# A novel multi-scale, multi-compartment model of oxygen transport – Towards in-silico clinical trials in the entire human brain

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## 1. Introduction

The in-silico clinical trials for the treatment of acute ischemic stroke (INSIST) consortium is a multi-disciplinary, multi-sectorial undertaking aiming to advance the understanding and treatment of ischemic stroke through computational simulations and clinical trials. The work presented here is a part of this project which aims to model oxygen transport and metabolism in the entire human brain. This will form the backbone of the in-silico trials as this model, coupled with the multi-scale model of the blood flow in the human brain presented elsewhere in this conference[1], will predict regions of hypoxia post-stroke, and hence will predict tissue death. This can then be validated against an available large database of stroke patients.

Modelling the oxygen transport in the entire brain is not a trivial matter, in particular due to the multiple spatial scales and time scales over which oxygen is transported and metabolised. Prior efforts at modelling oxygen transport in the brain have primarily involved modelling small regions of the vasculature (in the order of millimetres) due to computational constraints e.g. [1]. It was then demonstrated how the mass transport equation can be up-scaled through the use of homogenization [2,4] - and that a few key parameters can be pre-computed from the micro-scale which encapsulate the geometry and connectivities of the blood vessel networks. We here extend the homogenization procedure previously applied to the capillary bed [2,3] to deal with the multiple spatial-scales of the vasculature in the brain (from the tissue bed up to the pial vessels). We thus develop a multi-compartment, multi-scale coupled model of the oxygen transport in the entire human brain. The key parameters are computed from micro-scale simulations and are then used in an idealised one compartment simulation of oxygen transport in the arterioles.

## 2. Methods

**Theory** – We extend the work of Shipley and Chapman [2] here by reiterating the homogenization procedure over multiple spatial scales. In brief, at each scale e.g. the penetrating vessel scale, the mass transport equation describes the flow of oxygen through the penetrating vessels. The vessels at the scale below are treated as a porous medium (in this example the capillary bed) and boundary conditions are imposed between the vessels and porous medium that relate to the coupling of blood flow (and hence bulk transport of oxygen) and the transport of oxygen into the tissue across the vessel walls. After non-dimensionalizing these equations, the scale separation of the problem is exploited, and the leading order problem is extracted [2,3,4]. This homogenization procedure is reiterated from the tissue scale

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to the pial vessel scale. The result is a set of coupled partial differential equations (1) – (4):

$$\frac{\partial c_a^{(0)}}{\partial t} + \left(\langle \boldsymbol{u_a^{(0)}} \rangle_{\boldsymbol{a}} . \nabla_x c_a^{(0)}\right) = -\frac{\gamma_a S_a}{V_a}\left(c_a^{(0)} - c_t^{(0)}\right) - \beta_{ac}\left(p_a^{(0)} - p_c^{(0)}\right)c_a^{(0)} \quad (1)$$

$$\frac{\partial c_v^{(0)}}{\partial t} + \left(\langle \boldsymbol{u_v^{(0)}} \rangle_{\boldsymbol{v}} . \nabla_x c_v^{(0)}\right) = \beta_{cv}\left(p_c^{(0)} - p_v^{(0)}\right)c_c^{(0)} \quad (2)$$

$$\frac{\partial c_c^{(0)}}{\partial t} + \left(\langle \boldsymbol{u_c^{(0)}} \rangle_c\right) . \nabla_x c_c^{(0)}) = \nabla_x . \left[\boldsymbol{D_2^{dif}} \nabla_x c_c^{(0)}\right] - \frac{\gamma_c S_c}{V_c}\left(c_c^{(0)} - c_t^{(0)}\right) + \beta_{ac}\left(p_a^{(0)} - p_c^{(0)}\right)c_i^{(0)} + \beta_{cv}\left(p_v^{(0)} - p_c^{(0)}\right)c_c^{(0)} \quad (3)$$

$$\frac{\partial c_t^{(0)}}{\partial t} = \nabla_x . \left[\boldsymbol{D_2^{dif}} \nabla_x c_t^{(0)}\right] + \frac{\gamma_a S_a}{V_t}\left(c_a^{(0)} - c_t^{(0)}\right) + \frac{\gamma_c S_c}{V_t}\left(c_c^{(0)} - c_t^{(0)}\right) - f(c_t^{(0)}) \quad (4)$$

Subscripts t, c, a, and v refer to tissue, capillaries, arterioles, and venules respectively. $c^{(0)}$ is the leading order concentration, $S$ the surface area of the given vessels in the compartment, $V$ the volume of the compartment, and $p^{(0)}$ is the leading order pressure in the given compartment. $\gamma$ is the wall transport coefficient (from the vessels to the tissue), $\boldsymbol{D_2^{dif}}$ is the macro-scale diffusion tensor for oxygen in the capillaries and tissue, and $f(c_t^{(0)})$ is a non-linear metabolism term (Hill equation). Finally, $\beta_{ac}$ is the blood flow coupling coefficient from the arteriole to capillary compartment, $\beta_{cv}$ is the blood flow coupling coefficient from the capillary to the venule compartment, and $\langle \boldsymbol{u_i^{(0)}} \rangle_i$ is the Darcy velocity where $i$ refers to any of the four compartments (t, a, v, and c).

This set of equations can be solved over the entire brain, resulting in a 4-compartment coupled model of oxygen transport and metabolism. The Darcy velocity and pressure are computed from the homogenized blood flow equations detailed elsewhere[2].

The main parameters that derive from the homogenization procedure - that encapsulate the micro-scale structure of the networks - must be pre-computed before simulating over the macro-scale. These are the surface-area-to-volume ratios of the capillary and arteriole network $\left(\frac{S_c}{V_c}, \frac{S_a}{V_a}\right)$, the volume fractions of the capillary and arteriole network $\left(\frac{V_c}{V_T}, \frac{V_a}{V_T}\right)$ – where $V_T$ is the total volume of the compartment, and the effective diffusion coefficient $\boldsymbol{D_2^{dif}}$.

Simulation – We firstly run simulations on our micro-scale networks to extract the necessary parameters [3,5]. It is found that the diffusion tensor is isotropic and can be approximated as constant and equal to the original diffusion coefficient D. The surface-area-to-volume ratios of the arteriolar and capillary networks are calculated for steadily increasing cube sizes until the parameters converge. At this point, the parameters can be described as the effective parameters of the network, as they now encapsulate enough heterogeneities of the network that any further increase in cube size won't influence the effective parameters.

We then simulate oxygen transport in a 2 mm x 2 mm x 2 mm voxel for the arteriolar compartment, solving the continuum model using the FEniCS open source computing platform. Equation (1) is implemented without the coupling term and with a small diffusion term to observe what effect an occlusion has on the steady state oxygen distribution, along with a constant tissue concentration. A Dirichlet boundary condition is imposed on the pial surface of the compartment relating to a concentration of 1 $mm^3$ $O_2$ /$mm^3$, along with periodic boundary conditions on the 4 sides of the cube, and a no flow Neumann boundary condition at the grey/white matter interface. The diffusion coefficient is $1.8x10^{-3}$ $mm^2$/s, the Darcy velocity vector is [0,0,0.18] mm/s (imposing a velocity down the cortical column from the pial surface to the white matter), the tissue concentration is assumed constant and equal to 0.335 $mm^3$ $O_2$ /$mm^3$, and the wall transport coefficient $\gamma_a$ is 4.2 x $10^{-4}$ mm/s.

The simulation is initialised with zero concentration throughout the voxel and the time taken to reach steady state is recorded. An occlusion is then introduced on the pial surface which results in a step change in velocity, with the velocity vector dropping to 10% of its original value, and the time to reach steady state is again observed.

## 3. Results and Discussion

The mico-scale parameters of interested were generated for increasing cube sizes of networks. Their values are plotted, and the converged effective parameters are extracted (see Figure 1). For the capillaries, the value of the surface-area-to-volume ratio converges to ≈ 615 $mm^2/mm^3$ and the volume fraction converges to 1.4% (not shown). For the arterioles, the values are ≈ 188 $mm^2/mm^3$ for the surface-area-to-volume ratio, and 1.8% for the volume fraction (not shown). These compare well with values in the literature.

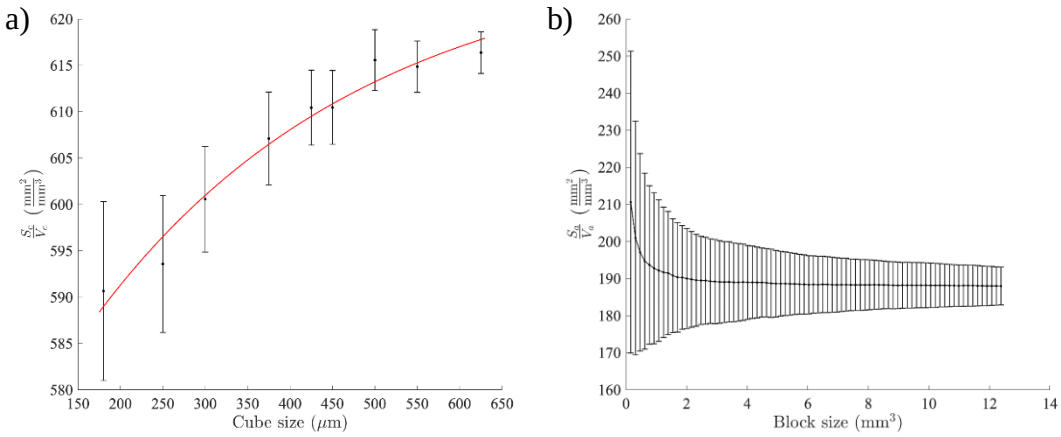


***Figure 1*** *a) Effective surface-area-to-volume ratio for the capillary network. b) Effective surface-area-to-volume ratio for the arteriolar network.*

This converged value of the surface-area-to-volume ratio for the arteriolar network is then used in the continuum simulation of oxygen transport in the arteriolar compartment. The voxel used, and the results pre- and post-occlusion can be found in Figure 2. After initialisation, the

voxel takes approximately 20 seconds to reach a steady state oxygen concentration. After imposing the blockage and a step change in velocity (at t=25s), it takes approximately 65 seconds for the cube to reach a similar steady state, giving us an indication of the time scales involved in oxygen transport through the cortex.

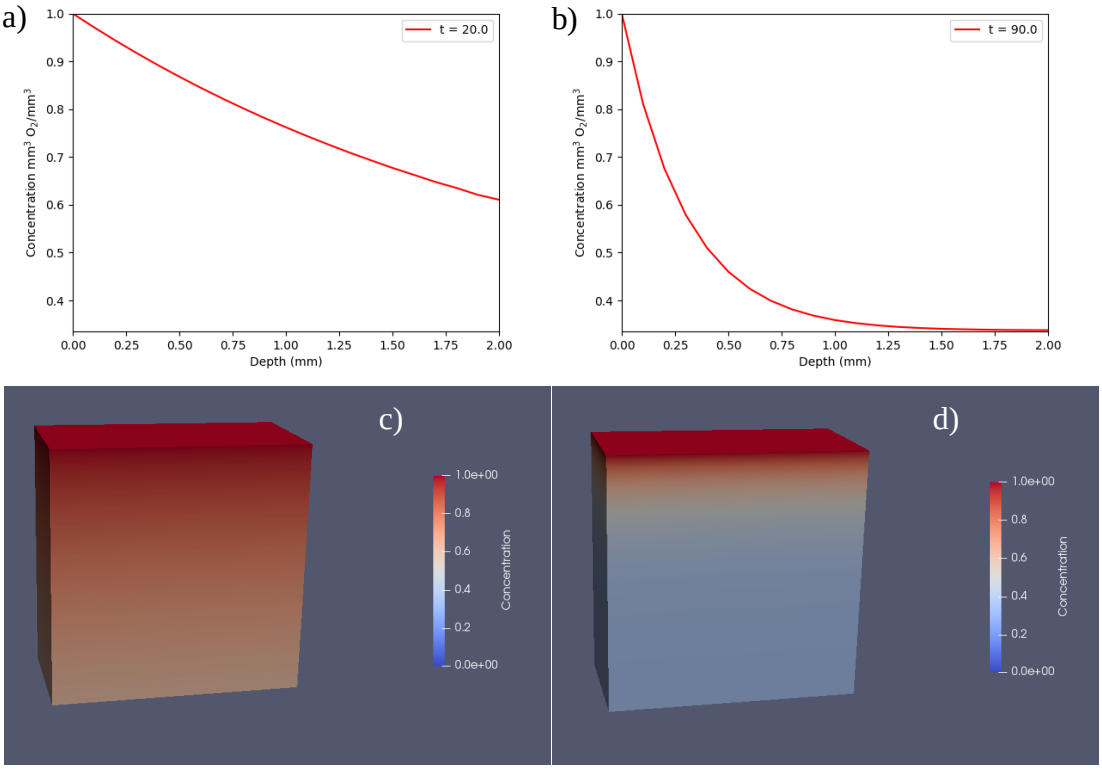


***Figure 2*** *a) The steady-state variation of concentration with depth through the voxel at t=20s. b) The steady-state variation of concentration with depth through the voxel at t=90s. c) A cut halfway through the voxel (in the x-z plane) showing the concentration distribution at t=20s. d) Similar to c) but at t=90s*

## 4. Conclusion

A fully coupled mathematical model for oxygen transport across the disparate length scales of the human vasculature (from capillary bed to pial surface) has been developed. We have calculated the parameters that are required to model oxygen transport over large regions of the brain in the continuum scale and have applied the continuum model to a single (passive) arteriolar compartment, imposing a step change in velocity and observing the time-scales required to reach steady-state. Applying this fully coupled model to a realistic geometry of the human brain is currently in progress, which in turn will be validated against a large database of stroke patient data.

## References

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