

Mathematical modelling of flow and nutrient transport in hollow fibre membrane bioreactors



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Abstract

Hollow fibre membrane bioreactors comprise permeable tubes situated within a bioreactor chamber. Nutrients and growth factors flow through the fibre lumen, transporting across the porous membrane to external cells, while external flow removes residual nutrients and cellular waste. Given cellular sensitivity to their local microenvironment, mathematical modelling can be used to predict and optimise bioreactor performance.

In this thesis, we develop a series of continuum models describing fluid flow and metabolite transport in poroelastic hollow fibre membrane bioreactors, inspired by human vasculature, for applications in tissue engineering. We model flow across the membrane wall using Darcy's law, which is coupled to flow through the bioreactor governed by Navier-Stokes equations. The membrane is able to deform under the action of fluid stress, modelled as a poroelastic material using Terzaghi's principle. Exploiting disparate parameter ratios such as the long thin bioreactor geometry, large membrane stiffness and small cell layer thickness, we utilise asymptotic techniques to systematically reduce the complexity of our system, revealing mechanistic insight into the local chemical and mechanical environment of the tissue culture.

We extend existing models by considering fluid-structure interaction in a poroelastic hollow fibre membrane under steady viscous flow. We later extend consideration to pulsatile flow through our bioreactor system, where we derive generalisations of the Womersley solution for a deformable porous tube wall. These models reveal how fluid pressure, membrane compressibility, permeability and thickness, effect distributions of stress and strain through the tissue scaffold, and thus modulate the local cell environment. Coupling to advection-diffusion-reaction equations for generalised nutrient uptake kinetics, we reveal how the membrane permeability can be tuned to achieve uniform nutrient uptake and facilitate uniform tissue growth. Finally, we consider the canonical problem of high laminar Reynolds flow through two long thin channels mediated by a porous wall. We do so to emulate larger, more physiologically-relevant fluid shear stresses that cells would likely experience in arteries and large-diameter vessels. We explore the intricate boundary layer structure that emerges across a range of laminar Reynolds number regimes, validated by full numerical simulations, which provides an in-depth analysis of the coupled transitions from plug to lubrication flow.

The analysis we present in this thesis provides novel methods to investigate flow and metabolite transport in a poroelastic hollow fibre membrane bioreactor setup. Furthermore, our modelling framework facilitates quick and efficient sensitivity analysis to understand the impact of varying key structural and operating parameters on

the local chemical and mechanical cell environment, which can be used to inform and optimise experimental bioreactor design.

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Chapter 1

Introduction

In this introduction, we present a broad overview of tissue engineering as a research field, alongside its successes and limitations. In particular, we discuss different tissue engineering methods, before focusing on recent developments in hollow fibre membrane bioreactor technology. We then introduce the experimental motivation inspiring our overarching research aims, and consider how mathematical modelling can aid in the design and optimisation of tissue engineering methods. We follow with a review of existing mathematical modelling methods in tissue engineering, with a focus on identifying current gaps in the literature. We conclude with a summary of the work in this thesis.

1.1 Tissue engineering

1.1.1 Background

The world is facing a global ageing population crisis. With an anticipated surge in individuals over the age of 60, projected to double to 2.1 billion by 2050 [1], the demand for innovative solutions to address age-associated health challenges is paramount. Ageing is associated with a myriad of health issues including bone defects, liver, kidney and heart-related illnesses as organs begin to show signs of extensive wear and tear over one's lifetime [2]. When damage to organs, tissue or vasculature poses a health risk, we rely on organ transplants and tissue donation to replace them. However, this is typically a bottleneck in the healthcare delivery process. In the UK alone, 7,200 people in 2023 are currently on the organ transplant waiting list due to a lack of available and bio-compatible donors [3, 4]. Of these, 6% died while on the waiting list in 2022 [5]. Among those lucky enough to receive transplants, a significant proportion of organs and tissue are rejected due to poor bio-compatibility,

with a 60-90% survival rate five years post-transplant [6]. Surviving patients remain on immuno-suppressants for the rest of their lives, weakening the body's immune system and thus dramatically increasing the risk of serious infections and health complications [7].

Tissue engineering is a field of research aimed at circumventing the need for organ and tissue donation by artificially repairing and replacing damaged organs, tissue and vasculature through a variety of experimental techniques. Using autologous cells, tissue can be grown that avoids rejection and issues related to bio-compatibility. Tissue engineering techniques have a wide variety of applications, such as bypass surgeries treating cardiovascular disease and engineered liver replacements [8, 9]. Allowing control over the geometry and functionality of engineered tissue, this technology has the potential to facilitate previously impossible treatments, ushering in a new age in personalised healthcare. To meet the demand for artificial tissue replacement, tissue engineering relies on the research and development of high-throughput methods of culturing 3D tissue quickly and efficiently.

The field of tissue engineering, as we now recognise it, emerged in the 1990s, when researchers first identified the necessity for *in vitro* tissue and organ synthesis [10]. Traditionally, cells had been cultured in labs using time-consuming, low-yield flask-based batch processes. Although useful and highly popular in research settings for controlled experiments, such techniques cannot meet the scale and efficiency required for growing 3D tissues. Nowadays, tissue engineering techniques typically require three key components - the cells of interest, a scaffold on which to seed cells, and nutrient delivery/waste removal for the cells to grow and proliferate. Such techniques can be broadly categorised as *in vivo* or *in vitro*. *In vivo* methods involve seeding cells to a scaffold that is implanted directly into the human body, relying on the body to deliver growth factors and nutrients to the cells. Although this allows for direct integration with the native environment, *in vivo* techniques do not offer control over the local chemical and mechanical conditions in which cells are grown. Additionally, direct implantation of artificial scaffolds can often lead to heightened rejection rates, cell dedifferentiation and poor structural tissue formation [11, 12]. To address these issues, *in vitro* methods culture cells externally on a scaffold in a controlled environment such as a bioreactor. Given the diverse shapes, sizes and functions of tissue and organs, many tissue engineering bioreactor and bioreactor scaffold designs have been developed to engineer functional tissue which we explore in the following sections.

1.1.2 Bioreactors

A bioreactor is a manufactured device that aims to provide the optimal conditions to handle and produce biologically active material of interest from starting materials. In the context of tissue engineering, bioreactors offer careful, automated control over the local mechanical and chemical environment experienced by the cell. Parameters such as pH, nutrient concentration, temperature, oxygen content and mechanical stress are critical in maintaining an optimal cell growth environment, as well as providing the required cues for cells to differentiate into functional 3D tissue [13].

Particular care in bioreactor design is given to managing the local mechanical environment of the cell. Cells directly sense and respond to their local mechanical environment, with mechanical stimuli (e.g. fluid shear stress) known to promote the production of molecules which affect cell response via cell signalling, a process known as mechanotransduction [14]. Mechanical stress has been observed to enhance cell proliferation and promote organisational structure in smooth muscle cells in engineered vasculature [15, 16]. However, excessive fluid shear can be detrimental to cell growth, resulting in detachment from the scaffold and even cell death [17]. As such, a careful balance must be struck between fluid flow and nutrient delivery in bioreactor design to ensure the optimal mechanical environment for cell growth.

An additional challenge in bioreactor design is overcoming mass transport limitations, ensuring that cells have access to available nutrients for cell growth, and are able to remove waste cell metabolites. For example, local oxygen concentration plays a key role in the production of the extracellular matrix (ECM) material important in cartilage engineering. This, in turn, relies on efficient mass transport to overcome rate-limiting diffusive mass transport [20]. One way to improve diffusive mass transport is via advection with fluid flows. However, fluid flows provide fluid shear stress. Therefore, one must balance the tension between enhancing flows to promote advective mass transfer, while ensuring mechanical stress such as fluid shear stress does not adversely impact the cell environment. Several bioreactor designs aim to deal with this issue, and can be classified into fixed-wall or rotating-wall bioreactors depending on how fluid transport is driven to overcome mass transport limitations.

Rotating-wall-vessel (RWV) bioreactors (Figure 1.1a) contain a mixture of nutrients and cells, with a rotating outer wall to drive fluid flow, ensuring nutrient is well-mixed and available for cell uptake [21]. RWV bioreactors typically operate by balancing gravitational forces with the centrifugal forces generated from the rotating outer wall, simulating a microgravity-like environment with cells in a constant state of free-falling [22]. These bioreactors are typically very good at maintaining a

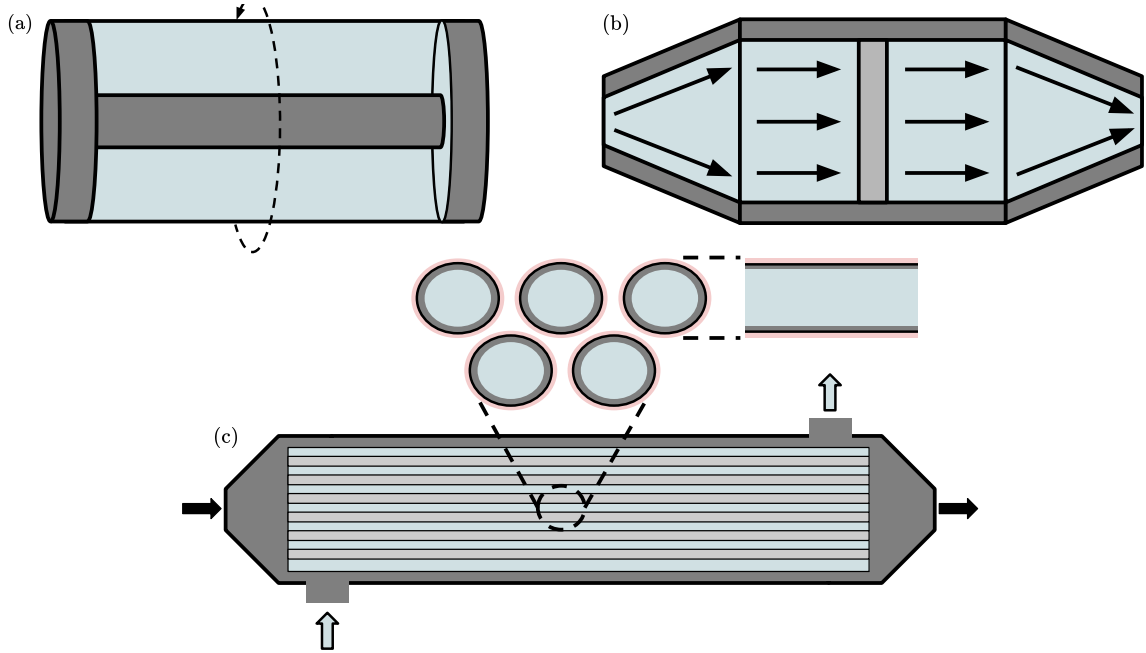


Figure 1.1: Examples of tissue engineering bioreactor setups adapted from Martin et al. [18], with permission from Elsevier, and Burova et al. [19], permitted under a Creative Commons license. (a) Rotating-wall-vessel bioreactor, in which the outer wall rotates to drive fluid flow through the system and mix cells with the surrounding nutrients; (b) Direct-perfusion bioreactor, whereby fluid flow through the porous cell scaffold delivers nutrients and growth factors directly to the cells seeded to the scaffold surface; (c) Hollow fibre membrane bioreactor, constructed of bundles of porous hollow fibre membranes with cells seeded to their surface, and nutrients delivered to the cell site through luminal fluid flow.

low shear stress environment, and have found particular use in cardiac and cartilage engineering where homogeneous mixing of different cell types is required for tissue functionality [23, 24]. Some designs also utilise microcarrier beads - small spherical scaffolds which cells can be pre-seeded to provide structural support and aid in tissue aggregation to engineer larger tissue constructs. However, mass transport to the centre of these microcarriers or cell aggregates is diffusion-limited. Whilst work has been considered to promote the mixing of nutrients and cell aggregates [25], RWV bioreactors are typically less suitable for engineering larger tissue constructs [26].

Fixed-wall systems describe a family of bioreactors that hold the tissue construct in place, utilising continuous flow to deliver growth factors and remove waste products. For example, direct-perfusion bioreactors (Figure 1.1b) hold a permeable tissue scaffold (explored in Section 1.1.3) perpendicular to the direction of fluid flow. The fluid flow is forced through the scaffold, carrying growth factors directly to the cells

seeded on the scaffold surface. This reduces the chances of developing hypoxic regions compared to rotating-wall bioreactors, and has been shown to produce a more uniform cell distribution in some scenarios [27]. Direct-perfusion bioreactors have had particular relevance in bone engineering, producing clinically relevant amounts of human bone tissue in preliminary experimental work [28, 29]. However, the large pressure drop across the membrane scaffold driving the fluid transport can cause significant mechanical disruption within the local cellular environment, even causing the scaffold to rupture. Additionally, direct-perfusion setups can become blocked as cell numbers increase which, in turn, further exacerbates the potentially disruptive pressures within the system. Hence, careful consideration should be made for the flow rate and maturation stage of the cells in question during bioreactor design [18, 30]. As such, direct perfusion systems are more suitable for slower flow rates and for cells more tolerant to higher fluid stresses.

To provide efficient mass transfer in fixed-wall systems while also minimising mechanical disruption, more recent research has focused on the development of hollow-fibre membrane bioreactors (HFMBs) [31]. As shown in Figure 1.1c, cells are seeded on the surface of rigid fibre membranes mimicking *in vivo* vasculature, with growth factors and nutrients delivered via fluid and mass transport through the fibre lumen. Nutrients can then travel across the porous fibre wall to the cells, thus avoiding direct fluid stresses applied to the cell [32]. An additional co-current or counter-current flow in the extra-capillary space (ECS) can also be introduced to wash away waste metabolites and provide physiological load. HFMBs are scalable, as multiple fibres can be bundled together to maximise the surface area-volume ratio available for cell growth. HFMBs have been particularly effective in culturing sensitive but highly-metabolic cell lines, such as hepatocytes for bio-artificial livers [33]. Early HFMB iterations have also shown proof of concept growing smooth muscle and endothelial cells for engineered vasculature [34–36]. Away from tissue engineering, HFMB setups have also been successful in stem cell amplification [37–39]. In particular, stem cells have been expanded with a view towards improving personalised medicine, allowing for the treatment of cranial and anterior mandibular defects [40].

Universal to each bioreactor design is the requirement of a scaffold suitable for supporting tissue growth. As a result, great emphasis on HFMB research is placed on scaffold design, which we now consider in Section 1.1.3.

1.1.3 Tissue scaffolds

Tissue scaffolds are designed to provide structural support for tissue, to guide the eventual desired tissue geometry, and to provide biochemical cues for cell proliferation and differentiation [9]. There is a long list of design criteria that must be met by tissue engineering scaffolds. For example, scaffolds must be bio-compatible and permit cell adhesion to their surface, allow for efficient mass transport of nutrients to the seeded cells, and provide sufficient structural support to maintain shape and prevent mechanical damage [41, 42]. Metal alloys and ceramics have traditionally been popular in orthopaedic surgical methods as strong, inert structures, presenting a good first step towards tissue engineering scaffolds [43]. However, the strength and rigidity of these materials can puncture or damage cells when used in soft tissue environments. Instead, porous synthetic polymers such as polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL) and polyhydroxyl alkenoates (PHAs), as well as natural polymers, such as chitosan, elastin and collagen, have been used in tissue engineering applications [44, 45]. Such materials aim to match the mechanical properties of the tissue to be grown, and have been shown to promote cell proliferation as a result [45]. Given that synthetic polymers are artificially engineered, they allow for control over material properties compared to natural polymer scaffolds. In particular, electrospinning technology allows for tight control over scaffold geometry as well as material properties such as membrane porosity and permeability [46, 47]. Additional scaffold properties such as biodegradability are helpful in a tissue engineering context as auto-removal of the scaffold can encourage greater bio-compatibility by avoiding rejection of the scaffold by the body [42]. By matching rates of scaffold degradation with the rate of ECM deposition, it is then possible to achieve physical and mechanical matching between the body and the engineered construct.

Existing membrane scaffolds are typically designed as rigid porous membranes, offering little compliance under the action of fluid stress. Furthermore, the inflexibility of rigid fibres limits the geometry of the tissue to be grown to simple, fixed geometries. To address these limitations, one can look to nature for inspiration for suitable tissue engineering scaffolds. Arguably one of the best tissue engineering “bioreactors” is the human body, which has successfully grown tissue and organs for millions of years through mammalian evolution. We rely on our vascular system to deliver nutrients to cells throughout the body under significant fluid pressures, utilising the deformability and distensibility of native vasculature to navigate the complex geometry of

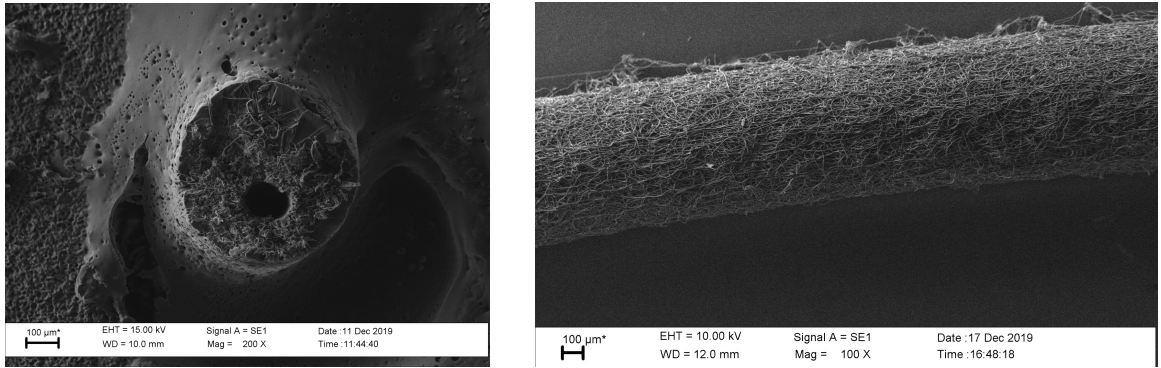


Figure 1.2: Scanning electron microscopy (SEM) images of deformable electrospun hollow fibre membranes developed by Risto Martin, a collaborator at the IBME.

the human body. Inspired by the human body, more recent experimental HFMB research has taken careful consideration of deformable scaffolds when designing tissue engineering systems.

1.2 Project motivation

Prof Cathy Ye at the Institute of Biomedical Engineering (IBME) and Prof Pierre-Alexis MOUTHUY at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) have partnered to develop a deformable tissue engineering scaffold for application in a HFMB setup. This novel material is made from a polydioxanone/polycaprolactone blend and is electrospun to construct a poroelastic hollow fibre inspired by human vasculature (Figure 1.2). These fibres take the place of traditional hollow fibre membranes in a HFMB setup. Similarly to rigid fibres, the fluid transport through the lumen should provide growth factors and nutrients to cells seeded on the scaffold surface, and external flow in the ECS region should wash away waste cell metabolites. These fibres therefore experience both internal and external fluid stresses, causing the fibres to deform while remaining clamped at the inlet and outlet. To experimentally characterise these fibres, laboratory-based experiments focus on a single-fibre bioreactor setup as shown in Figure 1.3. Inspired by this experimental setup, this DPhil project aims to develop mathematical models to describe the implications of using a poroelastic membrane fibre in a HFMB setup. Motivated by this, in the following section, we detail existing literature on mathematical models of tissue engineering bioreactors.

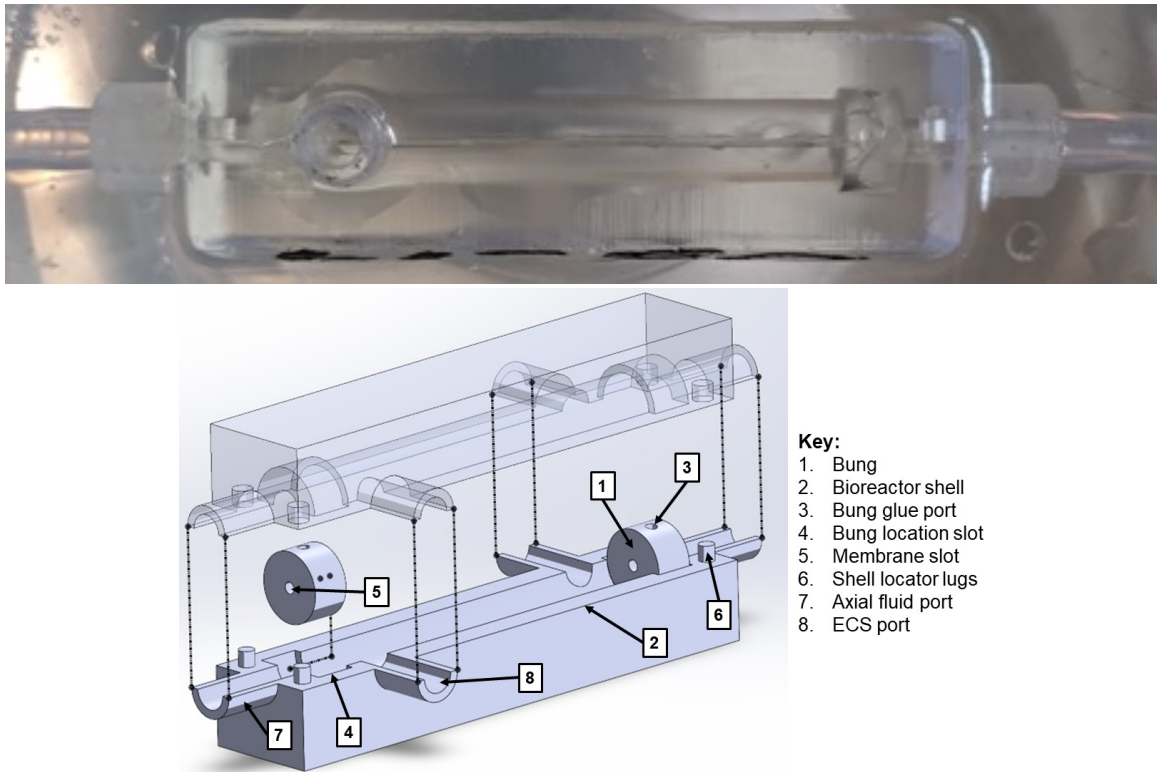


Figure 1.3: Single-fibre HFMB, designed by a collaborator at the IBME, Alexander Witt. Top: Experimental setup of a single-fibre HFMB with a poroelastic electrospun scaffold. Bottom: Schematic of single-fibre HFMB design.

1.3 Mathematical modelling

Mathematical modelling can be used to inform bioreactor design in tissue engineering, providing a fundamental understanding of the underlying processes involved in culturing 3D tissue [48]. Owing to the wide range of bioreactor and scaffold designs, a variety of modelling techniques have been employed to accurately capture the mechanics and biochemistry of each problem. Tissue engineering models can be broadly categorised as static or dynamic tissue culture models [48]. Static models typically focus on diffusion-limited problems where local nutrient availability is of primary concern, whereas dynamic models describe the transport of cell metabolites, often with additional focus on the local chemical and mechanical environment of cell cultures. In this thesis, we take a particular interest in how flow is utilised to enhance mass transport in tissue engineering bioreactors. Therefore, we continue with a review of mathematical methods for modelling dynamic tissue culture.

1.3.1 Discrete vs continuum modelling

Broadly, mathematical models of cell behaviour can be categorised into discrete or continuous models. Continuum cell growth models aim to describe the overall behaviour of a system through a set of partial differential equations (PDEs), modelling the dynamics of the cell population density. Conversely, discrete models consider individual cells to describe cell movement, proliferation and cell-cell interaction via a set of pre-prescribed rules. At an individual cell level, discrete models typically provide a more natural framework to explicitly model biochemical and biomechanical interactions within a population [48]. Discrete models have been used to incorporate information regarding cell signalling interactions, motility, proliferation and reaction dynamics in cell populations. Ouchi et al. use the cellular Potts model to describe cell-cell interactions that describe morphogenetic processes in tissue formation [49]. Additional considerations of cell interactions with their local environment have also been postulated by Meineke et al. through a system of over-damped springs connecting cell centres [50], which has been further developed to consider cell signalling mechanisms [51].

Unfortunately for cell growth simulations, discrete models typically become extremely computationally intensive as the cell number increases. Homogenisation techniques instead have been used to average over a lengthscale larger than individual cells, but smaller than the cell population, to derive continuum models that capture the mechanics of the underlying discrete system, while allowing for analytical or numerical analysis with a system of PDEs [52–54]. Furthermore, continuum mathematical methods present a natural framework to model the spatial and temporal dynamics of fluid flow and cell metabolite transport via conservation of mass and momentum arguments. With this in mind, we proceed by reviewing continuum mathematical models of fluid flow and metabolite transport in the context of tissue engineering, before focusing on mathematical models of hollow fibre membrane bioreactors.

1.3.2 Fluid flow

Advection of cell nutrients and waste metabolites is important in overcoming diffusive mass transport limitations in dynamic tissue culture. The continuity equation and Navier-Stokes equations famously present a system of differential equations that describe conservation of mass and momentum in fluid flow problems [55], and can be used to describe fluid flow in dynamic tissue engineering bioreactor systems. For fluid flow through porous media (e.g. porous tissue engineering scaffolds), Darcy’s

law can be utilised to model the relationship between fluid flux and pressure [55]. Darcy’s law can be derived from the Navier-Stokes equations via a homogenisation procedure appropriate for small Reynolds number flows where viscous forces dominate fluid inertia [56]. We note that we would typically see slow viscous flows in tissue engineering bioreactor setups, and thus porous flow models where macroscale viscous effects become important (e.g. Brinkman equations [57]), are not considered here.

In the context of tissue engineering bioreactors, single-phase fluid flow delivering cell nutrients (modelled by the Navier-Stokes equations) is often coupled to multi-phase flow through the porous tissue scaffold (modelled by Darcy’s law). Therefore, consideration must be made to correctly couple the flow between each region mathematically. Whilst continuity of normal flux and normal fluid stress are intuitive interfacial conditions, the condition on the tangential component of flow past a porous wall is an open research topic in fluid mechanics. Single-phase fluid-solid interfaces are typically characterised by a no tangential slip condition, and fluid-fluid interfaces are characterised by continuity of tangential stress and kinematic boundary conditions. However by homogenising over the porous domain, consisting of a biphasic mixture of solid matrix and saturated fluid pores, it is not immediately clear how to resolve flow past a surface comprised of fluid and solid phases. In 1967, Beavers & Joseph experimentally showed that the tangential slip between bulk flow and porous flow is proportional to the rate of change of the tangential velocity normal to the interface [58], which was later mathematically confirmed by Saffman utilising the method of matched asymptotic expansions [59]. The proportionality between these two quantities is defined as the slip coefficient, which can be experimentally characterised. However, in work by Shipley et al. [61], it was later confirmed by mathematical and experimental validation that in the context of slow viscous flow through a single porous hollow fibre, employing a Beavers-Joseph slip condition has negligible impact on the flow solution, and has qualitatively little difference to using a no-slip condition. Therefore when modelling flow in a HFMB setup, we prescribe a no-tangential-slip condition.

To make analytic progress in solving the Navier-Stokes equations, a number of assumptions can be made to reduce model complexity. In scenarios where flow is expected to remain constant in time, time derivatives in the Navier-Stokes equations can be neglected. Furthermore, in the small Reynolds number limit, Navier-Stokes simplifies to the Stokes flow equations [55]. This is valid for slow flow rates in a regime where viscous forces dominate inertia. Slower flow rates lead to a smaller fluid stress. Therefore in the context of advective mass transport in tissue engineering,

steady Stokes flow equations are often used in tissue engineering models to minimise mechanical disruption to cells [48]. In native vasculature, however, this is not the case. Blood flow *in vivo* is not steady, but in fact pulsatile, following the pulsatile pressure drop generated by the heart driving flow through the circulatory system. Womersley first considered the long timescale periodic solutions to pulsatile flow through straight rigid vasculature by neglecting nonlinear inertial effects [62]. Future work has adapted the periodic pressure drop condition considered by Womersley to consider 1D models of flow through pulsatile bioreactor systems in the context of vascular tissue engineering to pre-condition the vascular walls [63, 64]. However, these models do not account for spatial variations in fluid stress, which are key to understanding mechanical stress throughout the bioreactor.

Furthermore, flow through major vessels in the circulatory system is not accurately described by slow viscous Stokes flow models. Flow through large-diameter vessels such as arteries exhibit Reynolds numbers upward of 500 [65], representing fast flow rates where nonlinear inertial forces are important. Flow entering arteries from the heart is also not fully-developed, and thus accounting for entrance effects becomes important [66]. Fast flows generate significantly larger fluid shear stresses, which are important in regulating smooth muscle cell and endothelial cell morphology, as well as ensuring quick and efficient transport of oxygen and cell metabolites around the body [14, 67]. Extensive asymptotic and numerical modelling of large Reynolds flow in human vasculature has been considered in the literature (see Carvalho et al. [68]). In tissue engineering modelling, recent work by Dalwadi et al. considers large Reynolds flows in a RWV bioreactor to understand how flow transitions from a plug to Poiseuille profile entering and leaving a porous tissue scaffold, which is used to determine the fluid pressure drop across the porous region [69]. However, to our knowledge, large Reynolds flows have not been considered in the context of hollow fibre membrane bioreactors.

1.3.3 Metabolite transport

Transport of cell metabolites can be modelled as a dilute species by its concentration via the advection-diffusion-reaction equations, formed by considering conservation of mass in a continuum framework [70]. Advection describes the transport of dilute species via an underlying fluid velocity field, whereas diffusion describes the net spread of material down concentration gradients via random motion. The introduction of a reaction term accounts for the production or removal of a given species, which can be modelled by a function describing reaction kinetics. For example, the

Michaelis-Menten (M-M) equation is a popular empirical law describing enzymatic reaction kinetics in a well-mixed system [71]. M-M kinetics are parameterised by a maximum reaction rate V_{max} and the Michaelis constant K_M , which defines the concentration at which the reaction rate is half of V_{max} . The M-M reaction kinetics have found particular prominence in mathematical biology for accurately modelling reaction kinetics across a wide range of biological systems which exhibit a maximum rate V_{max} [71].

An implicit assumption in the derivation of M-M reaction kinetics is that the concentration of the intermediate complex remains constant over the timescale in which the product is formed. This is shown to be true of many biological reactions such as antigen-antibody binding, protein-protein interactions and production/uptake of cell metabolites [72]. Further extensions of Michaelis-Menten reaction kinetics have been subsequently proposed. For example, Hill kinetics can be thought of as a generalisation of the M-M equations with the exponent n that describes positive cooperative binding ($n > 1$) and negative cooperative binding ($n < 1$) [73]. Similarly, Haldane kinetics describe substrate inhibition through the addition of the inhibition constant K_i in the denominator of the M-M equations [74]. However, given the simplicity of the form of M-M kinetics and its strong quantitative agreement across a wide range of biological systems, it continues to be widely adopted in mathematical biology applications.

We now consider the interface of flow and metabolite transport modelling in the context of tissue engineering bioreactors.

1.3.4 Bioreactor modelling

Macroscale modelling of fluid flow through porous tissue engineering scaffolds is typically based on Darcy’s law. For example, Whittaker et al. model forced fluid flow through a porous scaffold based on Darcy’s law to examine nutrient and shear stress distributions throughout a perfusion bioreactor [75]. The use of a multiphase model such as Darcy’s law does not require a detailed understanding of the underlying microstructure of the porous membrane wall, and thus provides a fast and robust method to model macroscale porous flow.

However, biological tissue is inherently a complex mixture of different interacting constituents including different types of cells, cellular deposits and interstitial fluid. Multiphase modelling, or mixture theory, can be employed to describe fluid-structure interactions between different components by working within a continuum framework whereby different material phases can occupy the same space. Mass and momentum

balances alongside constituent relations are used to describe interactions between the different phases, describing the mechanics of a composite material as a function of the material properties and volume fractions of each component [76]. Early examples of this include multiphase models of rigid porous scaffolds formulated by Lemon and co-workers incorporating cell, water and scaffold phases [77, 78]. These models aim to understand how cell-cell interactions influence the distribution or aggregation of cells across the scaffold. This is built upon by O’Dea et al. and Osborne et al. in the design of direct-perfusion bioreactors, where it is found that cell density and aggregation has a significant effect on cell motility [79, 80]. In HFMB design, mixture theory has also been used to model the coexistence of a rigid porous scaffold, cells and nutrient media in the ECS of a hollow fibre membrane to understand how to maintain a uniform cell distribution through manipulating the fluid flow rate [81], as well as understanding how cell growth is impacted by fluid stress [82].

By coupling these multiphase regions to single-phase flow entering and leaving the bioreactor system, one can quantify the impact of varying operating parameters on the chemical and mechanical environment in the bioreactor. Finite element models of flow and nutrient transport in a HFMB setup have been developed to understand the impact of bioreactor flow rates, as well as membrane thickness and permeability, on nutrient concentration distributions [83]. Whilst computational methods are able to capture the mechanics of complex transport problems in complex geometries, their large computational cost prohibits detailed resolution of the metabolite field and the ability to comprehensively explore parameter space [84, 85]. Alternatively, reduced-order modelling relies on asymptotic methods to systematically reduce the complexity of mathematical problems by identifying and retaining the important physics. In tissue engineering, reduced-order models help reveal the dominant transport mechanisms at play under certain asymptotic limits, and can often yield explicit analytic solutions for the fluid velocity and metabolite concentration. For example, Shipley et al. compare analytic and numerical models for determining the optimal operating parameters for steady hollow fibre bioreactor operation [60]. By exploiting the long thin bioreactor geometry and assuming constant nutrient uptake throughout the ECS, it was possible to determine a fully analytic expression for the nutrient concentration profile throughout the bioreactor for all ratios of advective to diffusive mass transport effects (Péclet numbers). This also motivated future work on characterising the importance of flow in the ECS for nutrient delivery and uptake, by comparing an open and closed ECS port [86]. By retaining important terms and reducing computational cost, Shipley et al. find good quantitative agreement with full numerical simulations,

whilst revealing an explicit dependency of bioreactor nutrient concentration on bioreactor geometry, membrane permeability, thickness and flow rate. Chapman et al. build on these models with the incorporation of a time-dependent cell growth layer on the scaffold surface governed by a simple growth law, showing how cell growth inhibits fluid and mass transport within the bioreactor [87]. Chapman shows how the evolution of the free boundary of the cell layer increases proportionally to the local oxygen concentration, and decreases if local fluid stress exceeds the maximum shear stress the specific cell type can experience.

In each of these cases [86, 87], a constant nutrient uptake rate by cells was assumed. This is true if the bioreactor is saturated with nutrients. In practice, however, it is not always feasible to provide these nutrients in excess due to their significant cost and limited availability. Therefore, a key goal in tissue engineering models is to consider the minimum inlet concentration of nutrients required to sustain a cell population. However, models that can account for a full range of inlet nutrient concentrations by utilising full Michaelis-Menten uptake kinetics usually rely on computationally-expensive numerical methods such as COMSOL Multiphysics® to solve the full transport problem. Furthermore, the assumption of slow steady viscous flow in these systems limits the applicability of these results, and does not account for pulsatile or large Reynolds flows, where inertia plays an important role in fluid flow.

1.4 Thesis outline

In this thesis, we present a series of reduced-order models describing fluid flow and nutrient transport in a single-fibre HMFB for applications in tissue engineering. Inspired by the poroelastic fibre bioreactor developed by experimental collaborators, the motivation behind this work is to establish a framework to better understand transport in these bioreactor setups, as well as understand theoretically optimal structural and operating conditions for HFMB design. We begin each Chapter with a brief literature review of relevant research in each area, before describing our contributions.

In Chapter 2, we review existing models of poroelastic hollow fibre membranes used in tissue engineering bioreactors. We then present a 2D axisymmetric continuum model of Stokes flow through the lumen, membrane and ECS of a poroelastic single-fibre bioreactor of constant permeability. This model setup is inspired by the experimental model setup considered by our experimental collaborators. Utilising our analysis, we consider the effect of structural and operating model parameters

on distributions of stress and strain in the membrane wall, and explore how we can determine a theoretically optimal heterogeneous membrane permeability distribution that delivers uniform flux across the membrane wall. This is analogous to uniform nutrient delivery to cells seeded at the outer membrane wall in an advection-dominated transport regime.

In Chapter 3, we extend the model considered in Chapter 2 to consider pulsatile flow through our poroelastic bioreactor setup. We consider the asymptotic sublimit whereby flow is slow and viscous such that we neglect nonlinear inertia, however, the oscillatory nature of the flow means that we retain the time-dependent linear inertia term in the Navier-Stokes equations. We prescribe a pulsatile axial pressure drop through the lumen of the poroelastic fibre, and determine the pulsatile flow solution, distributions of membrane displacement, stress and strain. Through varying the frequency of the applied pressure oscillations, we characterise the pressure-flux phase lag, and utilise asymptotic analysis to determine the behaviour of the system at large oscillation frequencies.

Moving to Chapter 4, we consider the advection and diffusion of cell nutrients and waste metabolites in the bioreactor system described in Chapter 2, with the addition of nutrient uptake/waste production in a cell layer external to the membrane wall modelled by Michaelis-Menten kinetics. Utilising asymptotic techniques, we again exploit the long thin bioreactor geometry as well as the small cell layer thickness relative to typical radial length scales. To reduce the dimensionality of our governing equations, we also consider the non-trivial curvilinear coordinate transformation from 2D axisymmetric coordinates to a streamfunction-arclength formulation. We derive a reduced-order model that reveals how dilute species are transported in a long thin bioreactor system. We determine the set of model parameters that maximise nutrient delivery and waste removal in the system. Additionally, we utilise the optimal permeability distribution determined in Chapter 2 to understand how we can deliver a uniform nutrient concentration to cells seeded to the membrane scaffold, independent of the Péclet number.

In Chapter 5, we consider the literature surrounding the asymptotic analysis of laminar plug-to-Poiseuille flow transitions. Building on this work, we establish a 2D model of plug-to-lubrication flow transitions in two long thin parallel channels separated by a porous membrane, considered in the context of a hollow fibre membrane bioreactor. We reveal how the complex nested boundary layer structure varies as a function of the Reynolds number, in particular, to understand the local mechanical

environment cells are likely to experience when faster, more physiologically-relevant flow rates are used in a tissue engineering setup.

Finally in Chapter 6, we conclude with a summary of the work presented in this thesis, alongside a discussion of proposed applications and extended future work.

Chapter 2

Steady flow in poroelastic scaffolds

2.1 Introduction

In Section 1, the existing HFMB models explored typically assume that membrane fibres are rigid. This is not necessarily the case in practice, as polymer membrane fibres are flexible and can deform under the action of fluid stress. Given the sensitivity of cells to their local mechanical environment, the deformation of these fibres may in turn impact cell growth. Therefore, to more accurately describe cell growth with deformable scaffolds, more recent work has focused on the formulation of models based on fluid-structure interaction with elastic and poroelastic scaffolds. A range of experimental setups have been modelled by Kumar and co-workers utilising mixture theory to model a poroelastic scaffold region as a mixture of scaffold and nutrient-rich media. Setups include single-phase fluid flow through the lumen of a poroelastic fibre with a fixed and closed outer wall (Figure 2.1a) [88], as well as single-phase fluid flow through the lumen of a rigid porous membrane with cells seeded to a poroelastic scaffold in the surrounding ECS (Figure 2.1b) [89]. Both papers exploit the disparate time scales between cell growth and advection-diffusion of solutes to consider a short time-scale that neglects cell growth, death and differentiation. Additionally, the small aspect ratio of the HFMBs motivate the use of asymptotic techniques to make analytic progress with the respective fluid transport problems. Detailed analyses also aim to understand how parameters such as scaffold deformability, porosity, permeability and pressure gradient affect local nutrient concentration.

However, the experimental setups modelled by Kumar et al. do not reflect the setup we aim to model as described in Section 1.2. In each of their scenarios, the deformable scaffold is constrained in the radial direction, and they do not consider an outer membrane wall that is free to deform under the action of fluid stress. A prescribed fluid flux in the ECS region has also not been modelled here, although has

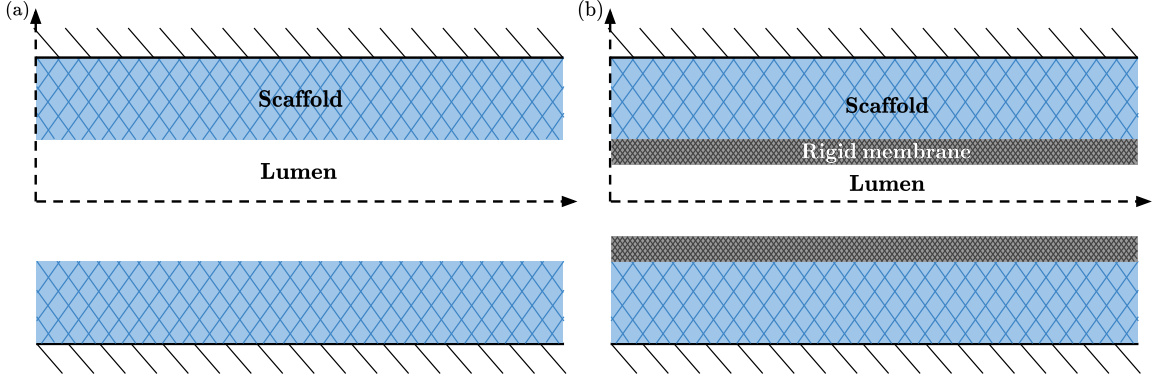


Figure 2.1: Model setups adapted from Kumar et al. describing: (a) Single-phase fluid transport through the lumen of a poroelastic cell scaffold with a closed rigid outer wall [88], reproduced with permission from John Wiley and Sons; (b) Single-phase fluid transport through the lumen of a rigid fibre membrane surrounded by a poroelastic cell scaffold with a closed rigid outer wall [89], reproduced with permission from AIP Publishing.

been utilised in many existing rigid HFMB models to promote the removal of waste metabolites [60, 86, 87].

The work presented in this Chapter extends the flow problem considered by Shipley et al. [86] combining with a poroelastic membrane wall to understand the deformation, stress and strain distributions through a deformable hollow fibre tissue engineering scaffold. We adopt the constitutive laws governing poroelastic deformation as considered by Kumar et al., however extend their analysis to account for deformation under the action of two single-phase flow regions, as well as membrane clamping at each axial end. Additionally, we consider the effect of heterogeneous membrane permeability distributions similarly to Dalwadi et al. [90], in the context of membrane filtration, to understand how permeability gradients can redirect the flow field to achieve uniform transport across the membrane wall.

2.2 Model setup

In this Chapter, we consider flow within a single-fibre HFMB. We model the HFMB as a long and thin poroelastic membrane with fluid transport prescribed through the lumen and in the surrounding extra-capillary space (ECS). In cylindrical coordinates (r^*, θ^*, z^*) , with the longitudinal axis coinciding with the cylinder axis, we define $\hat{\mathbf{e}}_r, \hat{\mathbf{e}}_\theta, \hat{\mathbf{e}}_z$ as unit vectors in the radial, azimuthal and axial directions respectively. We assume the system is axisymmetric along the cylinder axis, and therefore neglect azimuthal components and derivatives henceforth. The membrane consists of

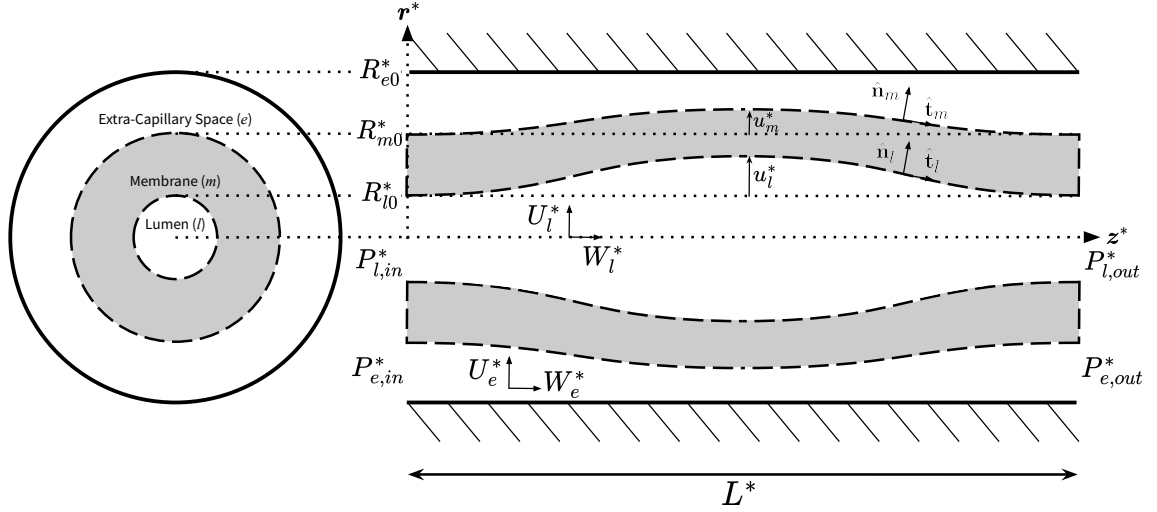


Figure 2.2: Axisymmetric description of a poroelastic hollow fibre membrane of circular cross-section and length L^* . Fluid flow along the lumen and extra-capillary space is driven by a pressure drop, $P_{i,in}^* - P_{i,out}^*$, where $i = l, e$ denotes the lumen and ECS respectively. Fluid can travel across the membrane wall under radial and axial pressure gradients. The fluid velocity has radial (U_i^*) and axial (W_i^*) components. Each deformed fluid-poroelastic interface is characterised by a unit outward-facing normal vector $\hat{\mathbf{n}}_j$ with corresponding tangent vector $\hat{\mathbf{t}}_j$ that vary spatially as a result of radial (u_j) and axial (w_j) membrane deformations, with $j = l, m$.

a poroelastic annulus of circular cross-section with length L^* , and undeformed internal and external radii of $r^* = R_{l0}^*$ and $r^* = R_{m0}^*$ respectively (with $R_{m0}^* > R_{l0}^*$) at ambient pressure. The membrane is clamped at the fluid inlet ($z^* = 0$) and outlet ($z^* = L^*$) to keep the membrane in place and to set the axial gradient of out-of-plane displacements. Additionally, a rigid wall surrounds the membrane at $r^* = R_{e0}^*$ (where $R_{e0}^* > R_{m0}^*$). The membrane deforms under the action of hydrodynamic stress, but is constrained by the clamped ends and the surrounding rigid wall.

2.3 Governing equations

2.3.1 Poroelastic deformation

We describe stress in the poroelastic membrane wall using Terzaghi's principle [91, 92], whereby on a scale of many pores the fluid stress in a poroelastic material averages to the fluid pore pressure. Therefore, the net stress in the material can be described by a combination of the fluid pore pressure and the elastic stress via

$$\boldsymbol{\tau}^* = -P_m^* \mathbf{I} + \boldsymbol{\tau}_e^*. \quad (2.1)$$

Here, $P_m^*(r^*, z^*)$ is the fluid pore pressure in the membrane, $\mathbf{I}$ is the identity matrix, and $\boldsymbol{\tau}_e^*$ denotes the elastic contribution of stress. Assuming the membrane is isotropic, we can define the elastic stress in terms of effective Lamé constants, λ_{eff}^* and μ_{eff}^* ,

$$\boldsymbol{\tau}_e^* = \lambda_{\text{eff}}^* \mathbf{I} \text{Tr}(\mathbf{e}) + 2\mu_{\text{eff}}^* \mathbf{e}. \quad (2.2)$$

The effective Lamé constants describe the effective mechanical properties of the poroelastic material assumed to comprise the solid scaffold and the saturated fluid pores. The Lamé constants can be expressed in terms of an effective Young's modulus (E^*) and compressibility factor (δ), such that

$$\lambda_{\text{eff}}^* = \frac{E^*(1-\delta)}{\delta(3-\delta)}, \quad \mu_{\text{eff}}^* = \frac{E^*}{3-\delta}. \quad (2.3)$$

Assuming displacement gradients are small, we relate material strain to material displacement through the infinitesimal strain tensor

$$\mathbf{e} = \frac{1}{2} \left(\nabla^* \mathbf{u}^* + (\nabla^* \mathbf{u}^*)^\top \right), \quad (2.4)$$

where the displacement $\mathbf{u}^* = u^* \hat{\mathbf{e}}_r + w^* \hat{\mathbf{e}}_z$, and the dependent variables are functions of r^* and z^* . Assuming the system is in equilibrium, and neglecting external body forces, we relate the above stresses (2.1) using the equilibrium condition

$$\nabla^* \cdot \boldsymbol{\tau}^* = \mathbf{0}. \quad (2.5)$$

Substituting (2.1)–(2.4) into Equations (2.5), we obtain the following equilibrium equations in terms of the displacement

$$\frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \left(\frac{\partial^2 u^*}{\partial r^{*2}} + \frac{1}{r^*} \frac{\partial u^*}{\partial r^*} - \frac{u^*}{r^{*2}} \right) + \frac{\partial^2 w^*}{\partial r^* \partial z^*} + \delta \frac{\partial^2 u^*}{\partial z^{*2}} \right] = \frac{\partial P_m^*}{\partial r^*}, \quad (2.6a)$$

$$\frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial^2 w^*}{\partial z^{*2}} + \frac{\partial^2 u^*}{\partial r^* \partial z^*} + \frac{1}{r^*} \frac{\partial u^*}{\partial z^*} + \delta \left(\frac{\partial^2 w^*}{\partial r^{*2}} + \frac{1}{r^*} \frac{\partial w^*}{\partial r^*} \right) \right] = \frac{\partial P_m^*}{\partial z^*}, \quad (2.6b)$$

with corresponding axisymmetric expressions for membrane wall stress

$$\tau_{rr}^* = -P_m^* + \frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial u^*}{\partial r^*} + (1-\delta) \left(\frac{u^*}{r^*} + \frac{\partial w^*}{\partial z^*} \right) \right], \quad (2.7a)$$

$$\tau_{\theta\theta}^* = -P_m^* + \frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \frac{u^*}{r^*} + (1-\delta) \left(\frac{\partial u^*}{\partial r^*} + \frac{\partial w^*}{\partial z^*} \right) \right], \quad (2.7b)$$

$$\tau_{zz}^* = -P_m^* + \frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial w^*}{\partial z^*} + (1-\delta) \left(\frac{u^*}{r^*} + \frac{\partial u^*}{\partial r^*} \right) \right], \quad (2.7c)$$

$$\tau_{rz}^* = \tau_{zr}^* = \frac{E^*}{3-\delta} \left[\frac{\partial w^*}{\partial r^*} + \frac{\partial u^*}{\partial z^*} \right], \quad (2.7d)$$

$$\tau_{\theta z}^* = \tau_{z\theta}^* = \tau_{r\theta}^* = \tau_{\theta r}^* = 0. \quad (2.7e)$$

2.3.2 Fluid flow

We model the fluid transport through the lumen and ECS by the steady Stokes equations for an incompressible Newtonian viscous fluid of constant density, ρ^* , and dynamic viscosity, μ^* ,

$$\nabla^* \cdot \mathbf{U}_i^* = 0, \quad \nabla^* P_i^* = \mu^* \nabla^{*2} \mathbf{U}_i^*, \quad (2.8)$$

where the fluid velocity vector $\mathbf{U}_i^* = U_i^* \hat{\mathbf{e}}_r + W_i^* \hat{\mathbf{e}}_z$, P_i^* is fluid pressure, and $i = l, e$ refers to the lumen or ECS regions respectively. In the poroelastic membrane, we model fluid transport via Darcy's law

$$\nabla^* \cdot \mathbf{U}_m^* = 0, \quad \phi \mathbf{U}_m^* = -\frac{k^*}{\mu^*} \nabla^* P_m^*, \quad (2.9)$$

where the membrane fluid pore velocity $\mathbf{U}_m^* = U_m^* \hat{\mathbf{e}}_r + W_m^* \hat{\mathbf{e}}_z$, k^* is the membrane permeability and ϕ is the constant uniform membrane porosity. Therefore, $\phi \mathbf{U}_m^*$ denotes the Darcy flux through the membrane. In general, we let $k^* = k^*(z^*)$ vary across the length of the domain, emphasising that it is independent of the radial position r^* , justified by manufacturing constraints for a long, thin membrane.

2.4 Boundary conditions

The fluid-poroelastic interfaces refer to the deformed inner lumen-membrane and outer membrane-ECS interfaces. At equilibrium and assuming axisymmetry, the membrane wall is displaced radially and axially under the action of fluid transport from its undeformed reference state to a new, deformed position. Though we will later find that we are in the linear poroelasticity regime, for completeness of the full problem statement we note that the equilibrium continuity conditions at each

interface should, strictly speaking, be evaluated at the deformed interfaces. The position of the deformed inner and outer membrane interfaces can be defined through its material displacement at each interface,

$$r^* = R_{j0}^* + u_j^*, \quad z^* = z_0^* + w_j^*, \quad (2.10)$$

where $j = l, m$ denotes the inner and outer interfaces respectively, $u_j^* = u^*|_{R_{j0}^*, z_0^*}$, and $w_j^* = w^*|_{R_{j0}^*, z_0^*}$. We proceed by defining the following interfacial conditions evaluated at the deformed inner and outer interfaces.

We first prescribe continuity of stress at the deformed lumen-membrane and membrane-ECS interfaces

$$\boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j = \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j, \quad (2.11)$$

where $\hat{\mathbf{n}}_j$ denotes the outward-facing unit normal vector to the surface of the membrane. The viscous fluid stress tensor, $\boldsymbol{\sigma}_i^*$ is related to fluid pressure and fluid velocity by the following relationship

$$\boldsymbol{\sigma}_i^* = -P_i^* \mathbf{I} + \mu^* (\nabla^* \mathbf{U}_i^* + (\nabla^* \mathbf{U}_i^*)^\top). \quad (2.12)$$

The unit outward facing normal vector to the surface of the deformed inner and outer membrane walls are defined as

$$\hat{\mathbf{n}}_l = \frac{\left(1 + \frac{\partial w_l^*}{\partial z^*}\right) \hat{\mathbf{e}}_r - \frac{\partial u_l^*}{\partial z^*} \hat{\mathbf{e}}_z}{\sqrt{\left(1 + \frac{\partial w_l^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_l^*}{\partial z^*}\right)^2}}, \quad \hat{\mathbf{n}}_m = \frac{\left(1 + \frac{\partial w_m^*}{\partial z^*}\right) \hat{\mathbf{e}}_r - \frac{\partial u_m^*}{\partial z^*} \hat{\mathbf{e}}_z}{\sqrt{\left(1 + \frac{\partial w_m^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_m^*}{\partial z^*}\right)^2}}. \quad (2.13)$$

The unit tangent vector to the unit normal vector, $\hat{\mathbf{t}}_j$, at the inner and outer boundaries become

$$\hat{\mathbf{t}}_l = \frac{\frac{\partial u_l^*}{\partial z^*} \hat{\mathbf{e}}_r + \left(1 + \frac{\partial w_l^*}{\partial z^*}\right) \hat{\mathbf{e}}_z}{\sqrt{\left(1 + \frac{\partial w_l^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_l^*}{\partial z^*}\right)^2}}, \quad \hat{\mathbf{t}}_m = \frac{\frac{\partial u_m^*}{\partial z^*} \hat{\mathbf{e}}_r + \left(1 + \frac{\partial w_m^*}{\partial z^*}\right) \hat{\mathbf{e}}_z}{\sqrt{\left(1 + \frac{\partial w_m^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_m^*}{\partial z^*}\right)^2}}. \quad (2.14)$$

In addition to continuity of stress, we specify that the normal component of fluid stress in the lumen and ECS is balanced by the fluid pore pressure at the deformed lumen-membrane and membrane-ECS interfaces

$$\hat{\mathbf{n}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j = -P_m^*. \quad (2.15)$$

Typically, flow past porous media can be modelled by imposing a Beavers-Joseph slip condition on the tangential component of fluid stress, where the slip coefficient is experimentally derived [58]. However, Shipley et al. show that accounting for slip at a porous interface in a typical bioreactor setup has negligible impact on the flow solution [61]. Therefore, we instead impose a no-slip condition at the lumen-membrane and membrane-ECS interfaces

$$\mathbf{U}_i^* \cdot \hat{\mathbf{t}}_j = 0, \quad (2.16)$$

alongside a continuity of normal flux condition

$$\mathbf{U}_i^* \cdot \hat{\mathbf{n}}_j = \phi \mathbf{U}_m^* \cdot \hat{\mathbf{n}}_j. \quad (2.17)$$

The above set of interfacial boundary conditions are evaluated at the deformed inner and outer membrane interfaces, which vary as a function of axial and radial position. To simplify we take a first-order Taylor expansion about the undeformed membrane geometry, the details of which are shown in Appendix A.

In the fluid flow problem, we prescribe a fluid stress at the inlet and outlet of both the lumen and ECS,

$$\boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{e}}_z = P_{i,in}^* \quad \text{at} \quad z^* = 0, \quad (2.18a)$$

$$\boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{e}}_z = P_{i,out}^* \quad \text{at} \quad z^* = L^*, \quad (2.18b)$$

with a specified inlet velocity profile. We note that we could also determine the inlet pressure conditions (2.18) from a prescribed set of volumetric flow rates, defined by

$$Q_{i,in}^* = 2\pi \int_{R_1^*}^{R_2^*} r^* W_i^* dr^* \quad \text{at} \quad z^* = 0, \quad (2.19)$$

for $i = l, e$, where R_1^*, R_2^* define the inner and outer radial boundaries of the respective region. Equation (2.19) is used to determine the appropriate inlet pressure conditions corresponding to the inlet flow rates used from literature summarised in Table 2.1.

To bound the fluid transport problem, we prescribe no flux at each end of the membrane

$$\mathbf{U}_m^* \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at} \quad z^* = 0, L^*, \quad (2.20)$$

noting that the dimensionality of the Darcy equation (2.9) only permits specification of a normal velocity condition here. Additionally, we prescribe a symmetry condition at the lumen centreline

$$\mathbf{U}_l^* \cdot \hat{\mathbf{e}}_r = \nabla^* (\mathbf{U}_l^* \cdot \hat{\mathbf{e}}_z) \cdot \hat{\mathbf{e}}_r = 0 \quad \text{at} \quad r^* = 0, \quad (2.21)$$

and no slip/flux at the rigid outer wall of the ECS

$$\mathbf{U}_e^* = \mathbf{0} \quad \text{at} \quad r^* = R_{e0}^*. \quad (2.22)$$

To model membrane clamping, we prescribe no displacement, and zero gradient of out-of-plane displacements, at the inlet and outlet

$$\mathbf{u}^* \cdot \hat{\mathbf{e}}_r = \nabla^* (\mathbf{u}^* \cdot \hat{\mathbf{e}}_r) \cdot \hat{\mathbf{e}}_z = \mathbf{u}^* \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at} \quad z^* = 0, L^*. \quad (2.23)$$

Equations governing membrane deformation (2.6) are solved subject to boundary conditions (2.11), (2.23) to determine radial u^* and axial w^* components of displacement. Fluid flow equations (2.8) – (2.9) are solved subject to (2.15) – (2.22) for radial U_i^* and axial W_i^* fluid velocity components, as well as fluid pressure P_i^* . Typical parameter values are given in Table 2.1. Where possible, parameter values have been sourced from literature on the experimental and mathematical characterisation of a single-fibre HFMB setup considered by Shipley et al. [61]. The Young's modulus (E^*) and compressibility factor (δ) parameters were experimentally determined for the electrospun polydioxanone/polycaprolactone fibre developed by collaborators at the IBME with compressive and tensile stress tests, which is currently part of an internal unpublished dataset.

2.5 Nondimensionalisation

Pre-empting the important balances in the outer regions, away from the clamped walls, we use the following scalings

$$(r^*, z^*) = L^* (\varepsilon r, z), \quad (u^*, w^*) = \frac{\mu^* \overline{W}^*}{\varepsilon^2 E^*} (\varepsilon u, w), \quad (P_i^*, P_m^*) = \frac{\mu^* \overline{W}^*}{\varepsilon^2 L^*} (P_i, P_m), \\ (U_i^*, W_i^*, U_m, W_m) = \overline{W}^* (\varepsilon U_i, W_i, \varepsilon U_m, \varepsilon^2 W_m), \quad (2.24)$$

where $\varepsilon = R_{i0}^*/L^*$ is the lumen aspect ratio.

In (2.24), we scale the axial and radial coordinates relative to the length and radius of the lumen respectively. As summarised in Figure 2.3, we scale fluid velocities

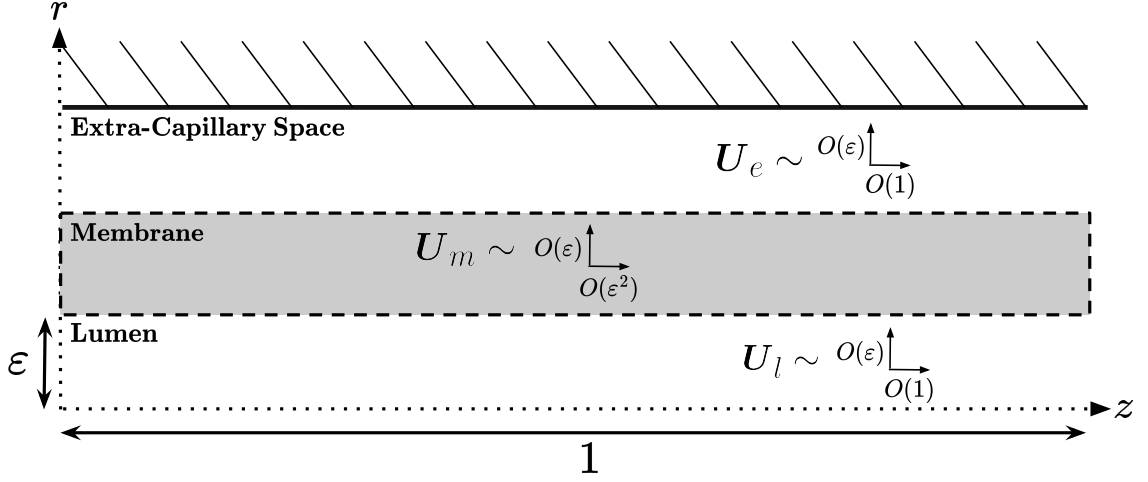


Figure 2.3: Schematic of relative fluid velocity and flux scalings in the lumen, membrane and ECS. Fluid flux scalings in the membrane are scaled to maintain a balance of terms in Darcy’s law (2.9). To maintain a balance of terms in the continuity of radial flux condition (2.17), radial velocities in the lumen and ECS are scaled the same as radial membrane flux. Applying lubrication scalings in the lumen and ECS means that axial velocity scalings are scaled $O(\varepsilon)$ larger than radial velocities.

in the lumen and ECS relative to the typical axial fluid velocity in the lumen, $\overline{W}^*$, with radial fluid velocity scaled an order of ε smaller than axial velocity scalings to remain consistent with lubrication theory in a long thin geometry. Given continuity of radial flux at the lumen-membrane and membrane-ECS interfaces, we scale radial velocity in the porous membrane with the same scalings as for radial flux in the lumen and ECS. Axial velocity scalings in the membrane are motivated by a balance of terms coming from Darcy’s law (2.9), requiring that axial velocity is scaled an order of ε smaller than the radial velocity scaling. We choose viscous pressure scalings reflecting a balance between pressure gradients and viscous terms. We choose displacement scalings to balance as many terms as possible in the continuity of normal stress boundary conditions. We emphasise that these scalings are valid where dominant stresses arise as a result of fluid-solid interaction, away from the clamped walls. Towards the ends of the membrane, stresses induced due to clamping will dominate and result in different balances, requiring different scalings.

Using the scalings in (2.24), the membrane deformation governing equations (2.6) become

$$\frac{1}{\delta(3-\delta)} \left[(1+\delta) \left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r} \frac{\partial u}{\partial r} - \frac{u}{r^2} \right) + \frac{\partial^2 w}{\partial r \partial z} + \varepsilon^2 \delta \frac{\partial^2 u}{\partial z^2} \right] = \frac{\partial P_m}{\partial r}, \quad (2.25a)$$

$$\frac{1}{\delta(3-\delta)} \left[\delta \left(\frac{\partial^2 w}{\partial r^2} + \frac{1}{r} \frac{\partial w}{\partial r} \right) + \varepsilon^2 \left((1+\delta) \frac{\partial^2 w}{\partial z^2} + \frac{\partial^2 u}{\partial r \partial z} + \frac{1}{r} \frac{\partial u}{\partial z} \right) \right] = \varepsilon^2 \frac{\partial P_m}{\partial z}. \quad (2.25b)$$

In the lumen and the ECS, fluid flow governing equations (2.8) become

$$\frac{1}{r} \frac{\partial}{\partial r} (r U_i) + \frac{\partial W_i}{\partial z} = 0, \quad (2.26a)$$

$$\frac{\partial P_i}{\partial r} = \varepsilon^2 \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial U_i}{\partial r} \right) - \frac{U_i}{r^2} \right) + \varepsilon^4 \frac{\partial^2 U_i}{\partial z^2}, \quad (2.26b)$$

$$\frac{\partial P_i}{\partial z} = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial W_i}{\partial r} \right) + \varepsilon^2 \frac{\partial^2 W_i}{\partial z^2}, \quad (2.26c)$$

and Darcy's law in the membrane region (2.9) becomes

$$\frac{1}{r} \frac{\partial}{\partial r} (r U_m) + \varepsilon^2 \frac{\partial W_m}{\partial z} = 0, \quad (2.27a)$$

$$\phi U_m = -\kappa \frac{\partial P_m}{\partial r}, \quad \phi W_m = -\kappa \frac{\partial P_m}{\partial z}, \quad (2.27b)$$

where $\kappa(z) = k^*(z^*)/\varepsilon^4 L^{*2}$, which we take to be an $O(1)$ quantity.

The parameter κ can be interpreted as the nondimensional permeability, quantifying the relative resistance to fluid flow across the membrane wall versus along the fibre lumen. To demonstrate this, we consider Stokes flow along a rigid pipe of radius R_{l0}^* and length L^* , which has resistance to fluid flow $F_l = \pi R_{l0}^{*4}/8L^*\mu^*$ assuming a simplified network model $Q = F\Delta P$. For unidirectional Darcy flow across a membrane fibre wall of permeability k^* , thickness $R_{m0}^* - R_{l0}^*$ and length L^* , we find that $F_m = 2\pi R_{l0}^* k^* L^*/\mu^* (R_{m0}^* - R_{l0}^*) \approx 2\pi k^* L^*/\mu^*$. Then, taking the ratio of the two, we find that

$$\frac{F_m}{F_l} = \frac{16k^* L^{*2}}{R_{l0}^{*4}} \approx \frac{k^* L^{*2}}{R_{l0}^{*4}} = \kappa. \quad (2.28)$$

At the rigid outer wall, we maintain no-slip and no-flux boundary conditions (2.22),

$$\mathbf{U}_e = \mathbf{0} \quad \text{at} \quad r = R_{e0}, \quad (2.29)$$

and at the inlet and outlet of the lumen and ECS our continuity of fluid stress (2.18) becomes an inlet and outlet pressure condition

$$P_i|_{z=0} = P_{i,in}, \quad P_i|_{z=1} = P_{i,out}. \quad (2.30)$$

The inlet pressure condition (2.30) is determined from the nondimensional inlet flow rate coming from (2.19)

$$Q_{i,in} = \int_{R_1}^{R_2} W_i r \, dr \quad \text{at} \quad z = 0, \quad (2.31)$$

where $Q_{i,in} = Q_{i,in}^*/2\pi\varepsilon^2 L^{*2} \bar{W}^*$ is determined from Table 2.1. We note that $Q_{lin} \equiv 1$, which sets the velocity scaling $\bar{W}^*$. The no-flux membrane condition (2.20) becomes

$$W_m = 0 \quad \text{at} \quad z = 0, 1, \quad (2.32)$$

and the symmetry condition (2.21) becomes

$$U_l = \frac{\partial W_l}{\partial r} = 0 \quad \text{at} \quad r = 0. \quad (2.33)$$

Lastly, the clamped wall boundary conditions (2.23) become

$$u = \frac{\partial u}{\partial z} = w = 0 \quad \text{at} \quad z = 0, 1. \quad (2.34)$$

We present details of how fluid-poroelastic interfacial conditions (2.11)–(2.17) are nondimensionalised in Appendix A.

2.6 Model solution

In nondimensionalising our problem, we find that two small dimensionless parameter groupings appear. Namely, ε which denotes the lumen aspect ratio, and $\gamma = \mu^* \bar{W}^* / \varepsilon^2 L^* E^*$ which represents the ratio of viscous forces to the stiffness of the membrane, or the relative membrane stiffness. Motivated by the typical parameter values outlined in Table 2.1, and remaining consistent with the theory of linear poroelasticity, we will consider the limit in which ε and γ are small. Further, we consider the most general case (i.e. the distinguished limit) where $\gamma \sim \varepsilon^2 \ll 1$. To do this, we let $\gamma = b\varepsilon^2$ where $b = \gamma/\varepsilon^2 = O(1)$, and investigate $\varepsilon \rightarrow 0$. In doing so we retain the parameter b , though we will later find that our leading-order solution is independent of b given our assumption of infinitesimal strain. Since we consider the problem with small material displacement, the leading-order flow problem decouples from the membrane deformation. Therefore, we solve the flow problem first.

Table 2.1: Typical model parameters.

Parameter	Description	Typical value (Units)
Dimensional parameters		
Bioreactor dimensions		
L^*	Bioreactor length	0.1 (m) [61]
R_{l0}^*	Lumen radius	2×10^{-4} (m) [61]
R_{m0}^*	Outer membrane wall radius	4×10^{-4} (m) [61]
R_{e0}^*	ECS wall radius	1×10^{-3} (m) [61]
Membrane properties		
E^*	Young's modulus	2.64 (MPa) [†]
k^*	Permeability	2.39×10^{-16} (m ²) [93]
Fluid transport		
μ^*	Fluid dynamic viscosity	1×10^{-3} (Pa s) [94]
$Q_{l,in}^*$	Typical lumen inlet flow rate	3.33×10^{-8} (m ³ s ⁻¹) [61]
$Q_{e,in}^*$	Typical ECS inlet flow rate	3.33×10^{-9} (m ³ s ⁻¹) [61]
$P_{l,in}^*$	Typical lumen inlet pressure	108900 (Pa) [61]
$P_{e,in}^*$	Typical ECS inlet pressure	18.6 (Pa) [61]
$P_{l,out}^*$	Typical lumen outlet pressure	105500 (Pa) [61]
$P_{e,out}^*$	Typical ECS outlet pressure	0 (Pa) [61]
Dimensionless parameters		
Bioreactor dimensions		
$\varepsilon = R_{l0}^*/L^*$	Lumen aspect ratio	2×10^{-3}
$R_{m0} = R_{m0}^*/\varepsilon L^*$	Outer membrane wall radius	2
$R_{e0} = R_{e0}^*/\varepsilon L^*$	ECS wall radius	5
Membrane properties		
δ	Compressibility factor	0.5 [†]
ϕ	Porosity	0.77 [95]
$\kappa = k^*/\varepsilon^4 L^{*2}$	Typical permeability	1.5×10^{-3}
$\gamma = \mu^* \bar{W}^* \varepsilon^2 L^* E^*$	Relative membrane stiffness	1.24×10^{-4}
Fluid transport		
$P_{l,in} = \varepsilon^2 P_{l,in}^* L^* / \mu^* \bar{W}^*$	Lumen inlet pressure	331.8
$P_{e,in} = \varepsilon^2 P_{e,in}^* L^* / \mu^* \bar{W}^*$	ECS inlet pressure	0.06
$P_{l,out} = \varepsilon^2 P_{l,out}^* L^* / \mu^* \bar{W}^*$	Lumen outlet pressure	321.4
$P_{e,out} = \varepsilon^2 P_{e,out}^* L^* / \mu^* \bar{W}^*$	ECS outlet pressure	0

[†] Parameters determined from internal unpublished experimental data.

2.6.1 Fluid flow

At leading order, our fluid flow governing equations in the lumen and ECS (2.26) become

$$\frac{1}{r} \frac{\partial}{\partial r}(rU_i) + \frac{\partial W_i}{\partial z} = 0, \quad (2.35a)$$

$$\frac{\partial P_i}{\partial r} = 0, \quad (2.35b)$$

$$\frac{\partial P_i}{\partial z} = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial W_i}{\partial r} \right), \quad (2.35c)$$

and governing equations in the poroelastic membrane (2.27) become

$$\frac{1}{r} \frac{\partial}{\partial r}(rU_m) = 0, \quad (2.36a)$$

$$\phi U_m = -\kappa \frac{\partial P_m}{\partial r}, \quad (2.36b)$$

$$\phi W_m = -\kappa \frac{\partial P_m}{\partial z}. \quad (2.36c)$$

We drop the axial derivative of axial flux at leading order in (2.36a) due to the scaling of the axial membrane flux in (2.24), which is consistent with lubrication flow coupled to porous medium problems in other contexts [96].

To solve the fluid transport problem, we require the leading order conditions of fluid stress, flux and velocity at the fluid-poroelastic interface. At leading order, the normal fluid stress condition (A.14) reduces to continuity of fluid pressure,

$$P_i = P_m \quad \text{at} \quad r = 1, R_{m0}. \quad (2.37)$$

We maintain no slip (A.16) and continuity of flux (A.18),

$$U_i = \phi U_m, \quad W_i = 0 \quad \text{at} \quad r = 1, R_{m0}. \quad (2.38)$$

Equations (2.29) - (2.33) remain unchanged at leading order. For completeness, these are the no-slip condition (2.29)

$$\mathbf{U}_e = \mathbf{0} \quad \text{at} \quad r = R_{e0}, \quad (2.39)$$

the inlet and outlet pressure conditions (2.30)

$$P_i|_{z=0} = P_{i,in}, \quad P_i|_{z=1} = P_{i,out}, \quad (2.40)$$

the membrane no-flux condition (2.32)

$$W_m = 0 \quad \text{at} \quad z = 0, 1, \quad (2.41)$$

and the symmetry condition (2.33)

$$U_l = \frac{\partial W_l}{\partial r} = 0 \quad \text{at} \quad r = 0. \quad (2.42)$$

From (2.35b) we see the leading order fluid pressure in the lumen and ECS is a function of axial position only, consistent with standard lubrication theory. This allows us to make significant analytic progress in solving the system, as we now demonstrate. Starting with fluid transport in the lumen ($i = l$), we integrate (2.35c) with respect to r , subject to (2.38), (2.42) to find

$$W_l = \frac{1}{4} \frac{dP_l}{dz} (r^2 - 1). \quad (2.43)$$

Substituting (2.43) in to the continuity equation in (2.35a), we can rearrange and integrate subject to (2.42) to find

$$U_l = \frac{r}{16} \frac{d^2 P_l}{dz^2} (2 - r^2). \quad (2.44)$$

Then, following a similar process in the ECS, we integrate (2.35c) with $i = e$ subject to (2.38) at $r = R_{m0}$ and (2.39) to find

$$W_e = \frac{1}{4} \frac{dP_e}{dz} \left(r^2 - R_{e0}^2 + \frac{(R_{e0}^2 - R_{m0}^2) \ln(r/R_{e0})}{\ln(R_{m0}/R_{e0})} \right). \quad (2.45)$$

Substituting (2.45) in to (2.35a) and solving subject to (2.39) we find

$$U_e = \frac{1}{16r \ln(R_{m0}/R_{e0})} \frac{d^2 P_e}{dz^2} \left(2r^2 (R_{m0}^2 - R_{e0}^2) \ln(r/R_{e0}) - (r^2 - R_{e0}^2) (R_{m0}^2 - R_{e0}^2 + (r^2 - R_{e0}^2) \ln(R_{m0}/R_{e0})) \right). \quad (2.46)$$

From Equations (2.43)–(2.46), we now have the fluid velocities in the lumen and ECS in terms of the fluid pressures. To solve for the fluid pressures P_l and P_e , we must first solve the fluid transport problem in the membrane. Integrating (2.36a) tells us that rU_m is constant. Using this information to integrate (2.36b) and imposing continuity of pressure conditions (2.37), we deduce that the pore pressure in the membrane is

$$P_m = \frac{(P_e - P_l)}{\ln R_{m0}} \ln r + P_l. \quad (2.47)$$

Then, we use (2.36b)–(2.36c) to determine the components of fluid flux through the membrane in terms of the pressure, as follows

$$\phi U_m = \frac{\kappa(P_l - P_e)}{r \ln R_{m0}}, \quad \phi W_m = \kappa \left(\frac{\ln r}{\ln R_{m0}} \left(\frac{dP_l}{dz} - \frac{dP_e}{dz} \right) - \frac{dP_l}{dz} \right). \quad (2.48)$$

Now with expressions for U_l (2.44), U_m (2.48) and U_e (2.46) in terms of the fluid pressure, we utilise the continuity of flux condition in (2.38) evaluated at the inner and outer interfaces to determine the governing equations for the pressure. This leads to a system of coupled ODEs in terms of P_l and P_e

$$\frac{A}{\kappa} \frac{d^2 P_l}{dz^2} = P_l - P_e, \quad \frac{B}{\kappa} \frac{d^2 P_e}{dz^2} = P_l - P_e, \quad (2.49)$$

where

$$A = \frac{\ln R_{m0}}{16}, \quad (2.50a)$$

$$B = -\frac{\ln R_{m0}}{16 \ln(R_{m0}/R_{e0})} [(R_{e0}^2 - R_{m0}^2)^2 + (R_{e0}^4 - R_{m0}^4) \ln(R_{m0}/R_{e0})]. \quad (2.50b)$$

Given we now have a solution for the flow in terms of the operating parameters of the system, we now explore various aspects of this flow. We first solve the system analytically for a homogeneous permeability. Then, for reasons we discuss below, we investigate how to choose a heterogeneous permeability distribution that delivers a uniform flux to the cells.

2.6.1.1 Case I: Homogeneous permeability

We proceed by first considering the case where κ is constant. Substituting our ODE for P_l into our ODE for P_e in (2.49) we obtain a fourth-order linear ODE in P_l with constant coefficients, the characteristic equation of which is solved by $\lambda_{1,2} = \pm \sqrt{\kappa(B-A)/BA}$, $\lambda_{3,4} = 0$. Given that $\kappa(B-A)/BA > 0$ for all possible values of R_{m0}, R_{e0}, κ as shown in Appendix B, we solve (2.49) subject to (2.40) to find

$$P_l = c_1 z + c_2(1 - z) + B [c_3 \sinh \lambda z + c_4 \sinh \lambda(1 - z)], \quad (2.51a)$$

$$P_e = c_1 z + c_2(1 - z) + A [c_3 \sinh \lambda z + c_4 \sinh \lambda(1 - z)], \quad (2.51b)$$

where

$$\lambda = \sqrt{\frac{\kappa(B-A)}{BA}}, \quad (2.52a)$$

$$c_1 = \frac{AP_{l,out} - BP_{e,out}}{A - B}, \quad c_2 = \frac{AP_{l,in} - BP_{e,in}}{A - B}, \quad (2.52b)$$

$$c_3 = \frac{P_{l,out} - P_{e,out}}{(B - A) \sinh \lambda}, \quad c_4 = \frac{P_{l,in} - P_{e,in}}{(B - A) \sinh \lambda}, \quad (2.52c)$$

yielding a fully analytic solution for P_l and P_e .

2.6.1.2 Case II: Uniform flux

A common objective of bioreactor systems is to deliver nutrients uniformly to cells to ensure uniform growth. For a homogeneous cell population with uniform seeding density at the outer wall of the fibre membrane, this corresponds to an axially uniform nutrient flux across the membrane wall, for nutrient delivered largely via advection. We see from our solution (2.51) that this cannot be achieved with a homogeneous permeability. This is due to axial variations in fluid pressure, leading to axial variations in transmural membrane flux. We now investigate if a heterogeneous permeability can generate a radial membrane flux that is independent of axial position at the outer wall.

From (2.48), we see that the axial dependency in membrane flux comes from the lumen and ECS fluid pressures. Axial pressure gradients drive fluid through our bioreactor system and thus cannot be eliminated. Instead, we note that a uniform flux is possible if we are able to prescribe the membrane permeability such that

$$\kappa(z) = \frac{1}{P_l(z) - P_e(z)}, \quad (2.53)$$

where P_l, P_e are yet to be solved for, as in this scenario, (2.48) becomes

$$\phi U_m = \frac{1}{r \ln R_{m0}}. \quad (2.54)$$

The flux delivered to the outer membrane wall where cells would be seeded can be determined by evaluating (2.54) at $r = R_{m0}$, and we see that this generates a uniform flux.

Using (2.53), Equations (2.49) decouple, simplifying to

$$\frac{d^2 P_l}{dz^2} = \frac{1}{A}, \quad \frac{d^2 P_e}{dz^2} = \frac{1}{B}. \quad (2.55)$$

Solving (2.55) subject to inlet and outlet pressures (2.40), we find

$$P_l = \frac{z(z-1)}{2A} + (P_{l,out} - P_{l,in})z + P_{l,in}, \quad (2.56a)$$

$$P_e = \frac{z(z-1)}{2B} + (P_{e,out} - P_{e,in})z + P_{e,in}. \quad (2.56b)$$

Combining (2.53) and (2.56), we can determine the heterogeneous permeability that generates a uniform flux at the membrane-ECS interface.

We note several important limitations of this calculation. Firstly, from (2.53) it is clear that we encounter a singularity when $P_l = P_e$. This is because pressure differences drive flow, so zero pressure difference cannot drive a (non-zero) uniform flow. Additionally, we cannot have negative permeability, so this analysis only holds for $P_l > P_e$ at each value of z . Therefore, for this to hold, we must also ensure $P_{l,in} > P_{e,in}$ and $P_{l,out} > P_{e,out}$.

We note that since the flow problem decouples from the poroelasticity problem, the leading-order problem we have solved for both Case I & II are equivalent to the problems of fluid flow prescribed through the lumen and ECS for a rigid porous hollow fibre membrane. In the next section, we use our results to understand the membrane deformation under the action of this fluid stress.

2.6.2 Poroelastic deformation

We now investigate the deformation of the poroelastic membrane. Following the analysis of the previous section, we pose an asymptotic expansion in even powers of ε for displacements u and w , i.e.

$$(u, w) = (u_0, w_0) + \varepsilon^2(u_2, w_2) + O(\varepsilon^4) \quad \text{as } \varepsilon \rightarrow 0. \quad (2.57)$$

Collecting terms of $O(1)$, the membrane wall governing equations (2.25) become

$$\frac{1}{\delta(3-\delta)} \left[(1+\delta) \left(\frac{\partial^2 u_0}{\partial r^2} + \frac{1}{r} \frac{\partial u_0}{\partial r} - \frac{u_0}{r^2} \right) + \frac{\partial^2 w_0}{\partial r \partial z} \right] = \frac{\partial P_m}{\partial r}, \quad (2.58a)$$

$$\frac{\partial^2 w_0}{\partial r^2} + \frac{1}{r} \frac{\partial w_0}{\partial r} = 0, \quad (2.58b)$$

which must be solved subject to the leading-order form of boundary conditions from (A.10) and (A.12),

$$\frac{1}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial u_0}{\partial r} + (1-\delta) \left(\frac{u_0}{r} + \frac{\partial w_0}{\partial z} \right) \right] - P_m = -P_i, \quad (2.59a)$$

$$\frac{\partial w_0}{\partial r} = 0, \quad (2.59b)$$

evaluated at $r = 1, R_{m0}$. Given we have continuity of pressure at leading order from (2.37), the boundary condition (2.59a) becomes

$$(1+\delta) \frac{\partial u_0}{\partial r} + (1-\delta) \left(\frac{u_0}{r} + \frac{\partial w_0}{\partial z} \right) = 0. \quad (2.60)$$

Since Equation (2.58b) decouples from (2.58a), and is a linear ODE, its solution can be expressed in the form

$$w_0 = C(z) \log(r) + D(z). \quad (2.61)$$

Then, imposing the boundary condition (2.59b) on (2.61) implies that $C = 0$, and hence we see $w_0 = D(z)$ is solely a function of z that must be determined by imposing a solvability condition at higher orders. Meanwhile, we can solve for u_0 as a function of w_0 in (2.58a) subject to continuity of normal stress in (2.60), which yields

$$u_0 = \frac{(3-\delta)}{2(1+\delta)r} \left[\left(\frac{R_{m0}^2 + \delta r^2}{R_{m0}^2 - 1} \right) \left(2\delta \int_1^{R_{m0}} r P_m dr - (1+\delta)(P_e - P_l) \right) - 2\delta \int_r^{R_{m0}} r P_m dr - (1+\delta)\delta r^2 P_e \right] - \frac{(1-\delta)}{2} \frac{dw_0}{dz} r. \quad (2.62)$$

Equations (2.61) – (2.62) represent the outcomes of our analysis at $O(1)$. To solve for the unknown function $D(z)$ we proceed to $O(\varepsilon^2)$ terms in Equations (2.25) which generates the following axial membrane wall governing equation

$$\frac{1}{\delta(3-\delta)} \left[\delta \left(\frac{\partial^2 w_2}{\partial r^2} + \frac{1}{r} \frac{\partial w_2}{\partial r} \right) + \left((1+\delta) \frac{d^2 w_0}{dz^2} + \frac{\partial^2 u_0}{\partial r \partial z} + \frac{1}{r} \frac{\partial u_0}{\partial z} \right) \right] = \frac{\partial P_m}{\partial z}, \quad (2.63)$$

subject to continuity of tangential stress (A.12)

$$\frac{1}{(3-\delta)} \left(\frac{\partial w_2}{\partial r} + \frac{\partial u_0}{\partial z} \right) = \frac{\partial W_i}{\partial r}, \quad (2.64)$$

evaluated at the inner ($r = 1, i = l$) and outer ($r = R_{m0}, i = e$) membrane wall interfaces. Substituting (2.61) and (2.62) into (2.63) and solving subject to (2.64), we can derive the following solvability condition for w_0

$$\frac{d^2 w_0}{dz^2} = \delta \frac{dP_l}{dz} - \left(\delta + \frac{(R_{e0}^2 - R_{m0}^2) \ln R_{m0}}{(R_{m0}^2 - 1) \ln(R_{m0}/R_{e0})} \right) \frac{dP_e}{dz}. \quad (2.65)$$

To solve (2.65), we require boundary conditions in z . While the boundary conditions (2.34) hold at $z = 0, 1$, the solutions we have derived in this section are outer solutions (in the language of matched asymptotic expansions), and only hold away from the boundaries at $z = 0, 1$. Specifically, away from inner regions of width $O(\varepsilon)$ from each boundary. One way to determine the correct boundary conditions to impose on the outer problem is to solve the relevant inner problem and match to the outer problem using Van Dyke's matching principle [97]. However, we can largely bypass the complexity of deriving full solutions in these inner regions to gain the matching information we require. This is because we are able to gain the leading-order information we require by solely considering the asymptotic scalings that take us into the inner region. That is, near $z = 0$ and $z = 1$, the appropriate inner regions have widths of $O(\varepsilon)$, and within these regions the axial displacement also scales with ε , i.e. $w = O(\varepsilon)$. Given the latter, asymptotic matching yields

$$\lim_{z \rightarrow 0,1} w_0 = 0. \quad (2.66)$$

Hence, the correct effective boundary conditions to impose for w_0 are

$$w_0 = 0 \quad \text{at} \quad z = 0, 1. \quad (2.67)$$

Finally, solving (2.65) subject to (2.67), we can solve for the axial component of membrane displacement in terms of the fluid pressure

$$w_0 = \int_0^z \delta P_l - \left(\delta + \frac{(R_{e0}^2 - R_{m0}^2) \ln R_{m0}}{(R_{m0}^2 - 1) \ln(R_{m0}/R_{e0})} \right) P_e dz - z \int_0^1 \delta P_l - \left(\delta + \frac{(R_{e0}^2 - R_{m0}^2) \ln R_{m0}}{(R_{m0}^2 - 1) \ln(R_{m0}/R_{e0})} \right) P_e dz. \quad (2.68)$$

2.7 Results

2.7.1 Typical operating conditions

We begin by considering steady fluid flow and membrane deformation in our bioreactor model under the typical operating conditions outlined in Table 2.1. Motivated by typical parameter values, our asymptotic analysis places us in a regime of high membrane stiffness. Taking a Taylor expansion of the membrane interfacial conditions

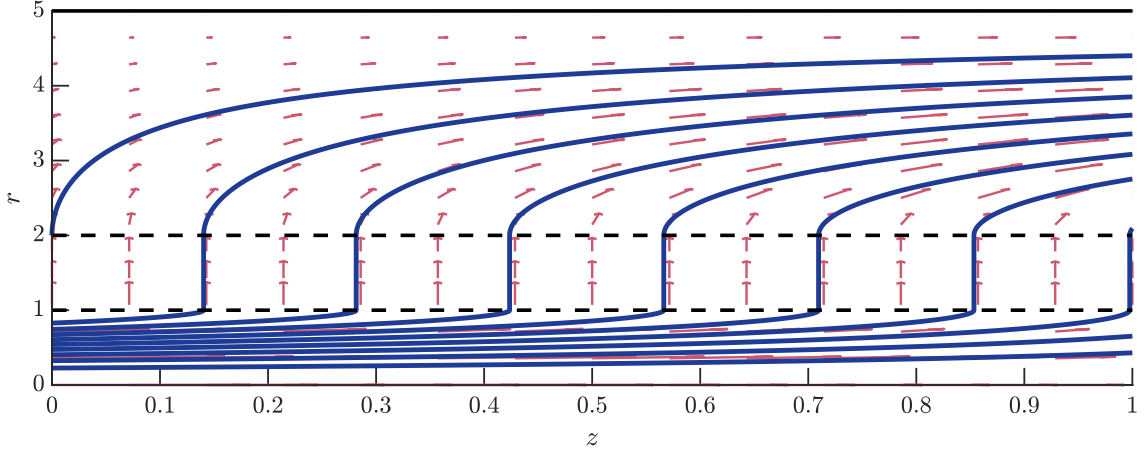


Figure 2.4: Steady fluid flow through the lumen ($r \in (0, 1)$), membrane ($r \in (1, 2)$) and ECS ($r \in (2, 5)$) under typical operating conditions outlined in Table 2.1. Red arrows denote the direction of flow, and blue lines are contours of the streamfunction representing streamlines of the flow.

about the undeformed position in Appendix A, our analysis is reduced to a one-way coupling at leading order in ε whereby fluid flows through an effective rigid bioreactor geometry, and the membrane is deformed under the action of the resulting fluid stress. Unlike non-linear poroelasticity theory, the deformation of the membrane wall is sufficiently small that it does not impact the geometry through which fluid flows through. As such, we first consider fluid flow in a rigid bioreactor geometry, before utilising these results to determine membrane deformation.

In Figure 2.4 we illustrate the path of fluid flow through the lumen, membrane and ECS of our bioreactor setup under typical operating conditions. Fluid entering through the lumen inlet at $z = 0$ can either transport along the lumen and through the outlet at $z = 1$, or across the membrane wall and into the surrounding ECS. An axial pressure drop across the ECS drives flow entering through the ECS inlet or from the membrane-ECS interface out via the ECS outlet. We note that because inlet and outlet boundary conditions (2.40) are set by fluid pressures, it is possible to reverse the direction of flow along the lumen/ECS as well as radially across the membrane wall by prescribing a negative pressure drop. However, because we are interested in the physically-relevant scenario whereby nutrient is introduced via the lumen inlet, we do not consider flow reversal here.

In Figure 2.5, we see cross-sections of components of displacement in the membrane wall. From Equation (2.62), radial membrane displacements are driven by the transmural pressure drop across the membrane wall, and are inversely proportional to the radial membrane position r . Therefore under typical operating conditions given

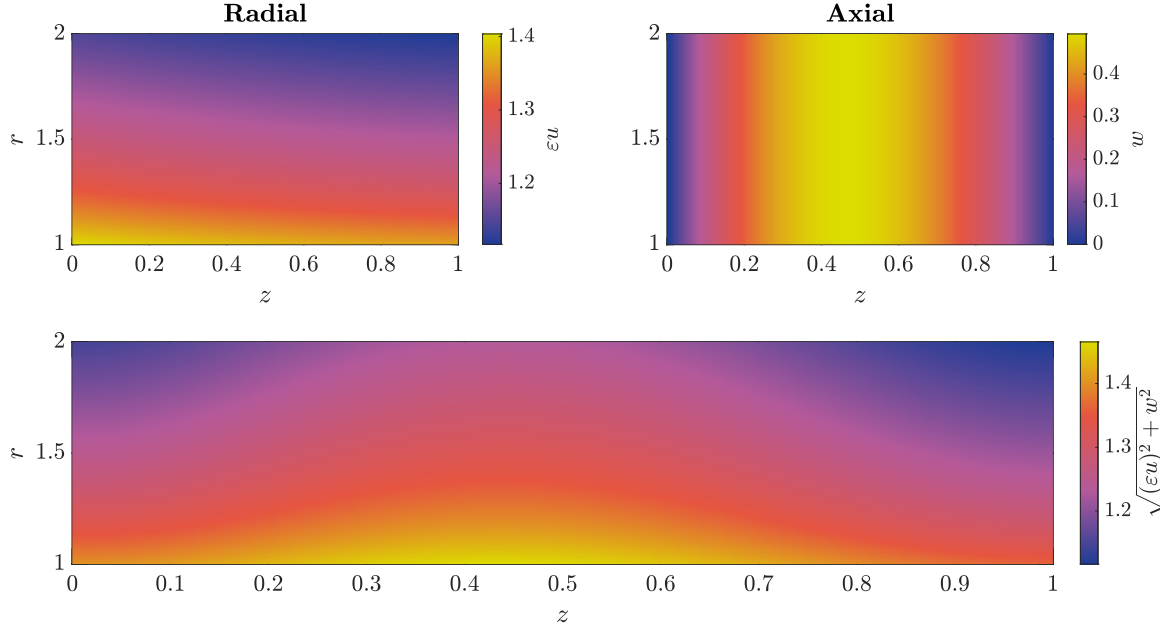


Figure 2.5: Axial cross-section describing radial (top left), axial (top right) and the overall magnitude (bottom) of displacement of the membrane wall under typical operating conditions outlined in Table 2.1. We scale radial displacement u by ϵ to remain comparable with axial displacement w as given by the nondimensionalisation scalings (2.24).

in Table 2.1, near the lumen inlet at $z = 0$ where the lumen and ECS pressures are greatest, we observe the greatest transmural pressure drop and thus the greatest radial displacement. We note that Equation (2.62) is valid in the outer membrane region at distances $> O(\epsilon)$ away from each axial clamped end. To formally prescribe the clamped wall boundary conditions (2.34) for the radial component of displacement, we would need to scale into a boundary layer of $O(\epsilon)$ thickness at each end and match into the outer solution. In these boundary layer regions, radial displacements would sharply decrease to zero near the inlet and outlet. Given that this behaviour occurs over a small axial length-scale, and that the inlet and outlet regions are not of fundamental interest in their own right, understanding the outer problem is sufficient to understand the dominant contributions of stress and strain in this bioreactor setup.

Axial displacements w in (2.68) are proportional to the integral of the transmural pressure drop along the length of the membrane. This dependency comes from prescribing continuity of tangential fluid stress at the lumen-membrane and membrane-ECS interfaces, coming from the derivation of the solvability condition for w_0 in (2.65). Axial displacement is a function of axial position only at leading order, however is constrained by the clamped wall conditions (2.34) at each axial end. As

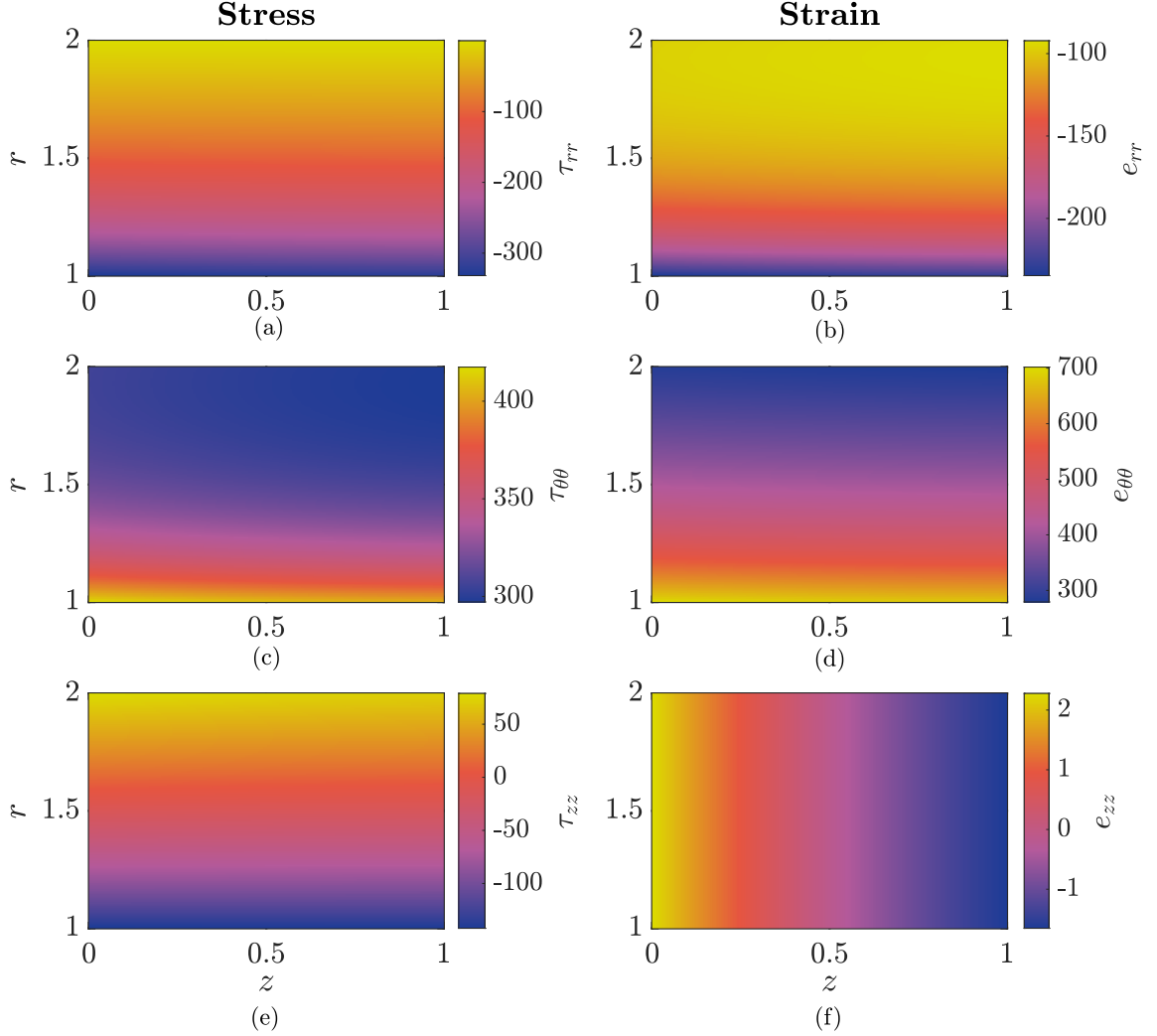


Figure 2.6: Distributions of the leading-order components of stress (a),(c),(e), and strain (b),(d),(f), through a cross-section of the membrane wall.

might be physically expected, the maximum axial displacement occurs near $z = 0.5$, i.e. at the furthest point away from each of the clamped ends where the membrane is free to deform.

To better understand the local mechanical environment that cells may experience in our bioreactor setup, we can visualise distributions of the dominant components of stress and strain through the membrane wall in Figure 2.6. At leading order in ε we identify three dominant components of material stress, namely the radial stress τ_{rr} (Figure 2.6a), hoop stress $\tau_{\theta\theta}$ (Figure 2.6c) and axial stress τ_{zz} (Figure 2.6e). Each component of stress depends on the membrane fluid pore pressure P_m and the material strain as given by Terzaghi's principle (2.1). The transmural pressure across the membrane wall generates significant compressive radial stress as evidenced

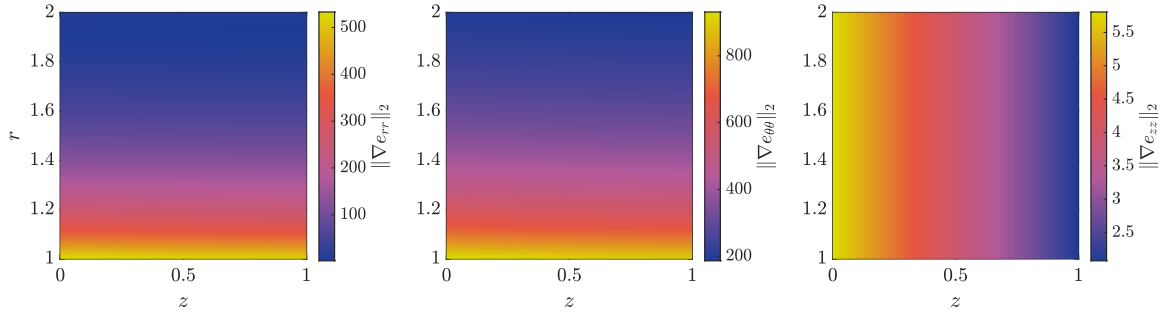


Figure 2.7: Euclidean norm of strain gradients through the membrane wall under typical operating conditions from Table 2.1.

by Figure 2.6a, leading to a corresponding compressive strain in the positive radial direction (Figure 2.6b). Taking a force balance over a finite element of the porous membrane wall (as shown in Appendix C) reveals that radial compression induces a corresponding positive hoop stress. This hoop stress acts to deform the membrane in the azimuthal direction under tension, leading to significant azimuthal hoop strain (Figure 2.6d).

In Figure 2.6e, we see a smaller but significant axial stress that increases in the positive radial direction from compressive axial stress at $r = 1$ to tensile axial stress at $r = R_{m0}$. This is because each component of stress depends on the membrane pore pressure P_m , which decreases in the positive radial direction under the operating conditions prescribed in Table 2.1. Therefore, this radial decrease in the magnitude of stress is observed across each of the three stress components. Given that axial displacements are a function of axial position only at leading order, we observe an axial variation only in the axial component of membrane strain (Figure 2.6f). This is a result of flow above and below the membrane wall effectively pulling the membrane along with it while remaining clamped at each of its axial ends. As a result, we observe notable tensile strain near the bioreactor inlet $z = 0$, which decreases to a negative compressive strain at the bioreactor outlet $z = 1$.

Whereas strain informs us of material displacement relative to its original configuration, strain gradients inform us of material displacement relative to its surroundings. If we think of this in terms of cells seeded to the material's surface, regions of high strain gradient correspond to displacement of cells closer to each other, locally increasing cell density in these regions. Relating this to Figure 2.7, we see that cells seeded on the lumen wall experience 4-5 times the magnitude of radial and hoop strain gradients compared to the ECS wall, resulting in an increased heterogeneous distribution of cells. Conversely, we see a small axial strain gradient that is radially-

uniform throughout the membrane wall, meaning cells will experience the same axial strain gradient irrespective of which wall they are seeded to.

2.7.2 Controlling distributions of stress and strain

A key consideration in tissue engineering bioreactor design is to modulate the local mechanical environment that cells are likely to experience. Cells are typically seeded on the inner or outer membrane wall in a hollow fibre bioreactor setup. Our systematic model reduction reveals insights into the effect of varying structural and operating conditions on distributions of mechanical stress in the fibre membrane, which are indicative of the local mechanical environment we can expect cells to experience.

2.7.2.1 Varying operating conditions

One way in which we can modulate mechanical stress is to change the inlet pressures in the lumen and ECS. In Figure 2.8, we investigate how variations in inlet lumen and ECS pressures impact each component of stress in the membrane, measured at the inner and outer membrane wall. From Figure 2.8, we see that variations in the inlet lumen pressure $P_{l,in}$ increase the flow rate through the lumen, and therefore increase the magnitude of each component of stress measured at the inner wall. In particular in Figures 2.8a and 2.8c, we observe a significant increase in average compressive radial stress τ_{rr} and tensile hoop stress $\tau_{\theta\theta}$, as well as an increase in the range of stress values measured at the inner wall. The relative increase in compressive axial stress τ_{zz} in Figure 2.8e is negligible, suggesting that increasing the lumen flow rate is not an important mechanism for modulating axial stress at the inner wall. At the outer wall, we see an increase in $P_{l,in}$ does not increase τ_{rr} in Figure 2.8b, but does lead to a significant increase in tensile stress for $\tau_{\theta\theta}$ (Figure 2.8d) and τ_{zz} (Figure 2.8f). This suggests that as the pressure inside the lumen increases, stress is preferentially distributed in the radial and azimuthal direction near the lumen-membrane interface, but is distributed in the azimuthal and axial direction near the membrane-ECS interface.

When we increase the ECS inlet pressure $P_{e,in}$ corresponding to an increase in the ECS inlet flow rate, we see a significant increase in components of stress acting to compress the membrane wall. The increase in fluid pressure in the ECS increases the membrane pore pressure at the membrane-ECS interface, thus increasing the compressive contributions of all components of stress at the outer membrane wall. At the inner wall we note similar trends in compressive hoop stress $\tau_{\theta\theta}$ and axial stress

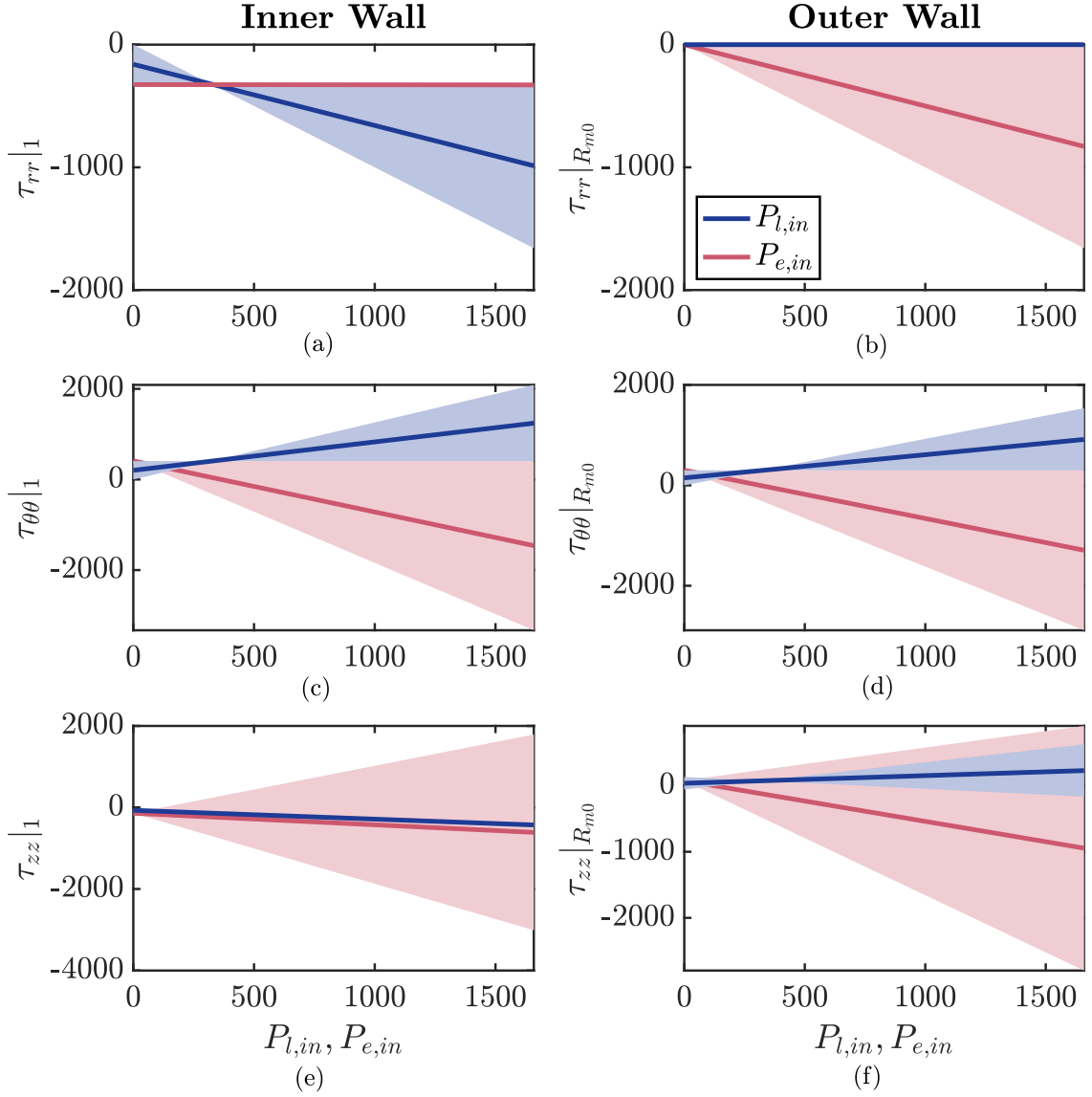


Figure 2.8: A sensitivity analysis to show how variations in the inlet lumen pressure $P_{l,in}$ and ECS pressure $P_{e,in}$ impact the components of radial stress τ_{rr} (a)–(b), hoop stress $\tau_{\theta\theta}$ (c)–(d) and axial stress τ_{zz} (e)–(f) measured at the inner $r = 1$ and outer $r = R_{m0}$ membrane walls. Solid blue and red lines denote the average component of stress at each interface when varying $P_{l,in}$ and $P_{e,in}$ respectively. Shaded regions of the same colour denote the range of corresponding stress values measured at each interface.

τ_{zz} in Figures 2.8c and 2.8e, however we observe a negligible dependency of radial stress τ_{rr} on $P_{e,in}$ in Figure 2.8a. This suggests that further away from the membrane-ECS interface, mechanical stress is favourably distributed in the azimuthal and axial directions only. Across the remaining components of stress, we note that an increase in $P_{e,in}$ significantly increases the range of stress values measured at both the inner and outer membrane wall. This suggests that increasing the flow rate through the ECS has a significant role to play in modulating mechanical stress in the membrane.

2.7.2.2 Varying structural conditions

In addition to selecting bioreactor operating conditions in our model, we have control over the bioreactor geometry and membrane properties. Figure 2.9 describes how variations in the membrane and ECS thickness impact mean components of stress $\bar{\tau}_{ii}$ measured at the inner and outer membrane wall interfaces. Broadly, we see a strong dependency of membrane thickness on each component of stress. As the membrane thickness R_{m0} increases, we note a decrease in all mean components of stress measured at the inner membrane wall. This corresponds to a significant increase in compressive axial stresses (Figure 2.9e) and a decrease in hoop stress tension (Figure 2.9c), and a small but quantifiable increase in compressive radial stress (Figure 2.9a).

At the outer membrane wall, we see how an increase in membrane thickness leads to an increase in components of stress in the radial and axial directions in Figures 2.9b and 2.9f, which is the opposite effect identified at the inner membrane wall. Hoop stress at the outer wall in Figure 2.9d follows a similar trend to hoop stress at the inner wall, leading to a decrease in azimuthal tension. Our analysis suggests that as the membrane wall becomes thicker, the resistance to azimuthal stretching increases, and thus stress is preferentially distributed in the radial and axial directions instead. Towards the inner membrane wall, stress is distributed more favourably in the axial direction, whereas at the outer membrane wall, stress is more favourably distributed in the radial direction. Our analysis also suggests that membrane stress is largely independent of the ECS outer radius R_{e0} . This is because we prescribe the axial fluid pressure drop across the ECS which is independent of the radial ECS width.

In Figure 2.10, we vary the compressibility factor δ and permeability κ to understand their impact on mechanical stress through the membrane wall. From Figures 2.10a and 2.10b, we see how an increase in membrane permeability beyond $\kappa \sim 10^{-3}$ leads to a relatively small increase in the magnitude of the average radial stress $\bar{\tau}_{rr}$ at both the inner and outer membrane interfaces. For $\kappa < 10^{-3}$, we see that changing

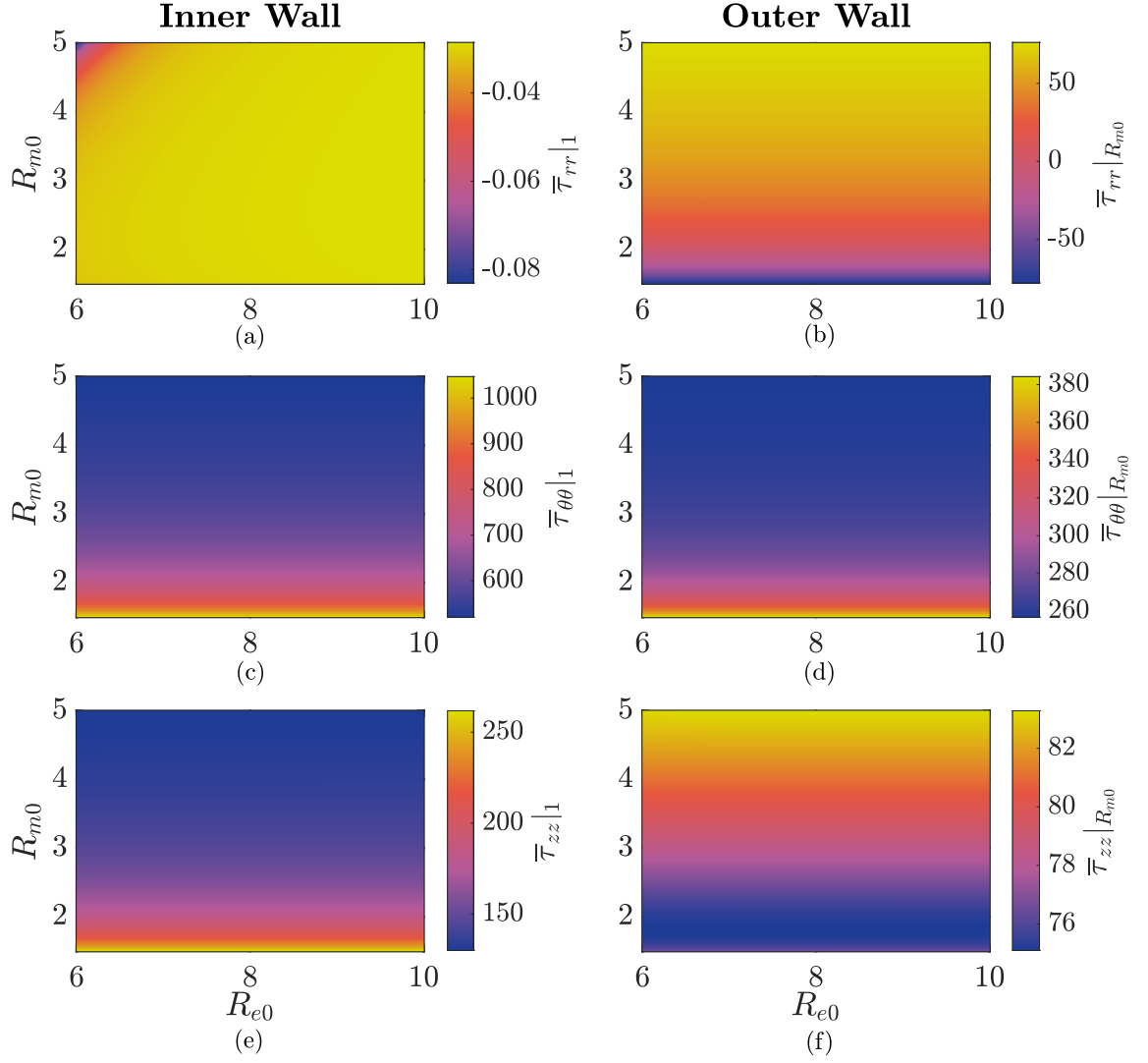


Figure 2.9: Investigating the effect of varying the membrane thickness R_{m0} and ECS thickness R_{e0} on the mean components of stress $\bar{\tau}_{ii}$ in the poroelastic membrane evaluated at the inner (left) and outer (right) membrane walls.

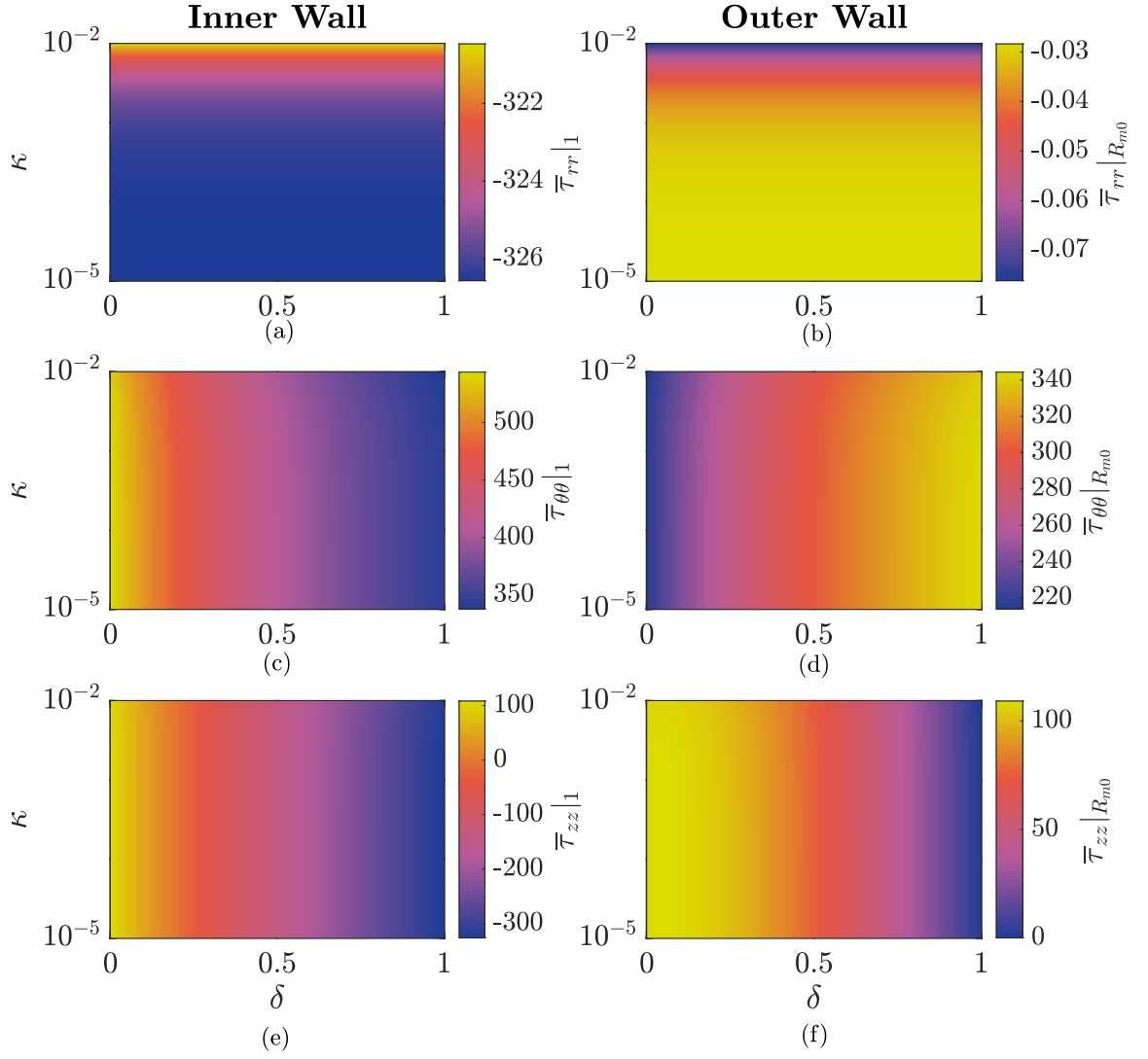


Figure 2.10: Investigating the effect of varying the membrane compressibility factor δ and permeability κ on the mean components of stress $\bar{\tau}_{ii}$ in the poroelastic membrane evaluated at the inner (left) and outer (right) membrane walls.

the permeability has a negligible impact on radial stress. This is likely due to the increase in resistance to fluid flow across the membrane wall as permeability decreases, meaning less fluid is able to cross the wall, thus decreasing contributions of stress in the radial direction. For an isotropic poroelastic membrane, the compressibility factor $\delta \in (0, 1)$. Varying the compressibility factor across this range, we see that there is a negligible change in radial stress.

Conversely, hoop stress $\tau_{\theta\theta}$ and axial stress τ_{zz} both exhibit a strong dependence on δ . As δ increases in Figure 2.10c, the magnitude of the average hoop stress at the inner wall decreases, leading to a reduction in azimuthal tension. Conversely, increasing δ in Figure 2.10d leads to an increase in azimuthal tension at the outer membrane wall. Therefore if the membrane becomes more compressible and compliant, we see a relaxation in hoop stress at the inner wall and an increase in azimuthal stretching at the outer wall. Additionally, we see an increase in δ in Figures 2.10e and 2.10f leads to a decrease in axial stress components τ_{zz} , with significant average axial compression near the inner membrane wall at large δ . We note that $\tau_{\theta\theta}$ and τ_{zz} appear to be independent of variations in κ , suggesting that membrane compressibility is the dominant membrane property in controlling distributions of membrane stress.

Across all parameter values explored in our sensitivity analysis, we find that $\tau_{\theta\theta}$ provides the biggest contribution to mechanical stress. Additionally, it is clear that each component of stress at the outer membrane wall is smaller than the equivalent stress components measured at the inner membrane wall. Therefore in determining which surface to seed cells to in a bioreactor setup, seeding on the outer membrane wall minimises the mechanical stress experienced by cells under a wide range of structural and operating conditions explored in this study.

2.7.3 Homogeneous vs heterogeneous membrane permeability distributions

In Section 2.6.1.2 we derived an expression for a heterogeneous permeability distribution that leads to axially-uniform radial fluid flux across the membrane wall. This is a desirable result for cells seeded to the outer bioreactor wall, as uniform advective mass transport of nutrient across the membrane wall would promote uniform nutrient uptake and therefore uniform tissue growth. In the case of a constant homogeneous membrane permeability, radial flux across the wall can vary as a result of variations in transmural pressure across the length of the bioreactor, therefore cells seeded in regions of low transmural pressure risk receiving insufficient nutrient to grow and proliferate, generating biologically unhelpful necrotic regions.

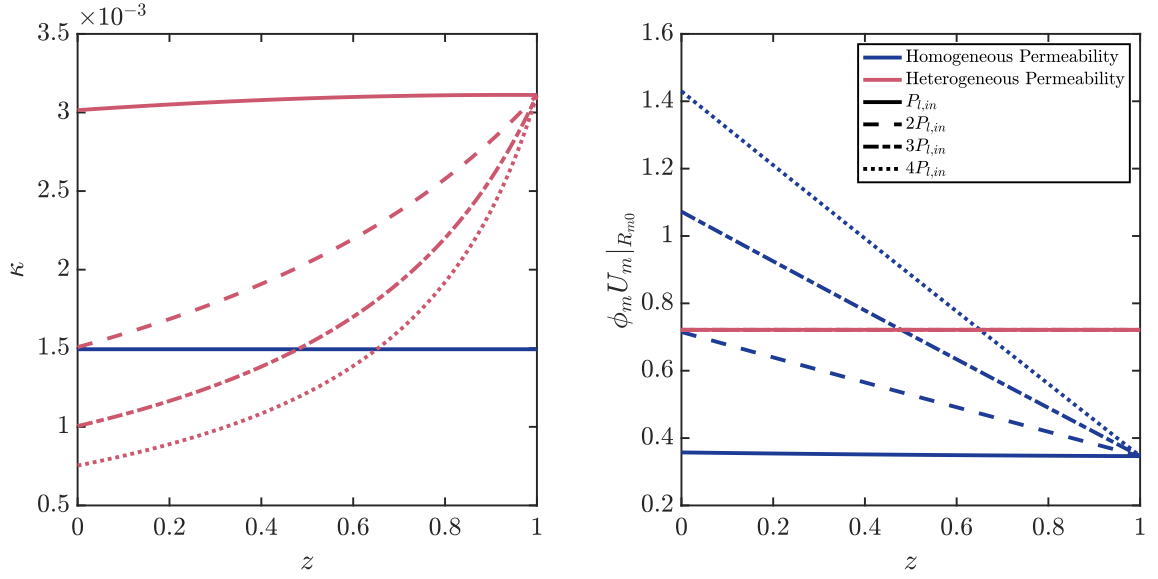


Figure 2.11: Comparing the radial fluid flux at the outer membrane wall using a homogeneous (blue) and heterogeneous (red) membrane distribution. On the left, we plot permeability as a function of axial position under varying inlet lumen pressures $P_{l,in}$. On the right, we plot radial membrane flux as a function of axial position. Note that the homogeneous membrane permeability is independent of $P_{l,in}$, therefore changes in inlet pressure result in changes in the radial flux distribution only. Conversely, the heterogeneous permeability solution is a function of $P_{l,in}$, therefore any changes in the lumen inlet pressure alter the permeability distribution only, but lead to the same uniform constant radial flux at the outer membrane wall.

In Figure 2.11, we investigate the effect of utilising our heterogeneous permeability distribution on the radial fluid flux at the outer membrane wall, compared to a constant homogeneous membrane permeability. Under typical model parameters given in Table 2.1, we see that a homogeneous permeability leads to a relatively constant radial flux at the outer wall. If we increase the inlet lumen pressure, corresponding to an increased inlet flow rate, we see an increase in heterogeneity of flux delivered across the membrane wall. In regions of high transmural pressures, radial flux across the wall increases as given by (2.48). As fluid flows along the lumen and ECS, P_l and P_e decrease, leading to a smaller transmural pressure drop and thus a smaller radial membrane flux further along the bioreactor. This heterogeneity in radial flux means that in a regime of advection-dominated nutrient transport, cells near the bioreactor inlet are relieving significantly more nutrient compared to cells near the bioreactor outlet.

Conversely, we see that our theoretical permeability distribution under typical operating conditions delivers uniform radial flux to the outer membrane wall. The

heterogeneous permeability solution is a function of fluid pressure as given by (2.53), therefore an increase in inlet lumen pressure acts to change the permeability distribution as a function of axial position. As such, radial flux is independent of fluid pressure as given by (2.54). Therefore any change in fluid pressure does not change the radial membrane flux, which remains constant under all inlet pressures explored.

When conducting sensitivity analysis on components of membrane stress in a homogeneous vs heterogeneous permeability distribution, negligible difference was found between stress distributions. As shown in Figure 2.10, distributions of stress through the membrane wall are relatively independent of membrane permeability, therefore this result is consistent with our earlier analysis.

2.8 Discussion

In this Chapter we have developed an axisymmetric, linearly poroelastic model of fluid-structure interaction in and around a thick-walled poroelastic membrane clamped at either end. Exploiting the small aspect ratio of the bioreactor, we use the method of matched asymptotic expansions to derive analytic solutions for steady-state fluid flow and membrane wall displacements. Through the constitutive stress-strain relationship, we have gained a mechanistic understanding of the local mechanical environment we would expect cells to experience once seeded to the membrane's surface, which, when paired to experimentally-derived parameter values, can aid in understanding and predicting mechanotransduction pathways to promote cell amplification and proliferation [17, 98].

Our preliminary sensitivity analysis provides an understanding of how one can optimise mechanical stresses for a cell line of interest. As a result, we can tune the fluid flow, membrane geometry, deformability and permeability relative to the optimal stress requirements of the cell line in each region of the bioreactor. This will be particularly useful in scenarios where cells may be required to be seeded to both the inside and outside of the membrane wall, for example, when growing artificial vasculature featuring a layer of endothelial and smooth muscle cells. However, if the objective is to minimise local mechanical stress on the cellular environment, we show that the outer membrane wall experiences significantly less mechanical stress compared to the inner membrane wall under a typical range of model parameters. Therefore, in this case, the outer membrane wall would be the preferable surface to seed cells to in such a cylindrical geometry. In reality, however, care must be taken

in choosing which surface to seed cells to based on the optimal stress requirement of the cultured cell line.

Under the assumption of small material displacements, we have linearised our continuity of stress boundary condition onto the undeformed membrane wall boundary. This means that the fluid flow problem decouples from the solid mechanics problem at leading order. Enforcing the assumption of small material displacements requires

$$\gamma = \frac{\mu^* \overline{W}^*}{\varepsilon^2 L^* E^*} \sim \varepsilon^2 \ll 1. \quad (2.69)$$

We note that Equation (2.69) holds under typical structural and operating conditions for a HFMB setup, however, care must be taken when using the model presented in this Chapter to ensure the correct parameter regime is observed.

Utilising our understanding of fluid flow across the membrane wall, we also derive a solution for a heterogeneous membrane permeability distribution that exactly cancels out axial variations in radial membrane fluid flux. This is of particular utility for HFMBs operating in a regime of high Péclet number where advective nutrient transport mechanisms dominate, ensuring cells all receive the same amount of nutrient irrespective of where they are seeded on the outer membrane wall. In particular, we use the analysis in this Chapter to consider uniform nutrient delivery to cells in Chapter 4.

Chapter 3

Pulsatile flow in poroelastic scaffolds

3.1 Introduction

We now consider pulsatile flow through our single-fibre bioreactor setup. Pulsatile flow is characteristic of blood flow in larger vessels of the human vasculature, and therefore is often used in haemodynamic modelling to better understand how the local mechanical environment in the circulatory system varies as a function of time and space. Mechanical stress of course plays an important role in mechanotransduction signalling pathways for cell proliferation and differentiation. In particular, modulating the phase shift between stress and strain in pulsatile flows has been shown to help regulate and remodel mammalian vasculature by carefully tuning the physiological mechanisms that are stimulated by stress and strain [67].

Pulsatile flow in a straight rigid tube of circular cross-section with an impermeable wall was first considered by Womersley when modelling blood flow in arteries [62]. Womersley prescribed a pressure drop across the length of the pipe that varied sinusoidally as a function of time. By decomposing the flow into a steady and unsteady component, Womersley was able to solve for each problem separately to determine the overall time-dependent axial velocity. Assuming unidirectional flow and neglecting nonlinear inertial terms in the Navier-Stokes equations, Womersley determined that pulsatile flow is a function of the ratio of the timescale for viscous diffusion of vorticity to the timescale of the flow, which is now commonly known as the Womersley number $\alpha = R_{i0}^* \sqrt{\rho^* \omega^* / \mu^*}$. Therefore for $\alpha \ll 1$, viscous effects would be observed throughout the cross-section of the flow, whereas $\alpha \gg 1$ reduces viscous effects to a boundary layer near the channel wall. Extensions of the Womersley solution have been considered for a sinusoidal inlet flow through a straight rigid pipe lined with

a porous annulus [99]. However, the absence of a radial pressure drop provides no driving force for radial flow into the porous region, thus simplifying consideration to axial flow components only.

Mathematical modelling of pulsatile flow through a straight rigid tube with porous walls has been modelled by Chang et al. by enforcing a presupposed seepage velocity at the fluid-porous wall interface that varies as a linear function of distance along the length of the pipe [100]. This relationship implies a constant pressure drop along the lumen of the membrane, which is not strictly true for flow through permeable pipes, or in the case of coupled flow regions mediated by a porous wall. Models by Chang et al. have later been extended by Misra and Ghosh for pulsatile flow driven by the prescribed deformation of a poroelastic tube wall with a prescribed wall seepage velocity [101]. The pre-determined wall oscillations are solved by Kaimal for pulsatile flow in a distensible impermeable tube, neglecting longitudinal displacements [102]. As such, the two-way coupled fluid-structure interaction problem considered by Misra and Ghosh reduces to pulsatile flow induced by a moving wall. In each problem, consideration is relegated to $O(1)$ Womersley numbers only, and thus information is lost as to the asymptotic pressure-flux phase lag and oscillation amplitude behaviour at small and large Womersley numbers.

In this Chapter, inspired by existing models of pulsatile flow in large-diameter vasculature, we will consider pulsatile flow through the lumen of a poroelastic fibre membrane modelled using Darcy's law. As we have done previously in Chapter 2, we consider the regime where nonlinear inertia is negligible. However similarly to Womersley [62], we retain linear time-dependent inertia and consider the unsteady Stokes equations, assuming that the ratio of transient inertial forces to viscous forces (i.e. the Womersley number, α) is an $O(1)$ quantity. In doing so, we utilise our asymptotic model reduction to compare steady and pulsatile flow profiles, membrane deformation, and distributions of stress and strain at all values of α . We note that in contrast to existing literature, our model is systematically derived from constitutive laws governing fluid flow and poroelastic deformation, and is valid for an arbitrary number of modes of oscillation.

3.2 Model setup

We model the HFMB as a long, thin poroelastic membrane as shown in Figure 2.2. In cylindrical coordinates (r^*, θ^*, z^*) , with the longitudinal axis coinciding with the cylinder axis, we define $\hat{\mathbf{e}}_r, \hat{\mathbf{e}}_\theta, \hat{\mathbf{e}}_z$ as unit vectors in the radial, azimuthal and axial

directions respectively. We assume the system is axisymmetric along the cylinder axis, neglecting azimuthal components and derivatives henceforth. The membrane consists of a poroelastic annulus of circular cross-section with length L^* , and undeformed internal and external radii of $r^* = R_{l0}^*$ and $r^* = R_{m0}^*$ respectively (with $R_{m0}^* > R_{l0}^*$) at ambient pressure. The membrane is clamped at the fluid inlet ($z^* = 0$) and outlet ($z^* = L^*$) to keep the membrane in place and to set the axial gradient of out-of-plane displacements to zero. Additionally, a rigid wall surrounds the membrane at $r^* = R_{e0}^*$ (where $R_{e0}^* > R_{m0}^*$).

We prescribe fluid flow through the lumen via a periodic pulsatile pressure. This is achieved by prescribing an inlet lumen pressure $P_{l,in}^*$ and outlet lumen pressure $P_{l,out}^*$ that varies as a function of time t^* between zero and a maximum amplitude of oscillation, characterised by a prescribed angular frequency ω^* . The inlet/outlet ECS pressures $P_{e,in}^*, P_{e,out}^*$ are held constant. The membrane deforms under the action of pulsatile hydrodynamic stress, but is constrained by the clamped ends and the surrounding rigid wall. Neglecting initial transient effects at short timescales, we will solve for the long-timescale periodic solution for fluid flow through the lumen, membrane and ECS of our setup, in addition to the radial and axial membrane wall deformation.

3.2.1 Fluid flow

We model transport through the lumen and ECS by the unsteady Stokes equations for an incompressible Newtonian viscous fluid of constant density, ρ^* , and dynamic viscosity, μ^* ,

$$\nabla^* \cdot \mathbf{U}_i^* = 0, \quad (3.1a)$$

$$\rho^* \frac{\partial \mathbf{U}_i^*}{\partial t^*} + \nabla^* P_i^* = \mu^* \nabla^{*2} \mathbf{U}_i^*, \quad (3.1b)$$

for $i = l, e$. Motivated by the axisymmetric geometry, we take the fluid flow to be axisymmetric. In the membrane, we model fluid flow using the unsteady version of Darcy's law given by

$$\nabla^* \cdot \mathbf{U}_m^* = 0, \quad (3.2a)$$

$$\rho^* \phi \frac{\partial \mathbf{U}_m^*}{\partial t^*} + \frac{\mu^* \phi}{k^*} \mathbf{U}_m^* = -\nabla^* P_m^*, \quad (3.2b)$$

where ϕ, k^* are the membrane porosity and permeability respectively, which we assume to be constant and isotropic. The unsteady version of Darcy's law is a common

approximation in engineering literature for unsteady porous flow. However, we note that (3.2) can be formally derived from volume-averaging or mixture theory [103, 104].

3.2.2 Poroelastic deformation

We model deformation of the membrane wall using the same constitutive relations outlined in Chapter 2 from Equations (2.1) – (2.4), and thus our assumptions of axisymmetry, isotropy and infinitesimal strain remain the same. However to incorporate the effect of linear inertia due to pulsatile flow, our momentum balance (2.5) becomes

$$\rho_{\text{eff}}^* \frac{\partial^2 \mathbf{u}^*}{\partial t^{*2}} + \nabla^* \cdot \boldsymbol{\tau}^* = \mathbf{0}, \quad (3.3)$$

where ρ_{eff}^* is the constant effective density of the poroelastic domain comprising a solid scaffold and saturated fluid pores. Substituting our axisymmetric components of wall stress (2.7) into (3.3), our governing equations become

$$\rho_{\text{eff}}^* \frac{\partial^2 u^*}{\partial t^{*2}} + \frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \left(\frac{\partial^2 u^*}{\partial r^{*2}} + \frac{1}{r^*} \frac{\partial u^*}{\partial r^*} - \frac{u^*}{r^{*2}} \right) + \frac{\partial^2 w^*}{\partial r^* \partial z^*} + \delta \frac{\partial^2 u^*}{\partial z^{*2}} \right] = \frac{\partial P_m^*}{\partial r^*}, \quad (3.4a)$$

$$\rho_{\text{eff}}^* \frac{\partial^2 w^*}{\partial t^{*2}} + \frac{E^*}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial^2 w^*}{\partial z^{*2}} + \frac{\partial^2 u^*}{\partial r^* \partial z^*} + \frac{1}{r^*} \frac{\partial u^*}{\partial z^*} + \delta \left(\frac{\partial^2 w^*}{\partial r^{*2}} + \frac{1}{r^*} \frac{\partial w^*}{\partial r^*} \right) \right] = \frac{\partial P_m^*}{\partial z^*}. \quad (3.4b)$$

3.2.3 Boundary conditions

Equations governing fluid flow (3.1) – (3.2) are solved subject to the same boundary conditions as the steady state boundary conditions (2.11) – (2.22) in Chapter 2. Additionally, Equations governing membrane deformation (3.4) are solved subject to boundary conditions (2.11), (2.23). However, we present them here for completeness.

We first prescribe continuity of stress at the deformed lumen-membrane and membrane-ECS interfaces

$$\boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j = \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j, \quad (3.5)$$

where $j = l, m$ denotes the inner and outer interfaces respectively, and $\hat{\mathbf{n}}_j$ denotes the outward-facing unit normal vector to the surface of the membrane (2.13). The viscous fluid stress tensor, $\boldsymbol{\sigma}_i^*$ is given by (2.12). Additionally at each interface, we prescribe continuity of normal fluid stress

$$\hat{\mathbf{n}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j = -P_m^*, \quad (3.6)$$

continuity of normal flux

$$\mathbf{U}_i^* \cdot \hat{\mathbf{n}}_j = \phi \mathbf{U}_m^* \cdot \hat{\mathbf{n}}_j, \quad (3.7)$$

and no tangential slip

$$\mathbf{U}_i^* \cdot \hat{\mathbf{t}}_j = 0, \quad (3.8)$$

where $\hat{\mathbf{t}}_j$ denotes the unit tangent vector to the surface of the membrane (2.14). The above set of interfacial boundary conditions are evaluated at the deformed inner and outer membrane interfaces, the details of which are presented in Appendix A.

In the fluid flow problem, we prescribe a fluid stress at the inlet and outlet of both the lumen and ECS,

$$\boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{e}}_z = P_{i,in}^* \quad \text{at} \quad z^* = 0, \quad (3.9a)$$

$$\boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{e}}_z = P_{i,out}^* \quad \text{at} \quad z^* = L^*. \quad (3.9b)$$

Instead of a constant inlet/outlet lumen pressure (2.18), we assume that the inlet and outlet pressure can vary as a periodic function of time. As such, $P_{l,in}^*, P_{l,out}^*$ are given by

$$P_{l,in}^* = \Re \left(\sum_{n=0}^N P_{l,in(n)}^* e^{i n \omega^* t^*} \right) \quad \text{at} \quad z^* = 0, \quad (3.10a)$$

$$P_{l,out}^* = \Re \left(\sum_{n=0}^N P_{l,out(n)}^* e^{i n \omega^* t^*} \right) \quad \text{at} \quad z^* = L^*, \quad (3.10b)$$

where $\mathbf{i}$ is the imaginary unit, ω^* is the angular frequency of the first harmonic (i.e. $n = 1$), $\Re(\zeta)$ is the real component of complex number ζ , and $P_{l,in(n)}^*, P_{l,out(n)}^*$ are the amplitudes of each harmonic, n . By taking a Fourier series decomposition of our

inlet/outlet lumen pressures, we can generalise our analysis to prescribe an arbitrary number of independent oscillatory modes. We note that we can also determine the inlet flow rate in the lumen and ECS by

$$Q_{i,in}^* = 2\pi \int_{R_1^*}^{R_2^*} r^* W_i^* dr^* \quad \text{at} \quad z^* = 0, \quad (3.11)$$

for $i = l, e$, where R_1^*, R_2^* define the inner and outer radial boundaries of the respective region. To bound the fluid transport problem, we prescribe no flux at each end of the membrane

$$\mathbf{U}_m^* \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at} \quad z^* = 0, L^*. \quad (3.12)$$

Additionally, we prescribe a symmetry condition at the lumen centreline

$$\mathbf{U}_l^* \cdot \hat{\mathbf{e}}_r = \nabla^* (\mathbf{U}_l^* \cdot \hat{\mathbf{e}}_z) \cdot \hat{\mathbf{e}}_r = 0 \quad \text{at} \quad r^* = 0, \quad (3.13)$$

as well as no slip and no flux at the rigid outer wall of the ECS

$$\mathbf{U}_e^* = \mathbf{0} \quad \text{at} \quad r^* = R_{e0}^*. \quad (3.14)$$

The clamped wall boundary conditions are given by

$$\mathbf{u}^* \cdot \hat{\mathbf{e}}_r = \nabla^* (\mathbf{u}^* \cdot \hat{\mathbf{e}}_r) \cdot \hat{\mathbf{e}}_z = \mathbf{u}^* \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at} \quad z^* = 0, L^*. \quad (3.15)$$

Typical model parameter values are discussed in Section 2.4 and provided in Table 3.1.

3.3 Nondimensionalisation

We nondimensionalise Equations (3.1) – (3.15) using the scalings from (2.24) with parameter values given in Table 3.1. Additionally, we nondimensionalise t^* relative to the inverse of the angular frequency ω^* , such that

$$t^* = \frac{1}{\omega^*} t. \quad (3.16)$$

The nondimensional governing equations for fluid flow in the lumen and ECS (3.1) become

$$\frac{1}{r} \frac{\partial}{\partial r} (r U_i) + \frac{\partial W_i}{\partial z} = 0, \quad (3.17a)$$

$$\varepsilon^2 \alpha^2 \frac{\partial U_i}{\partial t} = -\frac{\partial P_i}{\partial r} + \varepsilon^2 \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial U_i}{\partial r} \right) - \frac{U_i}{r^2} \right) + \varepsilon^4 \frac{\partial^2 U_i}{\partial z^2}, \quad (3.17b)$$

$$\alpha^2 \frac{\partial W_i}{\partial t} = -\frac{\partial P_i}{\partial z} + \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial W_i}{\partial r} \right) + \varepsilon^2 \frac{\partial^2 W_i}{\partial z^2}, \quad (3.17c)$$

for $i = l, e$, where the Womersley number $\alpha = \varepsilon L^* \sqrt{\rho^* \omega^* / \mu^*}$ denotes the ratio of transient inertial forces to viscous forces in the fluid. We retain α in our model as an $O(1)$ quantity in this distinguished limit to capture the most general physical scenario, where we later explore the model behaviour in the limit $\alpha \ll 1$ and $\alpha \gg 1$.

In the membrane, the nondimensional fluid flow governing equations (3.2) become

$$\frac{1}{r} \frac{\partial}{\partial r} (r U_m) + \varepsilon^2 \frac{\partial W_m}{\partial z} = 0, \quad (3.18a)$$

$$\varepsilon^2 \alpha^2 \kappa \phi \frac{\partial U_m}{\partial t} + \phi U_m = -\kappa \frac{\partial P_m}{\partial r}, \quad (3.18b)$$

$$\varepsilon^2 \alpha^2 \kappa \phi \frac{\partial W_m}{\partial t} + \phi W_m = -\kappa \frac{\partial P_m}{\partial z}. \quad (3.18c)$$

The governing equations for membrane deformation (3.4) under these scalings become

$$\alpha_m^2 v \frac{\partial^2 u}{\partial t^2} + \frac{1}{\delta(3-\delta)} \left[(1+\delta) \left(\frac{\partial^2 u}{\partial r^2} + \frac{1}{r} \frac{\partial u}{\partial r} - \frac{u}{r^2} \right) + \frac{\partial^2 w}{\partial r \partial z} + \varepsilon^2 \delta \frac{\partial^2 u}{\partial z^2} \right] = \frac{\partial P_m}{\partial r}, \quad (3.19a)$$

$$\alpha_m^2 v \frac{\partial^2 w}{\partial t^2} + \frac{1}{\delta(3-\delta)} \left[\delta \left(\frac{\partial^2 w}{\partial r^2} + \frac{1}{r} \frac{\partial w}{\partial r} \right) + \varepsilon^2 \left((1+\delta) \frac{\partial^2 w}{\partial z^2} + \frac{\partial^2 u}{\partial r \partial z} + \frac{1}{r} \frac{\partial u}{\partial z} \right) \right] = \varepsilon^2 \frac{\partial P_m}{\partial z}, \quad (3.19b)$$

where $\alpha_m = \varepsilon L^* \sqrt{\rho_{\text{eff}}^* \omega^* / \mu^*}$ denotes the Womersley number in the membrane utilising the effective membrane density ρ_{eff}^* , and $v = \mu^* \omega^* / E^*$ denotes the ratio of viscous forces to the effective membrane stiffness.

At the inlet and outlet of the lumen and ECS our continuity of fluid stress (3.9) reduces to an inlet and outlet pressure

$$P_i|_{z=0} = P_{i,in}, \quad P_i|_{z=1} = P_{i,out}, \quad (3.20)$$

where the nondimensional pulsatile inlet/outlet lumen pressures (3.10) are given by

$$P_{l,in} = \Re \left(\sum_{n=0}^N P_{l,in(n)} e^{int} \right) \quad \text{at} \quad z = 0. \quad (3.21a)$$

$$P_{l,out} = \Re \left(\sum_{n=0}^N P_{l,out(n)} e^{int} \right) \quad \text{at} \quad z = 1. \quad (3.21b)$$

The inlet flow rate (3.11) becomes

$$Q_{i,in} = \int_{R_1}^{R_2} W_i r \, dr \quad \text{at} \quad z = 0, \quad (3.22)$$

where $Q_{i,in} = Q_{i,in}^* / 2\pi\varepsilon^2 L^{*2} \bar{W}^*$ is determined from Table 3.1. The no-flux membrane condition (3.12) becomes

$$W_m = 0 \quad \text{at} \quad z = 0, 1, \quad (3.23)$$

and the symmetry condition (3.13) becomes

$$U_l = \frac{\partial W_l}{\partial r} = 0 \quad \text{at} \quad r = 0. \quad (3.24)$$

At the rigid outer wall we maintain no-slip and no-flux boundary conditions (3.14),

$$\mathbf{U}_e = \mathbf{0} \quad \text{at} \quad r = R_{e0}, \quad (3.25)$$

Lastly, the clamped wall boundary conditions (3.15) become

$$u = \frac{\partial u}{\partial z} = w = 0 \quad \text{at} \quad z = 0, 1. \quad (3.26)$$

Nondimensionalisation of the fluid-poroelastic interfacial conditions (3.5) – (3.8) is considered in Appendix A.

The system of equations governing fluid flow (3.17) – (3.18) are solved subject to the boundary conditions (3.20) – (3.25), (A.14) – (A.19). Additionally, Equations (3.19) describing membrane deformation are solved subject to boundary conditions (3.26), (A.10) – (A.13).

3.4 Model solution

To solve for the pulsatile pressure profile through our system, we take a Fourier series decomposition similarly to (3.21) such that

$$P_i = \Re \left(\sum_{n=0}^N P_{i(n)} e^{int} \right). \quad (3.27)$$

Given that our problem is linear, we assume that the fluid velocity and membrane deformation have the same angular frequency of oscillation as P_i . As such, we take a Fourier series decomposition of dependent variables in our model such that

$$U_i = \Re \left(\sum_{n=0}^N U_{i(n)} e^{int} \right), \quad W_i = \Re \left(\sum_{n=0}^N W_{i(n)} e^{int} \right), \quad (3.28a)$$

$$u = \Re \left(\sum_{n=0}^N u_{(n)} e^{int} \right), \quad w = \Re \left(\sum_{n=0}^N w_{(n)} e^{int} \right). \quad (3.28b)$$

Substituting (3.27) – (3.28) into (3.17) – (3.26), (A.10) – (A.19), we decompose our system into N linearly independent problems evaluated for each mode of oscillation given by the pulsatile inlet/outlet lumen pressure condition (3.21). Solving for an arbitrary mode n , we can fully solve for all N oscillatory modes. We note however that for $n = 0$, the solution reduces to the steady flow problem described in Chapter 2.

The introduction of linear inertia and pulsatile flow into our model results in three small parameters upon nondimensionalising. We retain the square of the lumen aspect ratio ε^2 and the relative membrane stiffness γ as described in Section 2.6. We also identify $v = \mu^* \omega^* / E^*$ as the ratio of viscous forces to membrane stiffness, which is also small from experimental parameter values. From Tables 2.1 and 3.1 we see that $v \ll \varepsilon^2, \gamma \ll 1$. Formally, the small nature of v suggests an early-time transient (boundary layer) solution. We are more interested in the general system behaviour after this early-time transience has abated, so we proceed by simply neglecting v in our subsequent asymptotic analysis.

Then, we proceed by investigating the limit in which $\varepsilon, \gamma \rightarrow 0$. Since the system is linear, each harmonic is independent. We therefore solve the fluid flow and membrane displacement problem subject to boundary conditions (3.26), (3.31) – (3.36), (3.51), (3.54) applied to each harmonic n . The leading-order fluid transport problem does not rely on information from the deformation of the membrane wall, and thus we proceed by first solving for fluid flow independent of membrane displacement.

Table 3.1: Typical model parameters.

Parameter	Description	Typical value (Units)
Dimensional parameters		
Bioreactor dimensions		
L^*	Bioreactor length	0.1 (m) [61]
R_{l0}^*	Lumen radius	2×10^{-4} (m) [61]
R_{m0}^*	Outer membrane wall radius	4×10^{-4} (m) [61]
R_{e0}^*	ECS wall radius	1×10^{-3} (m) [61]
Membrane properties		
E^*	Young's modulus	2.64 (MPa) [†]
k^*	Permeability	2.39×10^{-16} (m ²) [93]
ρ_s^*	Density of membrane solid	1145 (kg m ⁻³) [105]
$\rho_{\text{eff}}^* = \phi \rho^* + (1 - \phi) \rho_s^*$	Effective membrane density	1033 (kg m ⁻³)
Fluid transport		
μ^*	Fluid dynamic viscosity	1×10^{-3} (Pa s) [94]
ρ^*	Fluid density	1000 (kg m ⁻³) [94]
ω^*	Typical angular frequency	1.17 (Hz) [94]
$P_{l,in}^*$	Typical lumen inlet pressure	108900 (Pa) [61]
$P_{e,in}^*$	Typical ECS inlet pressure	18.6 (Pa) [61]
$P_{l,out}^*$	Typical lumen outlet pressure	105500 (Pa) [61]
$P_{e,out}^*$	Typical ECS outlet pressure	0 (Pa) [61]
Dimensionless parameters		
Bioreactor dimensions		
$\varepsilon = R_{l0}^*/L^*$	Lumen aspect ratio	2×10^{-3}
$R_{m0} = R_{m0}^*/\varepsilon L^*$	Outer membrane wall radius	2
$R_{e0} = R_{e0}^*/\varepsilon L^*$	ECS wall radius	5
Membrane properties		
δ	Compressibility factor	0.5 [†]
ϕ	Porosity	0.77 [95]
$\kappa = k^*/\varepsilon^4 L^{*2}$	Typical permeability	1.5×10^{-3}
$\gamma = \mu^* \overline{W}^* \varepsilon^2 L^* E^*$	Relative membrane stiffness	1.24×10^{-4}
$v = \mu^* \omega^*/E^*$	Ratio of viscous forces to Young's modulus	4.43×10^{-10}
$\alpha_m = \varepsilon L^* \sqrt{\rho_{\text{eff}}^* \omega^*/\mu^*}$	Membrane Womersley number	0.22
Fluid transport		
$\alpha = \varepsilon L^* \sqrt{\rho^* \omega^*/\mu^*}$	Womersley number	0.22
$P_{l,in(0)} = P_{l,in(1)} = \varepsilon^2 P_{l,in}^* L^*/\mu^* \overline{W}^*$	0 th & 1 st harmonic lumen inlet pressure	331.8
$P_{l,out(0)} = P_{l,out(1)} = \varepsilon^2 P_{l,out}^* L^*/\mu^* \overline{W}^*$	0 th & 1 st harmonic lumen outlet pressure	321.4
$P_{e,in(0)} = \varepsilon^2 P_{e,in}^* L^*/\mu^* \overline{W}^*$	0 th harmonic ECS inlet pressure	0.06
$P_{e,out(0)} = \varepsilon^2 P_{e,out}^* L^*/\mu^* \overline{W}^*$	0 th harmonic ECS outlet pressure	0
$P_{e,in(1)}$	1 st harmonic ECS inlet pressure	0
$P_{e,out(1)}$	1 st harmonic ECS outlet pressure	0

[†] Parameters determined from internal unpublished experimental data.

3.4.1 Fluid flow

Substituting the Fourier series decomposition (3.27) – (3.28) into governing equations (3.17) – (3.18), we derive a system of equations for which we can solve for the amplitudes of each harmonic. At leading order in ε , (3.17) becomes

$$\frac{1}{r} \frac{\partial}{\partial r} (r U_{i(n)}) + \frac{\partial W_{i(n)}}{\partial z} = 0, \quad (3.29a)$$

$$\frac{\partial P_{i(n)}}{\partial r} = 0, \quad (3.29b)$$

$$\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial W_{i(n)}}{\partial r} \right) - \alpha^2 W_{i(n)} = \frac{\partial P_{i(n)}}{\partial z}, \quad (3.29c)$$

for $i = l, e$, and in the membrane (3.18) becomes

$$\frac{\partial}{\partial r} (r U_{m(n)}) = 0, \quad (3.30a)$$

$$\phi U_{m(n)} = -\kappa \frac{\partial P_{m(n)}}{\partial r}, \quad (3.30b)$$

$$\phi W_{m(n)} = -\kappa \frac{\partial P_{m(n)}}{\partial z}. \quad (3.30c)$$

To solve the fluid transport problem, we require our leading order conditions on fluid stress, flux and velocity at the fluid-poroelastic interface for each harmonic n . At leading order, our normal fluid stress condition (A.14) reduces to continuity of fluid pressure,

$$P_{i(n)} = P_{m(n)} \quad \text{at} \quad r = 1, R_{m0}. \quad (3.31)$$

We maintain no slip (A.16) and continuity of flux (A.18),

$$U_{i(n)} = \phi U_{m(n)}, \quad W_{i(n)} = 0 \quad \text{at} \quad r = 1, R_{m0}. \quad (3.32)$$

Equations (3.20) – (3.25) remain unchanged at leading order. For completeness, these are the no-slip condition (3.25)

$$\mathbf{U}_{e(n)} = \mathbf{0} \quad \text{at} \quad r = R_{e0}, \quad (3.33)$$

the inlet and outlet pressure conditions (3.20)

$$P_{i(n)}|_{z=0} = P_{i,in(n)}, \quad P_{i(n)}|_{z=1} = P_{i,out(n)}, \quad (3.34)$$

the membrane no-flux condition (3.23)

$$W_{m(n)} = 0 \quad \text{at} \quad z = 0, 1, \quad (3.35)$$

and the symmetry condition (3.24)

$$U_{l(n)} = \frac{\partial W_{l(n)}}{\partial r} = 0 \quad \text{at} \quad r = 0. \quad (3.36)$$

From (3.29b) we see that the lumen and ECS pressure $P_{i(n)} = P_{i(n)}(z)$. We solve (3.29c) subject to (3.32), (3.36) to find

$$W_{l(n)} = \frac{\mathbf{i}}{\alpha^2 n} \frac{dP_{l(n)}}{dz} \left(1 - \frac{J_0(\Lambda_{(n)} r)}{J_0(\Lambda_{(n)})} \right), \quad (3.37)$$

where $\Lambda_{(n)} = \mathbf{i}^{\frac{3}{2}} n^{\frac{1}{2}} \alpha$, and J_0 is the 0th order Bessel functions of the first kind as detailed in Appendix D. We take the square root branch cut in the complex plane to be along the negative real axis. Substituting (3.37) into (3.29a) and solving subject to (3.36) we find

$$U_{l(n)} = -\frac{\mathbf{i}r}{2\alpha^2 n} \frac{d^2 P_{l(n)}}{dz^2} \left(1 - \frac{2J_1(\Lambda_{(n)} r)}{\Lambda_{(n)} r J_0(\Lambda_{(n)})} \right), \quad (3.38)$$

where J_1 is the 1st order Bessel function of the first kind (summarised in Appendix D). Similarly for flow in the ECS, we solve (3.29c) subject to (3.32), (3.33) to find

$$W_{e(n)} = \frac{\mathbf{i}}{\alpha^2 n} \frac{dP_{e(n)}}{dz} \left(1 - \frac{\mathcal{A}_{(n)}(r)}{\mathcal{B}_{(n)}} \right), \quad (3.39)$$

where

$$\begin{aligned} \mathcal{A}_{(n)}(r) = J_0(\Lambda_{(n)} r) (Y_0(-\Lambda_{(n)} R_{e0}) - Y_0(-\Lambda_{(n)} R_{m0})) \\ + Y_0(-\Lambda_{(n)} r) (J_0(\Lambda_{(n)} R_{m0}) - J_0(\Lambda_{(n)} R_{e0})), \end{aligned} \quad (3.40a)$$

$$\mathcal{B}_{(n)} = J_0(\Lambda_{(n)} R_{m0}) Y_0(-\Lambda_{(n)} R_{e0}) - J_0(\Lambda_{(n)} R_{e0}) Y_0(-\Lambda_{(n)} R_{m0}), \quad (3.40b)$$

and Y_0 is the 0th order Bessel function of the second kind (as shown in Appendix D). Substituting (3.39) into (3.29a) and solving subject to the no-flux condition (3.33) we find

$$U_{e(n)} = -\frac{\mathbf{i}}{2\alpha^2 n r} \frac{d^2 P_{e(n)}}{dz^2} \left(r^2 - R_{e0}^2 + \frac{2\mathcal{C}_{(n)}(r)}{\Lambda_{(n)} \mathcal{B}_{(n)}} \right), \quad (3.41)$$

where

$$\begin{aligned} \mathcal{C}_{(n)}(r) = (r Y_1(-\Lambda_{(n)} r) - R_{e0} Y_1(-\Lambda_{(n)} R_{e0})) (J_0(\Lambda_{(n)} R_{m0}) - J_0(\Lambda_{(n)} R_{e0})) \\ - (r J_1(\Lambda_{(n)} r) - R_{e0} J_1(\Lambda_{(n)} R_{e0})) (Y_0(-\Lambda_{(n)} R_{e0}) - Y_0(-\Lambda_{(n)} R_{m0})), \end{aligned} \quad (3.42)$$

and Y_1 is the 1st order Bessel function of the second kind as summarised in Appendix D. Given our solutions from Equations (3.37) – (3.42), we can substitute into (3.28) to describe the full time-dependent solution for components of fluid velocity in the lumen and ECS.

At leading order in ε , we find that the governing equations for fluid flow in the membrane (3.30) reduce to the steady governing equations (2.36). Therefore, to solve for the amplitude of fluid velocities at each harmonic n in Equations (3.30b) - (3.30c), we can use the same analysis in Section 2.6.1.

In the membrane, we express the fluid pressure in terms of the lumen and ECS pressure. Substituting (3.30b) in to (3.30a) and solving subject to continuity of pressure conditions (3.31), we find

$$P_{m(n)} = \frac{(P_{e(n)} - P_{l(n)}) \ln r}{\ln R_{m0}} + P_{l(n)}, \quad (3.43)$$

therefore substituting in to (3.30b) – (3.30c) we find

$$\phi U_{m(n)} = \frac{\kappa(P_{l(n)} - P_{e(n)})}{r \ln R_{m0}}, \quad (3.44a)$$

$$\phi W_{m(n)} = \kappa \left(\frac{\ln r}{\ln R_{m0}} \left(\frac{dP_{l(n)}}{dz} - \frac{dP_{e(n)}}{dz} \right) - \frac{dP_{l(n)}}{dz} \right). \quad (3.44b)$$

To solve for the lumen and ECS pressures, we utilise our continuity of radial flux conditions (3.32) which result in a system of coupled ODEs of the same form as (2.49),

$$\frac{A_{(n)}}{\kappa} \frac{d^2 P_{l(n)}}{dz^2} = P_{l(n)} - P_{e(n)}, \quad \frac{B_{(n)}}{\kappa} \frac{d^2 P_{e(n)}}{dz^2} = P_{l(n)} - P_{e(n)}, \quad (3.45)$$

where

$$A_{(n)} = -\frac{i \ln R_{m0}}{2\alpha^2 n} \left(1 - \frac{2J_1(\Lambda_{(n)})}{\Lambda_{(n)} J_0(\Lambda_{(n)})} \right), \quad (3.46a)$$

$$B_{(n)} = -\frac{i \ln R_{m0}}{2\alpha^2 n} \left(R_{m0}^2 - R_{e0}^2 + \frac{2\mathcal{C}_{(n)}(R_{m0})}{\Lambda_{(n)} \mathcal{B}_{(n)}} \right). \quad (3.46b)$$

We solve (3.45) similarly to Section 2.6.1, except now subject to the pulsatile inlet and outlet pressure conditions (3.34) for each harmonic n , which gives

$$P_{l(n)} = c_1 z + c_2(1 - z) + B_{(n)} [c_3 \sinh \lambda z + c_4 \sinh \lambda(1 - z)], \quad (3.47a)$$

$$P_{e(n)} = c_1 z + c_2(1 - z) + A_{(n)} [c_3 \sinh \lambda z + c_4 \sinh \lambda(1 - z)], \quad (3.47b)$$

where

$$\lambda = \sqrt{\frac{\kappa(B_{(n)} - A_{(n)})}{B_{(n)}A_{(n)}}}, \quad (3.48a)$$

$$c_1 = \frac{A_{(n)}P_{l,out(n)} - B_{(n)}P_{e,out(n)}}{A_{(n)} - B_{(n)}}, \quad c_2 = \frac{A_{(n)}P_{l,in(n)} - B_{(n)}P_{e,in(n)}}{A_{(n)} - B_{(n)}}, \quad (3.48b)$$

$$c_3 = \frac{P_{l,out(n)} - P_{e,out(n)}}{(B_{(n)} - A_{(n)}) \sinh \lambda}, \quad c_4 = \frac{P_{l,in(n)} - P_{e,in(n)}}{(B_{(n)} - A_{(n)}) \sinh \lambda}. \quad (3.48c)$$

3.4.2 Poroelastic deformation

We now consider pulsatile membrane wall deformation in the asymptotic sublimit $v \ll \varepsilon^2, \gamma \ll 1$. Having taken the limit $v \rightarrow 0$, we find that (3.19) reduces to the steady membrane deformation equations (2.25). Therefore to find the leading-order amplitude of membrane displacements at each harmonic n , we follow the analysis from the steady state case in Chapter 2, but now coupled to the corresponding pulsatile flow solution solved in Section 3.4.1. As such, we proceed by substituting (3.27) – (3.28) into (2.25) and taking an asymptotic expansion of our dependent variables such that

$$(u_{(n)}, w_{(n)}) = (u_{0(n)}, w_{0(n)}) + \varepsilon^2(u_{2(n)}, w_{2(n)}) + O(\varepsilon^4) \quad \text{as } \varepsilon \rightarrow 0. \quad (3.49)$$

Then, at leading order, (3.19) becomes

$$\frac{1}{\delta(3 - \delta)} \left[(1 + \delta) \left(\frac{\partial^2 u_{0(n)}}{\partial r^2} + \frac{1}{r} \frac{\partial u_{0(n)}}{\partial r} - \frac{u_{0(n)}}{r^2} \right) + \frac{\partial^2 w_{0(n)}}{\partial r \partial z} \right] = \frac{\partial P_{m(n)}}{\partial r}, \quad (3.50a)$$

$$\frac{\partial^2 w_{0(n)}}{\partial r^2} + \frac{1}{r} \frac{\partial w_{0(n)}}{\partial r} = 0, \quad (3.50b)$$

The leading-order interfacial boundary conditions (A.10) and (A.12) become

$$(1 + \delta) \frac{\partial u_{0(n)}}{\partial r} + (1 - \delta) \left(\frac{u_{0(n)}}{r} + \frac{\partial w_{0(n)}}{\partial z} \right) = 0 \quad (3.51a)$$

$$\frac{\partial w_{0(n)}}{\partial r} = 0, \quad (3.51b)$$

evaluated at $r = 1, R_{m0}$. Utilising a similar analysis to that of Section 3.4.1, we can derive a solution for the leading-order amplitudes of radial membrane displacement

at each harmonic n . We do this by solving (3.50) subject to continuity of normal stress (3.51a) to find

$$u_{0(n)} = \frac{(3-\delta)}{2(1+\delta)r} \left[\left(\frac{R_{m0}^2 + \delta r^2}{R_{m0}^2 - 1} \right) \left(2\delta \int_1^{R_{m0}} r P_{m(n)} dr - (1+\delta)(P_{e(n)} - P_{l(n)}) \right) - 2\delta \int_r^{R_{m0}} r P_{m(n)} dr - (1+\delta)\delta r^2 P_{e(n)} \right] - \frac{(1-\delta)}{2} \frac{dw_{0(n)}}{dz} r. \quad (3.52)$$

From (3.50b) and (3.51b), we see that the leading-order amplitudes of axial membrane displacements $w_{0(n)}$ are a function of z only. To solve for $w_{0(n)}$, we must proceed to the $O(\varepsilon^2)$ expansion of (3.19) which yields

$$\frac{1}{\delta(3-\delta)} \left[\delta \left(\frac{\partial^2 w_{2(n)}}{\partial r^2} + \frac{1}{r} \frac{\partial w_{2(n)}}{\partial r} \right) + \left((1+\delta) \frac{d^2 w_{0(n)}}{dz^2} + \frac{\partial^2 u_{0(n)}}{\partial r \partial z} + \frac{1}{r} \frac{\partial u_{0(n)}}{\partial z} \right) \right] = \frac{\partial P_{m(n)}}{\partial z}. \quad (3.53)$$

Equation (3.53) is solved subject to (A.12) which becomes

$$\frac{1}{(3-\delta)} \left(\frac{\partial w_{2(n)}}{\partial r} + \frac{\partial u_{0(n)}}{\partial z} \right) = \frac{\partial W_{i(n)}}{\partial r}, \quad (3.54)$$

from which we can derive a solvability condition for $w_{0(n)}$ of the form

$$\frac{d^2 w_{0(n)}}{dz^2} = \frac{\mathcal{D}_{(n)} P'_{l(n)}(z) + \mathcal{E}_{(n)} P'_{e(n)}(z)}{\mathcal{F}_{(n)}}, \quad (3.55)$$

where

$$\mathcal{D}_{(n)} = \frac{n\alpha^2 ((R_{m0}^2 - 1)\delta - 2 \ln R_{m0}) + 4i(J_1(\Lambda_{(n)})/J_0(\Lambda_{(n)})) \ln R_{m0}}{2n(R_{m0}^2 - 1)\alpha^2 \ln R_{m0}}, \quad (3.56a)$$

$$\begin{aligned} \mathcal{E}_{(n)} = & \left[4i\Lambda_{(n)} R_{m0} \ln R_{m0} [J_1(\Lambda_{(n)} R_{m0})(Y_0(-\Lambda_{(n)} R_{e0}) - Y_0(-\Lambda_{(n)} R_{m0})) \right. \\ & \left. + Y_1(-\Lambda_{(n)} R_{m0})(J_0(\Lambda_{(n)} R_{e0}) - J_0(\Lambda_{(n)} R_{m0}))] \right] / \mathcal{B}_{(n)} \\ & - n\alpha^2 ((R_{m0}^2 - 1)\delta - 2R_{m0}^2 \ln R_{m0}), \quad (3.56b) \end{aligned}$$

$$\mathcal{F}_{(n)} = 2n(R_{m0}^2 - 1)\alpha^2 \ln R_{m0}. \quad (3.56c)$$

Solving (3.55) subject to the clamped wall boundary conditions (3.26), we find

$$w_{0(n)} = \int_0^z \frac{\mathcal{D}_{(n)}P_{l(n)}(z) + \mathcal{E}_{(n)}P_{e(n)}(z)}{\mathcal{F}_{(n)}} dz - z \int_0^1 \frac{\mathcal{D}_{(n)}P_{l(n)}(z) + \mathcal{E}_{(n)}P_{e(n)}(z)}{\mathcal{F}_{(n)}} dz. \quad (3.57)$$

3.5 Results

3.5.1 Typical operating conditions

We begin by investigating pulsatile flow under typical operating conditions, as described in Table 3.1. In this section, we consider only the steady component and the first oscillatory mode ($n = 0, 1$), noting that the model solution derived in this Chapter holds for arbitrary n . We prescribe a pulsatile lumen inlet pressure (as shown in Figure 3.1) that oscillates about an average pressure $P_{l,in(0)}$ equal to the inlet lumen pressure prescribed in the steady flow problem in Chapter 2. Similarly, we prescribe a pulsatile outlet lumen pressure that oscillates about an average pressure $P_{l,out(0)}$. We set the amplitude of oscillations for the first mode of the inlet/outlet lumen pressures to be equal to the average pressure (i.e. $P_{l,in(0)} = P_{l,in(1)}$, $P_{l,out(0)} = P_{l,out(1)}$). In doing so, we ensure that the inlet and outlet lumen pressures tend to zero halfway through one oscillatory cycle, ensuring the pressure drop across the lumen drops to zero, as would be expected in the human circulatory system. The remaining pressure conditions $P_{e,in}$, $P_{e,out}$ are held constant and equal to the steady conditions used in Chapter 2.

We visualise the pulsatile nature of the fluid flow solution through the bioreactor as a function of time in Figure 3.1. Nondimensionalising time relative to the angular frequency of oscillations, one full oscillation of the inlet pressure occurs over a 2π time interval for $n = 1$. From Figure 3.1a, we see that at typical operating conditions with low Womersley numbers where viscous forces dominate, the flow rate into the lumen is largely in phase with the pulsatile pressure profile as a function of time. This means that an increase or decrease in the fluid pressure driving flow in the lumen corresponds to a near-instantaneous response in fluid flux. We note that this will not be the case for faster-forcing frequencies, for which there will be an emergent lag, as we will show later. At the beginning of the oscillatory pressure cycle, we see that the fluid pressure is at its greatest, corresponding to the biggest inlet flux. From Figure

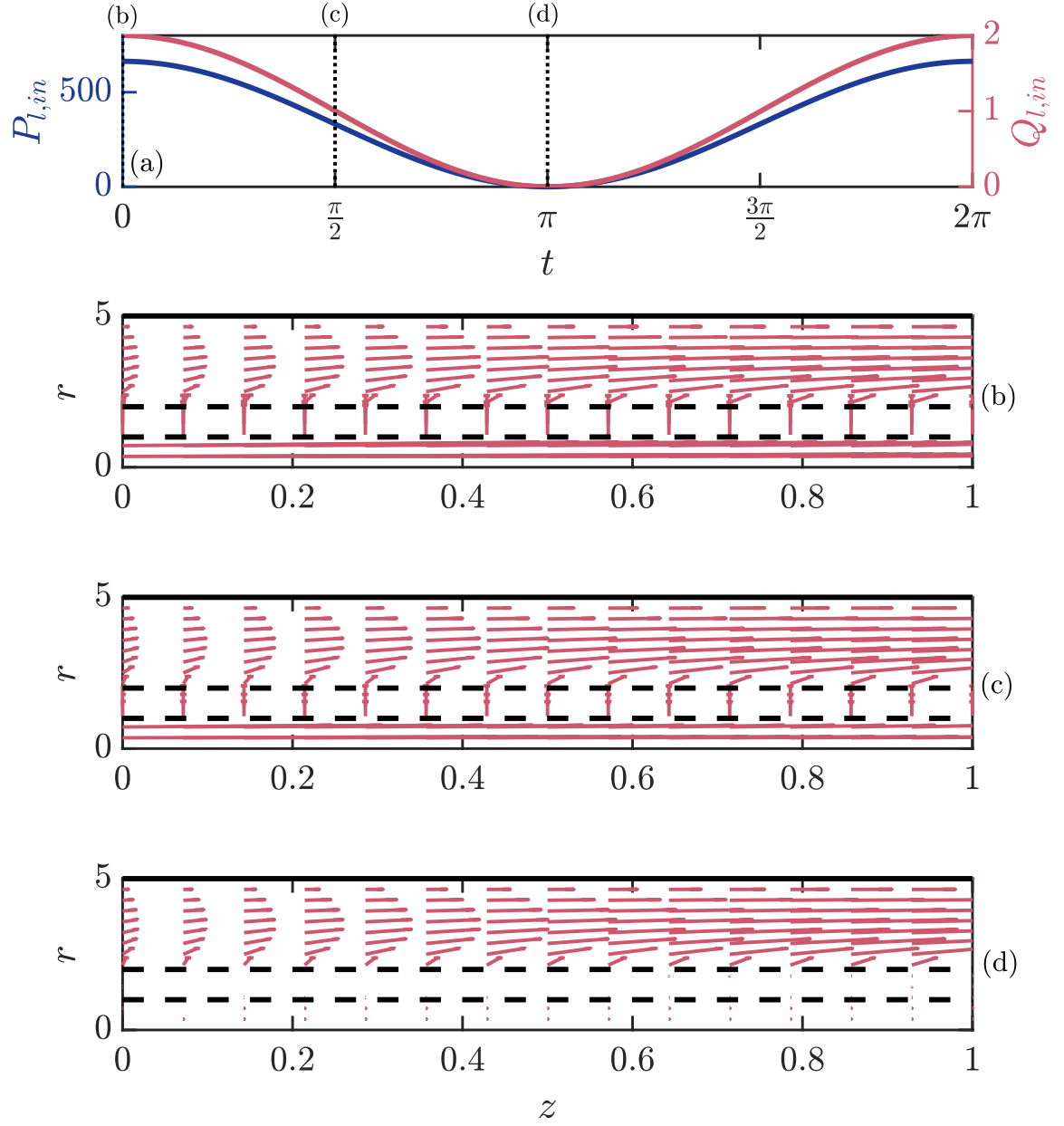


Figure 3.1: Pulsatile flow through the lumen, membrane and ECS under typical geometric and operating parameters outlined in Table 3.1. Figure (a) shows the total lumen inlet pressure and lumen inlet flux as a function of time during one cycle of oscillations. Figures (b) - (d) visualise the fluid velocity through a cross-section of the bioreactor at (b) $t = 0$, (c) $t = \pi/2$ and (d) $t = \pi$.

3.1, this corresponds to the maximum fluid velocity through the lumen $r \in (0, 1)$. As the inlet pressure decreases during the cycle, we see a proportional decrease in the inlet flux, corresponding to a decrease in the flow through the lumen in Figure 3.1c, tending towards a minimum near $t = \pi$ in Figure 3.1d. Beyond this point, the inlet pressure and flux increases and returns to its maximum at $t = 2\pi$. Throughout this cycle, we note that the flow through the ECS $r \in (2, 5)$ remains relatively constant. This is because the relative resistance to flow across the membrane is much higher compared to flow along the lumen. Therefore, when prescribing pulsatile flow through the lumen inlet, fluid will preferentially flow along the lumen, and thus pulsatile effects are felt less strongly in the ECS.

Under the same oscillatory inlet lumen pressure, we visualise the displacement of the poroelastic membrane wall as a function of time in Figure 3.2. Similarly to fluid flux under typical operating conditions, we see in Figure 3.2a that membrane displacements remain in phase with the inlet pulsatile lumen pressure. This is because the ratio of viscous forces to effective membranes stiffness $v \ll 1$, and thus in our model reduction, linear inertia in (3.19) is neglected at leading order. As the lumen inlet pressure decreases, both radial and axial displacements throughout the membrane also decrease to a minimum in Figure 3.2 when $P_{l,in} = P_{l,out} = 0$.

The periodic deformation of the membrane wall is induced by an applied periodic stress. In Figure 3.3, we visualise the leading-order components of stress and strain at the inner and outer membrane wall compared to the steady state case explored in Chapter 2. For all stress and strain components, it is clear that as the pulsatile lumen pressure is prescribed to oscillate about the steady lumen inlet pressure, stress and strain components oscillate about their steady values. The relative sign of each stress/strain component, corresponding to compressive or tensile stress/strain effects, remains the same throughout each oscillation. Therefore, it is only the magnitude of the stress/strain component that varies as a function of time. We note that halfway through each cycle where the lumen inlet/outlet pressure is zero, each component of stress and strain is also zero. As alluded to above, this is a direct consequence of the linear poroelastic problem being quasi-steady through the limit $v \ll 1$.

3.5.2 Pulsatile phase lag

By considering typical operating conditions where viscous forces dominate (i.e. $\alpha \ll 1$), we have seen that the time-dependent pressure-flux relationship remains relatively in phase. This means that an increase in the inlet lumen pressure leads to a near-instantaneous increase in the inlet lumen flux. However, at larger Womersley numbers

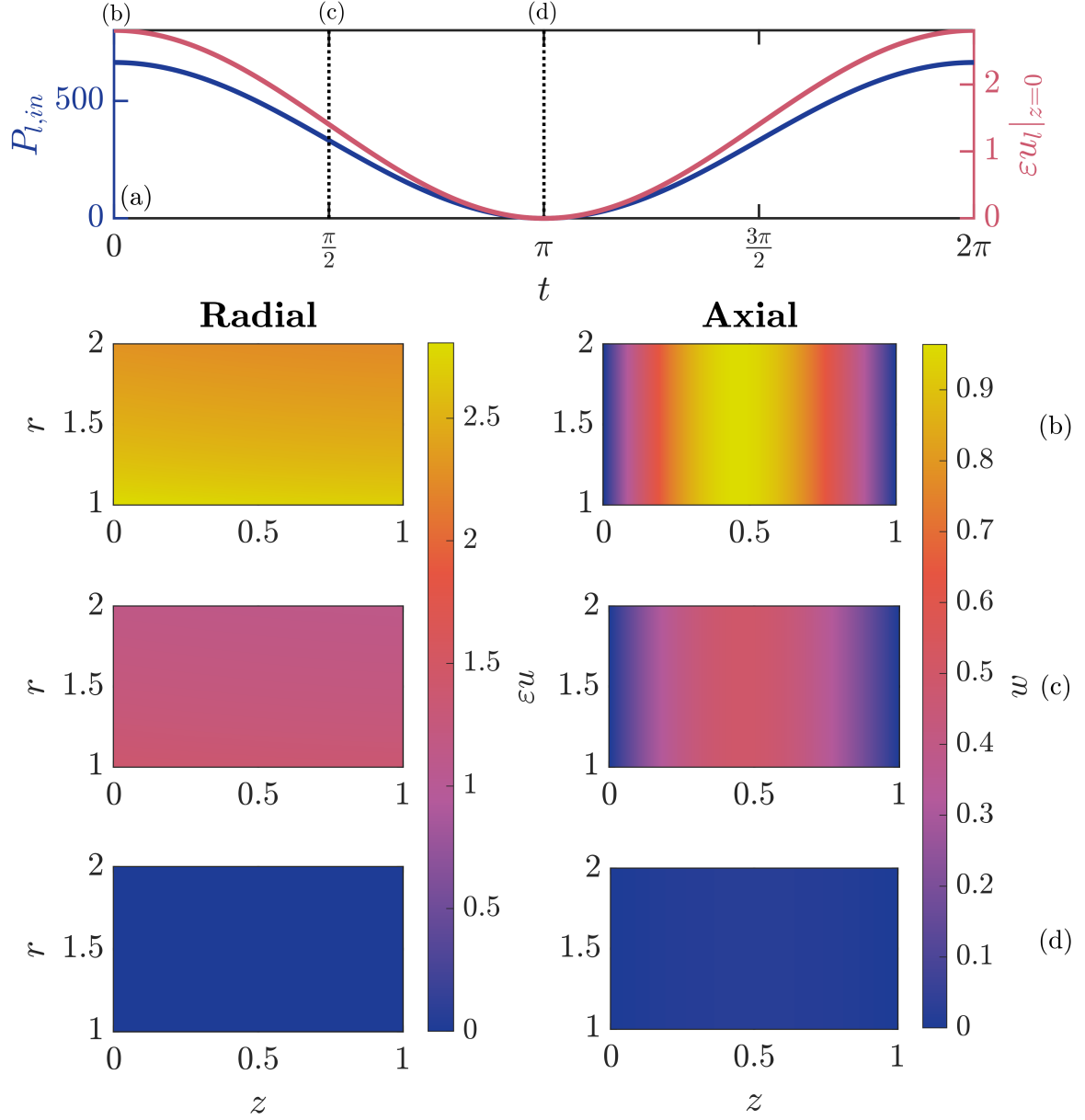


Figure 3.2: Pulsatile membrane displacements under typical geometric and operating parameters outlined in Table 3.1. Figure (a) shows the lumen inlet pressure and the radial displacement of the inner membrane wall at the inlet as a function of time. Figures (b) – (d) visualise the radial (left) and axial (right) membrane displacements through a cross-section of the membrane wall at (b) $t = 0$, (c) $t = \pi/2$ and (d) $t = \pi$.

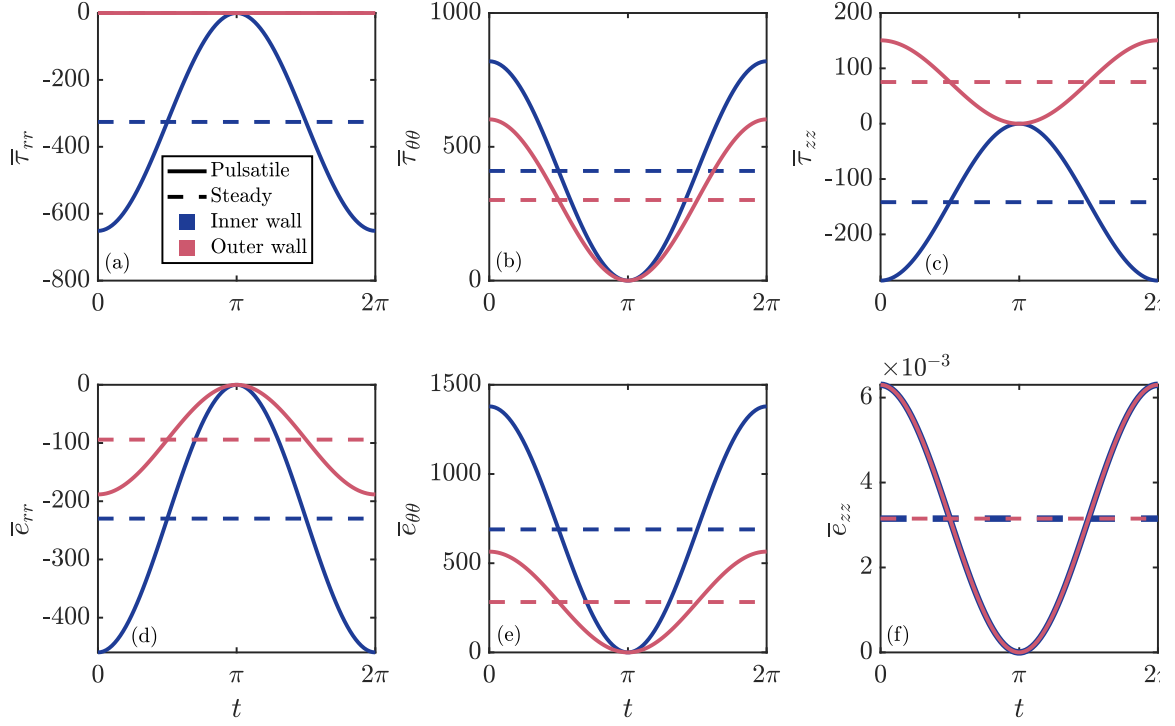


Figure 3.3: Average leading-order components of stress (a) – (c) and strain (d) – (f) evaluated at the inner (blue) and outer (red) membrane walls. Solid lines denote the pulsatile flow solution solved in Chapter 3, compared to the dotted line steady solution solved in Chapter 2.

where inertial effects dominate, this is not typically the case. In Figure 3.4, we visualise the pulsatile inlet lumen flux $Q_{l,in}$ compared to the inlet lumen pressure profile $P_{l,in}$ with increasing Womersley number (i.e. increasing oscillation frequency). As the Womersley number increases, we note an increasing phase lag, as well as a decrease in the amplitude of oscillations in the inlet flux. This is because at larger Womersley numbers where oscillatory inertial forces increase, the fluid has less time to respond to variations in the inlet pressure, and thus variations in flux are dampened.

In Figure 3.4, we can also see how the axial lumen inlet velocity profile $W_l|_{z=0}$ changes during one oscillation of the inlet pressure. At a low Womersley number where viscous forces dominate, we see a clear transition from a parabolic flow profile to a uniformly zero velocity profile that remains in phase with the driving lumen inlet pressure. As inertial effects dominate at larger α , the axial velocity tends to a near-steady velocity profile (e.g. $\alpha = 100$).

We can formally determine the phase lag φ between the oscillatory inlet lumen pressure and inlet flux for single-mode oscillations at varying Womersley numbers.

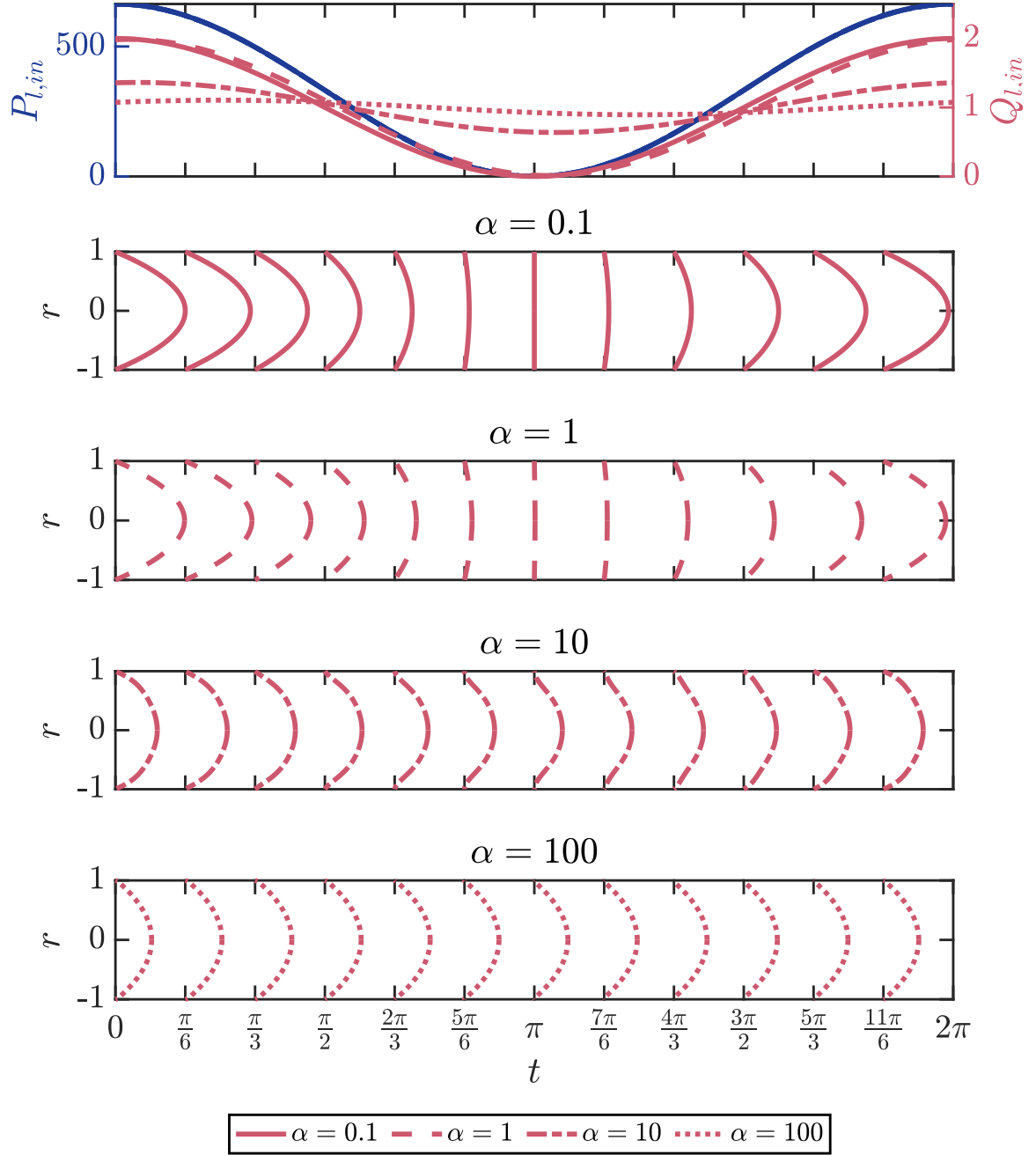


Figure 3.4: Comparison of the pressure-flux relationship (top), and visualisation of the lumen inlet axial velocity profile $W_l|_{z=0}$ during one oscillatory cycle under varying Womersley number α .

Combining our definition of the inlet lumen flux (3.22) and our Fourier series decomposition of the axial lumen velocity (3.28), we can express the inlet lumen flux in our system as

$$Q_{l,in} = Q_{l,in(0)} + \Re(Q_{l,in(1)}) \cos t - \Im(Q_{l,in(1)}) \sin t, \quad (3.58)$$

where

$$Q_{l,in(n)} = \int_0^1 r W_{l(n)}|_{z=0} dr, \quad (3.59)$$

and $\Im(\zeta)$ denotes the imaginary component of ζ . Since $\Im(Q_{l,in(1)}) \neq 0$, the phase angle, and thus the phase difference, is non-zero. The phase difference is given by

$$\varphi = \arctan \left(-\frac{\Im(Q_{l,in(1)})}{\Re(Q_{l,in(1)})} \right), \quad (3.60)$$

yielding a fully analytical pressure-flux phase relationship. We also note that the amplitude of flux oscillations is given by $|Q_{l,in(1)}|$.

Using (3.59) – (3.60), we visualise the dependency of the flux amplitude $|Q_{l,in(1)}|$ and the phase difference φ on the Womersley number α , as shown in Figure 3.5. As we increase α , corresponding to an increase in inertial forces, we see an increase in the phase shift φ between the inlet lumen pressure and lumen flow rate until a local maximum around $\alpha \approx 3 - 10$. This is analogous to the expected result for an increase in the Womersley number through a straight impermeable tube, where the increase in fluid inertia opposes, or impedes, the acceleration and deceleration of the fluid under oscillatory pressure gradients. However, in contrast to the case for flow through a rigid straight tube, the relationship for our scenario is non-monotonic. Beyond this local maxima, we note an initial decrease in φ . At $O(1)$ Womersley numbers, oscillations in the lumen flux appear to be dampened by the membrane and ECS flow regions, thus decreasing the phase lag. This dampening effect is overcome at larger Womersley numbers, where the phase difference increases and tends towards $\varphi = \pi/4$. This asymptotic behaviour is equivalent to the classic large Womersley number behaviour in a straight impermeable pipe as seen in Figure 3.6, and can be attributed to the fundamental phase lag in the system due to inertial impedance to flow in a regime where inertial forces dominate. However, rather than tending towards $\pi/2$ as in the classic Womersley solution, the dampening effect from the membrane and ECS leads to a $\pi/4$ asymptotic limit. This effect will be discussed later in this Section.

In Figure 3.5b, we see that an increase in the amplitude of oscillations in the inlet lumen pressure leads to a global increase in the inlet pressure-flux phase lag at

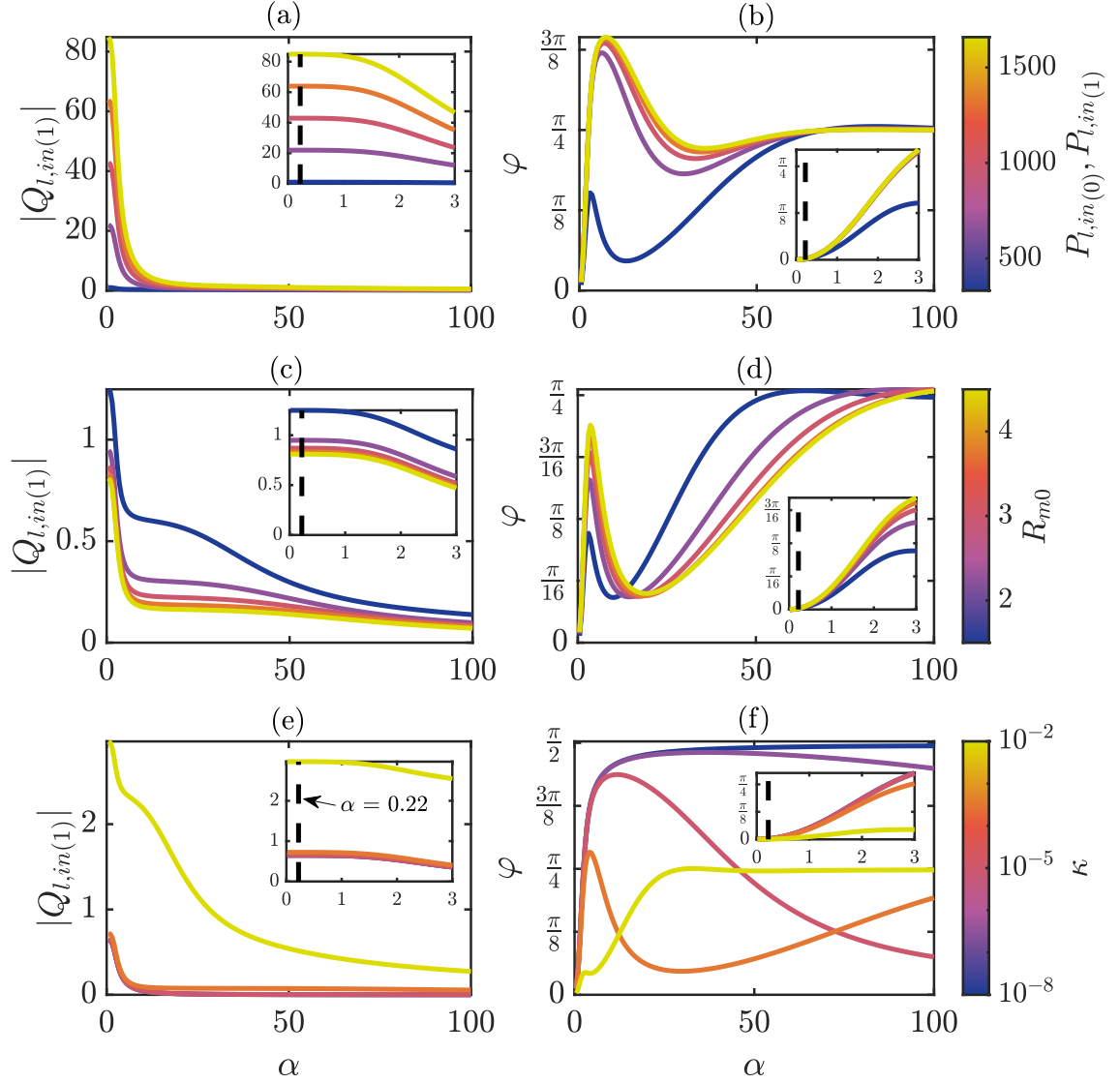


Figure 3.5: Amplitude of the lumen inlet flux oscillations $|Q_{l,in(1)}|$ (left) and the pressure-flux phase difference φ (right) as a function of the Womersley number α while varying (a) – (b) the magnitude of the inlet lumen pressure $P_{l,in(0)} = P_{l,in(1)}$, (c) – (d) the outer membrane wall position R_{m0} and (e) – (f) the membrane permeability κ . Remaining parameters are kept constant as given in Table 3.1.

each value of the Womersley number. This is because an increase in the inlet pressure corresponds to an increase in the magnitude of the inlet flux, as shown in Figure 3.5a. As a result, the fluid has greater inertia which impedes its acceleration or deceleration in response to oscillatory pressure gradients. The greater flow rate is slowed down less effectively at fixed α during each oscillation, leading to a greater phase lag. We note that in Figure 3.5a, the magnitude of inlet flux oscillations decreases exponentially with increasing α regardless of the inlet lumen pressure. This shows that as oscillation

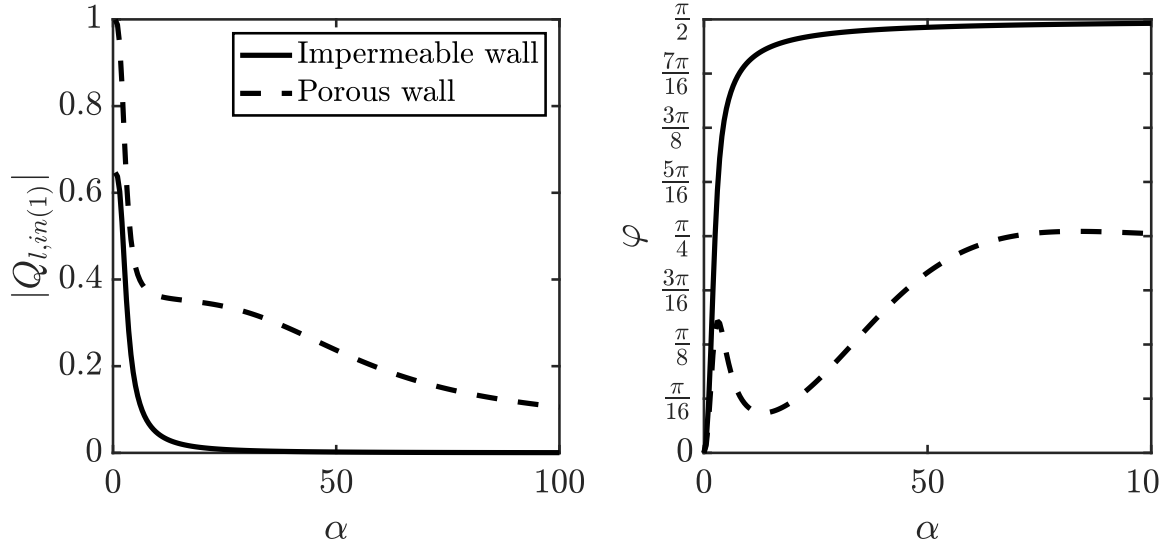


Figure 3.6: Comparing the amplitude of the inlet lumen oscillations $|Q_{l,in(1)}|$ (left) and the pressure-flux phase lag φ (right) as a function of the Womersley number in an impermeable tube wall and a porous membrane wall under typical operating conditions outlined in Table 3.1.

frequency increases, the inlet flow rate approaches a near-steady regime as visualised previously in Figure 3.4.

From Figures 3.5d and 3.5f, we see that an increase in the effective membrane thickness R_{m0} or a decrease in the membrane permeability κ leads to an increase in the peak phase lag, and delays the asymptotic phase lag plateau at larger Womersley numbers. This is because a thicker, less permeable membrane increases the resistance to flow between the lumen and ECS. Therefore, the dampening effect of the ECS flow is reduced, leading to a quicker initial increase in the phase lag. This also means that greater membrane resistances must be overcome by larger inertial forces, leading to a phase lag plateau at larger Womersley numbers.

In Figure 3.5f in particular, we see that at sufficiently small membrane permeabilities, the dampening effect has reduced such that the peak in phase lag appears to never decrease, and in fact asymptotes instead towards $\pi/2$ over the range of Womersley numbers considered. Therefore as the membrane permeability decreases, the phase lag profile appears to tend towards the phase lag profile for an impermeable pipe as shown in Figure 3.6. This qualitatively makes sense, as if we continue to decrease the membrane permeability, the resistance to flow across the membrane will tend towards that of a rigid impermeable pipe wall. We can formally investigate this behaviour by considering what happens to $Q_{l,in(1)}$ in the asymptotic limit $\alpha \rightarrow \infty$.

Substituting our solution for the axial lumen velocity (3.37) into our definition of the inlet lumen flux (3.59), we can express $Q_{l,in(1)}$ by

$$Q_{l,in(1)} = -\frac{i}{2\alpha^2} \frac{J_2(\Lambda_{(1)})}{J_0(\Lambda_{(1)})} \frac{dP_{l(1)}}{dz} \Big|_{z=0}. \quad (3.61)$$

As $\alpha \rightarrow \infty$, we find $\Lambda_{(1)} \sim e^{3\pi i/4} \infty$. In this limit, we find the ratio of the Bessel functions

$$\frac{J_2(\Lambda_{(1)})}{J_0(\Lambda_{(1)})} \sim -1. \quad (3.62)$$

From our solution to the pulsatile lumen pressure (3.47), we can express the pressure drop at the lumen inlet by

$$\frac{dP_{l(1)}}{dz} \Big|_{z=0} = c_1 - c_2 + B_{(1)} \lambda (c_3 - c_4 \cosh \lambda), \quad (3.63)$$

where coefficients c_i and λ depend on $A_{(1)}, B_{(1)}$ as shown in (3.48). Taking the limit $\alpha \rightarrow \infty$ in (3.46), we find

$$A_{(1)} \sim -\frac{i \ln R_{m0}}{2\alpha^2}, \quad (3.64a)$$

$$B_{(1)} \sim -\frac{i \ln R_{m0}}{2\alpha^2} (R_{m0}^2 - R_{e0}^2). \quad (3.64b)$$

Therefore substituting (3.64) into (3.48), (3.63), we find

$$\begin{aligned} \frac{dP_{l(1)}}{dz} \Big|_{z=0} &\sim \frac{P_{l,out(1)} - P_{l,in(1)} - (R_{e0}^2 - R_{m0}^2)(P_{e,out(1)} - P_{e,in(1)})}{(R_{e0}^2 - R_{m0}^2 + 1)} \\ &+ \frac{(R_{e0}^2 - R_{m0}^2)}{(R_{e0}^2 - R_{m0}^2 + 1)} \lambda \left[(P_{l,out(1)} - P_{e,out(1)}) \operatorname{csch} \lambda - (P_{l,in(1)} - P_{e,in(1)}) \coth \lambda \right], \end{aligned} \quad (3.65)$$

where

$$\lambda \sim \sqrt{\frac{2i\alpha^2 \kappa (R_{e0}^2 - R_{m0}^2 + 1)}{(R_{e0}^2 - R_{m0}^2) \ln R_{m0}}}, \quad (3.66)$$

which is complex with angle $\pi/4$. Therefore at large Womersley numbers, λ depends on the relative size of the membrane permeability compared to the square of the Womersley number, $\kappa\alpha^2$.

If we take κ to be sufficiently large such that $\kappa\alpha^2 \gg 1$, this means $\lambda \sim e^{i\pi/4} \infty$. Therefore, $\text{csch } \lambda \rightarrow 0$ and $\coth \lambda \rightarrow 1$, meaning that the last term in (3.65) dominates, giving

$$\left. \frac{dP_{l(1)}}{dz} \right|_{z=0} \sim - \frac{(R_{e0}^2 - R_{m0}^2)(P_{l,in(1)} - P_{e,in(1)})}{(R_{e0}^2 - R_{m0}^2 + 1)} \lambda. \quad (3.67)$$

Therefore as λ grows, the pressure gradient, and hence $Q_{l,in(1)}$ tends toward a complex number with angle $\pi/4$. Therefore as we increase the Womersley number in our system with $\kappa\alpha^2 \gg 1$, the phase lag $\varphi \rightarrow \pi/4$, thus validating our findings in Figure 3.5.

If we investigate the case of a small membrane permeability where $\kappa\alpha^2 \ll 1$, we see from (3.66) that $\lambda \rightarrow 0$, and thus we observe different asymptotic behaviour. In this limit, we find that $\text{csch } \lambda \rightarrow 1/\lambda$ and $\coth \lambda \rightarrow 1/\lambda$. Therefore, (3.65) simplifies to

$$\left. \frac{dP_{l(1)}}{dz} \right|_{z=0} \sim (P_{l,out(1)} - P_{l,in(1)}) - \frac{2(R_{e0}^2 - R_{m0}^2)(P_{e,out(1)} - P_{e,in(1)})}{(R_{e0}^2 - R_{m0}^2 + 1)}, \quad (3.68)$$

which is a real constant. Therefore from Equation (3.61), $Q_{l,in(1)}$ tends towards a purely imaginary number of decreasing amplitude, with angle $\pi/2$. As such when we take the small κ limit in our model, we recover the classical asymptotic behaviour of the Womersley solution for large α .

We also see from Figures 3.5c & 3.5e that a decrease in the membrane permeability or an increase in membrane thickness also decreases the amplitude of flux oscillations. Increasing the resistance to flow across the membrane also flattens the amplitude profile at larger Womersley numbers, converging to the profile for a straight impermeable tube (Figure 3.6), which is the expected result for the small κ limit.

We note that the peak phase lag, which we denote as φ_c , is a function of the model parameters explored in Figure 3.5. From Figure 3.7 we visualise the co-variance of R_{m0} and κ on the value of the peak phase lag φ_c and the corresponding Womersley number at which the peak phase lag occurs α_c . Broadly, we see that any change in a parameter that increases the resistance to flow across the membrane wall also acts to increase both φ_c and α_c . In particular, we see a dependency on the membrane permeability κ over two orders of magnitude, which leads to a significant increase in the value of φ_c . Any increase in membrane resistance makes it difficult for fluid to flow between the lumen and ECS, meaning that the phase lag dampening effect provided by the ECS is reduced, allowing flow in the lumen to initially become more and more out of phase.

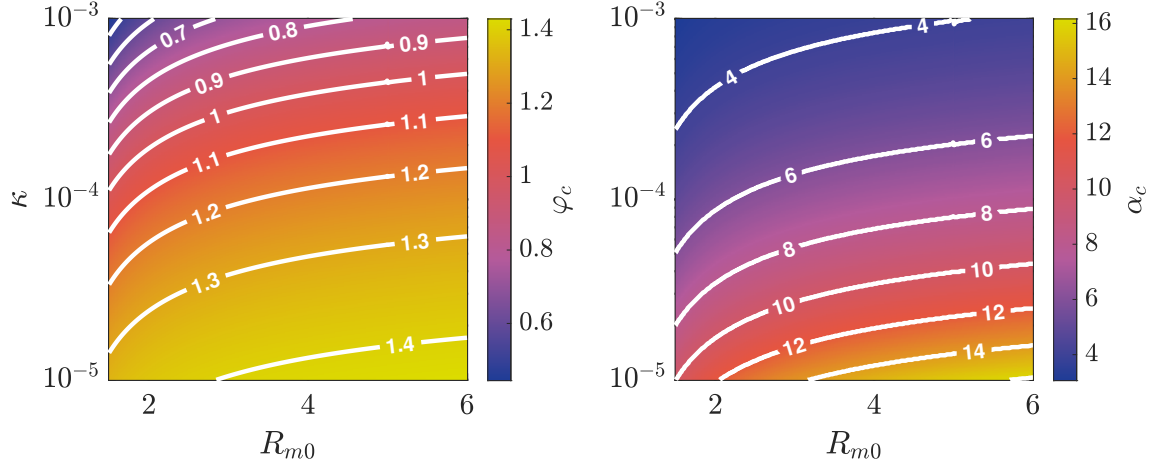


Figure 3.7: Identification of the peak phase lag φ_c (left) and the corresponding Womersley number α_c (right) at varying membrane thickness R_{m0} and permeability κ .

3.6 Discussion

In this Chapter, we extend our analysis from Chapter 2 to account for pulsatile fluid flow and membrane deformation in our poroelastic hollow fibre bioreactor setup. By prescribing a periodic inlet and outlet lumen pressure, we take a Fourier series decomposition of our dependent variables to simplify our problem into a linear sum of independent modes of oscillation. Therefore fluid flow and membrane deformation can be solved for subject to an inlet/outlet lumen pressure at each harmonic n . The framework presented in this chapter allows for scalable analysis of complex multi-modal pulsatile flow in our bioreactor system, which aims to better model more complex flow profiles.

By considering only the steady component and the first oscillatory mode, we have developed a preliminary insight into the pressure-flux response under typical operating conditions, and the impact this has on mechanical distributions of stress and strain in our bioreactor system. In the limit of high membrane stiffness ($\nu \ll 1$), we find that inertia due to oscillations in membrane displacements is negligible, leading to a near-instantaneous response to lumen pressure oscillations that is independent of the Womersley number α . We also find that under comparable operating conditions, components of membrane displacement, stress and strain oscillate sinusoidally about their steady values under the mean inlet lumen pressure, meaning that the average mechanical environment cells experience under pulsatile operation is equivalent to that experienced under steady operation. We note that we conduct an extended analysis of the impact of model parameters on membrane stress and strain in Chapter

2. This analysis is also applicable to the pulsatile flow problem.

From our leading-order analytical flow solution, we have derived the lumen inlet pressure-flux phase lag relationship which varies as a function of the Womersley number. Unlike the traditional Womersley solution through a straight rigid pipe, we identify a non-monotonic relationship between the phase lag φ and Womersley number α . Equation (3.60) gives a peak phase lag φ_c at a specified Womersley number α_c , which is a function of the resistance to fluid flow across the membrane wall. This peak phase lag is analogous to the resonant frequency of a driven damped harmonic oscillator, the amplitude of which is maximised by minimising the applied dampening effect. Drawing similarities with our own system, we have identified that flow in the membrane and ECS acts to dampen flow oscillations in the lumen. Therefore increasing the resistance to flow across the membrane wall (e.g. increasing R_{m0} , decreasing κ) acts to decrease the effect of dampening, thus maximising the amplitude of the phase lag at the corresponding resonant α_c . As we continue to increase the resistance to flow across the membrane, we recover the classic behaviour for pulsatile flow through a straight rigid pipe, with a phase lag that monotonically increases and asymptotes towards $\pi/2$ with increasing α .

Given that the phase lag φ is a function of our prescribed model parameters, we can tune our system to deliver the desired phase lag and mechanical stress at a prescribed Womersley number α . This insight is particularly useful for ensuring that we can accurately achieve the optimal mechanical environment for a given cell line of interest. Additionally, the existence of a characteristic peak phase lag φ_c and phase lag distribution has the potential to be used almost as a fingerprint to uniquely identify combinations of parameter values. In particular, we postulate that this analytical insight has the opportunity to identify key parameter values when fitted to experimental data. For example, if a series of experiments are conducted with a membrane of known thickness R_{m0} and inlet/outlet pressures across a range of Womersley number values (i.e. different pressure oscillation rates), it is theoretically possible to identify the membrane permeability from identification of the peak phase lag and the phase lag distribution. Such analysis would be much cheaper and simpler than traditional permeability characterisation studies, which traditionally require expensive equipment and time-consuming experimental setups (e.g. SEM/AFM imaging, gas/liquid permeation methods).

Chapter 4

Nutrient & waste metabolite transport

4.1 Introduction

In Chapter 2 we considered the coupled fluid flow problem through the lumen, membrane and extra-capillary space (ECS) compartments of our poroelastic bioreactor system (Figure 2.2). We showed that in the limit of large membrane stiffness, membrane deformation decouples from the fluid flow problem at leading order. As a result, the fluid flow problem effectively reduces to flow through a rigid geometry. Therefore when coupling fluid flow to solute transport, we do not need to consider the mechanical deformation of the poroelastic membrane to capture the dominant effects of advective mass transport. We now proceed with a rigid membrane geometry, as shown in Figure 4.1.

As mentioned in Section 1.3.4, many models of HFMB operation often simplify by assuming that the rate of nutrient uptake and waste metabolite production is constant [60, 87]. This assumption, while helpful for analytical ease, doesn't reflect the actual complexities in real-life scenarios. More accurate models that consider physiologically relevant reaction kinetics, alongside nutrient transport, instead require time-intensive numerical simulations [84, 85]. As such, there is a difficult trade-off between computational expediency and modelling accuracy.

We address this trade-off in Chapter 4 by deriving a reduced-order model of advection and diffusion of metabolites (cell nutrient/waste product) through our bioreactor system. Building on Chapter 2, we now introduce a cell layer located at the external membrane wall, where we model nutrient uptake and waste production modelled by Michaelis-Menten reaction kinetics. While the transport model presented in this Chapter holds for any generalised dilute species, we will consider the specific example

of transporting oxygen/removing carbon dioxide. Our motivation for this model is to understand the impact of varying structural and operating parameters to maximise nutrient delivery and waste metabolite removal. Additionally, we seek to understand how utilising the optimal permeability distribution we derived in Chapter 2, for a uniform fluid flux across the membrane wall, also facilitates a uniform nutrient uptake by cells seeded at the outer wall regardless of the balance between advective and diffusive mass transport effects.

4.2 Model setup

We consider solute transport in a viscous Newtonian fluid through a long thin bioreactor of length L^* , with geometry illustrated in Figure 4.1 and typical parameter values given in Table 4.1. We note that this is the same model geometry considered in Chapters 2 & 3, however now with the addition of a cell layer located at the outer membrane wall. In cylindrical coordinates (r^*, θ^*, z^*) with the longitudinal axis coinciding with the cylinder axis, we define $\hat{\mathbf{e}}_r, \hat{\mathbf{e}}_\theta, \hat{\mathbf{e}}_z$ as unit vectors in the radial, azimuthal and axial directions respectively. The model geometry considered in Figure 4.1 is axisymmetric around the cylinder axis. As such, we neglect azimuthal components and derivatives, reducing our problem to a 2D axisymmetric setup. We define a lumen of radius R_{l0}^* surrounded by a porous membrane of annular cross-section that extends the entire length of the bioreactor, with internal and external radii R_{l0}^* and R_{m0}^* respectively. A cell layer is seeded to the external membrane wall at $r^* = R_{m0}^*$ with an outer radius at $r^* = R_{c0}^*$. A rigid wall surrounds the bioreactor at $r^* = R_{e0}^*$, thus bounding our four key domains: the lumen (l), membrane (m), cell layer (c) and ECS (e). The nutrient and waste metabolite concentrations in region $i = l, m, c, e$ are denoted by c_i^* and w_i^* respectively, and the fluid velocity vector is denoted by $\mathbf{U}_i^* = U_i^* \hat{\mathbf{e}}_r + W_i^* \hat{\mathbf{e}}_z$. Although we are predominantly interested in solute transport in the flow field we derive in Chapter 2, for generality we present a model for a general flow field $\mathbf{U}_i^*$. We note, however, that we specifically use the lubrication flow results we generate in Chapter 2 when discussing the implications of our results in Section 4.9.

Nutrient enters the bioreactor at the lumen inlet. Nutrient can transport via advective and diffusive mass transport along the fibre lumen and out through the lumen outlet, or across the membrane wall. Cells seeded at the outer membrane wall consume the nutrient and produce waste metabolite, which are transported away through the ECS along with excess cell nutrient, again via advection and diffusion.

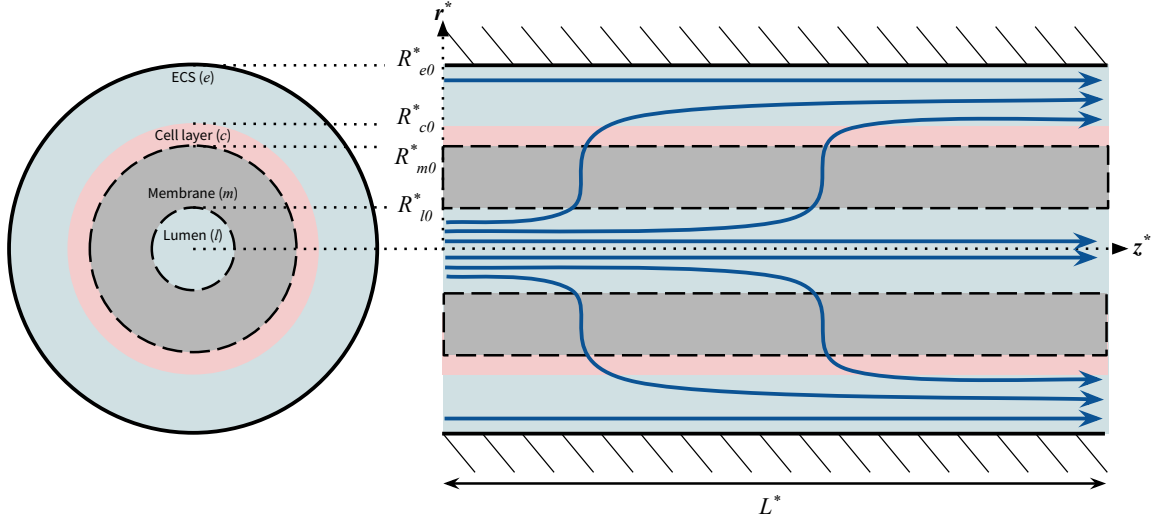


Figure 4.1: Axial (left) and radial (right) cross-section of the bioreactor setup. The fibre lumen (l) is enclosed by a porous fibre membrane wall (m) denoted by the grey region, with a cell layer (c) seeded to its outer surface represented by the pink region. The extra-capillary space (e) surrounds this, enclosed by an outer wall. Nutrient is introduced through the lumen inlet as indicated by the direction of the blue lines, denoting the different pathways available. Nutrient can transport via advection and diffusion either along the lumen or across the membrane wall to the cell layer. The cells can then consume the nutrients, producing waste metabolites, which are transported away with the excess nutrients along the ECS.

We consider the transport of both nutrient and waste products with typical parameter values outlined in Table 4.1. Motivated by the longer timescales for cell proliferation relative to advection, diffusion and uptake/production timescales, we neglect cell proliferation in this Chapter and focus on determining the steady nutrient distribution over transport timescales.

4.3 Governing equations

Everywhere except in the cell layer (where we have production/consumption of metabolites), we model the concentration of nutrient c_i^* in domain i using the following dimensional steady advection-diffusion equations representing conservation of mass

$$\mathbf{U}_i^* \cdot \nabla^* c_i^* = \nabla^* \cdot (\mathcal{D}_i^* \nabla^* c_i^*), \quad i = l, m, e. \quad (4.1)$$

Here $\mathcal{D}_i^*$ denotes the diffusivity of the solute in domain i which is taken to be homogeneous and isotropic. We assume the diffusivities are equal in the lumen and

ECS ($\mathcal{D}_l^* = \mathcal{D}_e^*$). We assume that the diffusivity of nutrient in the porous membrane and cell layer regions is proportional to the volume fraction of culture media (i.e. $\mathcal{D}_i^* = \phi_i \mathcal{D}_l^*$), where ϕ_i denotes the isotropic, homogeneous porosity in domain $i = m, c$. In the cell layer, in addition to advection and diffusion of nutrient, we introduce a reaction term to account for nutrient uptake as follows

$$\mathbf{U}_c^* \cdot \nabla^* c_c^* = \nabla^* \cdot (\mathcal{D}_c^* \nabla^* c_c^*) - \mathcal{R}^*(c_c^*), \quad \mathcal{R}^* = \frac{V_{max}^* c_c^*}{K_M^* + c_c^*}. \quad (4.2)$$

Here, V_{max}^* denotes the maximum uptake rate, and K_M^* is the Michaelis constant which denotes the nutrient concentration at which the uptake rate is half of V_{max}^* .

4.4 Boundary conditions

To couple metabolite flux between each domain, we require interfacial conditions at each domain interface. At the lumen-membrane, membrane-cell, and cell-ECS interfaces respectively, we prescribe continuity of concentration and concentration flux,

$$c_l^* = c_m^*, \quad (c_l^* \mathbf{U}_l^* - \mathcal{D}_l^* \nabla^* c_l^*) \cdot \hat{\mathbf{e}}_r = \phi_m (c_m^* \mathbf{U}_m^* - \mathcal{D}_m^* \nabla^* c_m^*) \cdot \hat{\mathbf{e}}_r \quad \text{at } r^* = R_{l0}^*, \quad (4.3a)$$

$$c_m^* = c_c^*, \quad \phi_m (c_m^* \mathbf{U}_m^* - \mathcal{D}_m^* \nabla^* c_m^*) \cdot \hat{\mathbf{e}}_r = \phi_c (c_c^* \mathbf{U}_c^* - \mathcal{D}_c^* \nabla^* c_c^*) \cdot \hat{\mathbf{e}}_r \quad \text{at } r^* = R_{m0}^*, \quad (4.3b)$$

$$c_c^* = c_e^*, \quad \phi_c (c_c^* \mathbf{U}_c^* - \mathcal{D}_c^* \nabla^* c_c^*) \cdot \hat{\mathbf{e}}_r = (c_e^* \mathbf{U}_e^* - \mathcal{D}_e^* \nabla^* c_e^*) \cdot \hat{\mathbf{e}}_r \quad \text{at } r^* = R_{c0}^*. \quad (4.3c)$$

Exploiting axisymmetry, we prescribe no diffusive flux at the lumen centreline,

$$(\mathcal{D}_l^* \nabla^* c_l^*) \cdot \hat{\mathbf{e}}_r = 0 \quad \text{at } r^* = 0, \quad (4.4)$$

and at the outer bioreactor wall, we prescribe a no flux condition,

$$(c_e^* \mathbf{U}_e^* - \mathcal{D}_e^* \nabla^* c_e^*) \cdot \hat{\mathbf{e}}_r = 0 \quad \text{at } r^* = R_{e0}^*, \quad (4.5)$$

noting that this is equivalent to no diffusive flux since the velocity, $\mathbf{U}_e^*$, vanishes on this boundary. At each of the axial ends, we prescribe no flux in the membrane and cell layer regions

$$(c_i^* \mathbf{U}_i^* - \mathcal{D}_i^* \nabla^* c_i^*) \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at } z^* = 0, L^*, \quad i = m, c. \quad (4.6)$$

We introduce fresh nutrient through the lumen inlet but not through the ECS inlet, captured via constant inlet concentration conditions,

$$c_l^* = C_{in}^*, \quad c_e^* = 0 \quad \text{at} \quad z^* = 0. \quad (4.7)$$

Finally, as solute exits the bioreactor via the lumen or ECS, we prescribe no diffusive flux at the outlet

$$(\mathcal{D}_i^* \nabla^* c_i^*) \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at} \quad z^* = L^*, \quad i = l, e. \quad (4.8)$$

4.5 Waste transport

We model the transport of waste metabolite w_i^* in the lumen, membrane and ECS using the governing equations defined in (4.1), where we replace c_i^* with w_i^* , and replace $\mathcal{D}_i^*$ with $\mathcal{D}_{w,i}$, respectively. We let $\mathcal{D}_{w,i}^*$ denote the diffusivity of waste metabolite in culture media. Therefore similarly to the nutrient transport problem, we let $\mathcal{D}_{w,i} = \phi_i \mathcal{D}_{w,l}$ denote the diffusivity of waste metabolite in the porous membrane and cell layer regions.

We assume that waste product is generated in the cell layer at a rate proportional to the nutrient uptake. The governing equation for waste transport in the cell layer is then

$$\mathbf{U}_c^* \cdot \nabla^* w_c^* = \mathcal{D}_{w,c}^* \nabla^{*2} w_c^* + \nu \mathcal{R}^*(c_c^*), \quad (4.9)$$

where ν denotes the constant of proportionality between nutrient consumption and waste production [106]. We also assume that no waste product is introduced to the system from the inlet ports, and so we prescribe a zero inlet concentration condition at the lumen and ECS inlet

$$w_i^* = 0 \quad \text{at} \quad z^* = 0, \quad i = l, e. \quad (4.10)$$

The remaining boundary conditions for w_i^* are equivalent to those in the nutrient transport problem, i.e. boundary conditions (4.3) – (4.6), (4.8) remain the same replacing c_i^* with w_i^* , and $\mathcal{D}_i^*$ with $\mathcal{D}_{w,i}^*$. We provide typical parameter values for both the nutrient and waste transport problem in Table 4.1.

4.6 Nondimensionalisation

Before systematically reducing the complexity of our model by exploiting the various disparate parameter ratios in this problem, we first non-dimensionalise. Using the

Table 4.1: Typical model parameters.

Parameter	Description	Typical value (Units)
Dimensional parameters		
Bioreactor dimensions		
L^*	Bioreactor length	0.1 (m) [61]
R_{l0}^*	Lumen radius	2×10^{-4} (m) [61]
R_{m0}^*	Outer membrane wall radius	4×10^{-4} (m) [61]
R_{c0}^*	Cell layer outer radius	4.1×10^{-4} (m) [107]
R_{e0}^*	ECS wall radius	1×10^{-3} (m) [61]
Fluid transport		
k_m^*	Typical membrane permeability	2.39×10^{-16} (m ²) [93]
μ^*	Fluid dynamic viscosity	1×10^{-3} (Pa s) [94]
$Q_{l,in}^*$	Typical lumen inlet flow rate	3.33×10^{-8} (m ³ s ⁻¹) [61]
$Q_{e,in}^*$	Typical ECS inlet flow rate	3.33×10^{-9} (m ³ s ⁻¹) [61]
$P_{l,in}^*$	Typical lumen inlet pressure	18.6 (Pa) [61]
$P_{e,in}^*$	Typical ECS inlet pressure	3.33×10^{-9} (m ³ s ⁻¹) [61]
$P_{l,out}^*$	Typical lumen outlet pressure	105500 (Pa) [61]
$P_{e,out}^*$	Typical ECS outlet pressure	0 (Pa) [61]
Oxygen transport		
C_{in}^*	Lumen inlet oxygen concentration	0.233 (mol m ⁻³) [†]
$\mathcal{D}_l^*$	Lumen oxygen diffusivity	3×10^{-9} (m ² s ⁻¹) [86]
V_{max}^*	Maximum reaction rate	8.39×10^{-2} (mol m ⁻³ s ⁻¹) [†]
K_M^*	Michaelis constant	1.12×10^{-6} (mol m ⁻³) [†]
Carbon dioxide transport		
$\mathcal{D}_{w,l}$	Lumen carbon dioxide diffusivity	2.88×10^{-9} (m ² s ⁻¹) [108]
Dimensionless parameters		
Bioreactor dimensions		
$\varepsilon = R_{l0}^*/L^*$	Lumen aspect ratio	2×10^{-3}
$\delta = (R_{c0}^* - R_{m0}^*)/L^*$	Cell layer thickness	1×10^{-4}
$R_{m0} = R_{m0}^*/\varepsilon L^*$	Outer membrane wall radius	2
$R_{c0} = R_{c0}^*/\varepsilon L^*$	Cell layer outer radius	2.05
$R_{e0} = R_{e0}^*/\varepsilon L^*$	ECS wall radius	5
Fluid transport		
$P_{l,in} = \varepsilon^2 P_{l,in}^* L^* / \mu^* \bar{W}^*$	Lumen inlet pressure	331.8
$P_{e,in} = \varepsilon^2 P_{e,in}^* L^* / \mu^* \bar{W}^*$	ECS inlet pressure	0.06
$P_{l,out} = \varepsilon^2 P_{l,out}^* L^* / \mu^* \bar{W}^*$	Lumen outlet pressure	321.4
$P_{e,out} = \varepsilon^2 P_{e,out}^* L^* / \mu^* \bar{W}^*$	ECS outlet pressure	0
ϕ_m	Typical membrane porosity	0.77 [95]
ϕ_c	Typical cell layer porosity	0.6 [86]
$\kappa = k_m^* / \varepsilon^4 L^{*2}$	Membrane permeability	1.5×10^{-3}
Oxygen transport		
$\varepsilon^2 \mathcal{P}_l = \varepsilon^2 \bar{W}^* L^* / \mathcal{D}_l^*$	Reduced lumen Péclet number	17.5
$V_{max} = V_{max}^* L^{*2} / C_{in}^* \mathcal{D}_c^*$	Maximum reaction rate	2×10^6
$K_M = K_M^* / C_{in}^*$	Michaelis constant	4.78×10^{-6}
Carbon dioxide transport		
$\varepsilon^2 \mathcal{P}_{w,l} = \varepsilon^2 \bar{W}^* L^* / \mathcal{D}_l^*$	Reduced lumen Péclet number	18.2

[†] Parameters determined from internal unpublished experimental data for growth of human endothelial cells.

flow scalings from Chapter 2, together with the nondimensionalisation of c_i^* and w_i^* with respect to the inlet lumen nutrient concentration, we impose

$$(r^*, z^*) = L^*(r, z), \quad (U_i^*, W_i^*) = \bar{W}^*(U_i, W_i), \quad (c_i^*, w_i^*) = C_{in}^*(c_i, w_i). \quad (4.11)$$

Axial and radial coordinates are scaled relative to the length of the bioreactor. Radial and axial velocity components are scaled relative to the axial velocity scaling in Equation (2.24). The nutrient transport governing equation (4.1) then becomes

$$\mathcal{P}_i \mathbf{U}_i \cdot \nabla c_i = \nabla^2 c_i, \quad i = l, m, e, \quad (4.12)$$

where $\mathcal{P}_i = \bar{W}^* L^* / \mathcal{D}_i^*$ is the Péclet number in domain i . We note that the relationship between the diffusivity in the porous and bulk flow regions means that we can express the Péclet number in the membrane and cell layer via the Péclet number in the lumen and ECS, such that $\mathcal{P}_i = \mathcal{P}_l / \phi_i$ for $i = m, c$. In the cell layer, (4.2) becomes

$$\mathcal{P}_c \mathbf{U}_c \cdot \nabla c_c = \nabla^2 c_c - \mathcal{R}(c_c), \quad (4.13)$$

where

$$\mathcal{R} = \frac{V_{max} c_c}{K_M + c_c}, \quad V_{max} = \frac{V_{max}^* L^{*2}}{C_{in}^* \mathcal{D}_c^*}, \quad K_M = \frac{K_M^*}{C_{in}^*}. \quad (4.14)$$

Here, V_{max} denotes the ratio between reaction and diffusion timescales, and K_M denotes the ratio of the Michaelis constant and the inlet lumen concentration.

Given continuity of concentration and continuity of radial fluid flux, advection terms in the continuity of solute flux condition balance and thus (4.3) becomes

$$c_l = c_m, \quad \frac{\partial c_l}{\partial r} = \phi_m^2 \frac{\partial c_m}{\partial r} \quad \text{at } r = \varepsilon, \quad (4.15a)$$

$$c_m = c_c, \quad \phi_m^2 \frac{\partial c_m}{\partial r} = \phi_c^2 \frac{\partial c_c}{\partial r} \quad \text{at } r = \varepsilon R_{m0}, \quad (4.15b)$$

$$c_c = c_e, \quad \phi_c^2 \frac{\partial c_c}{\partial r} = \frac{\partial c_e}{\partial r} \quad \text{at } r = \varepsilon R_{c0}, \quad (4.15c)$$

where $R_{i0} = R_{i0}^* / R_{l0}^*$ denotes the nondimensional radius of domain $i = m, c, e$, and $\varepsilon = R_{l0}^* / L^*$ denotes the lumen aspect ratio. We note that factors of ϕ_i^2 in (4.15) arise from the fact that $\mathcal{P}_i = \mathcal{P}_l / \phi_i$. As such, factors of ϕ_i^2 can be thought of as the porosity of domain i multiplied by the nondimensional diffusivity of solute in i .

The symmetry condition (4.4) becomes

$$\frac{\partial c_l}{\partial r} = 0 \quad \text{at} \quad r = 0, \quad (4.16)$$

and the no solute flux condition at the outer wall (4.5) combined with the no fluid flux condition (2.22) becomes

$$\frac{\partial c_e}{\partial r} = 0 \quad \text{at} \quad r = \varepsilon R_{e0}. \quad (4.17)$$

The no axial flux condition (4.6) becomes

$$\frac{\partial c_i}{\partial z} = 0 \quad \text{at} \quad z = 0, 1, \quad i = m, c, \quad (4.18)$$

noting that W_i vanishes at each boundary. Finally, the inlet concentration conditions (4.7) become

$$c_l = 1, \quad c_e = 0 \quad \text{at} \quad z = 0, \quad (4.19)$$

and the no-diffusive-flux conditions (4.8) become

$$\frac{\partial c_l}{\partial z} = 0, \quad \frac{\partial c_e}{\partial z} = 0 \quad \text{at} \quad z = 1. \quad (4.20)$$

For the waste transport problem, we find that (4.12), (4.15) – (4.18), (4.20) remain the same as the nutrient transport governing equations, having exchanged c_i for w_i , and replacing $\mathcal{P}_i$ with $\mathcal{P}_{w,i}$. We let $\mathcal{P}_{w,l}$ denote the Péclet number representing waste metabolite transport in the lumen. Similarly to the nutrient transport problem, we let $\mathcal{P}_{w,l} = \mathcal{P}_{w,e}$, and $\mathcal{P}_{w,i} = \mathcal{P}_{w,l}/\phi_i$ denote the Péclet number for waste metabolite transport in the porous membrane and cell layer regions. The governing equations for waste transport in the cell layer (4.9) becomes

$$\mathcal{P}_{w,c} \mathbf{U}_c \cdot \nabla w_c = \nabla^2 w_c + \nu \mathcal{R}(c_c). \quad (4.21)$$

As previously, our inlet concentration conditions for waste product (4.10) become

$$w_i = 0 \quad \text{at} \quad z = 0, \quad i = l, e. \quad (4.22)$$

4.7 Model reduction

We provide typical model parameter values in Table 4.1. We use parameter values from literature where possible as described in Section 2.4. Reaction kinetic parameters (V_{max}^*, K_M^*) are fitted from internal unpublished experimental data from the IBME for growth of human endothelial cells in a single fibre HFMB setup subject to an experimentally prescribed inlet oxygen concentration (C_{in}^*) . To mathematically simplify the metabolite transport problem (4.12) – (4.22), we exploit the geometry of our problem to derive a reduced-order system of equations that are more amenable to analytic study.

4.7.1 Cell layer reduction

We start by investigating nutrient transport and uptake in the cell layer of thickness $\delta = \varepsilon(R_{c0} - R_{m0})$. As justified by the parameter values in Table 4.1, we investigate the physically relevant asymptotic limit $\delta \ll \varepsilon \ll 1$. We transform the radial coordinate r such that $r = n + \varepsilon(R_{m0} + R_{c0})/2$. In doing so, we take the axial centreline of the cell layer to be $n = 0$, where $n \in (-\delta/2, \delta/2)$ in the cell layer. A schematic is shown in Figure 4.2, where we let $\mathbf{Q}_i = \mathcal{P}_l c_i \mathbf{U}_i - \phi_i \nabla c_i$ for $i = m, c$, and $\mathbf{Q}_e = \mathcal{P}_l c_e \mathbf{U}_e - \nabla c_e$. Given that we are considering the asymptotic limit in which $\delta \ll \varepsilon \ll 1$, we introduce an inner scaling $n = \delta N$ such that $N = O(1)$. Also given that $\mathcal{R} = O(\delta^{-1})$, we define $\bar{\mathcal{R}} = O(1)$ such that $\mathcal{R} = \bar{\mathcal{R}}/\delta$. We then pose an asymptotic expansion in δ for c_i i.e.

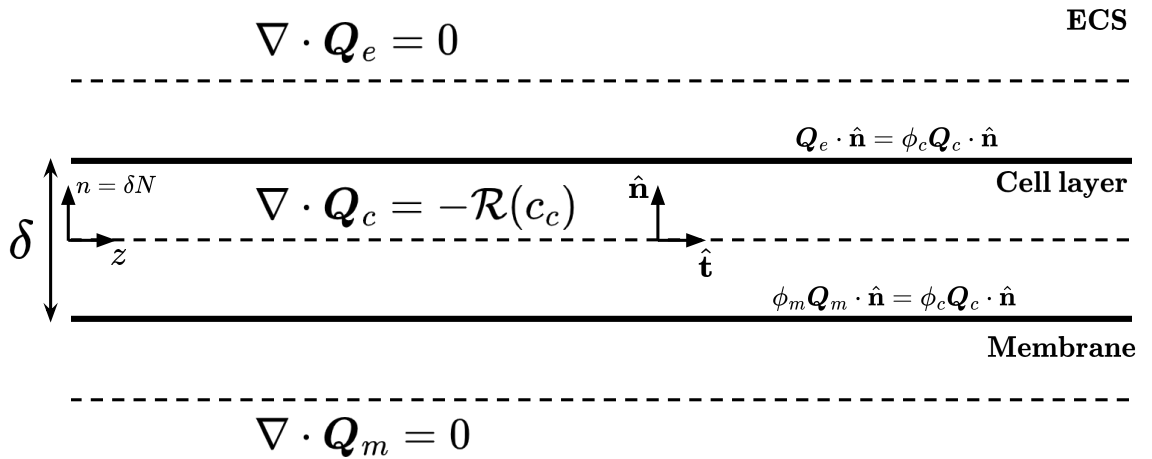


Figure 4.2: Cell layer with thickness δ . The central dotted line denotes the centreline along which we define $N = 0$, and the external dotted lines above and below denote the boundary of the inner problem in the outside membrane and ECS regions which we scale into.

$$c_i \sim c_{i0} + \delta c_{i1} + \cdots \quad \text{as } \delta \rightarrow 0. \quad (4.23)$$

Collecting $O(\delta^{-2})$ terms, (4.12) – (4.13) become

$$\frac{\partial^2 c_{m0}}{\partial N^2} = \frac{\partial^2 c_{c0}}{\partial N^2} = \frac{\partial^2 c_{e0}}{\partial N^2} = 0. \quad (4.24)$$

Equations (4.24) have solution

$$c_{c0} = A_c(z)N + B_c(z), \quad c_{i0} = A_i(z)N + B_i(z), \quad i = m, e. \quad (4.25)$$

We note that in the cell layer, $N = O(1)$ and bounded. In the membrane and ECS however, N can tend to $\pm\infty$. Since concentrations in the outer regions will be bounded as $\delta \rightarrow 0$, matching these inner solutions for c_{m0}, c_{e0} as $N \rightarrow \pm\infty$ with the outer solutions as $n \rightarrow 0$, we obtain the matching condition $A_i \equiv 0$ for $i = m, e$, so that

$$c_{m0} = B_m(z), \quad c_{e0} = B_e(z). \quad (4.26)$$

From the continuity of concentration and flux boundary conditions (4.15), we then find $A_c(z) = 0$, and $B_m(z) = B_c(z) = B_e(z)$. Therefore, concentration c_c is constant at leading order in the boundary layer, and therefore

$$c_{c0} = c_{m0}|_{n=0} = c_{e0}|_{n=0}. \quad (4.27)$$

Collecting terms at $O(\delta^{-1})$, (4.12) – (4.13) become

$$\frac{\partial}{\partial N} \left(\mathcal{P}_c (\mathbf{U}_c \cdot \hat{\mathbf{n}}) c_{c0} - \frac{\partial c_{c1}}{\partial N} \right) = -\overline{\mathcal{R}}(c_{c0}), \quad (4.28a)$$

$$\frac{\partial}{\partial N} \left(\mathcal{P}_i (\mathbf{U}_i \cdot \hat{\mathbf{n}}) c_{i0} - \frac{\partial c_{i1}}{\partial N} \right) = 0, \quad (4.28b)$$

for $i = m, e$, where $\hat{\mathbf{n}}$ is the unit normal vector in the positive N -direction. From (4.28) we see that the flux in the inner regions of the membrane and cell layer domains is conserved. Multiplying (4.28a) by the square of the porosity of the cell layer, ϕ_c^2 , and noting that $\mathcal{P}_i = \mathcal{P}_l/\phi_i$, we integrate from $N = -1/2$ to $N = 1/2$ to find

$$\phi_c \left(\mathcal{P}_l (\mathbf{U}_c \cdot \hat{\mathbf{n}}) c_{c0} - \phi_c \frac{\partial c_{c1}}{\partial N} \right) \Bigg|_{-1/2}^{1/2} = -\phi_c^2 \overline{\mathcal{R}}(c_{c0}). \quad (4.29)$$

Noting the continuity of flux boundary conditions (4.3) and that $\mathcal{P}_i = \mathcal{P}_l/\phi_i$, we see

$$\phi_c \left(\mathcal{P}_l(\mathbf{U}_c \cdot \hat{\mathbf{n}}) c_{c0} - \phi_c \frac{\partial c_{c1}}{\partial N} \right) \Big|_{-\frac{1}{2}} = \phi_m \left(\mathcal{P}_l(\mathbf{U}_m \cdot \hat{\mathbf{n}}) c_{m0} - \phi_m \frac{\partial c_{m1}}{\partial N} \right) \Big|_{-\frac{1}{2}}, \quad (4.30a)$$

$$\phi_c \left(\mathcal{P}_l(\mathbf{U}_c \cdot \hat{\mathbf{n}}) c_{c0} - \phi_c \frac{\partial c_{c1}}{\partial N} \right) \Big|_{\frac{1}{2}} = \left(\mathcal{P}_l(\mathbf{U}_e \cdot \hat{\mathbf{n}}) c_{e0} - \frac{\partial c_{e1}}{\partial N} \right) \Big|_{\frac{1}{2}}. \quad (4.30b)$$

We also note that by continuity of fluid flux and continuity of concentration, the advective terms in (4.30) cancel out. Matching into the outer problem in the membrane and ECS, we find that

$$\frac{\partial c_m}{\partial n} \Big|_{n \uparrow 0} \sim \frac{1}{\delta} \frac{\partial}{\partial N} (c_{m0} + \delta c_{m1}) \Big|_{N=-\frac{1}{2}} = \frac{\partial c_{m1}}{\partial N} \Big|_{N=-\frac{1}{2}}, \quad (4.31a)$$

$$\frac{\partial c_e}{\partial n} \Big|_{n \downarrow 0} \sim \frac{1}{\delta} \frac{\partial}{\partial N} (c_{e0} + \delta c_{e1}) \Big|_{N=\frac{1}{2}} = \frac{\partial c_{e1}}{\partial N} \Big|_{N=\frac{1}{2}}. \quad (4.31b)$$

Therefore, using the results of (4.28) – (4.31), we may derive the following effective boundary condition

$$\phi_m^2 \frac{\partial c_m}{\partial n} - \frac{\partial c_e}{\partial n} = -\phi_c^2 \overline{\mathcal{R}}(c_{c0}), \quad (4.32)$$

noting that $c_c \sim c_{c0}$. Transforming back into the radial coordinate r , (4.27), (4.32) become

$$c_m = c_e, \quad \phi_m^2 \frac{\partial c_m}{\partial r} - \frac{\partial c_e}{\partial r} = -\phi_c^2 \overline{\mathcal{R}}(c_m) \quad \text{at} \quad r = \varepsilon R_{m0}, \quad (4.33)$$

thus reducing our problem to fluid flow and nutrient transport in the lumen, membrane and ECS only. Formally, (4.33) replaces Equations (4.15b) – (4.15c) as $R_{c0} \rightarrow R_{m0}$. Physically, Equation (4.33) states that the effective jump in diffusive flux across the membrane wall is due to nutrient uptake by the cells. Similarly to the derivation of (4.33), the effective boundary condition at the membrane/ECS interface for the waste transport problem becomes

$$w_m = w_e, \quad \phi_m^2 \frac{\partial w_m}{\partial r} = \frac{\partial w_e}{\partial r} + \nu \phi_c^2 \overline{\mathcal{R}}(c_e) \quad \text{at} \quad r = \varepsilon R_{m0}. \quad (4.34)$$

4.7.2 Streamfunction-arclength formulation

Given that the long, thin bioreactor geometry means that a single numerical simulation of this problem takes several minutes to compute over a coarse grid, it is

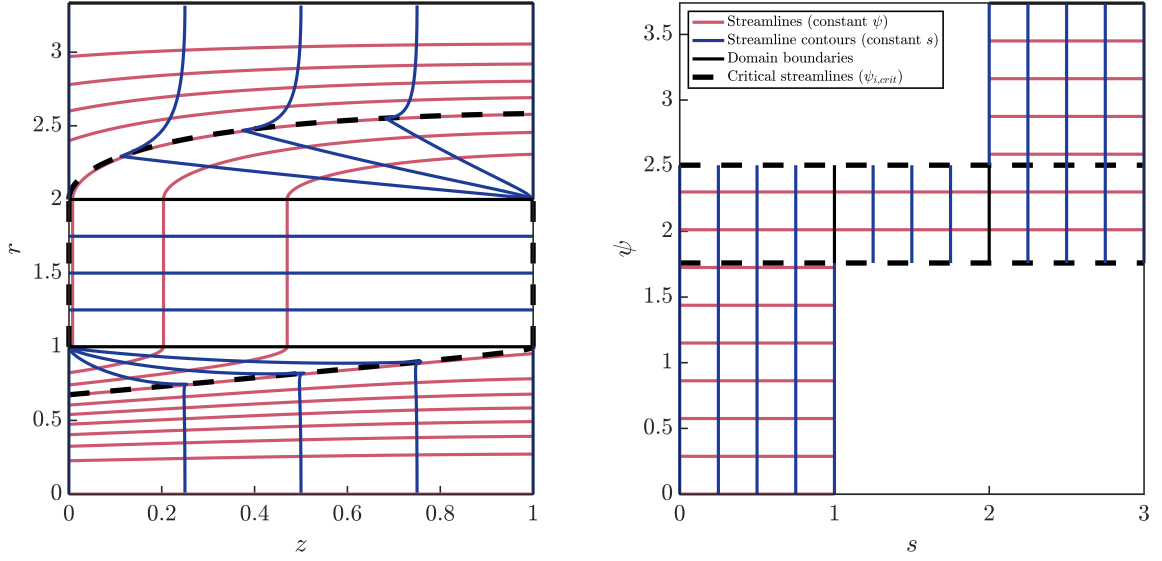


Figure 4.3: Transformation from an axisymmetric coordinate system (r, z) on the left, to a streamfunction-arclength coordinate system (ψ, s) on the right. Red lines denote streamlines of constant ψ , blue lines denote contours of constant s along streamlines, black solid lines denote the boundary of each physical domain, and dotted black lines denote the critical streamlines $\psi_{i,crit}$ which divide where fluid enters or leaves.

prudent to exploit the small lumen aspect ratio ε and apply lubrication scalings to our model, as we did for the fluid flow problem in Chapter 2. However, given the current form of the advection-diffusion equations, exploiting this limit requires some care. In particular, while the bioreactor does have a long, thin geometry, the flow is fast enough for advective transport to remain important. In particular, we show later that the reduced Péclet number in all domains, $\overline{\mathcal{P}}_i = \varepsilon^2 \mathcal{P}_i = O(1)$. This means that the advective terms are retained at leading order to balance with radial diffusion. While this does represent a reduction in the complexity of the system (given that we lose the axial diffusion term), the spatially 2D nature of the advective terms means that a numerical solution of this system is still challenging.

To circumvent this issue, we transform into a streamfunction-arclength coordinate system as shown in Figure 4.3. We note this is similar to the approach in Cummings and Waters [25] (for a different geometry). In our system, the solute is advected along streamlines (lines of constant streamfunction value), and therefore advective terms become spatially 1D with respect to arclength.

To ensure we accurately account for factors of r associated with the transformation from Cartesian to cylindrical coordinates, we consider the full transformation of our system from a 3D Cartesian coordinate system to a streamfunction-arclength formulation defined in axisymmetric cylindrical coordinates, $(x, y, z) \mapsto (\psi, \theta, s)$. However,

given that our solutions to the fluid flow problem are known in an axisymmetric cylindrical coordinate system, it is prudent to express our Cartesian coordinate system in terms of cylindrical coordinates, such that

$$x = r(\psi, s) \cos \theta, \quad y = r(\psi, s) \sin \theta, \quad z = z(\psi, s). \quad (4.35)$$

The metrics of this transformation can be expressed as

$$H_\psi \equiv \left| \frac{\partial \mathbf{x}}{\partial \psi} \right| = \sqrt{x_\psi^2 + y_\psi^2 + z_\psi^2} = \sqrt{r_\psi^2 (\cos^2 \theta + \sin^2 \theta) + z_\psi^2} = \left| \frac{\partial \mathbf{r}}{\partial \psi} \right|, \quad (4.36a)$$

$$H_\theta \equiv \left| \frac{\partial \mathbf{x}}{\partial \theta} \right| = r \sqrt{\cos^2 \theta + \sin^2 \theta} = r, \quad (4.36b)$$

$$H_s \equiv \left| \frac{\partial \mathbf{x}}{\partial s} \right| = \sqrt{x_s^2 + y_s^2 + z_s^2} = \sqrt{r_s^2 (\cos^2 \theta + \sin^2 \theta) + z_s^2} = \left| \frac{\partial \mathbf{r}}{\partial s} \right|, \quad (4.36c)$$

where $\mathbf{x} = x\mathbf{e}_x + y\mathbf{e}_y + z\mathbf{e}_z$ and $\mathbf{r} = r\mathbf{e}_r + \theta\mathbf{e}_\theta + z\mathbf{e}_z$.

The streamfunction (ψ) relates to the fluid velocity in domain i by

$$\mathbf{U}_i = \nabla \times \psi, \quad (4.37)$$

where $\psi = (0, 0, \psi)$. Having previously solved for components of the fluid velocity in cylindrical coordinates in Chapter 2, Equation (4.37) can be written as

$$U_i = -\frac{1}{r} \frac{\partial \psi}{\partial z}, \quad W_i = \frac{1}{r} \frac{\partial \psi}{\partial r}, \quad (4.38)$$

Therefore,

$$\left| \frac{\partial \psi}{\partial \mathbf{r}} \right| = \sqrt{\left(\frac{\partial \psi}{\partial r} \right)^2 + \left(\frac{\partial \psi}{\partial z} \right)^2} = r \sqrt{U_i^2 + W_i^2} = r \tilde{U}_i. \quad (4.39)$$

We can relate (4.39) to the metric of transformation H_ψ by

$$\frac{\partial \psi}{\partial \mathbf{r}} \cdot \frac{\partial \mathbf{r}}{\partial \psi} = \left| \frac{\partial \psi}{\partial \mathbf{r}} \right| \left| \frac{\partial \mathbf{r}}{\partial \psi} \right| \cos \theta. \quad (4.40)$$

Given that both vectors are tangential and align in the direction of constant s , this means that $\theta = 0$, and thus $\cos \theta = 1$. The left-hand side of (4.40) can be simplified if we consider the Jacobian of the transformation $(r, z) \mapsto (\psi, s)$,

$$\left| \frac{\partial (r, z)}{\partial (\psi, s)} \right| = \begin{pmatrix} r_\psi & r_s \\ z_\psi & z_s \end{pmatrix} = \begin{pmatrix} \psi_r & \psi_z \\ s_r & s_z \end{pmatrix}^{-1} = \frac{1}{\psi_r s_z - \psi_z s_r} \begin{pmatrix} s_z & -\psi_z \\ -s_r & \psi_r \end{pmatrix}. \quad (4.41)$$

Therefore, the left-hand side of (4.40) becomes

$$\frac{\partial\psi}{\partial\mathbf{r}} \cdot \frac{\partial\mathbf{r}}{\partial\psi} = \psi_r r_\psi + \psi_z z_\psi = \frac{\psi_r s_z - \psi_z s_r}{\psi_r s_z - \psi_z s_r} = 1, \quad (4.42)$$

as a direct result of the inverse function theorem. Therefore,

$$\left| \frac{\partial\psi}{\partial\mathbf{r}} \right| \left| \frac{\partial\mathbf{r}}{\partial\psi} \right| = 1 \quad \Rightarrow \quad \left| \frac{\partial\mathbf{r}}{\partial\psi} \right| = \left| \frac{\partial\psi}{\partial\mathbf{r}} \right|^{-1} = \frac{1}{r\tilde{U}}. \quad (4.43)$$

The normalised arclength (s) parameterises the distance along streamlines. Without loss of generality, we impose $0 \leq s \leq 1$ in the lumen, $1 \leq s \leq 2$ in the membrane, and $2 \leq s \leq 3$ in the ECS. We let $\mathcal{L}_i$ denote the actual arclength of a streamline in domain i , which varies between 0 and the total length of the streamline, $l_{\psi,i}$. The arclength $\mathcal{L}_i$ and normalised arclength s are therefore related by

$$\mathcal{L}_i = l_{\psi,i} (s - n_i), \quad (4.44)$$

where $n_i = 0, 1, 2$ for the lumen, membrane and ECS respectively. We also know that along a streamline of constant ψ , we can relate the arclength of a streamline to axisymmetric coordinates such that

$$d\mathcal{L}_i^2 = dr^2 + dz^2. \quad (4.45)$$

With ψ fixed, $\mathcal{L}_i$ varies only with s . Combining (4.44) – (4.45), this means that

$$\left(\frac{\partial\mathcal{L}_i}{\partial s} \right)^2 = \left(\frac{\partial r}{\partial s} \right)^2 + \left(\frac{\partial z}{\partial s} \right)^2 = l_{\psi,i}^2, \quad (4.46a)$$

$$\Rightarrow \left| \frac{\partial\mathbf{r}}{\partial s} \right| = \sqrt{\left(\frac{\partial r}{\partial s} \right)^2 + \left(\frac{\partial z}{\partial s} \right)^2} = l_{\psi,i}. \quad (4.46b)$$

Substituting (4.43), (4.46) in to (4.36), we can determine the metrics of the transformation to be

$$H_\psi = \frac{1}{r\tilde{U}_i}, \quad H_\theta = r, \quad H_s = l_{\psi,i}. \quad (4.47)$$

In these transformed coordinates, (4.12) becomes

$$\mathcal{P}_i \frac{\tilde{U}_i}{H_s} \frac{\partial c_i}{\partial s} = \frac{1}{H_\psi H_\theta H_s} \left[\frac{\partial}{\partial\psi} \left(\frac{H_\theta H_s}{H_\psi} \frac{\partial c_i}{\partial\psi} \right) + \frac{\partial}{\partial s} \left(\frac{H_\psi H_\theta}{H_s} \frac{\partial c_i}{\partial s} \right) \right]. \quad (4.48)$$

Finally, substituting in our metrics of transformation (4.47) into (4.48), we recover

$$\mathcal{P}_i \frac{\partial c_i}{\partial s} = \frac{\partial}{\partial \psi} \left(r^2 l_{\psi,i} \tilde{U}_i \frac{\partial c_i}{\partial \psi} \right) + \frac{\partial}{\partial s} \left(\frac{1}{l_{\psi,i} \tilde{U}_i} \frac{\partial c_i}{\partial s} \right). \quad (4.49)$$

To transform the boundary conditions from axisymmetric to streamfunction-arclength formulation, we make use of the fact that

$$\frac{\partial}{\partial r} = \frac{\partial \psi}{\partial r} \frac{\partial}{\partial \psi} + \frac{\partial s}{\partial r} \frac{\partial}{\partial s} = r W_i \frac{\partial}{\partial \psi} + \frac{U_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial}{\partial s}, \quad (4.50a)$$

$$\frac{\partial}{\partial z} = \frac{\partial \psi}{\partial z} \frac{\partial}{\partial \psi} + \frac{\partial s}{\partial z} \frac{\partial}{\partial s} = -r U_i \frac{\partial}{\partial \psi} + \frac{W_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial}{\partial s}. \quad (4.50b)$$

With this, continuity of concentration and solute flux (4.15a) becomes

$$c_l = c_m, \quad (4.51a)$$

$$r W_l \frac{\partial c_l}{\partial \psi} + \frac{U_l}{l_{\psi,l} \tilde{U}_l} \frac{\partial c_l}{\partial s} = \phi_m^2 \left(r W_m \frac{\partial c_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial c_m}{\partial s} \right) \quad \text{at } s = 1, \psi \in [\psi_{l,crit}, \psi_{l,max}), \quad (4.51b)$$

and the effective cell layer condition (4.33) becomes

$$c_m = c_e, \quad (4.52a)$$

$$\phi_m^2 \left(r W_m \frac{\partial c_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial c_m}{\partial s} \right) = \left(r W_e \frac{\partial c_e}{\partial \psi} + \frac{U_e}{l_{\psi,e} \tilde{U}_e} \frac{\partial c_e}{\partial s} \right) - \phi_c^2 \bar{\mathcal{R}}(c_e) \quad \text{at } s = 2, \psi \in (\psi_{e,min}, \psi_{e,crit}]. \quad (4.52b)$$

The symmetry condition (4.16) and the no flux condition at the outer wall (4.17) become

$$r W_i \frac{\partial c_i}{\partial \psi} + \frac{U_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial c_i}{\partial s} = 0 \quad \text{at } \psi = 0, \psi_{e,max}, \quad (4.53)$$

and the no-diffusive-flux outlet conditions (4.20) become

$$\frac{W_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial c_i}{\partial s} - r U_i \frac{\partial c_i}{\partial \psi} = 0 \quad \text{at } s = 1, \psi \in (0, \psi_{l,crit}] \quad \text{and } s = 3. \quad (4.54)$$

The inlet concentration conditions (4.19) remain the same,

$$c_l = 1 \quad \text{at} \quad s = 0, \quad (4.55a)$$

$$c_e = 0 \quad \text{at} \quad s = 2, \psi \in (\psi_{e,crit}, \psi_{e,max}]. \quad (4.55b)$$

For waste metabolite transport, the governing equations (4.49) remain the same, swapping c_i for w_i and $\mathcal{P}_i$ for $\mathcal{P}_{w,i}$. The jump condition (4.34) becomes

$$w_m = w_e \quad (4.56a)$$

$$\begin{aligned} \phi_m^2 \left(rW_m \frac{\partial w_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial w_m}{\partial s} \right) &= \left(rW_e \frac{\partial w_e}{\partial \psi} + \frac{U_e}{l_{\psi,e} \tilde{U}_e} \frac{\partial w_e}{\partial s} \right) + \nu \phi_c^2 \overline{\mathcal{R}}(w_e) \\ &\quad \text{at} \quad s = 2, \psi \in (\psi_{e,min}, \psi_{e,crit}], \end{aligned} \quad (4.56b)$$

and the inlet concentration (4.22) condition becomes

$$w_l = 0 \quad \text{at} \quad s = 0, \quad (4.57a)$$

$$w_e = 0 \quad \text{at} \quad s = 2, \psi \in (\psi_{e,crit}, \psi_{e,max}]. \quad (4.57b)$$

The remaining boundary conditions (4.51), (4.53) – (4.54) remain the same as for nutrient transport, exchanging c_i for w_i .

4.7.3 Long-thin reduction

From (4.49), we see that the governing equations in streamfunction-arclength formulation represent a balance between advective mass transport along streamlines, and diffusive mass transport along and between streamlines. Given the similarity to the original transport equation (4.12), it may not yet be clear what we have gained by performing this transformation. However, analogous to the lubrication analysis of the fluid flow section, we are now in a position to exploit the long thin bioreactor geometry to simplify our governing equations.

In the lumen and ECS, lubrication scalings for a long thin geometry mean that $r = \varepsilon r^*$, $U_i = \varepsilon U_i^*$, where $r^*, U_i^* = O(1)$. Since we have an $O(1)$ axial flow entering the lumen through a circular area of $O(\varepsilon)$ radius, fluid flux through the bioreactor is $O(\varepsilon^2)$, and hence the streamfunction ψ scales with ε^2 . Hence, we scale the streamfunction via $\psi = \varepsilon^2 \psi^*$. With these scalings and dropping the superscript $\star$ for ease of notation, (4.49) becomes

$$\bar{\mathcal{P}}_i \frac{\partial c_i}{\partial s} = \frac{\partial}{\partial \psi} \left(r^2 l_{\psi,i} \tilde{U}_i \frac{\partial c_i}{\partial \psi} \right) + \varepsilon^2 \frac{\partial}{\partial s} \left(\frac{1}{l_{\psi,i} \tilde{U}_i} \frac{\partial c_i}{\partial s} \right), \quad (4.58)$$

for $i = l, e$ where

$$\tilde{U}_i = \sqrt{\varepsilon^2 U_i^2 + W_i^2}, \quad (4.59)$$

and the reduced Péclet number $\bar{\mathcal{P}}_i = \varepsilon^2 \mathcal{P}_i$ which we take to be an $O(1)$ quantity.

In the membrane, we again scale $r = \varepsilon r^*$, $U_i = \varepsilon U_i^*$, $\psi = \varepsilon^2 \psi^*$, where r^* , U_i^* , $\psi^* = O(1)$. However, our analysis in Chapter 2 suggest that leading-order streamlines now align with the radial axis, which is an $O(\varepsilon)$ length scale compared to the bioreactor length. Hence, $l_{\psi,m}$ scales with ε in the membrane, and so we write $l_{\psi,m} = \varepsilon l_{\psi,m}^*$, where $l_{\psi,m}^* = O(1)$. For the fluid velocity in the membrane, the appropriate velocity scalings from the fluids problem for a long, thin geometry mean that

$$\tilde{U}_m = \sqrt{\varepsilon^2 U_m^{*2} + \varepsilon^4 W_m^{*2}} = \varepsilon \sqrt{U_m^{*2} + \varepsilon^2 W_m^{*2}} \sim \varepsilon \tilde{U}_m^*, \quad (4.60)$$

where we let $\tilde{U}_m = \varepsilon \tilde{U}_m^*$. Using these scalings and dropping the superscript $\star$, the governing equation in the membrane (4.49) becomes

$$\bar{\mathcal{P}}_m \frac{\partial c_m}{\partial s} = \varepsilon^2 \frac{\partial}{\partial \psi} \left(r^2 l_{\psi,m} \tilde{U}_m \frac{\partial c_m}{\partial \psi} \right) + \frac{\partial}{\partial s} \left(\frac{1}{l_{\psi,m} \tilde{U}_m} \frac{\partial c_m}{\partial s} \right), \quad (4.61)$$

where the reduced Péclet number in the membrane $\bar{\mathcal{P}}_m = \varepsilon^2 \mathcal{P}_m = \varepsilon^2 \mathcal{P}_l / \phi_m$ which we take to be an $O(1)$ quantity.

Utilising the appropriate scalings above, continuity of concentration and solute flux (4.51) becomes

$$c_l = c_m, \quad (4.62a)$$

$$r W_l \frac{\partial c_l}{\partial \psi} + \varepsilon^2 \frac{U_l}{l_{\psi,l} \tilde{U}_l} \frac{\partial c_l}{\partial s} = \phi_m^2 \left(\varepsilon^2 r W_m \frac{\partial c_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial c_m}{\partial s} \right) \quad \text{at } s = 1, \psi \in [\psi_{l,crit}, \psi_{l,max}], \quad (4.62b)$$

and the effective cell layer condition (4.52) becomes

$$c_m = c_e, \quad (4.63a)$$

$$\phi_m^2 \left(\varepsilon^2 r W_m \frac{\partial c_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial c_m}{\partial s} \right) = \left(r W_e \frac{\partial c_e}{\partial \psi} + \varepsilon^2 \frac{U_e}{l_{\psi,e} \tilde{U}_e} \frac{\partial c_e}{\partial s} \right) - \varepsilon \phi_c^2 \overline{\mathcal{R}}(c_m) \quad \text{at } s = 2, \psi \in (\psi_{e,min}, \psi_{e,crit}]. \quad (4.63b)$$

The symmetry condition and the no flux condition at the outer wall (4.53) become

$$r W_i \frac{\partial c_i}{\partial \psi} + \varepsilon^2 \frac{U_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial c_i}{\partial s} = 0 \quad \text{at } \psi = 0, \psi_{e,max}, \quad (4.64)$$

and the no-diffusive-flux outlet conditions (4.54) become

$$\frac{W_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial c_i}{\partial s} - r U_i \frac{\partial c_i}{\partial \psi} = 0 \quad \text{at } s = 1, \psi \in (0, \psi_{l,crit}] \quad \text{and } s = 3. \quad (4.65)$$

The inlet concentration conditions (4.55) remain the same,

$$c_l = 1 \quad \text{at } s = 0, \quad (4.66a)$$

$$c_e = 0 \quad \text{at } s = 2, \psi \in (\psi_{e,crit}, \psi_{e,max}]. \quad (4.66b)$$

Again, Equations (4.58) – (4.62), (4.64) – (4.65) remain the same for waste metabolite transport exchanging c_i for w_i . The effective boundary condition (4.56) becomes

$$w_m = w_e, \quad (4.67a)$$

$$\phi_m^2 \left(\varepsilon^2 r W_m \frac{\partial w_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial w_m}{\partial s} \right) = \left(r W_e \frac{\partial w_e}{\partial \psi} + \varepsilon^2 \frac{U_e}{l_{\psi,e} \tilde{U}_e} \frac{\partial w_e}{\partial s} \right) - \varepsilon \phi_c^2 \overline{\mathcal{R}}(w_m) \quad \text{at } s = 2, \psi \in (\psi_{e,min}, \psi_{e,crit}], \quad (4.67b)$$

and the inlet concentration condition remains the same as (4.57).

4.8 Model solution

We now consider the solution for metabolite concentration in our bioreactor setup. Until now, we have considered metabolite transport for an arbitrary flow field in a long thin geometry, exploiting the standard lubrication scalings. To make further analytic progress with our solution, we proceed utilising the flow field solved in Chapter 2. Therefore, we note that the metabolite transport problem considered from this point onward is valid for lubrication flow in a long thin geometry as considered in Chapter 2.

4.8.1 Membrane solution

From Equation (4.60), we see that $\tilde{U}_m = U_m$ at leading order in ε . Equation (4.61) becomes

$$\overline{\mathcal{P}}_m \frac{\partial c_m}{\partial s} = \frac{\partial}{\partial s} \left(\frac{1}{l_{\psi,m} U_m} \frac{\partial c_m}{\partial s} \right), \quad (4.68)$$

noting that $U_m > 0$ throughout our problem. Equation (4.68) is then solved subject to continuity of concentration (4.62a) and the leading-order effective cell layer boundary condition (4.63b), which becomes

$$\frac{\phi_m^2}{l_{\psi,m}} \frac{\partial c_m}{\partial s} = -\varepsilon \phi_c^2 \overline{\mathcal{R}}(c_m) \quad \text{at} \quad s = 2, \psi \in (\psi_{e,min}, \psi_{e,crit}], \quad (4.69)$$

noting that W_e vanishes at the membrane-ECS interface as per (2.38). For generality, we retain $\varepsilon \overline{\mathcal{R}}$ as an $O(1)$ quantity. Having previously solved the fluid transport problem analytically in Chapter 2 to obtain U_m , we know that streamlines in the membrane align with the radial axis as demonstrated in Figure 4.3. Therefore, we can relate the radial coordinate to the normalised arclength in the membrane via the relationship

$$r = (s - 1)(R_{m0} - 1) + 1, \quad (4.70)$$

and streamline lengths throughout the membrane become

$$l_{\psi,m} = R_{m0} - 1. \quad (4.71)$$

On this basis, we can express the fluid velocity along a streamline in the membrane wall by the radial velocity in (2.48), having transformed the radial coordinate by (4.70) to give

$$\tilde{U}_m = U_m = \frac{\kappa(P_l - P_e)}{\phi_m [(s - 1)(R_{m0} - 1) + 1] \ln R_{m0}}. \quad (4.72)$$

Substituting (4.70) – (4.72) into (4.68), we can integrate subject to continuity of concentration (4.62a) and the effective membrane-ECS interfacial condition (4.69) to determine that

$$c_m = c_l|_{[l,m]} + \mathcal{A} \left([(s - 1)(R_{m0} - 1) + 1]^{-\xi} - 1 \right), \quad \xi = \frac{\overline{\mathcal{P}}_l \kappa(P_e - P_l)}{\phi_m^2 \ln R_{m0}}, \quad (4.73)$$

where $c_l|_{[l,m]}$ denotes the unknown lumen concentration at the lumen-membrane interface and $\mathcal{A}$ depends on $c_l|_{[l,m]}$. These unknowns depend on the solution to nutrient

concentration in the lumen which in turn is coupled to the membrane concentration. To determine this coupling, we now consider the nutrient concentration in the lumen and ECS.

4.8.2 Lumen/ECS solution

4.8.2.1 Boundary layer analysis

Equation (4.58) is a singular perturbation problem, due to the small parameter ε^2 multiplying the highest order derivative in s . Investigating the dominant balance of terms suggests the existence of a boundary layer at the end of the streamlines in the lumen and ECS, where diffusion along streamlines dominates. Therefore, care must be taken in matching the outer solution to the respective boundary conditions.

We first investigate the putative boundary layer at the lumen and ECS exits. To maintain a dominant balance of advection and diffusion along streamlines, s must scale with ε^2 . We introduce an $O(1)$ variable $\hat{s}$ and scale such that $s = n + \varepsilon^2 \hat{s}$ where $n = 1, 3$ in the lumen and ECS respectively. Equation (4.58) then becomes

$$\bar{\mathcal{P}}_i \frac{\partial \hat{c}_i}{\partial \hat{s}} = \varepsilon^2 \frac{\partial}{\partial \psi} \left(r^2 l_{\psi,i} \tilde{U}_i \frac{\partial \hat{c}_i}{\partial \psi} \right) + \frac{\partial}{\partial \hat{s}} \left(\frac{1}{l_{\psi,i} \tilde{U}_i} \frac{\partial \hat{c}_i}{\partial \hat{s}} \right), \quad (4.74)$$

subject to

$$\frac{W_i}{l_{\psi,i} \tilde{U}_i} \frac{\partial \hat{c}_i}{\partial \hat{s}} - \varepsilon^2 r U_i \frac{\partial \hat{c}_i}{\partial \psi} = 0 \quad \text{at} \quad \hat{s} = 0, \quad \psi \in [0, \psi_{l,crit}) \text{ and } \psi \in (\psi_{e,min}, \psi_{e,max}), \quad (4.75)$$

at the bioreactor outlet. At leading order in ε , (4.74) – (4.75) becomes

$$\bar{\mathcal{P}}_i \frac{\partial \hat{c}_i}{\partial \hat{s}} = \frac{\partial}{\partial \hat{s}} \left(\frac{1}{l_{\psi,i} \tilde{U}_i} \frac{\partial \hat{c}_i}{\partial \hat{s}} \right), \quad (4.76)$$

subject to

$$\frac{\partial \hat{c}_i}{\partial \hat{s}} = 0 \quad \text{at} \quad \hat{s} = 0, \quad \psi \in [0, \psi_{l,crit}) \text{ and } \psi \in (\psi_{e,min}, \psi_{e,max}). \quad (4.77)$$

Equation (4.76) is satisfied by the general solution

$$\hat{c}_i = A_1(\psi) + A_2(\psi) \exp \left(\bar{\mathcal{P}}_i l_{\psi,i} \int \tilde{U}_i d\hat{s} \right), \quad (4.78)$$

and solving subject to (4.77) we see that $A_2 = 0$. A_1 can be solved for by matching into the outer solution, which shows that the concentration remains constant along

streamlines in the boundary layer and equal to the concentration entering the boundary layer. Therefore, this region is not a boundary layer at leading order (though we note it would affect higher-order terms).

We now investigate the lumen boundary layer at the lumen-membrane interface. This boundary layer is of $O(\varepsilon)$ thickness, given that in this region it is consistent to scale r and W_l as well as s . Therefore, we scale $s = 1 + \varepsilon\hat{s}$, $r = 1 + \varepsilon\hat{r}$ and $W_l = \varepsilon\hat{W}_l$ in the lumen. Using these scalings, (4.58) becomes

$$\bar{\mathcal{P}}_l \frac{\partial \hat{c}_l}{\partial \hat{s}} = \varepsilon^2 \frac{\partial}{\partial \psi} \left((1 + \varepsilon\hat{r})^2 l_{\psi,i} \hat{U}_l \frac{\partial \hat{c}_l}{\partial \psi} \right) + \frac{\partial}{\partial \hat{s}} \left(\frac{1}{l_{\psi,i} \hat{U}_l} \frac{\partial \hat{c}_l}{\partial \hat{s}} \right), \quad (4.79)$$

where

$$\tilde{U}_l = \sqrt{\varepsilon^2 U_l^2 + W_l^2} = \sqrt{\varepsilon^2 U_l^2 + \varepsilon^2 \hat{W}_l^2} = \varepsilon \sqrt{U_l^2 + \hat{W}_l^2} = \varepsilon \hat{\tilde{U}}_l, \quad (4.80)$$

and we let $\tilde{U}_l = \varepsilon \hat{\tilde{U}}_l$. The lumen-membrane interfacial condition (4.62) becomes

$$\varepsilon(1 + \varepsilon\hat{r})W_l \frac{\partial \hat{c}_l}{\partial \psi} + \frac{U_l}{l_{\psi,l} \hat{\tilde{U}}_l} \frac{\partial \hat{c}_l}{\partial \hat{s}} = \phi_m^2 \left(\varepsilon^2 r W_m \frac{\partial c_m}{\partial \psi} + \frac{U_m}{l_{\psi,m} \tilde{U}_m} \frac{\partial c_m}{\partial s} \right) \quad \text{at } \hat{s} = 0, \psi \in [\psi_{l,crit}, \psi_{l,max}]. \quad (4.81)$$

At $O(1)$, (4.79) reduces to (4.76) and thus gives the general solution (4.78). Equation (4.81) becomes

$$\frac{1}{l_{\psi,l}} \frac{\partial \hat{c}_l}{\partial \hat{s}} = \frac{\phi_m^2}{l_{\psi,m}} \frac{\partial c_m}{\partial s} \quad \text{at } \hat{s} = 0, \psi \in [\psi_{l,crit}, \psi_{l,max}], \quad (4.82)$$

noting that $\tilde{U}_m = U_m$ at leading order, and $\hat{W}_l = 0$ given by the no-slip condition at the lumen-membrane interface (2.38) means that $\hat{\tilde{U}}_l = U_l$. We know the solution to c_m in terms of the concentration at the lumen-membrane interface $c_l|_{[l,m]}$ given by Equation (4.73). Substituting (4.78) and (4.73) into (4.82), we find that $A_2 = \mathcal{A}$, and from matching into the outer solution in the lumen, we know that $A_1 = c_l|_{s \uparrow 1}$, giving

$$\hat{c}_l = c_l|_{s \uparrow 1} + \mathcal{A} \exp \left(\bar{\mathcal{P}}_l l_{\psi,l} \int \tilde{U}_l d\hat{s} \right). \quad (4.83)$$

From the continuity of normal fluid flux condition (2.38), we can write

$$\int \tilde{U}_l d\hat{s} \Big|_{\hat{s}=0} = \int U_l d\hat{s} \Big|_{\hat{s}=0} = \phi_m \int U_m ds \Big|_{s=1} = 0, \quad (4.84)$$

and thus using (4.83) we can express the lumen-membrane interfacial concentration as

$$c_l|_{[l,m]} = c_l|_{s\uparrow 1} + \mathcal{A}. \quad (4.85)$$

Therefore

$$c_m = c_l|_{s\uparrow 1} + \mathcal{A}((s-1)(R_{m0}-1)+1)^{-\xi}, \quad (4.86)$$

where $\mathcal{A}$ can be solved for using (4.69) to give

$$\mathcal{A} = \frac{-b - \sqrt{b^2 - 4ac}}{2a}, \quad (4.87)$$

and

$$a = \phi_m^2 \xi R_{m0}^{-(2\xi+1)}, \quad (4.88a)$$

$$b = \phi_m^2 \xi R_{m0}^{-(\xi+1)} (K_M + c_l|_{s\uparrow 1}) - \varepsilon \delta \phi_c^2 V_{max} R_{m0}^{-\xi}, \quad (4.88b)$$

$$c = -\varepsilon \delta \phi_c^2 V_{max} c_l|_{s\uparrow 1}. \quad (4.88c)$$

4.8.2.2 Lumen/ECS outer solution

From Equation (4.59), $\tilde{U}_i = W_i$ at leading order in ε . Equation (4.58) at leading order becomes

$$\varepsilon^2 \mathcal{P}_i \frac{\partial c_i}{\partial s} = \frac{\partial}{\partial \psi} \left(r^2 l_{\psi,i} W_i \frac{\partial c_i}{\partial \psi} \right), \quad i = l, e, \quad (4.89)$$

noting that $W_i \geq 0$ in our problem. Equation (4.89) takes the form of a coupled system of nonlinear 1D heat equations with non-constant coefficients (i.e. parabolic PDEs) with s as our time-like variable. Owing to our asymptotic reduction, we see that Equation (4.89) is first-order with respect to s . Therefore, we require initial conditions in s to solve for transport in the lumen and ECS, which come from inlet conditions (4.63a), (4.66). Additionally, the symmetry and no flux condition at leading order becomes

$$\frac{\partial c_i}{\partial \psi} = 0, \quad \text{at } \psi = 0, \psi_{e,max}. \quad (4.90)$$

We solve (4.89) using the Method of Lines, whereby we discretise along the ψ -coordinate, resulting in a linear system of ODEs with respect to s which can be solved readily using MATLAB's in-built ODE solvers.

4.8.3 Waste transport

We solve the waste transport problem similarly to the nutrient transport problem. As in the derivation of nutrient transport concentration in the membrane (4.86), we solve (4.68) swapping c_i for w_i and $\mathcal{P}_i$ for $\mathcal{P}_{w,i}$ subject to continuity of concentration

$$w_l = w_m \quad \text{at} \quad s = 1, \psi \in [\psi_{l,crit}, \psi_{l,max}), \quad (4.91)$$

and the leading-order effective boundary condition

$$\frac{\phi_m^2}{l_{\psi,m}} \frac{\partial w_m}{\partial s} = \varepsilon \phi_c^2 \overline{\mathcal{R}}(c_m) \quad \text{at} \quad s = 2, \psi \in (\psi_{e,min}, \psi_{e,crit}], \quad (4.92)$$

giving

$$w_m = w_l|_{s \uparrow 1} + \mathcal{B}((s-1)(R_{m0}-1)+1)^{-\xi}, \quad (4.93)$$

where $\mathcal{B}$ is

$$\mathcal{B} = -\frac{\varepsilon \phi_c^2 \overline{\mathcal{R}}(c_m) \ln R_{m0}}{\varepsilon^2 \mathcal{P}_{w,l} \kappa (P_e - P_l) R_{m0}^{-(\xi+1)}}. \quad (4.94)$$

We now proceed in Section 4.9 to solve for metabolite concentration throughout our bioreactor system, utilising typical parameter values outlined in Table 4.1

4.9 Results

4.9.1 Typical operating conditions

We first consider steady fluid flow and nutrient transport under typical bioreactor operating conditions (summarised in Table 4.1) as shown in Figure 4.4a. In the lumen, the transformed governing equation for metabolite transport (4.89) is a nonlinear diffusion equation. Solving subject to constant inlet concentration (4.55), the lumen concentration is constant along streamlines and therefore equal to the prescribed inlet concentration. There is a boundary layer in the lumen region at the lumen-membrane interface where streamwise advection and diffusion balance (4.83).

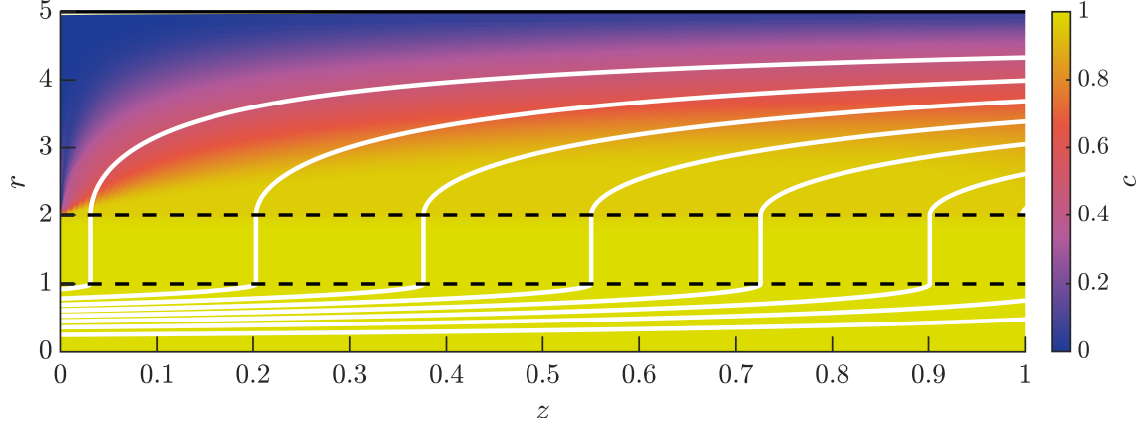
In Equations (4.73) and (4.86), we see that the membrane metabolite concentration depends on the ratio of advective to diffusive mass transport effects, characterised by the Péclet number featured in parameter ξ . An increase in the Péclet number, corresponding to an increase in advective mass transport effects, leads to a steeper decrease in metabolite concentration across the membrane wall. However, axial variations in the membrane metabolite concentration are a direct result of axial variations

in the transmural pressure only, which arise in the definition of parameter ξ . Therefore, although diffusive mass transport effects are important in determining nutrient transport across the membrane, it is advective mass transport effects that set the axial variation in membrane nutrient concentration. Therefore, we expect to see a higher nutrient concentration delivered to the cells where the radial pressure drop across the membrane wall is highest. Any leftover nutrient is then washed away by a prescribed flow in the ECS.

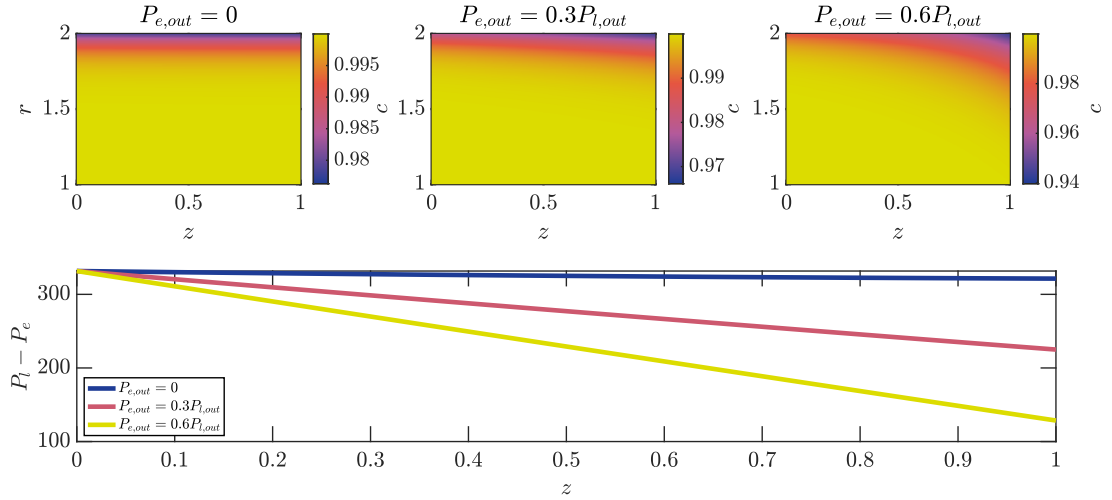
Focusing on the membrane in Figure 4.4b (left), we see that nutrient transport to the outer membrane interface under typical operating conditions is relatively uniform due to a transmural pressure drop that remains relatively constant in the axial direction. If we fix lumen and ECS inlet pressures and vary the transmural pressure drop at the outlet (e.g. by varying the ECS outlet pressure, $P_{e,out}$), we observe a strong dependence of nutrient delivery on the transmural pressure drop in Figure 4.4b. Towards the bioreactor outlet where the transmural pressure drop decreases, advective mass transport across the membrane wall decreases, and hence nutrient delivery also decreases (corresponding to a lower value of concentration). This spatial heterogeneity of nutrient delivery means that cells are receiving unequal amounts of nutrient depending on where they are seeded along the length of the membrane. This is of particular concern in engineering homogeneous tissue constructs, which have a uniform nutrient requirement, as heterogeneous nutrient delivery will lead to heterogeneous tissue growth. To achieve uniform nutrient delivery across the membrane wall requires a uniform transmural pressure drop irrespective of the given operating conditions.

4.9.2 Homogeneous vs. heterogeneous permeability distributions

As we established earlier in Equations (4.73) and (4.86), axial variations in membrane nutrient concentration arise solely from axial variations in advective mass transport, which is a function of the local permeability and transmural pressure drop. One way to generate uniform nutrient delivery across the membrane wall is to use a membrane with a heterogeneous permeability, similarly to Chapter 2. At positions where advective nutrient flux across the membrane wall is smaller due to a smaller transmural pressure, introducing a larger permeability will reduce the resistance for advective transport across these regions, thus raising the flux (and vice versa). In Chapter 2, we derive an analytic representation of this favourable permeability that exactly counteracts axial variations in transmural pressure (2.53). This heterogeneous permeability



(a) Nutrient concentration profile under typical experimental conditions as outlined in Table 4.1. The black dashed lines denote the interfaces between the lumen ($r \in (0,1)$), the membrane ($r \in (1,2)$) and the ECS ($r \in (2,5)$). Fresh nutrient enters through the lumen inlet at $z = 0$ and transports either along the length of the lumen or across the membrane wall to be consumed by cells seeded on the outer membrane surface at $r = 2$. Unreacted nutrient is washed away by flow in the ECS. Solid white lines denote streamlines beginning at the lumen inlet, which correspond to different particle paths that the nutrient can take.

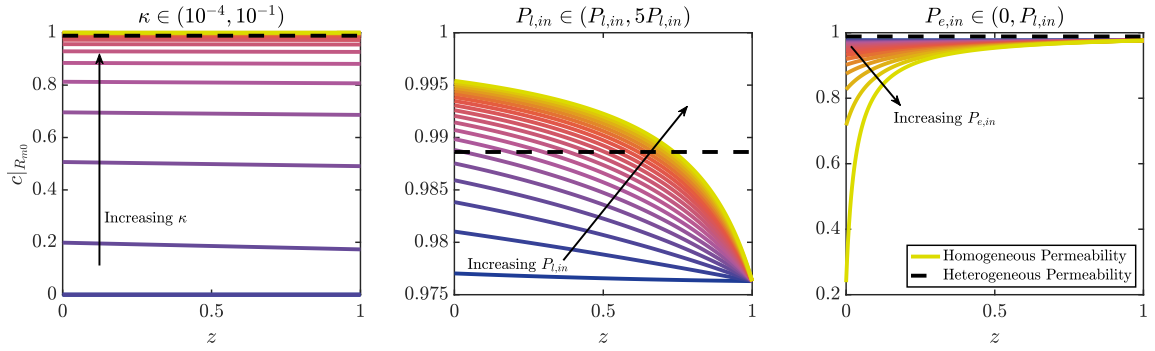


(b) Nutrient concentration profile in the membrane under varying axial pressure drops holding $P_{l,in}, P_{l,out}, P_{e,in}$ constant. Axial heterogeneity in nutrient concentration increases as axial variations in the transmembrane pressure drop increase. In particular, at a given axial position, the nutrient concentration delivered to the cells seeded at $r = 2$ decreases when the transmembrane pressure drop decreases.

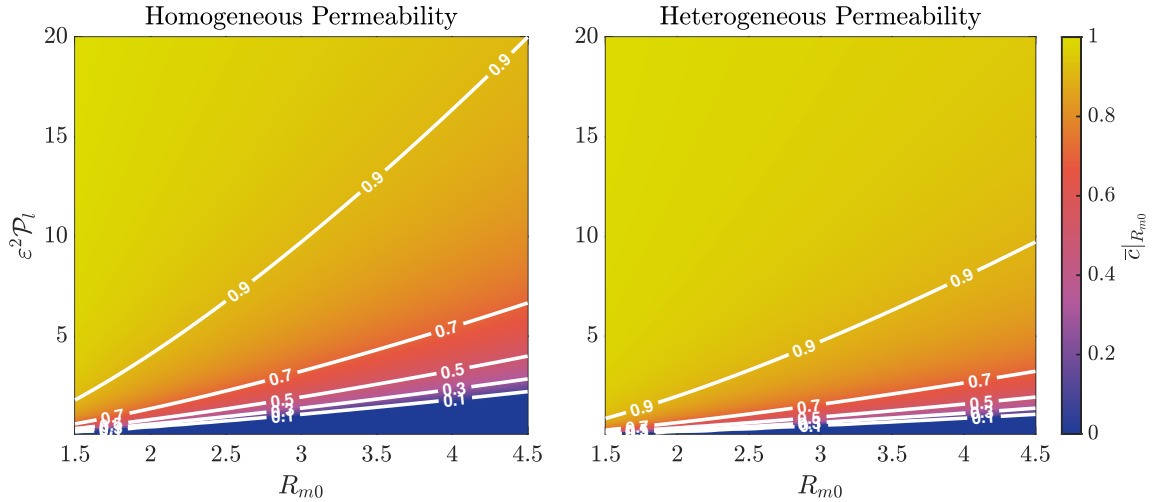
Figure 4.4: Nutrient concentration profiles across a cross-section of the bioreactor setup.

distribution can be applied here to achieve a uniform nutrient concentration at the cell layer, regardless of the balance between advective and diffusive mass transport effects.

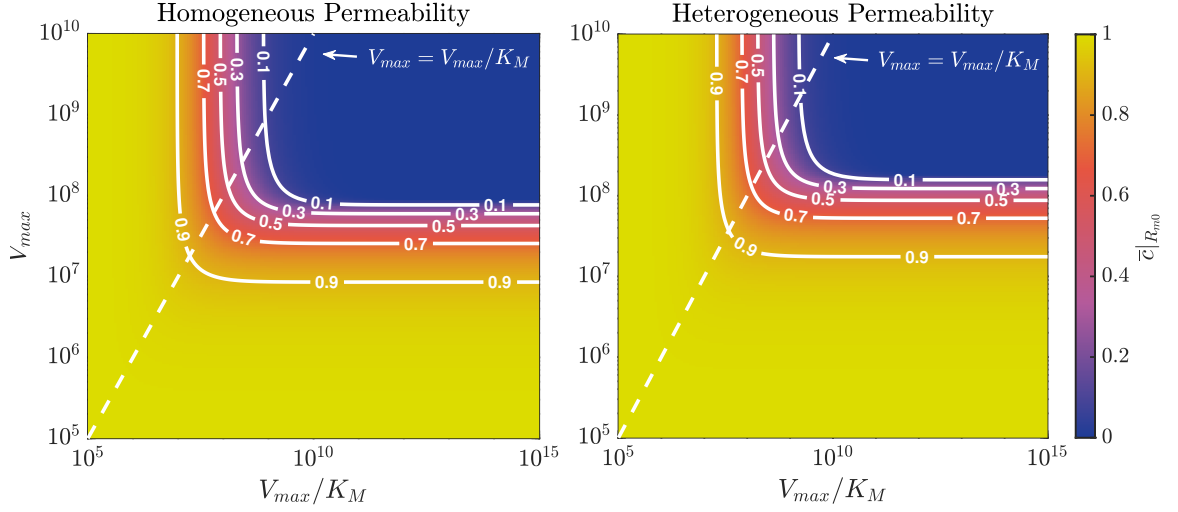
Figure 4.5a shows the concentration of nutrient delivered to cells seeded at the outer membrane wall as a function of the operating conditions, comparing a homogeneous membrane permeability to the heterogeneous permeability given in (2.53) under typical bioreactor operating conditions. As we can see, the heterogeneous permeability distribution exactly cancels out the axial variations in c_m from the transmural pressure drop, resulting in a membrane concentration profile that is axially uniform.



(a) Varying permeability, κ (left), lumen inlet pressure, $P_{l,in}$ (middle), and ECS inlet pressure $P_{e,in}$ (right). Coloured lines denote the concentration profile at R_{m0} with a homogeneous membrane permeability, and the black dotted line is the concentration profile with a heterogeneous membrane permeability. Note that the membrane concentration with a heterogeneous permeability is invariant to changes in the selected parameters.



(b) Comparing the average nutrient concentration at the outer membrane wall, $\bar{c}|_{R_{m0}}$ with a homogeneous vs ideal heterogeneous permeability (2.53) under varying membrane thicknesses R_{m0} and reduced Péclet numbers $\varepsilon^2 \mathcal{P}_l$. The solid white lines denote contours of constant nutrient concentration.



(c) Comparing the average nutrient concentration at the outer membrane wall, $\bar{c}|_{R_{m0}}$ with a homogeneous vs ideal heterogeneous permeability whilst varying the maximum nutrient uptake rate V_{max} and varying the ratio of kinetic parameters V_{max} to K_M . From (4.14), V_{max} and K_M scale with $1/C_{in}^*$. Therefore an increase in V_{max} whilst holding V_{max}/K_M constant corresponds to a decrease in dimensional inlet concentration C_{in}^* .

Figure 4.5: Comparing the nutrient concentration delivered to the outer membrane wall with a homogeneous vs a heterogeneous membrane permeability under varying structural and operating conditions.

For the considered model parameters, the heterogeneous permeability distribution also leads to a larger average nutrient concentration. As the desired heterogeneous permeability distribution is a function of the lumen and ECS fluid pressures, any variations in $P_{l,in}$ and $P_{e,in}$ will alter the appropriate permeability distribution. However, because this will cancel out the fluid pressure terms in our solution to c_m , our concentration profile remains unchanged by variations in these parameters.

Our theoretically favourable solution does, however, depend on both the membrane thickness and the lumen Péclet number. Figure 4.5b shows how increasing the membrane thickness decreases the nutrient concentration at the outer wall as the radial membrane fluid flux decreases, thus decreasing advective mass transport. As might be expected, an increase in the lumen Péclet number increases advective mass transport, therefore increasing nutrient delivery across the membrane wall. In both cases, the theoretically optimal membrane permeability distribution (2.53) delivers a much higher nutrient concentration to the outer wall compared to a membrane with constant membrane permeability. This suggests that in all scenarios, a heterogeneous permeability distribution is of significant benefit for both efficient and uniform nutrient transport.

Utilising Michaelis-Menten reaction kinetics in our model means that we can investigate nutrient delivery to cells even in regimes of limited nutrient availability. In Figure 4.5c, we investigate how a decrease in inlet nutrient concentration, corresponding to an increase in V_{max} , impacts the average concentration at the outer membrane wall. Given that both V_{max} , K_M are inversely proportional to C_{in}^* as given by (4.14), we plot $V_{max}/K_M = V_{max}^* L^{*2}/K_M^* \mathcal{D}_c^*$ on the x -axis so that C_{in}^* varies along the y -axis only. Variations in the positive x -direction therefore correspond to an increase in the ratio of dimensional kinetic parameters V_{max}^*/K_M^* , an increase in bioreactor length L^* or a decrease in the cell-layer solute diffusivity $\mathcal{D}_c^*$.

When the Michaelis constant K_M is small compared to the maximum uptake rate V_{max} , nutrient uptake is constant and limited predominantly by the maximum uptake rate, as might be expected physically. Therefore as V_{max} increases when V_{max}/K_M is large, nutrient uptake increases and thus the concentration at the outer membrane wall decreases. This means that when C_{in}^* is decreased (V_{max} is increased) while holding V_{max}/K_M constant, a larger proportion of the inlet nutrient is taken up by the cells.

Conversely when V_{max}/K_M is small, the Michaelis constant K_M is the limiting parameter. In this scenario, variations in V_{max} have little impact on nutrient uptake, corresponding to little change in the concentration at the outer membrane wall. In the interval $V_{max}/K_M \in (10^7, 10^{10})$, we note a transitional region where both V_{max} and K_M are of comparable importance in nutrient uptake. For a sufficiently large maximum reaction rate $V_{max} \geq V_{max}/K_M$, nutrient uptake in this regime is a function of V_{max}/K_M only. Variations in V_{max} , corresponding to variations in inlet concentration, do not impact uptake rate due to a dominant balance of kinetic parameters in the expression for Michaelis-Menten reaction kinetics in (4.14).

Figure 4.5c also reveals that the nutrient concentration at the membrane-ECS interface is greater in the ideal heterogeneous membrane case for corresponding values of V_{max} and K_M . This tells us that, for a given set of kinetic parameters, we can introduce less nutrient into the inlet of a heterogeneous membrane bioreactor (corresponding to a greater V_{max}), yet still deliver the same amount of nutrient to the cell layer seeded at the outer wall of a homogeneous membrane bioreactor. This is important in understanding how much nutrient is actually required to be introduced into the bioreactor to understand and optimise operating efficiency, especially in the case where nutrient is expensive or in limited availability. Across a range of dimensional inlet nutrient concentrations and kinetic parameters, the nutrient uptake rate in the

cell layer is greater when using the ideal heterogeneous membrane permeability setup compared to a homogeneous membrane permeability setup.

4.9.3 Waste metabolite transport

Using the same methodology as Section 4.9.2, we can model waste metabolite transport through our bioreactor system. This is of particular interest in understanding the intrinsic relationship between maximising nutrient delivery and waste removal, and how both factors can be affected by changes in structural and operating parameters.

Figure 4.6 shows how the mean and range of waste metabolite concentrations at the outer wall varies under different operating conditions. Similarly to nutrient concentration in Figure 4.5, we see that any change in parameter value which increases advective mass transport (either by increasing the pressure drop or decreasing resistance to flow across the membrane) increases flux across and out of the membrane. For the same reasons that this increases nutrient concentration delivery to the outer membrane wall, this increase in advective mass transport also washes away any waste metabolite produced more efficiently, thus decreasing the waste metabolite concentration at the outer wall. Interestingly, we see that increasing the inlet ECS pressure, corresponding to an increase in flow rate in the ECS, actually increases waste concentration at the outer membrane wall compared to lower ECS pressures. As the inlet ECS pressure increases towards the inlet lumen pressure, the pressure drop across the membrane decreases, and thus fluid flux across the membrane wall also decreases. Therefore, waste product is removed less easily. These results suggest that the most important mechanism for waste product removal in HFMBs is maximising fluid flow across the membrane wall rather than increasing the axial flow rate through the ECS.

Similarly to before, we note that the heterogeneous permeability distribution we derive results in both a uniform production of waste metabolite, and an overall reduction in waste concentration compared to a homogeneous permeability for the majority of parameter values. We conclude that the heterogeneous membrane allows for the delivery of a uniform nutrient concentration at higher concentrations compared to the homogeneous case under the same operating conditions, and washes away waste metabolites more efficiently.

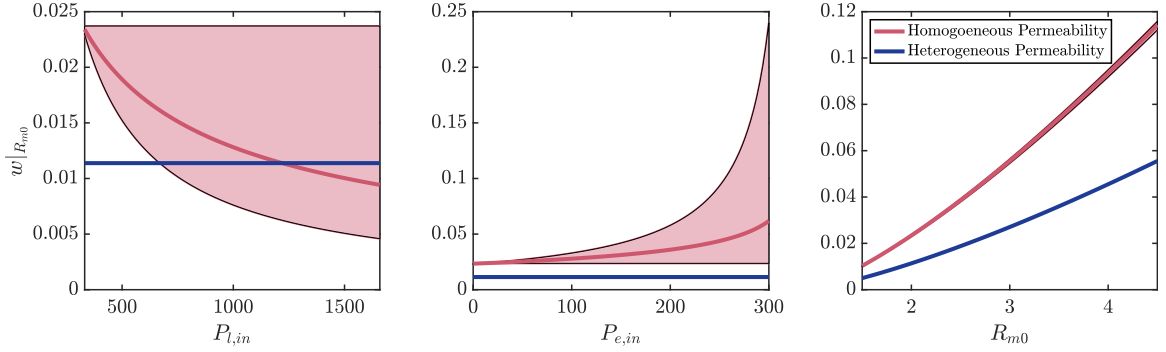


Figure 4.6: Waste metabolite concentration at the outer membrane wall under varying lumen inlet pressure (left), ECS inlet pressure (middle) and membrane wall thickness (right). The red line denotes the average concentration with a homogeneous permeability with the shaded red region denoting the maximum and minimum concentrations. The blue line denotes the concentration under the heterogeneous permeability distribution.

4.10 Discussion

In this Chapter, we present a 2D axisymmetric model for nutrient and waste transport through a hollow fibre membrane bioreactor. Exploiting the long, thin geometry and utilising a coordinate transformation into a streamfunction-arclength formulation, we used an asymptotic analysis to systematically reduce the dimensionality of our governing equations and derive a reduced-order system which we solved efficiently using the Method of Lines. We interpreted the results of our analysis to understand how the membrane permeability can be manipulated to achieve uniform nutrient transport to the cell layer, as well as to understand how to tune physical operating and geometric parameters to improve the balance between nutrient delivery and waste product removal.

Our systematic derivation of a reduced model means that we can solve for the nutrient transport problem with greater speed and efficiency compared to full multiphysics simulations in software packages such as COMSOL. A full simulation of nutrient transport through our bioreactor design under typical operating conditions using a fine mesh takes on average around seven minutes to compute in COMSOL on a standard desktop computer. Alternatively, a full simulation of our reduced model takes around 1 minute for a comparative mesh size. Better still, we are able to solve for the nutrient concentration profile through the membrane and at the outer membrane wall using our analytic solution as per Equation (4.73). Our analysis provides us with a full mechanistic understanding of nutrient delivery across the membrane,

which reveals to us the impact of system parameters on the model solution, and also speeds up sensitivity analysis considerably.

This model reduction and analytic solution allows us to understand the role of heterogeneous permeability distributions in achieving uniform nutrient delivery. From Equation (4.73), we have an explicit relationship between the nutrient concentration in the membrane and the membrane permeability, as well as an explicit understanding of how axial variations in the membrane flux leads to axial variations in nutrient concentration. This means that we can determine an analytic expression for the optimal membrane permeability that would cancel out these axial variations and lead to uniform nutrient delivery to the cell site. This is of particular importance for experimental design, whereby appropriate mathematical modelling can help inform the manufacture of membranes with the heterogeneous permeability distribution under desired operating conditions.

The heterogeneous permeability distribution corresponds to that which results in a uniform delivery of nutrient to a spatially-uniform cell layer of uniform cell type and seeding density. In the case of a heterogeneous cell seeding density or in a setup containing several different cell types, the effect of a spatially-varying nutrient demand will impact how the nutrient would be delivered most optimally, which in turn changes the corresponding heterogeneous permeability distribution. This Chapter presents a robust framework to carry out this analysis. If we know the explicit axial dependency of nutrient uptake in our cell layer, we can use the setup presented in this Chapter to determine a heterogeneous permeability that depends not only on advection across the membrane wall, but also on the spatially-varying reaction kinetics.

In our analysis of the nutrient and waste transport problem, it is clear that promoting advective mass transport not only improves nutrient delivery to the cell site, but also promotes the removal of waste products. However, in practice, an increase in advective mass transport comes at a cost of increased mechanical stress imparted on the cells. Cells are particularly sensitive to their local mechanical environment, which is of importance in regulating cell morphology and for mechanotransduction signalling pathways [14–16]. Excessive shear stresses can damage and even detach cells seeded to the membrane wall in an experimental setup, presenting a difficult trade-off between optimising the local chemical and mechanical cell environment. In our current model, the indirect impact of mechanical stress on nutrient uptake is not accounted for. However the derivation of the effective membrane-ECS interfacial condition holds for a generalised nutrient uptake reaction term, and therefore introducing reaction kinetics that depend on the local mechanical stress would allow us

to pursue this analysis further. Furthermore, the semi-analytic nature of the framework presented in this study presents a quick and efficient method for implementing optimisation methods to determine the optimal selection of structural and operating conditions that would lead to the desired trade-off between nutrient delivery and mechanical disruption.

This work is of particular importance in extending beyond traditional hollow fibre bioreactors to consider faster, more physiologically-relevant fluid flow problems. The framework presented in this Chapter can be used alongside any underlying 2D lubrication flow field, provided we can determine the accompanying streamfunction, either analytically or numerically.

The modelling approaches presented in this Chapter present a robust and flexible framework for analysis of nutrient transport in hollow fibre membrane bioreactor systems. With these tools, we have developed a mechanistic understanding of the system's response to varying structural and operating parameters, and the impact this has on the nutrient delivery/waste removal problem. This lays the groundwork for a plethora of mathematical extensions that more accurately describe the local chemical and mechanical environment of the cell layer, and provide us the tools to quickly and accurately traverse a large parameter space to determine the optimal bioreactor setup for uniform nutrient delivery to the cells.

Chapter 5

Boundary layer analysis of plug-to-lubrication flow transitions mediated by a porous medium

5.1 Introduction

Until now, we have focused on solutions to lubrication flow where viscous forces dominate nonlinear inertia (i.e. the reduced Reynolds number $\varepsilon Re = \varepsilon \rho^* W_{l,in}^* R_{l0}^* / \mu^* \ll 1$). While this regime is valid for many types of bioreactor operating conditions explored theoretically in the literature, it fails to be valid if we seek to emulate faster flows. This is of particular interest if we wish to provide larger mechanical stresses to cells *in vitro*, as well as capture transitional (laminar) behaviour from inlet plug flow to lubrication flow.

The asymptotic structure of plug-to-Poiseuille flow transitions in a straight rigid tube with impermeable walls was first considered by Van Dyke [109] and Wilson [110], and was subsequently validated numerically by Bodoia and Osterle [111]. It was found that Blasius boundary layers at the channel walls grow proportionally to the square root of the distance from the inlet at large Reynolds numbers, flanking an inviscid core of plug flow.

In aeronautical engineering, the transition from plug flow to Poiseuille flow at high Reynolds numbers past a porous plate with constant suction was considered by Thwaites as a mechanism to postpone boundary layer separation [112]. Thwaites showed that in the boundary layer near the porous surface, for distances close to the inlet, the solution is the same as the Blasius solution without suction. Iglisch later obtained a complete numerical solution by taking the von Mises transformation of the boundary layer equations obtained by Thwaites [113]. For large distances from the

leading edge, Griffith and Meredith showed that the boundary layer under constant suction reaches a spatially uniform thickness [114], unlike Blasius boundary layers which grow proportionally to the square root of the distance from the leading edge. However, we note the solution becomes more complex with the consideration of a spatially-dependent suction profile [115].

In this Chapter, we consider the canonical problem of 2D plug-to-lubrication flow transitions in channels mediated by a porous membrane region. A plug flow profile is prescribed at the inlet of the lumen and ECS channels, which then transitions to a parabolic flow profile along each channel. The boundary layer structure describing the flow transitions depends on the Reynolds number of the flow. We seek to understand this asymptotic structure, and to determine under what Reynolds number flows and channel lengths do we recover lubrication flow in the outer flow problem. We note that in the context of this Chapter, “transitional” flow refers to transitions from plug flow to lubrication flow. We present this problem in a 2D Cartesian geometry to provide fundamental insights into the coupled flow transition, which can then be applied to a wide range of physical problems (e.g. extend to axisymmetric geometries).

Considering the long thin limit (i.e. $\varepsilon = R_{i0}^*/L^* \ll 1$), we consider two further sublimits: moderate Reynolds number ($Re = O(1)$) and large Reynolds number ($Re \gg 1$) flow, in each case in the laminar regime. In the first sublimit, we identify an inlet boundary layer in the lumen and ECS, with comparable transverse and axial length, that describes the plug-to-lubrication flow transition via the 2D Navier-Stokes equations. In the second sublimit, we identify the formation of Blasius boundary layers at the lumen and ECS channel walls with an inviscid core of plug flow. Once the boundary layers have grown such that they are not asymptotically small relative to the inviscid core, we identify another (transitional) boundary layer in the lumen, membrane and ECS. These boundary layers characterise the full plug-to-lubrication flow transition in the lumen and ECS, coupled by flow across the membrane wall. The transitional boundary layer persists over a length scale proportional to the Reynolds number of the flow Re , indicating that faster flows will transition from plug to lubrication flow over a larger length scale.

5.2 Model setup

To capture the most general transitional flow behaviour across all length scales, we consider steady two-dimensional flow through two parallel channels of infinite length, separated by a porous membrane, as illustrated in Figure 5.1. While we consider

an infinite length, we later consider how the magnitude of the reduced Reynolds number, εRe , affects the observable boundary layer structure in a finite channel. For mathematical convenience, we proceed with a 2D Cartesian geometry with spatial coordinates $\mathbf{y}^* = (y^*, z^*)$, noting that results will be qualitatively comparable to the 2D axisymmetric geometry in the experimental setup. With the longitudinal z^* -axis coinciding with the lumen centreline, we define $\hat{\mathbf{e}}_y, \hat{\mathbf{e}}_z$ as unit vectors in the positive transverse y^* -direction and axial z^* -direction respectively. We define a lumen of height R_{l0}^* , above which sits a porous membrane that interfaces with the lumen at $y^* = R_{l0}^*$ and has thickness $R_{m0}^* - R_{l0}^*$. Above the membrane is the parallel channel, an extra-capillary space (ECS) which is bounded by a rigid impermeable outer wall of height $y^* = R_{e0}^* > R_{m0}^*$. Plug flow of uniform axial velocity $W_{l,in}^*$ and $W_{e,in}^*$ enters the lumen and ECS respectively at $z^* = 0$. Fluid can transport across the length of the lumen and ECS or across the membrane wall. The model is symmetric about the lumen centreline $y^* = 0$, and we present results for positive y^* only.

5.3 Governing equations

In the lumen and ECS, we describe fluid flow using steady Navier–Stokes equations for an incompressible Newtonian fluid of constant density ρ^* and dynamic viscosity μ^* , and neglect external body forces,

$$\nabla^* \cdot \mathbf{U}_i^* = 0, \quad \rho^* (\mathbf{U}_i^* \cdot \nabla^*) \mathbf{U}_i^* = -\nabla^* P_i^* + \mu^* \nabla^{*2} \mathbf{U}_i^*, \quad (5.1)$$

where $\mathbf{U}_i^* = U_i^* \hat{\mathbf{e}}_y + W_i^* \hat{\mathbf{e}}_z$ is the fluid velocity vector, P_i^* is the fluid pressure, and $i = l, e$ denotes the lumen and ECS respectively. In the membrane, we model flow using steady incompressible Darcy equations

$$\nabla^* \cdot \mathbf{U}_m^* = 0, \quad \phi \mathbf{U}_m^* = -\frac{k^*}{\mu^*} \nabla^* P_m^*, \quad (5.2)$$

where $\mathbf{U}_m^* = U_m^* \hat{\mathbf{e}}_y + W_m^* \hat{\mathbf{e}}_z$ is the membrane fluid velocity vector, P_m^* is the membrane fluid pressure, and ϕ and k^* are the membrane porosity and permeability respectively, which are assumed to be constant and isotropic.

5.4 Boundary Conditions

To drive fluid flow through the lumen and ECS inlet, we prescribe an inlet plug flow with uniform axial velocity, so that

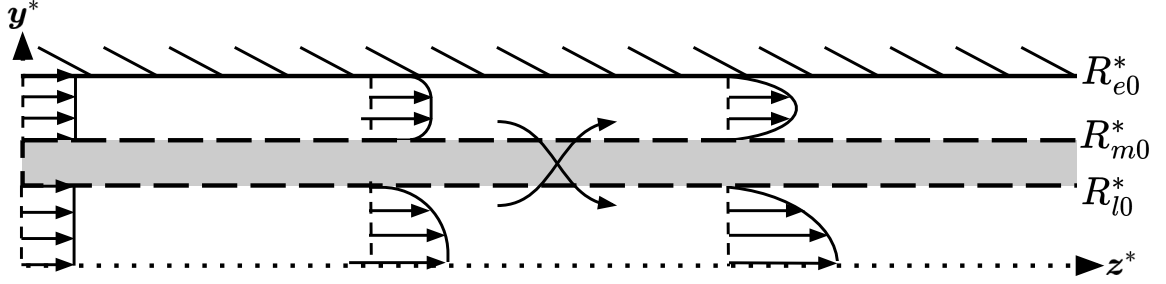


Figure 5.1: Dimensional model description. Plug flow enters from the lumen and ECS inlet, which transitions to lubrication flow in the positive z^* -direction. Fluid can also flow across the membrane between the lumen and ECS.

$$\mathbf{U}_i^* \cdot \hat{\mathbf{e}}_z = W_{i,in}^* \quad \text{at} \quad z^* = 0. \quad (5.3)$$

We also enforce that the downstream flow is finite in the far-field. At the lumen centreline, we prescribe symmetry conditions

$$U_l^* = \frac{\partial W_l^*}{\partial y^*} = 0 \quad \text{at} \quad y^* = 0, \quad (5.4)$$

and at the lumen–membrane ($y^* = R_{l0}^*$) and membrane–ECS ($y^* = R_{m0}^*$) interfaces, we prescribe continuity of normal flux, no axial slip, and continuity of normal stress

$$\mathbf{U}_i^* \cdot \hat{\mathbf{e}}_y = \phi \mathbf{U}_m^* \cdot \hat{\mathbf{e}}_y, \quad \mathbf{U}_i^* \cdot \hat{\mathbf{e}}_z = 0, \quad \hat{\mathbf{e}}_y \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{e}}_y = -P_m^*, \quad (5.5)$$

where $\boldsymbol{\sigma}_i^*$ is the viscous fluid stress tensor defined in (2.12). At the outer ECS wall, we prescribe no slip and no flux conditions

$$\mathbf{U}_e^* = \mathbf{0} \quad \text{at} \quad y^* = R_{e0}^*. \quad (5.6)$$

Lastly, we prescribe no flux through the axial end of the membrane wall

$$\mathbf{U}_m^* \cdot \hat{\mathbf{e}}_z = 0 \quad \text{at} \quad z^* = 0. \quad (5.7)$$

5.5 Nondimensionalisation

In contrast to the lubrication scalings we have used in previous chapters, here (and with the benefit of hindsight) we scale space with the lumen channel height R_{l0}^* , velocity with the inlet lumen velocity $W_{l,in}^*$, and we choose a pressure scaling where we presuppose that an axial pressure gradient eventually balances viscous terms. This

will allow us to conduct our analysis in the order in which information propagates through the system (largely with the flow). Nondimensional scalings are given by

$$\mathbf{y}^* = R_{l0}^* \mathbf{y}, \quad (\mathbf{U}_i^*, \mathbf{U}_m^*) = W_{l,in}^* (\mathbf{U}_i, \mathbf{U}_m), \quad (P_i^*, P_m^*) = \frac{\mu^* W_{l,in}^*}{\varepsilon R_{l0}^*} (P_i, P_m), \quad (5.8)$$

where $\varepsilon = R_{l0}^*/L^*$ is the characteristic lumen aspect ratio given a characteristic axial length scale L^* . The continuity equation and the Navier–Stokes equations in the lumen and ECS (5.1) become

$$\nabla \cdot \mathbf{U}_i = 0, \quad \varepsilon Re (\mathbf{U}_i \cdot \nabla) \mathbf{U}_i = -\nabla P_i + \varepsilon \nabla^2 \mathbf{U}_i, \quad (5.9)$$

where the Reynolds number $Re = \rho^* W_{l,in}^* R_{l0}^*/\mu^*$. The Darcy equations in the membrane (5.2) becomes

$$\nabla \cdot \mathbf{U}_m = 0, \quad \phi \mathbf{U}_m = -\varepsilon \kappa \nabla P_m, \quad (5.10)$$

where $\kappa = k^*/\varepsilon^2 R_{l0}^{*2}$. Boundary conditions (5.3) – (5.7) become

$$W_l = 1, \quad W_m = 0, \quad W_e = W_{e,in} \quad \text{at} \quad z = 0, \quad (5.11a)$$

$$U_l = \frac{\partial W_l}{\partial y} = 0 \quad \text{at} \quad y = 0, \quad (5.11b)$$

$$U_i = \phi U_m, \quad W_i = 0, \quad -P_i + 2\varepsilon \frac{\partial U_i}{\partial y} = -P_m \quad \text{at} \quad y = 1, R_{m0}, \quad (5.11c)$$

$$U_e = W_e = 0 \quad \text{at} \quad y = R_{e0}. \quad (5.11d)$$

5.6 Parameter regimes

We consider the asymptotic structure of the flow profile for $\varepsilon \ll 1$ under two different operating regimes. We first consider $Re = O(1)$ as $\varepsilon \rightarrow 0$, and show that at leading order in ε , the outer flow problem is lubrication flow in the lumen and ECS outer regions and Darcy flow across the membrane wall. The transition from plug to lubrication flow occurs in an $O(1)$ inner region at the inlet. It is worth noting here that $Re \ll 1$ is a regular limit of this problem. Then, we consider the large Reynolds number case $Re \gg 1$. To do so, it is helpful to consider the distinguished limit $\varepsilon Re = O(1)$ where $1 \ll 1/\kappa \ll 1/\varepsilon \sim Re$. We later see that the weakly-permeable wall limits $1 \ll 1/\kappa \ll Re \ll 1/\varepsilon$ and $1 \ll 1/\kappa \ll 1/\varepsilon \ll Re$ are regular limits of this formulation. Throughout our analysis we note that the nondimensional permeability

κ is small but is formally retained as an $O(1)$ quantity for mathematical convenience. This is similar to the approach adopted by Dalwadi et al. [69].

5.7 Moderate Reynolds number: $Re = O(1)$

Using the method of matched asymptotic expansions, we seek a solution to fluid flow through our system by exploiting the small parameter ε . In this regime we take $Re = O(1)$, noting that the limit $Re \ll 1$ is a regular limit of the same problem.

5.7.1 Asymptotic structure for $Re = O(1)$

The asymptotic structure is shown in Figure 5.1a, where each region is labelled I – VI. We show that the leading-order outer solution for flow in the lumen and ECS (regions IV & VI) is lubrication flow subject to no axial slip at the transverse interfaces. This is incompatible with the inlet plug flow condition at $z = 0$, implying the existence of an inlet boundary layer (regions I & III) characterised by an $O(1)$ length scale that accounts for the transition from plug to lubrication flow. Each region is also coupled to the membrane flow at the lumen-membrane and membrane-ECS interfaces by a continuity of pressure and transverse flux condition.

5.7.1.1 Inner regions I – III

In the inner regions I – III, we pose an asymptotic expansion for the dependent variables in powers of ε such that

Table 5.1: Typical model parameters.

Parameter	Description	Typical value (Units)
Bioreactor dimensions		
$\varepsilon = R_{l0}^*/L^*$	Lumen aspect ratio	2×10^{-3}
$R_{m0} = R_{m0}^*/R_{l0}^*$	Outer membrane wall height	2
$R_{e0} = R_{e0}^*/R_{l0}^*$	ECS wall height	3
Membrane properties		
$\kappa = k^*/\varepsilon^2 R_{l0}^{*2}$	Permeability	0.01
Fluid transport		
$W_{l,in}$	Lumen inlet axial velocity	1
$W_{e,in}$	ECS inlet axial velocity	1

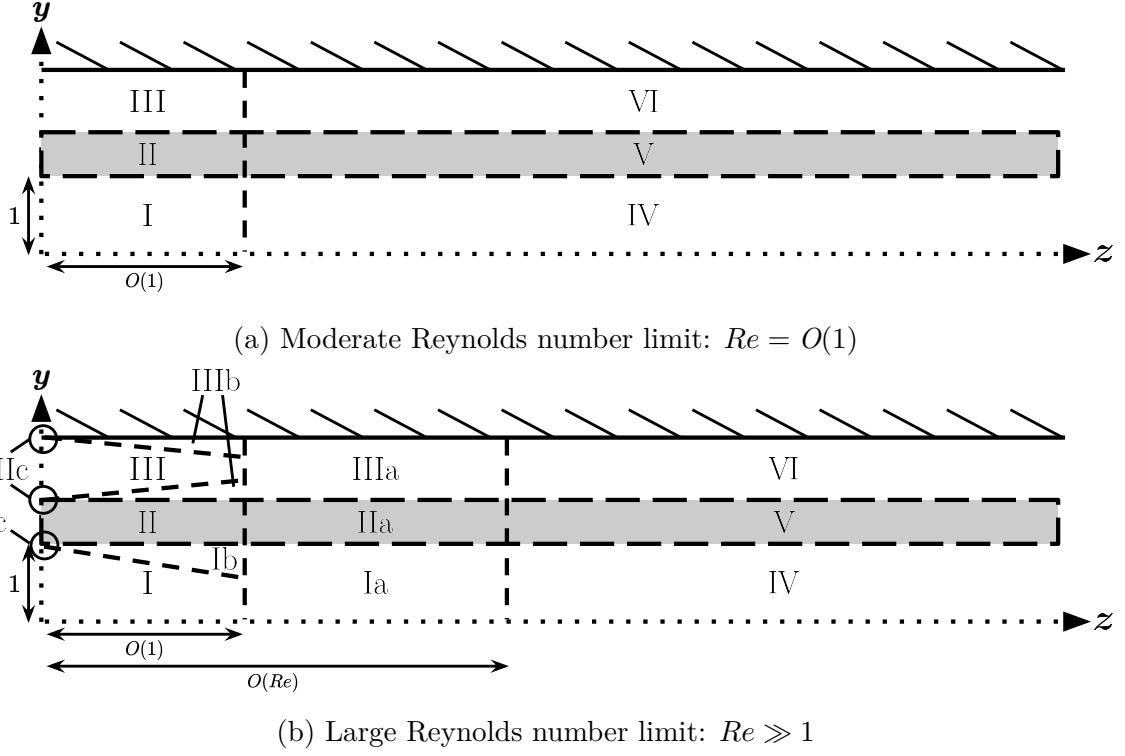


Figure 5.2: Boundary layer structure for all Reynolds number regimes. Regions IV – VI denote the outer lubrication regions.

$$(\mathbf{U}_i, P_i) = (\mathbf{U}_{i0}, P_{i0}) + \varepsilon (\mathbf{U}_{i1}, P_{i1}) + O(\varepsilon^2) \quad \text{as } \varepsilon \rightarrow 0. \quad (5.12)$$

Substituting (5.12) into (5.9), we find at leading order that

$$\nabla \cdot \mathbf{U}_{i0} = 0, \quad \nabla P_{i0} = 0. \quad (5.13)$$

Therefore, P_{i0}, P_{e0} are constant in regions I & III respectively. We find that the leading-order fluid flow in regions I & III is driven by the first correction to pressure, obtained by proceeding to $O(\varepsilon)$ in (5.9) to give

$$Re (\mathbf{U}_{i0} \cdot \nabla) \mathbf{U}_{i0} = -\nabla P_{i1} + \nabla^2 \mathbf{U}_{i0}. \quad (5.14)$$

We see the solution to the leading-order flow problem in regions I & III depends on the Reynolds number, Re . In region II, we again take an asymptotic expansion of the dependent variables in integer powers of ε , where at leading order (5.10) becomes

$$\mathbf{U}_{m0} = \mathbf{0}. \quad (5.15)$$

Therefore, the transverse flow arises at a higher order within the membrane in region II than in the lumen and ECS in regions I and III. Substituting (5.15) into the continuity of normal flux condition (5.11c), we recover no slip and no flux at the lumen-membrane interface

$$U_{i0} = W_{i0} = 0 \quad \text{at} \quad y = 1, R_{m0}. \quad (5.16)$$

Equations (5.13) – (5.14) represent the 2D steady incompressible Navier-Stokes equations, which can be solved numerically for $\mathbf{U}_{l0}, \mathbf{U}_{e0}$ subject to the inlet plug flow conditions (5.11a), the no slip and no flux condition at the lumen-membrane, membrane-ECS interfaces and ECS outer wall interfaces (5.11d), (5.16), and the lumen symmetry condition (5.11b). Since the highest derivatives are in the viscous terms, $Re \ll 1$ is a regular limit of this case, which reduces (5.14) to Stokes flow in regions I & III.

In the $O(\varepsilon)$ expansion of (5.10) in region II, we find that an $O(1)$ transmural pressure drop drives an $O(\varepsilon)$ transverse velocity

$$\nabla \cdot \mathbf{U}_{m1} = 0, \quad \phi \mathbf{U}_{m1} = -\kappa \nabla P_{m0}. \quad (5.17)$$

We later show that this is similar to the flow behaviour in Region V. Utilising the continuity of transverse flux condition (5.11c), this means that there is an $O(\varepsilon)$ transverse velocity entering or leaving region II via the lumen region I or ECS region III across a $O(1)$ cross-section, thus giving an $O(\varepsilon)$ flux. Solving (5.17) subject to (5.11c), we find

$$P_{m0} = \frac{(P_{e0} - P_{l0})}{(R_{m0} - 1)} (y - 1) + P_{l0}, \quad \phi U_{m1} = \kappa \frac{(P_{l0} - P_{e0})}{(R_{m0} - 1)}. \quad (5.18)$$

Given that P_{l0}, P_{e0} are constant in regions I & III, we deduce that U_{m1} is also constant in region II.

5.7.1.2 Outer regions IV – VI

To investigate the flow in the outer regions IV – VI, we scale $z = \varepsilon^{-1} \bar{z}$, and $(U_i, U_m) = \varepsilon(\bar{U}_i, \bar{U}_m)$, motivated by the continuity equation and the classic lubrication scalings. We use overbar notation and let $(y, W_i, W_m, P_i, P_m) = (\bar{y}, \bar{W}_i, \bar{W}_m, \bar{P}_i, \bar{P}_m)$ denote outer variables in regions IV – VI. We again take an asymptotic expansion of the dependent variables in integer powers of ε such that

$$f = f_0 + \varepsilon f_1 + O(\varepsilon^2) \quad \text{as} \quad \varepsilon \rightarrow 0 \quad \text{for} \quad f \in \{\bar{U}_i, \bar{U}_m, \bar{P}_i, \bar{P}_m\}. \quad (5.19)$$

Utilising these scalings and substituting (5.19) into the governing equations (5.9), the leading-order governing equations in regions IV and VI simplify to the lubrication equations

$$\frac{\partial \bar{U}_{i0}}{\partial \bar{y}} + \frac{\partial \bar{W}_{i0}}{\partial \bar{z}} = 0, \quad \frac{\partial \bar{P}_{i0}}{\partial \bar{y}} = 0, \quad \frac{\partial \bar{P}_{i0}}{\partial \bar{z}} = \frac{\partial^2 \bar{W}_{i0}}{\partial \bar{y}^2}. \quad (5.20)$$

Substituting (5.19) into (5.10), the leading-order governing equations in the membrane (region V) become

$$\frac{\partial \bar{U}_{m0}}{\partial \bar{y}} + \frac{\partial \bar{W}_{m0}}{\partial \bar{z}} = 0, \quad \phi \bar{U}_{m0} = -\kappa \frac{\partial \bar{P}_{m0}}{\partial \bar{y}}, \quad \bar{W}_{m0} = 0. \quad (5.21)$$

Equations (5.20) – (5.21) are equivalent to the flow problem considered in Chapter 2 in axisymmetric coordinates. At leading order, the boundary conditions (5.11) become

$$\bar{U}_{l0} = \frac{\partial \bar{W}_{l0}}{\partial \bar{y}} = 0 \quad \text{at} \quad \bar{y} = 0, \quad (5.22a)$$

$$\bar{U}_{i0} = \phi \bar{U}_{m0}, \quad \bar{P}_{i0} = \bar{P}_{m0}, \quad \bar{W}_{i0} = 0 \quad \text{at} \quad \bar{y} = 1, R_{m0}, \quad (5.22b)$$

$$\bar{U}_{e0} = \bar{W}_{e0} = 0 \quad \text{at} \quad \bar{y} = R_{e0}, \quad (5.22c)$$

$$\bar{W}_{m0} = 0 \quad \text{at} \quad \bar{z} = 0. \quad (5.22d)$$

Solving (5.20) subject to (5.22), we find

$$\bar{W}_{l0} = \frac{1}{2} \frac{d\bar{P}_{l0}}{d\bar{z}} (\bar{y}^2 - 1), \quad \bar{U}_{l0} = \frac{\bar{y}}{6} \frac{d^2 \bar{P}_{l0}}{d\bar{z}^2} (3 - \bar{y}^2), \quad (5.23)$$

in the lumen (region IV), and

$$\bar{W}_{e0} = \frac{1}{2} \frac{d\bar{P}_{e0}}{d\bar{z}} (\bar{y} - R_{m0}) (\bar{y} - R_{e0}), \quad (5.24a)$$

$$\bar{U}_{e0} = \frac{1}{12} \frac{d^2 \bar{P}_{e0}}{d\bar{z}^2} (R_{e0} - \bar{y})^2 (3R_{m0} - 2\bar{y} - R_{e0}), \quad (5.24b)$$

in the ECS (region VI), where $\bar{P}_{l0}, \bar{P}_{e0}$ are as-of-yet unknown. We note that flow solutions (5.23) – (5.24) are analogous to Poiseuille flow if we removed membrane cross-flow. We can, however, solve for the flow in region V in terms of unknown $\bar{P}_{l0}, \bar{P}_{e0}$ by solving (5.21) subject to (5.22). This procedure yields the relationship

$$\bar{P}_{m0} = \frac{(\bar{P}_{e0} - \bar{P}_{l0})}{(R_{m0} - 1)} (\bar{y} - 1) + \bar{P}_{l0}, \quad \phi \bar{U}_{m0} = \kappa \frac{(\bar{P}_{l0} - \bar{P}_{e0})}{(R_{m0} - 1)}. \quad (5.25)$$

Finally, we obtain governing equations for $\bar{P}_{l0}$ and $\bar{P}_{e0}$. From (5.23) – (5.25), we use the continuity of transverse flux condition (5.22b) evaluated at $\bar{y} = 1, R_{m0}$ to obtain a coupled system of second order ODEs for $\bar{P}_{l0}, \bar{P}_{e0}$

$$\frac{A}{\kappa} \frac{d^2 \bar{P}_{l0}}{d\bar{z}^2} = \bar{P}_{l0} - \bar{P}_{e0}, \quad \frac{B}{\kappa} \frac{d^2 \bar{P}_{e0}}{d\bar{z}^2} = \bar{P}_{l0} - \bar{P}_{e0}. \quad (5.26)$$

Here,

$$A = \frac{R_{m0} - 1}{3}, \quad B = -\frac{(R_{m0} - 1)(R_{e0} - R_{m0})^3}{12}. \quad (5.27)$$

Equations (5.26) are satisfied by the general solutions

$$\bar{P}_{l0} = c_1 e^{\lambda \bar{z}} + c_2 e^{-\lambda \bar{z}} + c_3 \bar{z} + c_4, \quad (5.28a)$$

$$\bar{P}_{e0} = \frac{c_1 A}{B} e^{\lambda \bar{z}} + \frac{c_2 A}{B} e^{-\lambda \bar{z}} + c_3 \bar{z} + c_4, \quad (5.28b)$$

where $\lambda = \sqrt{\kappa(B - A)/BA}$, and the c_i are constants to be solved for. For a physical solution whereby the pressure gradient in the lumen and ECS does not exponentially increase as $\bar{z} \rightarrow \infty$ (which would lead to an unphysical exponentially growing flux in the far field), we require $c_1 = 0$. To solve for the remaining constants, we first utilise a conservation of flux matching condition between regions I & III and the outer regions IV & VI

$$\lim_{z \rightarrow \infty} \int_{y_1}^{y_2} W_{i0} dy = \lim_{\bar{z} \rightarrow 0} \int_{\bar{y}_1}^{\bar{y}_2} \bar{W}_{i0} d\bar{y}, \quad (5.29)$$

where $\bar{y}_1, \bar{y}_2 = 0, 1$ in the lumen, and $\bar{y}_1, \bar{y}_2 = R_{m0}, R_{e0}$ in the ECS. From our asymptotic analysis, we note that the flux entering/leaving regions I & III across the membrane is of $O(\varepsilon)$, which is asymptotically smaller than the $O(1)$ axial flux entering and leaving regions I & III to regions IV & VI. Therefore for the purposes of determining the appropriate matching conditions for I & III into the outer regions IV & VI, it is consistent to neglect flux leaving or entering across the membrane in regions I & III in our leading-order model. We can then derive an analytic solution for the fluid pressure in regions IV & VI (5.26) by using the matching condition (5.29), which becomes

$$Q_{i,in} = \int_{y_1}^{y_2} W_{i,in} dy = \int_{\bar{y}_1}^{\bar{y}_2} \bar{W}_{i0} d\bar{y} \quad \text{as } \bar{z} \rightarrow 0, \quad (5.30)$$

Table 5.2: Asymptotic expansions within boundary layers in the moderate Reynolds number limit $Re = O(1)$.

Region	Asymptotic expansions	Relative scalings
I – III	$(\mathbf{U}_i, P_i) = (\mathbf{U}_{i0}, P_{i0})$ $+ \varepsilon(\mathbf{U}_{i1}, P_{i1}) + O(\varepsilon^2)$	
IV – VI	$(\bar{\mathbf{U}}_i, \bar{P}_i) = (\bar{\mathbf{U}}_{i0}, \bar{P}_{i0})$ $+ \varepsilon(\bar{\mathbf{U}}_{i1}, \bar{P}_{i1}) + O(\varepsilon^2)$	$U_i = \varepsilon \bar{U}_i, W_i = \bar{W}_i, P_i = \bar{P}_i,$ $y = \bar{y}, z = \varepsilon^{-1} \bar{z}$

where $W_{l,in}, W_{e,in}$ are the constant plug flow inlet velocities prescribed at the lumen and ECS inlet respectively. Substituting (5.23) – (5.24) into (5.30), we find that

$$\frac{d\bar{P}_{l0}}{d\bar{z}} \rightarrow -3, \quad \frac{d\bar{P}_{e0}}{d\bar{z}} \rightarrow -\frac{12W_{e,in}}{(R_{e0} - R_{m0})^2}, \quad \text{as } \bar{z} \rightarrow 0. \quad (5.31)$$

Then, finally, solving (5.28) subject to (5.31), the lumen and ECS pressures in regions IV & VI are given by

$$\bar{P}_{l0} \sim \frac{3((R_{e0} - R_{m0})^2 - 4W_{e,in})(R_{e0} - R_{m0})(\lambda\bar{z} + e^{-\lambda\bar{z}})}{\lambda(4 + (R_{e0} - R_{m0})^3)} - 3\bar{z}, \quad (5.32a)$$

$$\bar{P}_{e0} \sim \frac{3((R_{e0} - R_{m0})^2 - 4W_{e,in})((R_{e0} - R_{m0})^3\lambda\bar{z} - 4e^{-\lambda\bar{z}})}{\lambda(4 + (R_{e0} - R_{m0})^3)(R_{e0} - R_{m0})^2} - 3\bar{z}, \quad (5.32b)$$

which are unique up to an arbitrary constant c_4 , which we take to be zero without loss of generality.

5.8 Large Reynolds number: $Re \gg 1$

We now consider transitions from plug to lubrication flow in the asymptotic limit $Re \gg 1$. The transition from plug to lubrication flow at the lumen and ECS inlet will now depend on the Reynolds number, in a related manner to that considered by Dalwadi et al. [69], thus changing the asymptotic structure of the inner transition region. We illustrate the asymptotic structure in this limit in Figure 5.2b.

We conduct an asymptotic analysis by taking $1/Re \ll 1$. To generalise our analysis in this sublimit, we take the reduced Reynolds number εRe to be an $O(1)$ quantity as $\varepsilon \rightarrow 0$. We scale the governing equations (5.1) – (5.2) and boundary conditions (5.3) – (5.7) as before using the nondimensionalisation (5.8). However to balance

pressure in regions I & III with both viscous and inertial terms in Navier–Stokes equations, we now scale pressure to be

$$P_i^* = (1 + \varepsilon Re) \frac{\mu W_{l,in}^*}{\varepsilon R_{l0}^*} P_i, \quad (5.33)$$

where $Re = \rho^* W_{l,in}^* R_{l0}^* / \mu^*$. Equation (5.33) is equivalent to scaling $P_i \mapsto (1 + \varepsilon Re) P_i$ in the previous non-dimensional system (5.9) – (5.10). While this may seem unusual, introducing this scaling is equivalent to introducing a viscous and an inertial pressure. The specific formulation we introduce in (5.33) allows us to smoothly consider the limits of large and small εRe (in which the original pressure should scale with εRe and 1, respectively) without having to rescale the pressure separately. Therefore, in regions I & III, Equation (5.1) is now

$$\nabla \cdot \mathbf{U}_i = 0, \quad \varepsilon Re (\mathbf{U}_i \cdot \nabla) \mathbf{U}_i = -(1 + \varepsilon Re) \nabla P_i + \varepsilon \nabla^2 \mathbf{U}_i, \quad (5.34)$$

and Equation (5.2) in region II becomes

$$\nabla \cdot \mathbf{U}_m = 0, \quad \phi \mathbf{U}_m = -\varepsilon \kappa (1 + \varepsilon Re) \nabla P_m. \quad (5.35)$$

5.8.1 Asymptotic structure for $\varepsilon Re = O(1)$

5.8.1.1 Regions I & III

Since the inlet conditions (5.11a) are consistent with the governing equations in the inviscid regions I & III if we neglect $O(\varepsilon)$ terms in (5.34), we obtain the leading-order solution for free. However, we still need information about the higher-order terms in this region to match into subsequent asymptotic regions. Hence, in regions I & III, we pose an asymptotic expansion in Re such that

$$(\mathbf{U}_i, P_i) = (W_{i,in} \hat{\mathbf{e}}_z, P_{i0}) + Re^{-1/2} (\mathbf{U}_{i1}, P_{i1}) + O(Re^{-1}) \quad \text{as} \quad Re^{-1/2} \rightarrow 0, \quad (5.36)$$

where $W_{l,in} = 1$. Here the fractional order of Re arises from hindsight, due to matching into the boundary layer regions Ib & IIIb in Section 5.8.1.2. Substituting (5.36) into (5.9) we find the following groupings of terms at $O(1)$ and $O(Re^{-1/2})$ respectively

$$\nabla P_{i0} = 0, \quad \nabla \cdot \mathbf{U}_{i1} = 0, \quad (5.37a)$$

$$\varepsilon Re W_{i,in} \frac{\partial U_{i1}}{\partial z} = -(1 + \varepsilon Re) \frac{\partial P_{i1}}{\partial y}, \quad \varepsilon Re W_{i,in} \frac{\partial W_{i1}}{\partial z} = -(1 + \varepsilon Re) \frac{\partial P_{i1}}{\partial z}. \quad (5.37b)$$

Therefore the leading-order pressure P_{i0} is constant in region I & III. Upon cross-differentiating (5.37b) to eliminate pressure, and substituting into the continuity equation (5.37a), it follows that

$$\nabla^2 U_{i1} = 0. \quad (5.38)$$

Given that we only require the far-field behaviour of U_{i1} as $z \rightarrow \infty$ to match into regions Ia & IIIa, we do not need to fully solve (5.37b). Instead, we can solve (5.38) subject to the matching condition with region Ib later determined in (5.67). For convenience, we pre-emptively state it here as

$$U_{l1} = -\frac{\tilde{\beta}}{2z^{1/2}} \quad \text{as } y \rightarrow 1^-. \quad (5.39)$$

Then, using the symmetry condition (5.11b) and noting that (5.38) reduces to

$$\frac{\partial^2 U_{l1}}{\partial y^2} = 0 \quad \text{as } z \rightarrow \infty, \quad (5.40)$$

in the large- z limit, we may deduce the large- z solution

$$U_{l1} \sim -\frac{\tilde{\beta}y}{2z^{1/2}}, \quad \text{as } z \rightarrow \infty, \quad (5.41)$$

in the lumen. In the ECS, we solve (5.38) subject to the matching conditions determined in (5.74), which we give here to be

$$U_{e1} = \pm \frac{W_{e,in}^{1/2} \tilde{\beta}}{2z^{1/2}} \quad \text{as } y \rightarrow R_{m0}^+, R_{e0}^-. \quad (5.42)$$

Similarly to (5.40), Equation (5.38) reduces to

$$\frac{\partial^2 U_{e1}}{\partial y^2} = 0 \quad \text{as } z \rightarrow \infty, \quad (5.43)$$

therefore we can deduce the far-field behaviour for matching into region IIIa

$$U_{e1} \sim -\frac{W_{e,in}^{1/2} \tilde{\beta} (2y - R_{m0} - R_{e0})}{2(R_{e0} - R_{m0}) z^{1/2}} \quad \text{as } z \rightarrow \infty. \quad (5.44)$$

With the lumen far-field condition (5.41), we substitute into the continuity equation (5.37a) to obtain the far-field solution for W_{l1} in region I

$$W_{l1} \sim \tilde{\beta} z^{1/2} \quad \text{as } z \rightarrow \infty. \quad (5.45)$$

Substituting (5.45) into (5.37b), we can determine the far-field solution for P_{l1} to be

$$P_{l1} \sim -\frac{\varepsilon Re \tilde{\beta} z^{1/2}}{(1 + \varepsilon Re)} \quad \text{as } z \rightarrow \infty. \quad (5.46)$$

With the ECS far-field condition (5.44), we substitute into the continuity equation (5.37a) and solve to find

$$W_{e1} \sim \frac{2W_{e,in}^{1/2} \tilde{\beta} z^{1/2}}{(R_{e0} - R_{m0})} \quad \text{as } z \rightarrow \infty. \quad (5.47)$$

Then, substituting (5.47) into (5.37b), we can deduce that

$$P_{e1} \sim -\frac{2\varepsilon Re W_{e,in}^{3/2} \tilde{\beta} z^{1/2}}{(1 + \varepsilon Re)(R_{e0} - R_{m0})} \quad \text{as } z \rightarrow \infty, \quad (5.48)$$

in the ECS region III.

From (5.46) and (5.48), we see that the far-field pressure P_{i1} in regions I & III as $z \rightarrow \infty$ depends on the reduced Reynolds number εRe . In the regular limit $\varepsilon Re \rightarrow 0$, we see that

$$P_{l1} \sim 0, \quad P_{e1} \sim 0 \quad \text{as } z \rightarrow \infty, \quad (5.49)$$

meaning that the lumen and ECS pressures plateau at large- z . Conversely, if we take the large reduced Reynolds number limit $\varepsilon Re \rightarrow \infty$, we see that the fluid pressures scale such that

$$P_{l1} \sim -\tilde{\beta} z^{1/2}, \quad P_{e1} \sim -\frac{2W_{e,in}^{3/2} \tilde{\beta} z^{1/2}}{(R_{e0} - R_{m0})} \quad \text{as } z \rightarrow \infty, \quad (5.50)$$

suggesting that the lumen and ECS pressures decrease with decreasing gradient as z becomes large.

5.8.1.2 Regions Ib & IIIb

The leading-order plug flow profile in regions I and III do not satisfy the no-slip conditions at the transverse interfaces. Therefore, to satisfy the no-slip condition at the lumen-membrane, membrane-ECS and outer wall interfaces, we scale into a boundary layer region Ib in the lumen, and regions IIIb in the ECS (close to each interface) such that

$$y = 1 - Re^{-1/2} \hat{y}, \quad U_l = -Re^{-1/2} \hat{U}_l \quad \text{in region Ib,} \quad (5.51a)$$

$$y = R_{m0} + Re^{-1/2} \hat{y}, \quad U_e = Re^{-1/2} \hat{U}_e \quad \text{in region IIIb as } y \rightarrow R_{m0}, \quad (5.51b)$$

$$y = R_{e0} - Re^{-1/2} \hat{y}, \quad U_e = -Re^{-1/2} \hat{U}_e \quad \text{in region IIIb as } y \rightarrow R_{e0}. \quad (5.51c)$$

For the avoidance of doubt, we use hats to denote dimensionless variables in the boundary layers Ib & IIIb, so that $z = \hat{z}$, $W_i = \hat{W}_i$, $P_i = \hat{P}_i$. We pose the asymptotic expansion

$$(\hat{U}_i, \hat{P}_i) = (\hat{U}_{i0}, \hat{P}_{i0}) + O(Re^{-1}) \quad \text{as} \quad Re^{-1} \rightarrow 0. \quad (5.52)$$

Scaling and substituting (5.51)–(5.52) into (5.9) we find the leading-order governing equations to be

$$\frac{\partial \hat{U}_{i0}}{\partial \hat{y}} + \frac{\partial \hat{W}_{i0}}{\partial \hat{z}} = 0, \quad (5.53a)$$

$$\frac{\partial \hat{P}_{i0}}{\partial \hat{y}} = 0, \quad (5.53b)$$

$$\varepsilon Re \left(\hat{U}_{i0} \frac{\partial \hat{W}_{i0}}{\partial \hat{y}} + \hat{W}_{i0} \frac{\partial \hat{W}_{i0}}{\partial \hat{z}} \right) = -(1 + \varepsilon Re) \frac{\partial \hat{P}_{i0}}{\partial \hat{z}} + \varepsilon Re \frac{\partial^2 \hat{W}_{i0}}{\partial \hat{y}^2}, \quad (5.53c)$$

which are the classic Prandtl boundary layer equations with our pressure scalings [116]. The boundary conditions in this region become

$$\hat{U}_i = \phi \hat{U}_m, \quad \hat{W}_i = 0, \quad -\hat{P}_i + 2\varepsilon \frac{\partial \hat{U}_i}{\partial \hat{y}} = -\hat{P}_m \quad \text{at} \quad \hat{y} = 0, \quad (5.54)$$

for region Ib at the lumen-membrane interface, and IIIb at the membrane-ECS interface. The boundary condition for region IIIb at the outer ECS wall becomes

$$\hat{U}_e = 0, \quad \hat{W}_e = 0 \quad \text{at} \quad \hat{y} = 0. \quad (5.55)$$

We note that the matching condition with the leading-order axial velocity in regions I & III is

$$\hat{W}_{l0} \rightarrow 1, \quad \hat{W}_{e0} \rightarrow W_{e,in} \quad \text{as} \quad \hat{y} \rightarrow \infty, \quad (5.56)$$

which are independent of z . Then, considering the large- $\hat{y}$ limit of (5.53c), we deduce that

$$\frac{\partial \hat{P}_{i0}}{\partial \hat{z}} \rightarrow 0 \quad \text{as} \quad \hat{y} \rightarrow \infty. \quad (5.57)$$

Given that $\hat{P}_{i0}$ is independent of $\hat{y}$ from (5.53b), we can conclude that

$$\frac{\partial \hat{P}_{i0}}{\partial \hat{z}} \equiv 0, \quad (5.58)$$

and therefore $\hat{P}_{l0}, \hat{P}_{e0}$ are constant in regions Ib & IIIb respectively. Hence, (5.53) becomes

$$\frac{\partial \hat{U}_{i0}}{\partial \hat{y}} + \frac{\partial \hat{W}_{i0}}{\partial \hat{z}} = 0, \quad (5.59a)$$

$$\hat{U}_{i0} \frac{\partial \hat{W}_{i0}}{\partial \hat{y}} + \hat{W}_{i0} \frac{\partial \hat{W}_{i0}}{\partial \hat{z}} = \frac{\partial^2 \hat{W}_{i0}}{\partial \hat{y}^2}. \quad (5.59b)$$

To determine the appropriate boundary conditions at the lumen-membrane and membrane-ECS interfaces, we take an asymptotic expansion of (5.10) such that

$$(\mathbf{U}_m, P_m) = (\mathbf{U}_{m0}, P_{m0}) + O(Re^{-1}) \quad \text{as} \quad Re^{-1} \rightarrow 0. \quad (5.60)$$

Substituting into (5.35), the leading-order governing equations reduce to (5.15). That is,

$$\mathbf{U}_m = \mathbf{0}. \quad (5.61)$$

Hence, we find that there is no flow across region II at leading order from the lumen and ECS, similarly to the small Reynolds number case, and therefore the lumen-membrane and membrane-ECS interfacial conditions for regions Ib & IIIb (5.54) – (5.55) reduce to no slip and no flux (5.16). Alongside the no slip and no flux conditions at the outer wall interface, this means flow in regions Ib & IIIb reduce to Blasius boundary layers of $O((\hat{z}/Re)^{1/2})$ thickness along an impermeable 2D plate at leading order. This is a well-studied problem which has been shown to have a self-similar solution [116], given that the governing equations and boundary conditions are invariant under the transformation

$$\hat{y} \mapsto \alpha \hat{y}, \quad \hat{z} \mapsto \alpha^2 \hat{z}, \quad \hat{U}_{i0} \mapsto \alpha^{-1} \hat{U}_{i0}, \quad \hat{W}_{i0} \mapsto \hat{W}_{i0}, \quad (5.62)$$

where α is any positive constant. Using these classic invariant transformations, to solve (5.59) in regions Ib & IIIb, we substitute

$$\hat{U}_{i0} = \frac{\eta f'_i(\eta) - f_i(\eta)}{2\hat{z}^{1/2}}, \quad \hat{W}_{i0} = f'_i(\eta), \quad (5.63)$$

where $\eta = \hat{y}/\hat{z}^{1/2}$ is the similarity variable and f_i is the standard Blasius similarity solution. We note that the specific relationship between $\hat{U}_{i0}$ and $\hat{W}_{i0}$ in (5.63) follows from the continuity equation (5.59a), which is therefore trivially satisfied. Then, (5.59b) becomes

$$2f_i'''(\eta) + f_i''(\eta)f_i(\eta) = 0. \quad (5.64)$$

In the lumen region Ib, the no-slip and no-flux boundary conditions (5.16), and the matching condition (5.56) become

$$f_l(0) = f_l'(0) = 0, \quad f_l'(\infty) = 1. \quad (5.65)$$

The system for f_l (5.64) – (5.65), can be solved numerically (which we do below), and the behaviour of f_l is well studied. In particular, Boyd [117] shows that the behaviour of f_l up to exponentially small terms as $\eta \rightarrow \infty$ is given by

$$f_l \sim \eta - \tilde{\beta}, \quad (5.66)$$

where $\tilde{\beta} \approx 1.721$. Substituting (5.66) into (5.63) provides the matching condition between regions I and Ib for U_{l1} such that

$$U_{l1} = -\frac{\tilde{\beta}}{2z^{1/2}} \quad \text{as } y \rightarrow 1^-. \quad (5.67)$$

In the ECS region IIIb, the process is similar. Now, the no-slip and no-flux conditions (5.11d), (5.16) and the matching condition (5.56) are

$$f_e(0) = f_e'(0) = 0, \quad f_e'(\infty) = W_{e,in}. \quad (5.68)$$

To determine the behaviour of f_e as $\eta \rightarrow \infty$ for our matching condition, we can relate f_e to f_l by exploiting invariance of the Blasius differential equation (5.64) under the transformation

$$f_e(\eta) = \alpha F(x), \quad \eta = \frac{x}{\alpha}, \quad (5.69)$$

where α is an arbitrary positive constant. Substituting (5.69) into the Blasius differential equation (5.64) we recover

$$F'''(x) + 2F''(x)F(x) = 0, \quad (5.70)$$

as expected, and substituting (5.69) into the ECS boundary conditions (5.68), we find

$$F(0) = F'(0) = 0, \quad \alpha^2 F'(\infty) = W_{e,in}. \quad (5.71)$$

If we choose $\alpha = \sqrt{W_{e,in}}$ and substitute into (5.71), this gives us the boundary condition

$$F(0) = F'(0) = 0, \quad F'(\infty) = 1, \quad (5.72)$$

which are the same boundary conditions for the lumen region Ib in (5.65). With (5.70) and (5.72), we can conclude that $F(x) = f_l(\eta)$. Substituting $\alpha = \sqrt{W_{e,in}}$ into (5.69) and utilising the result derived by Boyd [117], we determine the behaviour for f_e as $\eta \rightarrow \infty$ in terms of $\tilde{\beta}$ by

$$f_e \sim W_{e,in}\eta - W_{e,in}^{1/2}\tilde{\beta}. \quad (5.73)$$

Therefore, the matching condition between regions III & IIIb from substituting (5.73) into (5.63) becomes

$$U_{e1} = \pm \frac{W_{e,in}^{1/2}\tilde{\beta}}{2z^{1/2}} \text{ as } y \rightarrow R_{m0}^+, R_{e0}^-. \quad (5.74)$$

We note that similarly to the classic Prandtl boundary layer problem [116], there exist additional boundary layers Ic & IIIc at the corner between the plug flow inlets and the channel walls to deal with the singularity that arises in the corner of the Prandtl boundary layers Ib & IIIb. No leading-order information propagates into the outer regions from these corner regions, so we relegate our consideration of these regions to Appendix E.

5.8.1.3 Regions Ia – IIIa

Given the similarity variable $\eta = \hat{y}/\hat{z}^{1/2}$ in the Prandtl boundary layers, and the transformation of the outer coordinate into the boundary layer coordinate scales with $1/\sqrt{Re}$, the boundary layer thickness grows like $\sqrt{z/Re}$. Since the asymptotic scalings will break down when the boundary layer thickness is of the same order as the channel height (i.e. $O(1)$), we see that there will be a new asymptotic balance when $z = O(Re)$. This new asymptotic balance identifies a transition from regions I & III to regions Ia & IIIa respectively, characterised by a balance between viscous and inertial effects across the full width of each channel. To understand these new asymptotic regions Ia and IIIa, we scale $z = Re\tilde{z}$. To ensure consistency in the continuity equation, we also scale $U_i = Re^{-1}\tilde{U}_i$. We introduce $y = \tilde{y}, W_i = \tilde{W}_i, P_i = \tilde{P}_i$ to denote dimensionless variables in regions Ia & IIIa. We then pose an asymptotic expansion in Re similarly to regions Ib & IIIb such that

$$(\tilde{U}_i, \tilde{P}_i) = (\tilde{U}_{i0}, \tilde{P}_{i0}) + O(Re^{-1}) \quad \text{as } Re^{-1} \rightarrow 0. \quad (5.75)$$

Table 5.3: Asymptotic expansions within boundary layers in the large Reynolds number limit $Re \gg 1$.

Region	Asymptotic expansions	Relative scalings
I	$(\mathbf{U}_l, P_l) = (\hat{\mathbf{e}}_z, P_{l0}) + Re^{-1/2}(\mathbf{U}_{l1}, P_{l1}) + O(Re^{-1})$	
Ia	$(\tilde{\mathbf{U}}_l, \tilde{P}_l) = (\tilde{\mathbf{U}}_{l0}, \tilde{P}_{l0}) + O(Re^{-1})$	$U_l = Re^{-1}\tilde{U}_l, W_l = \tilde{W}_l, P_l = \tilde{P}_l,$ $y = \tilde{y}, z = Re\tilde{z}$
Ib	$(\hat{\mathbf{U}}_l, \hat{P}_l) = (\hat{\mathbf{U}}_{l0}, \hat{P}_{l0}) + O(Re^{-1})$	$U_l = -Re^{-1/2}\hat{U}_l, W_l = \hat{W}_l, P_l = \hat{P}_l,$ $y = 1 - Re^{-1/2}\hat{y}, z = \hat{z}$
II	$(\mathbf{U}_m, P_m) = (\mathbf{U}_{m0}, P_{m0}) + O(Re^{-1})$	
IIa	$(\tilde{\mathbf{U}}_m, \tilde{P}_m) = (\tilde{\mathbf{U}}_{m0}, \tilde{P}_{m0}) + O(Re^{-1})$	$U_m = Re^{-1}\tilde{U}_m, W_m = \tilde{W}_m, P_m = \tilde{P}_m,$ $y = \tilde{y}, z = Re\tilde{z}$
III	$(\mathbf{U}_e, P_e) = (W_{e,in}\hat{\mathbf{e}}_z, P_{e0}) + Re^{-1/2}(\mathbf{U}_{e1}, P_{e1}) + O(Re^{-1})$	
IIIa	$(\tilde{\mathbf{U}}_e, \tilde{P}_e) = (\tilde{\mathbf{U}}_{e0}, \tilde{P}_{e0}) + O(Re^{-1})$	$U_e = Re^{-1}\tilde{U}_e, W_e = \tilde{W}_e, P_e = \tilde{P}_e,$ $y = \tilde{y}, z = Re\tilde{z}$
IIIb	$(\hat{\mathbf{U}}_e, \hat{P}_e) = (\hat{\mathbf{U}}_{e0}, \hat{P}_{e0}) + O(Re^{-1})$	$W_e = \hat{W}_e, P_e = \hat{P}_e,$ $y = R_{m0} + Re^{-1/2}\hat{y}, U_e = Re^{-1/2}\hat{U}_e$ as $y \rightarrow R_{m0},$ $y = R_{e0} - Re^{-1/2}\hat{y}, U_e = -Re^{-1/2}\hat{U}_e,$ as $y \rightarrow R_{e0},$ $z = \hat{z}$

Substituting into (5.9), we obtain the leading-order equations

$$\frac{\partial \tilde{U}_{i0}}{\partial \tilde{y}} + \frac{\partial \tilde{W}_{i0}}{\partial \tilde{z}} = 0, \quad (5.76a)$$

$$\frac{\partial \tilde{P}_{i0}}{\partial \tilde{y}} = 0, \quad (5.76b)$$

$$\varepsilon Re \left(\tilde{U}_{i0} \frac{\partial \tilde{W}_{i0}}{\partial \tilde{y}} + \tilde{W}_{i0} \frac{\partial \tilde{U}_{i0}}{\partial \tilde{z}} \right) = -(1 + \varepsilon Re) \frac{\partial \tilde{P}_{i0}}{\partial \tilde{z}} + \varepsilon Re \frac{\partial^2 \tilde{W}_{i0}}{\partial \tilde{y}^2}, \quad (5.76c)$$

which are the key flow transition equations in this region. In the membrane we equivalently scale into boundary layer IIa for U_m and P_m to achieve a balance of terms in the continuity of transverse flux condition (5.11c) such that $z = Re\tilde{z}, U_m = Re^{-1}\tilde{U}_m$. Using an equivalent asymptotic expansion to (5.75), the leading-order version of (5.35) in region IIa is

$$\frac{\partial \tilde{U}_{m0}}{\partial \tilde{y}} + \frac{\partial \tilde{W}_{m0}}{\partial \tilde{z}} = 0, \quad \phi \tilde{U}_{m0} = -\varepsilon Re \kappa (1 + \varepsilon Re) \frac{\partial \tilde{P}_{m0}}{\partial \tilde{y}}, \quad \tilde{W}_{m0} = 0. \quad (5.77)$$

Therefore, flow across the membrane in region IIa depends on the magnitude of the reduced Reynolds number εRe . Additionally from (5.77) and the interfacial conditions (5.11c), we can conclude that the membrane pressure in region IIa varies linearly in the $\tilde{y}$ -direction between the leading-order lumen and ECS pressures in regions Ia & IIIa respectively.

The leading-order matching conditions for the flow into region Ia are found by forming a composite expansion between the far-field conditions in regions I and Ib, and using Van Dyke's matching rule to match into Ia [97]. We determine the far-field expansion for region I in the limit $z \rightarrow \infty$ by combining the leading-order axial velocity and the first-order correction terms (5.36) to find

$$U_l \sim -\frac{\tilde{\beta}y}{2(Re z)^{1/2}}, \quad W_l \sim 1 + \tilde{\beta}(z/Re)^{1/2}. \quad (5.78)$$

Therefore, the far-field transverse and axial fluid velocity in region I decreases with increasing Re . With (5.78), we form the multiplicative composite expansion with the solution in the Blasius boundary layer (5.63). Writing the expansion (5.78) in terms of region Ia variables $\tilde{y} = y, \tilde{z} = Re^{-1}z$, the leading-order matching condition for region Ia as $\tilde{z} \rightarrow 0$ becomes

$$\tilde{U}_{l0} \sim -\frac{(\eta f'_l(\eta) - f_l(\eta))\tilde{y}}{2\tilde{z}^{1/2}}, \quad \tilde{W}_{l0} \sim (1 + \tilde{\beta}\tilde{z}^{1/2})f'_l(\eta), \quad (5.79)$$

where we can write $\eta = \hat{y}/\hat{z}^{1/2} = (1 - \tilde{y})/\tilde{z}^{1/2}$ in region Ia. Following the same procedure in the ECS region III, we combine the leading-order axial velocity and the first-order correction terms (5.36) to find

$$U_e \sim -\frac{W_{e,in}^{1/2}\tilde{\beta}(2y - R_{m0} - R_{e0})}{2(R_{e0} - R_{m0})(Re z)^{1/2}}, \quad W_e \sim W_{e,in} + \frac{2W_{e,in}^{1/2}\tilde{\beta}(z/Re)^{1/2}}{(R_{e0} - R_{m0})}. \quad (5.80)$$

We see here that the far-field transverse and axial fluid velocities in region IIIb also decrease as we increase the Reynolds number, which is to be expected. Finally, forming a multiplicative composite expansion with the solution in regions IIIb (5.63), we find

$$\tilde{U}_{e0} \sim -\frac{(2\tilde{y} - R_{m0} - R_{e0})}{2W_{e,in}^{1/2}\tilde{\beta}(R_{e0} - R_{m0})\tilde{z}^{1/2}} (\eta_{(a)}f'_e(\eta_{(a)}) - f_e(\eta_{(a)})) (\eta_{(b)}f'_e(\eta_{(b)}) - f_e(\eta_{(b)})), \quad (5.81a)$$

$$\tilde{W}_{e0} \sim \left(W_{e,in} + \frac{2W_{e,in}^{1/2}\tilde{\beta}\tilde{z}^{1/2}}{(R_{e0} - R_{m0})} \right) \frac{f'_e(\eta_{(a)})f'_e(\eta_{(b)})}{W_{e,in}^2}, \quad (5.81b)$$

where $\eta_{(a)} = (\tilde{y} - R_{m0})/\tilde{z}^{1/2}$ and $\eta_{(b)} = (R_{e0} - \tilde{y})/\tilde{z}^{1/2}$.

5.8.1.4 Regions IV – VI

In anticipation of the outer lubrication flow regions IV – VI, we scale $z = \varepsilon^{-1}\bar{z}$, and $(U_i, U_m) = \varepsilon(\bar{U}_i, \bar{U}_m)$, similarly to Section 5.7.1.2. We use overbar notation to denote outer variables in regions IV – VI. We then take an asymptotic expansion in integer powers of ε as in (5.19). Substituting into (5.34), we find that the leading-order governing equations in regions IV and VI become

$$\frac{\partial \bar{U}_{i0}}{\partial \bar{y}} + \frac{\partial \bar{W}_{i0}}{\partial \bar{z}} = 0, \quad (5.82a)$$

$$\frac{\partial \bar{P}_{i0}}{\partial \bar{y}} = 0, \quad (5.82b)$$

$$\varepsilon Re \left(\bar{U}_{i0} \frac{\partial \bar{W}_{i0}}{\partial \bar{y}} + \bar{W}_{i0} \frac{\partial \bar{W}_{i0}}{\partial \bar{z}} \right) = -(1 + \varepsilon Re) \frac{\partial \bar{P}_{i0}}{\partial \bar{z}} + \frac{\partial^2 \bar{W}_{i0}}{\partial \bar{y}^2}. \quad (5.82c)$$

Therefore flow in the outer regions IV & VI resembles the governing equations in regions Ia & IIIa (5.76). Substituting (5.19) into (5.35), the leading-order governing equations in the membrane (region V) become

$$\frac{\partial \bar{U}_{m0}}{\partial \bar{y}} + \frac{\partial \bar{W}_{m0}}{\partial \bar{z}} = 0, \quad \phi \bar{U}_{m0} = -\kappa(1 + \varepsilon Re) \frac{\partial \bar{P}_{m0}}{\partial \bar{y}}, \quad \bar{W}_{m0} = 0. \quad (5.83)$$

Before we proceed in solving (5.82) – (5.83), we must first recall the asymptotic regime we consider in this section. Up until now, we have determined that in the distinguished limit $\varepsilon Re = O(1)$, the flow transition region occurs over an $O(Re)$ length scale. Although we formally consider each channel to be infinitely long, in nondimensionalising our problem in (5.8), we define ε to be the ratio of the lumen channel height to a characteristic length scale, R_{i0}^*/L^* . Therefore the nondimensional characteristic length is given by $1/\varepsilon$. While we model an infinitely long geometry to capture all asymptotic regimes in this distinguished limit, we must consider the relative size of the characteristic length, $1/\varepsilon$, to the length scale over which flow transitions occur, Re , to determine which boundary layer regions would actually be observed in reality in each sublimit.

We can think of our characteristic length $1/\varepsilon$ as setting the observation window. If we consider $\varepsilon Re = O(1)$ (i.e. $1/\varepsilon \approx Re$), we see that flow transitions through the lumen and ECS over a length scale approximately equal to the characteristic channel length. Therefore, we would only observe the inlet regions I–III, the Blasius

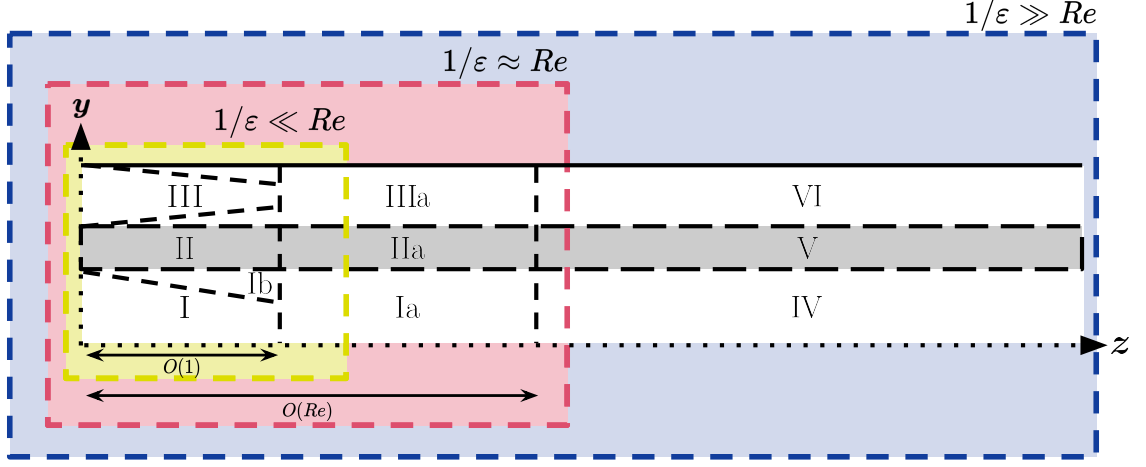


Figure 5.3: Illustration of observed flow transition regions through a finite channel of characteristic length $1/\varepsilon$, while varying the Reynolds number of the flow Re relative to the characteristic channel length.

boundary layer regions Ib and IIIb, and the formation of transition regions Ia – IIIa (as illustrated in Figure 5.3). However, we would not observe lubrication regions. The same is true if we consider $\varepsilon Re \gg 1$ in the asymptotic sublimit $1 \ll 1/\kappa \ll 1/\varepsilon \ll Re$. The characteristic channel length is much smaller than the transitional flow length scale, and thus any flow regions beyond this characteristic length would not be observed. Conversely, for $\varepsilon Re \ll 1$, such that $1 \ll 1/\kappa \ll Re \ll 1/\varepsilon$, the flow transitions over a length scale shorter than the channel length. Therefore, as illustrated in Figure 5.3, regions IV – VI are only observed if the channel length is sufficiently long relative to the Reynolds number (i.e. $\varepsilon Re \ll 1$).

Taking the limit $\varepsilon Re \rightarrow 0$ in (5.82) – (5.83), we recover the lubrication equations (5.20) coupled to radial membrane flow (5.21). To solve for the flow in regions IV – VI for $\varepsilon Re \ll 1$, we utilise the same analysis in Section 5.7.1.2. That is, we solve (5.20) – (5.21) subject to the leading-order symmetry condition (5.22a), interfacial conditions (5.22b), and an upstream matching condition to be determined. Because flux is not necessarily conserved from regions I to Ia and III to IIIa due to flow across the membrane region IIa, the matching condition (5.30) to solve for fluid pressure (5.26) no longer holds. Instead, we adapt the matching condition (5.30) to account for flux gained/lost across the membrane wall in region IIa. To begin, we define the matching condition between regions Ia/IIIa and regions IV/VI respectively by

$$\lim_{\tilde{z} \rightarrow \infty} \int_{\tilde{y}_1}^{\tilde{y}_2} \tilde{W}_{i0} d\tilde{y} = \lim_{\bar{z} \rightarrow 0} \int_{\bar{y}_1}^{\bar{y}_2} \bar{W}_{i0} d\bar{y}. \quad (5.84)$$

We can relate the flux leaving regions Ia/IIIa to the flux gained/lost across IIa by considering conservation of mass in regions Ia & IIIa

$$\lim_{\tilde{z} \rightarrow 0} \int_{\tilde{y}_1}^{\tilde{y}_2} \tilde{W}_{i0} d\tilde{y} - \lim_{\tilde{z} \rightarrow \infty} \int_{\tilde{y}_1}^{\tilde{y}_2} \tilde{W}_{i0} d\tilde{y} = \int_0^\infty \tilde{U}_i d\tilde{z}. \quad (5.85)$$

From Section 5.8.1.2, we know there is zero leading-order flux across region II. As such, flux entering the lumen/ECS is conserved when entering regions Ia & IIIa. Therefore, we can relate the lumen/ECS inlet flux to the region Ia/IIIa inlet flux via

$$Q_{i,in} = \int_{y_1}^{y_2} W_{i,in} dy = \int_{\tilde{y}_1}^{\tilde{y}_2} \tilde{W}_{i0} d\tilde{y} \quad \text{as } \tilde{z} \rightarrow 0. \quad (5.86)$$

Combining (5.84) – (5.86), we can relate the flux entering regions IV & VI to the flux entering the lumen/ECS and the flux gained/lost across region IIa by

$$\int_{\bar{y}_1}^{\bar{y}_2} \bar{W}_{i0} d\bar{y} = Q_{i,in} - \int_0^\infty \tilde{U}_i d\tilde{z} \quad \text{as } \bar{z} \rightarrow 0. \quad (5.87)$$

We note that in the limit $\varepsilon Re \rightarrow 0$, radial flux across the membrane wall in region IIa tends to zero as per (5.77). Therefore, the matching condition (5.87) reduces to (5.30).

Furthermore, we note that if we were to formally consider flow transitions through a geometry of finite length $1/\varepsilon$, we would need to prescribe an outlet condition (e.g. continuity of stress). As information largely flows in the direction of the fluid flow in this system, the analysis of flow transitions considered in this Chapter will hold for finite-length problems. However, depending on the relative size of the channel length $1/\varepsilon$ to the Reynolds number Re , we note that it may be required to match the transition flow problem into a boundary layer near the outlet to fully solve the problem. Given that we focus on modelling entrance effects only in this Chapter, we do not consider these outlet boundary layers further.

5.8.2 Results

We now utilise our asymptotic analysis to visualise the flow through our system in the high Reynolds number limit. The (nonlinear) leading-order system in regions Ia & IIIa (5.76) must be solved numerically. We note that numerical simulations of the same equations in analogous models with impermeable walls are considered by Dalwadi et al., which describe the solution for plug-to-lubrication flow transitions in a straight rigid 2D channel [69]. Hence, we focus on the inlet regions I – III and the Blasius boundary layer regions Ib & IIb.

In Section 5.8.1.2, we showed that there is no flow through region II at leading order, and that flow through regions I & III reduces to the standard Blasius solution for plug flow past an impermeable interface. We solve the system (5.64) – (5.65) numerically via the shooting method [118], and illustrate our results for the Blasius similarity solution in terms of the similarity variable η in Figure 5.4. This solution allows us to calculate the velocity profile through the boundary layer regions Ib & IIIb using Equation (5.63).

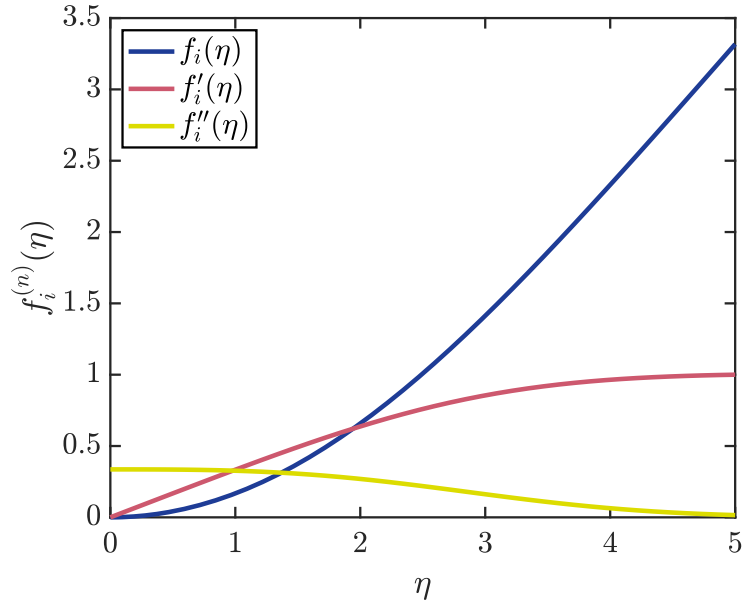


Figure 5.4: Solution to the Blasius similarity solution $f_i(\eta)$, alongside its first and second order derivatives $f'_i(\eta), f''_i(\eta)$ for an inlet velocity $W_{i,in} = 1$. We note that $\hat{W}_{i0} = f'_i(\eta)$.

In Figure 5.5, we illustrate the leading-order axial fluid velocity through the inner regions I & III, alongside boundary layers Ib & IIIb transformed into region I/III variables. Plug flow enters at the bioreactor inlet $z = 0$ and meets the channel walls, where the leading-order boundary conditions are given by no slip and no flux conditions (the transition from plug flow to no flow in these corner regions is considered in Appendix E). Blasius boundary layers with thickness of $O((z/Re)^{1/2})$ grow in the positive z -direction, bounding an inviscid core of plug flow through the centre of each channel. We see that as we increase the Reynolds number in each scenario, the rate at which the boundary layers grow, decreases, meaning that the central core of inviscid flow in regions I & III persists further through each channel.

To validate our asymptotic solution in the inner regions I – III, we also solve the full system of nondimensional equations using COMSOL Multiphysics® software. When

comparing our asymptotic and numerical solutions to the axial velocity in Figure 5.5, we see good qualitative agreement in the prediction of Blasius boundary layer formation near the channel walls. Additionally, we see that numerical simulations predict the decreasing boundary layer thickness at larger Reynolds numbers. At lower Reynolds numbers, we see that our COMSOL solution predicts the plug-to-lubrication transition to begin much earlier along the axial z -direction. At a larger Reynolds number, however, we see closer quantitative agreement with our asymptotic predictions of an inviscid core that persists through the centre of the channel. Our asymptotic and numerical simulations both predict negligible axial flow through the membrane in region II.

In Figure 5.6, we plot axial cross-sections of the axial velocity from Figure 5.5 to better compare our asymptotic and numerical models. In our asymptotic analysis of the large Reynolds number limit, we expand in powers of $Re^{-1/2}$ in regions I & III. Therefore, as the Reynolds number decreases, the contributions of higher-order terms increase. As such, we would expect to see larger discrepancies between the leading-order solution and full numerical simulations at smaller Reynolds numbers, as we see in Figure 5.6. We also see that our asymptotic and numerical solutions begin to diverge with increasing z , suggesting that the higher-order contributions in our asymptotic expansion contribute a z -dependency to the axial flow solution in these regions.

With good agreement between our asymptotic and numerical simulations, we can proceed to utilise our analysis to better understand fluid stresses induced by flow. Particularly in a tissue engineering scenario, the shear stress imparted on the porous scaffold wall is an important quantity to characterise to better understand the local mechanical environment cells might experience *in vitro*. In our 2D Cartesian geometry, the nondimensional leading-order shear stress in regions Ib & IIIb, transformed into region I & III variables, is given by

$$\sigma_{i,yz} = \frac{\partial W_i}{\partial y}. \quad (5.88)$$

In Figure 5.7, we see the shear stress evaluated at the membrane interface $y = 1$ in region Ib as a function of axial position z . We note that for $W_{e,in} = 1$, the equations and boundary conditions governing flow in regions Ib & IIIb are identical. As such, Figure 5.7 is also true for the shear stress evaluated at the membrane interface region IIIb (i.e. $\sigma_{l,yz}|_{y=1} = \sigma_{e,yz}|_{y=2} = \sigma_{yz}$). Towards $z = 0$ where plug flow enters our system, we can see the shear stress dramatically increases. This can be attributed to the inlet plug flow profile meeting the no slip and no flux condition at the channel

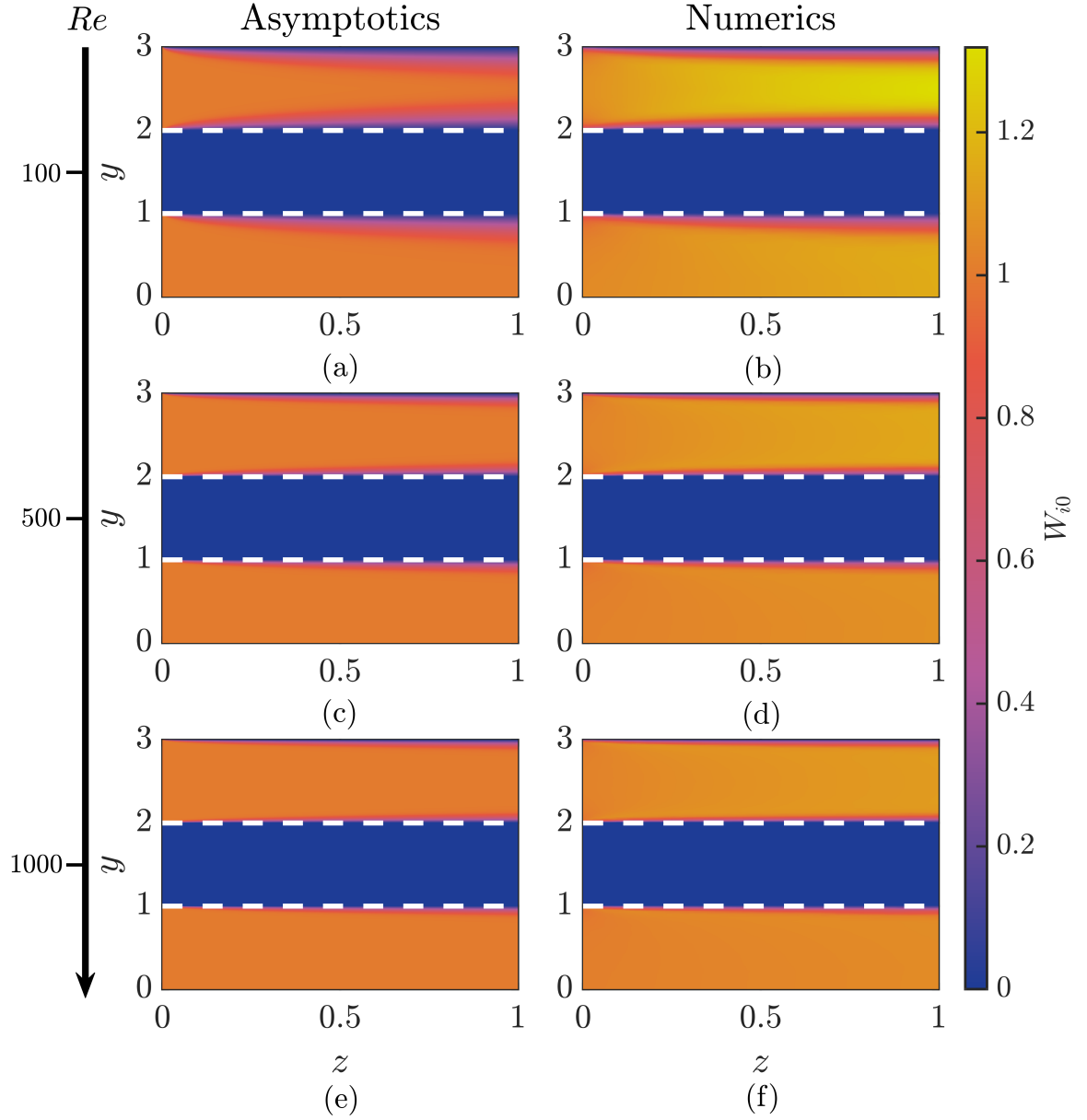


Figure 5.5: Comparing asymptotic (left) and numeric (right) solutions for the axial velocity profile through the inner regions I – III as a function of increasing Reynolds number, Re , using parameter values outlined in Table 5.1. Note the formation of Blasius boundary layer regions Ib & IIIb which grow in the positive z -direction.

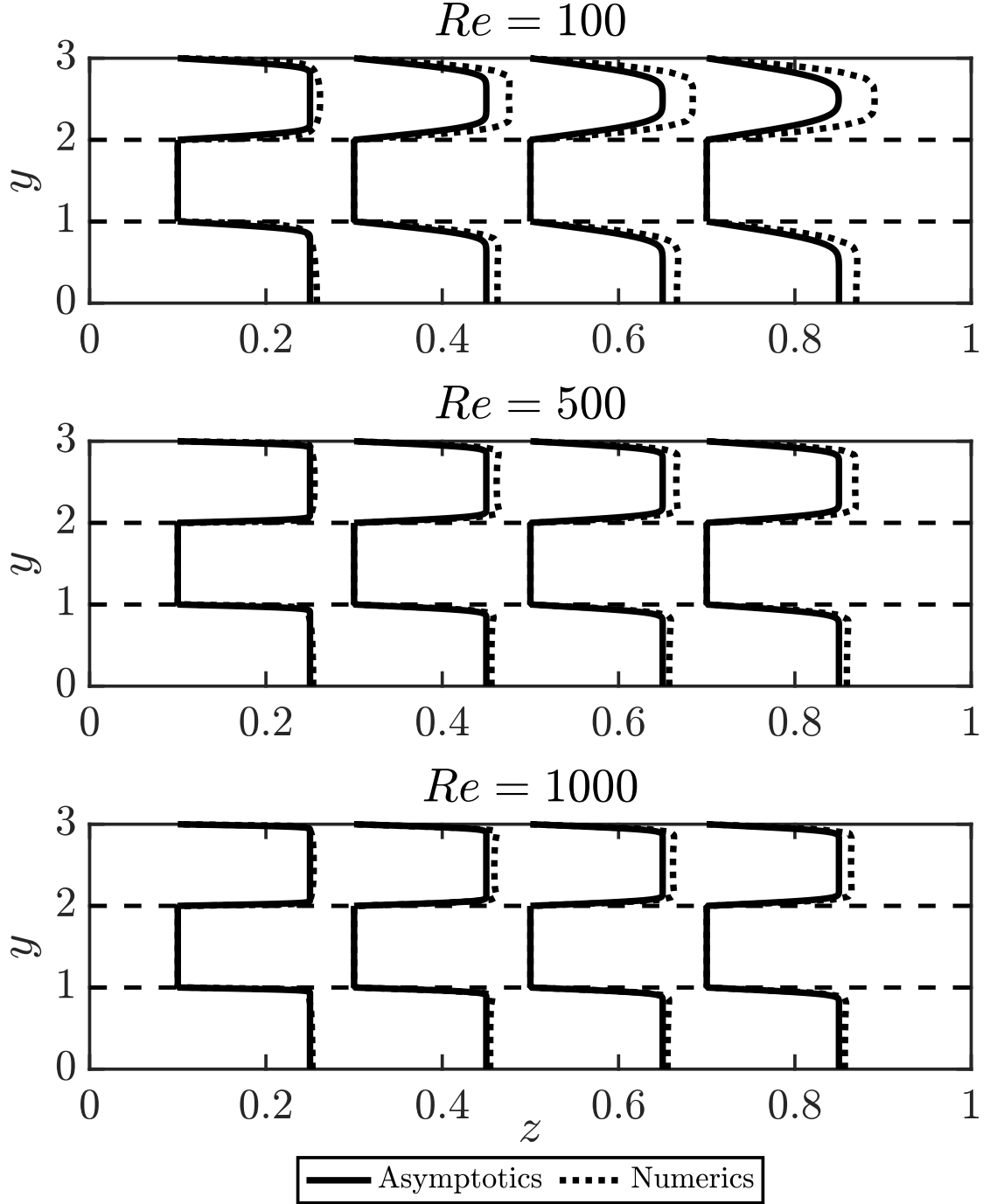


Figure 5.6: Comparison of the (normalised) axial velocity profiles at $z = 0.1, 0.3, 0.5, 0.7$ in regions I – III as predicted by our leading-order asymptotic solution and numerical solution computed using COMSOL Multiphysics®.

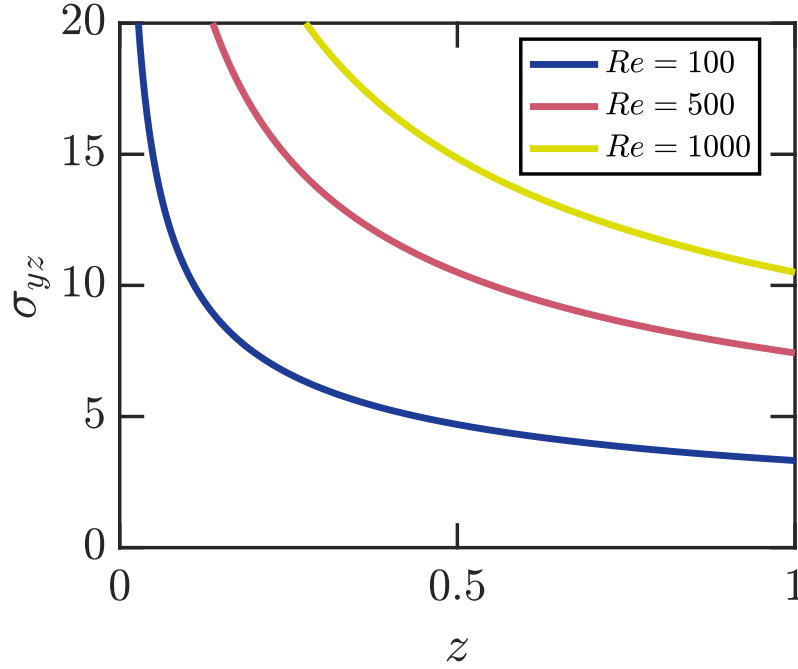


Figure 5.7: Shear stress at the membrane interface $y = 1$ in region Ib with varying Reynolds number. Note that the governing equations and boundary conditions for Ib & IIIb are the same in this scenario, and thus the results presented for region Ib are also true in region IIIb at the membrane interface $y = 2$.

walls. As such, flow decelerates rapidly in this region (as modelled by regions Ic/IIIc in Appendix E), thus contributing to large shear stresses near the inlet at the channel walls. As flow develops along the lumen and ECS, variations in the axial velocity profile decrease and thus the shear stress also decreases. As expected, we also see in Figure 5.7 that an increase in the Reynolds number Re , corresponding to larger fluid inertia, leads to an increase in the wall shear stress σ_{yz} . The Blasius similarity solution tells us that flow in regions Ib & IIIb is independent of the channel diameter, and is sensitive only to the Reynolds number Re and the inlet plug flow velocity $W_{i,in}$. Although not plotted, we note that increasing the inlet plug flow velocity also increases the shear stress at each axial wall position, following the same decreasing profile as in Figure 5.7.

5.9 Discussion

In this Chapter, we have investigated plug-to-lubrication flow transitions through two parallel long thin 2D channels mediated by a porous wall, evaluated across all values of laminar Reynolds numbers. In particular, we identify the emergent boundary layer

structure in the limits $Re = O(1)$ and $Re \gg 1$, and we derive the appropriate governing equations and matching conditions for the flow in each region, solving for the flow where feasible. In the large Re limit, we identify an intricate nested boundary layer structure, analogous to the setup considered by Dalwadi et al. [69] for rigid impermeable walls, that characterises the entrance length over which the plug-to-lubrication transition occurs. By considering a geometry of infinite length, we reveal how the magnitude of the reduced Reynolds number εRe dictates the observable boundary layer structure in a finite-length geometry. This analysis is key in understanding the flow structure for bioreactors operating at faster flow rates, allowing us to better understand the local mechanical environment cells might experience at different positions in our bioreactor setup. In transitional flow regions (i.e. near lumen/ECS inlets), we show that the fluid shear stress imparted on the membrane wall increases significantly. Therefore when considering cell seeding location, care must be taken to ensure that the desired cell line can withstand these predicted stresses.

In the large Reynolds number regime, we consider a full numerical simulation of the flow near the channel inlets to validate our leading-order asymptotic model. When solving for axial fluid velocities in this inner region, we find a strong qualitative and quantitative agreement between both approaches across a wide range of Reynolds numbers, which converge with increasing Re . Additionally, our numerical simulations validate our conclusions that, independent of the Reynolds number, we predict negligible flow in the membrane wall near the inlet. Together, this suggests that our reduced-order model provides an accurate mechanistic insight into the flow structure of our problem. However, further quantitative comparisons would be helpful to fully resolve and validate the intricate boundary layer structure for larger values of Re than we use here.

We note that the flow problem we consider in this Chapter is not unique to tissue engineering applications. Interactions between bulk flow and porous flows arise in a plethora of applied mathematics problems including filtration [119, 120], drug delivery [121] and tumour modelling [122, 123]. The analysis presented in this Chapter therefore provides a framework to extend investigations in these areas to gain a mechanistic insight into faster, more complex flow problems in a range of applications. The solutions presented in this Chapter can also be used in combination with the metabolite transport problem considered in Chapter 4 to model the transport of a given dilute species for an arbitrary Péclet number and (laminar) Reynolds number, providing a fast and flexible alternative to full numerical simulations such as COMSOL.

Chapter 6

Conclusion

6.1 Summary

In this thesis, we have developed a suite of continuum mathematical models to understand the flow, fluid-structure interaction, and metabolite transport in the context of poroelastic hollow fibre membrane bioreactors used for tissue engineering. We employed asymptotic methods to systematically reduce the system complexity, providing physical insight into the chemical and mechanical conditions experienced by cells *in vitro*. These insights facilitate the identification of a range of bioreactor operating strategies, and enable predictions of optimal operating parameter configurations (e.g. membrane thickness, permeability, lumen/ECS flow rates) that optimise nutrient delivery while mitigating undue mechanical stress.

In Chapter 2, we first consider 2D axisymmetric fluid-structure interaction in a poroelastic hollow fibre bioreactor. By exploiting the long thin bioreactor geometry and the large membrane stiffness relative to typical fluid pressures, we derive an analytic solution for steady Stokes flow in and around a linearly poroelastic annulus of circular cross-section, and compute membrane wall deformation. Our analysis reveals the intricate interplay between fluid flow and membrane deformation within a hollow fibre membrane bioreactor (HFMB) model, and allows us to efficiently visualise membrane deformation, stress and strain distributions. In particular, this allows us to understand how to control and modulate mechanical stress and strain distributions in the membrane wall. By varying operating conditions such as inlet pressures, structural factors including membrane thickness, and material properties such as compressibility and permeability, it is possible to tailor the mechanical environment to meet the specific requirements of cultured cell lines. We also show that flow decouples from membrane deformation at leading order in our model, thus simplifying to flow through a rigid porous hollow fibre. This means that we can consider

nutrient transport in Chapter 4 independently of membrane deformation. Furthermore, we introduce the concept of utilising a heterogeneous permeability distribution to achieve uniform radial fluid flux at the outer membrane wall, and characterise this using our framework. This presents an innovative approach to enhancing nutrient distribution within the bioreactor in an advection-dominated operating regime, with potential implications for optimising cell growth and tissue development. Our findings collectively underscore the significance of comprehensively understanding and manipulating the mechanical aspects of bioreactor systems in tissue engineering.

We extend this model in Chapter 3 to incorporate pulsatile flow and the resulting pulsatile membrane wall deformations. By considering a Fourier series decomposition of the dependent variables, we reduce our problem to a system of linearly independent unsteady Stokes flow problems that can be solved for each oscillatory mode. We compare membrane displacement, stress and strain distributions for the first oscillatory mode to the steady flow case, and show that in the limit of large membrane stiffness relative to viscous fluid forces (i.e. $v = \mu^* \omega^* / E^* \ll 1$), membrane inertia is lost at leading order, therefore membrane displacements remain in phase with the pulsatile lumen pressure profile for all oscillatory frequencies. Exploiting the long thin bioreactor geometry, we determine leading-order analytic expressions for the pressure-flux phase shift relationship, which exhibits non-monotonic behaviour as the oscillation frequency tends towards a natural resonant frequency. We show that in the limit of large oscillatory frequencies, the oscillatory phase lag tends towards $\pi/4$, unlike the traditional Womersley solution through a straight rigid pipe which tends towards $\pi/2$ [62]. We demonstrate that the asymptotic behaviour of the phase lag at large oscillatory frequencies in our problem depends on the membrane permeability relative to the oscillation frequency, and that as permeability decreases, the asymptotic behaviour in our porous-walled model tends towards the results captured by Womersley. Our work in Chapter 3 therefore represents a generalisation of the Womersley solution to compliant, poroelastic pipe walls, and captures the flow behaviour in an impermeable rigid pipe as a sublimit of this problem.

In Chapter 4, we model nutrient and waste metabolite transport in the HFMB. We consider the advection and diffusion of metabolites through our bioreactor at steady state, with nutrient uptake and waste production in a cell layer external to the membrane wall governed by Michaelis-Menten kinetics. By again exploiting the long thin bioreactor geometry and utilising a non-trivial curvilinear coordinate transformation, we can transform our advection-diffusion-reaction equations into a system of coupled 1D heat equations with non-constant coefficients, which we solve for numerically.

The insight provided by our model reduction generates a mechanistic understanding of metabolite transport in our system, and identifies the dominant transport mechanisms in each region of the bioreactor model. This reduction reveals that radial advection and diffusion play an important role in nutrient transport across the membrane wall, and that axial variations in nutrient uptake arise from axial variations in the transmural pressure drop. Therefore utilising the heterogeneous membrane distribution derived in Chapter 2, we can achieve uniform nutrient uptake in our cell region, as well as uniform waste removal. Lastly, we can use our reduced model to perform a comprehensive parameter sweep much quicker than full numerical simulations using standard engineering software such as COMSOL Multiphysics®. This allows us to identify combinations of structural and operating parameters that maximise nutrient delivery and waste removal.

Finally, we consider the canonical boundary layer structure for 2D plug flow transitioning to lubrication flow in two parallel channels connected via a porous medium, using the method of matched asymptotic expansions. We investigate the flow behaviour in the boundary layer regions for all (laminar) Reynolds number regimes, providing insight into the laminar transition from plug to lubrication flow. We explore in detail the complex nested boundary layer structure that emerges in the high Reynolds number limit. We present results for a range of Reynolds numbers and channel lengths, and systematically derive coupling conditions to match into the outer flow lubrication regions away from the channel inlets. Such analysis allows us to move away from modelling slow viscous flows in HFMBs towards introducing faster advective mass transport mechanisms.

6.2 Future work

In this thesis, we have made significant progress in the understanding of flow and transport in poroelastic HFMBs. Based on the contributions made in this thesis, we now propose future work that aims to extend the validity of our models, better emulate physiological flows, and provide further mechanistic insight into physical problems that involve interesting applied mathematics.

6.2.1 Biomimicry

The work conducted in this thesis is inspired by the poroelastic hollow fibre experimental setup described in Section 1.2, which is itself inspired by the geometry and mechanical properties of human vasculature. Therefore, a natural extension of this

work would be to consider physiologically-relevant flow profiles and geometries that better emulate flow in mammalian vasculature. While we considered a wide range of operating conditions including pulsatile flow and large Reynolds number flows, many of the simplifying assumptions made in our work begin to break down as we begin to compare to physiologically-relevant flow regimes. For example when considering pulsatile flow in large, thick-walled arteries, the driving pressure drop clearly does not vary sinusoidally, but rather follows the classic time-series profile for a human heart-beat. This is typically characterised by a sharp increase in pressure associated with heart contraction, known as systole, followed by an extended period of relaxation, known as diastole. If we are to better emulate the pressure drop profile experienced in human arteries, consideration must be made in our pulsatile flow problem to prescribe higher-order oscillatory modes, informed by experimental data, that better match *in vivo* pressure drop profiles. Additionally, fibre geometries would be chosen that better mimic the diameter, length, and wall thickness of the vasculature we wish to emulate.

Furthermore, our pulsatile flow solution in Chapter 3 neglects nonlinear inertial effects, and only considers transient inertia due to pulsatility. In arteries, the average Reynolds number $Re = \rho^* \overline{W}^* R_{i0}^* / \mu^* \approx 500$ [65], meaning that the reduced Reynolds number $\varepsilon Re \leq 1$ in a typical long thin fibre geometry. Therefore, the framework considered in Chapter 3 holds true for flow in arteries. However, to mimic pulsatile flow in larger arteries (e.g. $Re \approx 3000$ in the aorta [65]), our model begins to break down. Therefore, we would require an alternative methodology to investigate this, such as full 3D simulations of Navier-Stokes equations.

Lastly, we note that compliant arterial walls are held under tension *in vivo*. This allows for deformation and recoil of the vessel wall to help absorb excessive fluid pressures and drive flow through the circulatory system. Mathematically, this is prescribed by enforcing a tensile stress condition at each of the axial ends, as considered by Enderle et al. for a linearly elastic tube wall [65]. In Chapters 2 and 3 we do not consider pre-stress of the membrane wall, but instead prescribe clamped wall boundary conditions (2.34). This change in boundary condition will alter the mechanical stress predicted for cells seeded to the surface, as well as impact the deformation and strain gradient distributions throughout the membrane wall. For smaller-diameter vasculature such as arterioles, the effect of pre-stress is felt less strongly, therefore we postulate that our model can more accurately reflect the mechanics of smaller vessels. However, further comparisons between clamped and pre-stressed poroelastic

membranes would elucidate the importance of the prescribed axial boundary conditions.

6.2.2 Cell growth

Perhaps most important for bioreactor modelling is an understanding of tissue growth. In Chapter 4, we consider bioreactor operation on a timescale whereby nutrient transport and uptake is much faster than cell growth. Therefore we take the cell layer to be of constant thickness, and consider the steady solution for metabolite transport. However, if we want to account for time-dependent cell growth, we must extend our analysis to consider longer timescales. In Section 1.3.4, we discuss how Chapman et al. consider the time-dependent growth of a cell layer external to the membrane wall [87]. Experimentally, however, it can be observed that over long timescales, cells can detach as well as engraft in the membrane scaffold, blocking membrane pores and thus locally increasing the resistance of the membrane to transmural flux. If this continues over time, then the membrane risks blocking completely, restricting nutrient delivery to cells at the outer membrane wall. To account for this mathematically, we propose an extension to this model that considers an effective time-dependent membrane permeability that decreases proportionally to an empirical cell growth law. This is analogous to membrane fouling problems considered by Herterich et al. [124], whereby the inlet pressure required to sustain the same membrane flux increases in time as the effective membrane permeability decreases due to fouling. Such analysis would reveal how the efficiency of nutrient delivery in our system would vary as a function of time, giving experimentalists an estimate of the lifespan of a given tissue scaffold setup. Furthermore, such a setup would facilitate an explicit dependency of important parameters such as membrane thickness, permeability, and inlet flux on membrane fouling rate, to maximise the lifespan of a membrane.

6.2.3 Experimental and numerical validation

As is the case across applied mathematics research, validating mathematical models is essential to ensure that predictions are precise and accurate. Whilst experimental validation is desirable to ensure that models resemble the real-life physical scenario under consideration, often it is infeasible to collect data due to time and resource restrictions. One way to validate the reduction of the full model is via numerical validation. In Chapter 5, we consider full numerical simulations of plug-to-lubrication

flow transitions for large Reynolds numbers. These simulations show strong quantitative agreement with our asymptotic predictions, providing support for our analysis. However, full numerical simulations of the flow and transport problems considered in Chapters 2–4 would further validate the conclusions made in this thesis, as well as provide a platform to extend the complexity of models.

Additionally, and importantly, we would recommend experimental validation of the models considered in this thesis. This validation ensures that the models we have developed can accurately capture the biology and mechanics observed in real life when parameterised by experimental data. To do so, we recommend the following experimental setups:

- **Validation of fluid-structure interaction model**

In Chapter 2, we conclude that in the limit of large membrane stiffness, flow decouples from the deformation of the membrane wall. As such, the fluid flow problem reduces to classic lubrication flow in and around a rigid porous fibre, meaning that the resistance to flow across the membrane wall (i.e. the permeability and wall thickness) remains constant. To validate this, a series of experiments could be conducted that measures the outlet flow rates in the lumen and ECS under a range of inlet lumen flow rates. Quantitative agreement with model predictions would suggest that membrane wall deformations do not sufficiently compress membrane pores to alter its permeability, as per our predictions. Alternatively if data does not support model predictions, this may be indicative that there is significant deformation at the microstructure level unaccounted for by our modelling framework.

- **Validation of nutrient transport model**

In Chapter 4, experimental validation of the nutrient transport and uptake model could be considered by measuring the difference in nutrient concentration across the membrane wall to estimate the uptake rate of nutrients at each axial position along the fibre. This could then be compared to model predictions parameterised by literature values for nutrient kinetic and transport parameters, or could be fitted to the model via Bayesian inference methods to determine the goodness of fit. This would ensure that model assumptions of small cell layer thickness and strong nutrient uptake are grounded in experimental observations.

- **Uniform nutrient delivery**

With advancements in polymer electrospinning synthesis and control, it may

be possible to consider experimental observations of transport in a hollow fibre membrane with an optimal membrane permeability distribution as determined from Chapter 2 to validate if heterogeneous membrane permeability can lead to uniform tissue growth. This could be considered by measuring local nutrient concentration or estimating tissue growth rate along the length of the fibre in a single fibre HFMB setup as a function of time, comparing membranes with a homogeneous and heterogeneous permeability. Not only would this validate our findings that axial variations in membrane nutrient flux arise from axial variations in the transmural pressure drop, but would also contribute to the development of a hollow fibre bioreactor that facilitated uniform tissue growth.

- **Minimum concentration requirement**

In Chapter 4, we are able to show the impact of varying the inlet nutrient concentration on the nutrient concentration delivered to the cell layer. This analysis can help determine the minimum inlet nutrient concentration required to achieve a certain tissue growth rate, which is particularly useful for minimising operating costs for expensive nutrients and growth factors, as well as maximising bioreactor efficiency. To help validate these findings, it would be useful to conduct a series of experiments of decreasing inlet nutrient concentration (e.g. vascular endothelial growth factor (VEGF), an important and expensive growth factor essential in engineering and remodelling vasculature) whilst measuring the average nutrient concentration at the outer membrane wall to validate these model predictions.

With experimental and numerical validation, our reduced-order models provide a fast and robust framework to quickly explore parameter space, as well as infer model parameter distributions from experimental data using Bayesian inference methods. We propose that our models can also be used to consider the inverse problem whereby parameters that are difficult to determine from direct measurements (e.g. permeability, growth rate parameters) could be inferred from fitting data to our reduced-order models. As such, costly and time-intensive characterisation methods would be replaced by quick and easy computational inference methods that help directly describe and inform experimental design.

In this thesis, we make significant advancements towards understanding the complex dynamics within poroelastic HFMBs. The future endeavours, as outlined, promise to refine these models further, ensuring more accurate and experimentally verifiable predictions. By bridging mathematical modelling with experimental validation, we

inch closer to designing bioreactors that mimic natural cellular environments, thereby advancing regenerative medicine and unlocking new avenues in therapeutic applications.

Appendix A

Linearising the fluid-poroelastic interfacial conditions

In Section 2.4 we define a set of boundary conditions at the deformed inner and outer fluid-poroelastic interfaces. These consist of a continuity of stress condition, a continuity of fluid stress condition, a no-slip condition and a continuity of flux condition. Deformation at each interface is defined by the displacement of the membrane wall at a given point:

$$r^* = R_{j0}^* + u_j^*, \quad z^* = z_0^* + w_j^*, \quad (\text{A.1})$$

where $j = l, m$ at the inner and outer interfaces respectively. Therefore, the fluid-structure interfaces vary as a function of radial and axial position. To simplify this, we take a first-order Taylor expansion of each boundary condition in both the radial and axial directions with reference to the undeformed boundaries (R_{j0}^*, z_0^*) . For example, for an arbitrary function $f^*(r^*, z^*)$, a first-order Taylor expansion about the same interface would become

$$f^*(R_{j0}^* + u_j^*, z_0^* + w_j^*) \approx f^*(R_{j0}^*, z_0^*) + u_j^* \left. \frac{\partial f^*}{\partial r^*} \right|_{R_{j0}^*, z_0^*} + w_j^* \left. \frac{\partial f^*}{\partial z^*} \right|_{R_{j0}^*, z_0^*}. \quad (\text{A.2})$$

Applying (A.2) to (2.11), continuity of normal and tangential stress at each interface becomes

$$\begin{aligned} \boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j + u_j^* \frac{\partial}{\partial r^*} [\boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j] + w_j^* \frac{\partial}{\partial z^*} [\boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j] = \\ \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j + u_j^* \frac{\partial}{\partial r^*} [\boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j] + w_j^* \frac{\partial}{\partial z^*} [\boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j], \end{aligned} \quad (\text{A.3})$$

where

$$\hat{\mathbf{n}}_j \cdot \boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j = \frac{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 \tau_{rr}^* - 2 \left(1 + \frac{\partial w_j^*}{\partial z^*}\right) \frac{\partial u_j^*}{\partial z^*} \tau_{rz}^* + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2 \tau_{zz}^*}{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}, \quad (\text{A.4a})$$

$$\hat{\mathbf{t}}_j \cdot \boldsymbol{\tau}^* \cdot \hat{\mathbf{n}}_j = \frac{\left(\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 - \left(\frac{\partial u_j^*}{\partial z^*}\right)^2\right) \tau_{rz}^* + \left(1 + \frac{\partial w_j^*}{\partial z^*}\right) \frac{\partial u_j^*}{\partial z^*} (\tau_{rr}^* - \tau_{zz}^*)}{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}, \quad (\text{A.4b})$$

$$\hat{\mathbf{n}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j = \frac{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 \sigma_{i,rr}^* - 2 \left(1 + \frac{\partial w_j^*}{\partial z^*}\right) \frac{\partial u_j^*}{\partial z^*} \sigma_{i,rz}^* + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2 \sigma_{i,zz}^*}{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}, \quad (\text{A.4c})$$

$$\hat{\mathbf{t}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j = \frac{\left(\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 - \left(\frac{\partial u_j^*}{\partial z^*}\right)^2\right) \sigma_{i,rz}^* + \left(1 + \frac{\partial w_j^*}{\partial z^*}\right) \frac{\partial u_j^*}{\partial z^*} (\sigma_{i,rr}^* - \sigma_{i,zz}^*)}{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}. \quad (\text{A.4d})$$

Continuity of normal fluid stress (2.15) becomes

$$\begin{aligned} \hat{\mathbf{n}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j + u_j^* \frac{\partial}{\partial r^*} [\hat{\mathbf{n}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j] + w_j^* \frac{\partial}{\partial z^*} [\hat{\mathbf{n}}_j \cdot \boldsymbol{\sigma}_i^* \cdot \hat{\mathbf{n}}_j] = \\ - P_m^* - u_j^* \frac{\partial P_m^*}{\partial r^*} - w_j^* \frac{\partial P_m^*}{\partial z^*}. \end{aligned} \quad (\text{A.5})$$

The no axial slip condition (2.16) becomes

$$\mathbf{U}_i^* \cdot \hat{\mathbf{t}}_j + u_j^* \frac{\partial}{\partial r^*} [\mathbf{U}_i^* \cdot \hat{\mathbf{t}}_j] + w_j^* \frac{\partial}{\partial z^*} [\mathbf{U}_i^* \cdot \hat{\mathbf{t}}_j] = 0, \quad (\text{A.6})$$

where

$$\mathbf{U}_i^* \cdot \hat{\mathbf{t}}_j = \frac{\frac{\partial u_j^*}{\partial z^*} \mathbf{U}_i^* + \left(1 + \frac{\partial w_j^*}{\partial z^*}\right) \mathbf{W}_i^*}{\sqrt{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}}. \quad (\text{A.7})$$

Lastly, the continuity of flux condition (2.17) becomes

$$\begin{aligned} \mathbf{U}_i^* \cdot \hat{\mathbf{n}}_j + u_j^* \frac{\partial}{\partial r^*} [\mathbf{U}_i^* \cdot \hat{\mathbf{n}}_j] + w_j^* \frac{\partial}{\partial z^*} [\mathbf{U}_i^* \cdot \hat{\mathbf{n}}_j] = \\ \phi_m \mathbf{U}_m^* \cdot \hat{\mathbf{n}}_j + u_j^* \frac{\partial}{\partial r^*} [\phi_m \mathbf{U}_m^* \cdot \hat{\mathbf{n}}_j] + w_j^* \frac{\partial}{\partial z^*} [\phi_m \mathbf{U}_m^* \cdot \hat{\mathbf{n}}_j], \end{aligned} \quad (\text{A.8})$$

where

$$\mathbf{U}_i^* \cdot \hat{\mathbf{n}}_j = \frac{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right) U_i^* - \frac{\partial u_j^*}{\partial z^*} W_i^*}{\sqrt{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}}, \quad (\text{A.9a})$$

$$\phi_m \mathbf{U}_m^* \cdot \hat{\mathbf{n}}_j = \frac{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right) \phi_m U_m^* - \frac{\partial u_j^*}{\partial z^*} \phi_m W_m^*}{\sqrt{\left(1 + \frac{\partial w_j^*}{\partial z^*}\right)^2 + \left(\frac{\partial u_j^*}{\partial z^*}\right)^2}}. \quad (\text{A.9b})$$

Equations (A.3)–(A.9) are applied at the undeformed inner (R_{l0}^*, z^*) and outer (R_{m0}^*, z^*) membrane wall interfaces, with components of stress defined in (2.7).

Given the scalings in (2.24), we can now nondimensionalise our interfacial conditions to determine the relative order of terms. Continuity of normal stress (A.3) becomes

$$\mathcal{A} + \gamma u_j \frac{\partial \mathcal{A}}{\partial r} + \gamma w_j \frac{\partial \mathcal{A}}{\partial z} = \mathcal{B} + \gamma u_j \frac{\partial \mathcal{B}}{\partial r} + \gamma w_j \frac{\partial \mathcal{B}}{\partial z}, \quad (\text{A.10})$$

where

$$\begin{aligned} \mathcal{A} = & \left(1 + \gamma \frac{\partial w_j}{\partial z}\right)^2 \left(\frac{1}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial u_j}{\partial r} + (1-\delta) \left(\frac{u_j}{r} + \frac{\partial w_j}{\partial z} \right) \right] - P_m \right) \\ & - 2\gamma \left(1 + \gamma \frac{\partial w_j}{\partial z}\right) \frac{\partial u_j}{\partial z} \left(\frac{1}{(3-\delta)} \left[\frac{\partial w_j}{\partial r} + \varepsilon^2 \frac{\partial u_j}{\partial z} \right] \right) \\ & + (\gamma\varepsilon)^2 \left(\frac{\partial u_j}{\partial z} \right)^2 \left(\frac{1}{\delta(3-\delta)} \left[(1+\delta) \frac{\partial w_j}{\partial z} + (1-\delta) \left(\frac{\partial u_j}{\partial r} + \frac{u_j}{r} \right) \right] - P_m \right), \quad (\text{A.11a}) \end{aligned}$$

$$\begin{aligned} \mathcal{B} = & \left(1 + \gamma \frac{\partial w_j}{\partial z}\right)^2 \left(-P_i + 2\varepsilon^2 \frac{\partial U_i}{\partial r} \right) - 2\gamma\varepsilon^2 \left(1 + \gamma \frac{\partial w_j}{\partial z}\right) \frac{\partial u_j}{\partial z} \left(\frac{\partial W_i}{\partial r} + \varepsilon^2 \frac{\partial U_i}{\partial z} \right) \\ & + (\gamma\varepsilon)^2 \left(\frac{\partial u_j}{\partial z} \right)^2 \left(-P_i + 2\varepsilon^2 \frac{\partial W_i}{\partial z} \right). \quad (\text{A.11b}) \end{aligned}$$

Continuity of tangential stress (A.3) becomes

$$\mathcal{C} + \gamma u_j \frac{\partial \mathcal{C}}{\partial r} + \gamma w_j \frac{\partial \mathcal{C}}{\partial z} = \varepsilon^2 \left(\mathcal{D} + \gamma u_j \frac{\partial \mathcal{D}}{\partial r} + \gamma w_j \frac{\partial \mathcal{D}}{\partial z} \right), \quad (\text{A.12})$$

where

$$\begin{aligned} \mathcal{C} = & \left(\left(1 + \gamma \frac{\partial w_j}{\partial z}\right)^2 - (\gamma\varepsilon)^2 \left(\frac{\partial u_j}{\partial z} \right)^2 \right) \frac{1}{3-\delta} \left[\frac{\partial w_j}{\partial r} + \varepsilon^2 \frac{\partial u_j}{\partial z} \right] \\ & + \frac{2\gamma\varepsilon^2}{(3-\delta)} \frac{\partial u_j}{\partial z} \left(1 + \gamma \frac{\partial w_j}{\partial z}\right) \left[\frac{\partial u_j}{\partial r} - \frac{\partial w_j}{\partial z} \right], \quad (\text{A.13a}) \end{aligned}$$

$$\begin{aligned} \mathcal{D} = & \left(\left(1 + \gamma \frac{\partial w_j}{\partial z} \right)^2 - (\gamma \varepsilon)^2 \left(\frac{\partial u_j}{\partial z} \right)^2 \right) \left[\frac{\partial W_i}{\partial r} + \varepsilon^2 \frac{\partial U_i}{\partial z} \right] \\ & + 2\gamma \varepsilon^4 \frac{\partial u_j}{\partial z} \left(1 + \gamma \frac{\partial w_j}{\partial z} \right) \left[\frac{\partial W_i}{\partial z} - \frac{\partial U_i}{\partial r} \right]. \end{aligned} \quad (\text{A.13b})$$

The fluid stress condition (A.5) becomes

$$\mathcal{E} + \gamma u_j \frac{\partial \mathcal{E}}{\partial r} + \gamma w_j \frac{\partial \mathcal{E}}{\partial z} = - \left(P_m + \gamma u_j \frac{\partial P_m}{\partial r} + \gamma w_j \frac{\partial P_m}{\partial z} \right), \quad (\text{A.14})$$

where

$$\begin{aligned} \mathcal{E} = & \left(1 + \gamma \frac{\partial w_j}{\partial z} \right)^2 \left(-P_i + 2\varepsilon^2 \frac{\partial U_i}{\partial r} \right) - 2\gamma \varepsilon^2 \left(1 + \gamma \frac{\partial w_j}{\partial z} \right) \frac{\partial u_j}{\partial z} \left(\frac{\partial W_i}{\partial r} + \varepsilon^2 \frac{\partial U_i}{\partial z} \right) \\ & + (\gamma \varepsilon)^2 \left(\frac{\partial u_j}{\partial z} \right)^2 \left(-P_i + 2\varepsilon^2 \frac{\partial W_i}{\partial z} \right). \end{aligned} \quad (\text{A.15})$$

The no slip condition (A.6) becomes

$$\mathcal{F} + \gamma u_j \frac{\partial \mathcal{F}}{\partial r} + \gamma w_j \frac{\partial \mathcal{F}}{\partial z} = 0, \quad (\text{A.16})$$

where

$$\mathcal{F} = \varepsilon^2 \gamma \frac{\partial u_j}{\partial z} U_i + \left(1 + \gamma \frac{\partial w_j}{\partial z} \right) W_i. \quad (\text{A.17})$$

Finally, continuity of flux (A.8) becomes

$$\mathcal{G} + \gamma u_j \frac{\partial \mathcal{G}}{\partial r} + \gamma w_j \frac{\partial \mathcal{G}}{\partial z} = \mathcal{H} + \gamma u_j \frac{\partial \mathcal{H}}{\partial r} + \gamma w_j \frac{\partial \mathcal{H}}{\partial z}, \quad (\text{A.18})$$

where

$$\mathcal{G} = \left(1 + \gamma \frac{\partial w_j}{\partial z} \right) U_i - \gamma \frac{\partial u_j}{\partial z} W_i, \quad (\text{A.19a})$$

$$\mathcal{H} = \left(1 + \gamma \frac{\partial w_j}{\partial z} \right) \phi_m U_m - \gamma \varepsilon^2 \frac{\partial u_j}{\partial z} \phi_m W_m. \quad (\text{A.19b})$$

Equations (A.10) - (A.19) are evaluated at the undeformed inner (at $r = 1$, where $i = l, j = l$) and outer (at $r = R_{m0}$, where $i = e, j = m$) membrane wall interfaces. Note that we have identified two small parameters, namely ε as defined in (2.24) as the aspect ratio of the fibre lumen, and $\gamma = \mu^* \bar{W}^* / \varepsilon^2 L^* E^*$ which describes the ratio of viscous forces to the effective Young's modulus of the poroelastic fibre. To retain both small parameters in our asymptotic expansion, we let $\gamma = b\varepsilon^2$ where $b = \gamma/\varepsilon^2 \sim O(1)$. We then proceed with our model solution as detailed in Section 2.6.

Appendix B

Proof of real roots of the characteristic equation for fluid pressure

In this Appendix, we will solve for the lumen and ECS pressures P_l, P_e for steady flow considered in Chapter 2. From (2.49), we substitute our expression for P_e in terms of P_l into our ODE for P_e to obtain a fourth-order linear ODE in P_l with constant coefficients

$$\frac{AC}{\kappa^2} \frac{d^4 P_l}{dz^4} - \frac{(A+C)}{\kappa} \frac{d^2 P_l}{dz^2} = 0, \quad (\text{B.1})$$

where we let $C = -B$. Therefore, the characteristic equation for (B.1) is given by

$$\frac{AC}{\kappa^2} \lambda^4 - \frac{(A+C)}{\kappa} \lambda^2 = 0. \quad (\text{B.2})$$

Solving for the roots of the characteristic equation (B.2), we find that

$$\lambda_{1,2} = 0, \quad \lambda_{3,4} = \pm \sqrt{\frac{\kappa(A+C)}{AC}}. \quad (\text{B.3})$$

To solve for P_l , we must determine the behaviour of the roots to the equation $\lambda_{3,4}$ to determine the correct form of the general solution that solves (B.1). In this Appendix, we will prove that the solution to (B.2) yields real roots for all combinations of model parameter values.

For $\lambda_{3,4}$ to be real, we require that

$$\kappa(A+C)/AC > 0. \quad (\text{B.4})$$

The nondimensional permeability κ must be, by definition, a positive quantity. Additionally from inspection of (2.50a), we see that $A > 0$ for all possible values of R_{m0} .

Therefore if $C > 0$, then (B.4) holds true. Upon inspection of (2.50b), we find that $C > 0$ (or $B < 0$) when

$$\ln \left(\frac{R_{m0}}{R_{e0}} \right) < \frac{R_{m0}^2 - R_{e0}^2}{R_{m0}^2 + R_{e0}^2}. \quad (\text{B.5})$$

To simplify our analysis, we define $x = R_{e0}/R_{m0} > 1$. As such, (B.5) becomes

$$\ln x > \frac{x^2 - 1}{x^2 + 1}. \quad (\text{B.6})$$

Differentiating (B.6) with respect to x , we can rearrange to find that in the range of possible parameter values, this inequality holds when

$$x > 1 \quad \therefore \quad R_{e0} > R_{m0}. \quad (\text{B.7})$$

Given that $R_{e0} > R_{m0} > 1$ by definition in our problem, we show that $C > 0$ for any physically-relevant values of R_{m0} and R_{e0} . From this, we show that $\kappa(A+C)/AC > 0$ and thus the roots of the characteristic equation (B.2) are always real. Therefore, the general solution of (B.1) is given by (2.51).

Appendix C

Poroelastic membrane force balances

In this Appendix we conduct a force balance across a representative finite volume element in the outer region of this membrane wall, in order to physically describe the relationship between different components of material stress. Figure C.1 describes the components of stress acting on such a finite volume with radial thickness Δr^* and length Δz^* rotated through some angle $\Delta\theta^*$. Given the assumption of axisymmetry in our model, we find $\tau_{r\theta}^*$ and $\tau_{\theta z}^*$ are identically zero and thus do not feature in these force balances. From the diagram, we see that resolving components of hoop stress in the perpendicular horizontal and vertical components yields a balance of horizontal hoop stresses, which requires no further analysis.

C.1 Radial force balance

In the vertical direction, and at steady state under the action of no external accelerative forces, we have a balance between radial and hoop stresses of the form

$$\tau_{rr}^* r^* \Delta r^* + 2\tau_{\theta\theta}^* \Delta r^* \sin\left(\frac{\Delta\theta^*}{2}\right) = (\tau_{rr}^* + \Delta\tau_{rr}^*)(r^* + \Delta r^*)\Delta\theta^*. \quad (\text{C.1})$$

Given the angle $\Delta\theta^*$ is suitably small, we use the small angle approximation to approximate $\sin(\Delta\theta^*/2) \approx \Delta\theta^*/2$. Expanding out Equation (C.1) and negating products of small variables (e.g. $\Delta\tau_{rr}^* \Delta r^*$), we find

$$\tau_{\theta\theta}^* - \tau_{rr}^* = r^* \frac{\Delta\tau_{rr}^*}{\Delta r^*} \rightarrow r^* \frac{\partial\tau_{rr}^*}{\partial r^*}, \quad (\text{C.2})$$

in the limit $\Delta r^* \rightarrow 0$. Given the nondimensionalisation scalings defined in Equation (2.24), we can use our stress-displacement relationships in Equation (2.7) to define a

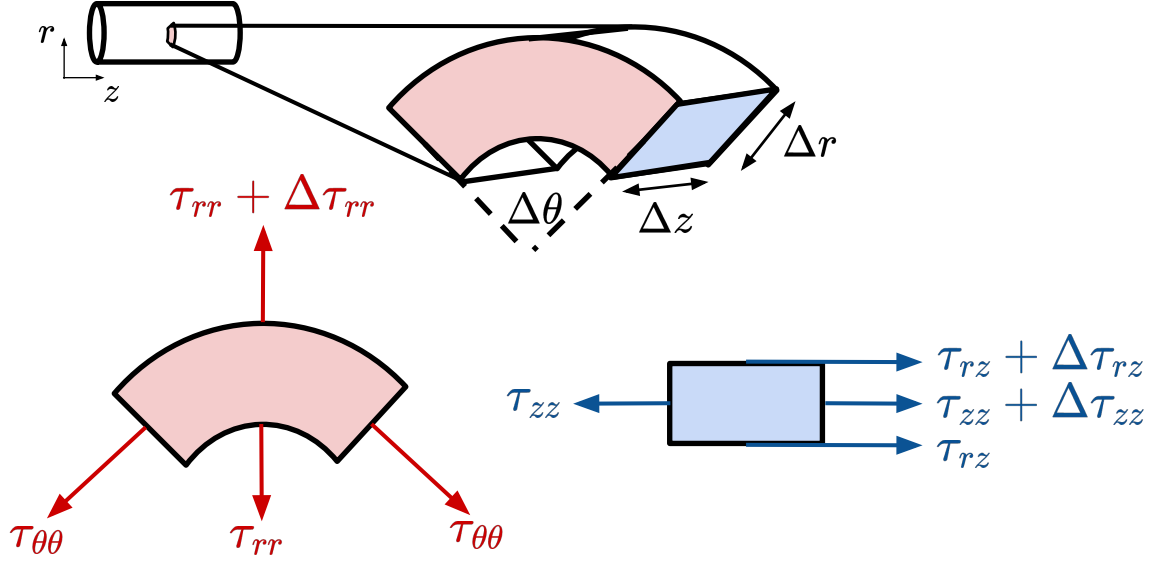


Figure C.1: Force balance over a finite control volume of the tube wall in the radial (bottom left) and axial (bottom right) directions.

set of scalings for components of stress such that

$$(\tau_{rr}^*, \tau_{\theta\theta}^*) = \tau_\star(\tau_{rr}, \tau_{\theta\theta}) \quad (\text{C.3})$$

where

$$\tau_\star = \frac{\mu^* \bar{W}^*}{\varepsilon^2 L^*}. \quad (\text{C.4})$$

Using these scalings, the nondimensional form of Equation (C.2) becomes

$$\tau_{\theta\theta} - \tau_{rr} = r \frac{\partial \tau_{rr}}{\partial r}. \quad (\text{C.5})$$

Thus, we demonstrate how hoop stress is directly proportional to radial stress and its radial derivative. Under typical operating conditions in Figure 2.6 we see that although compressive radial stress is negative due to continuity of normal stress with external fluid pressures, the gradient of radial stress is positive in the radial direction. Therefore through the relationship outlined in Equation (C.5), we can explain how compressive radial stress can induce a corresponding tensile hoop stress when $r \frac{\partial \tau_{rr}}{\partial r} > -\tau_{rr}$. We can integrate (C.5) across the tube wall using integration by parts to find that

$$\int_1^{R_{m0}} \tau_{\theta\theta} dr = [r \tau_{rr}]_1^{R_{m0}}. \quad (\text{C.6})$$

C.2 Axial force balance

Considering a balance of forces in the axial direction at steady state and under the action of no external accelerative forces, we find a balance between axial and shear stresses such that

$$\tau_{zz}^* z^* \Delta r^* = (z^* + \Delta z^*)(\tau_{zz}^* + \Delta \tau_{zz}^*) \Delta r^* + \tau_{rz}^* r^* \Delta z^* + (\tau_{rz}^* + \Delta \tau_{rz}^*)(r^* + \Delta r^*) \Delta z^* \quad (\text{C.7})$$

Expanding out and neglecting products of small variables as before, the axial force balance dramatically reduces down to

$$\tau_{rz}^* r^* \Delta z^* = 0, \quad (\text{C.8})$$

therefore for this to hold, $\tau_{rz}^* = \tau_{rz} = 0$. As a result, axial stress acts equally and oppositely over the finite element in the axial direction.

Appendix D

Bessel functions

In this Appendix, we provide further detail on Bessel functions, which arise in our solution to pulsatile flow through our hollow fibre bioreactor setup in Chapter 3. Bessel functions describe the canonical family of solutions $y(x)$ to Bessel's differential equation

$$x^2 \frac{d^2 y}{dx^2} + x \frac{dy}{dx} + (x^2 - \alpha^2)y = 0, \quad (\text{D.1})$$

where α is an arbitrary complex number. The general solution to (D.1) is given by

$$y = c_1 J_\alpha(x) + c_2 Y_\alpha(x), \quad (\text{D.2})$$

where J_α, Y_α are Bessel functions of the first and second kind of order α respectively, and c_1, c_2 are constants of integration to be solved for. Bessel functions of integer order often arise in cylindrical problems when deriving separable solutions to Laplace's equation in cylindrical coordinates, and in Chapter 3, we find that this too is the case.

Bessel functions are closely related to trigonometric functions. For large values of x , Bessel functions omit oscillatory behaviour similarly to sine and cosine graphs as shown in Figure D.1. For positive or integer values of α , Bessel functions of the first kind are finite at $x = 0$. Conversely, Bessel functions of the second kind have a singularity at the origin $x = 0$ and are multivalued. For $n \in \mathbb{Z}$, Bessel functions of the first kind can be expressed via the Hansen-Bessel formula [125]

$$J_n(x) = \frac{1}{\pi} \int_0^\pi \cos(n\tau - x \sin \tau) d\tau = \frac{1}{2\pi} \int_{-\pi}^\pi e^{i(n\tau - x \sin \tau)} d\tau, \quad (\text{D.3})$$

where i is the imaginary unit. Bessel functions of the second kind Y_α are generally related to J_α by

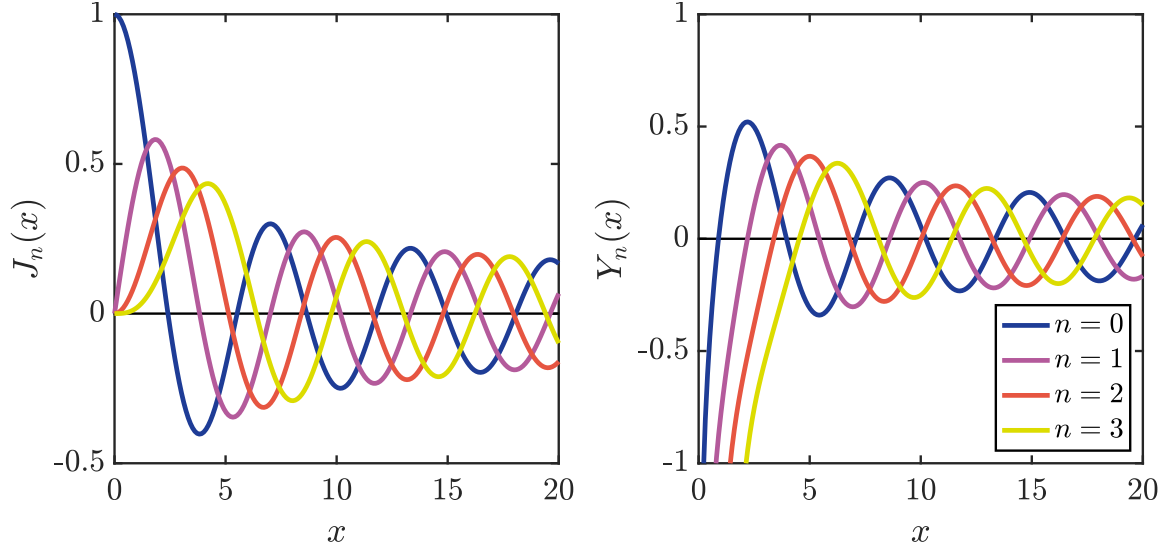


Figure D.1: Bessel functions of the first kind (left) and of the second kind (right) of integer order $n \in \{0, 1, 2, 3\}$.

$$Y_\alpha(x) = \frac{J_\alpha(x) \cos(\alpha\pi) - J_{-\alpha}(x)}{\sin(\alpha\pi)}, \quad (\text{D.4})$$

and thus for integer order n , we can express Y_n by taking the limit in which $\alpha \rightarrow n$

$$Y_n(x) = \lim_{\alpha \rightarrow n} Y_\alpha(x). \quad (\text{D.5})$$

To relate Bessel functions of the first and second kind of order α to lower or higher orders, we can utilise the recurrence relationships

$$\frac{2\alpha}{x} Z_\alpha(x) = Z_{\alpha-1}(x) + Z_{\alpha+1}(x), \quad (\text{D.6a})$$

$$2 \frac{dZ_\alpha(x)}{dx} = Z_{\alpha-1}(x) - Z_{\alpha+1}(x), \quad (\text{D.6b})$$

where $Z_\alpha = J_\alpha, Y_\alpha$. Combining Equations (D.6), it can be shown that

$$\left(\frac{1}{x} \frac{d}{dx} \right)^m [x^\alpha Z_\alpha(x)] = x^{\alpha-m} Z_{\alpha-m}(x), \quad (\text{D.7a})$$

$$\left(\frac{1}{x} \frac{d}{dx} \right)^m \left[\frac{Z_\alpha(x)}{x^\alpha} \right] = (-1)^m \frac{Z_{\alpha+m}(x)}{x^{\alpha+m}}. \quad (\text{D.7b})$$

Equations (D.7) can therefore be used to simplify expressions containing multiple orders of Bessel functions, as demonstrated in Chapter 3.

Appendix E

Additional plug flow boundary layers

In this Appendix, we expand on the boundary layer analysis in Chapter 5. In particular, we consider the boundary layers Ic & IIIc that deal with the singularities that arise at the corners of regions Ib & IIb. These singularities occur due to the conflict between the plug flow inlet condition meeting the no-axial-slip condition at the corners of each of the lumen and ECS inlets at $z = 0$, which is consolidated by a large radial and axial fluid pressure drop over a small region.

To scale into regions Ic & IIIc from regions I & III respectively, we scale the axial scaling $z = Re^{-1}\check{z}$, and scale the radial scaling y such that

$$y = 1 - Re^{-1}\check{y} \quad \text{in region Ic,} \quad (\text{E.1a})$$

$$y = R_{m0} + Re^{-1}\check{y} \quad \text{in region IIIc as } y \rightarrow R_{m0}, \quad (\text{E.1b})$$

$$y = R_{e0} - Re^{-1}\check{y} \quad \text{in region IIIc as } y \rightarrow R_{e0}. \quad (\text{E.1c})$$

For the avoidance of doubt, we let $U_i = \check{U}_i, W_i = \check{W}_i, P_i = \check{P}_i$ to denote variables in regions Ic & IIIc. Substituting these scalings into (5.34) and taking an asymptotic expansion in Re^{-1} of the form

$$(\check{U}_i, \check{P}_i) \sim (\check{U}_{i0}, \check{P}_{i0}) + O(Re^{-1}) \quad \text{as } Re^{-1} \rightarrow 0, \quad (\text{E.2})$$

we find the $O(1)$ expansion yields

$$\nabla \cdot \check{U}_{i0} = 0, \quad \varepsilon Re(\check{U}_{i0} \cdot \nabla)\check{U}_{i0} = -(1 + \varepsilon Re)\nabla\check{P}_{i0} + \varepsilon Re\nabla^2\check{U}_{i0}. \quad (\text{E.3})$$

Equation (E.3) represents the full 2D Navier-Stokes equations through regions Ic & IIIc, which are of $O(\varepsilon Re^{-1})$ in length. We are unable to solve these equations analytically, however for completeness, we provide the appropriate boundary conditions below. The leading-order boundary conditions at the membrane interfaces and the outer ECS wall (5.11c) become

$$\check{U}_{i0} = 0, \quad \check{W}_{i0} = 0 \quad \text{at} \quad \check{y} = 0 \quad \text{for} \quad \check{z} > 0, \quad (\text{E.4})$$

the inlet condition (5.11a) becomes

$$\check{W}_{l0} = 1, \quad \check{W}_{e0} = W_{e,in} \quad \text{at} \quad \check{z} = 0 \quad \text{for} \quad \check{y} > 0, \quad (\text{E.5})$$

and the matching conditions into regions Ib & IIIb are given by

$$\check{U}_{i0} \sim \frac{\check{\eta} f'_i(\check{\eta}) - f_i(\check{\eta})}{2\check{z}^{1/2}}, \quad \check{W}_{i0} \sim f'_i(\check{\eta}), \quad \check{P}_{i0} \rightarrow \hat{P}_{i0} \quad \text{as} \quad \check{y}^2 + \check{z}^2 \rightarrow \infty, \quad (\text{E.6})$$

where $\check{\eta} = \check{y}/\check{z}^{1/2}$.

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