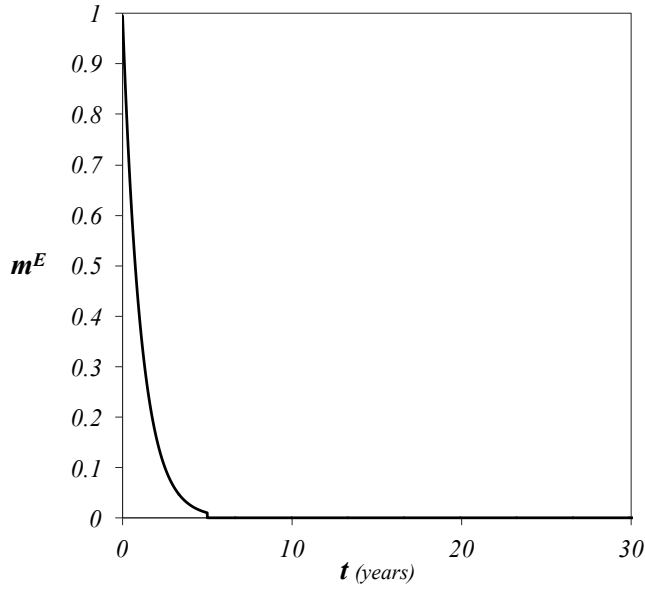


Figure 7.3: Plot demonstrating the prescribed exponential degradation of elastin over the first five years and the complete loss over the following 25 years.

The timescale of growth and remodelling (t) is measured in years. A plot of elastin mass density decrecence over a 30 year time period is shown in Figure 7.3.

Collagen adaptation

The collagen fabric is assumed to adapt (i.e. remodel and grow/atrophy) in order to compensate for the loss of load bearing elastin. It is hypothesised that new homeostasis is achieved by restoring the stretch in collagen towards to the fixed attachment stretch, λ_{AT}^C , throughout the whole domain. This is accomplished by individually modelling two different functionalities of fibroblasts: (i) adjusting the stretch at which collagen is recruited to bear load by remodelling of the recruitment configuration and (ii) increasing or decreasing collagen fibre concentration in response to fibre stretch.

- **Remodelling.** As the artery expands it is assumed that the newly deposited collagen fibres are always attached in a state of stretch. Watton et al. (2004) proposed that the collagen fabric evolves to maintain the strain of the collagen towards the attachment strain E_{AT}^C (equation 7.10). This is accomplished by remodelling the recruitment stretch using the following linear differential equation:

$$\frac{d\lambda^R}{dt} = \alpha \frac{[E_\phi^C - E_{AT}^C]}{E_{AT}^C} \quad (7.22)$$

The remodelling rate parameter α relates to the fibre turnover rate (ie. collagen half-life): the higher the remodelling rate, the higher the turnover of collagen. The value of α can be numerically determined so that it corresponds to a specific value of half-life. Watton (2002) achieved this by comparing two remodelling mechanisms: (i) the half-life model proposed by Humphrey (1999), whereby both the mechanical effects of fibre deposition and decay are modelled; (ii) the remodelling via a recruitment variable as outlined in equation (7.22). Using this method a value of $\alpha = 0.81\text{year}^{-1}$ was determined, which corresponds to a collagen half-life of 30 days.

• **Growth.** The evolution equation simulates fibroblasts sensing changes in the magnitude of cell stretch and responding by up(down) regulating collagen synthesis and down(up) regulating collagenase secretion. The rate of change of collagen density can thus be written,

$$\frac{dm^C}{dt} = \beta m^C \frac{[E_\phi^C - E_{AT}^C]}{E_{AT}^C}. \quad (7.23)$$

The growth parameter β phenomenologically relates to the rate at which fibroblasts synthesise or degrade collagen in response to variations in stretch. The lower the growth rate, the slower the increase in collagen concentration.

7.1.2 Thrombus propagation

Platelet adhesion and aggregation during the formation of a thrombus is intrinsically linked to local wall shear rates (WSR) (Weiss et al. (1986); Nesbitt et al. (2009)). Bowker et al. (2010) examined the spatial effects of WSR upon the growth of a thrombus within a 3D patient-generated aneurysm geometry and observed that modelling the propagation velocity as inversely proportional to the WSR constrained the clot to grow within the sac, without progressing into the parent artery. It is speculated that the WSR increases as the parent artery lumen diameter is recovered resulting in a slower propagation velocity. Based on these findings the propagation velocity for this model was set to the following:

$$V_{th} = \frac{\zeta}{\dot{\gamma}} \quad (7.24)$$

For a Newtonian fluid, the WSR at the inner wall of a cylinder is simply $\dot{\gamma} = 4Q/\pi r^3$, whereby Q is the flow rate through the cylinder. The radius r is the inner radius of the cylinder in contact with the flow, and so as the thrombus grows during aneurysm expansion the thrombus radius is defined as $r_{th} = r_e - h_{th}$ whereby r_e is the radius of the endothelium and h_{th} is the thrombus thickness. The propagation velocity of thrombus can hence be written as

$$V_{th} = \frac{\zeta \pi (r_e - h_{th})^3}{4Q} \quad |\dot{\gamma}| > |\dot{\gamma}_0|, \quad (7.25)$$

$$V_{th} = 0 \quad |\dot{\gamma}| \leq |\dot{\gamma}_0|. \quad (7.26)$$

The rate of thrombus growth is regulated by the constant ζ . It is assumed that thrombus growth halts if the WSR equals that of the ‘healthy’ artery (i.e. in the initial loaded configuration $\Omega^t(0)$): $|\dot{\gamma}| \leq |\dot{\gamma}_0|$, suggesting the original inner radius is recovered (i.e. the parent vessel is left unobstructed as in a successful occlusion of the sac).

In this first instance all efforts are concentrated on the possible detrimental effect to oxygen transport through this evolving thrombus layer, thus the possible stress contribution to the arterial wall are not taken into consideration here.

7.1.3 Steady state oxygen diffusion through two layers

The oxygen distribution through the thrombus and arterial wall layers of the model (Figure 7.4) are deemed to be through diffusion-only transport.

The 1D steady state diffusion equation of oxygen for a cylinder of radius r may be written:

$$D \frac{d}{dr} \left(\frac{dC}{dr} \right) = -r \dot{q}. \quad (7.27)$$

Whereby C and D are the concentration and the diffusivity of oxygen respectively. $\dot{q}$ is the oxygen consumption by cellular components.

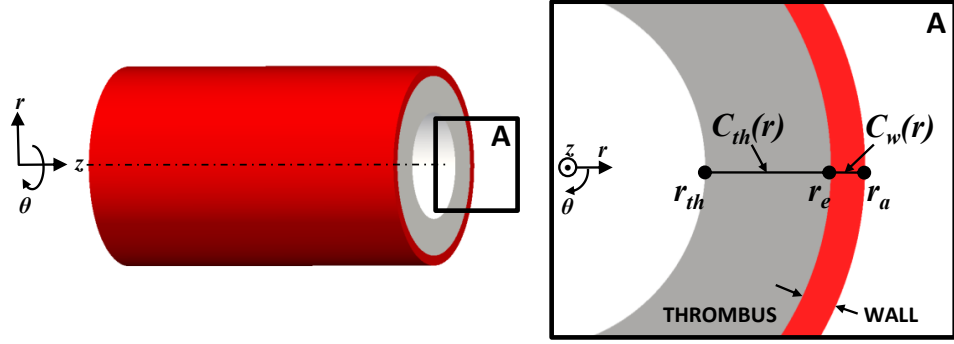


Figure 7.4: 1D oxygen mass transfer across two layers in the r -direction. $C_{th}(r)$ represents the change in oxygen concentration across the thrombus ($r \in [r_{th}, r_e]$) and $C_w(r)$ represents the change in oxygen concentration across the arterial wall ($r \in [r_e, r_a]$).

7.1.3.1 Diffusion through the thrombus

It is assumed that the thrombus layer consumes a negligible amount of oxygen and so equation (7.27) becomes

$$D_{th} \frac{d}{dr} \left(r \frac{dC_{th}}{dr} \right) = 0. \quad (7.28)$$

Whereby C_{th} and D_{th} are the concentration and diffusion terms for thrombus respectively. Derivation of the above equation yields the following:

$$C_{th}(r) = A_1 \ln r + B_1. \quad (7.29)$$

where $A_1, B_1 \in \mathbb{R}$, and are determined from boundary conditions.

7.1.3.2 Diffusion through the arterial wall

The diffusion of oxygen through the arterial wall takes into account the oxygen consumption rate by cells ($\dot{q}$),

$$D_w \frac{d}{dr} \left(r \frac{dC_w}{dr} \right) = -r \dot{q}. \quad (7.30)$$

C_w and D_w are the concentration and diffusivity of oxygen within the arterial layer. The concentration of oxygen at any point through the wall along the radius satisfies the following equation:

$$C_w(r) = -\frac{r^2 \dot{q}}{4D_w} + A_2 \ln r + B_2. \quad (7.31)$$

where $A_2, B_2 \in \mathbb{R}$, and are determined from boundary conditions.

7.1.3.3 Boundary conditions

Taking into account the boundary conditions at the lumen/thrombus interface ($r = r_{th}$) and the thrombus/wall interface (i.e. at the endothelium: $r = r_e$) equation (7.29) implies:

$$C_{th}(r_{th}) = C_0 \quad C_0 = A_1 \ln r_{th} + B_1, \quad (7.32)$$

$$C_{th}(r_e) = C_1 \quad C_1 = A_1 \ln r_e + B_1. \quad (7.33)$$

At the thrombus/wall ($r = r_e$) and adventitia ($r = r_a$) boundaries, equation (7.31) implies:

$$C_w(r_e) = C_1 \quad C_1 = -\frac{r_e^2 \dot{q}}{4D_w} + A_2 \ln r_e + B_2, \quad (7.34)$$

$$C_w(r_a) = C_2 \quad C_2 = -\frac{r_a^2 \dot{q}}{4D_w} + A_2 \ln r_a + B_2. \quad (7.35)$$

Continuous flux is applied to the interface boundary between the thrombus and the arterial wall:

$$D_{th} r_e \frac{dC_{th}}{dr} = D_w r_e \frac{dC_w}{dr} \quad (7.36)$$

Substituting the derivations of equations (7.29) and (7.31), equation (7.36) becomes:

$$A_1 = -\frac{r_e^2 \dot{q}}{2} + A_2. \quad (7.37)$$

The boundary oxygen concentrations at the lumen/thrombus interface (C_0) and at the adventitia (C_2) are known constants. This leaves five unknowns: C_1 , A_1 , B_1 , A_2 and B_2 , which are defined by simultaneously solving equations (7.32), (7.33), (7.34), (7.35) and (7.37). These are fully outlined in Appendix B. Substituting equations (B.9) to (B.12) back into equations (7.29) and (7.31) yields the following analytical solutions for oxygen concentration through the thrombus and arterial wall:

$$\begin{aligned} C_{th}(r) = & C_2 + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right) \\ & + \left[(C_2 - C_0) + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right) \right] \frac{\ln(r/r_a)}{\ln(r_a/r_{th})} \quad r \in [r_{th}, r_e] \end{aligned} \quad (7.38)$$

$$\begin{aligned}
C_w(r) = C_2 + \frac{\dot{q}}{4D_w} (r_a^2 - r^2) + \frac{r_e^2 \dot{q}}{2} \ln\left(\frac{r}{r_a}\right) \\
+ \left[(C_2 - C_0) + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln\left(\frac{r_e}{r_a}\right) \right] \frac{\ln(r/r_a)}{\ln(r_a/r_{th})} \quad r \in [r_e, r_a]
\end{aligned} \tag{7.39}$$

7.1.3.4 Oxygen consumption rate

As discussed in detail in Chapters 1 and 4, one of the primary phenomenological responses of cellular components to hypoxia is oxygen conformance, i.e. the cellular energy demand is adjusted to the minimum requirement for aerobic energy production through adaptive responses to hypoxia. Furthermore, the consumption of oxygen by the arterial wall is primarily undertaken by the SMCs present in the media, and the fibroblasts within the adventitia. As the aneurysm evolves the concentration of both these cell types varies. Thus, it is hypothesised that the oxygen consumption rate be a function of the normalised (relative to the initial lumen tension) average oxygen tension within the wall, $\overline{C_w}$, and the concentration of both SMCs and fibroblasts:

$$\dot{q} = \mathcal{F}(\overline{C_w}, m^{SMC}, m^{FIB}) \tag{7.40}$$

The apoptosis of SMCs is hypothesised to occur simultaneously with the deletion of elastinous constituents, thus it can be stated that the normalised mass density of SMCs, m^S , may be represented by the mass density of elastin, i.e. $m^S = m^E$. It is also assumed that the change in concentration of the collagenous constituents is dependent on the concentration of fibroblasts: $m^F = m^C$. Under these assumptions, the consumption rate of oxygen may be defined by the following expression.

$$\dot{q} = (V^S m^E + V^F m^C) \mathcal{Q}(\overline{C_w}), \quad \mathcal{Q}(\overline{C_w}) > \dot{q}_{min}, \tag{7.41}$$

$$\dot{q} = (V^S m^E + V^F m^C) \dot{q}_{min}, \quad \mathcal{Q}(\overline{C_w}) < \dot{q}_{min}. \tag{7.42}$$

Whereby $\dot{q}_{min}$ is the lowest possible oxygen respiration rate required by cells to maintain some functionality. The percentages, V^S and V^F , represent the normalised volume of oxygen consumed within SMCs and fibroblasts respectively,

whereby $V^S + V^F = 1$ for $\forall t$. The percentage of oxygen absorbed by the SMCs is believed to decay simultaneously with the apoptosis of SMCs (i.e. exponentially over the first 5 years). This is achieved by setting the following:

$$V^S(t) = V_0^S \left(\frac{0.01}{V_0^S} \right)^{t/5}, \quad 0 \leq t \leq 5 \quad (7.43)$$

$$V^S(t) = 0, \quad \forall t > 5. \quad (7.44)$$

The adaptive response to oxygen decrescence is believed to occur rapidly, thus the consumption rate is assumed to decrease exponentially relative to the decline in average oxygen concentration within the wall. Hence, the respiration function in equation 7.41 is set to the following:

$$\mathcal{Q}(\overline{C_w}) = \dot{q}_0 \left[\left(\frac{\dot{q}_{min}}{\dot{q}_0} \right) \exp \left(\frac{(\overline{C_w}) - (\overline{C_w})_0}{(\overline{C_w})_{min} - (\overline{C_w})_0} \right) \right]. \quad (7.45)$$

The choice for this particular function is based on the initial consumption rate and normalised average oxygen tension within the wall for a ‘healthy’ artery, $\dot{q}_0$ and $(\overline{C_w})_0$ respectively. The respiration rate is set to decrease to a minimum of 1% when the average oxygen tension has reached 1%: $\dot{q}_{min} = 0.01 \dot{q}_0$ when $(\overline{C_w})_{min} = 0.01 (\overline{C_w})_0$.

7.1.4 Influence of oxygen levels on fibroblast functionality

Steinbrech et al. (1999) carried out several experiments investigating the effect of hypoxia on fibroblast functionality. It was found that after a 48h exposure to oxygen levels between 0-2% O_2 , collagen synthesis was downregulated to $\sim 4\%$ of the baseline. From these findings it is hypothesised that the growth rate β decreases to a minimum of $4\% \beta_0$ when the oxygen levels reach a minimum of $(\overline{C_w})_{min} = 2\%$.

The rate at which reduced oxygen levels affects fibroblast functionality is explored by implementing the following power law function for the decrease in β rel-

ative to the average oxygen tension within the wall:

$$\beta = \beta_0 + (\beta_{min} - \beta_0) \left[\frac{(\overline{C_w})^i - (\overline{C_w})_0^i}{(\overline{C_w})_{min}^i - (\overline{C_w})_0^i} \right] \quad \overline{C_w} > 2\% \quad (7.46)$$

The exponential index i allows for a variation in the rate at which β decreases with $\overline{C_w}$. It is assumed that fibroblasts remain functional even in extreme hypoxic conditions and so a set minimal growth rate of $\beta = 0.04\beta_0$ is set for $\forall \overline{C_w} \leq 2\%$. All three growth functions are based on an initial value of $\beta_0 = 1.5$, chosen such that the circumferential stretch stabilises at $\lambda \approx 3.7$ after the first 15 years in the instance that the G&R model is not linked to the oxygen mass transfer model (based on findings by Watton et al. (2009b)).

A sensitivity analysis was conducted to explore the limits of the model described above to establish the impact of the combination of both the thrombus propagation rate ζ and the rate at which oxygen levels reduce fibroblast functionality β (by means of varying the exponential index i) on the expansion of the membrane. The following four growth functions (GF) presented within this Chapter demonstrated the most significant changes from the uncoupled G&R model and the relative importance of both ζ and β :

- GF1: $i = 1/16$, with a thrombus propagation rate of $\zeta = 2e^{-4}$ (eq. 7.25);
- GF2: $i = 1/4$, with a thrombus propagation rate of $\zeta = 2e^{-4}$ (eq. 7.25);
- GF3: $i = 1/4$, with a thrombus propagation rate of $\zeta = 5e^{-4}$ (eq. 7.25);
- GF4: $i = 1$, with a thrombus propagation rate of $\zeta = 2e^{-4}$ (eq. 7.25);

7.1.5 Summary of the coupled FSGT numerical model

The flowchart depicted in Figure 7.5 gives a visual summary of the iterative loop for solving the mathematical model of coupled FSGT. The governing equations for mechanical equilibrium of a cylindrical membrane (eqs. 7.18 and 7.19) are iteratively solved over a period of 30 years. A sensitivity analysis showed that a timestep of $dt = 0.005$ years is small enough to achieve independence in results whilst reducing computational costs. The membrane is set as the mid-plane through the arte-

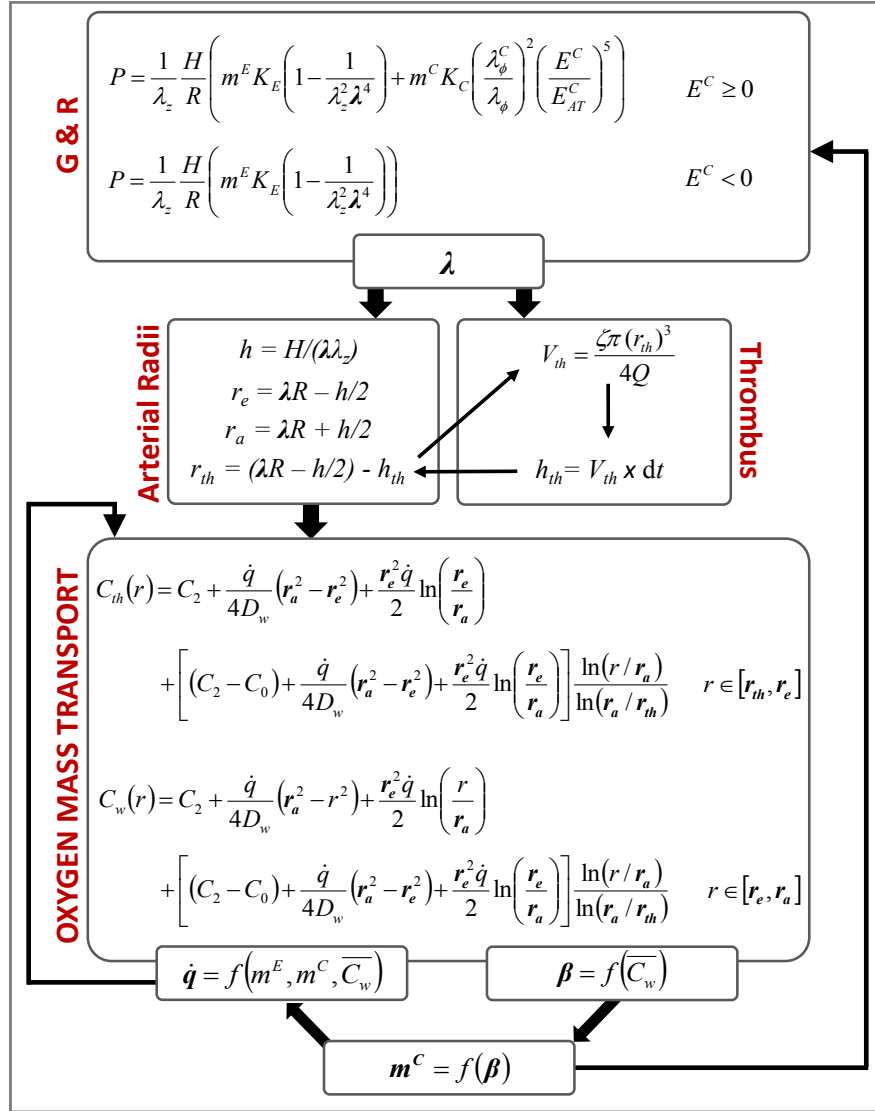


Figure 7.5: Iterative loop of the coupled growth and remodelling and oxygen mass transport model

rial wall, hence the endothelium and advential radii may be determined using the following expressions: $r_e = R\lambda - h/2$ and $r_a = R\lambda + h/2$. The thickness of the wall is calculated from the loaded configuration: $h = H/\lambda\lambda_z$ (as the cylinder is considered an incompressible material). The thrombus thickness is determined from the thrombus propagation velocity (eq. 7.25): $h_{th} = V_{th} \times dt$, allowing for the calculation of the inner thrombus radius $r_{th} = r_e - h_{th}$. The thickness of the thrombus and the wall are divided into 100 finite increments $dr_{th} : (r_a - r_e)/100$ and $dr_w : (h_{th})/100$

for which the oxygen concentration profiles $C_{th}(r_{th})$ and $C_w(r_w)$ are determined by solving equations (7.38) and (7.39) respectively. The average oxygen concentration through the arterial wall $\overline{C_w}$ allows for the computation of the new consumption rate $\dot{q}$ (eq. 7.41 and 7.42) and the new growth parameter β depending on the GF (eq. 7.46). The latter is then implemented into the linear differential equation for collagen concentration (7.23) when solving the governing equation for mechanical equilibrium in the next time step.

For comparison, the uncoupled G&R model is also simulated for $t = 30$ years, whereby λ is iteratively solved from the force balance equations (eqs. 7.18 and 7.19) with a constant collagen growth rate of $\beta = 1.5$.

7.2 ARTERIAL GEOMETRY, PHYSIOLOGICAL DATA AND MATERIAL PROPERTIES

All geometrical, physiological, material, flow, and mass transport properties are summarised in Table 7.1.

The dimensions of the cylinder are based on the internal carotid artery (ICA) such as the 3D patient-specific cases presented in Chapter 6: the average inlet radius was measured as 2.1 mm. The arterial wall thickness was taken as 20% of the vessel radius (Monson et al. (2005); Alastruey et al. (2007)). Based on this, the reference configuration radius of the mid-plane was calculated to be $R = 2.33\text{mm}$.

A constant volumetric flow rate is assumed through the section of ICA as the blood flow is continuously pumped around the Circle of Willis. Based on phenomenological data the initial shear rate is set to $\dot{\gamma}_0 = 400\text{s}^{-1}$ (Forsberg et al. (2000)). Given this, the volumetric flow rate for the healthy artery was calculated to be $Q = \dot{\gamma}\pi(r_e)_0^3/4 = 7.7e^{-6} \text{ m}^3/\text{s}$, whereby the initial endothelium radius is $(r_e)_0 = R\lambda - H/2 = 2.89\text{mm}$.

It is hypothesised that elastin initially bears 80% of the load, i.e. the initial pro-

Parameter Name	Variable	Value
Arterial Geometry		
Reference configuration radius	R	2.33 mm
Reference wall thickness ^a	$H = 0.2R$	0.46mm
Applied pressures		
Systolic pressure	P	16 kPa (120mmHg)
Axial pre-stretch ^b	λ_z	1.3
Ratio Systolic to Diastolic diameter	λ_D^S	1.1
Stretch values		
Circumferential stretch at systole	λ_0	1.30
Circumferential stretch at diastole	λ^R	1.18
Collagen attachment stretch	λ_{AT}^C	1.07
Initial collagen stretch	$\lambda_\phi^C _{t=0} = \lambda_{AT}^C$	1.07
Initial elastin stretch resolved in collagen direction	$\lambda_\phi _{t=0}$	1.30
Initial recruitment stretch	$\lambda^R _{t=0}$	1.21
Material Properties		
<i>Elastin</i>		
Initial normalised density	m_0^E	1
Initial load-bearing capacity	$P_0^{E:C}$	0.80
Material parameter	K_E	105 kPa
<i>Collagen</i>		
Initial normalised density	m_0^C	1
Initial load-bearing capacity	$1 - P_0^{E:C}$	0.20
Material parameter	K_C	30 kPa
Flow Properties		
Fixed volumetric flow rate	Q	$7.7e^{-6} m^3/s$
Mass Transport Properties		
Lumen oxygen concentration	C_0	0.1076 mol/m^3
Adventitial oxygen concentration	C_2	0
Diffusivity of oxygen through the wall	D_w	$0.9e^{-9} \text{ m}^2/\text{s}$
Initial consumption rate	$\dot{q}_0$	$1e^{-4} \text{ mol/m}^3/\text{s}$
Initial thrombus thickness	$(h_{th})_0$	0 mm
Initial endothelium radius	$(r_e)_0$	2.89 mm
Initial adventitial radius	$(r_a)_0$	3.17 mm

^a Monson et al. (2005)^b Monson et al. (2003)**Table 7.1:** Simulation input parameters for coupled G&R and mass transfer model of a cylindrical membrane

portion of load of the elastin is set to be $P_0^{E:C} = 0.8$. This enables automatic determination of the material constants K_E and K_C from equation (7.18) when $t = 0$:

$$K_E = P_0^{E:C} \frac{PR\lambda_z}{H} \left(1 - \frac{1}{\lambda_z^2 \lambda_0^4} \right)^{-1}, \quad K_C = (1 - P_0^{E:C}) \frac{PR\lambda_z}{H} \frac{\lambda_0^2}{(\lambda_{AT}^C)^2}. \quad (7.47)$$

Whereby the initial stretch in the collagen is equal to the attachment stretch: $\lambda_\phi^C|_{(t=0)} = \lambda_{AT}^C$. The pitch of collagen fibres is set to $\pm\phi = 30^\circ$ (considered that of collagen fibres within the medial layer (Holzapfel (2000))).

The properties of oxygen mass transport are those detailed in Chapters 4 and 6. An observation made from the coupled flow and mass transfer models in these previous chapters is that the normalised oxygen concentration throughout the lumen stabilises at 96% of that set at the inlet. With this in mind the value of oxygen at the lumen/wall (and subsequently the lumen/thrombus interface) was set to $C_0 = 0.1076 \text{ mol/m}^3$. Assuming that the oxygen diffused through the wall of the ICA is sufficient to supply the entire wall, the concentration at the adventitial boundary was set to $C_2 = 0$.

The phenomenological value of cellular respiration is believed to vary radially between $1e^{-3}$ and $1e^{-4} \text{ mol/m}^3/\text{s}$ (as discussed in greater detail in Chapters 4 and 6). From these results it is hypothesised that the lower of these two values allows for full oxygenation through the wall whilst maintaining a baseline oxygen tension value after cellular respiration, believed to allow for a rapid response should cells require oxygenation; such as is observed in *in vivo* trans-arterial measurements (Ninikoski et al. (1973); Santilli et al. (1995, 2000)). Implementing a initial value of $\dot{q}_0 = 1e^{-4} \text{ mol/m}^3/\text{s}$ within the mass transport equations (7.38) and (7.39) for the ‘healthy’ artery leaves an average baseline tension of $\left(\overline{C_w}\right)_0 = 48\%$ of the luminal value. Within a ‘healthy’ muscular cerebral artery the SMCs occupy approximately 70% of the medial layer (Walmsley (1983)), thus the initial percentage volume of respiration by SMCs within the wall is set to $V_0^S = 0.7$.

7.3 RESULTS

The iterative cycle shown in Figure 7.5 demonstrates the dependability of each parameter on each other: i.e. the WSR is dependent on the inner radius in contact with blood flow (i.e the thrombus/lumen interface r_{th}), which itself is dependent on the inner radius of the wall (r_e), and thus on the computed circumferential stretch (λ). λ is however dependent on the concentration of collagen fibres, which is regulated by the growth parameter β , calculated from the normalised average concentration of oxygen within the wall ($\overline{C_w}$), which itself is dependent on the thickness of thrombus in contact with the wall ($h_{th} = r_e - r_{th}$). For this reason, the results detailed in this section shall be presented in a somewhat linear manner so as demonstrate the consequence of one variable on the next: starting with the results of WSR for each GF ($\dot{\gamma}$). This is followed by results for the calculated thrombus propagation velocity V_{th} , the thrombus thickness h_{th} , the wall thickness h , the resulting normalised oxygen concentrations in the wall ($\overline{C_w}$) and thrombus ($\overline{C_{th}}$) layers, the calculated oxygen consumption rate $\dot{q}$ and collagen growth rate β . The latter is followed by the concentration of collagen m^C , the stretch in the collagen fibre λ_ϕ^C and the circumferential stretch λ . Lastly, the resulting radii calculated from λ : r_a , r_e and r_{th} are shown, from which h , h_{th} , and $\dot{\gamma}$ are defined, thus completing the cycle.

Figure 7.6 depicts the WSR at the lumen/thrombus interface for cases GF1, GF2, GF3 and GF4 over time. The inset A is a close up of the results after 5 years. Within the first five years the WSR drops from the initial physiological value of $\dot{\gamma}_0 = 400\text{s}^{-1}$ down to 40s^{-1} for all four cases. From this point in time, the WSR profiles demonstrate a power law decay over time of varying rates. At $t = 30$ years, $\dot{\gamma} = 10.6\text{s}^{-1}$ for GF1, $\dot{\gamma} = 8.4\text{s}^{-1}$ for GF2, $\dot{\gamma} = 3.5\text{s}^{-1}$ for GF3 and $\dot{\gamma} = 1.9\text{s}^{-1}$ for GF4.

The propagation velocity of thrombus V_{th} calculated from the local shear rates (eq. 7.25) for each case over time are shown in Figure 7.7. Within the first five years, the GF1, GF2 and GF4 profiles are identical, given the identical values of WSR and propagation rate ζ ; $V_{th} = 4.8e^{-3}\text{mm/year}$ at $t = 5$ years. Whilst cases

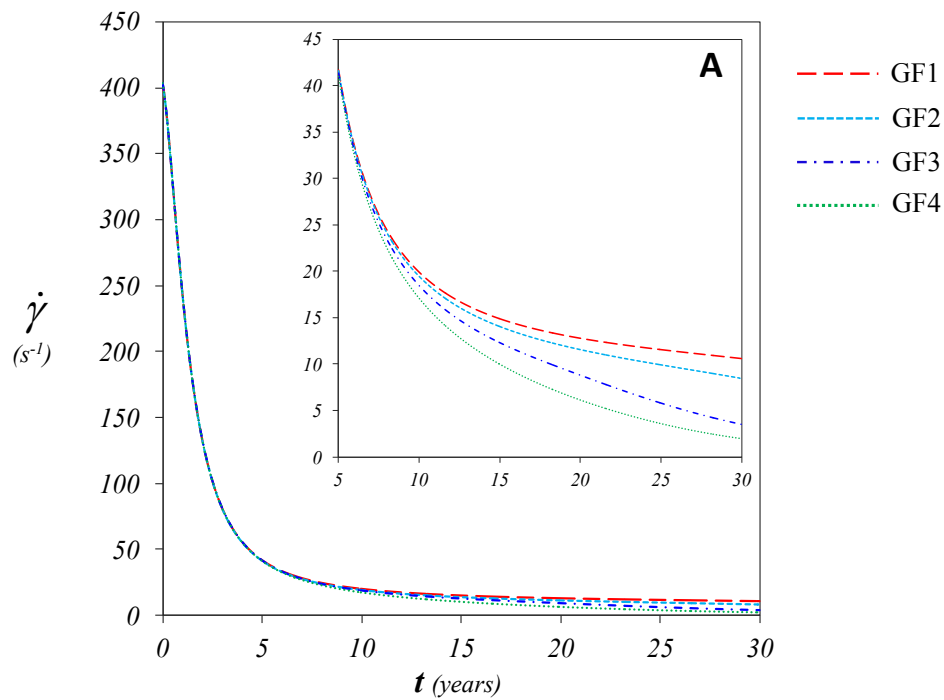


Figure 7.6: Shear rate at the inner radius (i.e. the lumen/thrombus interface r_{th}) over 30 years for each growth function. Inset A within the graph allows a closer look at the variation in shear rate after the first 5 years.

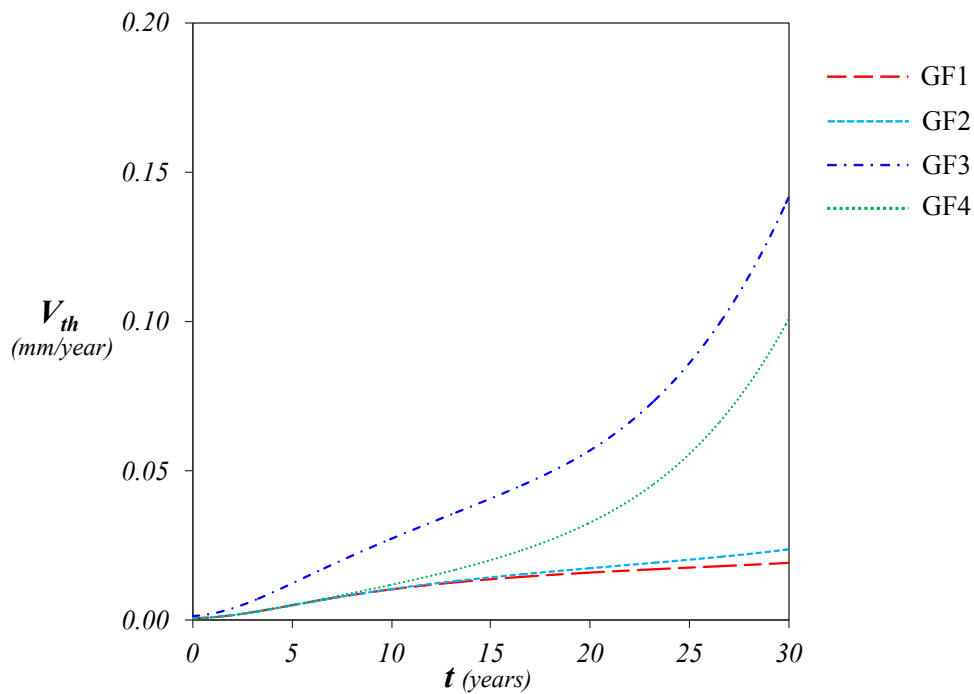


Figure 7.7: Thrombus propagation velocity (V_{th}) over 30 years for each growth function.

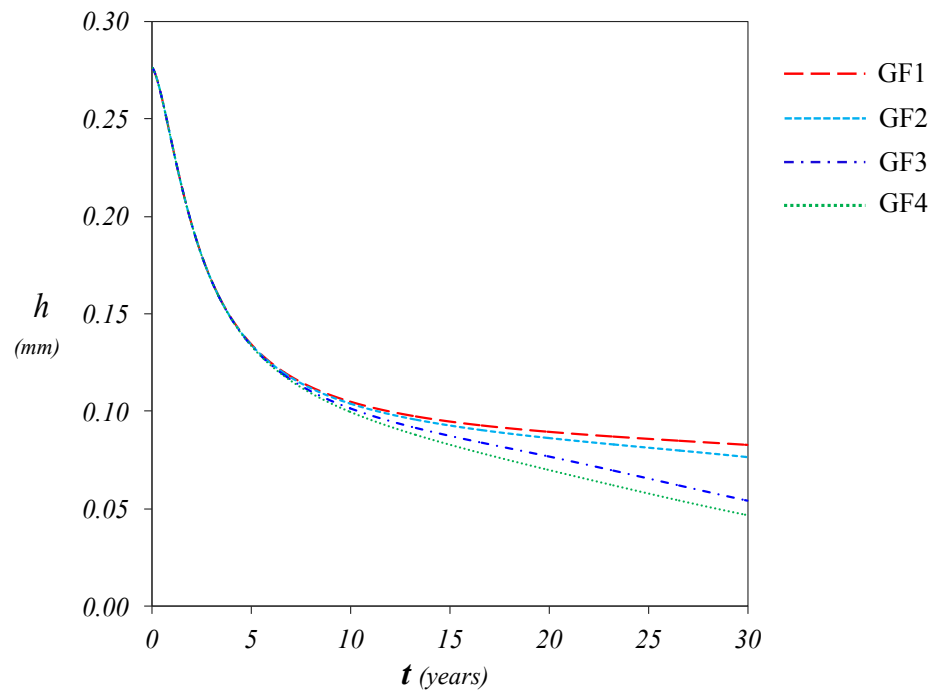


Figure 7.8: The thickness of the wall layer, h , with time for each GF

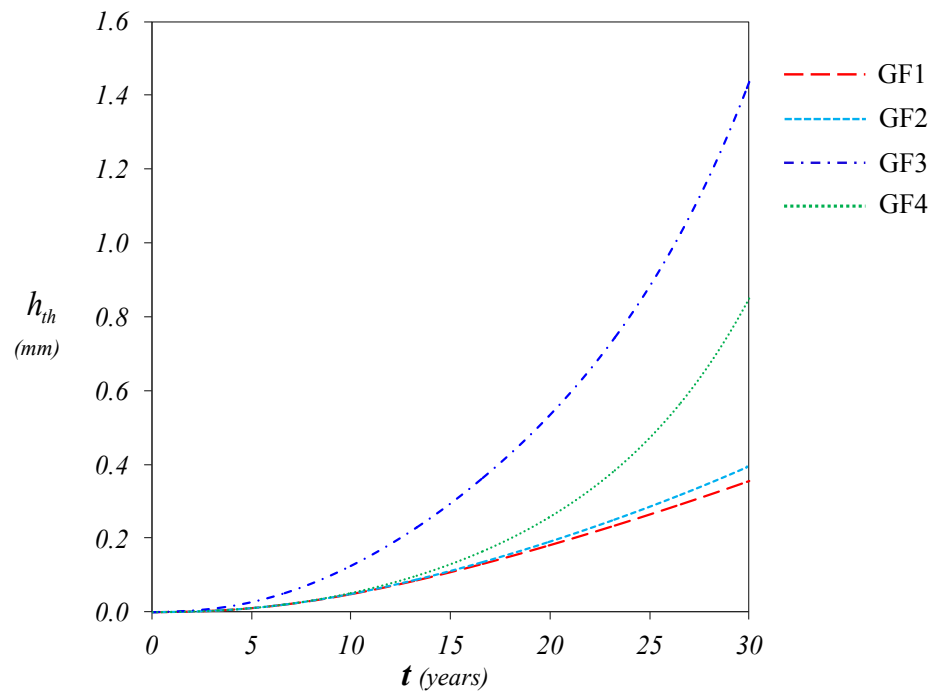


Figure 7.9: The thickness of the thrombus layer, h_{th} , with time for each GF

GF1 and GF2 demonstrate an approximately linear increase in V_{th} , the greater increase for GF4 is proportional to the greater drop in WSR: the final velocities are $V_{th} = 1.9e^{-2}$ mm/year for GF1, $V_{th} = 2.4e^{-2}$ mm/year for GF2 and $V_{th} = 0.1$ mm/year for GF3. The higher propagation rate, and greater decreases in WSR for GF3 results in a larger increase of V_{th} over time: $V_{th} = 1.2e^{-2}$ mm/year at $t = 5$ years and $V_{th} = 0.14$ mm/year at $t = 30$ years.

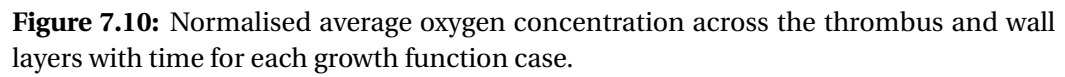
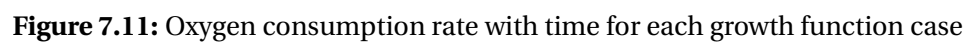
Figures 7.8 and 7.9 depict the wall thickness, h , and thrombus thickness, h_{th} with time respectively, for all four cases. As the arterial wall is assumed incompressible the thickness of the wall $h = H/\lambda\lambda_z$ (i.e. $h = r_a - r_e$) reduces as the cylinder radius increases. At $t = 5$ years, the thickness for all four cases has reduced from 0.27 down to 0.13mm, after which point the wall thickness reduces at different rates for each GFs. By $t = 30$ years, $h = 0.083$ mm for G&R, $h = 0.076$ mm for GF1, $h = 0.054$ mm for GF2, $h = 0.047$ mm for GF3 and $h = 0.040$ mm for GF4. The rate at which thrombus thickness increases is proportional to the propagation velocities. The initial development of thrombus over the first 10 years is concurrent for the GF1, GF2 and GF4 cases for which $\zeta = 1e^{-4}$: at $t = 10$ years the thickness is $h_{th} = 0.05$ mm in all three cases. Case GF3 has a higher thrombus propagation rate of $\zeta = 5e^{-4}$ which leads to a greater thickness of $h_{th} = 0.126$ mm within the first 5 years. Due to the diverging radial growth thereafter, the difference between each case is greater at the end of the simulation with final thicknesses of $h_{th} = 0.35$ mm for GF1, $h_{th} = 0.39$ mm for GF2, $h_{th} = 1.43$ mm for GF3, and $h_{th} = 0.85$ mm for GF4.

The average normalised oxygen concentration plots through the thrombus and wall layers, $\overline{C_{th}}$ and $\overline{C_w}$ respectively, for each GF are shown in Figure 7.10. The drop in $\overline{C_w}$ is proportional to the decrease in $\overline{C_{th}}$ over time for all four cases. For the first 9 years the drop in average oxygen concentration in both the thrombus and the wall is identical for Cases GF1, GF2 and GF4. The small difference in thrombus thicknesses between GF1 and GF2, lead to a very slight difference in $\overline{C}$ over the following 21 years; at $t = 30$ years the average oxygen tension within the wall has dropped from the initial value of $\overline{C_w} = 48\%$ to 2% for GF1 and 1% for GF2. The greater prop-

agation velocity of thrombus for GF4 results in a more significant drop in $\bar{C}$: the wall is completely devoid of oxygen by approximately 25 years. The significantly faster thrombus growth for GF3 also results in oxygen depletion within the wall by approximately 21 years. At the instance of complete oxygen depletion the average concentration across the thrombus has reached $\bar{C}_{th} = 48\%$ for both cases. Interestingly, the thrombus thicknesses for each GF does vary slightly: $h_{th} = 0.60\text{mm}$ for GF3 and $h_{th} = 0.46\text{mm}$ for GF4.

Figure 7.11 shows oxygen respiration rates versus time for all four cases. Cellular respiration is dependent on the average oxygen concentration within the wall, as well as the cellular content (i.e. the mass density of elastin and collagen). The first 5 years demonstrate a sigmoidal increase in oxygen consumption rate as a consequence of the changing mass densities of elastin and collagen (eq. 7.41 and 7.42). GF1, GF2 and GF4 reach a maximum respiration rate in the range of $2.75e^{-4}$ mol/m³/s. Due to the faster growth rate of thrombus and resulting faster drop in $\bar{C}_w$ for GF3 the respiration function $\mathcal{Q}(\bar{C}_w)$ (eq. 7.45) has a greater influence on the resulting respiration rate than the cellular content, thus $\dot{q}$ only reaches a maximum of $1.8e^{-4}$ mol/m³/s. After this point the oxygen consumption rate for all GFs rapidly decreases, the rate of which is proportional to the decrease in average oxygen tension across the wall. The final respiration rate reaches $\dot{q} = 0.42e^{-4}$ mol/m³/s for GF1 and $\dot{q} = 0.38e^{-4}$ mol/m³/s for GF2. As the average oxygen tension across the wall $\bar{C}_w \rightarrow 0$ the respiration rates for GF3 and GF4 reach a minimum of $\dot{q} = 0.27e^{-4}$ mol/m³/s and $\dot{q} = 0.28e^{-4}$ respectively.

Figure 7.12 demonstrates the collagen growth rate β versus time for all four cases. The growth parameter maintains the initial value of $\beta_0 = 1.5$ for the first 2 years, subsequently all four cases decrease towards the minimum $\beta_{min} = 4\%\beta_0$. The growth functions GF1, GF2 and GF3 are defined as power law functions that relate the decline in collagen growth rate to the average wall oxygen tension. Profiles for GF1, GF2 and GF3 decrease approximately linearly with time. For GF1, which has a smaller exponential index ($i = 1/16$) than cases GF1 and GF2 ($i = 1/4$), β declines



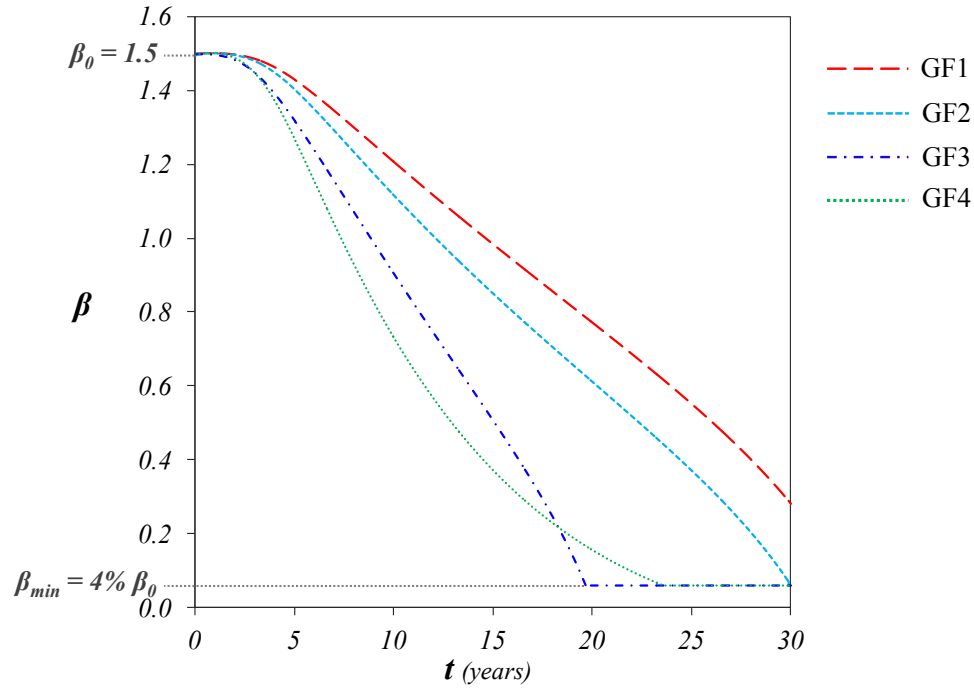


Figure 7.12: Collagen growth rate β with time for each growth function case

at the slowest rate. Given that the propagation rate of thrombus is larger for case GF3 ($\zeta = 5e^{-4}$) the greater decrease in oxygen tension over time leads to a faster downregulation of collagen production. Function GF4, which dictates a linear decrease in β with respect to $\overline{C_w}$ (i.e. a faster decrease than the power law functions), demonstrates a fairly quadratic decrease of collagen growth rate with time. The initial decrease is faster than GF3, but then decelerates as $\beta \rightarrow \beta_{min}$ (as $\overline{C_w} \rightarrow 0$) at approximately $t = 25$ years.

Figures 7.13, 7.14 and 7.15 illustrate the evolution of the concentration of collagen fibres m^C , collagen fibre stretch λ_ϕ^C and circumferential stretch λ with respect to time respectively. The dark blue and green dots demonstrate the temporal points at which the average oxygen concentration within the wall has reached naught for the GF3 and GF4 cases respectively. In the instance of the uncoupled G&R case, the growth of the membrane becomes stabilised over the course of time. The exponential decay of elastinous material (see Figure 7.3) results in the exponential increase in collagen stretch in the first 5 years due to the transference of load from the elastin to the collagen. Over time, the rate at which collagen concentration increases allows

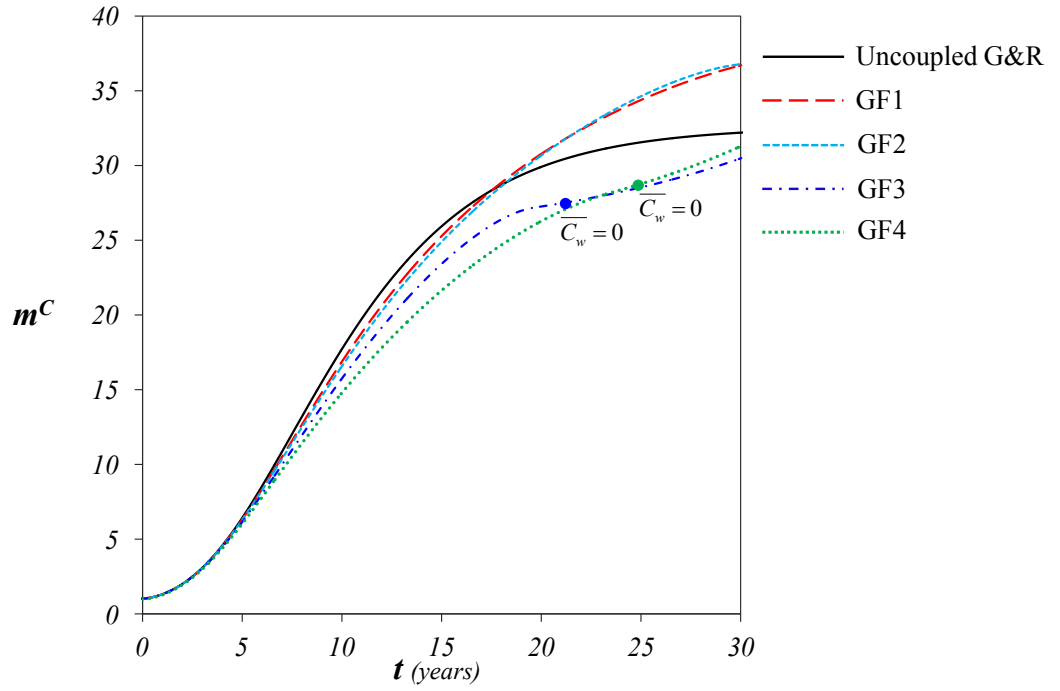


Figure 7.13: Comparison of collagen mass density evolution with time for the uncoupled G&R and coupled GRM models. Dark blue and green dots highlight the temporal points at which $\overline{C_w} = 0$ for GF3 and GF4 respectively.

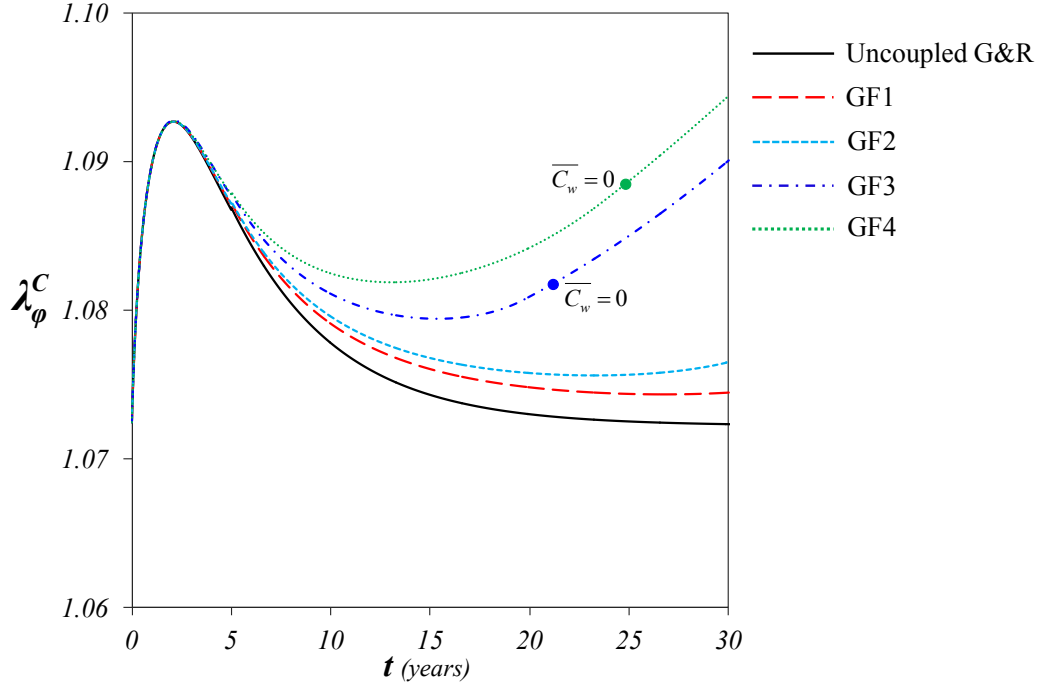


Figure 7.14: Stretch in the collagen fibres for the uncoupled G&R and coupled GRM models. Dark blue and green dots highlight the temporal points at which $\overline{C_w} = 0$ for GF3 and GF4 respectively.

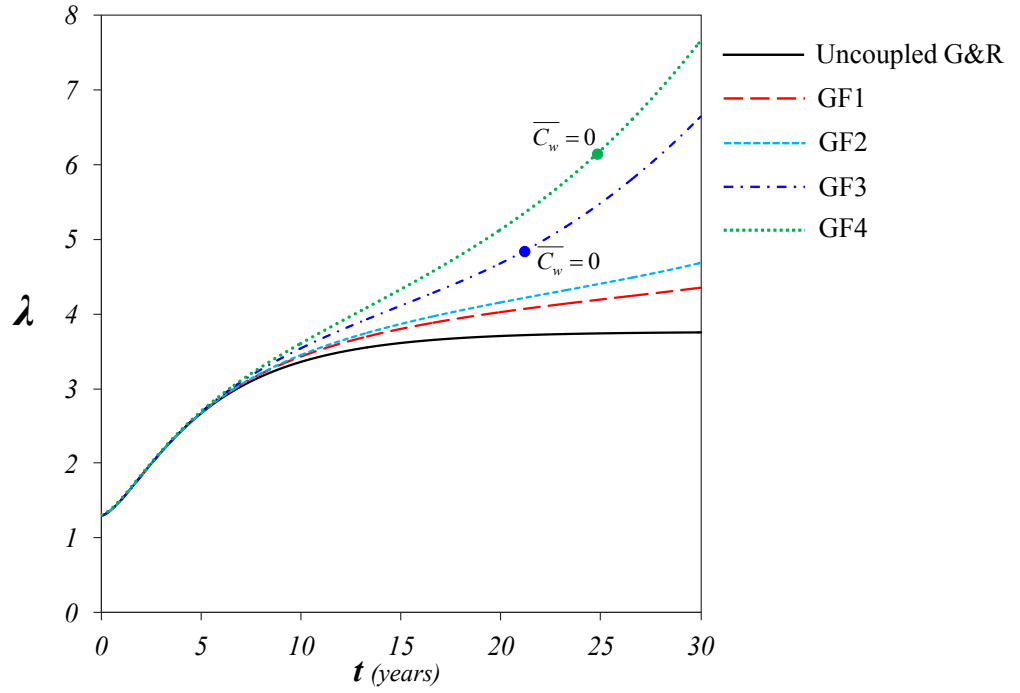


Figure 7.15: Circumferential stretch of the cylinder with time for the uncoupled G&R and coupled GRM models. Dark blue and green dots highlight the temporal points at which $\overline{C_w} = 0$ for GF3 and GF4 respectively.

for the stretch in collagen to be restored towards the attachment stretch as a consequence of maintaining mechanical equilibrium. By $t = 15$ years, $\lambda_\phi^C \rightarrow \lambda_{AT}^C = 1.07$ and the rate at which collagen fibre concentration increases begins to decelerate towards a stable value of $m^C = 32$, resulting in the stabilisation of the membrane as the circumferential stretch tends towards $\lambda = 3.75$.

Conversely, the continual increase in λ with time for cases GF1, GF2, GF3 and GF4 all demonstrate the continual enlargement of the cylindrical membrane when coupling wall oxygen tension to collagen production rates. Over the first 5 years, the insignificant growth of thrombus, and consequently the limited reduction in oxygen concentration within the wall does not significantly decrease the rate of collagen production. Thus, the initial values for λ , λ_ϕ^C and m^C do not differ from the uncoupled G&R case. After this 5 year time point, the overall decline of β leads to a slower production rate of collagen fibres. The notable difference in β values for GF1 and GF2 lead to a relatively insignificant difference in m^C values between these two

cases. In both instances the mass of collagen is fractionally lower than the uncoupled case up until $t \sim 18$ years, after which point the continually evolving membrane leads to the continual increase until a maximum value of $m^C = 37$. For cases GF3 and GF4 the rate of increase in m^C is significantly slower, once more in proportion to the respective β profiles over time: the value reaches a maximum of $m^C = 30$ for GF3 and $m^C = 31$ for GF4. The stretch in collagen λ_ϕ^C initially tends towards λ_{AT}^C for all four cases before diverging away as the concentration of collagen fibres is not sufficiently upregulated to reach a new mechanical equilibrium. The rate at which the divergence occurs is far greater for cases GF3 and GF4 than for GF1 and GF2. At $t = 30$ years the stretch in the collagen is $\lambda_\phi^C = 1.074$ for GF1, $\lambda_\phi^C = 1.076$ for GF2, $\lambda_\phi^C = 1.09$ for GF3 and $\lambda_\phi^C = 1.094$ for GF4.

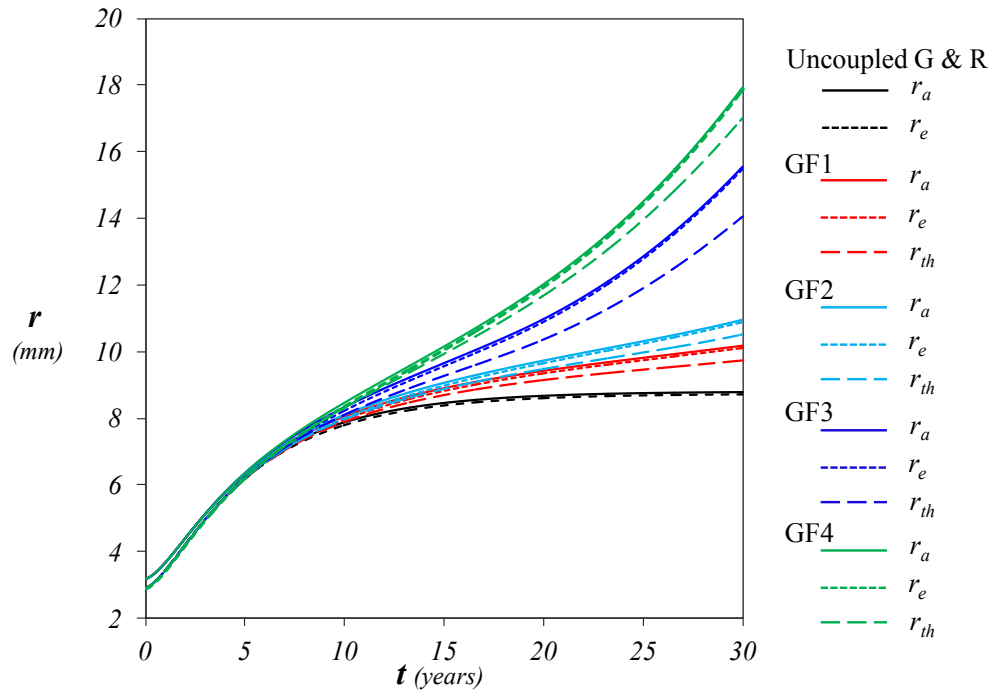


Figure 7.16: Endothelium, adventitia and thrombus radii versus time for uncoupled G&R model and coupled GRM model with varying growth functions.

Figure 7.16 shows the resulting radial expansion of the cylinder with time: the endothelium and adventitia radii, r_e and r_a respectively, demonstrate the growth of the cylinder (and thinning of the wall) over time, whilst the thrombus radius r_{th}

shows its propagation. It can be seen that the uncoupled G&R case begins to stabilise after 15 years of growth with a final endothelium radius of $r_e \approx 8.7\text{mm}$. In correlation with the development of circumferential stretch λ , the GF1, GF2, GF3 and GF4 models do not reach a stable radius during the 30 year time frame. The radii for all four GFs do not differ from the uncoupled case when $0 < t < 5$ years. Thereafter, GF1 and GF2 show a fairly linear expansion over time, whilst GF3 and GF4 demonstrate a cubic expansion over time. The final endothelial radii at $t = 30$ years is $r_e = 10.1\text{mm}$ for GF1, $r_e = 10.9\text{mm}$ for GF2, $r_e = 15.5\text{mm}$ for GF3 and $r_e = 17.9\text{mm}$ for GF4. The final thrombus radii (i.e the lumen/thrombus interface) at $t = 30$ years is $r_{th} = 9.75\text{mm}$ for GF1, $r_{th} = 10.51\text{mm}$ for GF2, $r_{th} = 14.07\text{mm}$ for GF3 and $r_{th} = 17.05\text{mm}$ for GF4. In each instance, the inner radii diverge away from the original value of $(r_e)_0 = 2.89\text{ mm}$, resulting in the continual decrease in WSR as displayed in Figure 7.6. Thus, completing the iterative cycle.

7.4 DISCUSSION AND FUTURE CONSIDERATIONS

GF1 and GF2 define the decline in β relative to the average oxygen tension $\overline{C_w}$ by means of a power law function (eq. 7.46) with exponential indices $i = 1/16$ and $i = 1/4$ respectively (i.e $\beta(i = 1/16)$ declines at a slower rate than $\beta(i = 1/4)$) and a thrombus propagation rate of $\zeta = 2e^{-4}$ for both cases. The ensuing thrombus propagation velocity computed for these two GFs does not vary greatly and thus the difference in average consumption rates across the thrombus and wall layers is fairly insignificant. However, the thrombus thickness is great enough to lead to $\overline{C_w} \rightarrow 0$, and hence $\beta \rightarrow \beta_{min}$ as $t \rightarrow 30$ years. The difference in decrescence rates between $\beta(i = 1/16)$ versus $\beta(i = 1/4)$ results in a very small difference between values for m^C in each case. Although this difference may seem slight, the stretch in the collagen fibre λ_ϕ^C required to maintain mechanical equilibrium is greater for GF2, highlighting the sensitivity of this variable. GF3 demonstrates the effect of a higher thrombus propagation rate ($\zeta = 5e^{-4}$) on the collagen growth rate. The specific function for β is the same as GF2, nonetheless, the faster development of thrombus results in $\overline{C_w} \rightarrow 0\%$

and $\beta = \beta_{min}$ by $t = 21$ years. The faster decrease in β leads to a slower increase in m^C than GF1 and GF2, resulting in an even greater increase in collagen fibre stretch in order to maintain mechanical equilibrium. In comparison to the three other GFs, GF4 prescribes a linear decrease in β with $\overline{C_w}$, whilst maintaining the slower thrombus propagation rate of $\zeta = 2e^{-4}$. Although the initial decrease in $\overline{C_w}$ is approximately identical with GF1 and GF2 within the first 13 years, β has reduced to a third of the initial value. The significantly slower rate of collagen formation for GF4 at this time point leads to the greatest divergence in λ_ϕ^C away from λ_{AT}^C , and thus the greatest expansion of the membrane (i.e the largest λ) over time. Nonetheless, this case does not simulate the greatest increase in thrombus thickness even though there is a point in time at which the wall is subject to anoxia: when $\overline{C_w} = 0\%$ the thrombus thickness is $h_{th} = 0.60\text{mm}$ for GF3 and $h_{th} = 0.46\text{mm}$ for GF4. The respiration function $\mathcal{Q}(\overline{C_w})$ (eq. 7.45) is equal for each case, however the mass density of collagen is actually greater for GF4, resulting in the higher rate of $\dot{q} = 0.28e^{-4}\text{mol/m}^3/\text{s}$ compared to $\dot{q} = 0.27e^{-4}\text{mol/m}^3/\text{s}$ for GF3. This compounds the idea that the possible hypoxic environment created by the presence of a thrombus may not only be related to the thrombus thickness, but also to the increased cellular composition of the wall and the respective O_2 consumption rates as a consequence of aneurysm expansion.

Overall, all four GFs proposed resulted in the continual expansion of the membrane over the 30 year timeframe. The mass density of collagen is limited by the gradually hypoxic conditions within the wall as a result of the growing thrombus layer. If the concentration in collagen fibres does not increase at a sufficient rate, the existing fibres undergo a greater stretch in order to maintain mechanical equilibrium: i.e λ_ϕ^C diverges away from λ_{AT}^C , resulting in an unstable evolving membrane over time.

It is important at this point to state why the continual growth of the membrane may be considered unstable. Collagen can only undergo a 3-5% extension in length before rupturing (Kroon (2010)). Should the normal stretch in collagen fibres have a normal physiological (stable) value of $\lambda_\phi^C = \lambda_{AT} = 1.07$, this means the ‘rupture’

stretch would be in the range of 1.10 to 1.20. Although none of the cases have reached this point, should the aneurysm continue to expand after the 30 year time-frame, it is possible to speculate that all four GFs could result to fatal rupture of the collagen fabric. However, this is assuming that the fibroblast may survive for such long periods in anoxic conditions. The temporal points in Figures 7.15, 7.14 and 7.13 (dark blue for GF3 and green for GF4) show the point at which $\overline{C_w} = 0\%$. Fibroblasts, like any other cells, require a minimum of oxygen in order to function. Should the hypoxic environment become chronic, or gradually anoxic, then cells will ultimately die, either through energy depletion or through oxidative damage (discussed in greater detail in Section 1.5.2). In this instance, the cessation of fibre deposition by fibroblasts and the decay of already deposited collagen fibres (which have a 30 day half life) could result in the yielding of the aneurysm wall. Thus, it is possible to hypothesise that all four cases would predict aneurysm rupture through anoxia, even before mechanical failure as the stretch in the collagen reaches the critical ‘rupture’ fibre stretch.

The work presented within this Chapter demonstrates the potential of modelling the possible detrimental effects of thrombus on IA progression. Nonetheless, this conceptual 1D-cylindrical FSGT model has its limitations which can only be approved upon so as to gradually step closer to a fully multi-scale, multi-physics model of IA evolution. For example, the effect of local oxygen tension on fibroblast functionality merits further development. As discussed in Chapter 1, fibroblasts have a crucial role in lesion repair. Injury to the artery wall may result in a hypoxic microenvironment due to obstruction of oxygen delivery to the affected area. The proliferative capacity of fibroblasts is significantly regulated by this stimulus (Agocha et al. (1997); Stenmark et al. (2002); Sakamoto and Seiki (2010)). As these cells invade the wound, several mechanisms are triggered at once. In the first instance the synthesis of ‘immature’ collagen is upregulated and MMPs are downregulated in order to rebuild the ECM. The simultaneous release of growth factors, such as vascular endothelial growth factor (VEGF) leads to angiogenesis, providing a new network of

oxygen supply to the affected site (which is also clinically observed in both the wall and the thrombus layers of partially thrombosed IAs (as shown in Figure ??)). The fresh delivery of oxygen not only restores cellular aerobic respiration, but also allows for the hydroxylation (an oxidative process) of collagen molecules for fibril formation. The latter is essential for the deposition of ‘mature’, stable collagen into the ECM (Yamauchi and Shiiba (2008)). Whilst this model does take into account the effect of chronic hypoxia on the functionality of fibroblasts, it does not take into account the adaptive responses to transient hypoxia. Although Steinbrech et al. (1999) demonstrated that a prolonged exposure to hypoxic conditions ($\sim 2\%O_2$) lead to a downregulation of collagen synthesis by fibroblasts to $\sim 4\%$ of the baseline value, it was also shown that within the first 24hrs the synthesis is actually greatly increased to 170% of the baseline. Furthermore the same studies demonstrated a 470% increase in VEGF mRNA. Thus, the FSGT model could be adapted to take into consideration the preliminary upregulation of collagen fibre density, as well neovascularisation, in the preliminary ‘transient’ instances of hypoxia during the first stages of thrombus formation.

In terms of thrombus growth, a basic WSR-modulated propagation velocity is utilised for this mathematical model. Although this formulation successfully demonstrates the dynamic progression of thrombus as a consequence of IA evolution it is an oversimplification of the biocomplexity that is the coagulation cascade (Figure 1.8). Modelling of the coagulation cascade is out of scope for this work but it has substantial potential for future developments of multi-scale FSGT. Whilst exhaustive models of the coagulation cascade are already in development (e.g Bowker et al. (2010); Xu et al. (2010)) it is speculated that the computational demands of direct coupling to G&R models may still be too expensive. Thus, in the short term, it is suggested that further developments should be limited to a refined shear-modulated thrombus growth models.

Furthermore, it is important to note that the thrombus was modelled as a homogeneous solid which has no effect on the stress distribution throughout the wall.

Nonetheless thrombus is a biologically active material which not only affects the local inflammatory and proteolytic environment of both the thrombus and wall (see Section 1.4.4.1), but also affects local stress distributions (see Section 1.4.3). In terms of biomechanics, thrombus is speculated to exhibit a poroviscoelastic behaviour (Thubrikar et al. (2003); Boschetti et al. (2007)). The porosity of the material is believed to allow the transport of pressure through the pores themselves, hence reducing the observed pressure drop across the thrombus (Speelman et al. (2010)). Moreover it is speculated that the mechanical properties of thrombus evolve as the clot expands (Karsaj and Humphrey (2009)), as a result of variations in elasticity and extensibility as the fibrinous clot forms (Liu et al. (2006); Vande Geest et al. (2006); Lee et al. (2007)): i.e. the added mechanical contribution of the collagenous material as the thrombus becomes a stabilised tissue. Hence it may be speculated that there is some counterbalance to the detrimental effect of oxygen depletion should the mechanical properties of thrombus be taken into account within adaptations to this model. Adapting to model to be a porous medium, not only from a biomechanical perspective but it also offers the possibility of modelling neovascularisation through the thrombus and wall domains by adapting the domain porosity and permeability to oxygen.

Looking at the G&R model itself, the theoretical framework implements an elastinous and collagenous cylindrical membrane as a representation of an artery. The wall was represented as a single homogeneous layer, whereby the majority of collagen G&R is assumed to be that of the medial layer. However, the distribution and orientation of collagen fibres differs between the adventitia and medial layers, each providing a specific support to the mechanical equilibrium of the vessel (Canham et al. (1999)). Thus, a heterogeneous multi-layered approach is necessary to take into consideration the individual contribution of both the medial and adventitial layer of the arterial wall. Furthermore, this FGST model only takes into account the passive mechanical response of the elastin and collagen within the ECM, whilst disregarding the passive and active responses provided by the SCMs

within the medial layer. Nonetheless, experimental data demonstrates the significant impact of SMC contraction and relaxation on stress distributions within the artery (Matsumoto et al. (1996)). Based on this, a limited number of studies (in comparison to the extensive models incorporating solely the passive responses of elastin and collagen) have proposed constitutive models for incorporating both passive and active responses of SMCs (e.g. Rachev and Hayashi (1999); Masson et al. (2008); Yosibash and Priel (2012)). These models relate SMC contribution to the circumferential stretch (whereby the SMCs are circumferentially aligned) and the local chemical concentration. In terms of the later, the SMCs respond to intracellular biochemical signals by means of mechanotransduction (Shi and Tarbell (2011)); in particular, vessel vasoconstriction and vasodilation in response to local pressures has been linked to the SMC response to the concentration of intracellular free calcium, Ca^{2+} (Hill et al. (2001)). To a smaller extent, the local levels of CO_2 and O_2 have also been shown to affect the regulation of SMC contractility. Thus, the incorporation of models such as that proposed by Murtada et al. (2010), which link Ca^{2+} to SMC activation, could be sophisticated to also take into consideration the possible regulation of SMCs by O_2 , thus strengthening the biochemical formulation of the FSGT model. To take it one step further, the SMC phenotype could also be taken into consideration. As discussed in Section 1.1.2.1, the sessile contractile phenotype can dedifferentiate to a synthetic phenotype during disease or injury in order to migrate, proliferate and synthesise matrix proteins - the occurrence of the latter will ultimately disrupt the mechanical balance within the wall. Further sophistication (and most importantly understanding) is thus required in order to link the complex interplay between the mechanical environment and SMC functionality.

The initiation of membrane expansion was prescribed by an exponential decay of elastin over the first five years, therefore triggering the growth and remodelling of the collagenous fabric in order to maintain the mechanical equilibrium of the membrane. Taking example from Watton et al. (2011a,b), the critical WSS at which EC may dysfunction could be explicitly linked to the subsequent degradation of the

elastinous constituents. Thus, by linking the cyclic deformation of the membrane (i.e. solving for pulsatile flow) to the FSGT model it would be possible to link physiologically realistic haemodynamic stimuli to the propagation of thrombus (i.e. WSR) and the degradation of elastin (i.e. WSS). Based on comparative simulations carried out by Back (1976) and Tada (2010), which demonstrated qualitatively similar mass transport distribution patterns in both steady and pulsatile flow conditions over the course of multiple cardiac cycles, the simulations carried out within this thesis have assumed a steady flow in order to keep computational costs to a minimum. However, due to the pulsatile nature of blood flow, the variability of convective flux induces a variation in oxygen concentration over the cardiac cycle itself, which may or may not affect the biomechanical stability of the wall. To the Author's knowledge this is the first coupled G&R and oxygen mass transport model, and thus the possible effects of pulsatility need to be explored. It has already been mentioned that the thrombus and wall layers may better be represented as porous mediums. Experimental measurements of filtration velocities through the arterial wall (Back (1976); Tedgui and Lever (1984)) and calculated filtration velocities through the thrombus (Chapter 4) are 2-3 orders of magnitude lower than oxygen diffusion velocities, thus why radial convective transport was disregarded for this preliminary model, nonetheless their inclusion would not only add phenomenological precision, but would also allow for the modulation of convection velocities as the cellular content alters (i.e. such as the increased porosity as a result of neovascularisation as an adaptive response to hypoxia).

Another key element of the transport model is the consumption term $\dot{q}$, which regulates the rate at which cells respire: it was shown that $\dot{q}$ also has an effect on how quickly the wall may be depleted of oxygen due to the increase in cellular demand as the aneurysm evolves. The concentrations of SMCs and fibroblasts are deemed proportional to the mass density of elastin and collagen respectively, however this may not be phenomenologically accurate. The earlier proposed heterogeneous multi-layered adaptation to the G&R framework would allow for a greater ap-

proximation of cellular density, and also the possibility of including the radial variability of $\dot{q}$ observed within experimental data (Buerk and Goldstick (1982); Crawford et al. (1983); Barron et al. (1996)). In particular, a greater consumption rate is observed within the medial layer (Buerk and Goldstick (1982)) which is believed to be linked to the energy required by SMCs to maintain vascular tone. This point reinforces the need for including SMC within the FSGT model, thus permitting the direct link between the local oxygen levels and SMC concentration and functionality.

For simplicity, a consumption term was not allocated to the transport of oxygen within the thrombus layer, as the layer is deemed to be composed of very few cellular components. However, the differentiation of blood cells into fibroblasts, macrophages, ECs and SMCs during thrombus organisation (Leu et al. (1988); Szikora et al. (2006a); Lee et al. (2007)) would suggest a degree of respiration by these cells in order to function (even though fibroblasts and macrophages only require a minimum due to their proliferative capacities in hypoxic conditions). Therefore, a consumption term for the thrombus layer would need to be taken into account when solving the convection-diffusion of O_2 so as to establish whether this would further deplete the arterial wall of oxygen.

7.5 CONCLUDING REMARKS

The proposed FSGT model links the average oxygen tension within the wall to the rate at which the fibroblasts synthesise collagen fibres. Two different parameters are explored: the rate at which thrombus propagates relative to the local WSR (ζ), and the rate at which the collagen synthesis is downregulated as the oxygen tension within the artery is reduced due to the presence of thrombus (β). In all instances it was observed that the wall is subjected to hypoxic conditions as a result of thrombus propagation. Furthermore, when coupling this oxygen deficiency to fibroblast functionality, the rate at which collagen fibre mass density increased was not fast enough to compensate for the transfer in load from the deleted elastin to the colla-

gen, thus resulting in the over stretch of the fibres that are already deposited, and thus the continual expansion of the membrane. Furthermore this occurs regardless of the rate of thrombus propagation or the rate at which fibroblasts downregulated the production of collagen, these parameters simply dictate the timeframe in which this occurs. To date, the thickness of the thrombus has been greatly discussed as a major parameter leading to hypoxia, however an increase in collagen fibres concentration as a consequence of rapid expansion of the wall accentuates the dominance of cellular respiration rates on oxygen distribution across the wall.

Although, the variables within the proposed framework were defined with a phenomenological basis behind them, this 1D cylindrical model has its limitations. The biomechanical and biochemical representations of both the wall and thrombus layers merit further development before FSGT models such this can be implemented to patient-specific modelisation of IAs. Nevertheless, this novel chemo-mechano-biological mathematical model of intracranial aneurysm evolution is a step further towards modelling of the whole cycle of IA evolution, from its initiation and progression, to the possible detrimental effects of embolisation.

CONCLUSIONS AND CONSIDERATIONS FOR MODEL DEVELOPMENT

Preliminary feasibility studies of oxygen transport were conducted in a 2D axisymmetric computational fluid dynamics (CFD) model of a thrombosed artery in the aim of setting up simulation parameter for the subsequent 3D modelling of patient-specific aneurysms. Based on the conclusive findings of published computational studies of oxygen transport within arteries, the coupled FM model proposed takes into consideration the ‘fluid-side’ and ‘wall-side’ mass transport of oxygen. The arterial wall and thrombus were considered homogeneous layers across which convection-diffusion-reaction equations were solved. The convection and diffusion of oxygen within the blood filled lumen took into consideration both the oxygen present as dissolved free state in plasma, and that bound to haemoglobin. A uniform consumption rate ($\dot{q}$) was applied to the wall layer to take into account the respiration of oxygen by arterial cells (e.g. ECs, SMCs, fibroblasts). The variability of reported consumption rates within the literature led to the evaluation of varying degrees of respiration on oxygen wall tension. A total of five thickness values are modelled to establish whether there is a correlation between the thrombus depth and the level of hypoxia within the wall: $\delta_{th} = 0.025, 0.05, 0.1, 0.15$ and 0.2mm . The parametric studies conducted demonstrate the importance of both cellular respiration and thrombus thickness on oxygen distribution throughout the wall. Universally, the presence of thrombus, however thick, will limit the delivery of oxygen to the wall to some extent. However, the greater the cellular demands, the greater the impedance of the thrombus on oxygen delivery to the thrombus/wall interface: for a thickness of $\delta_{th} = 0.2\text{mm}$, a consumption rate of $\dot{q} = 1e^{-4}\text{mol/m}^3/\text{s}$ results in a $\approx 10\%$ reduction from the oxygen tension observed in the ‘healthy’ (i.e. no throm-

bus) artery case, whilst a consumption rate of $\dot{q} = 1e^{-3}\text{mol/m}^3/\text{s}$ results in a $\approx 55\%$ reduction. When modelling thrombus as a porous medium, the added filtration velocity through the layer has an evident influence on oxygen transport to the wall when the thrombus is relatively thin. The contribution of convective oxygen flux becomes less significant as the thrombus thickness $\delta_{th} \rightarrow 0.2\text{mm}$, i.e. the transport distance is such that oxygen transport becomes diffusion limited.

This 2D axisymmetric model was subsequently adapted to simulate coupled FM of oxygen transport within patient-specific IAs, with the aim of exploring factors thought to predispose the formation of thrombus, as well as the effect of a thrombus layer on oxygen tension levels within the aneurysm dome and wall. The ‘fluid-side’ and ‘wall-side’ mass transport properties of O_2 remained as defined within the 2D model. However, due to the computational intensity of solving the convection-diffusion of oxygen through a porous medium, and the substantial thickness of majority of the layer ($\delta_{th} = 0.4\text{mm}$), the convective flux was disregarded when simulating oxygen transport within these patient-specific IA models. Once again, a single oxygen consumption was implemented; the higher physiological rate of $\dot{q} = 1e^{-3}\text{mol/m}^3/\text{s}$ was chosen in order to take into account the higher respiratory demands of certain cells within the wall (i.e SMCs). Two particular patient-specific geometries were modelled: named the VISC and the OX12 cases. A comparison of both cases highlights the limiting effect of low velocity recirculations within the dome on oxygen distribution in an IA presenting with a very high aspect ratio (i.e a narrow neck and high sack height) such as case OX12: approximately 50% of the dome surface is completely deprived of oxygen due to the diffusion limited transport in regions of near-stagnant flow and the high cellular demands of the wall. The VISC case was also manipulated so as to explore two different scenarios: (i) untreated versus treated and (ii) presenting with a layer of thrombus of varying thickness: $0 < d_{th} < 0.4\text{mm}$. A reduction in intrasaccular flow as a consequence of stent deployment across the neck resulted in a difference in the rate at which ‘fresh’ oxygenated blood reaches the lumen/wall interface within the sac, nonethe-

less over the course of time (i.e. when steady state is achieved) the O_2 levels within the aneurysmal wall itself does not differ from that of the untreated case. The presence of thrombus results in a dramatic reduction in oxygen delivery to the wall as $d_{th} \rightarrow 0.4\text{mm}$: the levels observed are considered hypoxic as $\hat{C}_{O_2} \rightarrow 1\%$. Should the lumen/wall interface reach the maximum available oxygen tension, the high respiration rate prescribed to the wall results in complete absorption of the available oxygen within 50% of the wall thickness. This reduces down to 1% of the wall thickness in the instance that the oxygen level at the thrombus/wall interface tends towards $\hat{C}_{O_2} \rightarrow 1\%$. Thus, as observed within the 2D framework, the overall oxygen distribution through the wall layer is limited by the imposed uniform cellular respiration rate.

Finally, a novel fluid-solid-growth-mass transport (FSGT) mathematical model was conceived to explore the possible detrimental effect of thrombus on the evolution of an IA. The importance of haemodynamic and mechanical factors on aneurysm progression have led to the emergence of mathematical modelling of aneurysm evolution governed by the Growth and Remodelling (G&R) of collagenous material as an adaptation to redistributions in load as other components degrade. A conceptual cylindrical G&R model was extended to include (i) model dynamic thrombus propagation with respect to local wall shear rates; (ii) mass transport of oxygen through the enlarging thrombus and thinning wall; (iii) link local oxygen levels to the rate at which fibroblasts synthesise collagen fibres as the IA evolves. Two different parameters were explored: the rate at which thrombus propagates relative to the local WSR (ζ), and the rate at which the collagen synthesis is downregulated as the oxygen tension within the artery decreases due to the presence of thrombus (β). In each case, the mass density of collagen is limited by the gradually hypoxic conditions within the wall as a result of the growing thrombus layer. As the concentration in collagen fibres does not increase at a sufficient rate, the existing fibres undergo a greater stretch in order to maintain mechanical equilibrium: i.e λ_ϕ^C diverges away from λ_{AT}^C , resulting in an unstable evolving membrane over time. Variation in the

aforementioned parameters dictates the rate at which aneurysm expansion occurs: the greatest instability is observed when thrombus propagation and the decrease in β with respect to local oxygen concentrations is accelerated.

Whether as a result of obstruction due to the presence of thrombus, or due to the limit transport of O_2 as a consequence of near-stagnant intrasaccular flow, the observed hypoxic environment is hypothesised to predict a higher risk of wall rupture as cells subjected to anoxia will ultimately die, either through energy depletion or through oxidative damage. These findings validate the need for a greater understanding of the possible detrimental impact of a hypoxic environment on wall functionality so as to ensure optimum patient care when diagnosing risk of rupture and choosing a tailored treatment plan. The ultimate goal of this line of research is a full multiscale, multiphysics system for evaluating patient-specific long-term vascular behaviour, such as demonstrated in the Schematic depicted in Figure 8.1.

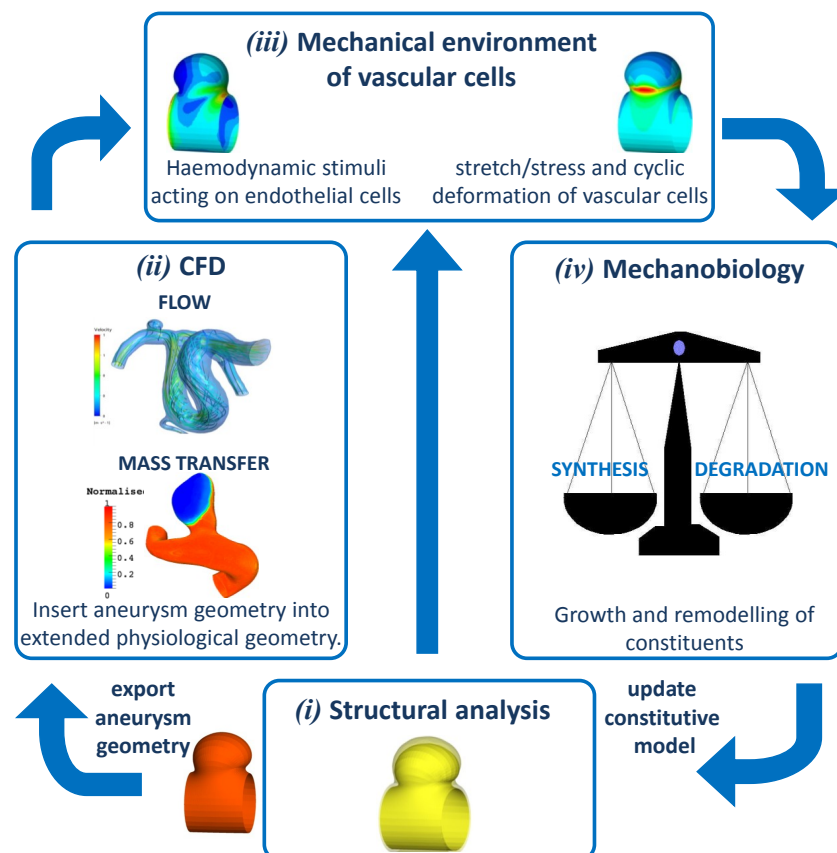


Figure 8.1: Coupled flow, mass transfer and GR modelling cycle.

The two different frameworks investigated in this thesis, the coupling of haemodynamics and oxygen mass transport within patient-specific models of IA, and the coupling of haemodynamics, collagen G&R, thrombus propagation and oxygen mass transport within an idealised representation of IA evolution, are a good basis on which to build on. Nonetheless these models have their limitations which need to be addressed in order to achieve a fully integrated system. In particular, the biomechanical and biochemical representations of both the wall and thrombus layers merit further development before this goal will be achieved. The following improvements are suggested:

- decomposition of the homogeneous arterial wall layer into three distinct layers of the intima, media and adventitia;
- definition of the wall thickness as a function of local arterial radius;
- implementation of a radial variation in oxygen consumption rates dependent on the individual cellular requirement and the volume of respiring cells of the wall layers;
- sophistication of adaptive responses to oxygen deficiency: i.e the possible decrease in oxygen respiration due to oxygen conformance, or the increase supply of oxygen as a result of neovascularisation through the wall and thrombus layers.
- take consideration of the different mechanical support offered by the differing distribution and orientation of collagen fibres within medial and adventitial layers;
- addition of the active and passive responses of SMCs within the G&R framework;
- take into account more realistic effects from flow phenomena, such as anatomy-specific pulsatility, transmural pressure and WSS;

- application of WSS mediated degradation of elastinous constituents;
- sophistication of shear-modulated thrombus propagation velocity;
- an evaluation of the possible cellular composition of organised thrombus and the relevant diffusion, convection and consumption properties;
- adaptation of the coupled FSGT 1D cylindrical model to a 3D spherical one, as a step towards modelling of an aneurysm dome;

In terms of coupled FM models, multi-layered models have so far been restricted to idealised 2D axisymmetric representations of the artery whereby the varying transport properties through the endothelium, intima, IEL, media and adventitia are taken into account. To the author's knowledge this has only been achieved (and validated against experimental data) for the distribution of LDL (e.g. Prosi et al. (2005); Yang and Vafai (2006, 2008)). However, this method requires various parameters for each layer (i.e. permeability, porosity, consumption rates, diffusion coefficients, reactions rates), many of which are still not reliably obtained from current measurement techniques, simply adding multiple unknowns and uncertainties to the computations. Nevertheless, one of the most attractive qualities of computational models is the ability to carry out significant parametric studies (even more so with the increased ease of parallelisation) in order to observe the effect of various parameters, in the hope that validation will follow shortly. Moreover, the specificity of imaging modalities will need to be enhanced in order to allow the segmentation of each individual layer so that this technique may be applied to 3D patient-specific models.

The work presented within this thesis has concentrated solely on the transport of oxygen so as to explore the potential of hypoxia in IAs. The underlying outcome of hypoxia is cell death due to complete energy depletion, i.e. the chronic lack of O_2 would result in the significant reduction in ATP production through anaerobic glycolysis (cf Section 1.5.1.1). Thus on the molecular scale, a more comprehensive

model could also encompass the possible effect of local O_2 levels on ATP production, including such reactions as the switch from aerobic to anaerobic glycolysis within the wall tissue. Furthermore, it has been brought to light that erythrocytes are not only responsible of carrying oxygen molecules, but that they also regulate the release of ATP in response to decreased in oxyhaemoglobin saturation levels, i.e as a consequence of a reduction in local oxygen partial pressure (Bergfeld and Forrester (1992); Ellsworth et al. (1995); Jagger et al. (2001); González-Alonso (2012b,a)). This suggests that the availability of ATP to the cells within the wall should not only take into consideration the synthesis of ATP from oxygen delivered to the wall interface by means of modelling both the free oxygen within the plasma and that subsequently unbound from haemoglobin, but also by modelling the transport of ATP released from erythrocytes as a response to low O_2 . Although the analysis into ATP transport in idealised 3D saccular IAs has already been conducted by Imai et al. (2010), the coupled FM CFD model proposes that the ATP concentration in the lumen be set to a uniform value representative of the normal level found in blood and thus disregards any fluctuations as a consequence of local oxygen tension. A model of the dynamic pathway of ATP release within blood flow, such as an adaptation of that proposed by Goldman et al. (2012) which numerically simulates the steady-state ATP transport within the capillary network, coupled to the oxygen mass transport model presented in this thesis would give a greater insight into the adaptation to hypoxia on a molecular level, and thus a better interpretation of the detrimental effect of hypoxia on the cellular level.

Until an exhaustive multi-layered FSGT model is achieved, and validated against *in vivo* data, only then will it be possible to verify whether the presence of thrombus in a stable or expanding IA results in possibly fatal hypoxic conditions. The greater the knowledge acquired on the functioning of the arterial wall on a cellular level, the more confidence will be gained in computational results obtained from multiscale, multiphysics models.

REFERENCES

- AALKJAER, C. AND LOMBARD, J. H. Effect of hypoxia on force, intracellular pH and Ca²⁺ concentration in rat cerebral and mesenteric small arteries. *The Journal of Physiology*, 482 (Pt 2:409–19, January 1995.
- ABRUZZO, T., SHENGELAIA, G. G., DAWSON, R. C., OWENS, D. S., CAWLEY, C. M., AND GRAVANIS, M. B. Histologic and morphologic comparison of experimental aneurysms with human intracranial aneurysms. *American Journal of Neuroradiology*, 19(7):1309–14, August 1998.
- ADOLPH, R., VORP, D. A., STEED, D. L., WEBSTER, M. W., KAMENEVA, M. V., AND WATKINS, S. C. Cellular content and permeability of intraluminal thrombus in abdominal aortic aneurysm. *Journal of Vascular Surgery*, 25(5):916–26, May 1997.
- AENIS, M., STANCAMPANO, A. P., WAKHLOO, A. K., AND LIEBER, B. B. Modeling of flow in a straight stented and nonstented side wall aneurysm model. *Journal of Biomedical Engineering*, 119:206–212, May 1997.
- AGOCHA, A., LEE, H. W., AND EGHBALI-WEBB, M. Hypoxia regulates basal and induced DNA synthesis and collagen type I production in human cardiac fibroblasts: effects of transforming growth factor-beta1, thyroid hormone, angiotensin II and basic fibroblast growth factor. *Journal of Molecular and Cellular Cardiology*, 29(8):2233–44, August 1997.
- AIMES, R. T. AND QUIGLEY, J. P. Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. *The Journal of Biological Chemistry*, 270 (11):5872–6, March 1995.
- ALASTRUEY, J., PARKER, K. H., PEIRO, J., BYRD, S. M., AND SHERWIN, S. J. Modelling the circle of Willis to assess the effects of anatomical variations and occlusions on cerebral flows. *Journal of Biomechanics*, 40:1794–1805, 2007.
- ALBERTS, B., JOHNSON, A., LEWIS, J., RAFF, M., ROBERTS, K., AND WALTER, P. *Molecular Biology of the Cell*. Garland Science, New York, 5th edition, 2008.
- AMBROSIO, G., TRITTO, I., AND GOLINO, P. Reactive oxygen metabolites and arterial thrombosis. *Cardiovascular Research*, 34(3):445–52, June 1997.
- AOKI, T., KATAOKA, H., ISHIBASHI, R., NOZAKI, K., AND HASHIMOTO, N. Cathepsin B, K, and S are expressed in cerebral aneurysms and promote the progression of cerebral aneurysms. *Stroke*, 39(9): 2603–10, September 2008.
- AOKI, T., KATAOKA, H., ISHIBASHI, R., NOZAKI, K., MORISHITA, R., AND HASHIMOTO, N. Reduced collagen biosynthesis is the hallmark of cerebral aneurysm: contribution of interleukin-1beta and nuclear factor-kappaB. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 29(7):1080–6, July 2009.
- AOKI, T., KATAOKA, H., MORIMOTO, M., NOZAKI, K., AND HASHIMOTO, N. Macrophage-derived matrix metalloproteinase-2 and -9 promote the progression of cerebral aneurysms in rats. *Stroke*, 38(1): 162–9, January 2007a.
- AOKI, T., KATAOKA, H., MORIWAKI, T., NOZAKI, K., AND HASHIMOTO, N. Role of TIMP-1 and TIMP-2 in the progression of cerebral aneurysms. *Stroke*, 38(8):2337–45, August 2007b.
- APPANABOYINA, S., MUT, F., LÖHNER, R., PUTMAN, C. M., AND CEBRAL, J. R. Computational fluid dynamics of stented intracranial aneurysms using adaptive embedded unstructured grids. *International Journal for Numerical Methods in Fluids*, 57 (5):475–493, June 2008.
- APPANABOYINA, S., MUT, F., LÖHNER, R., PUTMAN, C., AND CEBRAL, J. Simulation of intracranial aneurysm stenting: Techniques and challenges. *Computer Methods in Applied Mechanics and Engineering*, 198(45-46):3567–3582, September 2009.
- ARAUZ, A., LOPEZ, M., CANTU, C., AND BARINAGARREMENTERIA, F. Nonaneurysmal subarachnoid hemorrhage. Study of long-term follow-up. *Neurologia*, 22:502–506, October 2007.
- ARNAOUT, M. A. The vasculopathy of autosomal dominant polycystic kidney disease: insights from animal models. *Kidney International*, 58(6):2599–610, December 2000.

- ARZANI, A. AND SHADDEN, S. C. Characterization of the transport topology in patient-specific abdominal aortic aneurysm models. *Physics of Fluids*, 24(8):81901, August 2012.
- ASARI, S. AND OHMOTO, T. Growth and rupture of unruptured cerebral aneurysms based on the intraoperative appearance. *Acta Medica Okayama*, 48(5):257–62, October 1994.
- AUGSBURGER, L., FARHAT, M., REYMOND, P., FONCK, E., KULCSAR, Z., STERGIOPULOS, N., AND RÜFENACHT, D. A. Effect of flow diverter porosity on intraaneurysmal blood flow. *Klinische Neuroradiologie*, 19(3):204–14, August 2009.
- AYDIN, F. Do human intracranial arteries lack vasa vasorum? A comparative immunohistochemical study of intracranial and systemic arteries. *Acta Neuropathologica*, 96:22–28, July 1998.
- AZIZ, S., MORRIS, J. L., PERRY, R. A., AND STABLES, R. H. Stent expansion: a combination of delivery balloon underexpansion and acute stent recoil reduces predicted stent diameter irrespective of reference vessel size. *Heart (British Cardiac Society)*, 93(12):1562–6, December 2007.
- BACK, L. Analysis of oxygen transport in the avascular region of arteries. *Mathematical Biosciences*, 31(3-4):285–306, 1976.
- BACK, L. H. Theoretical investigation of mass transport to arterial walls in various blood flow regions—II. oxygen transport and its relationship to lipoprotein accumulation. *Mathematical Biosciences*, 27(3-4):263–285, 1975.
- BAEK, S., RAJAGOPAL, K. R., AND HUMPHREY, J. D. Competition Between Radial Expansion and Thickening in the Enlargement of an Intracranial Saccular Aneurysm. *Journal of Elasticity*, 80(1-3):13–31, November 2005.
- BAEK, S., RAJAGOPAL, K. R., AND HUMPHREY, J. D. A Theoretical Model of Enlarging Intracranial Fusiform Aneurysms. *Journal of Biomechanical Engineering*, 128(1):142, 2006.
- BAMFORD, J., SANDERCOCK, P., DENNIS, M., BURN, J., AND WARLOW, C. A prospective-study of acute cerebrovascular-disease in the community - the oxfordshire community stroke project 1981-86 .2. incidence, case fatality rates and overall outcome at 1 year of cerebral infarction, primary intracerebral and subarachnoid haemod. *Journal of Neurology Neurosurgery and Psychiatry*, 53(1):16–22, January 1990.
- BARRON, J. T., KOPP, S. J., TOW, J., AND PARRILLO, J. E. Substrate-dependent alteration in O₂ consumption and energy metabolism in vascular smooth muscle. *The American Journal of Physiology*, 270(6 Pt 2):H1869–77, June 1996.
- BASCIANO, C., KLEINSTREUER, C., HYUN, S., AND FINOL, E. A. A relation between near-wall particle-hemodynamics and onset of thrombus formation in abdominal aortic aneurysms. *Annals of Biomedical Engineering*, 39(7):2010–26, July 2011.
- BECK, J., ROHDE, S., BERKEFELD, J., SEIFERT, V., AND RAABE, A. Size and location of ruptured and unruptured intracranial aneurysms measured by 3-dimensional rotational angiography. *Surgical Neurology*, 65(1):18–25; discussion 25–7, January 2006.
- BENNDORF, G., CAMPI, A., SCHNEIDER, G. H., WELLNHOFER, E., AND UNTERBERG, A. Overlapping stents for treatment of a dissecting carotid artery aneurysm. *Journal of Endovascular Therapy*, 8(6):566–70, December 2001a.
- BENNDORF, G., HERBON, U., SOLLMANN, W. P., AND CAMPI, A. Treatment of a ruptured dissecting vertebral artery aneurysm with double stent placement: case report. *American Journal of Neuroradiology*, 22(10):1844–8, 2001b.
- BERG, D., YODIM, M. B., AND RIEDERER, P. Redox imbalance. *Cell and Tissue Research*, 318(1):201–213, 2004.
- BERGE, J., BIONDI, A., MACHI, P., BRUNEL, H., PIEROT, L., GABRILLARGUES, J., KADZIOŁKA, K., BARREAU, X., DOUSSET, V., AND BONAFÉ, A. Flow-diverter silk stent for the treatment of intracranial aneurysms: 1-year follow-up in a multicenter study. *American Journal of Neuroradiology*, 33(6):1150–5, June 2012.
- BERGFELD, G. R. AND FORRESTER, T. Release of ATP from human erythrocytes in response to a brief period of hypoxia and hypercapnia. *Cardiovascular Research*, 26(1):40–7, January 1992.
- BERGOEING, M. P., ARIEF, B., HACKMANN, A. E., ENNIS, T. L., THOMPSON, R. W., AND CURCI, J. A. Cigarette smoking increases aortic dilatation without affecting matrix metalloproteinase-9 and -12 expression in a modified mouse model of aneurysm formation. *Journal of Vascular Surgery*, 45(6):1217–1227, June 2007.

- BERNARDINI, A., LARRABIDE, I., PETRINI, L., PENNATI, G., FLORE, E., KIM, M., AND FRANGI, A. F. Deployment of self-expandable stents in aneurysmatic cerebral vessels: comparison of different computational approaches for interventional planning. *Computer Methods in Biomechanics and Biomedical Engineering*, 15(3):303–11, January 2010.
- BERNARDINI, A., LARRABIDE, I., MORALES, H. G., PENNATI, G., PETRINI, L., CITO, S., AND FRANGI, A. F. Influence of different computational approaches for stent deployment on cerebral aneurysm haemodynamics. *Interface Focus*, 1(3): 338–48, June 2011.
- BHARADVAJ, B. K., MABON, R. F., AND GIDDENS, D. P. Steady flow in a model of the human carotid bifurcation. Part I-flow visualization. *Journal of Biomechanics*, 15(5):349–62, January 1982a.
- BHARADVAJ, B. K., MABON, R. F., AND GIDDENS, D. P. Steady flow in a model of the human carotid bifurcation. Part II-laser-Doppler anemometer measurements. *Journal of Biomechanics*, 15(5):363–78, January 1982b.
- BIRK, D. E., ZYCBAND, E. I., WINKELMANN, D. A., AND TRELSTAD, R. L. Collagen fibrillogenesis in situ. Discontinuous segmental assembly in extracellular compartments. *Annals of the New York Academy of Sciences*, 580:176–94, January 1990.
- BLUESTEIN, D., DUMONT, K., DE BEULE, M., RICOTTA, J., IMPELLIZZERI, P., VERHEGGHE, B., AND VERDONCK, P. Intraluminal thrombus and risk of rupture in patient specific abdominal aortic aneurysm - FSI modelling. *Computer Methods in Biomechanics and Biomedical Engineering*, 12(1):73–81, February 2009.
- BOLSOVER, S. R., HYAMS, J., SHEPHARD, E. A., WHITE, H., AND WIEDEMANN, C. *Cell Biology: A Short Course*. John Wiley and Sons Ltd., Hoboken, NJ, USA, 2nd edition, 2004.
- BONITA, R. Epidemiology of stroke. *Lancet*, 339:342–344, February 1992.
- BORDEN, N. M. *3D Angiographic Atlas of Neurovascular Anatomy and Pathology*. Cambridge University Press, 2007.
- BOSCHETTI, F., DI MARTINO, E., AND GIODA, G. A poroviscoelastic model of intraluminal thrombus from abdominal aortic aneurysms. In *Proceedings of the 2007 Summer Bioengineering Conference 2007*, Keystone CO., 2007.
- BOWKER, T. J., WATTON, P. N., SUMMERS, P. E., BYRNE, J. V., AND VENTIKOS, Y. Rest versus exercise hemodynamics for middle cerebral artery aneurysms: a computational study. *American Journal of Neuroradiology*, 31(2):317–23, February 2010.
- BOWKER, T. J. *A computational model for thrombus prediction*. PhD thesis, University of Oxford, 2010.
- BRENNER, D. J. AND HALL, E. J. Computed tomography—an increasing source of radiation exposure. *The New England journal of medicine*, 357(22):2277–84, November 2007.
- BRILSTRA, E. H., RINKEL, G. J. E., VAN DER GRAAF, Y., VAN ROOIJ, W. J. J., AND ALGRA, A. Treatment of intracranial aneurysms by embolization with coils - A systematic review. *Stroke*, 30:470–476, February 1999.
- BRISMAN, J. L., SONG, J. K., AND NEWELL, D. W. Medical progress: Cerebral aneurysms. *New England Journal of Medicine*, 355:928–939, August 2006.
- BROOKS, A. AND HUGHES, T. Streamline upwind/ Petrov-galerkin formulations for convective dominated flow with particular emphasis on incompressible Navier-Stokes equations. *Computational methods in applied methods and engineering*, 32:199–259, 1982.
- BROWN, C. H., LEVERETT, L. B., LEWIS, C. W., ALFREY, C. P., AND HELLUMS, J. D. Morphological, biochemical, and functional changes in human platelets subjected to shear stress. *The Journal of Laboratory and Clinical Medicine*, 86(3):462–71, September 1975.
- BROWNLEE, R. D., TRANMER, B. I., SEVICK, R. J., KARMY, G., AND CURRY, B. J. Spontaneous thrombosis of an unruptured anterior communicating artery aneurysm. An unusual cause of ischemic stroke. *Stroke*, 26(10):1945–9, October 1995.
- BRUNO, G., TODOR, R., LEWIS, I., AND CHYATTE, D. Vascular extracellular matrix remodeling in cerebral aneurysms. *Journal of Neurosurgery*, 89(3): 431–40, September 1998.
- BUERK, D. G. AND GOLDSTICK, T. K. Arterial wall oxygen consumption rate varies spatially. *The American Journal of Physiology*, 243(6):H948–58, December 1982.
- BURKE, B., GIANNOUDIS, A., CORKE, K. P., GILL, D., WELLS, M., ZIEGLER-HEITBROCK, L., AND LEWIS,

- C. E. Hypoxia-induced gene expression in human macrophages: implications for ischemic tissues and hypoxia-regulated gene therapy. *The American Journal of Pathology*, 163(4):1233–43, October 2003.
- BYRNE, J. V., BELTECHI, R., YARNOLD, J. A., BIRKS, J., AND KAMRAN, M. Early experience in the treatment of intra-cranial aneurysms by endovascular flow diversion: a multicentre prospective study. *PloS One*, 5(9), January 2010.
- BYRNE, J. V. AND SZIKORA, I. Flow Diverters in the Management of Intracranial Aneurysms: A Review. *EJMINT Original Article*, 1225000057, 2012.
- BYUN, H. S. AND RHEE, K. CFD modeling of blood flow following coil embolization of aneurysms. *Medical Engineering & Physics*, 26:755–761, November 2004.
- CAIRD, J., NAPOLI, C., TAGGART, C., FARRELL, M., AND BOUCHIER-HAYES, D. Matrix metalloproteinases 2 and 9 in human atherosclerotic and non-atherosclerotic cerebral aneurysms. *European Journal of Neurology*, 13(10):1098–105, October 2006.
- CANHAM, P. B., FINLAY, H. M., DIXON, J. G., AND FERGUSON, S. E. Layered collagen fabric of cerebral aneurysms quantitatively assessed by the universal stage and polarized light microscopy. *The Anatomical Record*, 231(4):579–92, December 1991.
- CANHAM, P. B., FINLAY, H. M., KIERNAN, J. A., AND FERGUSON, G. G. Layered structure of saccular aneurysms assessed by collagen birefringence. *Neurological Research*, 21(7):618–26, October 1999.
- CARROLL, K., SHAHED, M., ELIAHOO, J., AND AZEEM, M. Stroke incidence and risk factors in a population - based prospective cohort study. *Office of National Statistics Health Statistics Quarterly*, Winter: 18–26, 2001.
- CASTRO, M. A., PUTMAN, C. M., AND CEBRAL, J. R. Patient-specific computational modeling of cerebral aneurysms with multiple avenues of flow from 3D rotational angiography images. *Academic Radiology*, 13:811–821, July 2006.
- CAVAZZUTI, M., ATHERTON, M. A., COLLINS, M. W., AND BAROZZI, G. S. Non-Newtonian and flow pulsatility effects in simulation models of a stented intracranial aneurysm. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, 225(6):597–609, June 2011.
- CEBRAL, J. R. AND LÖHNER, R. Efficient simulation of blood flow past complex endovascular devices using an adaptive embedding technique. *IEEE Transactions on Medical Imaging*, 24(4):468–76, April 2005.
- CHIEN, A., SAYRE, J., AND VIÑUELA, F. Comparative Morphological Analysis of the Geometry of Ruptured and Unruptured Aneurysms. *Neurosurgery*, 69(2):349–356, August 2011.
- CHIEN, S. Effects of disturbed flow on endothelial cells. *Annals of Biomedical Engineering*, 36(4):554–62, April 2008.
- CHIQUET, M., RENEDO, A. S., HUBER, F., AND FLÜCK, M. How do fibroblasts translate mechanical signals into changes in extracellular matrix production? *Matrix Biology*, 22(1):73–80, March 2003.
- CHUONG, C. J. AND FUNG, Y. C. Three-dimensional stress distribution in arteries. *Journal of Biomechanical Engineering*, 105(3):268–74, August 1983.
- CHYATTE, D., BRUNO, G., DESAI, S., AND TODOR, D. R. Inflammation and intracranial aneurysms. *Neurosurgery*, 45(5):1137–46; discussion 1146–7, November 1999.
- CLARENÇON, F., PIOTIN, M., PISTOCCHI, S., BABIC, D., AND BLANC, R. Evaluation of stent visibility by flat panel detector CT in patients treated for intracranial aneurysms. *Neuroradiology*, 54(10):1121–5, October 2012.
- CLARK, A., FEDERSPIEL, W. J., CLARK, P. A. A., AND COKELET, R. Oxygen delivery from red-cells. *Biophysical Journal*, 47:171–181, 1985.
- CLIFTON, A. G. MR angiography. *British medical bulletin*, 56(2):367–77, January 2000.
- COOKE, J. P., STAMLER, J., ANDON, N., DAVIES, P. F., MCKINLEY, G., AND LOSCALZO, J. Flow stimulates endothelial cells to release a nitrovasodilator that is potentiated by reduced thiol. *The American Journal of Physiology*, 259(3 Pt 2):H804–12, September 1990.
- COPPOLA, G. AND CARO, C. Oxygen mass transfer in a model three-dimensional artery. *Journal of the Royal Society, Interface / the Royal Society*, 5(26):1067–75, September 2008.
- CRAWFORD, D. W., COLE, M. A., AND BACK, L. H. Evidence for the blood oxygen boundary layer pO₂ gradient (ΔpO_2) as a significant determinant

- of intimal (PW) and lowest medial pO₂ (p delta n) in the vivo dog femoral artery. *Advances in Experimental Medicine and Biology*, 159:197–209, January 1983.
- CRAWFORD, T. Some observations on the pathogenesis and natural history of intracranial aneurysms. *Journal of Neurology, Neurosurgery, and Psychiatry*, 22:259–66, November 1959.
- CROMPTON, M. R. Mechanism of growth and rupture in cerebral berry aneurysms. *British Medical Journal*, 1(5496):1138–42, May 1966.
- CUNNINGHAM, K. S. AND GOTLIEB, A. I. The role of shear stress in the pathogenesis of atherosclerosis. *Laboratory Investigation*, 85(1):9–23, January 2005.
- DAVID, C. A., VISHTEH, A. G., SPETZLER, R. F., LEMOLE, M., LAWTON, M. T., AND PARTOVI, S. Late angiographic follow-up review of surgically treated aneurysms. *JOURNAL OF NEUROSURGERY*, 91: 396–401, September 1999.
- DAVIES, P. F. Flow-mediated endothelial mechanotransduction. *Physiological Reviews*, 75(3):519–60, July 1995.
- DEHDASHTI, A. R., THINES, L., WILLINSKY, R. A., AND TYMIANSKI, M. Symptomatic enlargement of an occluded giant carotido-ophthalmic aneurysm after endovascular treatment: the vasa vasorum theory. *Acta Neurochirurgica*, 151(9):1153–8, September 2009.
- DELFINO, A., STERGIOPULOS, N., MOORE, J. E., AND MEISTER, J. J. Residual strain effects on the stress field in a thick wall finite element model of the human carotid bifurcation. *Journal of Biomechanics*, 30(8):777–86, August 1997.
- DENG, S. X., TOMIOKA, J., DEBES, J. C., AND FUNG, Y. C. New experiments on shear modulus of elasticity of arteries. *The American Journal of Physiology*, 266(1 Pt 2):H1–10, January 1994.
- DENG, X., KING, M., AND GUIDOIN, R. Localization of atherosclerosis in arterial junctions. Modeling the release rate of low density lipoprotein and its breakdown products accumulated in blood vessel walls. *ASAIO journal (American Society for Artificial Internal Organs)*, 39(3):M489–95, 1993.
- DENG, X., KING, M. W., AND GUIDOIN, R. Localization of atherosclerosis in arterial junctions. Concentration distribution of low density lipoproteins at the luminal surface in regions of disturbed flow. *ASAIO journal (American Society for Artificial Internal Organs)*, 41(1):58–67, 1995.
- DEPAOLA, N., GIMBRONE, M. A., DAVIES, P. F., AND DEWEY, C. F. Vascular endothelium responds to fluid shear stress gradients. *Arteriosclerosis and Thrombosis : a journal of Vascular Biology*, 12(11): 1254–7, November 1992.
- DEWEY, C. F., BUSSOLARI, S. R., GIMBRONE, M. A., AND DAVIES, P. F. The dynamic response of vascular endothelial cells to fluid shear stress. *Journal of Biomechanical Engineering*, 103(3):177–85, August 1981.
- DHAR, S., TREMMEL, M., MOCCO, J., KIM, M., YAMAMOTO, J., SIDDIQUI, A. H., HOPKINS, L. N., AND MENG, H. Morphology parameters for intracranial aneurysm rupture risk assessment. *Neurosurgery*, 63(2):185–96; discussion 196–7, August 2008.
- DI MARTINO, E. S. AND VORP, D. A. Effect of variation in intraluminal thrombus constitutive properties on abdominal aortic aneurysm wall stress. *Annals of Biomedical Engineering*, 31(7):804–9, 2003.
- DIAMOND, S. L. Engineering design of optimal strategies for blood clot dissolution. *Annual Review of Biomedical Engineering*, 1:427–62, January 1999.
- DIMMELER, S., HAENDELER, J., RIPPMMANN, V., NEHLS, M., AND ZEIHNER, A. M. Shear stress inhibits apoptosis of human endothelial cells. *FEBS Letters*, 399 (1-2):71–4, December 1996.
- DOBRIN, P. B. AND MRKVICKA, R. Failure of elastin or collagen as possible critical connective tissue alterations underlying aneurysmal dilatation. *Cardiovascular Surgery*, 2(4):484–8, August 1994.
- DOERFLER, A., WANKE, I., EGELHOF, T., STOLKE, D., AND FORSTING, M. Double-stent method: therapeutic alternative for small wide-necked aneurysms. Technical note. *Journal of Neurosurgery*, 100(1):150–4, January 2004.
- DONEA, J. AND HUERTA, A. *Finite Element Methods for Flow Problems*. 2003.
- DONNAN, G. A., FISHER, M., MACLEOD, M., AND DAVIS, S. M. Stroke. *Lancet*, 371:1612–1623, May 2008.
- DOUGHAN, A. K., HARRISON, D. G., AND DIKALOV, S. I. Molecular mechanisms of angiotensin II-mediated mitochondrial dysfunction: linking mitochondrial oxidative damage and vascular endothelial dysfunction. *Circulation Research*, 102(4): 488–96, February 2008.

- D'URSO, P. I., LANZINO, G., CLOFT, H. J., AND KALLMES, D. F. Flow diversion for intracranial aneurysms: a review. *Stroke*, 42(8):2363–8, August 2011.
- EHRlich, L. W. AND FRIEDMAN, M. H. Steady convective diffusion in a bifurcation. *IEEE Transactions on Bio-medical Engineering*, 24(1):12–8, January 1977.
- ELLSWORTH, M. L., FORRESTER, T., ELLIS, C. G., AND DIETRICH, H. H. The erythrocyte as a regulator of vascular tone. *The American Journal of Physiology*, 269(6 Pt 2):H2155–61, December 1995.
- ERIKSSON, T., KROON, M., AND HOLZAPFEL, G. A. Influence of medial collagen organization and axial in situ stretch on saccular cerebral aneurysm growth. *Journal of Biomechanical Engineering*, 131(10):101010, October 2009.
- ESI-CFD. CFD-ACE+ User manual, 2010.
- FENG, Y., WADA, S., ISHIKAWA, T., TSUBOTA, K.-I., AND YAMAGUCHI, T. A Rule-Based Computational Study on the Early Progression of Intracranial Aneurysms Using Fluid-Structure Interaction: Comparison between Straight Model and Curved Model. *Journal of Biomechanical Science and Engineering*, 3(2):124–137, 2008.
- FERNANDEZ-PATRON, C., MARTINEZ-CUESTA, M. A., SALAS, E., SAWICKI, G., WOZNIAC, M., RADOMSKI, M. W., AND DAVIDGE, S. T. Differential regulation of platelet aggregation by matrix metalloproteinases-9 and -2. *Thrombosis and Haemostasis*, 82(6):1730–5, December 1999.
- FERZIGER, J. H. AND PERIC, M. *Computational Methods for Fluid Dynamics*. Springer, 2002.
- FINLAY, H. M., MCCULLOUGH, L., AND CANHAM, P. B. Three-dimensional collagen organization of human brain arteries at different transmural pressures. *Journal of Vascular Research*, 32(5):301–12, 1995.
- FINOL, E. A. AND AMON, C. H. Flow dynamics in anatomical models of abdominal aortic aneurysms: computational analysis of pulsatile flow. *Acta Científica Venezolana*, 54(1):43–9, January 2003.
- FIGORELLA, D., ALBUQUERQUE, F., GONZALEZ, F., MCDUGALL, C. G., AND NELSON, P. K. Reconstruction of the right anterior circulation with the Pipeline embolization device to achieve treatment of a progressively symptomatic, large carotid aneurysm. *Journal of Neurointerventional Surgery*, 2(1):31–7, March 2010.
- FIGORELLA, D., ALBUQUERQUE, F. C., DESHMUKH, V. R., AND MCDUGALL, C. G. Usefulness of the neuroform stent for the treatment of cerebral aneurysms: Results at initial (3-6-mo) follow-up. *Neurosurgery*, 56:1191–1201, June 2005.
- FIGORELLA, D., LYLYK, P., SZIKORA, I., KELLY, M. E., ALBUQUERQUE, F. C., MCDUGALL, C. G., AND NELSON, P. K. Curative cerebrovascular reconstruction with the Pipeline embolization device: the emergence of definitive endovascular therapy for intracranial aneurysms. *Journal of NeuroInterventional Surgery*, 1(1):56–65, June 2009.
- FIGORELLA, D., ALBUQUERQUE, F. C., DESHMUKH, V. R., WOO, H. H., RASMUSSEN, P. A., MASARYK, T. J., AND MCDUGALL, C. G. Endovascular reconstruction with the Neuroform stent as monotherapy for the treatment of uncoilable intradural pseudoaneurysms. *Neurosurgery*, 59:291–299, August 2006.
- FIGORELLA, D., ALBUQUERQUE, F. C., HAN, P., AND MCDUGALL, C. G. Preliminary experience using the Neuroform stent for the treatment of cerebral aneurysms. *Neurosurgery*, 54(1):6–16; discussion 16–7, January 2004.
- FISCHER, S., VAJDA, Z., AGUILAR PEREZ, M., SCHMID, E., HOPE, N., BÄZNER, H., AND HENKES, H. Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections. *Neuroradiology*, 54(4):369–82, April 2012.
- FISHER, C. AND ROSSMANN, J. S. Effect of non-newtonian behavior on hemodynamics of cerebral aneurysms. *Journal of biomechanical engineering*, 131(9):091004, September 2009.
- FLYNN, L. E. The use of decellularized adipose tissue to provide an inductive microenvironment for the adipogenic differentiation of human adipose-derived stem cells. *Biomaterials*, 31(17):4715–24, June 2010.
- FONTAINE, V., JACOB, M.-P., HOUARD, X., ROSSIGNOL, P., PLISSONNIER, D., ANGLES-CANO, E., AND MICHEL, J.-B. Involvement of the mural thrombus as a site of protease release and activation in human aortic aneurysms. *The American Journal of Pathology*, 161(5):1701–10, November 2002.

- FORSBERG, F., MORVAY, Z., RAWOOL, N. M., DEANE, C. R., AND NEEDLEMAN, L. Shear rate estimation using a clinical ultrasound scanner. *Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine*, 19(5):323–7, May 2000.
- FREEDMAN, J. E. Oxidative stress and platelets. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 28(3):s11–6, March 2008.
- FRIEDMAN, J. A., NICHOLS, D. A., MEYER, F. B., PICHELMANN, M. A., MCIVER, J. I., TOUSSAINT, L. G., AXLEY, P. L., AND BROWN, R. D. Guglielmi detachable coil treatment of ruptured saccular cerebral aneurysms: Retrospective review of a 10-year single-center experience. *American Journal of Neuroradiology*, 24:526–533, March 2003.
- FRIEDMAN, M. H. AND EHRLICH, L. W. Effect of spatial variations in shear on diffusion at the wall of an arterial branch. *Circulation Research*, 37(4):446–54, October 1975.
- FRIEDRICH, P. AND REININGER, A. J. Occlusive thrombus formation on indwelling catheters: in vitro investigation and computational analysis. *Thrombosis and Haemostasis*, 73(1):66–72, January 1995.
- FRÖSEN, J., PIIPPO, A., PAETAU, A., KANGASNIEMI, M., NIEMELÄ, M., HERNESNIEMI, J., AND JÄÄSKELÄINEN, J. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. *Stroke*, 35(10):2287–93, October 2004.
- FUJIMOTO, K. 'Medial defects' in the prenatal human cerebral arteries: an electron microscopic study. *Stroke*, 27(4):706–8, April 1996.
- FUNG, Y. C., FRONEK, K., AND PATITUCCI, P. Pseudoe-lasticity of arteries and the choice of its mathematical expression. *The American Journal of Physiology*, 237(5):H620–31, November 1979.
- FURIE, B. AND FURIE, B. C. In vivo thrombus formation. *Journal of Thrombosis and Haemostasis*, 5 Suppl 1:12–7, July 2007.
- FURIE, B. AND FURIE, B. C. Mechanisms of thrombus formation. *The New England Journal of Medicine*, 359(9):938–49, August 2008.
- GAETANI, P., TARTARA, F., TANCIONI, F., RODRIGUEZ Y BAENA, R., CASARI, E., ALFANO, M., AND GRAZIO-OLI, V. Deficiency of total collagen content and of deoxypyridinoline in intracranial aneurysm walls. *FEBS Letters*, 404(2-3):303–6, March 1997.
- GASSER, T. C., OGDEN, R. W., AND HOLZAPFEL, G. A. Hyperelastic modelling of arterial layers with distributed collagen fibre orientations. *Journal of the Royal Society, Interface*, 3(6):15–35, February 2006.
- GEERS, A. J., LARRABIDE, I., MORALES, H. G., AND FRANGI, A. F. Comparison of steady-state and transient blood flow simulations of intracranial aneurysms. In *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, volume 2010, pages 2622–5, January 2010.
- GERBER, S., DORMONT, D., SAHEL, M., GROB, R., FONCIN, J. F., AND MARSAULT, C. Complete spontaneous thrombosis of a giant intracranial aneurysm. *Neuroradiology*, 36(4):316–7, May 1994.
- GIBBONS, G. H. AND DZAU, V. J. The emerging concept of vascular remodeling. *The New England Journal of Medicine*, 330(20):1431–8, May 1994.
- GOLDMAN, D., FRASER, G. M., ELLIS, C. G., SPRAGUE, R. S., ELLSWORTH, M. L., AND STEPHENSON, A. H. Toward a multiscale description of microvascular flow regulation: o(2)-dependent release of ATP from human erythrocytes and the distribution of ATP in capillary networks. *Frontiers in Physiology*, 3:246, January 2012.
- GOLDSTICK, T., SCHNEIDERMAN, G., AND MOCKROS, L. Effects of womersley-type blood-flow pulsatility on arterial wall oxygen-supply. *Federation Proceedings*, 36(3):513–513, 1977.
- GONZALEZ, C. F., CHO, Y. I., ORTEGA, H. V., AND MORET, J. Intracranial aneurysms: flow analysis of their origin and progression. *American Journal of Neuroradiology*, 13(1):181–8, 1992.
- GONZÁLEZ-ALONSO, J. A novel role for the red blood cell in the regulation of tissue O₂ supply. *The Journal of Physiology*, 590(Pt 20):4983–4, October 2012a.
- GONZÁLEZ-ALONSO, J. ATP as a mediator of erythrocyte-dependent regulation of skeletal muscle blood flow and oxygen delivery in humans. *The Journal of Physiology*, 590(Pt 20):5001–13, October 2012b.
- GRAVES, E. J. Detailed diagnoses and procedures, National Hospital Discharge Survey. *Vital Health Statistics*, 13:1–225, 1999.
- GREENBERG, M. S. *Handbook of Neurosurgery*. Springer Berlin / Heidelberg, 2000.

- GRODEN, C., LAUDAN, J., GATCHELL, S., AND ZEUMER, H. Three-dimensional pulsatile flow simulation before and after endovascular coil embolization of a terminal cerebral aneurysm. *Journal of Cerebral Blood Flow and Metabolism*, 21:1464–1471, December 2001.
- GROSS, B. A. AND FRERICHS, K. U. Stent usage in the treatment of intracranial aneurysms: past, present and future. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84(3):244–53, March 2013.
- GUGLIELMI, G., VINUELA, F., DION, J., AND DUCKWILER, G. Electrothrombosis of saccular aneurysms via endovascular approach .2. preliminary clinical-experience. *Journal of Neurosurgery*, 75:8–14, July 1991.
- GUPTA, V. AND GRANDE-ALLEN, K. J. Effects of static and cyclic loading in regulating extracellular matrix synthesis by cardiovascular cells. *Cardiovascular Research*, 72(3):375–83, December 2006.
- GUYTON, J. R. AND KLEMP, K. F. The lipid-rich core region of human atherosclerotic fibrous plaques. Prevalence of small lipid droplets and vesicles by electron microscopy. *The American Journal of Pathology*, 134(3):705–17, March 1989.
- HALLIWELL, B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *Lancet*, 344(8924):721–4, September 1994.
- HANSEN, F., MANGELL, P., SONESSON, B., AND LÄNNE, T. Diameter and compliance in the human common carotid artery-variations with age and sex. *Ultrasound in Medicine & Biology*, 21(1):1–9, January 1995.
- HARTER, L. P., GROSS, B. H., CALLEN, P. W., AND BARTH, R. A. Ultrasonic evaluation of abdominal aortic thrombus. *Journal of Ultrasound in Medicine*, 1(8):315–8, October 1982.
- HASSAN, T., TIMOFEEV, E. V., SAITO, T., SHIMIZU, H., EZURA, M., MATSUMOTO, Y., TAKAYAMA, K., TOMINAGA, T., AND TAKAHASHI, A. A proposed parent vessel geometry-based categorization of saccular intracranial aneurysms: computational flow dynamics analysis of the risk factors for lesion rupture. *Journal of Neurosurgery*, 103(4):662–80, October 2005.
- HEIL, M. THE STABILITY OF CYLINDRICAL SHELLS CONVEYING VISCOUS FLOW. *Journal of Fluids and Structures*, 10(2):173–196, February 1996.
- HENROTIN, Y. E., BRUCKNER, P., AND PUJOL, J.-P. L. The role of reactive oxygen species in homeostasis and degradation of cartilage. *Osteoarthritis and Cartilage*, 11(10):747–55, October 2003.
- HIGASHIDA, R. T., SMITH, W., GRESS, D., URWIN, R., DOWD, C. F., BALOUSEK, P. A., AND HALBACH, V. V. Intravascular stent and endovascular coil placement for a ruptured fusiform aneurysm of the basilar artery - Case report and review of the literature. *Journal of Neurosurgery*, 87:944–949, December 1997.
- HIGASHIDA, R. T., HALBACH, V. V., DOWD, C. F., JURAVSKY, L., AND MEAGHER, S. Initial clinical experience with a new self-expanding nitinol stent for the treatment of intracranial cerebral aneurysms: the Cordis Enterprise stent. *American Journal of Neuroradiology*, 26(7):1751–6, August 2005.
- HIJIDRA, A., VAN GIJN, J., NAGELKERKE, N., VERMEULEN, M., AND VANCREVEL, H. Prediction of delayed cerebral-ischemia, rebleeding, and outcome after aneurysmal subarachnoid hemorrhage. *Stroke*, 19:1250–1256, October 1988.
- HILL, A. The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *Journal of Physiology*, 40, 1910.
- HILL, M. A., ZOU, H., POTOCNIK, S. J., MEININGER, G. A., AND DAVIS, M. J. Invited review: arteriolar smooth muscle mechanotransduction: Ca(2+) signaling pathways underlying myogenic reactivity. *Journal of Applied Physiology*, 91(2):973–83, August 2001.
- HIMBURG, H. A., GRZYBOWSKI, D. M., HAZEL, A. L., LAMACK, J. A., LI, X.-M., AND FRIEDMAN, M. H. Spatial comparison between wall shear stress measures and porcine arterial endothelial permeability. *American Journal of Physiology. Heart and Circulatory Physiology*, 286(5):H1916–22, May 2004.
- HIRASAWA, T., TSUBOKAWA, T., KATAYAMA, Y., KOIKE, Y., UENO, Y., HIRAYAMA, T., AND HIMI, K. Growth of a giant aneurysm following complete thrombosis by detachable balloon occlusion. *Surgical Neurology*, 38(4):283–6, October 1992.
- HOFFMAN, M. Remodeling the blood coagulation cascade. *Journal of Thrombosis and Thrombolysis*, 16(1-2):17–20, 2004.
- HOI, Y., MENG, H., WOODWARD, S. H., BENDOK, B. R., HANEL, R. A., GUTERMAN, L. R., AND HOPKINS, L. N. Effects of arterial geometry on

- aneurysm growth: three-dimensional computational fluid dynamics study. *Journal of Neurosurgery*, 101(4):676–81, October 2004.
- HOLME, P. A., ORVIM, U., HAMERS, M. J., SOLUM, N. O., BROSSTAD, F. R., BARSTAD, R. M., AND SAKARIASSEN, K. S. Shear-induced platelet activation and platelet microparticle formation at blood flow conditions as in arteries with a severe stenosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 17(4):646–53, April 1997.
- HOLZAPFEL, G. A. AND OGDEN, R. W. Constitutive modelling of arteries. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 466(2118):1551–1597, March 2010.
- HOLZAPFEL, G. A. AND WEIZSÄCKER, H. W. Biomechanical behavior of the arterial wall and its numerical characterization. *Computers in Biology and Medicine*, 28(4):377–92, July 1998.
- HOLZAPFEL, G. A. *Nonlinear Solid Mechanics: A Continuum Approach for Engineering*. John Wiley and Sons Ltd., Chichester, UK, 2000.
- HOLZAPFEL, G. A. Collagen in Arterial Walls: Biomechanical Aspect. In FRATZL, P., editor, *Collagen: Structure and Mechanics*, chapter 11, pages 285–384. Springer Science+Business Media, New York, USA, 2008.
- HOLZAPFEL, G. A., GASSER, T. C., AND OGDEN, R. W. A new constitutive framework for arterial wall mechanics and a comparative study of material models. *Journal of Elasticity*, 61(1-3):1–48, 2000.
- HORNEBECK, W., ADNET, J. J., AND ROBERT, L. Age dependent variation of elastin and elastase in aorta and human breast cancers. *Experimental Gerontology*, 13(5):293–8, January 1978.
- HOWINGTON, J. U., HANEL, R. A., HARRIGAN, M. R., LEVY, E. I., GUTERMAN, L. R., AND HOPKINS, L. N. The Neuroform stent, the first microcatheter-delivered stent for use in the intracranial circulation. *Neurosurgery*, 54(1):2–5, January 2004.
- HUANG, P. Y. AND HELLUMS, J. D. Aggregation and disaggregation kinetics of human blood platelets: Part II. Shear-induced platelet aggregation. *Biophysical Journal*, 65(1):344–53, July 1993.
- HUMPHREY, J. D. Mechanics of the arterial wall: review and directions. *Critical Reviews in Biomedical Engineering*, 23(1-2):1–162, January 1995.
- HUMPHREY, J. D. Review: Computer Methods in Membrane Biomechanics. *Computer Methods in Biomechanics and Biomedical Engineering*, 1(3):171–210, January 1998.
- HUMPHREY, J. D. Remodeling of a collagenous tissue at fixed lengths. *Journal of Biomechanical Engineering*, 121(6):591–7, December 1999.
- HUMPHREY, J. D. AND RAJAGOPAL, K. R. A constrained mixture model for growth and remodeling of soft tissues. *Mathematical Models and Methods in Applied Sciences*, 12(3):407–430, 2002.
- HUMPHREY, J. D. AND TAYLOR, C. A. Intracranial and abdominal aortic aneurysms: similarities, differences, and need for a new class of computational models. *Annual Review of Biomedical Engineering*, 10:221–46, January 2008.
- HUSTON, J., TORRES, V. E., SULLIVAN, P. P., OFFORD, K. P., AND WIEBERS, D. O. Value of magnetic resonance angiography for the detection of intracranial aneurysms in autosomal dominant polycystic kidney disease. *Journal of the American Society of Nephrology*, 3(12):1871–7, June 1993.
- IDE, T., TSUTSUI, H., HAYASHIDANI, S., KANG, D., SUEMATSU, N., NAKAMURA, K., UTSUMI, H., HAMASAKI, N., AND TAKESHITA, A. Mitochondrial DNA damage and dysfunction associated with oxidative stress in failing hearts after myocardial infarction. *Circulation Research*, 88(5):529–35, March 2001.
- IIHARA, K., MURAO, K., SAKAI, N., SOEDA, A., ISHIBASHI-UEDA, H., YUTANI, C., YAMADA, N., AND NAGATA, I. Continued growth of and increased symptoms from a thrombosed giant aneurysm of the vertebral artery after complete endovascular occlusion and trapping: the role of vasa vasorum. Case report. *Journal of Neurosurgery*, 98(2):407–13, February 2003.
- IMAI, Y., SATO, K., ISHIKAWA, T., COMERFORD, A., DAVID, T., AND YAMAGUCHI, T. ATP transport in saccular cerebral aneurysms at arterial bends. *Annals of Biomedical Engineering*, 38(3):927–34, March 2010.
- INTENGAN, H. D. AND SCHIFFRIN, E. L. Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. *Hypertension*, 38(3 Pt 2):581–7, September 2001.

- INTERNATIONAL STUDY OF UNRUPTURED INTRACRANIAL ANEURYSMS INVESTIGATORS. Unruptured intracranial aneurysms-risk of rupture and risks of surgical intervention. *The New England Journal of Medicine*, 339(24):1725–33, December 1998.
- IRACE, C., CORTESE, C., FIASCHI, E., CARALLO, C., FARINARO, E., AND GNASSO, A. Wall shear stress is associated with intima-media thickness and carotid atherosclerosis in subjects at low coronary heart disease risk. *Stroke*, 35(2):464–8, February 2004.
- JACKSON, Z. S., GOTLIEB, A. I., AND LANGILLE, B. L. Wall tissue remodeling regulates longitudinal tension in arteries. *Circulation Research*, 90(8):918–25, May 2002.
- JAGGER, J. E., BATEMAN, R. M., ELLSWORTH, M. L., AND ELLIS, C. G. Role of erythrocyte in regulating local O₂ delivery mediated by hemoglobin oxygenation. *American Journal of Physiology*, 280(6):H2833–9, June 2001.
- JEAN-CLAUDE, J., NEWMAN, K. M., LI, H., GREGORY, A. K., AND TILSON, M. D. Possible key role for plasmin in the pathogenesis of abdominal aortic aneurysms. *Surgery*, 116(2):472–8, August 1994.
- JO, H., DULL, R. O., HOLLIS, T. M., AND TARBELL, J. M. Endothelial albumin permeability is shear dependent, time dependent, and reversible. *The American Journal of Physiology*, 260(6 Pt 2):H1992–6, June 1991.
- JOSHI, M. S., PONTHER, J. L., AND LANCASTER, J. R. Cellular antioxidant and pro-oxidant actions of nitric oxide. *Free Radical Biology & Medicine*, 27(11-12):1357–66, December 1999.
- JOU, L. D., WONG, G., DISPENSA, B., LAWTON, M. T., HIGASHIDA, R. T., YOUNG, W. L., AND SALONER, D. Correlation between lumenal geometry changes and hemodynamics in fusiform intracranial aneurysms. *American Journal of Neuroradiology*, 26:2357–2363, October 2005.
- JOU, L.-D. AND MAWAD, M. E. Hemodynamic effect of Neuroform stent on intimal hyperplasia and thrombus formation in a carotid aneurysm. *Medical Engineering & Physics*, 33(5):573–80, June 2011.
- KAAZEMPUR-MOFRAD, M., WADA, S., MYERS, J., AND ETHIER, C. Mass transport and fluid flow in stenotic arteries: Axisymmetric and asymmetric models. *International Journal of Heat and Mass Transfer*, 48(21-22):4510–4517, October 2005.
- KAAZEMPUR-MOFRAD, M. R. AND ETHIER, C. R. Mass transport in an anatomically realistic human right coronary artery. *Annals of Biomedical Engineering*, 29(2):121–7, February 2001.
- KAIM, G. AND DIMROTH, P. ATP synthesis by F₁F₀-type ATP synthase is obligatorily dependent on the transmembrane voltage. *The European Molecular Biology Organization Journal*, 18(15):4118–4127, 1999.
- KAKALIS, N. M. P., MITSOS, A. P., BYRNE, J. V., AND VENTIKOS, Y. The haemodynamics of endovascular aneurysm treatment: A computational modelling approach for estimating the influence of multiple coil deployment. *IEEE Transactions on Medical Imaging*, 27:814–824, June 2008.
- KALLMES, D. F., HELM, G. A., HUDSON, S. B., ALTES, T. A., DO, H. M., MANDELL, J. W., AND CLOFT, H. J. Histologic evaluation of platinum coil embolization in an aneurysm model in rabbits. *Radiology*, 213(1):217–22, October 1999.
- KALLMES, D. F., DING, Y. H., DAI, D., KADIRVEL, R., LEWIS, D. A., AND CLOFT, H. J. A new endoluminal, flow-disrupting device for treatment of saccular aneurysms. *Stroke*, 38(8):2346–52, August 2007.
- KANG, H., BAYLESS, K. J., AND KAUNAS, R. Fluid shear stress modulates endothelial cell invasion into three-dimensional collagen matrices. *American Journal of Physiology. Heart and Circulatory Physiology*, 295(5):H2087–97, November 2008.
- KARNER, G., PERKTOL, K., AND ZEHENTNER, H. P. Computational Modeling of Macromolecule Transport in the Arterial Wall. *Computer Methods in Biomechanics and Biomedical Engineering*, 4(6):491–504, January 2001.
- KARSAJ, I. AND HUMPHREY, J. D. A mathematical model of evolving mechanical properties of intraluminal thrombus. *Biorheology*, 46(6):509–27, January 2009.
- KASELL, N. F. AND TORNER, J. C. Size of intracranial aneurysms. *Neurosurgery*, 12(3):291–7, March 1983.
- KASELL, N. F., TORNER, J. C., HALEY, E. C., JANE, J. A., ADAMS, H. P., AND KONGABLE, G. L. The international-cooperative-study-on-the-timing-of-aneurysm-surgery .1. overall management results. *Journal of Neurosurgery*, 73:18–36, July 1990a.

- KASSELL, N. F., TORNER, J. C., JANE, J. A., HALEY, E. C., AND ADAMS, H. P. The international cooperative study on the timing of aneurysm surgery .2. surgical results. *Journal of Neurosurgery*, 73:37–47, July 1990b.
- KATAOKA, K., TANEDA, M., ASAI, T., KINOSHITA, A., ITO, M., AND KURODA, R. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. *Stroke*, 30(7): 1396–401, July 1999.
- KAZI, M. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. *Journal of Vascular Surgery*, 38(6): 1283–1292, December 2003.
- KEHRER, J. P. Free radicals as mediators of tissue injury and disease. *Critical Reviews in Toxicology*, 23(1): 21–48, January 1993.
- KELMAN, G. R. Digital computer subroutine for conversion of oxygen tension into saturation. *Journal of Applied Physiology*, 21:1375–8, 1966.
- KIM, M. S., BHANG, S.-H., YANG, H. S., RIM, N. G., JUN, I., KIM, S. I., KIM, B.-S., AND SHIN, H. Development of functional fibrous matrices for the controlled release of basic fibroblast growth factor to improve therapeutic angiogenesis. *Tissue Engineering. Part A*, 16(10):2999–3010, October 2010.
- KIM, M., TAULBEE, D. B., TREMMEL, M., AND MENG, H. Comparison of two stents in modifying cerebral aneurysm hemodynamics. *Annals of Biomedical Engineering*, 36(5):726–41, May 2008.
- KIRK, J. E., EFFERSØ E, P. G., AND CHIANG, S. P. The rate of respiration and glycolysis by human and dog aortic tissue. *Journal of Gerontology*, 9(1):10–53, January 1954.
- KIRK, J. E. AND LAURSEN, T. J. Diffusion coefficients of various solutes for human aortic tissue, with special reference to variation to tissue permeability with age. *Journal of Gerontology*, 10(3):288–302, July 1955.
- KONDO, S., HASHIMOTO, N., KIKUCHI, H., HAZAMA, E., NAGATA, I., AND KATAOKA, H. Cerebral aneurysms arising at nonbranching sites. An experimental Study. *Stroke*, 28(2):398–403; discussion 403–4, February 1997.
- KONDO, S., HASHIMOTO, N., KIKUCHI, H., HAZAMA, E., NAGATA, I., AND KATAOKA, H. Apoptosis of medial smooth muscle cells in the development of saccular cerebral aneurysms in rats. *Stroke*, 29(1):181–8; discussion 189, January 1998.
- KOSHIBA, N., ANDO, J., CHEN, X., AND HISADA, T. Multiphysics simulation of blood flow and LDL transport in a porohyperelastic arterial wall model. *Journal of Biomechanical Engineering*, 129(3):374–85, June 2007.
- KRAYENBUEHL, H. AND YASARGIL, M. G. *Cerebral Angiography*. Thieme, 1982.
- KRINGS, T., ALVAREZ, H., REINACHER, P., OZANNE, A., BACCIN, C. E., GANDOLFO, C., ZHAO, W. Y., REINGES, M. H. T., AND LASJAUNIAS, P. Growth and rupture mechanism of partially thrombosed aneurysms. *Interventional Neuroradiology : Journal of Peritherapeutic Neuroradiology, Surgical Procedures and Related Neurosciences*, 13(2):117–26, June 2007.
- KRISANDA, J. M. AND PAUL, R. J. Energetics of isometric contraction in porcine carotid artery. *The American Journal of Physiology*, 246(5 Pt 1):C510–9, May 1984.
- KROLL, M. H., HELLUMS, J. D., MCINTIRE, L. V., SCHAFER, A. I., AND MOAKE, J. L. Platelets and shear stress. *Blood*, 88(5):1525–41, September 1996.
- KROON, M. Modeling of fibroblast-controlled strengthening and remodeling of uniaxially constrained collagen gels. *Journal of Biomechanical Engineering*, 132(11):111008, November 2010.
- KROON, M. AND HOLZAPFEL, G. A. A model for saccular cerebral aneurysm growth by collagen fibre remodelling. *Journal of Theoretical Biology*, 247(4): 775–87, August 2007.
- KROON, M. AND HOLZAPFEL, G. A. Modeling of saccular aneurysm growth in a human middle cerebral artery. *Journal of biomechanical engineering*, 130(5):051012, October 2008.
- KROON, M. AND HOLZAPFEL, G. A. A theoretical model for fibroblast-controlled growth of saccular cerebral aneurysms. *Journal of Theoretical Biology*, 257(1):73–83, March 2009.
- KU, D. N., GIDDENS, D. P., PHILLIPS, D. J., AND STRANDNESS, D. E. Hemodynamics of the normal human carotid bifurcation: in vitro and in vivo studies. *Ultrasound in Medicine & Biology*, 11(1): 13–26, 1985.

- KUIVANIEMI, H., PROCKOP, D. J., WU, Y., MADHATHERI, S. L., KLEINERT, C., EARLEY, J. J., JOKINEN, A., STOLLE, C., MAJAMAA, K., AND MYLLYLÄ, V. V. Exclusion of mutations in the gene for type III collagen (COL3A1) as a common cause of intracranial aneurysms or cervical artery dissections: results from sequence analysis of the coding sequences of type III collagen from 55 unrelated patients. *Neurology*, 43(12):2652–8, December 1993.
- KULCSÁR, Z., HOUDART, E., BONAFÉ, A., PARKER, G., MILLAR, J., GODDARD, A. J. P., RENOWDEN, S., GÁL, G., TUROWSKI, B., MITCHELL, K., GRAY, F., RODRIGUEZ, M., VAN DEN BERG, R., GRUBER, A., DESAL, H., WANKE, I., AND RÜFENACHT, D. A. Intra-aneurysmal thrombosis as a possible cause of delayed aneurysm rupture after flow-diversion treatment. *American Journal of Neuroradiology*, 32(1):20–5, January 2011.
- KYRIACOU, S. K. AND HUMPHREY, J. D. Influence of size, shape and properties on the mechanics of axisymmetric saccular aneurysms. *Journal of Biomechanics*, 29(8):1015–22, August 1996.
- LANGILLE, B. L. Arterial remodeling: relation to hemodynamics. *Canadian Journal of Physiology and Pharmacology*, 74(7):834–41, July 1996.
- LARRABIDE, I., KIM, M., AUGSBURGER, L., VILLARIOL, M. C., RÜFENACHT, D., AND FRANGI, A. F. Fast virtual deployment of self-expandable stents: Method and in vitro evaluation for intracranial aneurysmal stenting. *Medical Image Analysis*, May 2010.
- LARRABIDE, I., RADAELLI, A., AND FRANGI, A. Fast Virtual Stenting with Deformable Meshes: Application to Intracranial Aneurysms. In *Medical Image Computing and Computer-Assisted Intervention - MICCAI 2008, Pt II, PROCEEDINGS - Lecture notes in Computer Science*, volume 5242 of *LECTURE NOTES IN COMPUTER SCIENCE*, pages 790–797, 2008.
- LASHERAS, J. C. The Biomechanics of Arterial Aneurysms. *Annual Review of Fluid Mechanics*, 39(1):293–319, January 2007.
- LEBLANC, R., LOZANO, A. M., VAN DER REST, M., AND GUTTMANN, R. D. Absence of collagen deficiency in familial cerebral aneurysms. *Journal of Neurosurgery*, 70(6):837–40, June 1989.
- LEE, D., YUKI, I., MURAYAMA, Y., CHIANG, A., NISHIMURA, I., VINTERS, H. V., WANG, C. J., NIEN, Y.-L., ISHIL, A., WU, B. M., AND VIÑUELA, F. Thrombus organization and healing in the swine experimental aneurysm model. Part I. A histological and molecular analysis. *Journal of Neurosurgery*, 107(1):94–108, July 2007.
- LEE, V. Y., MCCLINTOCK, D. S., SANTORE, M. T., BUDINGER, G. R. S., AND CHANDEL, N. S. Hypoxia sensitizes cells to nitric oxide-induced apoptosis. *The Journal of Biological Chemistry*, 277(18):16067–74, May 2002.
- LEE, Y.-J., KIM, D. J., SUH, S. H., LEE, S.-K., KIM, J., AND KIM, D. I. Stent-assisted coil embolization of intracranial wide-necked aneurysms. *Neuroradiology*, 47(9):680–9, September 2005.
- LEIPZIG, T. J., REDELMAN, K., AND HORNER, T. G. Reducing the risk of rebleeding before early aneurysm surgery: A possible role for antifibrinolytic therapy. *Journal of Neurosurgery*, 86:220–225, February 1997.
- LEU, H., FEIGL, W., SUSANI, M., AND ODERMATT, B. Differentiation of Mononuclear Blood Cells into Macrophages, Fibroblasts and Endothelial Cells in Thrombus Organization. *Pathobiology*, 56(4):201–210, 1988.
- LI, Y.-S. J., HAGA, J. H., AND CHIEN, S. Molecular basis of the effects of shear stress on vascular endothelial cells. *Journal of Biomechanics*, 38(10):1949–71, October 2005.
- LIBBY, P. Inflammation in atherosclerosis. *Nature*, 420(6917):868–74, 2002.
- LIEBER, B. B., STANCAMPANO, A. P., AND WAKHLOO, A. K. Alteration of hemodynamics in aneurysm models by stenting: influence of stent porosity. *Annals of Biomedical Engineering*, 25(3):460–9, 1997.
- LIU, T.-M., LI, Y.-C., AND WANG, T.-C. Hemodynamics altered by placing helix stents in an aneurysm at a 45 degrees angle to the curved vessel. *Physics in Medicine and Biology*, 53(14):3763–76, July 2008.
- LIU, C. Y., ESKIN, S., AND HELSUMS, J. The oxygen permeability of cultured endothelial cell monolayers. In PLENUM, editor, *Oxygen Transport to Tissue XV*. New York, 1992.
- LIU, W., JAWERTH, L. M., SPARKS, E. A., FALVO, M. R., HANTGAN, R. R., SUPERFINE, R., LORD, S. T., AND GUTHOLD, M. Fibrin fibers have extraordinary extensibility and elasticity. *Science (New York, N.Y.)*, 313(5787):634, August 2006.

- LOSCALZO, J. Oxidative stress in endothelial cell dysfunction and thrombosis. *Pathophysiology of Haemostasis and Thrombosis*, 32(5-6):359–60, 2002.
- LOSSO, J. N. AND BAWADI, H. A. Hypoxia inducible factor pathways as targets for functional foods. *Journal of Agricultural and Food Chemistry*, 53(10): 3751–68, May 2005.
- LU, G., HUANG, L., ZHANG, X. L., WANG, S. Z., HONG, Y., HU, Z., AND GENG, D. Y. Influence of hemodynamic factors on rupture of intracranial aneurysms: patient-specific 3D mirror aneurysms model computational fluid dynamics simulation. *American journal of neuroradiology*, 32(7):1255–61, August 2011.
- LUBICZ, B., LECLERC, X., GAUVRIT, J. Y., LEJEUNE, J. P., AND PRUVO, J. P. Giant vertebrobasilar aneurysms: Endovascular treatment and long-term follow-up. *Neurosurgery*, 55:316–323, August 2004.
- LUO, B., YANG, X., WANG, S., LI, H., CHEN, J., YU, H., ZHANG, Y., ZHANG, Y., MU, S., LIU, Z., AND DING, G. High shear stress and flow velocity in partially occluded aneurysms prone to recanalization. *Stroke; a journal of cerebral circulation*, 42(3):745–53, March 2011.
- LYLYK, P., COHEN, J. E., CERATTO, R., FERRARIO, A., AND MIRANDA, C. Combined endovascular treatment of dissecting vertebral artery aneurysms by using stents and coils. *Journal of Neurosurgery*, 94(3):427–32, March 2001.
- LYLYK, P., FERRARIO, A., PABON, B., MIRANDA, C., AND DOROSZUK, G. Buenos aires experience with the neuroform self-expanding stent for the treatment of intracranial aneurysms. *Journal of Neurosurgery*, 102:235–241, February 2005.
- LYLYK, P., MIRANDA, C., CERATTO, R., FERRARIO, A., SCRIVANO, E., LUNA, H. R., BEREZ, A. L., TRAN, Q., NELSON, P. K., AND FIORELLA, D. Curative endovascular reconstruction of cerebral aneurysms with the pipeline embolization device: the Buenos Aires experience. *Neurosurgery*, 64(4):632–42; discussion 642–3; quiz N6, April 2009.
- MA, B., HARBAUGH, R. E., AND RAGHAVAN, M. L. Three-dimensional geometrical characterization of cerebral aneurysms. *Annals of Biomedical Engineering*, 32(2):264–73, February 2004.
- MA, P., LI, X., AND KU, D. N. Convective mass transfer at the carotid bifurcation. *Journal of Biomechanics*, 30(6):565–71, June 1997.
- MALEK, A. M., ALPER, S. L., AND IZUMO, S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA: Journal of the American Medical Association*, 282:2035–2042, December 1999.
- MARUISHI, M., SHIMA, K., CHIGASAKI, H., AND TSUCHIYA, K. Giant intracranial aneurysm with rapid thrombus formation and intramural hemorrhage—case report. *Neurologia Medico-Chirurgica*, 34(12):829–31, December 1994.
- MASSON, I., BOUTOUYRIE, P., LAURENT, S., HUMPHREY, J. D., AND ZIDI, M. Characterization of arterial wall mechanical behavior and stresses from human clinical data. *Journal of Biomechanics*, 41(12):2618–27, August 2008.
- MATSUMOTO, T., TSUCHIDA, M., AND SATO, M. Change in intramural strain distribution in rat aorta due to smooth muscle contraction and relaxation. *The American journal of physiology*, 271(4 Pt 2):H1711–6, October 1996.
- MAYBERG, M. R., BATJER, H. H., DACEY, R., DIRINGER, M., HALEY, E. C., HEROS, R. C., STERNAU, L. L., TORNER, J., ADAMS, H. P., FEINBERG, W., AND THIES, W. Guidelines for the management of aneurysmal subarachnoid hemorrhage - a statement for health-care professionals from a special writing group of the stroke-council, American-Heart-Association. *Stroke*, 25:2315–2328, November 1994.
- MENG, H., WANG, Z., HOI, Y., GAO, L., METAXA, E., SWARTZ, D. D., AND KOLEGA, J. Complex hemodynamics at the apex of an arterial bifurcation induces vascular remodeling resembling cerebral aneurysm initiation. *Stroke*, 38(6):1924–31, June 2007.
- MERICLE, R. A., LANZINO, G., WAKHLOO, A. K., GUTERMAN, L. R., AND HOPKINS, L. N. Stenting and secondary coiling of intracranial internal carotid artery aneurysm: Technical case report. *NEUROSURGERY*, 43:1229–1233, November 1998.
- MITCHELL, P. AND JAKUBOWSKI, J. Estimate of the maximum time interval between formation of cerebral aneurysm and rupture. *Journal of Neurology, Neurosurgery, and Psychiatry*, 69(6):760–7, December 2000.
- MOAKE, J. L., TURNER, N. A., STATHOPOULOS, N. A., NOLASCO, L., AND HELLUMS, J. D. Shear-induced platelet aggregation can be mediated by vWF released from platelets, as well as by exogenous large

- or unusually large vWF multimers, requires adenosine diphosphate, and is resistant to aspirin. *Blood*, 71(5):1366–74, May 1988.
- MOLYNEUX, A. J., KERR, R. S. C., YU, L. M., CLARKE, M., SNEADE, M., YARNOLD, J. A., SANDERCOCK, P., AND ISAT COLLABORATIVE GRP. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and . *Lancet*, 366(9488):809–817, September 2005.
- MONSON, K. L., GOLDSMITH, W., BARBARO, N. M., AND MANLEY, G. T. Axial mechanical properties of fresh human cerebral blood vessels. *Journal of Biomechanical Engineering*, 125(2):288–94, April 2003.
- MONSON, K. L., GOLDSMITH, W., BARBARO, N. M., AND MANLEY, G. T. Significance of source and size in the mechanical response of human cerebral blood vessels. *Journal of Biomechanics*, 38(4):737–44, April 2005.
- MOORE, J. A. AND ETHIER, C. R. Oxygen mass transfer calculations in large arteries. *Journal of Biomechanical Engineering*, 119(4):469–75, November 1997.
- MOORE, J. E., BÜRKI, E., SUCIU, A., ZHAO, S., BURNIER, M., BRUNNER, H. R., AND MEISTER, J. J. A device for subjecting vascular endothelial cells to both fluid shear stress and circumferential cyclic stretch. *Annals of Biomedical Engineering*, 22(4):416–22, 1994.
- MOORE, S., DAVID, T., CHASE, J. G., ARNOLD, J., AND FINK, J. 3D models of blood flow in the cerebral vasculature. *Journal of biomechanics*, 39(8):1454–63, January 2006.
- MORALES, H., LARRABIDE, I., MACHO, J., BLASCO, J., SAN ROMAN, L., AND FRANGI, A. Evaluation of Patient-Specific Intra-Aneurysmal Hemodynamics after Endovascular Treatments by CFD Models. In *Proceedings of the 2011 SCATh Joint Workshop on New Technologies for Computer/Robot Assisted Surgery*, 2011.
- MOWER, W., QUINONES, W., AND GAMBHIR, S. Effect of intraluminal thrombus on abdominal aortic aneurysm wall stress. *Journal of Vascular Surgery*, 26(4):602–608, October 1997.
- MURAYAMA, Y., NIEN, Y. L., DUCKWILER, G., GOBIN, Y. P., JAHAN, R., FRAZEE, J., MARTIN, N., AND VINUELA, F. Guglielmi Detachable Coil embolization of cerebral aneurysms: 11 years experience. *Journal of Neuroradiology*, 98:959–966, May 2003.
- MURAYAMA, Y., VIÑUELA, F., SUZUKI, Y., AKIBA, Y., ULIOA, A., DUCKWILER, G. R., GOBIN, Y. P., VINTERS, H. V., IWAKI, M., AND ABE, T. Development of the biologically active Guglielmi detachable coil for the treatment of cerebral aneurysms. Part II: an experimental study in a swine aneurysm model. *American Journal of Neuroradiology*, 20(10):1992–9, 1999.
- MURRAY, C. J. L. AND LOPEZ, A. D. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*, 349:1436–1442, May 1997a.
- MURRAY, C. J. L. AND LOPEZ, A. D. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*, 349:1269–1276, May 1997b.
- MURRAY, J. D. On the molecular mechanism of facilitated oxygen diffusion by haemoglobin and myoglobin. *Proceedings of the Royal Society of London. Series B, Containing papers of a Biological character. Royal Society (Great Britain)*, 178(50):95–110, June 1971.
- MURTADA, S.-I., KROON, M., AND HOLZAPFEL, G. A. A calcium-driven mechanochemical model for prediction of force generation in smooth muscle. *Biomechanics and Modeling in Mechanobiology*, 9(6):749–62, December 2010.
- NAGAHIRO, S., TAKADA, A., GOTO, S., KAI, Y., AND USHIO, Y. Thrombosed growing giant aneurysms of the vertebral artery: growth mechanism and management. *Journal of Neurosurgery*, 82(5):796–801, May 1995.
- NAKAJIMA, N., NAGAHIRO, S., SANO, T., SATOMI, J., AND SATOH, K. Phenotypic modulation of smooth muscle cells in human cerebral aneurysmal walls. *Acta Neuropathologica*, 100(5):475–80, November 2000.
- NEIL-DWYER, G., BARTLETT, J. R., NICHOLLS, A. C., NARCISI, P., AND POPE, F. M. Collagen deficiency and ruptured cerebral aneurysms. A clinical and biochemical study. *Journal of Neurosurgery*, 59(1):16–20, July 1983.

- NELSON, P. K., LYLYK, P., SZIKORA, I., WETZEL, S. G., WANKE, I., AND FIORELLA, D. The pipeline embolization device for the intracranial treatment of aneurysms trial. *American Journal of Neuroradiology*, 32(1):34–40, January 2011.
- NESBITT, W. S., WESTEIN, E., TOVAR-LOPEZ, F. J., TOLOUEI, E., MITCHELL, A., FU, J., CARBERRY, J., FOURAS, A., AND JACKSON, S. P. A shear gradient-dependent platelet aggregation mechanism drives thrombus formation. *Nature Medicine*, 15(6):665–73, June 2009.
- NIHLB. National Institutes of Heart Lungs and Blood. Morbidity & mortality: 2009 Chart Book on cardiovascular, lung and blood diseases. Technical report, 2009.
- NIINIKOSKI, J., HEUGHAN, C., AND HUNT, T. Oxygen tensions in the aortic wall of normal rabbits. *Atherosclerosis*, 17(3):353–359, May 1973.
- NISSEN, R., CARDINALE, G. J., AND UDENFRIEND, S. Increased turnover of arterial collagen in hypertensive rats. *Proceedings of the National Academy of Sciences of the United States of America*, 75(1):451–3, January 1978.
- OHTA, M., WETZEL, S. G., DANTAN, P., BACHELET, C., LOVBLAD, K. O., YILMAZ, H., FLAUD, P., AND RUFENACHT, D. A. Rheological changes after stenting of a cerebral aneurysm: A finite element modeling approach. *Cardiovascular and Interventional Radiology*, 28:768–772, 2005.
- OSTERGAARD, J. R. AND OXLUND, H. Collagen type III deficiency in patients with rupture of intracranial saccular aneurysms. *Journal of neurosurgery*, 67(5): 690–6, November 1987.
- OWENS, G. K. Regulation of differentiation of vascular smooth muscle cells. *Physiological Reviews*, 75(3): 487–517, July 1995.
- PACKHAM, M. A., ROWSELL, H. C., JORGENSEN, L., AND MUSTARD, J. F. Localized protein accumulation in the wall of the aorta. *Experimental and Molecular Pathology*, 7(2):214–32, October 1967.
- PAGE-MCCAW, A., EWALD, A. J., AND WERB, Z. Matrix metalloproteinases and the regulation of tissue remodelling. *Nature Reviews. Molecular cell biology*, 8(3):221–33, March 2007.
- PARKINSON, R. J., EDDLEMAN, C. S., BATJER, H. H., AND BENDOK, B. R. Giant intracranial aneurysms: Endovascular challenges. *Neurosurgery*, 62:1336–1345, June 2008.
- PATANKAR, S. V. *Numerical Heat Transfer and Fluid Flow*. Hemisphere Publishing Corporation, 1980.
- PEERLESS, S. J. AND DRAKE, C. G. Treatment of giant cerebral aneurysms of the anterior circulation. *Neurosurgical Review*, 5(4):149–154, December 1982.
- PENN, M. S., SAIDEL, G. M., AND CHISOLM, G. M. Relative significance of endothelium and internal elastic lamina in regulating the entry of macromolecules into arteries in vivo. *Circulation Research*, 74(1):74–82, January 1994.
- PENTIMALLI, L., MODESTI, A., VIGNATI, A., MARCHESE, E., ALBANESE, A., DI ROCCO, F., COLETTI, A., DI NARDO, P., FANTINI, C., TIRPAKOVA, B., AND MAIRA, G. Role of apoptosis in intracranial aneurysm rupture. *Journal of Neurosurgery*, 101(6): 1018–25, December 2004.
- PHELPS, J. E. AND DEPAOLA, N. Spatial variations in endothelial barrier function in disturbed flows in vitro. *American Journal of Physiology. Heart and Circulatory Physiology*, 278(2):H469–76, February 2000.
- PIETILÄ, K. AND JAAKKOLA, O. Effect of hypoxia on the synthesis of glycosaminoglycans and collagen by rabbit aortic smooth muscle cells in culture. *Atherosclerosis*, 50(2):183–90, February 1984.
- PITTMAN, R. N. AND DULING, B. R. Oxygen sensitivity of vascular smooth muscle. I. In vitro studies. *Microvascular Research*, 6(2):202–11, September 1973.
- PROSI, M., ZUNINO, P., PERKTOLD, K., AND QUARTERONI, A. Mathematical and numerical models for transfer of low-density lipoproteins through the arterial walls: a new methodology for the model set up with applications to the study of disturbed luminal flow. *Journal of Biomechanics*, 38:903–917, April 2005.
- PURVES, W. K., SADAVA, D., ORIAN, G. H., AND HELLER, H. C. *Life: the science of biology*. Sinauer Associates Inc, 6th edition, 2001.
- QIU, Y. AND TARBELL, J. M. Numerical Simulation of Oxygen Mass Transfer in a Compliant Curved Tube Model of a Coronary Artery. *Annals of Biomedical Engineering*, 28(1):26–38, January 2000.
- RACHEV, A. AND HAYASHI, K. Theoretical Study of the Effects of Vascular Smooth Muscle Contraction on Strain and Stress Distributions in Arteries. *Annals of Biomedical Engineering*, 27(4):459–468, July 1999.

- RADAELLI, A. G., AUGSBURGER, L., CEBRAL, J. R., OHTA, M., RUEFENACHT, D. A., BALOSSINO, R., BENNDORF, G., HOSE, D. R., MARZO, A., METCALFE, R., MORTIER, P., MUT, F., REYMOND, P., SOCCI, L., VERHEGHE, B., AND FRANGI, A. F. Reproducibility of haemodynamical simulations in a subject-specific stented aneurysm model - A report on the Virtual Intracranial Stenting Challenge 2007. *Journal of Biomechanics*, 41:2069–2081, July 2008.
- RAFTOPOULOS, C. Is surgical clipping becoming underused? *Acta Neurochirurgica*, 147:117–124, February 2005.
- RAGHAVAN, M. L., MA, B., AND HARBAUGH, R. E. Quantified aneurysm shape and rupture risk. *Journal of Neurosurgery*, 102(2):355–62, March 2005.
- RAPPITSCH, G. AND PERKTOLD, K. Pulsatile Albumin Transport in Large Arteries: A Numerical Simulation Study. *Journal of Biomechanical Engineering*, 118(4):511, 1996a.
- RAPPITSCH, G., PERKTOLD, K., AND PERNKOPF, E. Numerical modelling of shear-dependent mass transfer in large arteries. *International Journal for Numerical Methodes in Fluids*, 25(7):847–857, October 1997.
- RAPPITSCH, G. AND PERKTOLD, K. Computer simulation of convective diffusion processes in large arteries. *Journal of Biomechanics*, 29(2):207–15, February 1996b.
- RAY, J. B., ARAB, S., DENG, Y., LIU, P., PENN, L., COURTMAN, D. W., AND WARD, M. E. Oxygen regulation of arterial smooth muscle cell proliferation and survival. *American Journal of Physiology. Heart and Circulatory Physiology*, 294(2):H839–52, February 2008.
- RAYZ, V. L., BOUSSEL, L., GE, L., LEACH, J. R., MARTIN, A. J., LAWTON, M. T., MCCULLOCH, C., AND SALONER, D. Flow residence time and regions of intraluminal thrombus deposition in intracranial aneurysms. *Annals of Biomedical Engineering*, 38(10):3058–69, October 2010.
- RAYZ, V. L., BOUSSEL, L., LAWTON, M. T., ACEVEDO-BOLTON, G., GE, L., YOUNG, W. L., HIGASHIDA, R. T., AND SALONER, D. Numerical modeling of the flow in intracranial aneurysms: Prediction of regions prone to thrombus formation. *Annals of Biomedical Engineering*, 36:1793–1804, November 2008.
- REININGER, A. J., HEINZMANN, U., REININGER, C. B., FRIEDRICH, P., AND WURZINGER, L. J. Flow mediated fibrin thrombus formation in an endothelium-lined model of arterial branching. *Thrombosis Research*, 74(6):629–41, June 1994.
- REYMOND, P., BOHRAUS, Y., PERREN, F., LAZEYRAS, F., AND STERGIOPULOS, N. Validation of a patient-specific one-dimensional model of the systemic arterial tree. *American journal of physiology. Heart and circulatory physiology*, 301(3):H1173–82, September 2011.
- REYMOND, P., MERENDA, F., PERREN, F., RÜFENACHT, D., AND STERGIOPULOS, N. Validation of a one-dimensional model of the systemic arterial tree. *American journal of physiology. Heart and circulatory physiology*, 297(1):H208–22, July 2009.
- RINKEL, G. J. E., DJIBUTI, M., ALGRA, A., AND VAN GIJN, J. Prevalence and risk of rupture of intracranial aneurysms - A systematic review. *Stroke*, 29(1):251–256, January 1998.
- RISSANEN, E., TRANBERG, H. K., AND NIKINMAA, M. Oxygen availability regulates metabolism and gene expression in trout hepatocyte cultures. *American Journal of Physiology: Regulatory Integrative and Comparative Physiology*, 291(5):R1507–R1515, 2006.
- RIVERO-ARIAS, O., GRAY, A., AND WOLSTENHOLME, J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. *Cost Effectiveness and Resource Allocation : C/E*, 8:6, January 2010.
- ROACH, M. R. AND BURTON, A. C. The reason for the shape of the distensibility curves of arteries. *Canadian Journal of Biochemistry and Physiology*, 35(8):681–90, August 1957.
- ROOS, Y. AND VERMEULEN, M. Prevention of early rebleeding. *Journal of Neurosurgery*, 98:1148–1149, May 2003.
- ROSAMOND, W., FLEGAL, K., FURIE, K., GO, A., GREENLUND, K., HAASE, N., HAILPERN, S. M., HO, M., HOWARD, V., KISSELA, B., KITTNER, S., LLOYD-JONES, D., MCDERMOTT, M., MEIGS, J., MOY, C., NICHOL, G., O'DONNELL, C., ROGER, V., SORLIE, P., STEINBERGER, J., THOM, T., WILSON, M., HONG, Y., AND AMERICAN HEART ASSOC STAT COMM STROKE. Heart disease and stroke statistics - 2008 update - A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, 117:E25–E146, January 2008.

- ROSS, R. The smooth muscle cell. II. Growth of smooth muscle in culture and formation of elastic fibers. *The Journal of Cell Biology*, 50(1):172–86, July 1971.
- ROSS, R. Atherosclerosis—an inflammatory disease. *The New England Journal of Medicine*, 340(2):115–26, January 1999.
- RUBANYI, G. M. AND VANHOUTTE, P. M. Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. *The American Journal of Physiology*, 250(5 Pt 2):H822–7, May 1986.
- RUCKLIDGE, G., MILNE, G., MCGAW, B., MILNE, E., AND ROBINS, S. Turnover rates of different collagen types measured by isotope ratio mass spectrometry. *Biochimica et Biophysica Acta (BBA) - General Subjects*, 1156(1):57–61, December 1992.
- RUGGERI, Z. M. Structure of von Willebrand factor and its function in platelet adhesion and thrombus formation. *Best Practice & Research. Clinical Haematology*, 14(2):257–79, June 2001.
- RUGGERI, Z. M. The role of von Willebrand factor in thrombus formation. *Thrombosis Research*, 120 Suppl:S5–9, January 2007.
- RUGGIERI, P. M., POULOS, N., MASARYK, T. J., ROSS, J. S., OBUCHOWSKI, N. A., AWAD, I. A., BRAUN, W. E., NALLY, J., LEWIN, J. S., AND MODIC, M. T. Occult intracranial aneurysms in polycystic kidney disease: screening with MR angiography. *Radiology*, 191(1):33–9, April 1994.
- SAKAKI, T., KOHMURA, E., KISHIGUCHI, T., YUGUCHI, T., YAMASHITA, T., AND HAYAKAWA, T. Loss and apoptosis of smooth muscle cells in intracranial aneurysms. Studies with in situ DNA end labeling and antibody against single-stranded DNA. *Acta neurochirurgica*, 139(5):469–74; discussion 474–5, January 1997.
- SAKAMOTO, N., OHASHI, T., AND SATO, M. Effect of fluid shear stress on migration of vascular smooth muscle cells in cocultured model. *Annals of Biomedical Engineering*, 34(3):408–15, March 2006.
- SAKAMOTO, T. AND SEIKI, M. A membrane protease regulates energy production in macrophages by activating hypoxia-inducible factor-1 via a non-proteolytic mechanism. *The Journal of Biological Chemistry*, 285(39):29951–64, September 2010.
- SANCHORAWALA, H. AND KEANEY, J. F. J. Physiology of Vascular Homeostasis. In BECKER, R. C., editor, *Textbook of Coronary Thrombosis and Thrombolysis*, chapter 9, pages 139–154. Kluwer Academic Publishers, Norwell, Massachusetts 02061, USA, 1997.
- SANTILLI, S. M., STEVENS, R. B., ANDERSON, J. G., PAYNE, W. D., AND CALDWELL, M. D. Transarterial wall oxygen gradients at the dog carotid bifurcation. *The American Journal of Physiology*, 268(1 Pt 2):H155–61, January 1995.
- SANTILLI, S. M., TRETINYAK, A. S., AND LEE, E. S. Transarterial wall oxygen gradients at the deployment site of an intra-arterial stent in the rabbit. *American Journal of Physiology - Heart and Circulatory Physiology*, 279:H1518–H1525, October 2000.
- SATTA, J., LÄÄRÄ, E., AND JUVONEN, T. Intraluminal thrombus predicts rupture of an abdominal aortic aneurysm. *Journal of Vascular Surgery*, 23(4):737–9, April 1996.
- SAWICKI, G., SANDERS, E. J., SALAS, E., WOZNIAK, M., RODRIGO, J., AND RADOMSKI, M. W. Localization and translocation of MMP-2 during aggregation of human platelets. *Thrombosis and Haemostasis*, 80(5):836–9, November 1998.
- SCHEBESCH, K.-M., DOENITZ, C., ZOEPHEL, R., FINKENZELLER, T., AND BRAWANSKI, A. T. Recurrent subarachnoid hemorrhage caused by a de novo basilar tip aneurysm developing within 8 weeks after clipping of a ruptured anterior communicating artery aneurysm: case report. *Neurosurgery*, 62(1):E259–60; discussion E260, January 2008.
- SCHIEVINK, W. I. Genetics of intracranial aneurysms. *Neurosurgery*, 40(4):651–62; discussion 662–3, April 1997a.
- SCHIEVINK, W. I. Intracranial aneurysms. *New England Journal of Medicine*, 336:28–40, April 1997b.
- SCHIEVINK, W. I., PIEPGRAS, D. G., AND WIRTH, F. P. Rupture of previously documented small asymptomatic saccular intracranial aneurysms. Report of three cases. *Journal of Neurosurgery*, 76(6):1019–24, June 1992.
- SCHNEIDERMAN, G. *Arterial wall oxygen transport system: computer simulation and experimental study, including a theoretical analysis of various tissue oxygenation microelectrodes*. PhD thesis, Northwestern University, 1975.
- SCHNEIDERMAN, G. AND GOLDSTICK, T. Significance of luminal plasma layer resistance in arterial wall oxygen supply. *Atherosclerosis*, 31(1):11–20, September 1978a.

- SCHNEIDERMAN, G. AND GOLDSTICK, T. K. Carbon monoxide-induced arterial wall hypoxia and atherosclerosis. *Atherosclerosis*, 30(1):1–15, May 1978b.
- SCHNEIDERMAN, G., GOLDSTICK, T., AND ZUCKERMAN, L. Simulation of the oxygen transport system in the human arterial wall. In *Paper 13d at the 67th Annual Meeting of the American Institute of Chemical Engineers*, Washington, D.C., 1974.
- SCHNEIDERMAN, G., MOCKROS, L. F., AND GOLDSTICK, T. K. Effect of pulsatility on oxygen transport to the human arterial wall. *Journal of Biomechanics*, 15(11):849–858, January 1982.
- SCHRIEFL, A. J., ZEINDLINGER, G., PIERCE, D. M., REGITNIG, P., AND HOLZAPFEL, G. A. Determination of the layer-specific distributed collagen fibre orientations in human thoracic and abdominal aortas and common iliac arteries. *Journal of the Royal Society, Interface*, 9(71):1275–86, June 2012.
- SCHUBIGER, O., VALAVANIS, A., AND WICHMANN, W. Growth-mechanism of giant intracranial aneurysms; demonstration by CT and MR imaging. *Neuroradiology*, 29(3):266–71, January 1987.
- SCHULTZ, G. S. AND GRANT, M. B. Neovascular growth factors. *Eye*, 5 (Pt 2):170–80, January 1991.
- SCHULZ, E., JANSEN, T., WENZEL, P., DAIBER, A., AND MÜNDEL, T. Nitric oxide, tetrahydrobiopterin, oxidative stress, and endothelial dysfunction in hypertension. *Antioxidants & Redox Signaling*, 10(6):1115–26, June 2008.
- SCHULZE-BAUER, C. A. J., MÖRTH, C., AND HOLZAPFEL, G. A. Passive biaxial mechanical response of aged human iliac arteries. *Journal of Biomechanical Engineering*, 125(3):395–406, June 2003.
- SCHULZE-BAUER, C. A. J., REGITNIG, P., AND HOLZAPFEL, G. A. Mechanics of the human femoral adventitia including the high-pressure response. *American Journal of Physiology. Heart and Circulatory Physiology*, 282(6):H2427–40, June 2002.
- SCOTT, N. A., CIPOLLA, G. D., ROSS, C. E., DUNN, B., MARTIN, F. H., SIMONET, L., AND WILCOX, J. N. Identification of a potential role for the adventitia in vascular lesion formation after balloon overstretch injury of porcine coronary arteries. *Circulation*, 93(12):2178–87, June 1996.
- SEKHAR, L. N. AND HEROS, R. C. Origin, growth, and rupture of saccular aneurysms: a review. *Neurosurgery*, 8(2):248–60, February 1981.
- SEMENZA, G. L. Life with oxygen. *Science*, 318(5847):62–4, October 2007a.
- SEMENZA, G. L. Oxygen-dependent regulation of mitochondrial respiration by hypoxia-inducible factor 1. *The Biochemical Journal*, 405(1):1–9, July 2007b.
- SERBINEN, F. A. Balloon catheterization and occlusion of major cerebral vessels. *Journal of Neurosurgery*, 41:125–145, 1974.
- SHANKARAN, H., ALEXANDRIDIS, P., AND NEELAMEGHAM, S. Aspects of hydrodynamic shear regulating shear-induced platelet activation and self-association of von Willebrand factor in suspension. *Blood*, 101(7):2637–45, April 2003.
- SHAPIRO, S. D., ENDICOTT, S. K., PROVINCE, M. A., PIERCE, J. A., AND CAMPBELL, E. J. Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-aspartate and nuclear weapons-related radiocarbon. *The Journal of Clinical Investigation*, 87(5):1828–34, May 1991.
- SHARMA, B. S., GUPTA, A., AHMAD, F. U., SURI, A., AND MEHTA, V. S. Surgical management of giant intracranial aneurysms. *Clinical Neurology and Neurosurgery*, 110(7):674–81, July 2008.
- SHEKHONIN, B. V., DOMOGATSKY, S. P., MUZYKANTOV, V. R., IDELSON, G. L., AND RUKOSUEV, V. S. Distribution of type I, III, IV and V collagen in normal and atherosclerotic human arterial wall: immunomorphological characteristics. *Collagen and Related Research*, 5(4):355–68, September 1985.
- SHERIFF, J., BLUESTEIN, D., GIRDHAR, G., AND JESTY, J. High-shear stress sensitizes platelets to subsequent low-shear conditions. *Annals of Biomedical Engineering*, 38(4):1442–50, April 2010.
- SHI, Z.-D. AND TARBELL, J. M. Fluid flow mechanotransduction in vascular smooth muscle cells and fibroblasts. *Annals of biomedical engineering*, 39(6):1608–19, June 2011.
- SHOJIMA, M., OSHIMA, M., TAKAGI, K., TORII, R., HAYAKAWA, M., KATADA, K., MORITA, A., AND KIRINO, T. Magnitude and role of wall shear stress on cerebral aneurysm - Computational fluid dynamic study of 20 middle cerebral artery aneurysms. *Stroke*, 35:2500–2505, November 2004.

- SHULTZ, P. J. AND RAIJ, L. Endogenously synthesized nitric oxide prevents endotoxin-induced glomerular thrombosis. *Journal of Clinical Investigation*, 90 (5):1718–1725, 1992.
- SIOW, R. C. M., MALLAWAARACHCHI, C. M., AND WEISSBERG, P. L. Migration of adventitial myofibroblasts following vascular balloon injury: insights from in vivo gene transfer to rat carotid arteries. *Cardiovascular Research*, 59(1):212–21, July 2003.
- SMITH, S. A. The cell-based model of coagulation. *Journal of Veterinary Emergency and Critical Care*, 19(1):3–10, February 2009.
- SOMER, J. B. AND SCHWARTZ, C. J. Focal (3 H)cholesterol uptake in the pig aorta. 2. Distribution of (3 H)cholesterol across the aortic wall in areas of high and low uptake in vivo. *Atherosclerosis*, 16(3):377–88, 1972.
- SPEELMAN, L., SCHURINK, G. W. H., BOSBOOM, E. M. H., BUTH, J., BREEUWER, M., VAN DE VOSSE, F. N., AND JACOBS, M. H. The mechanical role of thrombus on the growth rate of an abdominal aortic aneurysm. *Journal of Vascular Surgery*, 51(1):19–26, 2010.
- STALLING, D. AND ZOCKLER, M. Amira User Guide. *Zuse Institute Berlin and Graphics Template Software Inc., San Diego, USA*, 2001.
- STAMATOPOULOS, C., MATHIOULAKIS, D. S., PAPA-HARILAOU, Y., AND KATSAMOURIS, A. Experimental unsteady flow study in a patient-specific abdominal aortic aneurysm model. *Experiments in Fluids*, 50(6):1695–1709, December 2010.
- STANGEBY, D. K. AND ETHIER, C. R. Computational Analysis of Coupled Blood-Wall Arterial LDL Transport. *Journal of Biomechanical Engineering*, 124(1): 1, 2002a.
- STANGEBY, D. K. AND ETHIER, C. R. Coupled computational analysis of arterial LDL transport – effects of hypertension. *Computer Methods in Biomechanics and Biomedical Engineering*, 5(3):233–41, June 2002b.
- STANLEY, J. R., WOODLEY, D. T., KATZ, S. I., AND MARTIN, G. R. Structure and function of basement membrane. *The Journal of Investigative Dermatology*, 79 Suppl 1:69s–72s, July 1982.
- STARK, D. D., BRADLEY, W. G., AND BRADLEY, W. G. *Magnetic Resonance Imaging*. C.V. Mosby, 3rd edition, 1999.
- STAVENOW, L. AND BERG, A. L. Effects of hypoxia and other injurious stimuli on collagen secretion and intracellular growth stimulating activity of bovine aortic smooth muscle cells in culture. *Artery*, 14(4): 198–208, January 1987.
- STEBBENS, W. E. Ultrastructure of aneurysms. *Archives of Neurology*, 32(12):798–807, December 1975.
- STEINBRECH, D. S., LONGAKER, M. T., MEHRARA, B. J., SAADEH, P. B., CHIN, G. S., GERRETS, R. P., CHAU, D. C., ROWE, N. M., AND GITTES, G. K. Fibroblast response to hypoxia: the relationship between angiogenesis and matrix regulation. *The Journal of Surgical Research*, 84(2):127–33, June 1999.
- STEINMAN, D. A., MILNER, J. S., NORLEY, C. J., LOWNIE, S. P., AND HOLDSWORTH, D. W. Image-based computational simulation of flow dynamics in a giant intracranial aneurysm. *American Journal of Neuroradiology*, 24:559–566, April 2003.
- STENMARK, K. R., GERASIMOVSKAYA, E., NEMENOFF, R. A., AND DAS, M. Hypoxic activation of adventitial fibroblasts: role in vascular remodeling. *Chest*, 122(6 Suppl):326S–334S, December 2002.
- STRONG, K., MATHERS, C., AND BONITA, R. Preventing stroke: saving lives around the world. *Lancet Neurology*, 6:182–187, February 2007.
- STUHNE, G. R. AND STEINMAN, D. A. Finite-element modeling of the hemodynamics of stented aneurysms. *Journal of Biomedical Engineering*, 126:382–387, June 2004.
- SUH, G.-Y., LES, A. S., TENFORDE, A. S., SHADDEN, S. C., SPILKER, R. L., YEUNG, J. J., CHENG, C. P., HERFKENS, R. J., DALMAN, R. L., AND TAYLOR, C. A. Quantification of particle residence time in abdominal aortic aneurysms using magnetic resonance imaging and computational fluid dynamics. *Annals of Biomedical Engineering*, 39(2):864–83, February 2011.
- SUN, N., LEUNG, J. H., WOOD, N. B., HUGHES, A. D., THOM, S. A., CHESHIRE, N. J., AND XU, X. Y. Computational analysis of oxygen transport in a patient-specific model of abdominal aortic aneurysm with intraluminal thrombus. *The British Journal of Radiology*, 82 Spec No:S18–23, January 2009.
- SUN, N., WOOD, N. B., HUGHES, A. D., THOM, S. A. M., AND XU, X. Y. Fluid-wall modelling of mass transfer in an axisymmetric stenosis: effects

- of shear-dependent transport properties. *Annals of biomedical engineering*, 34(7):1119–28, July 2006.
- SUN, N., WOOD, N. B., HUGHES, A. D., THOM, S. A. M., AND XU, X. Y. Influence of pulsatile flow on LDL transport in the arterial wall. *Annals of Biomedical Engineering*, 35(10):1782–90, October 2007.
- SZIKORA, I., BERENTEI, Z., KULCSAR, Z., BARATH, K., BEREZ, A., BOSE, A., AND NYARY, I. Endovascular treatment of intracranial aneurysms with parent vessel reconstruction using balloon and self expandable stents. *Acta Neurochirurgica*, 148(7):711–23; discussion 723, July 2006a.
- SZIKORA, I., BERENTEI, Z., KULCSAR, Z., MAROSFOI, M., VAJDA, Z. S., LEE, W., BEREZ, A., AND NELSON, P. K. Treatment of intracranial aneurysms by functional reconstruction of the parent artery: the Budapest experience with the pipeline embolization device. *American Journal of Neuroradiology*, 31(6):1139–47, June 2010.
- SZIKORA, I., SEIFERT, P., HANZELY, Z., KULCSAR, Z., BERENTEI, Z., MAROSFOI, M., CZIRJAK, S., VAJDA, J., AND NYARY, I. Histopathologic evaluation of aneurysms treated with Guglielmi detachable coils or matrix detachable microcoils. *American Journal of Neuroradiology*, 27(2):283–8, February 2006b.
- SZIKORA, I., WAKHLOO, A. K., GUTERMAN, L. R., CHAVIS, T. D., DAWSON, R. C., HERGENROTHER, R. W., TWYFORD, R. H., AND HOPKINS, L. N. Initial experience with collagen-filled Guglielmi detachable coils for endovascular treatment of experimental aneurysms. *American Journal of Neuroradiology*, 18(4):667–72, April 1997.
- SZIKORA, I., PAAL, G., UGRON, A., NASZTANOVICS, F., MAROSFOI, M., BERENTEI, Z., KULCSAR, Z., LEE, W., BOJTAR, I., AND NYARY, I. Impact of aneurysmal geometry on intraaneurysmal flow: a computerized flow simulation study. *Neuroradiology*, 50(5):411–21, May 2008.
- SZYMANSKI, M. P., METAXA, E., MENG, H., AND KOLEGA, J. Endothelial cell layer subjected to impinging flow mimicking the apex of an arterial bifurcation. *Annals of Biomedical Engineering*, 36(10):1681–9, October 2008.
- TADA, S. Numerical study of oxygen transport in a carotid bifurcation. *Physics in Medicine and Biology*, 55(14):3993–4010, July 2010.
- TADA, S. AND TARBELL, J. M. Oxygen mass transport in a compliant carotid bifurcation model. *Annals of Biomedical Engineering*, 34(9):1389–99, September 2006.
- TAGGART, M. J. AND WRAY, S. Hypoxia and smooth muscle function: key regulatory events during metabolic stress. *The Journal of Physiology*, 509 (Pt 2):315–25, June 1998.
- TAKABA, M., ENDO, S., KURIMOTO, M., KUWAYAMA, N., NISHIJIMA, M., AND TAKAKU, A. Vasa Vasorum of the Intracranial Arteries. *Acta Neurochirurgica*, 140(5):411–416, May 1998.
- TAKEMURA, Y., HIRATA, Y., SAKATA, N., NABESHIMA, K., TAKESHITA, M., AND INOUE, T. Histopathologic characteristics of a saccular aneurysm arising in the non-branching segment of the distal middle cerebral artery. *Pathology, Research and Practice*, 206(6):391–6, June 2010.
- TARBELL, J. M. Mass transport in arteries and the localization of atherosclerosis. *Annual Review of Biomedical Engineering*, 5:79–118, 2003.
- TARBELL, J. M., LEVER, M. J., AND CARO, C. G. The effect of varying albumin concentration of the hydraulic conductivity of the rabbit common carotid artery. *Microvascular Research*, 35(2):204–20, March 1988.
- TARBELL, J. M. AND QIU, Y. Arterial Wall Mass Transport: The Possible Role of Blood Phase Resistance in the Localization of Arterial Diseases. In BRONZINO, J. D., editor, *The Biomedical Engineering Handbook*, chapter 100. CRC Press LLC, Boca Raton, FL, USA, 2nd edition, 2000.
- TARBELL, J. M. Bioengineering studies of the endothelial transport barrier. *BMES Bulletin*, 17:35–39, 1993.
- TARBELL, J. M. Shear stress and the endothelial transport barrier. *Cardiovascular Research*, 87(2):320–30, July 2010.
- TATESHIMA, S., MURAYAMA, Y., VILLABLANCA, J. P., MORINO, T., NOMURA, K., TANISHITA, K., AND VIÑUELA, F. In vitro measurement of fluid-induced wall shear stress in unruptured cerebral aneurysms harboring blebs. *Stroke*, 34(1):187–92, January 2003.
- TEDGUI, A. AND LEVER, M. J. Filtration through damaged and undamaged rabbit thoracic aorta. *The American Journal of Physiology*, 247(5 Pt 2):H784–91, November 1984.

- TENG, M. M.-H., NASIR QADRI, S. M., LUO, C.-B., LIRNG, J.-F., CHEN, S.-S., AND CHANG, C.-Y. MR imaging of giant intracranial aneurysm. *Journal of Clinical Neuroscience*, 10(4):460–4, July 2003.
- THORNTON, J., BASHIR, Q., ALETICH, V. A., DEBRUN, G. M., AUSMAN, J. I., AND CHARBEL, F. T. What percentage of surgically clipped intracranial aneurysms have residual necks? *Neurosurgery*, 46: 1294–1298, June 2000.
- THUBRIKAR, M. J., ROBICSEK, F., LABROSSE, M., CHERVENKOFF, V., AND FOWLER, B. L. Effect of thrombus on abdominal aortic aneurysm wall dilation and stress. *The Journal of Cardiovascular Surgery*, 44(1):67–77, February 2003.
- TODOR, D. R., LEWIS, I., BRUNO, G., AND CHYATTE, D. Identification of a serum gelatinase associated with the occurrence of cerebral aneurysms as pro-matrix metalloproteinase-2. *Stroke*, 29(8):1580–3, August 1998.
- TONG, F. C., CLOFT, H. J., AND DION, J. E. Endovascular treatment of intracranial aneurysms with Guglielmi Detachable Coils: emphasis on new techniques. *Journal of Clinical Neuroscience*, 7: 244–253, May 2000.
- TOPPER, J. N., CAI, J., FALB, D., AND GIMBRONE, M. A. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. *Proceedings of the National Academy of Sciences of the United States of America*, 93(19):10417–22, September 1996.
- TREMMEL, M., DHAR, S., LEVY, E. I., MOCCO, J., AND MENG, H. Influence of intracranial aneurysm-to-parent vessel size ratio on hemodynamics and implication for rupture: results from a virtual experimental study. *Neurosurgery*, 64:622–630, April 2009.
- TULAMO, R., FROSEN, J., HERNESNIEMI, J., AND NIEMELA, M. Inflammatory changes in the aneurysm wall: a review. *Journal of NeuroInterventional Surgery*, 2(2):120–130, March 2010.
- TUROWSKI, B., MACHT, S., KULCSÁR, Z., HÄNGGI, D., AND STUMMER, W. Early fatal hemorrhage after endovascular cerebral aneurysm treatment with a flow diverter (SILK-Stent): do we need to rethink our concepts? *Neuroradiology*, 53(1):37–41, January 2011.
- UEDA, A., SHIMOMURA, M., IKEDA, M., YAMAGUCHI, R., AND TANISHITA, K. Effect of glycocalyx on shear-dependent albumin uptake in endothelial cells. *American Journal of Physiology*, 287(5): H2287–94, November 2004.
- UJIE, H., TAMANO, Y., SASAKI, K., AND HORI, T. Is the aspect ratio a reliable index for predicting the rupture of a saccular aneurysm? *Neurosurgery*, 48(3):495–502; discussion 502–3, March 2001.
- VALENCIA, A., MUNOZ, F., ARAYA, S., RIVERA, R., AND BRAVO, E. Comparison between computational fluid dynamics, fluid-structure interaction and computational structural dynamics predictions of flow-induced wall mechanics in an anatomically realistic cerebral aneurysm model. *International Journal of Computational Fluid Dynamics*, 23(9):649–666, October 2009.
- VALENCIA, A. A., GUZMÁN, A. M., FINOL, E. A., AND AMON, C. H. Blood flow dynamics in saccular aneurysm models of the basilar artery. *Journal of biomechanical engineering*, 128(4):516–26, August 2006.
- VAN DEN BERG, J. S., PALS, G., ARWERT, F., HENNEKAM, R. C., ALBRECHT, K. W., WESTERVELD, A., AND LIMBURG, M. Type III collagen deficiency in saccular intracranial aneurysms. Defect in gene regulation? *Stroke*, 30(8):1628–31, August 1999.
- VAN DOORMAAL, J. P. AND RAITHBY, G. D. Enhancements of the the simple method for predicting incompressible fluid flows. *Numerical Heat Transfer*, 7(2):147–163, April 1984.
- VAN GIJN, J. AND RINKEL, G. J. E. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain*, 124:249–278, February 2001.
- VAN GIJN, J. AND VAN DONGEN, K. Computerized-tomography in subarachnoid hemorrhage - difference between patients with and without an aneurysm on angiography. *Neurology*, 30:538–539, 1980.
- VAN MUNSTER, C. E. P., FRAUNBERG, M. V. U. Z., RINKEL, G. J. E., RINNE, J., KOIVISTO, T., AND RONKAINEN, A. Differences in Aneurysm and Patient Characteristics Between Cohorts of Finnish and Dutch Patients With Subarachnoid Hemorrhage Time Trends Between 1986 and 2005. *Stroke*, 39(12):3166–3171, December 2008.

- VANDE GEEST, J. P., SACKS, M. S., AND VORP, D. A. A planar biaxial constitutive relation for the luminal layer of intra-luminal thrombus in abdominal aortic aneurysms. *Journal of Biomechanics*, 39(13): 2347–54, January 2006.
- VANNINEN, R., MANNINEN, H., AND RONKAINEN, A. Broad-based intracranial aneurysms: thrombosis induced by stent placement. *American Journal of Neuroradiology*, 24(2):263–6, February 2003.
- VELTHUIS, B. K., RINKEL, G. J. E., RAMOS, L. M. P., WITKAMP, T. D., VAN DER SPENKEL, J. W. B., VANDERTOP, W. P., AND VAN LEEUWEN, M. S. Subarachnoid hemorrhage: Aneurysm detection and preoperative evaluation with CT angiography. *Radiology*, 208:423–430, August 1998.
- VITA, J. A. AND MITCHELL, G. F. Effects of shear stress and flow pulsatility on endothelial function. *Journal of the American College of Cardiology*, 42(12): 2096–2098, December 2003.
- VLAKE, M. H. M., RINKEL, G. J. E., GREEBE, P., VAN DER BOM, J. G., AND ALGRA, A. Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study. *Stroke*, 42(7): 1878–82, July 2011a.
- VLAKE, M. H., ALGRA, A., BRANDENBURG, R., AND RINKEL, G. J. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurology*, 10(7): 626–36, July 2011b.
- VON DER MARK, K. Localization of collagen types in tissues. *International Review of Connective Tissue Research*, 9:265–324, January 1981.
- VORP, D. A., FEDERSPIEL, W. J., AND WEBSTER, M. W. Does laminated intraluminal thrombus within abdominal aortic aneurysm cause anoxia of the aortic wall? *Journal of Vascular Surgery*, 23(3):540–1, March 1996.
- VORP, D. A., LEE, P. C., WANG, D. H. J., MAKAROUN, M. S., NEMOTO, E. M., OGAWA, S., AND WEBSTER, M. W. Association of intraluminal thrombus in abdominal aortic aneurysm with local hypoxia and wall weakening. *Journal of Vascular Surgery*, 34: 291–299, August 2001.
- VORP, D. A., WANG, D. H. J., WEBSTER, M. W., AND FEDERSPIEL, W. J. Effect of intraluminal thrombus thickness and bulge diameter on the oxygen diffusion in abdominal aortic aneurysm. *Journal of Biomechanical Engineering - Transactions of the ASME*, 120:579–583, October 1998.
- WADA, S. AND KARINO, T. Theoretical study on flow-dependent concentration polarization of low density lipoproteins at the luminal surface of a straight artery. *Biorheology*, 36(3):207–23, January 1999.
- WADA, S. AND KARINO, T. Theoretical prediction of low-density lipoproteins concentration at the luminal surface of an artery with a multiple bend. *Annals of Biomedical Engineering*, 30(6):778–91, June 2002.
- WALMSLEY, J. G. Vascular smooth muscle orientation in straight portions of human cerebral arteries. *Journal of Microscopy*, 131(Pt 3):361–75, September 1983.
- WALMSLEY, J. G. AND CANHAM, P. B. Orientation of nuclei as indicators of smooth muscle cell alignment in the cerebral artery. *Blood Vessels*, 16(1):43–51, January 1979.
- WANG, D. H., MAKAROUN, M., WEBSTER, M. W., AND VORP, D. A. Mechanical properties and microstructure of intraluminal thrombus from abdominal aortic aneurysm. *Journal of Biomechanical Engineering*, 123(6):536–9, December 2001.
- WANG, D. H. J., MAKAROUN, M. S., WEBSTER, M. W., AND VORP, D. A. Effect of intraluminal thrombus on wall stress in patient-specific models of abdominal aortic aneurysm. *Journal of Vascular Surgery*, 36(3): 598–604, September 2002.
- WANG, G. L., JIANG, B. H., RUE, E. A., AND SEMENZA, G. L. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O₂ tension. *Proceedings of the National Academy of Sciences of the United States of America*, 92(12): 5510–4, June 1995.
- WANG, Z. J. AND SRINIVASAN, K. An adaptive Cartesian grid generation method for ‘Dirty’ geometry. *International Journal for Numerical Methods in Fluids*, 39:703+, July 2002.
- WANKE, I., DOERFLER, A., SCHOCH, B., STOLKE, D., AND FORSTING, M. Treatment of wide-necked intracranial aneurysms with a self-expanding stent system: initial clinical experience. *American Journal of Neuroradiology*, 24(6):1192–9, 2003.
- WANKE, I. AND FORSTING, M. Stents for intracranial wide-necked aneurysms: more than mechanical protection. *Neuroradiology*, 50:991–998, December 2008.

- WATANABE, H., NAKANISHI, I., YAMASHITA, K., HAYAKAWA, T., AND OKADA, Y. Matrix metalloproteinase-9 (92 kDa gelatinase/type IV collagenase) from U937 monoblastoid cells: correlation with cellular invasion. *Journal of Cell Science*, 104 (Pt 4:991–9, April 1993.
- WATTON, P. N. AND HILL, N. A. Evolving mechanical properties of a model of abdominal aortic aneurysm. *Biomechanics and Modeling in Mechanobiology*, 8(1):25–42, February 2009.
- WATTON, P. N., HILL, N. A., AND HEIL, M. A mathematical model for the growth of the abdominal aortic aneurysm. *Biomechanics and Modeling in Mechanobiology*, 3(2):98–113, September 2004.
- WATTON, P. N., SELIMOVIC, A., RABERGER, N. B., HUANG, P., HOLZAPFEL, G. A., AND VENTIKOS, Y. Modelling evolution and the evolving mechanical environment of saccular cerebral aneurysms. *Biomechanics and Modeling in Mechanobiology*, 10 (1):109–32, February 2011a.
- WATTON, P. N. *Mathematical modelling of the abdominal aortic aneurysm*. PhD thesis, University of Leeds, 2002.
- WATTON, P. N., RABERGER, N. B., HOLZAPFEL, G. A., AND VENTIKOS, Y. Coupling the hemodynamic environment to the evolution of cerebral aneurysms: computational framework and numerical examples. *Journal of Biomechanical Engineering*, 131 (10):101003, October 2009a.
- WATTON, P. N., VENTIKOS, Y., AND HOLZAPFEL, G. A. Modelling the growth and stabilization of cerebral aneurysms. *Mathematical Medicine and Biology*, 26(2):133–64, June 2009b.
- WATTON, P. N., VENTIKOS, Y., AND HOLZAPFEL, G. A. Modelling cerebral aneurysm evolution. In MCGLOUGHLIN, T., editor, *Biomechanics and Mechanobiology of Aneurysms*, chapter 12, pages 373–400. Springer-Verlag Berlin, Heidelberg, 2011b.
- WEBER, W., BENDSZUS, M., KIS, B., BOULANGER, T., SOLYMOSI, L., AND KÜHNE, D. A new self-expanding nitinol stent (Enterprise) for the treatment of wide-necked intracranial aneurysms: initial clinical and angiographic results in 31 aneurysms. *Neuroradiology*, 49(7):555–61, July 2007.
- WEIR, B., DISNEY, L., AND KARRISON, T. Sizes of ruptured and unruptured aneurysms in relation to their sites and the ages of patients. *Journal of Neurosurgery*, 96(1):64–70, January 2002.
- WEISEL, J. O. P. S. O. M. Penn Researchers Show That Protein Unfolding is Key for Understanding Blood Clot Mechanics, 2009. URL http://health.upenn.edu/news/news_releases/2009/08/fibrin-blood-clot-structure/image.html.
- WEISS, H. J., TURITTO, V. T., AND BAUMGARTNER, H. R. Role of shear rate and platelets in promoting fibrin formation on rabbit subendothelium. Studies utilizing patients with quantitative and qualitative platelet defects. *The Journal of Clinical Investigation*, 78(4):1072–82, October 1986.
- WEITZ, J. I., CROWLEY, K. A., LANDMAN, S. L., LIPMAN, B. I., AND YU, J. Increased neutrophil elastase activity in cigarette smokers. *Annals of Internal Medicine*, 107(5):680–2, November 1987.
- WEMPNER, G. *Mechanics of Solids*. McGraw-Hill, New York, 1973.
- WHEREAT, A. F. Oxygen consumption of normal and atherosclerotic intima. *Circulation Research*, 9: 571–5, May 1961.
- WHITTLE, I. R., DORSCH, N. W., AND BESSER, M. Spontaneous thrombosis in giant intracranial aneurysms. *Journal of Neurology, Neurosurgery, and Psychiatry*, 45(11):1040–7, November 1982.
- WIEBERS, D. O., WHISNANT, J. P., SUNDT, T. M., AND O'FALLON, W. M. The significance of unruptured intracranial saccular aneurysms. *Journal of Neurosurgery*, 66(1):23–9, January 1987.
- WIEBERS, D. O., FEIGIN, V. L., AND BROWN, R. D. J. *Handbook Of Stroke*. Lippincott Williams and Wilkins, 2006.
- WILLIAMS, J. K. AND HEISTAD, D. D. Structure and function of vasa vasorum. *Trends in Cardiovascular Medicine*, 6(2):53–7, February 1996.
- WILLINSKY, R. A., TAYLOR, S. M., TERBRUGGE, K., FARB, R. I., TOMLINSON, G., AND MONTANERA, W. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. *Radiology*, 227(2):522–8, May 2003.
- WILSON, W. R. W., SCHWALBE, E. C., JONES, J. L., BELL, P. R. F., AND THOMPSON, M. M. Matrix metalloproteinase 8 (neutrophil collagenase) in the pathogenesis of abdominal aortic aneurysm. *The British Journal of Surgery*, 92(7):828–33, July 2005.

- WILSON, W. R. W., ANDERTON, M., SCHWALBE, E. C., JONES, J. L., FURNESS, P. N., BELL, P. R. F., AND THOMPSON, M. M. Matrix metalloproteinase-8 and -9 are increased at the site of abdominal aortic aneurysm rupture. *Circulation*, 113(3):438–45, January 2006.
- WOLF, Y. G., THOMAS, W. S., BRENNAN, F. J., GOFF, W. G., SISE, M. J., AND BERNSTEIN, E. F. Computed tomography scanning findings associated with rapid expansion of abdominal aortic aneurysms. *Journal of Vascular Surgery*, 20(4):529–35; discussion 535–8, October 1994.
- XIANG, J., NATARAJAN, S. K., TREMMEL, M., MA, D., MOCCO, J., HOPKINS, L. N., SIDDIQUI, A. H., LEVY, E. I., AND MENG, H. Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. *Stroke*, 42(1):144–52, January 2011.
- XU, Z., LIOI, J., MU, J., KAMOCKA, M. M., LIU, X., CHEN, D. Z., ROSEN, E. D., AND ALBER, M. A multiscale model of venous thrombus formation with surface-mediated control of blood coagulation cascade. *Biophysical Journal*, 98(9):1723–32, May 2010.
- YAGI, T., SATO, A., SHINKE, M., TAKAHASHI, S., TOBE, Y., TAKAO, H., MURAYAMA, Y., AND UMEZU, M. Experimental insights into flow impingement in cerebral aneurysm by stereoscopic particle image velocimetry: transition from a laminar regime. *Journal of the Royal Society, Interface / the Royal Society*, 10(82):20121031, January 2013.
- YAMAUCHI, M. AND SHIIBA, M. Lysine hydroxylation and cross-linking of collagen. *Methods in Molecular Biology*, 446:95–108, January 2008.
- YANG, N. AND VAFAI, K. Modeling of low-density lipoprotein (LDL) transport in the artery—effects of hypertension. *International Journal of Heat and Mass Transfer*, 49(5-6):850–867, 2006.
- YANG, N. AND VAFAI, K. Low-density lipoprotein (LDL) transport in an artery—A simplified analytical solution. *International Journal of Heat and Mass Transfer*, 51(3-4):497–505, February 2008.
- YASARGIL, M. *Microneurosurgery. Clinical Considerations, Sugery of the Intracranial Aneurysms and Results*. Thieme, Stuttgart, 1984.
- YASUHARA, T., TAMIYA, T., SUGIU, K., INOUE, S., AND OHMOTO, T. De novo formation and rupture of an aneurysm. Case report. *Journal of Neurosurgery*, 97(3):697–700, September 2002.
- YONEOKA, Y., TAKEDA, N., AKIRA, I., IBUCHI, Y., KUMAGAI, T., SUGAI, T., TAKEDA, K.-I., AND UEDA, K. Ruptured de novo intracranial aneurysms. *Acta Neurochirurgica*, 146(9):979–81; discussion 981, September 2004.
- YOSIBASH, Z. AND PRIEL, E. Artery active mechanical response: High order finite element implementation and investigation. *Computer Methods in Applied Mechanics and Engineering*, 237-240:51–66, September 2012.
- ZEMPO, N., KENAGY, R. D., AU, Y. P., BENDECK, M., CLOWES, M. M., REIDY, M. A., AND CLOWES, A. W. Matrix metalloproteinases of vascular wall cells are increased in balloon-injured rat carotid artery. *Journal of Vascular Surgery*, 20(2):209–17, August 1994.
- ZIEGLER, T., BOUZOURÈNE, K., HARRISON, V. J., BRUNNER, H. R., AND HAYOZ, D. Influence of oscillatory and unidirectional flow environments on the expression of endothelin and nitric oxide synthase in cultured endothelial cells. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 18(5):686–92, May 1998.



GOVERNING EQUATIONS

A.1 2D AXISYMMETRIC CONSERVATION EQUATIONS

A.1.1 Navier-Stokes equations for a fluid domain

A.1.1.1 Conservation of momentum

In cylindrical polar coordinates (r, θ, z) the conservation of momentum equations for an incompressible flow of velocity $\mathbf{U}(u_r, u_\theta, u_z)$ are: in the r -direction,

$$\begin{aligned} \rho \left(\frac{\partial u_r}{\partial t} + u_r \frac{\partial u_r}{\partial r} + \frac{u_\theta}{r} \frac{\partial u_r}{\partial \theta} + u_z \frac{\partial u_r}{\partial z} - \frac{u_\theta^2}{r} \right) = - \frac{\partial p}{\partial r} \\ + \mu \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_r}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 u_r}{\partial \theta^2} + \frac{\partial^2 u_r}{\partial z^2} - \frac{u_r}{r^2} - \frac{2}{r^2} \frac{\partial u_\theta}{\partial \theta} \right) + \rho g_r \end{aligned} \quad (\text{A.1})$$

in the θ -direction,

$$\begin{aligned} \rho \left(\frac{\partial u_\theta}{\partial t} + u_r \frac{\partial u_\theta}{\partial r} + \frac{u_\theta}{r} \frac{\partial u_\theta}{\partial \theta} + u_z \frac{\partial u_\theta}{\partial z} - \frac{u_r u_\theta}{r} \right) = - \frac{1}{r} \frac{\partial p}{\partial \theta} \\ + \mu \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_\theta}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 u_\theta}{\partial \theta^2} + \frac{\partial^2 u_\theta}{\partial z^2} - \frac{u_\theta}{r^2} + \frac{2}{r^2} \frac{\partial u_r}{\partial \theta} \right) + \rho g_\theta \end{aligned} \quad (\text{A.2})$$

in the z -direction,

$$\begin{aligned} \rho \left(\frac{\partial u_z}{\partial t} + u_r \frac{\partial u_z}{\partial r} + \frac{u_\theta}{r} \frac{\partial u_z}{\partial \theta} + u_z \frac{\partial u_z}{\partial z} \right) = - \frac{\partial p}{\partial z} \\ + \mu \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_z}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 u_z}{\partial \theta^2} + \frac{\partial^2 u_z}{\partial z^2} \right) + \rho g_z. \end{aligned} \quad (\text{A.3})$$

For a 2D axisymmetric system of equations it is assumed that there is no tangential velocity, u_θ , and that r and z are independent of θ . Also ignoring gravitational acceleration, ρg_i ($i = r, z$), the system of equations reduces to:

in the r -direction,

$$\rho \left(\frac{\partial u_r}{\partial t} + u_r \frac{\partial u_r}{\partial r} + u_z \frac{\partial u_r}{\partial z} \right) = - \frac{\partial p}{\partial r} + \mu \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_r}{\partial r} \right) + \frac{\partial^2 u_r}{\partial z^2} - \frac{u_r}{r^2} \right) \quad (\text{A.4})$$

in the z -direction,

$$\rho \left(\frac{\partial u_z}{\partial t} + u_r \frac{\partial u_z}{\partial r} + u_z \frac{\partial u_z}{\partial z} \right) = - \frac{\partial p}{\partial z} + \mu \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_z}{\partial r} \right) + \frac{\partial^2 u_z}{\partial z^2} \right). \quad (\text{A.5})$$

A.1.1.2 Conservation of mass

The continuity equation in cylindrical polar coordinates is:

$$\frac{\partial \rho}{\partial t} + \frac{1}{r} \frac{\partial (\rho r u_r)}{\partial r} + \frac{1}{r} \frac{\partial (\rho u_\theta)}{\partial \theta} + \frac{\partial (\rho u_z)}{\partial z} = 0. \quad (\text{A.6})$$

which reduces to the following equation for an incompressible axisymmetric flow, with no tangential velocity:

$$\frac{1}{r} \frac{\partial (r u_r)}{\partial r} + \frac{\partial (u_z)}{\partial z} = 0. \quad (\text{A.7})$$

A.1.2 Navier-stokes equations for a porous medium

The following conservation equations take into account the isotropic porosity ε and the permeability κ in 2D axisymmetric coordinate system.

A.1.2.1 Conservation of momentum

In the r -direction,

$$\varepsilon \rho \left(\frac{\partial u_r}{\partial t} + u_r \frac{\partial u_r}{\partial r} + u_z \frac{\partial u_r}{\partial z} \right) = -\varepsilon \frac{\partial p}{\partial r} + \frac{\varepsilon^2 \mu}{\kappa} \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_r}{\partial r} \right) + \frac{\partial^2 u_r}{\partial z^2} - \frac{u_r}{r^2} \right). \quad (\text{A.8})$$

In the z -direction,

$$\varepsilon \rho \left(\frac{\partial u_z}{\partial t} + u_r \frac{\partial u_z}{\partial r} + u_z \frac{\partial u_z}{\partial z} \right) = -\varepsilon \frac{\partial p}{\partial z} + \frac{\varepsilon^2 \mu}{\kappa} \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u_z}{\partial r} \right) + \frac{\partial^2 u_z}{\partial z^2} \right). \quad (\text{A.9})$$

A.1.2.2 Conservation of mass

$$\frac{\varepsilon}{r} \frac{\partial (r u_r)}{\partial r} + \varepsilon \frac{\partial (u_z)}{\partial z} = 0. \quad (\text{A.10})$$

A.2 3D CARTESIAN CONSERVATION EQUATIONS

A.2.1 Navier-Stokes equations

A.2.1.1 Conservation of momentum

In cartesian coordinates (x, y, z) the conservation of momentum equations for an incompressible flow of velocity $\mathbf{U}(u, v, w)$ are:

in the x -direction,

$$\rho \left(\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + v \frac{\partial u}{\partial y} + w \frac{\partial u}{\partial z} \right) = -\frac{\partial p}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + \rho g_x \quad (\text{A.11})$$

in the y -direction,

$$\rho \left(\frac{\partial v}{\partial t} + u \frac{\partial v}{\partial x} + v \frac{\partial v}{\partial y} + w \frac{\partial v}{\partial z} \right) = -\frac{\partial p}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) + \rho g_y \quad (\text{A.12})$$

in the z -direction,

$$\rho \left(\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial x} + v \frac{\partial w}{\partial y} + w \frac{\partial w}{\partial z} \right) = -\frac{\partial p}{\partial z} + \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right) + \rho g_z. \quad (\text{A.13})$$

A.2.1.2 Conservation of mass

For an incompressible flow, the continuity equation simply becomes:

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0 \quad (\text{A.14})$$

A.2.2 Convection-diffusion equations

The 3D Cartesian convection-diffusion equations for the lumen, thrombus and wall layers of the model are as follows:

A.2.2.1 Convection-diffusion of oxygen within the lumen

For free oxygen,

$$\begin{aligned} \frac{\partial C_{O_2}}{\partial t} - D_b \left[\frac{\partial^2 C_{O_2}}{\partial x^2} + \frac{\partial^2 C_{O_2}}{\partial y^2} + \frac{\partial^2 C_{O_2}}{\partial z^2} \right] \\ + \left[u \frac{\partial C_{O_2}}{\partial x} + v \frac{\partial C_{O_2}}{\partial y} + w \frac{\partial C_{O_2}}{\partial z} \right] = R_{Hb}. \end{aligned} \quad (\text{A.15})$$

For oxygen bound to haemoglobin,

$$\begin{aligned} [Hb] \frac{\partial C_{HbO_2}}{\partial t} - [Hb] D_{Hb} \left[\frac{\partial^2 C_{HbO_2}}{\partial x^2} + \frac{\partial^2 C_{HbO_2}}{\partial y^2} + \frac{\partial^2 C_{HbO_2}}{\partial z^2} \right] \\ + [Hb] \left[u \frac{\partial C_{HbO_2}}{\partial x} + v \frac{\partial C_{HbO_2}}{\partial y} + w \frac{\partial C_{HbO_2}}{\partial z} \right] = -R_{Hb}. \end{aligned} \quad (\text{A.16})$$

A.2.2.2 Diffusion of oxygen across the thrombus layer

$$\frac{\partial C_{O_2}}{\partial t} - D_w \left[\frac{\partial^2 C_{O_2}}{\partial x^2} + \frac{\partial^2 C_{O_2}}{\partial y^2} + \frac{\partial^2 C_{O_2}}{\partial z^2} \right] = -\dot{q}. \quad (\text{A.17})$$

A.2.2.3 Diffusion of oxygen across the arterial wall

$$\frac{\partial C_{O_2}}{\partial t} - D_{th} \left[\frac{\partial^2 C_{O_2}}{\partial x^2} + \frac{\partial^2 C_{O_2}}{\partial y^2} + \frac{\partial^2 C_{O_2}}{\partial z^2} \right] = 0. \quad (A.18)$$

SOLUTION TO SIMULTANEOUS EQUATIONS OF 1D DIFFUSION EQUATIONS

C_1 , A_1 , B_1 , A_2 and B_2 are defined by solving the following set of simultaneous equations (as outlined in Section 7.1.3.3:

$$C_0 = A_1 \ln r_{th} + B_1 \quad (\text{B.1})$$

$$C_1 = A_1 \ln r_e + B_1 \quad (\text{B.2})$$

$$C_1 = -\frac{r_e^2 \dot{q}}{4D_w} + A_2 \ln r_e + B_2 \quad (\text{B.3})$$

$$C_2 = -\frac{r_a^2 \dot{q}}{4D_w} + A_2 \ln r_a + B_2 \quad (\text{B.4})$$

$$A_1 = -\frac{r_e^2 \dot{q}}{2} + A_2 \quad (\text{B.5})$$

Substituting equation B.5 into equation B.4 and rearranging yields:

$$B_2 = C_2 + \frac{r_a^2 \dot{q}}{4D_w} - A_1 \ln r_a - \frac{r_e^2 \dot{q}}{2} \ln r_a. \quad (\text{B.6})$$

And then equation B.6 into B.3:

$$C_1 = C_2 + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + A_1 \ln \left(\frac{r_e}{r_a} \right) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right). \quad (\text{B.7})$$

And equation B.7 into B.2 gives:

$$B_1 = C_2 + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right) + A_1 \ln r_a. \quad (\text{B.8})$$

An expression for A_1 is achieved by substituting equation B.8 into B.2,

$$A_1 = \left[(C_2 - C_0) + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right) \right] \frac{1}{\ln(r_a/r_e)} \quad (\text{B.9})$$

B_1 can hence be defined by substituting the above expression of A_1 back into equation B.8,

$$\begin{aligned} B_1 = & C_2 + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right) \\ & + \left[(C_2 - C_0) + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln \left(\frac{r_e}{r_a} \right) \right] \frac{\ln r_a}{\ln(r_a/r_{th})} \end{aligned} \quad (\text{B.10})$$

Subsequently an expression for A_2 is obtained by equating B.9 and B.5:

$$A_2 = \frac{r_e^2 \dot{q}}{2} + [(C_2 - C_0) + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln\left(\frac{r_e}{r_a}\right)] \frac{1}{\ln(r_a/r_{th})} \quad (\text{B.11})$$

Finally, an expression for B_2 is achieved by substituting the equation B.9 and B.6, which yields:

$$B_2 = C_2 + \frac{r_a^2 \dot{q}}{4D_w} - \frac{r_e^2 \dot{q} \ln r_a}{2} - \left[(C_2 - C_0) + \frac{\dot{q}}{4D_w} (r_a^2 - r_e^2) + \frac{r_e^2 \dot{q}}{2} \ln\left(\frac{r_e}{r_a}\right) \right] \frac{\ln r_a}{\ln(r_a/r_{th})} \quad (\text{B.12})$$