A two-compartment BOLD model of an infusion of contrast agent

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INTRODUCTION

The BOLD response to neural activation is often used to study brain function, yet the technique is not fully understood. It is hoped that through suitable experiments and simulations the mechanisms underlying the technique can be more thoroughly elucidated. The work of Buxton [1] and others provides a model of the BOLD response that may be tested experimentally. We present a simulation of the effect of an infusion of a gadolinium-chelate contrast agent (CA) on the BOLD haemodynamic response function. Comparison is then made with experimental measurements [3]. An infusion of this type [2] is often used to quantify oxygenation and blood volume changes.

THEORY

We model the BOLD signal change to be the sum of intra- (IV) and extra-vascular (EV) signals, and separate the vasculature into arterioles and venules. This neglects the capillary contribution, which is assumed to have constant volume and mixed oxygenation levels, and is shared between these compartments. Arterial volume change is simulated using the *arterial compliance* model [4] and venous volume change using the standard *balloon* model [1] incorporating viscoelastic effects. Numerical simulations in MATLAB [5] were performed to produce time-courses of arterial volume (v_a), venous volume (v_v) and venous deoxyhaemoglobin (q_v). An *in vivo* CA concentration time-course (*[Gd]*) was also simulated [6]. The BOLD signal is modelled as a function of volume, deoxyhaemoglobin ([dHb]) content and gadolinium ([Gd]) concentration, following the approach of Obata *et al.* [7]. The total signal is considered to be a weighted sum of IV and EV signals dependent on changes in transverse relaxation rate (ΔR_2^*) between *initial resting* state (Eqn. 1) and *later* states with altered [dHb] and [Gd] (Eqn. 2),

$$S_0 = (1-V_{a0}-V_{v0})F_{v0}S_{E0} + (1-V_{a0}-V_{v0})F_{a0}S_{E0} + V_{v0}S_{I0v} + V_{a0}S_{I0a} \quad (1)$$

$$S = (1-V_a-V_v)F_vS_{E0}e^{-TE\Delta R_{2Ev}^*} + (1-V_a-V_v)F_aS_{E0}e^{-TE\Delta R_{2Ea}^*} + V_vS_{I0v}e^{-TE\Delta R_{2Iv}^*} + V_aS_{I0a}e^{-TE\Delta R_{2Ia}^*} \quad (2)$$

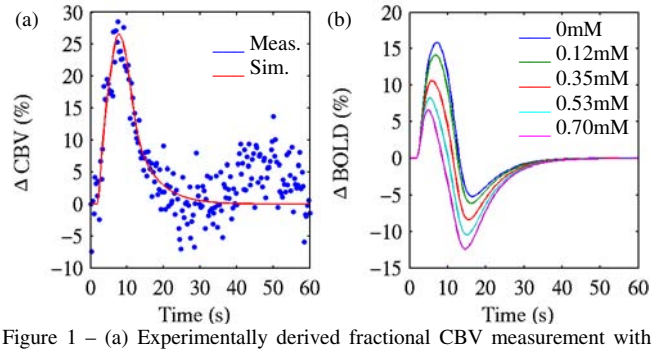
where F_v and F_a apply a volume weight to the EV signals, V_0 is resting volume fraction with subscripts a and v representing arterial and venous compartments and subscripts E and I representing the EV and IV compartments. We derived expressions for ΔR_2^* (Eqn. A-D) as functions of volume, [Gd] and [dHb] and substituted these into Eqn. 1 and 2. By deriving the fractional signal change and rearranging in terms of normalised volume, v, and deoxyhaemoglobin content, q, we yield Eqn. 7.

$$\frac{\Delta S_{tot}}{S_{tot}} \approx V_{vo}\left[k_1F_v(1-q_v) - k_2(q_v-v_v) - k_3(1-v_v) - k_4F_vv_v[Gd] - k_5v_v[Gd]\right] + V_{a0}\left[-k_6F_av_a[Gd] - k_7v_a[Gd] - k_8(1-v_a)\right] \quad (3)$$

Constants k_1 to k_8 are listed (below right), where χ and r are the volume susceptibilities and 3T relaxivities. Finally, ε is the ratio of the venous IV signal to EV signal and β is the ratio of venous IV signal to arterial IV signal, at initial resting state ([Gd]=0).

RESULTS

In order to compare model predictions with experimental data, simulated results were fitted to a CBV time-course obtained from an infusion experiment [3] (Fig1(a)). The balloon model viscoelastic time constants were estimated to be 10.17s during inflation and 12.88s during deflation. The neuronal efficacy, signal decay and flow feedback constants were found to be 0.51s^{-2}, 1.71s^{-1}, 0.46s^{-2}. Additionally the maximum normalised arterial radius was 1.30 and the delay to onset of volume change was 2.34s. These findings are similar to Behzadi *et al.* These parameters were used to simulate the expected BOLD signal during the infusion experiment, Fig. 1(b), and compared to the experimental data, Fig. 1(c). Whilst the reduction in the overshoot, with increasing [Gd], is relatively consistent with the experimental data, the post-stimulus undershoot is not. The post-stimulus undershoot and its change with increasing [Gd] is too large when compared with experimental data.



$$\Delta R_{2Ea}^* = \tfrac{4}{3}\pi\omega_0V_{a0}v_a[Gd]\chi_{gd} \quad (A)$$

$$\Delta R_{2Ia}^* = r_{gd}[Gd] \quad (B)$$

$$\Delta R_{2Ev}^* = \tfrac{4}{3}\pi\omega_0V_{v0}\left[E_0(q_v-1)\chi_{dhb} + v_v[Gd]\chi_{gd}\right] \quad (C)$$

$$\Delta R_{2Iv}^* = r_{dhb}E_0\left(\tfrac{q_v}{v_v}-1\right) + r_{gd}[Gd] \quad (D)$$

$$k_1 = \tfrac{4}{3}\pi\omega_0TE\chi_{dhb}E_0 \qquad k_2 = \varepsilon TEE_0r_{dhb}$$

$$k_3 = \varepsilon - 1 \qquad k_4 = \tfrac{4}{3}\pi\omega_0TE\chi_{gd}$$

$$k_5 = \varepsilon TEr_{gd} \qquad k_6 = \tfrac{4}{3}\pi\omega_0TE\chi_{gd}$$

$$k_7 = \tfrac{\varepsilon}{\beta}TEr_{gd} \qquad k_8 = \tfrac{\varepsilon}{\beta} - 1$$

Figure 1 – (a) Experimentally derived fractional CBV measurement with model fitted curve, (b) simulated BOLD response with increasing CA concentration, (c) measured BOLD response during infusion experiment [3]. Paradigm: 20 visual stimulus cycles; 4 pre-infusion, 16 during infusion. BOLD signal data is averaged in blocks of 4 cycles to improve SNR.

DISCUSSION

The two-compartment BOLD signal model described above allows more comprehensive tests of the balloon model to be performed. This approach is necessary in experiments where exogenous contrast is used to probe the BOLD response. Some differences between the simulated and experimental data (Fig. 1(b) and Fig. 1(c)) may be accounted for by uncertainty in various parameters including the fractional volume of each compartment (V_{a0}=0.01, V_{v0}=0.03). The results suggest that the underlying mechanism of the post-stimulus undershoot requires further investigation. In the current implementation of the balloon model the post-stimulus undershoot is dominated by volume change. These results are consistent with the suggestion [8] that oxygenation may play an important role in the form of the post-stimulus undershoot. Future work will consider these anomalies.

REFERENCES

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Funded by the MRC