1 **Identifying the myogenic and metabolic components of cerebral autoregulation**

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Abstract

Cerebral autoregulation is the term used to describe a number of mechanisms that act together to maintain a near constant cerebral blood flow in response to changes in arterial blood pressure. These mechanisms are complex and known to be affected in a range of cerebrovascular diseases. However, it can be difficult to assign an alteration in cerebral autoregulation to one of the underlying physiological mechanisms without the use of a complex mathematical model. In this paper, we thus set out a new approach that enables these mechanisms to be related to the autoregulation behaviour and hence inferred from experimental measurements. We show that the arteriolar response is a function of just three parameters, which we term the elastic, the myogenic and the metabolic sensitivity coefficients, and that the full vascular response is dependent upon only seven parameters. The ratio of the strengths of the myogenic and the metabolic responses is found to be in the range 2.5 to 5 over a wide range of pressure, indicating that the balance between the two appears to lie within this range. We validate the model with existing experimental data both at the level of an individual vessel and across the whole vasculature, and show that the results are consistent with findings from the literature. We then conduct a sensitivity analysis of the model to demonstrate which parameters are most important in determining the strength of static autoregulation, showing that autoregulation strength is predominantly set by the arteriolar sensitivity coefficients. This new approach could be used in future studies to help to interpret the components of the autoregulation response and how they are affected under different conditions, providing a greater insight into the fundamental processes that govern autoregulation.

Variable	Meaning	Variable	Meaning
f	Fraction	S_E	Elastic sensitivity coefficient
f_a	Resistance fraction of large arterial vessels	S_M	Myogenic sensitivity coefficient
f_r	Resistance fraction of regulating vessels	S_V	Metabolic sensitivity coefficient
f_v	Resistance fraction of venous vessels	Δ	Change
F	Force	λ	Stretch
h	Wall thickness	σ	Stress
k	Stiffness	τ	Shear stress
p	Pressure		
q	Flow	∇	Gradient
r	Radius	$\mathcal{R}$	Resistance
RAP	Resistance-Area Product		
S	Sensitivity coefficient		

1 Introduction

The brain is one of the most tightly regulated organs in the human body, with cerebral blood flow being matched both locally and globally to metabolic needs through a number of different mechanisms. One of the most important aspects of control is that cerebral blood flow is maintained near constant over a wide range of arterial blood pressure (ABP): this is known as cerebral autoregulation [1], first quantified by [2] in its static form. Later studies then explored the dynamic response to changes in ABP, determining its characteristic biphasic response [3]. In response to decreases in ABP, CBF shows a rapid decrease due to the immediate reduction in ABP; this is then followed by a rise caused by feedback mechanisms that act to increase arteriole vessel diameter and hence to reduce resistance to flow. The steady state result is that the fractional decrease in CBF is much smaller than that in ABP.

The physiological processes that act to adjust arteriolar diameter are essentially a balance between vasoconstricting and vasodilating factors that set the phosphorylation of smooth muscle cells in the walls of the arterioles. By adjusting the stiffness of these cells through a number of feedback pathways, the relationship between radius and pressure is altered allowing the vasculature to establish a new equilibrium state in response to changes in ABP. These vessels are then one component of the cerebral vasculature that can be characterised in terms of a relationship between changes in arterial blood pressure and changes in cerebral blood flow (or more often cerebral blood flow velocity, CBFV, due to the fact that transcranial Doppler, the most commonly used measurement technique, actually only measures flow velocity, most commonly in the middle cerebral artery). This relationship is often modelled using the instantaneous relationship:

$$V = \frac{P_a - P_c}{RAP} (1)$$

where CBFV is denoted by V , arterial blood pressure, ABP, by P_a , critical closing pressure, CrCP, by P_c , and resistance-area product, RAP, by RAP . The product of resistance and area results from the use of CBFV, rather than CBF, in Equation 1.

The critical closing pressure thus represents the intersection with the x axis on a plot of CBFV changes against ABP changes and it has received considerable attention [4], with a number of methods being used to estimate it experimentally, see for example [5]. A number of studies have also quantified the contributions of the myogenic and metabolic mechanisms to the parameters in Equation 1, showing that RAP appears to be associated primarily with the myogenic mechanisms and that CrCP is primarily associated with the metabolic mechanisms [6], although there is some cross-over. Other studies have investigated how this is affected in subject populations, for example with the myogenic response being found to be impaired in acute ischaemic stroke patients [7].

To help in interpreting cerebral autoregulation, a number of physiological models have been proposed, see [8-16] and others. These models have adopted a wide range of complexity, although nearly all use the same fundamental concepts with an equivalent electrical circuit and a feedback mechanism that adjusts arteriolar stiffness (or compliance); some also consider the neural response as well as the autoregulation behaviour, for example [14]. Many of them have been partially validated using experimental data, although there is rarely sufficient data to validate all of the different parameter values used in the model, given the complexity of the response. Their complexity also makes it difficult to consider their behaviour explicitly in terms of the myogenic and metabolic components of the response and hence to relate to studies into these parameters.

We therefore take a different approach here, by considering the autoregulation response to comprise a simple balance between a vasoconstricting (myogenic) mechanism and a vasodilating (metabolic) mechanism that act on the arteriolar bed within the context of a simple electrical equivalent model. The aim of this approach is essentially to help to interpret the balance between the two mechanisms that control vascular tone through the construction of a mathematical model of

autoregulation. This, much simpler, approach enables us to examine the relative influences of the myogenic and metabolic responses more directly, particularly in a way that can be compared with experimental data. The aim is to identify the relative strengths of the two components without going into further detail about the pathways, such that they can be related directly to experimental data.

It should be noted that we associate the myogenic response with vasoconstriction and the metabolic response with vasodilation in our terminology here, as will be explained below. We do this for simplicity, although it is likely that the responses are a mixture of these pathways: if preferred the responses could be thought of as the responses governed by direct stress and shear stress respectively (as will be presented below).

The use of the mathematical model proposed here enables us to provide a means for interpreting experimental data in a more rigorous manner; through the use of experimental data, it could then be possible to separate out the two components and to understand how they link to experimental measurements that can be routinely made. This will then allow for changes in this balance to be identified more easily, helping to interpret the different components that act to maintain cerebral blood flow and thus to identify their relative importance, in particular how this balance is altered in diseased states. The aim is that this will help to drive treatment of impaired autoregulation through a better understanding of precisely what it is that is impaired under different conditions.

2 Theory

We note at the start that we will only consider static autoregulation here, for simplicity. It would be possible in future to adapt the proposed static model to a dynamic one.

2.1 Single vessel model

We thus begin by considering a single arteriole in steady state. The Laplace law relates wall stress, σ , to internal pressure, p , radius, r , and wall thickness, h :

$$\sigma = \frac{pr}{h} \quad (2)$$

For small changes about a baseline point, denoted by Δ , this can be written in the form:

$$\Delta\sigma^* = \Delta p^* + \Delta r^* - \Delta h^* \quad (3)$$

where we use the star superscript to denote a value as a fraction of its baseline value. Note that throughout the paper we are primarily concerned with variables as fraction of their baseline values: this is done to simplify the analysis since it reduces very substantially the number of variables in the resulting equations.

Similarly, the wall force can be related to internal pressure and radius:

$$F = pr \quad (4)$$

and hence:

$$\Delta F^* = \Delta p^* + \Delta r^* \quad (5)$$

We then assume that this force is dependent in some (as yet unspecified) way upon the smooth muscle cell stiffness (which will be related to the level of phosphorylation), k , and the stretch, λ , giving:

$$\Delta F^* = S_{F,k} \Delta k^* + S_{F,\lambda} \Delta \lambda^* \quad (6)$$

where the stretch is related to changes in radius:

$$\Delta \lambda^* = S_{\lambda,r} \Delta r^* \quad (7)$$

through geometric considerations. Note that we use $S_{i,j}$ here to denote the sensitivity of variable i to variable j . We also assume that the volume of the vessel wall remains constant and that hence:

$$0 = \Delta r^* - \Delta h^* \quad (8)$$

We then assume that the stiffness responds to two stimuli, one related to stress and one to shear stress, with these acting in opposite directions:

$$\Delta k^* = S_{k,\sigma} \Delta \sigma^* - S_{k,\tau} \Delta \tau^* \quad (9)$$

where shear stress, τ , is straightforwardly a function of radius and pressure gradient, ∇p :

$$\Delta \tau^* = \Delta r^* + \Delta(\nabla p)^* \quad (10)$$

Note that Equation 9 is a very simple approximation to the underlying response, whereby we assume that the vessel wall stiffness is adjusted by feedback mechanisms that can be summarised in terms of a response to direct stress and to shear stress. More sophisticated models could be used, but we adopt this formulation here deliberately as a starting point for simplicity.

These are sufficient to derive a relationship of the form:

$$\Delta r^* = S_{r,p} \Delta p^* + S_{r,\nabla p} \Delta(\nabla p)^* \quad (11)$$

where the sensitivity coefficients are given by:

$$S_{r,p} = \frac{1 - S_M}{2S_M - S_V + S_E - 1} \quad (12)$$

$$S_{r,\nabla p} = \frac{S_V}{2S_M - S_V + S_E - 1} \quad (13)$$

and we define:

$$S_{F,k} S_{k,\sigma} = S_M \quad (14)$$

$$S_{F,k} S_{k,\tau} = S_V \quad (15)$$

$$S_{F,\lambda} S_{\lambda,r} = S_E \quad (16)$$

as being respectively the myogenic, metabolic and elastic components to the overall response. As noted in the Introduction, this terminology is adopted for convenience here, where we assume that

the response pathway governed by direct stress is the key component of the myogenic response and that governed by shear stress is the key component of the metabolic response.

Note that we have, as yet, said nothing about the forms of many of the relationships: we do not need to do so, since we can characterise the overall response in terms of just a handful of sensitivity coefficients. The importance of the results in Equations 12 and 13 is that the overall sensitivity of vessel radius to both pressure and pressure gradient is dependent upon just three parameters (an elastic response that characterises the mechanical behaviour of the wall, as well as the myogenic and metabolic responses). This means that only six experimental data points (yielding three difference values) are required to calculate all three of these sensitivity coefficients. In the absence of any active response, the model of course reduces to the passive ‘inflation’ response.

2.2 Vascular model

Before considering the numerical values of these sensitivity coefficients, we next incorporate this model of arteriolar regulation within a full vascular model in order to relate the arteriolar response to the overall response of the cerebral vasculature. For this, we use an adapted version of the model proposed by [14], as this has already been validated against a number of experimental data. The model is shown in Figure 1, where there is a large artery and non-regulating arteriolar (subscript ‘la’) compartment upstream of the regulating compartment, and a capillary and venous (subscript ‘cv’) compartment downstream of the regulating compartment. We take the pressure in the regulating compartment as being that mid-way along the compartment, with the pressure gradient being equivalent to the pressure drop across this compartment. The other pressures within the system are arterial blood pressure, P_a , critical closing pressure, P_c , and intracranial pressure, P_{ic} . Note that CrCP is used in this model rather than venous blood pressure since we are only considering small static perturbations and hence Equation 1 applies.

Figure 1 Schematic of vascular model

The inverse relationship between vessel resistance and radius to the power four means that:

$$\Delta \mathcal{R}^* = -4 \Delta r^* \quad (17)$$

where the total resistance is given by:

$$\mathcal{R}_T = \mathcal{R}_{la} + \mathcal{R} + \mathcal{R}_{cv} \quad (18)$$

and the intramural pressure in the regulating vessels is given by:

$$p = \frac{1}{\mathcal{R}_T} \left[P_a \left(\frac{\mathcal{R}}{2} + \mathcal{R}_{cv} \right) + P_c \left(\mathcal{R}_{la} + \frac{\mathcal{R}}{2} \right) \right] - P_{ic} \quad (19)$$

where P_{ic} denotes intracranial pressure, and the pressure gradient by:

$$\nabla p = \frac{\mathcal{R}}{\mathcal{R}_T} (P_a - P_c) \quad (20)$$

The flow through the vessel is then given by:

$$q = \frac{(P_a - P_c)}{\mathcal{R}_T} \quad (21)$$

Note that Equation 21 is the same as Equation 1, but re-written in terms of flow and resistance

rather than velocity and RAP, since this is how the model is most easily formulated. It does however

assume that flow and velocity are directly proportional, which we will examine in more detail in the

Discussion section.

We now consider small perturbations in CrCP and total resistance about their baseline values, assuming that ICP remains constant. Re-arranging Equations 17-21 together with Equation 11 yields:

$$\Delta q^* = S_{q,\mathcal{R}} \Delta \mathcal{R}_T^* + S_{q,c} \Delta P_c^* \quad (22)$$

where the two sensitivity coefficients are given by:

$$S_{q,\mathcal{R}} = - \frac{\frac{1}{4f_r} + \left(\frac{\bar{P}_a - \bar{P}_c}{2\bar{p}} \right) S_{r,p} + \frac{1}{f_r} S_{r,\nabla p}}{\left(\frac{f_r}{2} + f_v \right) \left(\frac{\bar{P}_a}{\bar{p}} \right) S_{r,p} + \left(\frac{\bar{P}_a}{\bar{P}_a - \bar{P}_c} \right) S_{r,\nabla p}} \quad (23)$$

$$S_{q,c} = - \frac{\left(\frac{\bar{P}_c}{\bar{p}} \right) S_{r,p}}{\left(\frac{f_r}{2} + f_v \right) \left(\frac{\bar{P}_a}{\bar{p}} \right) S_{r,p} + \left(\frac{\bar{P}_a}{\bar{P}_a - \bar{P}_c} \right) S_{r,\nabla p}} \quad (24)$$

where the overbar is again used to denote baseline conditions and $\bar{p}$ is the baseline value of Equation 19. The resistance fractions are given by:

$$f_a = \frac{\mathcal{R}_{la}}{\bar{\mathcal{R}}_T} \quad (25)$$

$$f_r = \frac{\mathcal{R}}{\bar{\mathcal{R}}_T} \quad (26)$$

$$f_v = \frac{\mathcal{R}_{cv}}{\bar{\mathcal{R}}_T} \quad (27)$$

which sum to one. The additional number of degrees of freedom is thus just four (two resistance fractions and two baseline pressure ratios).

Finally, we consider the response of flow to changes in ABP, assuming that all other parameters remain constant. This results in an expression of the form:

$$\Delta q^* = S_{q,a} \Delta P_a^* \quad (28)$$

where:

$$S_{q,a} = \left(\frac{\bar{P}_a}{\bar{P}_a - \bar{P}_c} \right) \left[\frac{\frac{1}{4f_r} + \left(\frac{\bar{P}_a - \bar{P}_c}{2\bar{p}} \right) S_{r,p} + \frac{1}{f_r} S_{r,\nabla p}}{\frac{1}{4f_r} + \left(\frac{\bar{P}_a - \bar{P}_c}{2\bar{p}} \right) (1 - f_r - 2f_v) S_{r,p} + \left(\frac{1}{f_r} - 1 \right) S_{r,\nabla p}} \right] \quad (29)$$

This can be considered to be the measure of the strength of (static) autoregulation (i.e. the fractional change in flow for a fractional change in pressure). Note that this is now only a function of the resistance ratios and the baseline pressures.

3 Results

We now examine the numerical values of these parameters. We begin by considering the single vessel model, with its three sensitivity coefficients. Despite only having three values to estimate, there are few experimental studies in the literature that are sufficiently detailed to perform this analysis. Here, we use the data of [17], which considered arterioles under three different conditions: ‘passive’ whilst bathed in a solution preventing calcium being available to the vascular smooth muscle cells; ‘no-flow’ when the pressures at each end of the vessel are increased equally; and ‘with flow’ when there is also a pressure difference along the vessel to generate flow through the vessel.

From these, we can calculate the sensitivity of radius to pressure under ‘passive’ conditions, when both the myogenic and vasodilating components are ‘switched off’, hence $S_{r,p} = 1/(S_E - 1)$ under these conditions, enabling us to calculate S_E . In the ‘no-flow’ case, the metabolic component is ‘switched off’, hence $S_{r,p} = (1 - S_M)/(2S_M + S_E - 1)$, enabling us to calculate S_M . Finally, the sensitivity of radius to pressure gradient, through Equation 13, yields the value of S_V . We use a central difference approximation from the data points presented by [17]: this yields the values shown in Figure 2 for the three sensitivity coefficients as functions of pressure.

Figure 2 Variation in elastic, myogenic and metabolic coefficients with driving pressure

It is noticeable that there are very large changes in all three sensitivity coefficients over this range of driving pressure, although all three coefficients show the same characteristic style of behaviour, with a peak at medium values of pressure and decreasing in magnitude either side. The precise values of these sensitivity coefficients should, of course, be taken with caution, since they are based on the numerical calculations of gradients from a relatively small number of data points from a single source; however, it is encouraging that the data do show a clear trend in the values of all three sensitivity coefficients, indicating good consistency across pressure. The ratio of myogenic to metabolic sensitivity coefficients (which indicates the relative strength of the vasoconstricting and vasodilating responses) is also shown in Figure 2, indicating that the ratio is in the range 2.5 to 5 over this (large) pressure range.

We next examine the behaviour in the full vascular model. For this we use the values of resistance proposed by [14], which are based on the earlier models of Ursino and colleagues; these give values of $f_a = 0.0547$, $f_r = 0.6881$ and $f_v = 0.2572$. Typical values of arterial, critical closing and intracranial pressures in healthy subjects are 100 mmHg, 30 mmHg and 15 mmHg respectively [4, 14]. Using these values, we plot the radius and flow sensitivity coefficients in Figure 3, where we show the radius sensitivity coefficients as functions of the myogenic and metabolic sensitivity coefficients in (a) and (b) and the flow sensitivity coefficients similarly in (c) and (d). Note that for simplicity of plotting, we assume that the elastic sensitivity coefficient is fixed at $S_E = 12$ (approximately the average value shown in Figure 2).

Figure 3 Variation in sensitivity coefficients with myogenic and metabolic sensitivity coefficients ($S_E = 12$): (a) radius-pressure; (b) radius-driving pressure; (c) flow-resistance; (d) flow-CrCP.

The radius sensitivity coefficients show a predominant dependence on one variable, with the pressure coefficient (Figure 3a) being almost entirely a function of the myogenic strength but the pressure gradient coefficient (Figure 3b) being predominantly dependent upon the metabolic strength, except at very low values of myogenic strength. However, the flow sensitivity coefficients are more mixed, with both being dependent upon both the myogenic and metabolic response; however, at a mean pressure of 57 mmHg (the value of $\bar{p}$), we find that:

$$\frac{\partial S_{q,c}}{\partial S_M} > \frac{\partial S_{q,c}}{\partial S_V} \quad (30)$$

$$\frac{\partial S_{q,R}}{\partial S_M} < \frac{\partial S_{q,R}}{\partial S_V} \quad (31)$$

This means that the dependence of flow on CrCP is more sensitive to the myogenic response than to the metabolic response and that the dependence of flow on resistance is more sensitive to the metabolic response than to the myogenic response. This is in agreement with the results of [6], although it should be emphasised that this is not a direct comparison, since the methods used are different. It does however give an indication that the model appears to give the right general behaviour.

Finally, we examine the effect of the values of the myogenic and metabolic sensitivity coefficients on the strength of static autoregulation (the fractional change in flow as a ratio of the fractional change in pressure), as defined by Equation 29. This is shown in Figure 4, where we again assume a fixed value of $S_E = 12$. As might be expected, the response is predominantly dependent upon the strength of the myogenic response, with autoregulation strengthening (as shown by a reduction in the value of $S_{q,a}$) with an increase in the value of the myogenic sensitivity coefficient; conversely, autoregulation weakens with increased metabolic sensitivity coefficient. As would be expected, it is not possible to separate out the values of both of the coefficients from a single value of

autoregulation strength (and we have already assumed a fixed value of the other sensitivity coefficient).

Figure 4 Variation in autoregulation strength with myogenic and metabolic sensitivity coefficients ($S_E = 12$).

At the baseline values of all three sensitivity coefficients (Figure 2), the autoregulation strength is calculated to be 0.68, indicating a good level of autoregulation. The value of this static autoregulation strength has been reported within a wide range in the literature. A highly detailed meta-analysis of static autoregulation has been performed, based on 40 studies from the literature, by [18]. The resulting sensitivities were found to be $0.82 \pm 0.77 \text{ \%/\%}$ and $0.21 \pm 0.47 \text{ \%/\%}$ for decreases and increases from baseline respectively, with these values altering to $0.39 \pm 0.30 \text{ \%/\%}$ and $0.64 \pm 1.16 \text{ \%/\%}$ respectively when changes in PaCO_2 were corrected for. Our value of 0.68 $\text{ \%/\%}$ is thus highly comparable, although it should be noted that there is a very substantial variability

284 within the different studies that results in a very large value of standard deviation, making it difficult
285 to settle on a single ‘typical’ value for the strength of static autoregulation.

286 Other studies that examine the impulse and step responses show a final value of the step response
287 of approximately 0.2 %/%, see for example [3]. The Tiecks model of autoregulation [19], which is
288 very widely used to fit experimental data, also shows a static autoregulation strength of
289 approximately 0.1-0.2 for values of ARI of 4-5 (these being typical values found in healthy young
290 subjects). The discrepancies between the meta-analysis results, the Tiecks model and the new model
291 proposed here are somewhat puzzling and are worthy of further investigation, as this will help to
292 understand the precise level of static autoregulation. It should, however, be emphasised that our
293 value is based upon the behaviour of a single arteriolar bed within a vascular model, where we have
294 not attempted to fit the model responses to data.

295 The full vascular model of autoregulation shows that the strength of static autoregulation is
296 dependent upon the values of resistance fractions (with 2 degrees of freedom), the CrCP/ABP ratio,
297 the ICP/ABP ratio and the three sensitivity coefficients. Although this results in the model being
298 dependent upon 7 parameters in total, this is still a very substantial reduction from most other
299 available models. We next consider a sensitivity analysis of the model to explore which are the most
300 important factors in determining autoregulation strength.

301 For this we use the implementation of the Elementary Effects method, as originally proposed by [20],
302 contained in the SAFE toolbox [21]. This technique explores the variation in the model output, taken
303 here to be the value of $S_{q,a}$, with changes in the model parameters. Once ranges for all of the model
304 parameters have been set, taken here to be $\pm 20\%$ of their baseline values, trajectories through this
305 ‘hyper-cube’ in the parameter space are computed and two measures of sensitivity are calculated;
306 mean and standard deviation of the ‘elementary effects’. The resulting values are plotted in Figure 5,
307 where parameters located closer to the origin have less effect on the model output than parameters
308 found further away (note that we consider fractional changes in each parameter here, enabling

direct comparisons to be made). For a fuller discussion of the meaning of these metrics and of the techniques used to calculate them, the reader is referred to [21]: simply put, these measures respectively quantify the influence of each parameter and the non-linearity and/or interaction effects of each parameter on the variability of the output. Note that we have considered CrCP and ICP as fractions of ABP, since this is sufficient to describe the behaviour of the system.

Figure 5 Mean and standard deviation of elementary effects for autoregulation model based on fractional changes in each model parameter

It is clear from inspection of Figure 5 that it is the three sensitivity coefficients that dominate the value of autoregulation, with the resistance fractions and the pressure ratios being much less important. This means that the precise details of the vascular model are less important than the sensitivity coefficients that determine the regulation of flow through the arteriolar bed; this is a very interesting result as it implies that static autoregulation strength is fundamentally set by the relative

strengths of the arteriolar feedback mechanisms (and the elastic behaviour) and that hence these could in theory be inferred from measurements of static autoregulation. Of course, since static autoregulation strength cannot be used on its own to estimate all three of the sensitivity coefficients, other experimental data will be required and the dynamic response could well play an important part in determining the relative strengths of these components.

4 Discussion

The complexity of the vascular response to stimuli, with multiple pathways working within a multi-generational vascular bed, means that interpreting this response can be highly challenging. In particular, attempting to assign different responses to changes in the myogenic and vasodilating sensitivities can be very difficult, although some authors have begun to separate these out using sophisticated signal processing techniques, for example the autoregressive-moving average model of Panerai et al. [6]. The aim of the model presented here is to provide such analysis with a firmer mathematical footing. Most importantly, we have shown how the static arteriolar response can be broken down into just three sensitivity coefficients, which we have termed elastic, myogenic and vasodilating. By estimating these values as functions of pressure and incorporating them within a full vascular model, we have been able to show how these coefficients affect the strength of static autoregulation.

Such a method for disentangling the two different responses has significant potential in terms of interpreting the actual processes that govern the control of cerebral blood flow: by quantifying the strengths of the two primary feedback mechanisms, it will be possible to understand more clearly when these are altered and by what processes. This approach then opens up the possibility of being able to target the relevant mechanisms clinically. The mathematical model proposed here should be able to play a full part in this analysis, helping to identify and to understand better the effects of the different factors. With only seven parameters, it is a highly compact representation of the system, avoiding the sometimes highly complex physiological models that have been used by other authors:

for example, even the very simplified models of Payne [14] and Ursino et al. [11] have 26 and 24 parameters respectively (although these do consider more than one input and include the dynamic response that we have not considered here).

As a result, we have had to make many assumptions in the derivation of this model in order to retain simplicity, in addition to the assumption that we can use a linear model to simulate small changes about a baseline value. One key factor that we have not considered is the role of arterial partial pressure of CO₂, since hypercapnia has been widely found to reduce the strength of autoregulation (and is thus commonly used as a means of comparing normal and impaired autoregulation), see for example [22]. This impairment of autoregulation can be caused by a decrease in the myogenic response or an increase in the vasodilating response (or a mixture of the two); however, a more detailed study would be required to attempt to separate out these two potential factors. Additionally, it would be valuable to examine the behaviour of single arterioles in response to CO₂, in order to validate the model under alterations in this partial pressure.

We have also not considered here the neurovascular coupling, i.e. the response of the cerebral vasculature to changes in cellular metabolism. We have omitted this, as this is intrinsically a local response and thus requires a more detailed model that can consider local changes, rather than the whole brain model used here. Neither have we considered the role of the sympathetic response within this model, largely since this remains so poorly understood. However, it would indeed be possible to include this within the model, given suitable assumptions about its behaviour. Indeed, the mathematical framework presented here would be a highly suitable framework for examining such effects.

We have only considered the response of flow, rather than cerebral blood flow velocity, which is what is measured in most studies on cerebral autoregulation. For the two to be directly comparable, the assumption of constant MCA cross-sectional area has to be made. This remains a poorly understood assumption, particularly in the context of changes in ABP: for a more detailed discussion

of this see [1]. Our labelling of the feedback mechanisms that are driven by direct and shear stress as myogenic and metabolic is of course somewhat of a crude one that should be revisited in more detail in future.

Finally we note that the model that we have considered here has been a purely static one: although the inclusion of dynamic effects would be possible, this is somewhat more complicated, and we have thus chosen to focus purely on static analysis. Further work will include the effects of dynamic changes in ABP, which will open up the possibility of more detailed comparisons with experimental data. It will also include modelling the effects of changes in ICP, which will open up the possibility of considering the behaviour in patient populations where ICP changes, such as brain trauma patients.

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