

Perspectives on A Mathematical Model of Cerebral Blood Flow Control in Anaemia and  
Hypoxia by Duffin et al.

**Searching for the stimulus controlling brain oxygen supply**

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The control of cerebral blood flow (CBF) is of great physiological and clinical importance.

The brain acts to maintain homeostasis through a very tight balance between CBF and cerebral metabolism of oxygen and glucose, since only very small quantities of these can be stored. The brain adjusts CBF in response to a number of challenges: global changes (blood pressure, blood gas levels) and local changes (neural activity) alongside sympathetic control. Regardless of stimuli, however, CBF is fundamentally controlled through changes in vascular tone (despite some active debate at present as to where precisely in the vascular bed this predominantly takes place).

Clinically, this control is of great importance. As one example, dementia (including both Alzheimer's disease and vascular dementia) is now the largest cause of death in the UK. There is an increasing appreciation of the vascular component of dementia and of the importance of maintaining a healthy cerebral vasculature. Following stroke, the clinical setting of optimal blood pressure remains a significant challenge, particularly when the control of CBF can vary in its behaviour over time. We still don't know what role impaired control of CBF plays in a number of cerebrovascular diseases: it is a cause or a result of these diseased states? Should this impairment be a target for therapy and/or is it a metric that can aid diagnosis and treatment?

The danger, however, with asking these questions, is that it focusses on the end rather than the means, i.e. that we concern ourselves so much with the changes in vascular tone that we fail to appreciate how these changes are driven and by what. After all, the brain does not need blood, rather it needs the nutrients that the blood brings with it. Something must be driving changes in vascular tone and the question that the authors set out to address in

this modelling study is whether it is feasible to expect this to be the partial pressure of oxygen in brain tissue. This is an appealingly straightforward hypothesis that has been supported by a number of experimental studies, since it seems logical to expect any changes to be driven by the fundamental question of whether brain tissue is being adequately supplied with oxygen.

Duffin et al. [1] thus elegantly consider the control of CBF under several conditions, in particular anaemia and hypoxia, using a very simple mathematical model. The key question that they are trying to investigate is whether there is a brain oxygen tension sensor that drives changes in CBF in response to these different stimuli. Should this be the case, it would be expected then to follow that this would be the same under a range of different conditions.

The authors debunk this hypothesis in a most straightforward and clear manner, by showing that it is not plausible to explain the responses to both conditions. Although the model only considers the static behaviour, it links nicely to other work on the dynamics of the microcirculation, where the same hypothesis has been rejected on the grounds that the response time would be too slow for the characteristic autoregulation behaviour to be achieved [2]. This does illustrate how a variety of different models and different stimuli can be used to interrogate the same system with a view to understanding its behaviour more clearly (and encouraging us to think of the pathways to controlling vascular tone as having much in common between different challenges).

The question obviously remains of what is controlling vascular tone in response to the many stimuli that control CBF. The authors are perhaps a little cautious in attempting answering this question, but one fruitful avenue for further exploration would be the work that has been done in the context of physiological models of the neurovascular coupling (see for example the review by Buxton [3]) and the model by Arciero et al. of metabolic blood flow regulation [4].

In the former, the stimulus originates of course directly in the tissue, but it is now thought that the flow response runs in parallel with the increased activation, rather than being driven by changes in tissue oxygenation (the rationale for this is again the speed of the response, both the autoregulation and neurovascular coupling responses occurring in a matter of a few seconds). In the latter, the oxygen sensor is taken to be the red blood cells themselves, i.e. the red blood cells respond to changes in oxygen level within the bloodstream. The much faster dynamics of red blood cells (governed by convection rather than diffusion) means that any changes in response to, say, capillary haemoglobin levels can result in a very rapid response.

Although a more indirect measure of tissue oxygen, which still seems somewhat counterintuitive, this hypothesis has the merit of a very fast response, enabling supply to be matched to demand much more tightly. It would be very interesting to explore this alternative hypothesis using the model proposed here (picking up on their suggestion that cerebral blood flow could be governed by arterial oxygen concentration). This would undoubtedly help us to gain a more detailed understanding of the mechanics of this control. If the authors have persuaded other researchers to think about the control of cerebral blood

flow in a more integrated manner, through the use of the responses to multiple stimuli, this would also be of great benefit to the field.

## References

[1] Duffin J, Hare G and Fisher J. A mathematical model of cerebral blood flow control in anaemia and hypoxia. *Journal of Physiology*, in press.

[2] Payne SJ and Lucas C. Oxygen delivery from the cerebral microvasculature to tissue is governed by a single time constant of approximately 6 seconds. *Microcirculation*, **25**: e12428, 2018.

[3] Buxton RB Dynamic models of BOLD contrast. *Neuroimage*. 2012;**62**(2):953-961.

[4] Arciero JC, Carlson BE and Secomb TW. Theoretical model of metabolic blood flow regulation: roles of ATP release by red blood cells and conducted responses. *Am J Physiol Heart Circ Physiol*. 2008 Oct;**295**(4):H1562-71.