A new model for molecule exchange in the brain microvascular system: consequences of capillary occlusions in alzheimers disease

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Abstract

The brain microvascular system is a key actor in Alzheimer's disease (AD) development. Indeed, a significant decrease of cerebral blood flow is the earliest biomarker of AD [1].

In vivo TPLSM of cortical vasculature in APP/PS1 mice suggests the mechanism underlying the blood flow reduction is capillary occlusions. Leucocytes adhere to inflamed vessel walls and limit the flow.

The impact of capillary occlusions on blood flow has been quantified numerically in large (>10000 vessels) anatomical networks in humans and mice [2]. The regional blood flow has been found to depend linearly with no threshold effect on the fraction of capillary occlusions, so that a small fraction of stalls (2-4%) yields a significant decrease in blood flow (5-12%).

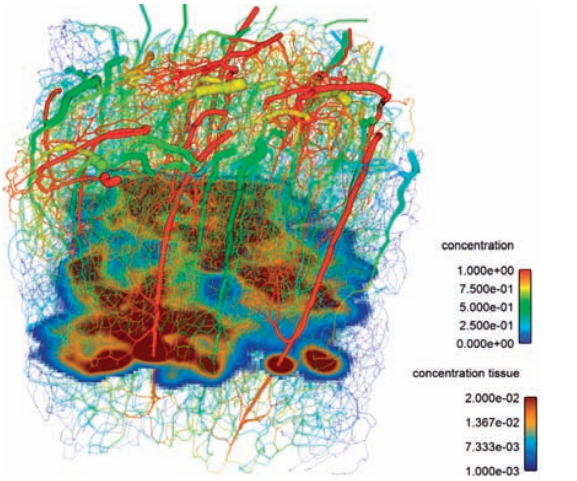
Such flow decrease has a strong impact on nutrient delivery and waste clearance. That is why we devised a new model to study the effect of capillary stalling on molecule

transport. The geometry of anatomical networks is too complex to use classic numerical approaches like finite elements. Instead, our model, inspired by pore-network approaches, reduces computational costs while capturing most of the underlying physics.

To derive this model, we apply upscaling methods [3] to the 3D transport equations within each vessel to obtain 1D average equations along the axis. Contrary to previous models, this new formulation describes accurately radial concentration gradients, capturing effects like longitudinal dispersion.

We further use a Green's function formulation inpired by [4] to calculate the concentration fields inside the tissue where diffusion and reaction occur. The coupling between vessels and tissues is modelled using a membrane condition [5] representing the blood brain barrier.

This new molecule transport model is coupled with our previously validated blood flow model to examine the effects of capillary stalling [2] on molecular exchange in transient and stationary regimes in anatomical networks. In particular, in stationnary regimes, we demonstrate an increase of the extraction coefficient with the proportion of stalled capillaries, which does not compensate for the associated blood flow reduction.



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