Simulation of intravoxel incoherent perfusion signal using a realistic capillary network of a mouse brain

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Purpose: To simulate the intravoxel incoherent perfusion magnetic resonance magnitude signal from the motion of blood particles in three realistic vascular network graphs from a mouse brain.

Methods: In three networks generated from the cortex of a mouse scanned by two-photon laser microscopy, blood flow in each vessel was simulated using Poiseuille’s law. The trajectories, flow speeds and phases acquired by a fixed number of simulated blood particles during a Stejskal-Tanner bipolar pulse gradient scheme were computed. The resulting magnitude signal was obtained by integrating all phases and the pseudo-diffusion coefficient $D^*$ was estimated by fitting an exponential signal decay. To better understand the anatomical source of the intravoxel incoherent motion (IVIM) perfusion signal, the above was repeated restricting the simulation to various types of vessel.

Results: The characteristics of the three microvascular networks were respectively vessel lengths (mean ± std. dev.) 67.2 ± 53.6 μm, 59.8 ± 46.2 μm and 64.5 ± 50.9 μm, diameters 6.0 ± 3.5 μm, 5.7 ± 3.6 μm and 6.1 ± 3.7 μm and simulated blood velocity 0.9 ± 1.7 μm/ms, 1.4 ± 2.5 μm/ms and 0.7 ± 2.1 μm/ms. Exponential fitting of the simulated signal decay as a function of $b$-value resulted in the following $D^*$-values [$10^{-3}$ mm$^2$/s]: 31.7, 40.4 and 33.4. The signal decay for low $b$-values was the largest in the larger vessels, but the smaller vessels and the capillaries accounted for more of the total volume of the networks.

Conclusion: This simulation improves the theoretical understanding of the IVIM perfusion estimation method by directly linking the MR IVIM perfusion signal to an ultra-high resolution measurement of the microvascular network and a realistic blood flow simulation.

INTRODUCTION

Measuring specifically microvascular perfusion is of particular clinical interest, because microvascular dysfunction plays an important role in many important diseases, such as vascular dementia, lacunar infarcts and diabetes. For example, microvascular complications in patients with diabetes are causes of blindness, renal failure and non-traumatic amputations, and powerful predictors of cardiovascular complications.

Abbreviations: IVIM, intravoxel incoherent motion; MR, magnetic resonance; RBC, red blood cell.
Microvascular perfusion can be assessed with intravoxel incoherent motion (IVIM) magnetic resonance (MR) perfusion imaging without injection of intravenous contrast agent. The method has seen a resurgence of research interest in the last decade, both in the brain and in the body, and many recent experimental and clinical studies have demonstrated the feasibility of measuring microvascular perfusion with IVIM. For example, IVIM perfusion has been shown to be altered early in patients with diabetes, and the dependence on the local microvascular perfusion has been used to assess the quality of collateral blood flow in the context of stroke or to detect vasospasm at the microvascular level after aneurysm rupture. However, the microscopic anatomical origin of the IVIM perfusion signal is not well understood. It is assumed to arise from motion of the blood inside the microvasculature, but an ultimate experimental validation of this assumption is lacking. In addition, the exact relationships between the IVIM perfusion parameters, the micro-vascular network structure and the blood flow are not clearly established.

The purpose of this study was to simulate blood flow in three realistic microvascular networks, which were imaged at ultra-high resolution, and to derive the expected IVIM MR magnitude signal and from this the expected IVIM pseudo-diffusion coefficient D*. The microvascular networks, embedded in a tissue volume of 1 mm³, were obtained using two-photon laser scanning microscopy in a previous work by Blinder et al. The networks contain on average 15 000 vessels and their network characteristics have been describe in detail in Reference 9. By assigning realistic pressure boundary conditions at all in- and outflows and by employing Poiseuille’s law, the flow rate in each vessel can be computed. An in-depth analysis of the flow field with focus on depth-dependent characteristics has been performed by Schmid et al. Here, the flow field is used to compute the trajectories of a fixed number of blood protons for a defined time interval, and to calculate the phase acquired by each blood proton during a standard Stejskal-Tanner bipolar pulse gradient scheme as used in a typical IVIM experiment. The sum of all phases resulted in the simulated MR magnitude signal as a function of the b-value, and the IVIM pseudo-diffusion coefficient D* was obtained by fitting an exponential signal decay. Finally, to better understand the anatomical source of the IVIM effect, we decomposed the signal by restricting the simulation to the various types of vessel: artery, arterioles, capillary bed, venules and veins.

2 | METHODS

2.1 | Microvascular networks

The three microvascular networks were acquired in a previous study by Blinder et al. using two-photon laser scanning microscopy. The networks were obtained from the vibrissa primary sensory cortex of three C57/BL6 male mice. Details regarding tissue preparation, two-photon imaging, image segmentation and vectorization are available in the work of Blinder et al. Each network is embedded in a tissue volume of approximately 1 mm³ and contains on average 15 000 vessels. An in-depth description of the pre-processing steps for the blood flow simulations is available in Reference 10. In brief, the microvascular networks are stored in a graph format, ie they consist of a set of nodes (bifurcations), which are connected by edges (vessels). The tortuosity of the vessels is stored in coordinates as edge attributes. Further edge attributes are the effective vessel diameter, the vessel length and the vessel type.

2.2 | Decomposition into vessel types

The vessel type was assigned by following individual penetrating vessels from the cortical surface and by applying a diameter criterion: if two consecutive vessel branches had diameter < 7 μm, the second branch and the following ones were considered to be part of the capillary bed. To obtain a capillary diameter distribution consistent with literature data, a histogram-based up-scaling approach was applied, which was based on a beta distribution with a mean of 4 μm and a standard deviation of 1 μm. The histogram-based up-scaling approach was necessary because tissue shrinkage can cause an underestimation of capillary diameters. The average capillary diameter in the raw data was below the commonly reported value of 4 μm (References 12–14) and some diameters were as small as 1.7 μm. As the flow resistance of a single vessel is inversely proportional to the power of four of the diameter, accurate estimates of capillary diameters are crucial to perform flow simulations and put forward the use of the histogram-based up-scaling approach. A three-dimensional representation of the microvascular networks under investigation is depicted in Figure 1.

2.3 | Blood flow simulation

In the following, a brief summary of the key aspects of the blood flow model is provided. A more detailed description is available in Reference 10. The blood flow model is based on the small Reynolds number in the microvasculature, which allows the use of Poiseuille’s law to compute the flow rate between vertices, ie
\[ q_{ij} = \pi d_{ij}^4 \left( \frac{p_i - p_j}{L_{ij}} \right) \]

where \( q_{ij} \) is the flow rate in the vessel connecting nodes \( i \) and \( j \), and \( d_{ij} \) and \( L_{ij} \) are the vessel diameter and length, respectively. The variables \( p_i \) and \( p_j \) are the pressures at nodes \( i \) and \( j \) respectively, and \( \mu_{\text{eff}} \) is the effective viscosity within the vessel. The effective viscosity is a function of the vessel diameter and the local red blood cell (RBC) density, i.e., the hematocrit, and is computed based on empirical equations. To compute the local hematocrit, we track individual RBCs through the microvascular network. Here, we account for the Fåhraeus-Lindqvist effect, Fåhraeus effect and phase separation. In non-capillaries, the fractional RBC flow at divergent bifurcations is obtained from empirical equations. At capillary bifurcations, the RBCs follow the path of the largest pressure force. By assigning pressure boundary conditions and a physiological inflow hematocrit of 0.3, a well-posed problem is obtained, which together with the continuity equation can be transformed into a linear system of equations. By solving the linear system of equations, the pressure value at each vertex can be computed. The blood flow rate, the flow velocity and the flow direction can be obtained for each vessel based on the pressure field. Subsequently, the RBCs are propagated for the time step \( \Delta t \) and the vessel resistances are updated based on the novel RBC distribution. This procedure is repeated until a statistical steady state is obtained. Due to the fluctuating RBC distribution the flow field is non-steady, and hence time-averaged simulation results are used for further analysis. To assign pressure boundary conditions at all inflows the procedure is different between larger vessels and capillaries. For larger vessels we assign pressure values based on in vivo measurements. To assign suitable pressure values at capillary level, we implant the realistic microvascular network in a large semi-realistic network and compute a simplified pressure field with constant hematocrit. For the simulation with RBC tracking we assign the pressure boundary conditions at capillaries based on the simplified simulation results (hierarchical pressure boundary condition approach). The time average simulation flow field including the assigned pressure boundary conditions is available in Reference 19. To validate the blood flow model we compare the time averaged simulation results against in vivo data and observe that RBC velocities, RBC fluxes and flow rates lie well within the range that has been observed in vivo (more details are provided in Reference 10).
2.4 | Particle tracking

The trajectories of a fixed number of 20,000 blood protons, without further differentiation of the exact location of those protons (i.e., inside the RBC or inside the plasma), was computed along the network architecture, using the simulated characteristic flow speed and pressure gradient obtained as described above, for a defined time interval corresponding to the diffusion time of the Stejskal-Tanner bipolar pulse gradient scheme (see below). The particle track was created as follows.

1. The particle was placed in a vessel chosen randomly. The starting position inside this vessel was itself chosen randomly as well, according to the relative volume of the vessel segment compared with the volume of the full vessel.
2. The velocity of the particle in this vessel segment was calculated by the flow within the vessel and its diameter.
3. The particle followed the tortuosity of the given vessel according to the tortuosity coordinates with the given velocity until it reached a branching point, at which it entered a new vessel with lower pressure gradient according to the relative flow of all vessels at this branching point.
4. Steps 2 and 3 were repeated until the defined time interval was reached.
5. If the particle left the network during the defined time interval, the particle was not considered in the signal simulation.

2.5 | IVIM MR magnitude signal simulation

A Stejskal-Tanner bipolar pulse gradient scheme was used for the simulation, with following parameters: \( b \)-values: 0–800 s/mm\(^2\); fixed diffusion time, \( T = 100 \) ms (corresponding to gradient strengths of 0–11 mT/m); fixed gradient time, \( \delta = 50 \) ms. The gradient strength used was calculated for 100 \( b \)-values between 0 and 800 s/mm\(^2\) using the following formula: \( b = e^a x - 1 \), with \( a = 0.0621661 \) and \( x = [0, 1, 2, ..., 100] \), giving a higher \( b \)-value density near \( b = 0 \) s/mm\(^2\) and a lower density for the larger \( b \)-values, near \( b = 800 \) s/mm\(^2\). The gradient ramps were neglected.

The track of each particle \( n \) was divided into parts \( i \) in each vessel segment with constant velocity and constant gradient \( g \). The accumulated phase acquired by this particle was

\[
\phi_{nk} = \gamma \int_{t_0}^{t_{\text{end}}} r(t) g \, dt = \gamma \sum_i \left[ r_0 g (t_{\text{end}} - t_{\text{end}}) + \frac{1}{2} v g (t_{\text{end}}^2 - t_{\text{end}}^2) \right]
\]

where \( \gamma \) is the gyromagnetic ratio of a proton, \( r \) the position, \( v \) the velocity and \( t \) the time. The signal amplitude over all \( N \) particles was

\[
S = \frac{1}{N} \left| \sum_{n=1}^{N} e^{i \phi_{nk}} \right|
\]

(2)

The gradient strengths of the Stejskal-Tanner bipolar standard sequence were calculated according to the following equation20:

\[
|g| = \frac{\sqrt{12b}}{\gamma T^{1/2}}
\]

(3)

where \( T \) is the diffusion time.

2.6 | IVIM MR signal fit

The trace of the MR signal was calculated with an applied gradient in \( x \)-, \( y \)- and \( z \)-directions. A mono-exponential fit of the trace of the signal was used to obtain the pseudo-diffusion coefficient \( D^* \):

\[
S = e^{-D^*}
\]

(4)

2.7 | Restriction of the simulation to the various anatomical vessel types

To better understand the anatomical source of the IVIM perfusion signal, the above was repeated restricting the simulation to the various types of vessel: capillaries, arterioles, venules and pial vessels. This was done by ignoring all of the particles outside the vessel under consideration, as well as by ignoring all of the particles leaving the vessel type under consideration in the signal simulation.
2.8 | Statistics

Statistical analysis was performed using MATLAB version 2015a (MathWorks, Natick, MA). Statistical significance was assessed using Student’s t-test Welch correction to compare significant differences of vessel characteristics between the three networks. Chi-square was used for comparing the distribution of the relative volume of different vessel types. The significance level $\alpha$ was set to 0.05. The square roots of the diagonal elements from the estimated covariance matrix were used as the errors in the fitting constants along different gradient directions. The error of the pseudo-diffusion was then calculated with standard error propagation.

3 | RESULTS

3.1 | Network characteristics

All three networks differed in their structures. Mean capillary segment lengths of the extracted capillary graphs were for Network 1 (mean ± std. dev.) 67.2 ± 53.6 $\mu$m, Network 2 59.8 ± 46.2 $\mu$m and Network 3: 64.5 ± 50.9 $\mu$m. The mean of the diameter distribution was for Network 1 6.0 ± 3.5 $\mu$m, Network 2 5.7 ± 3.6 $\mu$m and Network 3 6.1 ± 3.7 $\mu$m (Figure 2). Most capillary branches in all three networks were connected to three branches, with a maximum of six connections (Figure 3). All three networks differed in the distribution of the relative volume for artery, veins, arterioles, venules and capillaries (Table 1). All networks showed significant differences in length, diameter and distribution of relative volumes of the different vessel type (Table 2, $p < 0.05$).

3.2 | Blood flow simulation

The mean simulated blood speed was 0.9 ± 1.7 $\mu$m/ms in Network 1, 1.4 ± 2.5 $\mu$m/ms in Network 2 and 0.7 ± 2.1 $\mu$m/ms in Network 3 (Figure 2). All vessel types showed significant differences in blood speed ($p < 0.05$). Arteries showed, as expected, significantly higher blood velocities compared to capillaries (12.5 ± 10.2 versus 0.7 ± 1.1 $\mu$m/ms, $p < 0.05$); see Figure 3.

3.3 | MR signal simulation

The IVIM MR signal decay as a function of $b$-value was faster decaying at low $b$-value than a mono-exponential when a mono-exponential signal equation was fitted to the data for all three capillary networks (Figure 4). Exponential fitting resulted in the following IVIM pseudo-diffusion coefficients $D^*$: $31.7 \times 10^{-3}$ mm$^2$/s with an error of 0.5 (Network 1), $40.4 \times 10^{-3}$ mm$^2$/s with an error of 0.5 (Network 2) and $33.4 \times 10^{-3}$ mm$^2$/s with an error of 0.7 (Network 3).

3.4 | Dependence of the IVIM MR signal on the vessel type

The signal decay was strongly dependent on the type of vessel considered (Figure 5 and Table 1). The slowest signal decay for low $b$-values was seen in the capillary network ($D^*$ range for all three networks: 6.3–9.8 $\times 10^{-3}$ mm$^2$/s), a moderate decay for the descending arterioles ($21.7–40.4 \times 10^{-3}$ mm$^2$/s) and veins ($61.9–219.3 \times 10^{-3}$ mm$^2$/s) and a steep signal decay for the pial artery ($172.1–833.3 \times 10^{-3}$ mm$^2$/s). The contribution from the capillaries to the total volume of the network was the largest of all vessel types.

4 | DISCUSSION

We simulated blood motion in three realistic microvascular networks obtained by two-photon laser microscopy in the mouse brain and computed the effect of this motion on the MR IVIM perfusion signal for $b$-values between 0 and 800 s/mm$^2$. Our findings are in good agreement with the assumption of a microvascular source of the IVIM perfusion signal, although our simulation derived pseudo-diffusion coefficient $D^*$ values were in the upper range compared with the in vivo measured signal. The pseudo-diffusion coefficient $D^*$ has been reported$^{11,21,22}$ as between $7 \times 10^{-3}$ mm$^2$/s and $17 \times 10^{-3}$ mm$^2$/s for young healthy adults, but $D^*$ of $31 \times 10^{-3}$ mm$^2$/s has been reported in the gray matter after functional activation,$^{22}$ and between 28.49 and $73.96 \times 10^{-3}$ mm$^2$/s in regions of interest drawn in pathological hyperperfused lesions.$^{3}$
Interestingly, we found a steep decline of the IVIM signal at very low $b$-value. This correlates well with our in vivo experience, and steep declines at low $b$-value had already been reported; see for example Figure 6(i) and Figure 7(n) in Reference 3. This could also be linked with the recent observation that a two-pool model seems to better describe the IVIM cerebral perfusion in the rat. The question arises why this steeper decline is not always observed with in vivo measurements. This might possibly be due to dephasing effects by the imaging gradients or other sources of dephasing causing an underestimation of the real signal at $b = 0 \text{s/mm}^2$.

The largest part of the relative volume of the network consisted of the capillaries. The signal decay was strongly dependent on the specific type of vessel (capillaries, arterioles/venules or pial vessels) and we found that an important portion of the IVIM perfusion signal comes from the arteries and veins inside the voxel. Of importance, only the effects arising from motion inside a specific vessel type was studied here; the effects arising from the blood particles moving between the vessel types were not considered. Further, one should note that the sensitivity with respect to boundary conditions in the blood flow simulation is the highest in the pial vessels. However, while this might affect the absolute velocity values, the impact of the pressure boundary conditions on the velocity ratio between the different vessel types is likely very small. In summary, our findings suggest that the IVIM perfusion signal does arise from all components of the microvasculature, not only the capillary bed as suggested by early theoretical assumptions.

**FIGURE 2**  Velocity, vessel length, vessel diameter and connectivity distributions for all three networks. Note that only vessel diameters of 20 $\mu$m or less are displayed. In Networks 1, 2 and 3 we have 0.5%, 0.6% and 0.6% of vessels with a diameter less than 20 $\mu$m, which are not shown.
FIGURE 3  Velocity, vessel length, vessel diameter and connectivity distributions for all vessel types

TABLE 1  Decomposition of the source of IVIM perfusion signal as a function of the type of vessel, with $D^*$ [$10^{-3}$ mm²/s] as obtained from a mono-exponential fit for the simulated MR signal decay for $b$-values (0–800 s/mm²) and the relative volume of the whole network volume [%] of each vessel type

| Network 1 | Network 2 | Network 3 |
|-----------|-----------|-----------|
| $D^*$     | Relative volume | $D^*$ | Relative volume | $D^*$ | Relative volume |
| Whole network | 31.7 ± 0.5 | 40.4 ± 0.5 | 33.4 ± 0.7 |
| Artery | 284.9 ± 2.4 | 10.7 | 172.1 ± 2.9 | 20.1 | 833.3 ± 8.3 | 9.6 |
| Vein | 61.9 ± 0.5 | 18.7 | 98.7 ± 3.2 | 9.3 | 219.3 ± 1.7 | 18.4 |
| Arteriole | 21.9 ± 0.1 | 18.8 | 40.4 ± 1.0 | 17.4 | 21.7 ± 0.5 | 13.5 |
| Venule | 60.5 ± 1.9 | 11.7 | 38.8 ± 2.5 | 19.1 | 27.1 ± 0.9 | 24.8 |
| Capillary | 9.8 ± 0.1 | 40.1 | 12.7 ± 0.1 | 34.1 | 6.3 ± 0.3 | 33.7 |

This table shows that an important portion of the IVIM perfusion signal originates from the arteries and veins inside the voxel.

TABLE 2  The lengths, velocities and volume distributions of the vessel types are significantly different between the three networks; a Welch t-test was used for length and velocity comparison and a chi-square test was used for distribution comparison

| p-value | NW 1 vs NW 2 | NW 1 vs NW 3 | NW 2 vs NW 3 |
|---------|--------------|--------------|--------------|
| Length | <0.000001 | <0.000001 | <0.000001 |
| Velocity | <0.0001 | <0.0001 | <0.0001 |
| Volume distribution | <0.0001 | <0.0001 | <0.0001 |
An unexpected plateau in the MR signal was visible in the first and third networks below and around \( b = 100 \) s/mm\(^2\), but not in the second network. Interestingly, this effect disappeared when the veins were excluded from the simulation (data not shown), suggesting that this effect occurred in the veins. The low density of the veins might imply larger macroscopic effects because of their large relative volume and the possible higher global variation between the samples, but further investigation will be necessary to confirm this hypothesis.

Various strategies to mitigate the observed steep signal decline at low \( b \)-values should be explored in the context of IVIM perfusion imaging. Sources of field inhomogeneities, for example mechanical resonances, thermal effects, magnet drifts and eddy currents, should be minimized. During the acquisition, the use of direct magnetic field monitoring\(^{25}\) could be investigated to improve the precision of the effective \( b \)-value applied to the tissue. Oscillating gradients could be used to explore the acquisition of images with very low \( b \)-value and with very short diffusion time.\(^{26}\)

This study has several limitations. The signal from the extravascular compartment was not considered here, but the results presented are independent of the extravascular compartment. The volume of the extravascular compartment is much larger than that of the intravascular compartment, and its contribution is of particular importance when assessing the feasibility of various fitting methods to separate intravascular and extravascular compartments. This was outside the scope of the study, and should consider realistic signal-to-noise aspects. In addition, water exchange between vascular and interstitial/cellular compartments was not considered. Further, particles leaving the voxel under consideration were excluded from the calculation, which might limit the accuracy of the simulation results. Finally, the results found in this simulation apply to the specific tissue obtained for this study, and might not generalize to tissue obtained from other regions.

In conclusion, this simulation improves the theoretical understanding of the IVIM method, by directly linking the MR IVIM signal to ultra-high resolution measurements of the microvascular network and realistic blood flow simulation. The simulated pseudo-diffusion coefficient \( D^* \) was found to be in the upper range of corresponding in vivo measurements. Our results quantify the contributions of the various anatomical components of the microvascular network to the MR IVIM perfusion signal.
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DATA AVAILABILITY STATEMENT

Research data are not shared.

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