Estimating changes to brain oxygenation delivery through multi-scale modelling of the cerebral microvasculature

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Introduction

The brain requires a constant supply of oxygenated blood to maintain its function. This is partly achieved by the well-developed collateral circulation, which allows for multiple pathways, and the high degree of interconnectedness of the capillary network. The dynamics of oxygen transport within the cerebral vasculature are thus complex. A detailed understanding of the oxygen transport dependence on local network properties would be valuable in helping to interpret how oxygen supply is affected under different pathological conditions. For example, recent studies have proposed a heterogeneous capillary transit time which becomes more homogeneous during ischemic conditions [4-5] in order to improve oxygen supply to surrounding tissue [3]. Using a novel model of the microvasculature, we investigate the relationship between the residue function (the function measured experimentally in MRI that represents the amount of tracer remaining in the capillary bed at a given time) and the transit time for a physiologically realistic capillary network that matches experimentally obtained morphological data. The unsteady mass transport equation is solved to quantify local changes in concentration. This multi-scale modeling approach thus opens up the possibility of using residue function to gain quantitative information about the microvasculature in both healthy and pathological conditions, which could aid in clinical decision making for ischemic stroke patients.

Methods

A capillary network, within a cube with a length of $500\mu m$, matching both length and radial distribution obtained experimentally [1] is created based on Prim's algorithm [6]. The unsteady one-dimensional mass transport equation solely driven by convection is solved for the created capillary network assuming Poiseuille flow. We consider the pressure difference between the inlet and outlet to be 2000Pa, being a typical value. The concentration in the capillaries at a specific time is equal to the convolution of the inlet concentration with the residue function:

$$C(t) = C_a(t) * R(t). \quad (1)$$

The residue function can hence be obtained by deconvolving the inlet concentration with the capillary network concentration. A step impulse tracer concentration is considered at the inlet of our capillary network in order to observe the signal produced within the network. The concentration obtained for the capillary network is fitted to an exponential function of the form:

$$C(t) = A_0 + A_1 e^{-b_1 t} + A_2 e^{-b_2 t}. \quad (2)$$

Two exponential decay terms were considered as this was the minimum number of terms required to give a good fit. The transit time can then be obtained by taking the rate of change of the residue function:

$$h(t) = -dR/dt. \quad (3)$$

We consider first the case with a single inlet and outlet (1/1) and then the case when the numbers of inlets and outlets are matched to experimental data [2], 24 and 16 respectively for this volume of tissue (24/16). We also consider the cases for both a complete network and when 20% of the vessels are occluded.

Results and Discussion

Figure 1 shows the concentration, residue function and transit time for the different conditions. The first column considers the 1/1 case and the second column considers the 24/16 case; the solid and dashed lines representing the normal and 20% occluded cases respectively. The recovery in the concentration profile is faster as we increase the number of inlets and outlets as well as the number of vessels within the network. The residue function decays exponentially, the decay being faster for more inlets and outlets as well as for more vessels. There is a fast and a slow decay to replicate the variety between shorter and longer pathways. The difference between the normal case and the 20% occluded case is more significant for 1/1 than 24/16 as there are more available pathways in the latter case.

The residue function of a single vessel model can be expressed as a single exponentially decaying function. This single exponential decay approach has thus been considered in some studies. The capillary network, however, has many vessels connected in a complex manner, thus having numerous different pathways. It is thus not surprising that the residue function is not a single exponential decay. The decay is faster for increased numbers of inlets and outlets as there are more pathways available to the outlet. The transit time is heterogeneous for both conditions considered here, but further investigation will be required to observe whether the transit time becomes more homogeneous during ischemic conditions.

This model can thus provide information about the structure of the capillary network and its physiological conditions if the mass transport, residue function and/or transit time are known. An additional advantage of this model is that it could be used to analyse the effects of different perfusion levels, since we are able to quantify perfusion and how this will affect the residue function. This can be easily implemented by adding a perfusion term that depends on the concentration gradient as well as the diffusion coefficient along the vessel wall.

Conclusion

We have considered here a multi-scale model to estimate mass transport with different network conditions and hence to calculate the residue function and the transit time. A simple double exponential function can be used to fit the concentration in a complexly connected capillary network. The different network structures are found to lead to different concentration profiles and thus residue functions and transit time distributions. This has significant potential to provide additional information about the localized properties of the microvasculature in both healthy tissue and tissue affected by stroke, via the information contained in experimentally estimated residue functions.

More detailed analysis will need to be performed to quantify the precise nature of the relationship between residue function parameters and the microvascular properties. This will also need to include the statistical variation inherent to such properties: one advantage of the model used here is that the network generation is statistical in nature and as such can be used to quantify this variability. Such estimates will give the robustness needed for these measurements to be of valuable in clinical studies: such multi-scale modeling opens up a real possibility of bridging the gap between modelling and clinical practice.

References

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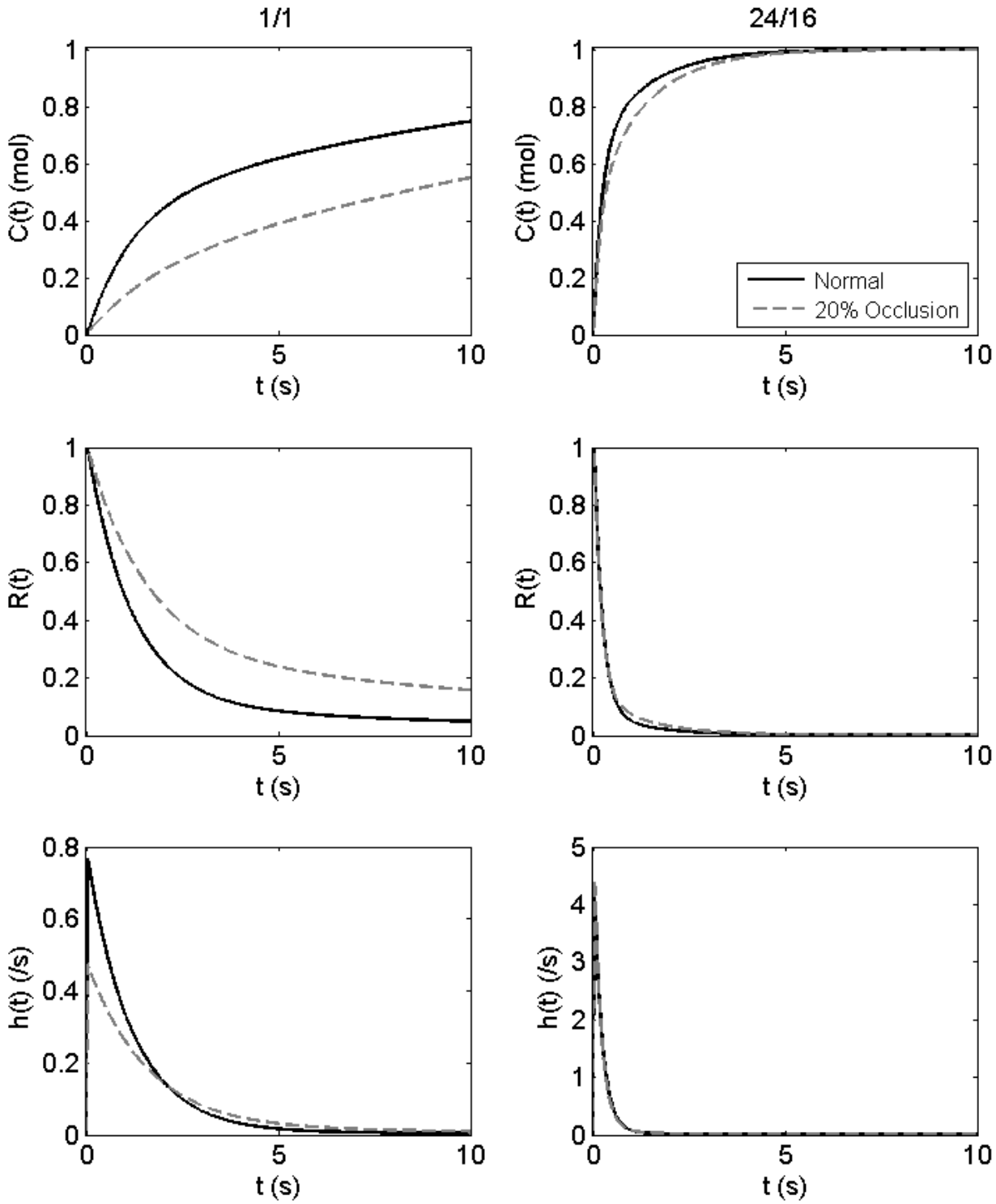

Figure 1. Plots of concentration, residue function and transit time for the different conditions.