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Arteries dominate volume changes during brief functional hyperemia: evidence from mathematical modelling

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Abstract

Variations in local neural activity are accompanied by rapid, focal changes in cerebral blood flow and volume. While a range of observations have shown that dilation occurs in cerebral arteries, there is conflicting evidence about the significance of volume changes in post-arteriole vessels. Here, we reconcile the competing observations using a new mathematical model of the hemodynamic response. First, we followed a ‘top down’ approach, without constraining the model, but using experimental observations at progressively more detailed scales to ensure physiological behaviour. Then, we blocked dilation of post-arteriole vessels, and predicted observations at progressively more aggregated scales (a ‘bottom up’ approach). Predictions of blood flow, volume, velocity, and vessel diameter changes were consistent with experimental observations. Interestingly, the model predicted small, slow increases in capillary and venous diameter in agreement with recent \textit{in vivo} data. Blocking dilation in these vessels led to erroneous volume predictions. The results are further evidence that arteries make up the majority of blood volume increases during brief functional activation. However, dilation of capillaries and veins appears to be increasingly significant during extended stimulation. These are important considerations when interpreting results from different neurovascular imaging modalities.

\textit{Keywords:} cerebral blood flow, cerebral blood volume, functional hyperemia,

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1. Introduction

Moment to moment variations in neural activity are accompanied by rapid changes in local cerebral blood flow (CBF) and volume (CBV); this is termed functional hyperemia. While the purpose (Buxton, 2010) and underlying mechanisms (Attwell et al., 2010) remain unclear, reports are beginning to emerge that offer a more consistent view of how this process unfolds.

In vivo observations at the single vessel scale have shown that arteries supplying an active cortical region dilate rapidly in response to stimulation (Takano et al., 2006), increasing the supply of blood and thus the delivery of oxygen and nutrients. Depth resolved microscopy suggests that this vasodilation originates deep within the cortex, at or below layer four, then propagates to upstream and surface vessels within seconds (Tian et al., 2010). Direct measurements of veins during functional hyperemia have observed no (Hillman et al., 2007) or small (Drew and Kleinfeld, 2011) increases in diameter.

Consistent with these microscopic observations, ‘bulk’ measurements of CBF and CBV made with MRI have shown increases in arterial CBV (CBV$_a$, Kim et al., 2007; Ho et al., 2010b; Kim and Kim, 2011). However, in conflict with the venous diameter measurements, observations made using MRI have demonstrated significant increases in venous CBV (CBV$_v$, Chen and Pike, 2009, 2010). Furthermore, it is widely thought that the balloon-like increases in CBV (Buxton et al., 1998; Obata et al., 2004) are an important component of the Blood Oxygenation Level Dependent (BOLD) functional MRI signal (Ogawa et al., 1990).

It is not clear whether these apparent differences between optical (Hillman et al., 2007; Drew and Kleinfeld, 2011) and MRI data (Chen and Pike, 2009, 2010) are significant. It is possible that the discrepancy may be due to methodological differences such as species, stimulation length, surgical preparation, or anesthesia. Or, differences in the spatial resolution of the imaging modalities
used may play a role.

In this study, we attempt to reconcile the competing observations using a dynamic, predictive mathematical model of the hemodynamic response that is based on fundamental biophysical mechanisms. To do so, we extend previous implementations of the widely known Windkessel model (Mandeville et al., 1999; Zheng et al., 2005; Huppert et al., 2007) and introduce a novel description of vascular compliance.

Initially we employ a ‘top down’ approach—assuming post-arteriole vessels are able to dilate. This approach imposes no a priori constraints on the behaviour of post-arteriole vessels, so we refer to this model as “top down (unconstrained)” . However, we use experimental observations at progressively more detailed scales to restrict the model to physiological behaviour. Subsequently, we prevent dilation in post-arteriole vessels, and use the same model to predict observations at progressively more aggregated scales, following a ‘bottom up’ approach. This approach constrains the behaviour of post-arteriole vessels, so we refer to this model as “bottom up (constrained)” .

2. Theory

[Insert Figure A.1 about here]

Recently, several compelling models have examined CBF and CBV in complex or anatomical geometries (Boas et al., 2008; Reichold et al., 2009; Lorthois et al., 2011). However, here we choose to focus in more detail on the bulk mechanisms and retain sufficient computational simplicity to consider transient effects. As such, we consider the problem domain as three lumped compartments representing arteries, capillaries, and veins, as shown in Figure A.1. These are referred to by the subscripts 1, 2, 3 respectively. The subscripts 0 and 4 refer to notional larger arterial and venous compartments.

The governing equations of the model are presented in the following sections, while Appendix A contains further details of the derivation and scaling. Table A.1 summarizes the dynamic variables used in the model. Extending a previous convention (Buxton et al., 2004), variables in upper case are absolute quantities,
while those in lower-case are dimensionless (see Appendix A.1). The superscript * (e.g. $v^*$) represents baseline values.

[Insert Table A.1 about here]

2.1. Fluid flow

The blood volume in a vascular compartment $i$, $v_i(t)$, varies when the flow in, $f_{i-1,i}(t)$, and out, $f_{i,i+1}(t)$, differ, according to

$$\frac{dv_i}{dt} = f_{i-1,i}(t) - f_{i,i+1}(t).$$

(1)

Following the path of the flow from the ground (see Figure A.1) up through the vascular compliance, $c_i(t)$, and the viscous resistance, $r_i(t)$, leads to an equation for the pressure at the entrance to each compartment, $p_i(t)$, such that

$$p_i(t) = \frac{1}{2} r_i(t) f_{i-1,i}(t) + \frac{v_i(t)}{c_i(t)};$$

(2)

where $c_i(t)$ is defined in Equation (5) and discussed in more detail in Section 2.2;

$$r_i(t) = \frac{l_i^3}{v_i(t)^2};$$

(3)

and $l_i$, the compartment length, is assumed constant. To eliminate $p_i(t)$ and express the equations in terms of flow and volume only, $p_i(t)$ can also be defined as the dimensionless form of Equation (A.5).

To complete the equations, the compartmental pressure losses must sum to the pressure boundary condition, $\Delta p_r$; mathematically:

$$\sum_{i=1}^{3} \Delta p_i(t) = \Delta p_r,$$

(4)

where $\Delta p_i(t)$, the pressure drop over a single compartment, is the dimensionless form of Equation (A.6). Allowing $i$ to range from 1 to 3 creates a system of seven differential algebraic equations (DAEs) in four flows and three volumes governed by Equations (1), (2), and (4). In this work we define CBF as the instantaneous volume weighted average of the four flows, as per the dimensionless form of Equation (A.11).
2.2. Compliance

In this study we propose a novel model of vascular compliance that includes three physiologically-observed features: (1) a linear compliance-volume relationship in the steady state, (2) dynamic viscoelastic effects, and (3) compliance changes that represent active smooth muscle dilation or contraction. The model is mathematically simple and agrees well with in vivo experimental data (Figure A.4). A complete description of the model and its parameters is given in Appendix A.2. Mathematically, compliance, $c_i(t)$, is described such that

$$c_i(t) = c_i^* - \kappa_i - v_i(t)/v_i^* - \nu_i \frac{dv_i(t)}{dt} + s_i(t), \quad (5)$$

where $c_i^*$ is the baseline compliance, $\kappa_i$ is a stiffness coefficient, $v_i^*$ is the baseline volume, $s_i(t)$ is the vasodilatory stimulus defined in Equation A.15 (see Section 2.3), and $\nu_i$ is a viscoelasticity coefficient.

2.3. Vasodilatory Stimulus

The CBF response to activation can take many forms. For brief stimuli, it typically exhibits a rapid increase, which quickly returns to baseline at the cessation of stimulation. During more extended stimulation, CBF typically reaches or approaches a plateau, but it is also common to see an initial overshoot. There may also be a post-stimulus CBF undershoot, but this is not always present and is often small (Buxton et al., 2004). Based on these typical experimental observations, we chose a plausible form for the stimulus that captures the dynamics of the CBF response. See Appendix A.3 and for a complete description and the mathematical definition of the stimulus. A diagram of the stimulus at three example lengths is shown in Figure A.5.

3. Methods

The model equations introduced in Section 2 have fifteen undefined parameters (degrees of freedom): three lengths, $l_i$; three baseline compliances, $c_i^*$; three stiffness coefficients, $\kappa_i$; three viscoelasticity coefficients, $\nu_i$; and three stimulus parameters, $s_{max}$, $s^*$, and $\tau_{decay}$ (see Appendix A.3). The model was restricted
to physiological behaviour and the number of these undefined parameters was
reduced by using experimental data: first at baseline, then during steady state
stimulation, and finally during dynamic stimulation. Table A.2 summarizes
these parameters and their values.

[Insert Table A.2 about here]

3.1. Baseline behaviour

As explained in Appendix A.1, our choice of scales yields the constraints

\[
\Delta p_r = 1; \quad \sum_{i=1}^{3} v_i^* = 1; \\
\sum_{i=1}^{3} r_i^* = 1, \\
\]  

where \( f^* \), \( v_i^* \), and \( r_i^* \) are the baseline flow, volumes, and resistances. In order to
restrict the model to physiological behaviour, experimental data from baseline
measurements were then used to fix \( v_i^* \) and \( r_i^* \) and therefore determine the three
lengths \( (l_i) \) and baseline compliances \( (c_i^*) \), as explained below.

Using macaque cortical sections, Weber et al. (2008) estimated the baseline
capillary vascular volume fraction to be 41%. Using Indian ink-injected human
cortical sections, Lauwers et al. (2008) reached a similar estimate of 48%. The
mean of these values, 44.5%, is significantly higher than the values used in
previous models (Huppert et al., 2007; Zheng et al., 2005; both use 15%).

While such microscopic techniques have been used to estimate the relative
number of arteries versus veins (Weber et al., 2008; Reichold et al., 2009), no
data exist for the volume fractions. However, studies have attempted to estimate
the volume fraction of arteries in the brain using lower resolution modalities such
as MRI and PET, obtaining values ranging from 23–39% (mean 0.29; Duong
and Kim, 2000; Lee et al., 2001; Ito et al., 2001a; An and Lin, 2002; Ito et al.,
2005; Kim et al., 2007). Veins must make up the remainder of the vascular
volume, and therefore we set the baseline volume fractions \( v^* \) (= \([v_1^*, v_2^*, v_3^*]\))
to be [0.29, 0.44, 0.27].

In the absence of suitable direct experimental data from the brain, we
used two indirect data sources to determine the baseline resistance distribution.
Firstly, we used measurements of the terminal pressure distribution in the
microcirculation of cat mesentery (Zweifach, 1974; Lipowsky, 2005). Assuming that CBF is constant through the different microcirculatory compartments, the measured pressure differences between points in the network are proportional to resistance. Secondly, we calculated baseline resistance fractions from a pseudo-synthetic data set developed for the sheep cerebrovascular system (Sharan et al., 1989); the two independent calculations produced similar results. Therefore, we set the baseline resistance fractions \( r^* \) to be the mean of these two data sources, [0.74, 0.08, 0.18].

Using these volume and resistance fractions, and setting all derivative terms to zero, the DAEs in Equations (1), (2), and (4) reduce to algebraic equations. Therefore, it is possible to calculate \( l_i \) from Equation (3), \( p^*_i \) from the dimensionless forms of Equations (A.5) and (A.6), and \( c^*_i \) from Equation (2) such that

\[
l_i = \left( r^*_i v^*_i \right)^{3/2}, \quad (7a)
\]

\[
p^*_i = \begin{cases} \Delta p_r & : i = 1 \\ \Delta p_r - f^* \sum_{j=1}^{i-1} r^*_j & : \text{otherwise, and} \end{cases} \quad (7b)
\]

\[
c^*_i = v^*_i / \left( p^*_i - \frac{1}{2} r^*_i f^* \right). \quad (7c)
\]

Model predictions of baseline velocities \( (u^*_i) \) and diameters \( (d^*_i) \) can be calculated from the dimensionless forms of Equations (A.10) and (A.9) so

\[
u^*_i = f^* l_i / v^*_i, \quad \text{and} \quad (8a)
\]

\[
d^*_i = \sqrt{v^*_i / l_i}. \quad (8b)
\]

The model predicted that baseline arterial velocity is higher than venous, which is higher than capillary; these predictions are broadly consistent with experimental observations Zweifach (1974).

3.2. Steady state simulation

The arterial stiffness \( (\kappa_1) \) was estimated using data obtained from rat pial arterioles by Baumbach and colleagues (Baumbach et al., 1989; Hajdu et al., 1990; Baumbach and Hajdu, 1993). As length, \( l_i \), is assumed constant in our
model, $\kappa_1$ is equivalent to the x-intercept of a linear fit to their compliance-area plots, normalized to baseline. We set $\kappa_1$ to be mean of the values calculated from these three independent data sets (control experiments only): 1.29 (range 1.24-1.33).

To our knowledge, no similar data exist to allow estimation of cerebral capillary and venous stiffness. As such, $\kappa_2$ and $\kappa_3$ were determined indirectly using experimentally observed CBF-CBV relationships and Grubb’s power law, $v = f^\alpha$ (Grubb et al., 1974), where $v$ and $f$ are CBF and CBV normalised to baseline. This equation has been used to describe the total (Grubb et al., 1974; Ito et al., 2001a; Jones et al., 2001; Lee et al., 2001; Jones et al., 2002; Ito et al., 2003; Kong et al., 2004; $\alpha = 0.26 - 0.40$, mean 0.34), arterial (Ho et al., 2010a,b; $\alpha = 0.55 - 0.69$, mean 0.62), and venous (Chen and Pike, 2009, 2010; $\alpha = 0.18 - 0.23$, mean 0.21) CBF-CBV relationships. However, as the MRI sequence used to estimate CBV changes is likely to be sensitive to capillary CBV too (Chen and Pike, 2009), we assume ‘venous’ CBV changes are in fact ‘non-arterial’, that is the sum of capillary and venous CBV changes.

For each $\kappa_2$ and $\kappa_3$ pair, we adjusted the vasodilatory stimulus to vary normalized CBF over the range 0.5-3 and calculated model predictions of CBV. In addition, we used the mean $\alpha$ values from the studies mentioned above to calculate the corresponding Grubb’s law predictions of CBV. The values of $\kappa_2$ and $\kappa_3$ were then varied simultaneously to minimize the error between the model and Grubb’s law predictions of CBV. All optimization was implemented in MATLAB R2010a (The MathWorks Inc., Natick, MA) using a constrained Nelder-Mead simplex algorithm (Lagarias et al., 1998), with initial parameter values chosen from a uniform random distribution. For this first stage of optimization, three repetitions with different initial guesses were sufficient to show that the values converged to an optimal solution.

### 3.3 Dynamic simulation

Experimental measurements of CBF and CBV changes during sensory stimulation (Mandeville et al., 1999) were used to determine the six remaining free
parameters: the three viscoelasticity coefficients \( \nu_i \) and stimulus parameters \( (s_{\text{max}}, s^*, \text{and } \tau_{\text{decay}}) \). We varied these six values simultaneously to minimize the relative error between the model predictions and experimental observations. This second stage of optimization was performed similarly to the first, but with seven repetitions.

3.4. Blocking post-arteriole dilation

To block post-arteriole dilation, we assumed the capillary and venous compartments tended towards infinite stiffness; mathematically, \( \kappa_2 \) and \( \kappa_3 \rightarrow 1 \). In the limiting case, this eliminates the volume term from Equation (2) and prevents any dilation. As the optimal values of the six remaining parameters \( (\nu_i, s_{\text{max}}, s^*, \text{and } \tau_{\text{decay}}) \) could differ under these conditions, we repeated the second stage of optimization (dynamic simulations) to determine them.

3.5. Sensitivity and statistical analyses

We conducted analyses to determine whether the model predictions were sensitive to changes in those quantities obtained directly from experimental data: baseline volume fractions, \( v^* \); baseline resistance fractions, \( r^* \); arterial stiffness, \( \kappa_1 \); and Grubb power law coefficients, \( \alpha \) (for top down simulations only). We independently perturbed each of these parameters by \( \pm 10\% \), and repeated the appropriate optimization stage(s) in each case.

Unless otherwise specified, numeric results are presented as the value obtained from the optimal simulation \( \pm \) the standard deviation of all values, including the sensitivity analysis simulations, where \( n = 21 \) (top down) or 15 (bottom up). To test for statistically significant differences between samples, we first checked for normality using the Lilliefors test. Where both samples were normally distributed, we used an unpaired t-test with either the equal or unequal variances assumption, depending on the results of an F-test. For all other cases, we used a non-parametric Wilcoxon rank sum test. In all analyses, two tailed tests were used unless specified otherwise, and results were considered significant for \( P < 0.05 \).
4. Results

4.1. ‘Top down’ (unconstrained) simulations

[Insert Figure A.2 about here]

The model predictions of the optimal total ($\alpha = 0.341 \pm 0.010$), arterial ($\alpha = 0.618 \pm 0.019$) and non-arterial ($\alpha = 0.209 \pm 0.004$) steady state flow volume relationships are shown in Figure A.2A. The optimal value of capillary stiffness, $\kappa_2$, was determined to be 1.51; however, the optimal value for venous stiffness, $\kappa_3$, was sufficiently large ($\approx 1000$) that the first term in Equation 5 was approximately constant. As such, venous compliance was assumed to be independent of static volume changes.

Optimal model predictions of CBF and CBV changes in response to 6 and 30 second stimulation are shown in Figure A.2B-C, with a summary of quantitative results presented in Supplementary Table 1. CBF increased rapidly at first then more slowly as stimulation continued, peaking 53.7 ± 1.1% above baseline under 6 second stimulation ($t_{\text{peak}} = 6.1 \pm 0.0$ seconds), and 65.4 ± 0.8% above baseline under 30 second stimulation ($t_{\text{peak}} = 30.1 \pm 0.1$ seconds). The time to 50% of the peak value, $t_{50}$, was 1.6 ± 0.2 seconds up and 2.6 ± 0.2 seconds down for the 6 second stimulation; and $t_{50}^{\text{up}} = 1.9 \pm 0.2$ seconds and $t_{50}^{\text{down}} = 2.6 \pm 0.2$ seconds for 30 second stimulation.

The CBV response was initially similar to the CBF, but under prolonged stimulation the continued rise was steeper than CBF. Quantitatively, CBV peaked 11.6 ± 0.5% ($t_{\text{peak}} = 6.1 \pm 0.0$ seconds) and 16.7 ± 0.3% ($t_{\text{peak}} = 30.0 \pm 0.0$ seconds) above baseline under 6 and 30 second stimulation. Temporally, $t_{50}^{\text{up}}$ and $t_{50}^{\text{down}}$ were 1.6 ± 0.2 seconds and 3.2 ± 0.2 seconds under 6 second stimulation, and 2.6 ± 0.2 seconds and 4.4 ± 0.3 seconds under 30 second stimulation. These $t_{50}^{\text{down}}$ values calculated from the CBV predictions were significantly larger than the corresponding metrics for the CBF predictions at both stimulation lengths (all $P < 0.001$, one tailed), suggesting that CBV was slower than CBF to return to baseline.

Arterial dilation accounted for 88.4 ± 2.5% of the total volume increase for the 6 second stimulation, while capillaries and veins made up 7.2 ± 3.0% and
For the 30 second stimulation, the proportion of volume change from arterial dilation decreased to 64.8 ± 5.3%, with 14.7 ± 5.1% and 21.5 ± 6.1% due to dilation in capillaries and veins.

Optimal model predictions of vessel diameter and blood velocity changes in response to 1, 10 and 30 second stimulation are shown in Figure A.2D-I; a summary of quantitative results is presented in Supplementary Table 1. Arteriolar diameter increased rapidly ($t_{50}^{up} = 1.4 ± 0.0$ seconds) to a plateau, peaking 17.3 ± 1.1% above baseline in response to 30 second stimulation. However, for the same stimulation capillary and venous diameter increased more slowly ($t_{50}^{up} = 12.0 ± 1.2$ and $12.5 ± 1.7$ seconds) to smaller peaks of 2.7 ± 0.9% and 6.5 ± 1.8% above baseline. While arterial diameter increased 6.4 ± 1.1% above baseline under 1 second stimulation, capillary and venous diameter increases were minimal at only 0.2 ± 0.1%, and 0.5 ± 0.2% above baseline.

Velocity increases followed a similar temporal profile in all three vessel types, but the magnitude of the relative changes were larger in capillaries and veins than in arteries. In response to 1 second stimulation, velocity in arteries, capillaries and veins increased 5.7 ± 1.0%, 19.5 ± 3.4%, and 19.3 ± 3.4% above baseline; under 30 second stimulation these values were 20.4 ± 2.7%, 56.8 ± 2.1%, and 50.3 ± 3.1% above baseline.

4.2. ‘Bottom up’ (constrained) simulations

[Insert Figure A.3 about here]

Optimal model predictions of changes in vessel diameter and blood velocity under the same conditions as the equivalent ‘top down’ simulations, but with dilation in capillaries and veins blocked, are shown in Figure A.3A-F. Summaries of quantitative results and statistical analyses are presented in Supplementary Tables 2 and 3. Blocking this dilation had a significant but relatively minor effect on the peak arterial diameter under 30 second stimulation ($P < 0.001$), with the optimal peak increasing to 21.4 ± 1.0% above baseline. The blocked arterial diameter predictions displayed a qualitatively similar temporal profile to the unblocked ones.
Predictions of peak velocity changes in arteries also changed significantly \((P < 0.001\) under 10 and 30 second stimulation), and displayed a much flatter profile. Under 1 second stimulation, arterial velocity peaked \(6.8 \pm 0.9\%\) above baseline, but the peaks under 10 second \((12.6 \pm 2.3\%)\) and 30 second \((13.0 \pm 2.5\%)\) stimulation were very similar. In capillaries and veins, blocking dilation had a significant effect on peak velocity increases \((P < 0.001\) under 10 and 30 second stimulation), with the optimal peaks under 30 second stimulation both increasing to \(66.6 \pm 1.3\%\) above baseline.

Optimal predictions of CBF and CBV under the blocked conditions are shown in Figure A.3G-H. Blocking dilation had a significant effect on peak CBF under 30 second stimulation \((all\ P < 0.01)\). Using the optimal parameters, the peak CBF increased slightly to \(54.5 \pm 1.5\%\) above baseline under 6 second stimulation, and \(66.6 \pm 1.3\%\) above baseline under 30 second stimulation. Temporally, \(t_{up}^{50}\) and \(t_{down}^{50}\) were \(1.4 \pm 0.1\) seconds and \(3.7 \pm 0.1\) seconds under 6 second stimulation, and \(1.8 \pm 0.1\) seconds and \(3.7 \pm 0.1\) seconds under 30 second stimulation.

Blocking dilation had a significant effect on peak CBV \((all\ P < 0.01)\), and the CBV response was almost identical in shape to the CBF response. Quantitatively, CBV peaked \(11.0 \pm 0.6\%\) and \(13.7 \pm 0.9\%\) above baseline under 6 and 30 second stimulation. Temporally, \(t_{up}^{50}\) and \(t_{down}^{50}\) were \(1.4 \pm 0.1\) seconds and \(3.5 \pm 0.1\) seconds under 6 second stimulation, and \(1.8 \pm 0.2\) seconds and \(3.5 \pm 0.1\) seconds under 30 second stimulation. There was no evidence that \(t_{down}^{50}\) calculated from the volume predictions was significantly larger than the corresponding metrics from the CBF predictions \((all\ P > 0.999,\ one\ tailed)\), suggesting that CBV was at least as fast as CBF to return to baseline under the blocked conditions.

The predictions of the total \((\alpha = 0.369 \pm 0.983,\ P < 0.001)\), arterial \((\alpha = 0.961 \pm 1.129,\ P < 0.001)\) and non-arterial \((\alpha = 0.0 \pm 0.00,\ P < 0.001)\) steady state CBF-CBV relationships all changed significantly under blocked conditions \((Figure\ A.3I)\). The standard deviations of these \(\alpha\) values were unexpectedly high due to one simulation in the sensitivity analysis. Excluding this simulation, in
which the arteries had to dilate well above physiological limits to achieve the full flow range, the standard deviations were 0.035 for the total and 0.062 for the arterial values.

5. Discussion

5.1. Summary of results

In this study we used a mathematical modelling approach, based on fundamental biophysical mechanisms, to test whether experimental observations of the hemodynamic response were consistent with one another across a range of different spatial and temporal scales. We were motivated by apparent discrepancies between MRI measurements of venous volume (Chen and Pike, 2009, 2010) and optical measurements of venous diameter (Hillman et al., 2007; Drew and Kleinfeld, 2011).

Assuming the bulk measurements to be correct (i.e. that post-arteriole vessels are able to dilate), we performed ‘top down’ (unconstrained) simulations and used experimental observations at progressively more detailed scales to constrain the model to physiological behaviour. To test the alternative, that there is no dilation in post-arteriolar vessels, we also performed ‘bottom up’ (constrained) simulations—where we blocked all dilation in capillaries and veins—and predicted the response at progressively more aggregated scales.

Ignoring the baseline distribution of volume and resistance, the broadest spatial and temporal scale we examined was the relationship between steady state CBF and CBV changes. A number of studies have found that this relationship is well described by a power law, \( v = f^\alpha \), first proposed by Grubb et al. (1974), and that this equation is valid for the total (Grubb et al., 1974; Ito et al., 2001b; Jones et al., 2001; Lee et al., 2001; Jones et al., 2002; Ito et al., 2003; Kong et al., 2004), arterial (Ho et al., 2010a,b) and non-arterial (Chen and Pike, 2009, 2010) relationships.

The optimal model predictions from our ‘top down’ simulations fit very well to the power law shape (Figure A.2A), and \( \alpha \) values from best fits of this law to
our predictions agreed closely with the mean of $\alpha$ values taken from experimental measurements. In the ‘bottom up’ simulations however, best fit $\alpha$ values for the arterial and venous relationship were significantly larger and smaller, respectively, than those determined experimentally. While the $\alpha$ value for the total relationship was within an acceptable range, the predictions were not well described by the power law. In fact, both the total and arterial flow-volume relationships displayed the opposite curvature to experimental observations (Figure A.3I).

Next, we fit the model to data from Mandeville et al. (1999) to predict dynamic changes in CBF and CBV. The optimal model predictions fit very well to the data at both brief (6 second) and extended (30 second) stimulation lengths in our ‘top down’ simulations (Figure A.2B-C). However, the ‘bottom up’ simulations were unable to reproduce some features of the data. In particular, they could not produce: the second, slower, phase of CBV increases (“slow ramp”) evident in the data during extended stimulation (Figure A.3H), and the slower return to baseline of CBV compared with flow evident in the data at both stimulation lengths.

These two phenomenon, while they appear especially pronounced in the data used here (Mandeville et al., 1999), are also present to a varying degree in many (Herman et al., 2009; Kida et al., 2006) but not all (Donahue et al., 2009) measurements of volume changes. Given the slow increases and decreases visible in the predictions of capillary and venous contributions to CBV (Figure A.2C), and the fact that blocking dilation in these compartments removes the effects, our results suggest that both these phenomena are caused by changes in the diameter of post-arteriole vessels that occur on a much slower timescale than those in arteries.

Finally, to consider changes at the single vessel scale, we compared model predictions to recent in vivo measurements of diameter and velocity changes obtained by Drew and Kleinfeld (2011). It is important to note that these data were not used to parameterize or fit the model, so also serve as an independent validation. Pleasingly, optimal model predictions of diameter changes from
our ‘top down’ simulations were consistent with the data at all three stimulus lengths: single puff (1 second in the model), 10 and 30 seconds.

Arterial diameter predictions were within an acceptable range of the data and occurred on the right timescale (Figure A.2D). However, the model was not able to produce the biphasic increase (an initial fast peak followed by a second, slower peak) in arterial diameter evident in the data. This may be due to the simplicity of the vasodilatory stimulus we used, which does not consider more complex arterial behaviour such as competing dilation and constriction (Devor et al., 2007). However, the data were obtained from single arteries (Drew and Kleinfeld, 2011), whereas our model considers the average behaviour of all arteries in a region. Given that this biphasic response was not necessary to produce volume changes consistent with the MRI data we used (Mandeville et al., 1999), it is possible that the biphasic response ‘disappears’ when the diameter changes of all arteries in a region are combined, subject to spatially varying dilation and constriction (Devor et al., 2007). In addition, there may be differences in the nature of the hemodynamic response between awake mice subject to air puff stimulation of the vibrissa (Drew and Kleinfeld, 2011) and alpha-chloralose anesthetized rats subject to electrical stimulation of the forepaw (Mandeville et al., 1999). There were no important differences in arterial diameter between the ‘top down’ and ‘bottom up’ simulations.

The model also predicted small, slow increases in capillary and venous diameter that would be difficult to detect with optical microscopy, particularly during brief stimulation. For example, Drew and Kleinfeld (2011) reported that they could not resolve changes in diameter of less than 0.2 µm using two-photon microscopy, meaning they were unable to detect “changes in venous diameter of less than 2% and changes in capillary diameter of less than 7%”. In our ‘top down’ predictions, capillary diameter peaked at only 2.7% above baseline in response to 30 second stimulation, and venous diameter did not increase beyond 2% until nearly 8 seconds after stimulus onset. As such, our findings are consistent with Drew and Kleinfeld (2011), and an earlier report that did not observe any venous dilation in response to 4 second stimulation (Hillman et al., 2007).
By definition, there was no dilation of capillaries and veins in the ‘bottom up’ simulations.

Drew and Kleinfeld (2011) reported only capillary velocity responses, and our predictions were consistent with these data (Figure A.2H). Similarly to the arterial diameter changes, the model was not able to produce the biphasic response in capillary velocity. However, our observations (unpublished) suggest that capillary velocity is strongly dependent on arterial diameter, as would be expected if arteries were the major resistance vessels. Thus, the possible reasons for the differences in arterial diameter between model and data may well explain the differences in capillary velocity too. Blocking dilation of capillaries and veins in the ‘bottom up’ simulations eliminated the slow ramp in arterial velocity and the undershoots in venous velocity. However, to our knowledge these features have not been observed experimentally and so their significance is unclear.

Taken together, these results suggest that—relying only on the mechanisms present in this model—dilation of capillaries and/or veins is necessary to predict experimental observations that are consistent across multiple spatial and temporal scales. We propose that dilation in capillaries and veins on the order of that predicted here does occur, but is not observed directly due to lack of resolution and the relatively brief length of stimulation typically used in optical imaging experiments. However, we suggest that the effects of this dilation are detectable during the prolonged stimulation typically used in bulk measurements of CBV changes, and measurements of the steady state CBF-CBV relationship.

5.2. Compartment specific CBV changes

Arteries make up a relatively small proportion of baseline CBV, in the vicinity of 25–35% (Duong and Kim, 2000; Lee et al., 2001; Ito et al., 2001a; An and Lin, 2002; Kim et al., 2007). Yet our results suggest that arterial dilation is large enough and fast enough that arteries dominate CBV changes during brief functional hyperemia. According to our model, they contribute just under 90% of the total CBV increase at 6 seconds following stimulation onset. This drops to just under 65% by 30 seconds post onset, but this proportion is still the
majority.

In addition to the data used here (Drew and Kleinfeld, 2011), our predictions of arterial diameter changes are consistent with other two photon microscopy observations in response to brief (1–4 second) electrical stimulation (Hillman et al., 2007; Devor et al., 2007; Tian et al., 2010). Furthermore, our predictions agree with MRI measurements of CBV in cats in response to longer (15-40 second) visual stimulation (Kim et al., 2007; Kim and Kim, 2010, 2011). Finally, our predictions also agree with measurements of the arterial-specific steady state CBF-CBV relationship made using MRI (Ho et al., 2010a,b).

While our (and others’) results suggest arteries dominate CBV changes during brief functional hyperemia, they also imply that dilation in post-arteriole vessels is necessary to make predictions consistent with experimental observations. Mechanistically, it appears that this occurs in the opposite manner to arteries: small, slow increases in capillary and venous diameter that become significant due to the large proportion of baseline CBV that these vessels represent.

With the recent exception of Drew and Kleinfeld (2011), measurements of the temporal profile of the hemodynamic response with optical imaging have typically used a stimulation length on the order of 1–5 seconds, on the basis that this approximates the behavioural time scale (Kleinfeld et al., 1998; Chaigneau et al., 2003; Devor et al., 2007). Our model suggests that this stimulation length is insufficient to observe dilation in post-arteriolar vessels.

However, dilation in capillaries and veins has been directly observed, although to our knowledge not the temporal profile. Following perfusion fixation, Duelli and Kuschinsky (1993) reported increases in diameter of 20% in rat capillaries, although this comparison was between hyper- and hypocapnic conditions. Using in vivo confocal microscopy, Villringer et al. (1994) observed 7% dilation in rat capillaries in response to hypercapnia. An in vivo two photon microscopy study observed 15% dilation in capillaries and 7% dilation venules and veins combined in response to hypercapnia (Hutchinson et al., 2006), and a subsequent study reported 10% increase in capillary CBV in response to 60 seconds
forepaw stimulation (Stefanovic et al., 2008). Our results are broadly consistent with all of these observations.

In addition, Kim and Kim (2011) suggest arterial and non-arterial volume contributions may be approximately equal after 40 seconds stimulation, on the basis of their measurements of CBV_a. Our model suggests that capillaries and veins contribute slightly under 40% of total CBV changes after 30 second stimulation, which is similar to their observations. Finally, our model also agrees with the measurements of the venous-specific steady state CBF-CBV relationship (Chen and Pike, 2009, 2010).

Thus, our results are consistent with the hypothesis proposed by Drew and Kleinfeld (2011): that arterial vessels act as a rapid ‘bagpipe’ to serve “as a reservoir of fresh blood to support the ongoing and anticipated increase in brain metabolic activity”. However, the slower ‘balloon’ effect of capillary and venous dilation remains significant during prolonged stimulation.

5.3. Methodological considerations

There are a number of limitations of the model which may affect interpretation of the results. We chose to trade spatial resolution for computational simplicity and represented the complex, tortuous network of cerebral blood vessels as three dimensionless compartments. While this approach removes the effect of any spatial heterogeneity, the Windkessel model we use is well established and has been shown to produce results in agreement with experimental observations in a wide range of cases, including here. In addition, measurements made with imaging modalities like MRI and PET are also spatially averaged to some degree, depending on the resolution.

To calculate vascular resistance we assume steady, fully-developed Poiseuille flow, which may be an underestimation. However, following the reasoning of Reichold et al. (2009), we suggest that this assumption is valid as Reynolds numbers in the cerebral circulation remain below the threshold for turbulent flow in all but the largest vessels. We also ignore the effects of energy loss at vessel bifurcations. However, our analyses show that the model predictions
are not sensitive to small changes in resistance fractions, which suggests that branching effects may be insignificant.

The model does not include any capillary recruitment. While including this mechanism might have an effect on the results, in vivo confocal microscopy in the rat brain has suggested that classical capillary recruitment (opening or closing of capillaries) is unlikely to be a significant factor in blood flow regulation (Villringer et al., 1994).

We ignore any active dilation of capillaries or veins in this model. There is evidence from retinal and cerebellar slices showing that pericytes are capable of inducing dilation or constriction of capillaries (Peppiatt et al., 2006). However, it remains unclear whether such dilation occurs in cortical capillaries in vivo, and if so, whether it occurs rapidly enough to have a significant effect during functional hyperemia. Regardless, it is possible that, if active dilation does occur (for example in response to increases in blood pressure or endothelial wall shear stress), some of this is included here as passive distension instead.

Finally, bulk CBF and CBV data, like that we used to identify the model’s dynamic parameters (Mandeville et al., 1999), does not provide sufficient information to discriminate between contributions from the capillary and venous compartments with complete certainty. This is an inherent limitation of the modality used to collect the data, rather than a feature of the particular data we used, or a problem with our optimization approach. Because of this, the model may misrepresent a small amount of the behaviour of the capillaries as that of veins, or vice versa. However, we believe that the important distinction—between arteries and post-arteriole vessels—is unaffected.

The major methodological advancement in this work is the development of a novel linear compliance model. There are many existing empirical models of compliance, which are often formulated using exponential (e.g. Mandeville et al., 1999) or arctangent functions (e.g. Langewouters et al., 1984; Drzewiecki et al., 1997). While these relations agree well with experimental data, they require a relatively large number of parameters to be estimated and do not describe dynamic effects.
The linear compliance model we propose here requires only two parameters: one ‘stiffness’ parameter, which in theory may be measured directly from experiments, and one dynamic ‘viscoelasticity’ parameter. In addition, the model seamlessly incorporates the effects of active dilation or constriction through the vasodilatory stimulus term. Thus, the linear compliance model is able to represent the principal mechanisms relevant during functional hyperemia, and do so in a much simpler form than previous compliance models.

Despite the limitations, the model performed extremely well. To our knowledge, this model is the first to accurately predict features of experimental observations of the hemodynamic response at four distinct spatial or temporal scales: baseline, the steady state relationships between bulk CBF and CBV, bulk measurements of dynamic CBF and CBV changes, and single vessel dynamic measurements of diameter and velocity changes following functional activation.

While the model is a powerful predictive tool, it remains mathematically and computationally simple, requiring only 7 differential algebraic equations to be solved. Using the model, we are able to integrate observations from multiple scales, experiments, and imaging modalities into a plausible, biophysically based framework. In addition, it is possible to predict observations under conditions that would be difficult or impossible to produce experimentally, such as blocking dilation in capillaries and veins.

6. Acknowledgements

The authors thank Richard Buxton for insightful discussions and comments on an early version of the manuscript, and Patrick Drew for helpful suggestions and generously sharing unpublished data.

7. References

References


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Appendix A. Mathematical Detail

Appendix A.1. Fluid Flow

Similarly to previous models (Zheng et al., 2005; Huppert et al., 2007), we treat fluid flow from compartment $i$ to $j$, $F_{i,j}(T)$, as analogous to current flow in an electrical circuit. Viscous resistance, $R_i(T)$, is analogous to electrical resistance, and vessel compliance, $C_i(T)$, is analogous to electrical capacitance. Following Reichold et al. (2009), we ignore inertial effects as the Reynolds number has been shown to remain less than 2 for all but the largest blood vessels in the brain.

The pressure drop (analogous to voltage drops) caused by component $X$, $\Delta P_X(T)$, is given by

$$\Delta P_R(T) = R(T)F(T), \quad \text{(A.1a)}$$
$$\Delta P_C(T) = \frac{V(T)}{C(T)}, \quad \text{(A.1b)}$$


where \( V(T) \) is the volume. Considering a cylindrical compartment of length \( L_i \) and diameter \( D_i(T) \), and assuming Poiseuille flow with a fluid of viscosity \( \mu \), we can describe the resistance of this compartment as

\[
R_i(T) = \frac{128 \mu L_i}{\pi D_i(T)^4}. \tag{A.2}
\]

The volume of this compartment, \( V_i(t) \), equals \( \frac{\pi}{4} D_i(T)^2 L_i \), and therefore (A.2) becomes

\[
R_i(T) = \frac{8\pi \mu L_i^3}{V_i(T)^2}. \tag{A.3}
\]

To conserve energy, pressure gains and losses around a loop must sum to zero; therefore, we can describe the pressure at the entrance of a compartment, \( P_i(T) \), from ground upwards as

\[
P_i(T) = \frac{1}{2} R_i(T) F_{i-1,i}(T) + \frac{V_i(T)}{C_i(T)} + P_{icp}, \tag{A.4}
\]

where \( P_{icp} \) is the intracranial pressure. To reduce the number of variables, \( P_i(T) \) can also be defined from \( P_{in} \), the inlet pressure boundary condition, down such that

\[
P_i(T) = \begin{cases} 
P_{in} & : i = 1 \\
P_{in} - \sum_{j=1}^{i-1} \Delta P_j(T) & : \text{otherwise.}
\end{cases} \tag{A.5}
\]

The pressure drop over a compartment, \( \Delta P_i(T) \), is defined as

\[
\Delta P_i(T) = \frac{1}{2} R_i(T) [F_{i-1,i}(T) + F_{i,i+1}(T)]. \tag{A.6}
\]

The pressure drops over all compartments must sum to difference between the inlet and outlet pressure boundary conditions, so

\[
\sum_{i=1}^{3} \Delta P_i(T) = P_{in} - P_{out} = \Delta P_r, \tag{A.7}
\]

where \( P_{out} \) is the outlet pressure boundary condition, and \( \Delta P_r \) is the total (reference) pressure difference.

To conserve mass, the compartment must change volume when flow in and out differs, so

\[
\frac{dV_i}{dT} = F_{i-1,i}(T) - F_{i,i+1}(T). \tag{A.8}
\]
Continuing the assumption of cylindrical geometry, vessel diameter, \( D_i(T) \), and blood velocity, \( U_i(T) \), are respectively given by

\[
D_i(T) = \sqrt{\frac{4V_i(T)}{\pi L_i}}, \quad \text{and} \\
U_i(T) = \frac{\bar{F}_i}{X_i} = \frac{L_i}{2V_i(T)} [F_{i-1,i}(T) + F_{i,i+1}(T)],
\]

where \( \bar{F}_i \) is the average flow, and \( X_i \) is the cross sectional area. Finally, we define CBF so

\[
CBF = \frac{\sum_{i=1}^{3} V_i(T) [F_{i-1,i}(T) + F_{i,i+1}(T)]}{2 \sum_{i=1}^{3} V_i(T)}.
\]

The preceding equations were nondimensionalized to simplify the system and improve numerical stability. Scales were chosen such that

\[
c_i(t) = \frac{c_i(T)}{C}; \quad d_i(t) = \frac{D_i(T)}{D}; \quad f_i(t) = \frac{F_i(T)}{F}; \quad l_i = \frac{L_i}{L}; \quad p_i(t) = \frac{P_i(T)-P_{icp}}{P}; \quad r_i(t) = \frac{R_i(T)}{R}; \quad t = \frac{T}{T}.
\]

\[
u_i(t) = \frac{U_i(T)}{U}; \quad \psi_i(t) = \frac{V_i(T)}{V}; \quad \frac{dti}{dt} = \frac{\hat{T}}{T} \frac{dF_i}{dT}, \quad \text{and} \quad \frac{dvi}{dt} = \frac{\hat{T}}{T} \frac{dV_i}{dT}.
\]

We defined the scales as

\[
\hat{P} = \Delta P_r; \quad \hat{F} = F^*; \quad \hat{V} = \sum_{i=1}^{3} V_i^*; \quad \hat{R} = \hat{P}/\hat{F}; \quad \hat{C} = \hat{V}/\hat{P}; \quad \hat{L} = \left( \frac{R^2 \mu^2}{8 \pi \mu F} \right) \frac{1}{4}; \quad \hat{T} = \hat{V}/\hat{F}; \quad \hat{D} = \sqrt{\frac{4\hat{V}}{\pi \hat{L}}},
\]

and \( \hat{U} = \hat{F} \hat{L}/\hat{V} \)

where \( \Delta P_r \), the reference pressure difference, is defined in Eq. (A.7) above; \( F^* \) is the flow at baseline; \( \sum_{i=1}^{3} V_i^* \) is the total volume of the three compartments at baseline; and \( \mu \) is the whole blood viscosity. Derived variables not specifically mentioned in Equation (A.12) are nondimensionalized using the scale with the correct dimensions. The dimensionless equations do not include any of these parameters, so the model results are independent of their value.
Appendix A.2. Compliance

[Insert Figure A.4 about here]

In this work we define compliance such that

\[ C(T) = \frac{V(T)}{P_t(T)} \] (A.14a)

\[ = L \frac{X(T)}{P_t(T)}, \] (A.14b)

where \( P_t(T) \) is transmural pressure, and \( X(T) \) is the vessel cross-sectional area. Length, \( L \), is assumed constant so \( V(T) \) and \( X(T) \) are proportional.

Using intravascular ultrasound and pressure transducers, Bank et al. (1995) reported the pressure-area relationships of human brachial arteries in vivo. Their data, which we replot here in Figure A.4, show that it is reasonable to approximate steady state compliance as a linear function of volume (proportional to area in this work) under physiological conditions. While cerebral arteries lack the external elastic lamina found in systemic arteries such as the brachial (Lee, 1995), this approximately linear relationship is also valid for data taken from cerebral arterioles (Baumbach et al., 1989; Hajdu et al., 1990; Baumbach and Hajdu, 1993; data not shown). Thus, we define a single ‘stiffness’ coefficient, \( \kappa \), as the maximum possible multiple of baseline volume; mathematically,

\[ v_{\text{max}} = \kappa v^* \] where \( v_{\text{max}} \) is the maximum volume to which a vessel may dilate.

In addition, the slope of this compliance relationship is near constant during changes in smooth muscle tone. As such, we describe dilation or constriction as a vertical shift (up or down, respectively) in steady state compliance caused by stimulus \( s(t) \) (see Figure A.4).

While viscoelastic effects are not significant under steady state or slowly varying conditions, they are relevant here because of the rapid changes that follow neural activation. Zheng and Mayhew (2009) proposed a ‘viscoelastic Windkessel’ model that shows good agreement with experimental data. However for simplicity, we represent viscoelasticity using a single linear viscoelasticity coefficient, \( \nu \).
The full mathematical description of the linear compliance model is given in Equation (5) in the main text.

Appendix A.3. Vasodilatory Stimulus

[Insert Figure A.5 about here]

There is a growing body of evidence suggesting that calcium dependent signalling in astrocytes may trigger the increase in CBF following activation (e.g. Metea and Newman, 2006; Takano et al., 2006; Gordon et al., 2008); however, the cellular signalling pathways remain unclear (for a review, see Attwell et al., 2010). In addition, some suggest that the vascular response is composed of competing dilation and constriction (Devor et al., 2007; Zheng et al., 2010). For simplicity, here we use an empirical vasodilatory stimulus to represent the combined effects of the putative neuron-astrocyte-vascular smooth muscle unit as a change in vessel compliance (see Section 2.2). Our stimulus is similar to the ‘neural response’ proposed by Buxton et al. (2004).

The vasodilatory stimulus applied to the arteries, \( s_1(t) \), (see Figure A.5) is described by

\[
 s_1(t) = \begin{cases} 
 s_{up}(t), & t < t_{max} \\ 
 s_{decay}(t), & t_{max} \leq t \leq t_{end} \\ 
 s_{down}(t), & t > t_{end} 
 \end{cases} 
\] (A.15)

where:

\[
 s_{up}(t) = \frac{1}{2} s_{max} \left[ 1 + \text{erf} \left( \frac{t - (t_0 + \frac{\tau_{up}}{2})}{\sqrt{2\tau_{up}}} \right) \right]; \quad (A.16a)
\]

\[
 s_{decay}(t) = (s_{max} - s^*) \exp \left( \frac{t_{max} - t}{\tau_{decay}} \right) + s^*; \quad (A.16b)
\]

\[
 s_{down}(t) = s_{end} \exp \left( \frac{t_{end} - t}{\tau_{down}} \right); \quad (A.16c)
\]

\( t_{max} \), the time at maximum stimulus, is equal to \( t_0 + \tau_{up} \); \( t_{end} \) is the time at the cessation of stimulation (where \( t_{end} \geq t_{max} \)); \( s_{max} \) is the peak value of the stimulus; \( \text{erf} \) is the error function; \( t_0 \) is the stimulus onset time; \( \tau_X \) are time constants (where \( X \in \{up, decay, down\} \)); \( s^* \) is the steady state value of the stimulus (where \( s^* \leq s_{max} \)); and \( s_{end} \), the stimulus value at \( t_{end} \), is given by \( s_{decay}(t_{end}) \).
The values of \( \tau_{up} \) and \( \tau_{down} \) were set to \( 1/\hat{T} \) and \( 1/4\tau_{up} \) respectively, while the values of \( s_{max}, s^*, \) and \( \tau_{decay} \) were determined using dynamic simulations (see Section 3.2). No stimulus was applied to the capillary or venous compartments; i.e. \( s_2(t) = s_3(t) = 0 \) for all \( t \).

Table A.1: List of dynamic variables

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c_i(t) )</td>
<td>Vessel compliance</td>
</tr>
<tr>
<td>( d_i(t) )</td>
<td>Vessel diameter</td>
</tr>
<tr>
<td>( f_{i,j}(t) )</td>
<td>Blood flow from ( i ) to ( j )</td>
</tr>
<tr>
<td>( p_i(t) )</td>
<td>Entrance blood pressure</td>
</tr>
<tr>
<td>( \Delta p_i(t) )</td>
<td>Blood pressure difference</td>
</tr>
<tr>
<td>( r_i(t) )</td>
<td>Viscous resistance</td>
</tr>
<tr>
<td>( s_i(t) )</td>
<td>Vasodilatory stimulus</td>
</tr>
<tr>
<td>( u_i(t) )</td>
<td>Blood velocity</td>
</tr>
<tr>
<td>( v_i(t) )</td>
<td>Blood volume</td>
</tr>
<tr>
<td>( x_i(t) )</td>
<td>Vessel cross-sectional area</td>
</tr>
</tbody>
</table>
Table A.2: List of optimal parameters for both the ‘top down’ (unconstrained) and ‘bottom up’ (constrained) models. Parameters with three values correspond to [arteries, capillaries, and veins].

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value (a.u.)</th>
<th>'Top Down'</th>
<th>'Bottom Up'</th>
<th>Determined Via</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c^*$</td>
<td>Baseline compliance</td>
<td>[0.46, 2.02, 2.97]</td>
<td>same</td>
<td>Indirect data; see Equation (7c)</td>
<td></td>
</tr>
<tr>
<td>$l$</td>
<td>Length</td>
<td>[0.39, 0.25, 0.23]</td>
<td>same</td>
<td>Indirect data; see Equation (7a)</td>
<td></td>
</tr>
<tr>
<td>$s^*$</td>
<td>Steady state stimulus</td>
<td>2.15</td>
<td>1.93</td>
<td>Fit to Mandeville et al. (1999)</td>
<td></td>
</tr>
<tr>
<td>$s_{\text{max}}$</td>
<td>Peak stimulus</td>
<td>2.87</td>
<td>5.19</td>
<td>Fit to Mandeville et al. (1999)</td>
<td></td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Stiffness coefficient</td>
<td>[1.29, 1.51, $\infty$]</td>
<td>[1.29, 1, 1]</td>
<td>Direct and indirect data; see main text</td>
<td></td>
</tr>
<tr>
<td>$\nu$</td>
<td>Viscelastic coefficient</td>
<td>[31, 163, 122]</td>
<td>[47, $\infty$, $\infty$]</td>
<td>Fit to Mandeville et al. (1999)</td>
<td></td>
</tr>
<tr>
<td>$\tau_{\text{decay}}$</td>
<td>Stimulus time constant</td>
<td>1.04</td>
<td>0.45</td>
<td>Fit to Mandeville et al. (1999)</td>
<td></td>
</tr>
</tbody>
</table>
Figure A.1: Model structure. Electrical circuit representation of the vascular model showing pressure boundary condition ($\Delta p_r$), blood flows ($f_{i,j}$), resistances ($r_i$), and compliances ($c_i$). Resistances are symmetric within arterial (Art.), capillary (Cap.), and venous (Ven.) compartments.
Figure A.2: Optimal predictions from ‘top down’ (unconstrained) simulations. (A) Normalized total (plus signs), arterial (Art., circles), and venous (Ven., triangles) steady state CBF-CBV relationships; and best fit of Grubb’s power law to the model predictions (solid lines), where α values are given in the legend. (B-C) Normalized total CBF (B) and CBV (C) changes in response to 6 and 30 second stimulation (black lines without markers); experimental data from Mandeville et al. (1999) (grey lines without markers); and contribution of arteries (circles), capillaries (squares) and venules (triangles) to total CBV changes. (D-F) Normalized diameter changes in arteries (D), capillaries (E) and veins (F) in response to 1, 10, and 30 second stimulation (dark lines); and experimental data from Drew and Kleinfeld (2011) (pale lines). (G-I) Normalized velocity changes in arteries (G), capillaries (H) and veins (I); stimulation and notation as per D-F.
Figure A.3. Optimal model predictions from ‘bottom up’ (constrained) simulations, with dilation blocked in capillaries and veins. (A-C) Normalized diameter changes in arteries (A), capillaries (B) and veins (C); stimulation and notation as per Figure A.2D-F. (D-F) Normalized velocity changes in arteries (D), capillaries (E) and veins (F); stimulation and notation as per Figure A.2G-I. (G-H) Normalized total CBF (G) and CBV (H) changes; stimulation and notation as per Figure A.2B-C. (I) Normalized steady state CBF-CBV relationships; notation as per Figure A.2A.
Figure A.4: Linear compliance relationship. Top: Experimentally measured relationship in brachial arteries under baseline, dilated, and constricted conditions. The data points (± s.d. in each axis) are replotted from Bank et al. (1995). Lines are linear regression fits. ‘Area’ on both axes is cross-sectional area and ‘Pressure’ is transmural pressure. Bottom: Diagram of the proposed linear relationship. The ‘stiffness’ parameter $\kappa$ represents the maximum possible volume. Stimulation, $s(t)$, shifts the relationship from baseline to dilated (or constricted).
Figure A.5: Schematic of vasodilatory stimulus. Following onset ($t_0$), the stimulus increases to a peak ($s_{\text{max}}$) at time $t_{\text{max}}$, with the rate governed by $\tau_{\text{up}}$. Then, it decays (rate constant $\tau_{\text{decay}}$) toward a steady state ($s^*$). At the cessation of stimulation ($t_{\text{end}}$), the stimulus returns to baseline, with the rate governed by $\tau_{\text{down}}$. Three possible forms of the stimulus are shown: a medium length (black line), a brief, and an extended form (both grey lines).
Highlights

- We model the hemodynamic response to functional activation at multiple scales.
- We propose a powerful new description of vascular compliance.
- Arteries, not veins, dominate volume changes.
- Capillary and/or venous dilation is required to produce consistent predictions.