Temporal Dynamics of BOLD fMRI at the Microscopic Level

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ABSTRACT

With the prospect of elucidating the BOLD fMRI phenomenon we consider the interactions between Cerebral Blood Flow (CBF), oxygen utilization \( (\text{CMRO}_2) \), haemoglobin reaction kinetics, and oxygen transport. This paper presents four cases that mimic the physiological response of the brain subject to cerebral activation/inactivation transitions and changes in CBF. Model results show that the system is more sensitive to changes in CBF rather than alterations in \( \text{CMRO}_2 \). Thus given the small magnitude of BOLD fMRI signal \((0.5\% \text{ to } 5\%)\)\[1\] the relative feedback reactions between \( \text{CMRO}_2 \) and CBF appear to play a pivotal role in elucidating BOLD fMRI.

Keywords: BOLD fMRI, capillary, oxygen saturation/transport

1 INTRODUCTION

Despite the fact that functional MRI (fMRI) is currently used to support clinical brain interventions, to study brain development and physiology, and to understand human cognition, the underlying Blood Oxygenation Level Dependent (BOLD) mechanism, upon which the modality is based is not completely understood. Considering an activated region, a drop in the capillary Oxygen Extraction Fraction (OEF), is believed to yield a higher ratio of oxy-to-deoxyhaemoglobin, in relation to the basal state \[2\], resulting in a visible increase in the BOLD signal.

In terms of MRI physics, the BOLD signal is caused by the discrepancies in magnetic susceptibilities between oxy- and deoxy-haemoglobin, allowing signal changes during brain stimulation to be measured relative to a resting reference level. During stimulation the signal increases, implying that the ratio of oxy- to deoxy-haemoglobin has also increased. This effect is counter-intuitive: during neuronal activation the metabolic rate, and therefore oxygen consumption, is higher, and a lower saturation (and consequently a lower BOLD signal) would be expected. Hypothesized physiological explanations are based on feedback reactions involving changes in CBF to the activated region, thus oversupplying the activated area with oxygenated blood. To quantitatively investigate this hypothesis, we consider the transient interactions between the two key parameters– oxygen consumption rate and CBF– using a computational system of a capillary.

2 METHODS

2.1 The Capillary-Tissue Model

The mathematical model consists of a straight cerebral capillary, 8\(\mu\)m in diameter by 200\(\mu\)m in length, subdivided into an erythrocyte and a cell depleted region (CDR) ending at 3.25\(\mu\)m and 4\(\mu\)m in the radial direction from the central axis, respectively. The blood vessel, surrounded by a coaxial tissue compartment 29\(\mu\)m in radius, is depicted in Figure 1. Both diffusion and convection of oxyhaemoglobin and oxygen are considered in the axial and radial directions.

Oxygen and haemoglobin diffusivity coefficients together with model particulars, are presented in Table 1. The model was developed using the multi-physics CFD-ACE+ platform.

Erythrocyte (RBC) Region. The rationale for having a continuous RBC zone derives from observations in similar diameter glass tube experiments where erythrocytes aggregate to form continuous columns \[4\]. The RBC region was treated as a rigid body moving with a constant velocity. In this domain the oxygen release and the concomitant drop in haemoglobin saturation is governed by the oxygen dissociation curve (ODC) \[5\]. Haemoglobin entering the RBC inlet had a saturation of 0.97 and the local partial oxygen pressure was 93.4mmHg.

Cell Depleted Region, CDR. In the CDR we solve the equations of flow. Here oxygen flux from the erythrocyte into the tissue region is influenced by both convec-

Figure 1: The cerebral capillary-tissue computational system.
tion and diffusion. The CDR was taken to be 0.75 μm [7] in thickness.

**Tissue Region.** Cerebral tissue was taken to consist of a constant neuronal cell density consuming a uniform amount of oxygen during basal-to-activated changes. Oxygen transport was governed by the generic transport equation (1) which considered only diffusion in this region. Carrier-mediated transport of oxygen in the cerebral tissue is accounted for within the oxygen diffusivity constant [10], [9] (See Table 1). CMRO₂ is considered as a sink term, -Sᵦ, added to the same equation (1), which changes with local oxygen concentration.

### 2.2 Governing Equations

The momentum conservation equation along with continuity were used to capture the behavior of the plasma in the CDR while the RBC region moved at a constant velocity. Haemoglobin transport, within the RBC domain, and oxygen flux from the same domain into the CDR and eventually into tissue is governed by appropriate mass transport equations, one for each species:

\[
\frac{\partial \rho \phi}{\partial t} + \nabla \cdot (\rho \mathbf{u} \phi) = \nabla \cdot (D \nabla \phi) \pm S \phi
\]  \hspace{1cm} (1)

The second term in the LHS and the first term in the RHS are the convection and diffusion terms respectively. Oxygen and haemoglobin, are the dependent scalar variables denoted by \( \phi \), whereas \( D \) are the diffusivity coefficients. Oxygen release and haemoglobin saturation, in the erythrocyte region, are governed by the source/sink term, \( S \phi \), that derives from the haemoglobin reaction rate [11], [12]:

\[
R_{ODC} = k_H \cdot C_H \cdot \left( \frac{sO_2\text{ Num} - sO_2\text{ ODC}}{1 - sO_2\text{ ODC}} \right)
\]  \hspace{1cm} (2)

In turn, equation (2) is based on the ODC [5]. Furthermore, \( k_H \) is the reaction rate of the oxyhaemoglobin dissociation, \( c_H \) is the oxygen carrying capacity of haemoglobin, and \( sO_2\text{ Num} \) and \( sO_2\text{ ODC} \) are the fractional saturation of haemoglobin, determined numerically and using the ODC, respectively. In the tissue domain oxygen consumption initially follows a linear profile to be subsequently bounded by the basal or activated amount. As

<table>
<thead>
<tr>
<th>Capillary</th>
<th>Erythrocyte Region</th>
<th>Cell Depleted Region</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length, L (μm)</td>
<td>( L_{RBC}=200 ) [6]</td>
<td>( L_{CDR}=200 ) [6]</td>
<td>( L_{Tissue}=200 ) [6]</td>
</tr>
<tr>
<td>Radius, D (μm)</td>
<td>( D_{RBC}=3.25 )</td>
<td>( D_{CDR}=4 ) [7]</td>
<td>( D_{Tissue}=29 ) [8]</td>
</tr>
<tr>
<td>Mass-density, ( \rho ) (kg/m³)</td>
<td>( \rho_{RBC}=1,160 )</td>
<td>( \rho_{CDR}=1,025 )</td>
<td>( \rho_{Tissue}=937.5 )</td>
</tr>
<tr>
<td>Dynamic Viscosity, ( \mu ) (kg/m-s)</td>
<td>-</td>
<td>( \mu_{CDR}=1.2 \times 10^{-3} )</td>
<td>-</td>
</tr>
<tr>
<td>( O_2 ) Diffusion Coeff., D (cm²/s)</td>
<td>( D_{O_2\ RBC}=8.8 \times 10^{-6} )</td>
<td>( D_{O_2\ CDR}=2.29 \times 10^{-5} )</td>
<td>( D_{O_2\ Tissue}=1.6 \times 10^{-5} ) [9]</td>
</tr>
<tr>
<td>( HbO_2 ) Diffusion Coeff., D (cm²/s)</td>
<td>( D_{HbO_2\ RBC}=1.42 \times 10^{-6} )</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 2: Tissue oxygen consumption profile. depicted in Figure 2, the tissue can not consume more oxygen than there is in its region.

### 2.3 CMRO₂ and CBF Transitions

To explore the non-linear temporal dynamics of the BOLD effect we examine the impact neuronal activation, in terms of CMRO₂ and CBF, has on the fractional haemoglobin saturation at the outlet of the capillary. This analysis is based on the hypothesis that following regional brain activity local CBF, rather than capillary recruitment, increases to satisfy local metabolic demands [13]. For the basal state we used a CMRO₂ value of 160μmol/100g-min [14] and a capillary velocity of 0.3mm/s [15] whereas for the activated scenario we consider a 50% increase in CMRO₂ [16] and a CBF of 1mm/s [17]. It is worth noting that blood velocity values in the capillaries found in the literature ranged from 0.3mm/s [15] to 4mm/s [20]. Detailed features of the regional, in-vivo oxygen utilization characteristics in humans during activation at the capillary level have been very difficult to identify. We assumed discrete transitions in CMRO₂ and CBF to occur as step changes. Mimicking this physiological brain behavior we considered four cases during which we mapped the haemoglobin saturation at the capillary outlet. It is worth emphasizing that for each consecutive case we have altered only one parameter, either CMRO₂ or CBF, at a time, while each case used as its initial conditions the previous case’s steady state findings. Sections 2.3.1-4 outline the characteristics of each scenario. Furthermore, the upper two plots in Figure 3 graphically portray the relative changes in CMRO₂ and CBF.

**2.3.1 Activated CMRO₂ and Resting CBF.**
assuming a basal blood flow this scenario is based on a CMRO$_2$ value of 240$\mu$mol/100g-min and a CBF of 0.3mm/s.

2.3.2 Activated CMRO$_2$ and Activated CBF. Given that cerebral activation triggers increases in CBF this case explores the coupled influence an increased CMRO$_2$ and CBF, of 240$\mu$mol/100g-min and 1.0mm/s respectively, have on the haemoglobin fraction.

2.3.3 Resting CMRO$_2$ and Activated CBF. Assuming that the stimulus duration is substantially smaller than the time scale of vascular adaptations in blood flow one can safely suppose that CMRO$_2$ can switch back to its basal state while CBF still retains its high velocity. Hence, CMRO$_2$ will drop to 160$\mu$mol/100g-min while CBF will remain at 1mm/s.

2.3.4 Resting CMRO$_2$ and Resting CBF. Finally, once the stimulus has been removed and the blood flow has abated one would expect cerebral autoregulation to revert the system back to its equilibrium state, thus a CBF value of 0.1mm/s and CMRO$_2$ of 160$\mu$mol/100g-min.

3 RESULTS

As depicted in the bottom schema of Figure 3, the overall shape of the the haemoglobin saturation curve correlates well with the BOLD signal from previous studies [18]. Despite a 50% increase in CMRO$_2$, during activation, scenario 2.3.1, with a drop of -7.98% in haemoglobin saturation does not exert an appreciable influence on the discharge haemoglobin saturation. This behavior is quantitatively captured by the time constant, $\tau$, which is a measure of the time it takes for haemoglobin saturation to reach half the value of its final steady state amount. This measure implies that the lower the $\tau$ value the more responsive the system is. Table 2.b presents the $\tau$ values for all four cases. Thus, the behavior of case 2.3.1 is reflected by its high $\tau$ value of 0.421s. However, given that the brain stores little energy and oxygen reserves while active neurons require a substantial amount of oxygen [19] this behavior is somewhat surprising. Indeed, the most striking behavior is that of scenario 2.3.2 when CBF is increased to 1mm/s. With the smallest $\tau$ value of 0.076 the haemoglobin saturation of this case increases dramatically (from 0.80 to 0.88) reaching 2/3 of its total steady state saturation amount in just 0.2s. Thereafter it takes another 2.8s for the haemoglobin saturation to reach its state steady value of 0.92.

Subsequently, reverting back to the basal state consumption, scenario 2.3.3, with a $\tau$ value of 0.33 reinforces the argument that the system is more responsive to perturbations in velocity and the availability of oxygenated blood. Finally, a reduction in blood velocity from 1 to 0.3mm/s brings about an appreciable drop in haemoglobin saturation (from 0.94) to 0.86. Despite the sudden decrease in velocity the reduction in saturation with a nearly linear trend results in the highest $\tau$ value of 0.599. The reason for this is that the neuron region is now replete with oxygen that has to be consumed before a gradient from the erythrocyte region is reestablished.

4 DISCUSSION

Model results show that the capillary-tissue system is more responsive to changes in velocity rather than alterations in CMRO$_2$. These results lend credibility to the hypothesis that supports increases in CBF, rather than capillary recruitment, as the mode of satisfying the brain’s metabolic demands. Evidently, both the threshold of the tissue oxygen content, that elicits changes in CBF, and the magnitude of the time delay between the signal for increase in flow and the actual delivery of the blood would have an appreciable effect on the haemoglobin saturation at the capillary outlet. Thus given the small magnitude of BOLD fMRI signal, between 0.5% and 5%, the relative temporal dynamics between CMRO$_2$ and CBF appear to play a vital role in understanding the contrast.

**Limitations.** These results are based on a straight cerebral capillary-tissue system. Another limitation is that the scenarios explored utilize a higher haematocrit that what is physiological for the cerebral microvasculature.
(Hct of 66% instead of the normal 45%). Apart from a small influence on the Hb saturation values this Hct is not expected to yield substantially different results. Similarly, although cerebral capillaries are not straight, certain parts of the cortex exhibit capillaries with a very significant straight section. Finally, the use of steady state initial conditions derive from the lack of experimental data.

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REFERENCES
[3] ESI Inc, Huntsville, AL, USA.