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# A dynamic model of oxygen transport from capillaries to tissue with moving red blood cells

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Running head: Capillary oxygen transport with moving red blood cells

Author contributions:

- Adrien Lücker
  - Development and implementation of the numerical model
  - Execution and evaluation of the simulations
  - Redaction of manuscript draft
- Bruno Weber and Patrick Jenny
  - Development of the principal idea of the investigation
  - Guiding and supervision of the project

Abstract

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Most oxygen required to support the energy needs of vertebrate tis-2 sues is delivered by diffusion from microvessels. The presence of red 3 blood cells (RBCs) makes blood flow in the microcirculation highly heterogeneous. Additionally, flow regulation mechanisms dynamically respond to changes in tissue energy demand. These spatio-temporal variations directly affect the supply of oxygen to parenchymal cells. Due to various limiting assumptions, current models of oxygen trans-8 port cannot fully capture the consequences of complex hemodynamic g effects on tissue oxygenation, and are often not suitable for study-10 ing unsteady phenomena. With our new approach based on moving 11 RBCs, the impact of blood flow heterogeneity on oxygen partial pres-12 sure  $(Po_2)$  in the tissue can be quantified. Oxygen transport was 13 simulated using parachute-shaped solid RBCs flowing through a cap-14 illary. Using a conical tissue domain with radii 19  $\mu$ m and 13  $\mu$ m 15 respectively, our computations indicate that  $Po_2$  at the RBC mem-16 brane exceeds  $Po_2$  between RBCs by 30 mmHg on average, and that 17 the mean plasma  $Po_2$  decreases by 9 mmHg over 50  $\mu$ m. These results 18 reproduce well recent intravascular  $Po_2$  measurements in the rodent 19 brain. We also demonstrate that instantaneous variations of capillary 20 hematocrit cause associated fluctuations of tissue Po<sub>2</sub>. Further, our 21 results suggest that homogeneous tissue oxygenation requires capil-22 lary networks to be denser on venular side than on arteriolar side. 23 Our new model for oxygen transport will make it possible to quantify 24 in detail the effects of blood flow heterogeneity on tissue oxygenation 25 in realistic capillary networks. 26

*Keywords:* oxygen transport, microcirculation, red blood cells, hematocrit, blood flow heterogeneity

#### <sup>29</sup> 1 Introduction

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The supply of oxygen to tissues is an essential function of the vertebrate cir-30 culatory system. Oxygen bound to hemoglobin is carried from the lungs by 31 the blood circulation to the target regions, and finally reaches individual cells 32 by diffusive transport from microvessels. Red blood cells (RBCs) make up 33 about 45% of the blood volume and contain hemoglobin, which is the main 34 oxygen carrier. Gas exchange mostly occurs in the microcirculation, where 35 erythrocytes and vessel diameters are similar in size. In particular, RBCs 36 need to deform in order to enter capillaries. The particulate nature of blood 37 has profound effects on hemodynamics and hence on oxygen transport. Blood 38 rheological properties and the complex geometry of microvascular networks 39 cause large variations of hematocrit which are specific to the microcircula-40 tion. Additionally, the microcirculation is a dynamic system that adapts to 41 changes in energy metabolism. In the brain, blood flow is controlled by arteri-42 oles as well as capillaries (13); in muscles, capillary recruitment increases the 43 surface area for diffusion in response to contractile activity (31). The tem-44 poral and spatial variations in the microcirculation render investigations by 45 both experiments and theoretical models challenging. However, new exper-46 imental techniques such as two-photon phosphorescence lifetime microscopy 47 were applied to measure in vivo oxygen tensions at depths up to 300  $\mu$ m 48 (19). In spite of these advances, control of physiological parameters and si-49

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<sup>50</sup> multaneous measurements at multiple locations remain difficult to achieve.
<sup>51</sup> Theoretical models for oxygen transport ideally complement experiments by
<sup>52</sup> providing precise control on all variables and making it possible to isolate
<sup>53</sup> their individual influence.

Oxygen modeling started with the seminal work of Krogh (18). For a 54 tissue cylinder with a capillary at its center, the Krogh-Erlang equation yields 55 an estimate of the oxygen gradient that is required to sustain a given rate 56 of oxygen consumption. In the 1970s, Hellums (14) modeled for the first 57 time oxygen transport with individual red blood cells and coined the term 58 "erythrocyte-associated transients" (EATs). The presence of EATs in the 59 blood was observed experimentally about thirty years later by Golub and 60 Pittman (11) and confirmed with micrometric resolution by Parpaleix et al. 61 (24). Further modeling studies have extended the original Krogh model and 62 considered microvascular networks. 63

Models for oxygen transport in the microcirculation were reviewed by 64 Goldman (8). Current models for oxygen transport from capillaries to tissue 65 generally employ two distinct approaches. The first class of models focuses 66 on the tissue and does not represent individual RBCs. Instead, they employ a 67 boundary condition at the capillary wall that accounts for oxygen transport 68 from the capillary. While the original Krogh model assumed a constant 69 oxygen tension at the capillary wall, more recent models often use a mass 70 transfer coefficient (MTC) that relates the  $Po_2$  drop from the RBC to the 71 oxygen flux across the capillary wall  $(j = k\Delta P)$ . Since these MTCs depend 72 on hematocrit (15, 5), this approach captures the influence of RBC flow on 73 tissue oxygenation. Besides, these models have the advantage that they do 74

not resolve the complex intravascular PO<sub>2</sub> field with individual RBCs, which
makes them applicable to capillary networks (9, 29, 10, 35). However, this
first class of models is dependent on other models that compute the oxygen
flux out of capillaries.

The second approach models intravascular oxygen transport in more de-79 tail and can be used to compute MTCs. Accurate MTC estimates re-80 quire discrete RBCs to be modeled (14, 6, 15) (as opposed to a continuous 81 hemoglobin solution) and extracapillary oxygen transport to be included (5). 82 Most models with individual RBCs carry out computations in the frame of 83 reference of the erythrocyte, which simplifies the numerical treatment of the 84 reaction between oxygen and hemoglobin in RBCs. In this moving frame, 85 the tissue has an apparent velocity opposite to the RBC velocity and appears 86 to move backwards. This idea was first used by Hellums (14) who used an 87 analytical model with a cylindrical RBC and the adjacent tissue to compute 88 MTCs. Eggleton et al. (5) built on this approach and used a model with con-89 centric layers around the capillary for wall, interstitial fluid and the tissue. 90 They investigated the dependence of MTCs on hematocrit, RBC velocity 91 and capillary radius. The resulting MTCs can then be used in simulations 92 of oxygen transport in complex capillary networks (9, 29, 10, 35). 93

Although the models for intravascular oxygen transport described above are convenient for numerical computations and useful for estimating MTCs, they suffer from limitations that restrict their scope. In the RBC frame of reference, the boundary condition at the distal end of the tissue cylinder has a considerable effect on tissue PO<sub>2</sub> since the PO<sub>2</sub> value at that boundary is advected backwards by the apparent tissue motion. Therefore, models that

use the RBC frame cannot fully capture the influence of RBC flow on tissue 100  $PO_2$ , which is essential in applications such as hypoxia. These models are also 101 inflexible in terms of geometry, since the backward motion of the tissue forces 102 the computational domain to have the same radial cross section along the 103 flow direction. For instance, local capillary dilations, as observed in vivo (13), 104 cannot be simulated with this class of models. Furthermore, the simulation 105 duration is limited to the time that RBCs spend in capillaries (100 to 300 ms 106 in the cerebral cortex (16)). For applications that require a larger simulation 107 time (e.g., functional hyperemia), it is also necessary to use the frame of 108 reference of the tissue, as done by models based on MTCs. Unlike other 109 studies, Groebe and Thews (12) modeled individual RBCs in a fixed tissue 110 region. However, their approach is limited to steady state situations and 111 relies on multiple simplifying assumptions that allow an analytic treatment 112 of the intra-erythrocyte  $PO_2$  field. 113

Finally, Goldman (8) pointed out that thorough model validations have 114 yet to be done. For intravascular PO<sub>2</sub>, this task puts constraints on both the 115 simulation method and the required experimental data. Since  $PO_2$  is gener-116 ally measured at one or more fixed locations, a convenient model validation 117 should be performed in the fixed frame of reference of the tissue. Besides, 118 a detailed comparison with measured intravascular  $Po_2$  requires high spa-119 tial and temporal resolution. Pioneering work by Vanzetta and Grinvald 120 (37) has revealed Po<sub>2</sub> transients related to neuronal activation and oxygen 121 metabolism with the use of phosphorescence lifetime microscopy. Using one-122 photon excitation with a lower excitation volume, Golub and Pittman (11) 123 measured EATs in the rat mesentery. However, until now, only two-photon 124

<sup>125</sup> phosphorescence lifetime microscopy achieved sufficiently high resolution to <sup>126</sup> enable *in vivo* measurements of the  $PO_2$  between RBCs in depth. This tech-<sup>127</sup> nique was applied by Parpaleix et al. (24) in the olfactory glomerulus of the <sup>128</sup> rodent brain. Sakadžić et al. (27) used it in the rat cerebral cortex, without <sup>129</sup> reporting details of the intravascular  $PO_2$  field. Due to the absence of other <sup>130</sup> detailed experimental studies, we compared our simulation results with the <sup>131</sup> data from (24).

We propose a new model of oxygen transport in the microcirculation that 132 is adapted for validation against experimental data. The main improvement 133 over previous models is the use of overlapping meshes, which simultaneously 134 allows the frame of reference of the tissue to be fixed and individual RBCs 135 to be modeled. Hence, the coupling between intravascular oxygen transport 136 and tissue  $PO_2$  can be captured together with the details of the  $PO_2$  field in-137 side and around capillaries. Individual RBCs are followed by moving meshes 138 that are used to compute hemoglobin diffusion and reaction with oxygen. 139 These moving meshes are mapped onto a fixed mesh, where oxygen advec-140 tion, diffusion and consumption in the tissue are computed. This approach 141 can capture the influence of heterogeneous RBC flow on tissue oxygenation 142 in a time-dependent manner. Situations with unsteady blood flow such as 143 functional hyperemia can be modeled by adapting blood velocity and hema-144 tocrit. A thorough comparison with the experimental data from Parpaleix 145 et al. (24) showed that both intra- and extravascular oxygen transport are 146 accurately simulated. For this comparison, an axisymmetric geometry based 147 on Eggleton et al. (5) with concentric layers for the plasma, the capillary 148 wall and tissue was used. However, we found that a cone-shaped geometry 149

as used by Hudetz (17) yields a better agreement with the measurements
than a cylinder with constant radius. MTCs were also compared with results
from previous models.

Although we apply this new model to an axially symmetric geometry, 153 our algorithm is formulated in a general way and can be applied to arbi-154 trary geometries. Therefore, using a model for RBC transport (e.g., (23)) to 155 compute RBC trajectories, oxygen transport can be simulated in arbitrary 156 capillary networks with realistic RBC dynamics. Our efficient time-stepping 157 scheme allows taking large time steps and makes our model tractable in 158 complex geometries. This will enable the investigation of the effects of 159 blood flow heterogeneity during physiologically relevant phenomena such as 160 microstrokes or capillary dilations (13). 161

## $_{162}$ 2 Methods

#### <sup>163</sup> 2.1 Mathematical model

Oxygen transport and consumption was modeled in a domain that consists of four regions: tissue, capillary wall, plasma and RBCs. Oxygen is consumed only in the tissue; the capillary wall does not consume oxygen and has a lower diffusion coefficient; in both plasma and RBCs, oxygen is convected by the blood flow. Finally, RBCs contain hemoglobin, which carries oxygen in bound form. In fact, due to the low solubility of oxygen in plasma, most oxygen in capillaries is bound to hemoglobin.

Dissolved oxygen can be quantified by its concentration  $C \, [mlO_2 \, cm^{-3}]$ 

and partial pressure  $P = Po_2$  [mmHg], which are related by Henry's law as

$$C = \alpha P, \tag{1}$$

where  $\alpha$  is the solubility coefficient in mlO<sub>2</sub> cm<sup>-3</sup> (mmHg)<sup>-1</sup>. The formulation of the conservation equation for oxygen in terms of  $C = \alpha P$  is most convenient for our purposes. Hemoglobin is expressed using the saturation S, which is the concentration ratio of oxyhemoglobin to total hemoglobin.

The reaction between oxygen and hemoglobin in RBCs is most completely described by the Adair equation (3). However, as in many previous studies, here we employ the Hill equation

$$S = \frac{P^n}{P_{50}^n + P^n} \tag{2}$$

to describe the equilibrium curve between P and S, where  $P_{50}$  is the oxygen partial pressure at hemoglobin half-saturation and n is the Hill exponent. This results in a one-step reaction for the four heme groups of the hemoglobin molecule. To model the reaction rates when oxygen and hemoglobin are in nonequilibrium, we followed the approach of Clark et al. (3) and used the function

$$f(P,S) = \begin{cases} k_{-} \left( S - (1-S) \left( \frac{P}{P_{50}} \right)^{n} \right) & \text{inside RBCs,} \\ 0 & \text{outside RBCs,} \end{cases}$$
(3)

where  $k_{-}$  is the dissociation rate. This function satisfies f = 0 when oxygen and hemoglobin are in equilibrium (Eq. (2)). Since no hemoglobin is present <sup>188</sup> in healthy blood plasma, the reaction term f(P, S) was only used within <sup>189</sup> RBCs.

Oxygen consumption was modeled using first-order Michaelis-Menten kinetics (8) and assumed to occur only in the tissue, which results in

$$M(P) = \begin{cases} M_0 \frac{P}{P_{\text{crit}} + P} & \text{inside tissue,} \\ 0 & \text{outside tissue,} \end{cases}$$
(4)

where  $M_0$  is the maximal metabolic rate of oxygen consumption in mlO<sub>2</sub> cm<sup>-3</sup> s<sup>-1</sup> and  $P_{\rm crit}$  is the oxygen level at which consumption is half of  $M_0$ . Since we compared our results with measurements performed in the rodent brain where no muscles are present, we did not consider myoglobin-facilitated diffusion of oxygen inside the tissue.

<sup>197</sup> Our model is based on a single equation for oxygen for all regions, that <sup>198</sup> is,

$$\frac{\partial \alpha P}{\partial t} + \boldsymbol{v} \cdot \nabla(\alpha P) = \nabla \cdot (D\alpha \nabla P) + cf(P, S) - M(P), \qquad (5)$$

where D is the diffusion coefficient and  $\boldsymbol{v}$  the advection velocity. The factor c is given by  $c = N_{\text{Hb}}V_{\text{mol},O_2}$ , where  $N_{\text{Hb}}$  is the molar density of heme groups and  $V_{\text{mol},O_2}$  is the molar volume of oxygen. Hemoglobin saturation is governed by the equation

$$\frac{\partial S}{\partial t} + \boldsymbol{v} \cdot \nabla S = \nabla \cdot (D_{\text{Hb}} \nabla S) - f(P, S), \qquad (6)$$

 $_{203}$  where  $D_{\rm Hb}$  is the diffusivity of hemoglobin in RBCs.

At interfaces between regions with different solubility or diffusion coef-

ficients, continuity of  $PO_2$  and oxygen flux across the interface have to be satisfied (39). For example, at the wall-tissue interface, the latter condition is

$$D_{\rm w}\alpha_{\rm w}\frac{\partial P}{\partial n} = D_{\rm t}\alpha_{\rm t}\frac{\partial P}{\partial n},\tag{7}$$

<sup>208</sup> where the subscripts refer to the wall and the tissue, respectively.

The choice of boundary conditions depends on the computational domain. 209 In this study, we considered representative domains with  $\partial P/\partial n = 0$  at the 210 tissue boundary. At the capillary entrance, a  $Po_2$  value is required since 211 oxygen is convected into the domain by the blood flow. When a RBC overlaps 212 with the domain boundary, the oxygen tension is interpolated from this RBC 213 to the capillary entrance. When plasma is flowing in, a constant  $Po_2$  value 214  $P_{\rm p,in}$  was used. At the capillary outlet, the boundary condition  $\partial P/\partial n = 0$ 215 was applied. 216

Since RBC membranes are impermeable for hemoglobin, the boundary condition for hemoglobin saturation is  $\partial S/\partial n = 0$ . Unlike hemoglobin, oxygen is soluble in lipids and can diffuse through cell membranes. The different solubility and diffusion coefficients of oxygen in lipid bilayers was not taken into account since RBC membranes are generally less than 10 nm thick (33), which is negligible compared to the cell size.

The entry of RBCs into the capillary plays a crucial role, since it determines the amount of oxygen in bound form that enters the domain. The oxygen tension in entering erythrocytes was set to a constant value  $P_{\rm rbc,in}$ . The simplest model for capillary spacing is a constant distance between each RBC pair. However, Chaigneau et al. (2) observed large instantaneous fluctuations of the RBC linear density. Moreover, they showed that variations of RBC flow were primarily caused by fluctuations of linear density, whereas instantaneous RBC velocity fluctuations were 2.5 times lower. Therefore, we treated RBC spacings as a random variable and modeled it using a lognormal random variable with independent values for each RBC pair. The parameters were chosen to match experimentally measured mean  $\mu_{LD}$  and standard deviation  $\sigma_{LD}$  of linear density.

The initial PO<sub>2</sub> field in RBCs was set to  $P_{\rm rbc,in}$  and hemoglobin saturation was set to equilibrium with oxygen. Outside RBCs, the initial PO<sub>2</sub> was set to  $P_{\rm p,in}$  in the plasma and to 22 mmHg in the tissue.

#### $_{238}$ 2.2 Discretization

The main objective of this study is to thoroughly compare simulation results 239 with experimental data. To allow an easy comparison with measurements, 240 the numerical model should reflect how experiments are carried out. Our 241 reference data (24) were acquired using two-photon phosphorescence lifetime 242 microscopy. Thus, measurements were obtained from the focal plane of the 243 microscope which may contain both capillaries and tissue. An easy compar-244 ison with these data requires a model that focuses on a fixed region. This 245 approach also enables capturing transient phenomena such as local changes 246 in RBC flow or metabolism. 247

The fixed frame of reference motivated above is problematic when solving Eq. (6). Hemoglobin is a large protein that cannot cross erythrocyte membranes. However, the discretization of the advection term would create numerical diffusion, which would in turn cause an unphysical leak of
hemoglobin out of RBCs. These problems can be circumvented by solving
Eq. (6) in a Lagrangian frame of reference that follows the moving RBC.
This approach enables the no-flux boundary condition for hemoglobin at the
RBC membrane to be exactly satisfied.

We therefore used a fixed computational domain for the capillaries and 256 the tissue, denoted by  $\Omega$ , as well as a moving domain for each RBC, denoted 257 by  $\Omega_{\rm rbc}$  (Fig. 1). Each domain is covered by its own computational mesh. 258 This overlapping mesh approach was adapted from the overset grid method 259 (26), which has been applied to aerodynamic problems with moving objects. 260 We will also refer to  $\Omega$  as Eulerian domain and to  $\Omega_{\rm rbc}$  as Lagrangian domain. 261 To simplify the notation, we omit RBC indices. Since RBCs are entering and 262 leaving  $\Omega$ , the Lagrangian domain  $\Omega_{\rm rbc}$  may be completely or partly inside 263 Ω. 264

Erythrocytes were assumed to have a fixed shape. While they actually 265 deform, this assumption avoided the expensive treatment of fluid-structure 266 interaction. Therefore, our modeled RBCs behaved similar to solid bodies 267 that follow the plasma flow. As a further simplification, we considered plasma 268 flow to be uniform along radial cross sections of capillaries. Note that the 269 detailed flow field around RBCs is not of importance here, since transport 270 of oxygen is diffusion dominated (see (36) for a corresponding study about 271 nitric oxide). Consequently, the blood velocity was given by v = Q/A, where 272 Q is the blood volume flow and A the capillary cross section. 273

Equation (5) for oxygen was solved in the Eulerian domain  $\Omega$ , whereas the hemoglobin equation (6) was solved in the Lagrangian domain  $\Omega_{\rm rbc}$ . Since  $\Omega_{\rm rbc}$  moves with the velocity  $\boldsymbol{v}_{\rm rbc}$ , the coordinate transformation  $\boldsymbol{x}' = \boldsymbol{x} + \boldsymbol{v}_{\rm rbc} t$  cancels the advection term and yields

$$\frac{\partial S}{\partial t} = \frac{\partial}{\partial x'_i} \left( D_{\rm Hb} \frac{\partial S}{\partial x'_i} \right) - f(P, S). \tag{8}$$

Since this equation is discretized in  $\Omega_{\rm rbc}$ , the oxygen partial pressure is also 278 needed in that domain. This field, denoted by  $P_{\rm rbc}$ , is obtained by inter-279 polation from  $\Omega$  to  $\Omega_{\rm rbc}$ . Likewise, since Eq. (5) is solved in  $\Omega$ , values of 280 S in the Eulerian domain, denoted by  $S_{\rm Euler},$  have to be interpolated from 281  $\Omega_{\rm rbc}$  (Fig. 1). The interpolation method may considerably affect simulation 282 results, since most oxygen in the blood is bound to hemoglobin. Thus, in-283 terpolation errors that cause inaccurate values of  $S_{\text{Euler}}$  may have a large 284 effect on the resulting  $Po_2$ . A conservative interpolation scheme is therefore 285 crucial. 286

To obtain  $P_{\rm rbc}$  and  $S_{\rm Euler}$ , we used a volume-based interpolation scheme that is discretely conservative in the sense that the integral of the interpolated field on any subset of the target mesh is conserved. For grid cells  $V_I$  and  $V_{{\rm rbc},J}$ in  $\Omega$  and  $\Omega_{\rm rbc}$ , respectively, interpolation weights were defined by

$$w_{I,J}^{\rm rbc} = \frac{|V_I \cap V_{\rm rbc,J}|}{|V_{\rm rbc,J}|} \tag{9}$$

291 and

$$w_{I,J}^{\text{Euler}} = \frac{|V_I \cap V_{\text{rbc},J}|}{|V_I|}.$$
(10)

 $_{\rm 292}~$  The interpolation formulas for  $P_{\rm rbc}$  and  $S_{\rm Euler}$  are then given by

$$P_{\rm rbc,J} = \sum_{I} w_{I,J}^{\rm rbc} P_I \tag{11}$$

293 and

$$S_{\text{Euler},I} = \sum_{J} w_{I,J}^{\text{Euler}} S_{J}.$$
 (12)

The discrete conservation property for the interpolated field  $S_{\text{Euler}}$  is shown as follows. Consider a subdomain  $\Omega' = \bigcup_{k=1}^{m} V_{I_k}$  that consists of m grid cells  $V_{I_k}$ . The integral of  $S_{\text{Euler}}$  on  $\Omega'$  is given by

$$\int_{\Omega'} S_{\text{Euler}} \, dV = \sum_{k=1}^{m} |V_{I_k}| S_{\text{Euler}, I_k} \tag{13}$$

$$=\sum_{k=1}^{m}\sum_{J}|V_{I_{k}}|\frac{|V_{I_{k}}\cap V_{\mathrm{rbc},J}|}{|V_{I_{k}}|}S_{J}$$
(14)

$$=\sum_{J}\sum_{k=1}^{m}|V_{I_k}\cap V_{\operatorname{rbc},J}|S_J\tag{15}$$

$$=\sum_{J} |\Omega' \cap V_{\mathrm{rbc},J}| S_J \tag{16}$$

$$= \int_{\Omega'} S \, dV. \tag{17}$$

<sup>297</sup> The same argument can be used for the integral of  $P_{\rm rbc}$  on a subset of  $\Omega_{\rm rbc}$ , <sup>298</sup> which shows that the interpolation scheme given by Eqs. (11) and (12) is <sup>299</sup> discretely conservative.

Grid cells in  $\Omega$  that overlap with the RBC border require special care. If the intersection of a grid cell  $V_I$  with  $\Omega_{\rm rbc}$  occupies a small volume,  $S_{\rm Euler,I}$ will be also small. This fact has to be accounted for in the discretization of the reaction term f(P, S). We introduce the RBC volume fraction

$$\gamma_I = \frac{|V_I \cap \Omega_{\rm rbc}|}{|V_I|}.\tag{18}$$

In  $V_I$ , we consider that the chemical reaction between hemoglobin and oxygen only occurs in a fraction of  $V_I$  with volume  $\gamma_I |V_I|$  where all the hemoglobin is contained. Since this volume fraction has hemoglobin saturation  $S_{\text{Euler},I}/\gamma_I$ , the discretized reaction term in  $\Omega$  is given by

$$f(P_I, S_{\text{Euler},I}) = \gamma_I k_- \left(\frac{S_{\text{Euler},I}}{\gamma_I} - \left(1 - \frac{S_{\text{Euler},I}}{\gamma_I}\right) \left(\frac{P_I}{P_{50}}\right)^n\right)$$
(19)

$$= k_{-} \left( S_{\text{Euler},I} - (\gamma_{I} - S_{\text{Euler},I}) \left( \frac{P_{I}}{P_{50}} \right)^{n} \right).$$
 (20)

Continuity of the oxygen flux at interfaces between regions with different 308 solubility or diffusion coefficient (Eq. (7)) is enforced by adequately interpo-309 lating the Krogh diffusion coefficient  $D\alpha$ . At cell faces, mass conservation 310 is enforced by using the harmonic average of  $D\alpha$  in both neighboring grid 311 cells (25). The boundary condition at the capillary inlets of  $\Omega$  also requires 312 interpolation. If a RBC overlaps a cell face at the capillary inlet, the  $Po_2$ 313 value at that face is obtained by bilinear interpolation of the RBC  $PO_2$  at the 314 corresponding location. Otherwise, the boundary  $Po_2$  is set to the constant 315 value  $P_{p,in}$ . 316

The governing equations were discretized using a finite-volume method with the central scheme for the divergence operator. For the Laplace operator, Gauss integration, centered differences for the surface normal gradient and harmonic interpolation for the diffusion coefficient were used. Time stepping and coupling between Eqs. (5) and (6) are addressed in Appendix A.
The algorithm was implemented using the open source software package
OpenFOAM® v.2.1.1.

#### 324 2.3 Model parameters

Our main goal is the validation of the method explained above against the experimental data from Parpaleix et al. (24). These data were acquired in the rodent olfactory glomerulus, which is an area with a high capillary density.

We used an axially symmetric geometry with a capillary at its center – similar to the classical Krogh model (18). Instead of a cylinder, we employed a cone-shaped domain with different radii at the proximal (arteriolar) and distal (venular) ends. Due to symmetry,  $\Omega$  can be represented by a twodimensional domain. As shown in Figure 2,  $\Omega$  consists of three regions, that is, the plasma, the capillary wall and the tissue region.

In the olfactory glomerulus, the average distance from any point to the nearest capillary is 10.8  $\mu$ m (20). In a hexagonal array of Krogh cylinders with a capillary diameter of 4  $\mu$ m, this corresponds to a radius of 16  $\mu$ m. Therefore, unless stated otherwise, the radii on the arteriolar and venular sides were set to  $r_{\rm t,a} = 19 \ \mu$ m and  $r_{\rm t,v} = 13 \ \mu$ m, respectively. The length of the capillary was set to 100  $\mu$ m.

The RBC shape was taken from Secomb et al. (30) for a RBC velocity of 1 mm s<sup>-1</sup>. This shape (computed for human RBCs) was scaled down to the size of mouse erythrocytes with volume  $V_{\rm rbc} = 59.0$  fl (32). We used the mean RBC velocity  $v_{\rm rbc} = 0.57$  mm s<sup>-1</sup> measured in the olfactory glomerulus  $_{344}$  by Chaigneau et al. (2).

The cerebral metabolic rate of oxygen consumption (CMRO<sub>2</sub>) is an essential model parameter. To our knowledge, no measurement of CMRO<sub>2</sub> in the olfactory glomerulus has been performed. Therefore, we chose the value CMRO<sub>2</sub> = 197  $\mu$ M s<sup>-1</sup> to obtain PO<sub>2</sub> values in the tissue between 15 and 20 mmHg approximately (using the perfect gas law at 36.9°C, this corresponds to  $M_0 = 5 \cdot 10^{-3}$  mlO<sub>2</sub> cm<sup>-3</sup> s<sup>-1</sup>). The resulting values of PO<sub>2</sub> in the plasma agree well with the results of Parpaleix et al. (24).

#### 352 **3** Results

We now show simulated oxygen tensions inside the sample capillary and 353 the surrounding tissue region shown on Figure 2. Whenever possible, we 354 compare our results with the data measured by Parpaleix et al. (24) us-355 ing two-photon phosphorescence lifetime microscopy in the rodent olfactory 356 glomerulus. They characterized intracapillary oxygen tensions by the three 357 following quantities: RBC PO<sub>2</sub>, mean PO<sub>2</sub> and inter-RBC PO<sub>2</sub>. RBC PO<sub>2</sub> is 358 the maximal oxygen tension in the plasma, which is attained at the erythro-359 cyte membrane. Mean PO<sub>2</sub> is the average PO<sub>2</sub> value between two erythrocytes 360 and inter-RBC  $PO_2$  is the minimal  $PO_2$  between two RBCs. The EAT am-361 plitude is the difference between RBC  $PO_2$  and inter-RBC  $PO_2$ . Throughout 362 this section, the coordinate x denotes the axial direction. 363

Using the parameters listed in Table 1, we obtained an averaged EAT amplitude of 29.7 mmHg (RBC  $PO_2 = 50.8$  mmHg, inter-RBC  $PO_2 = 21.1$ mmHg, mean  $PO_2 = 27.4$  mmHg). These values were obtained by sampling

 $Po_2$  on the capillary centerline at nine evenly spaced longitudinal locations 367 (between  $x = 10 \ \mu \text{m}$  and 90  $\mu \text{m}$ ). The maximal Po<sub>2</sub> in the plasma was 368 attained on the rear side of the RBC membrane. Parpaleix et al. (24) also 369 observed significant differences between these quantities (RBC  $PO_2 = 57.1 \pm$ 370 1.3 mmHg (mean  $\pm$  s.e.m.), inter-RBC PO<sub>2</sub> = 23.6  $\pm$  0.7 mmHg, mean PO<sub>2</sub> 371  $= 30.8 \pm 0.9$  mmHg). Since they performed 241 measurements, the results for 372 our sample capillary differ from these average values by less than one third 373 of a standard deviation. 374

Figure 3 shows instantaneous longitudinal profiles on the capillary cen-375 terline and at various radial distances from the capillary wall. In RBCs close 376 to the arteriolar end of the domain, the intracellular  $Po_2$  variation exceeds 377 30 mmHg and decreases to 15 mmHg at the venular end. These strong in-378 travascular oxygen variations extend to the nearby tissue. At 1  $\mu$ m from the 379 outer side of the wall, the amplitude of these fluctuations ranges from 12.7 380 mmHg to 4.2 mmHg. Away from the capillary entrance, these values agree 381 well with the mean pulse amplitude of 5.0 mmHg reported by Parpaleix et al. 382 (24) outside the vessel ( $< 2 \,\mu m$ ). At 5  $\mu m$  from the endothelium, these pulses 383 are almost entirely smeared out. The influence of instantaneous linear den-384 sity fluctuations on inter-RBC  $PO_2$  is clearly illustrated by the second and 385 the third RBC spacings. Since short RBC spacings cause higher inter-RBC 386  $Po_2$  values, the EAT amplitude drops when the instantaneous linear density 387 increases. 388

We then investigated longitudinal variations of PO<sub>2</sub> along our sample capillary. Figure 4 shows time-averaged oxygen partial pressures for the cone-shaped geometry (Fig. 2) and for a cylinder with equal tissue volume.

Since RBC PO<sub>2</sub> declines faster than inter-RBC PO<sub>2</sub>, the EAT amplitudes also 392 decrease along the capillary. Parpaleix et al. (24) reported longitudinal vari-393 ations of  $Po_2$  in single capillaries over a mean distance of 49.7  $\mu$ m. Table 2 394 contains these values as well as our simulated  $Po_2$  variations in the conical 395 and cylindrical geometries. The maximal gradients in the cone-shaped ge-396 ometry are a consequence of the high RBC  $PO_2$  at the capillary entrance. 397 However, the gradients away from the arteriolar end of the domain corre-398 spond very well to the experimental data, while in the cylinder geometry the 399 gradients of mean  $PO_2$  and inter-RBC  $PO_2$  are significantly higher than in 400 A better match could not be obtained in a cylindrical the reference data. 401 geometry by changing  $CMRO_2$ , since this would considerably decrease the 402 agreement of RBC  $PO_2$  and inter-RBC  $PO_2$  with experimental data. The 403 chosen geometry with  $r_{\rm t,a} = 19 \ \mu m$  and  $r_{\rm t,v} = 13 \ \mu m$  had the smallest taper 404 that yielded a good match with the measured longitudinal  $PO_2$  variations. 405 These results suggest that a cylindrical geometry is not a suitable model for 406 capillaries, at least in the brain region considered in this study. 407

Our model includes instantaneous variations of linear density similar to 408 those observed by Chaigneau et al. (2). Figure 5 shows values of RBC  $Po_2$ 409 and inter-RBC PO<sub>2</sub> that were collected during three seconds at 30  $\mu$ m from 410 the capillary entrance. The linear density on the horizontal axis was quanti-411 fied by the length occupied by RBCs over a given capillary segment divided 412 by the segment length. As previously observed in Figure 3, inter-RBC  $PO_2$ 413 is correlated with the linear density. The dependency of inter-RBC  $PO_2$  on 414 linear density agrees very well with the experimental data, but the simulated 415 RBC  $Po_2$  is almost constant, while the reference data exhibit a positive 416

correlation between linear density and RBC Po<sub>2</sub>. Our simulations did not 417 reproduce this trend, since a single capillary with constant RBC  $PO_2$  at 418 its arteriolar end was used. However, Parpaleix et al. (24) measured EAT 419 properties in 42 capillaries, which limits the scope of this comparison. This 420 difference between the pooled experimental data and our computations in 421 a single capillary indicates that capillaries with high average linear density 422 also have a higher  $PO_2$ . Besides, Parpaleix et al. (24) have observed that 423 inter-RBC  $PO_2$  attains similar values as  $PO_2$  in the neuropil. Figure 5 also 424 shows the difference between inter-RBC  $PO_2$  and tissue  $PO_2$  at 10  $\mu$ m from 425 the capillary wall as a function of linear density. For linear densities lower 426 than 0.25, this difference stays below 2.0 mmHg. For high hematocrit values, 427 this gap exceeds 10 mmHg. Thus, our results indicate that inter-RBC  $Po_2$ 428 may significantly exceed tissue  $Po_2$  for high linear densities. 429

Since linear density affects tissue  $Po_2$ , we investigated the influence of 430 the standard deviation  $\sigma_{LD}$  of linear density on tissue Po<sub>2</sub>. Figure 6 shows 431 tissue Po<sub>2</sub> at 10  $\mu$ m from the capillary wall and  $x = 50 \mu$ m for two different 432 values of  $\sigma_{LD}$ . The same random numbers were used and the parameters 433 of the log-normal distribution for RBC spacings were adjusted to obtain an 434 average linear density of 0.28 over four seconds and the desired standard 435 deviation. Only the last second of the simulation is shown. Random fluc-436 tuations of linear density led to large  $Po_2$  oscillations. For  $\sigma_{LD} = 0.08$ , the 437 difference between minimal and maximal  $Po_2$  was 5.7 mmHg, and for higher 438 fluctuations ( $\sigma_{LD} = 0.16$ ), it increased to 10.9 mmHg. This is a consequence 439 of RBC groups that are close to or far away from each other. Occasionally, a 440 large RBC spacing resulted in a sudden drop of tissue PO<sub>2</sub> by several mmHg. 441

Therefore, if linear density fluctuations as reported by Chaigneau et al. (2)
are present, PO<sub>2</sub> in the tissue cannot be considered to be constant.

Finally, we compare our results with previous works by examining the 444 intracapillary resistance to oxygen transport. MTCs were computed using 445 a constant linear density and compared with previously published values. 446 The MTC may be defined as  $k = j/(P^* - P_w)$ , where j is the oxygen flux 447  $(mlO_2 \ cm^{-2} \ s^{-1}), P^*$  is the oxygen tension in equilibrium with the mean 448 hemoglobin saturation in the RBC and  $P_{\rm w}$  is the average oxygen tension at 449 the capillary wall around a RBC. For a tube hematocrit of 0.25, we obtained 450  $k = 1.67 \cdot 10^{-6} \text{ mlO}_2 \text{ cm}^{-2} \text{ s}^{-1}$ , which exactly matches the results of Eggleton 451 et al. (5) for the same hematocrit and capillary radius ( $r_{\rm p} = 2.0 \ \mu {\rm m}$ ). This 452 consistency was expected, since the same equations as in (5) were solved 453 (except myoblogin-facilitated diffusion in the tissue) and similar diffusion 454 and solubility coefficients were chosen. 455

456 Comparison with earlier works can also be performed using the Nusselt457 number, which is defined by

$$Nu = \frac{jd_p}{D_p \alpha_p (P^* - P_w)},$$
(21)

where  $d_p$  is the capillary diameter. For tube hematocrit values between 0.15 and 0.36, we obtained Nusselt numbers from 0.48 to 1.7. Hellums et al. (15) summarized Nusselt numbers from various studies. For a diameter of 3.6  $\mu$ m and a tube hematocrit of 0.28, Secomb and Hsu (28) calculated Nu = 1.22 using a solid cylinder model. Our computed value for this tube hematocrit is 1.17. Therefore, our model reproduces oxygen fluxes from previous studies <sup>464</sup> in steady state situations.

#### 465 4 Discussion

Oxygen transport from a capillary with moving RBCs to the surrounding tissue has been simulated in an axisymmetric cone-shaped geometry. Oxygen partial pressure in the capillary and the tissue was compared with experimental data (24). Longitudinal oxygen variations and the influence of linear density were investigated. As an application of our model, we studied the impact of instantaneous hematocrit fluctuations on tissue oxygenation.

Our simulations reproduced a number of results from Parpaleix et al. 472 (24). Their average measured EAT amplitude was 33.5 mmHg, and similar 473 amplitudes were obtained in the first section of our sample capillary (Fig. 4). 474 At 30  $\mu$ m from the capillary entrance, the simulated EAT amplitude was 475 33.6 mmHg. Close to the venular end, RBC  $PO_2$  was lower due to oxygen 476 consumption in the tissue, which gave rise to smaller EATs (< 25 mmHg). 477 Therefore, our average EAT amplitude of 29.7 mmHg over the nine sampled 478 positions is slightly lower than that from Parpaleix et al. (24). Since the 479 experimental data were collected independently of the measurement position 480 in the vascular bed, it is difficult to further interpret these differences. How-481 ever, the dependency of EAT values on the distance from the arteriolar side 482 could for example be studied experimentally in the brain cortex. 483

The relationship between intracapillary oxygen tensions and tissue  $PO_2$ was also examined. For linear densities lower than 0.25, simulated inter-RBC  $PO_2$  exceeds tissue  $PO_2$  at 10  $\mu$ m from the capillary wall by less than

2.0 mmHg (Fig. 5), while this difference is larger than 10 mmHg for higher 487 hematocrit values. These findings are only in partial agreement with the ob-488 servation by Parpaleix et al. (24) that inter-RBC Po<sub>2</sub> attains similar values 489 as in the neuropil. However, measurements in capillaries and tissue were not 490 performed simultaneously and results were averaged over several seconds, 491 which filtered out  $PO_2$  fluctuations, whereas we report instantaneous snap-492 shots. Moreover, the influence of hematocrit fluctuations was not examined 493 in this part of the experiment. Therefore, our simulations indicate that inter-494 RBC  $PO_2$  is similar to tissue  $PO_2$  only close to the capillary or at low linear 495 densities. Since concentration gradients drive molecular diffusion, we sug-496 gest that inter-RBC  $PO_2$  is on average higher than tissue  $PO_2$  far away from 497 capillaries, provided they are not close to an arteriole. This hypothesis can 498 be tested in vivo by measuring the dependency of tissue  $Po_2$  on the distance 499 to the nearest capillary. 500

Our simulation setup with RBCs moving through a fixed capillary allows 501 the computation of longitudinal oxygen gradients. Motivated by the fact that 502 capillary segments with high oxygen tensions can supply a correspondingly 503 large tissue volume, we used a cone-shaped geometry (Fig. 2) similar to 504 Hudetz (17). We compared results obtained with this geometry and with a 505 simple cylindrical domain to the data (24), where longitudinal PO<sub>2</sub> variations 506 were measured in individual capillaries. While gradients of mean  $PO_2$  and 507 inter-RBC PO<sub>2</sub> in the classical Krogh cylinder geometry are much higher 508 than in the reference data (Table 2), the cone-shaped domain leads to a 509 very good agreement. Although a conical geometry is idealized, it appears 510 to be a suitable model to reproduce *in vivo* intracapillary oxygen gradients 511

in the brain. This finding may imply that capillary density increases along RBC paths through capillary networks. In other words, we suggest that an evenly distributed tissue PO<sub>2</sub> requires denser capillary networks on venular side. However, one should examine whether these simulation results hold in realistic networks, where capillary interactions and tortuosity are present.

Instantaneous variations of hematocrit as observed by Chaigneau et al. 517 (2) can be accounted for by our model, which overcomes a limitation of the 518 models based on MTCs. We treated linear density as a random process 519 governed by a log-normal RBC spacing distribution. The resulting depen-520 dency of inter-RBC  $PO_2$  on linear density agrees very well with the data (24) 521 (Fig. 5). On the other hand, RBC  $PO_2$  stayed constant, which means that 522 the drop in hemoglobin saturation along RBC paths was not influenced by in-523 stantaneous hematocrit fluctuations. Since our results were produced in one 524 sample capillary and the data from Parpaleix et al. (24) were pooled from 42 525 capillaries, we propose the following interpretation of this discrepancy: while 526 fast fluctuations of linear density do not influence RBC PO<sub>2</sub>, capillaries with 527 high average hematocrit have a higher RBC PO<sub>2</sub>. This explanation should 528 be investigated by measuring RBC  $PO_2$  in capillaries that have different av-529 erage linear densities. Additionally, these hematocrit fluctuations also affect 530 tissue PO<sub>2</sub> (Fig. 6). With a RBC length of 7.27  $\mu$ m, the standard devia-531 tion of linear density reported by Chaigneau et al. (2) is 0.12. Our results 532 show that for this value, oscillations of oxygen tension in the tissue approach 533 10 mmHg. During transient periods of low RBC density and/or velocity, it 534 therefore seems possible that tissue oxygenation drops at times below the 535 critical level for oxidative phosphorylation, although the average tissue  $Po_2$ 536

remains above this level. Since the geometry of complex capillary networks
affects tissue PO<sub>2</sub>, it will be essential to further study the influence of linear
density fluctuations.

Although multiple experimental results could be reproduced, the sim-540 ulation setup presented here has several limitations, in particular the ax-541 isymmetric geometry. While such a geometry is most relevant for parallel 542 capillary arrays in muscles, Krogh cylinder models fail to capture the min-543 imal tissue  $PO_2$  in the capillary beds of the brain cortex (29). Accordingly, 544 our conclusions on the relationship between inter-RBC  $PO_2$  and tissue  $PO_2$ 545 will certainly need to be refined for realistic networks. The hypothesis that 546 capillary networks are denser on venous side should also be verified in such 547 networks. Nevertheless, the simulated oxygen tensions in the plasma mainly 548 depend on hemoglobin saturation in nearby erythrocytes and should not be 549 directly affected by diffusive interactions between capillaries. This is con-550 firmed by the good agreement between the simulated inter-RBC  $Po_2$  and 551 experimental data (Fig. 5). 552

Other limitations include constant blood velocity, the absence of shifts of 553 the oxygen-hemoglobin dissociation curve and the uncertainty in the choice of 554 parameters. While RBC velocity undergoes fluctuations, their amplitude is 555 lower than that of linear density (2), hence we chose to keep it constant. How-556 ever, RBC velocity is an important factor for tissue oxygenation and should 557 be realistically modeled. Besides, variations of carbon dioxide concentration 558 and pH are known to shift the equilibrium curve modeled by Eq. (2). This 559 may be significant in regions with low  $PO_2$  and high  $CO_2$  concentration (4). 560 The inclusion of these shifts would require further modeling efforts. Finally, 561

tissue oxygenation highly depends on  $CMRO_2$ , which is difficult to measure 562 experimentally. Our chosen value (197  $\mu$ M s<sup>-1</sup>) is almost three times as high 563 as the CMRO<sub>2</sub> in the cortex of awake rats (73.5  $\mu$ M s<sup>-1</sup>), which was obtained 564 using the value 420  $\mu$ mol (100 g)<sup>-1</sup> min<sup>-1</sup> (7) and a brain density of 1.05 g 565  $cm^{-3}$  (22). Based on estimates by Nawroth et al. (21), the neuron density 566 in the olfactory glomerulus of the rat is  $6.9 \cdot 10^5$  cells per mm<sup>3</sup>, whereas this 567 value is  $1.17 \cdot 10^5$  in the mouse neocortex (34). The high density of neural 568 elements (possibly in combination with a high steady state firing rate) in the 569 olfactory glomerulus may explain why a high CMRO<sub>2</sub> value was needed to 570 reproduce the tissue  $PO_2$  observed by Parpaleix et al. (24). However, using 571 a theoretical energy budget, Nawroth et al. (21) obtained a CMRO<sub>2</sub> value of 572  $75 \ \mu M s^{-1}$  for the olfactory glomerulus, which is lower than our chosen value. 573 Further interpretation of this discrepancy would require actual measurements 574 of  $CMRO_2$  in the olfactory bulb. 575

In addition to model limitations, the comparison with experimental data 576 is also limited. To the author's knowledge, only the data from (24) allowed a 577 detailed comparison of simulated intracapillary PO<sub>2</sub>. A good agreement was 578 obtained by adapting  $CMRO_2$  and the initial  $PO_2$  in RBCs on the arteriolar 579 side, and by choosing a tapered cylinder. Further data on intracapillary  $Po_2$ 580 and its relationship to tissue PO<sub>2</sub> should be obtained and compared with 581 (24). The parameters mentioned above will most likely need to be modified 582 to reproduce further experiments. The computational model presented in 583 this study will be a useful tool to interpret possible differences between future 584 experimental data. 585

Although our model for oxygen transport was applied to a simple ax-

isymmetric geometry, the numerical algorithm is independent of the domain 587 topology and can be extended to realistic capillary networks provided ve-588 locities of single RBCs are known. This can be achieved by coupling our 589 method with a detailed model of RBC transport such as that of Obrist et al. 590 (23). This combined approach will remove the need for separately computed 591 mass transfer coefficients and is suitable for investigating unsteady scenar-592 ios. For example, Hall et al. (13) recently observed that capillary pericytes 593 participate in the regulation of cerebral blood flow. Our model will enable 594 quantifying the influence of capillary dilations on tissue oxygenation. There-595 fore, our present study is a first step toward an oxygen transport model that 596 can capture a wide range of dynamic physiological phenomena while taking 597 into account the complex properties of RBC flow. 598

In conclusion, we have developed a new model of oxygen transport from 599 capillaries with moving RBCs based on overlapping grids. We successfully 600 validated it against experimental data acquired in the rodent brain. EATs 601 and longitudinal gradients of  $PO_2$  could be reproduced using a cone-shaped 602 geometry. Instantaneous variations of hematocrit were shown to cause con-603 siderable fluctuations of oxygen tension in the tissue. Further work includes 604 the extension of the model to realistic capillary networks. The coupling 605 of RBC dynamics with oxygen transport will eventually allow simulations of 606 blood flow regulation mechanisms in health and disease with unprecedented 607 detail. 608

## <sup>609</sup> Appendix A Time integration

Generation of PO<sub>2</sub> maps in realistic capillary network may require simulations 610 with at least hundreds of red blood cells during several seconds. The ability 611 to use large time steps is therefore crucial to keep the computational time 612 sufficiently low. Special care is required to achieve this within our frame-613 work based on overlapping meshes. The nonlinear reaction term f(P, S)614 (Eq. (3)) combined with RBC displacements prevents from using an explicit 615 scheme. As observed by Clark et al. (3), the boundary layer inside erythro-616 cytes is a region of chemical nonequilibrium, such that large explicit time 617 steps inevitably cause overshooting. Another requirement is that the cou-618 pling between hemoglobin and oxygen equations conserves the total of free 619 and bound oxygen. 620

To achieve this, we use Godunov splitting for Eq. (5) and linearization of the reaction and consumption terms using Picard's method. While the equation for oxygen can be integrated without Godunov splitting, this unsplit approach would severely limit the maximal stable time step, since the linearization of the reaction term requires PO<sub>2</sub> values in  $\Omega$  to vary moderately. If RBCs undergo large displacements during one time step, the resulting large PO<sub>2</sub> variations would lead to instabilities.

Let the superscript k indicate the current time  $t^k$ . To integrate Eqs. (5) and (6) from  $t^k$  to  $t^k + \Delta t$ , an intermediate solution  $P^*$  is obtained by integrating only the advection term:

$$\frac{\alpha^* P^* - \alpha^k P^k}{\Delta t} + \boldsymbol{v} \cdot \nabla(\alpha^* P^*) = 0.$$
(22)

Here, the solubility  $\alpha^*$  corresponds to RBC positions after their displacement. The reaction term f(P, S) and the consumption term M(P) were both linearized and their linear part is treated implicitly as

$$\alpha^{*} \frac{P^{(\nu)} - P^{*}}{\Delta t} = \nabla \cdot (D\alpha^{*} \nabla P^{(\nu)}) + c \left[ f(P^{(\nu-1)}, S_{\text{Euler}}^{(\nu-1)}) + (P^{(\nu)} - P^{(\nu-1)}) \frac{\partial f}{\partial P} \left( P^{(\nu-1)}, S_{\text{Euler}}^{(\nu-1)} \right) \right] - \left( M(P^{(\nu-1)}) + (P^{(\nu)} - P^{(\nu-1)}) \frac{\partial M}{\partial P} (P^{(\nu-1)}) \right)$$
(23)

634 and

$$\frac{S^{(\nu)} - S^{k}}{\Delta t} = \nabla \cdot (D_{\rm Hb} \nabla S^{(\nu)}) - \left[ f(P_{\rm rbc}^{(\nu-1)}, S^{(\nu-1)}) + (S^{(\nu)} - S^{(\nu-1)}) \frac{\partial f}{\partial S} \left( P_{\rm rbc}^{(\nu-1)}, S^{(\nu-1)} \right) \right],$$
(24)

where  $\nu$  is the iteration number and  $P^{(0)} = P^*$ . The coupling between both equations conserves the total oxygen amount, if the integral of both terms in square brackets are equal. Although the volume-based interpolation method (Eqs. (11) and (12)) conserves P and S, it does not exactly conserve the integral of f(P, S) since the reaction term is nonlinear in P. However, this only causes a minimal amount of oxygen loss in the domain (less than 0.2% for total RBC discharge).

The moving meshes  $\Omega_{\rm rbc}$  are displaced during each time step by the increment  $\boldsymbol{v}_{\rm rbc}\Delta t$ . When a RBC leaves the domain  $\Omega$  and no longer overlaps it, the corresponding mesh is moved to the front of the RBC queue and placed at a distance to the next RBC, which is randomly generated based on a log-normal distribution. In the plasma, the coefficients  $\alpha$  and D have to be <sup>647</sup> updated to reflect RBC motion. In a grid cell  $V_I$ , the discretized coefficients <sup>648</sup> are given by

$$D_I = \gamma_I D_{\rm rbc} + (1 - \gamma_I) D_{\rm p}, \qquad (25)$$

$$\alpha_I = \gamma_I \alpha_{\rm rbc} + (1 - \gamma_I) \alpha_{\rm p}, \qquad (26)$$

<sup>649</sup> where the subscripts "rbc" and "p" refer to values in the RBCs and in the <sup>650</sup> plasma. The algorithm is summarized in Table 3.

The domain  $\Omega$  was discretized using a Cartesian grid with constant grid spacing  $\Delta x = 0.1 \,\mu\text{m}$  in the axial direction. In the radial direction, the grid cell spacing in the capillary was constant ( $\Delta y = 0.1 \,\mu\text{m}$ ) and decreasing in the tissue region, since oxygen gradients decrease away from capillaries. The ratio between the height of the top-most grid cell to the bottom-most in the tissue was set to four. This results in a grid with 333 × 29 grid cells.

<sup>657</sup> The RBC domain  $\Omega_{\rm rbc}$  consists of those Cartesian grid cells that lie en-<sup>658</sup> tirely inside the RBC shape, which results in a "staircase" geometry (Fig. 1). <sup>659</sup> A curvilinear shape-conforming mesh is not necessary for such an advection-<sup>660</sup> diffusion problem. Besides, the computation of the interpolation coefficients <sup>661</sup> defined in Eqs. (9) and (10) is easier for Cartesian grids.

The tolerance tol in the algorithm shown on Table 3 was set to  $10^{-4}$ . A smaller tolerance affected results by less than 0.1 mmHg. Unless stated otherwise, the time step  $\Delta t$  was set to 0.5 ms. All our simulations were run for four seconds. After one second, the influence of the initial condition disappeared. The results were collected during the following three seconds.

<sup>667</sup> The accuracy of the algorithm with a coarser Eulerian grid and larger

time steps was also examined. Table 4 shows absolute and relative errors 668 on the capillary centerline and in the tissue against a baseline case with 669  $\Delta t = 0.1$  ms and  $\Delta x = \Delta y = 0.1 \ \mu$ m in the capillary. The relative error 670 was normalized by the maximum  $PO_2$  value in the considered longitudinal 671 profile. When multiplying the grid spacing and the time step by three, the 672 relative error stays below 2.5%. With a 50 times larger timestep ( $\Delta t = 5$ 673 ms), the absolute error in the tissue is still smaller than 1 mmHg, while the 674 computational time is divided by 10. This is an indication that our numerical 675 algorithm is very robust in terms of time step size and grid spacing. This 676 property will allow for simulations of oxygen transport in larger capillary 677 networks. 678

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## 686 Disclosures

<sup>687</sup> The authors declare no conflict of interest.

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Figure 1



Figure 2



Figure 3



Figure 4



Figure 5



Figure 6

Parameter	Description	Value	Units	Reference
$\alpha_{ m rbc}$	$O_2$ solubility in RBCs	$3.38\cdot 10^{-5}$	$mlO_2 mmHg^{-1} cm^{-3}$	(5)
$\alpha_{\rm p}$	$O_2$ solubility in the plasma	$2.82\cdot 10^{-5}$	$\mathrm{mlO}_{2}\mathrm{mmHg}^{-1}\mathrm{cm}^{-3}$	(5)
$\alpha_{\rm w}$	$O_2$ solubility in the capillary wall	$3.89\cdot 10^{-5}$	$\mathrm{mlO}_{2}\mathrm{mmHg}^{-1}\mathrm{cm}^{-3}$	(5)
$lpha_{ m t}$	$O_2$ solubility in the tissue	$3.89\cdot 10^{-5}$	$\mathrm{mlO}_{2}\mathrm{mmHg}^{-1}\mathrm{cm}^{-3}$	(5)
$D_{ m rbc}$	$O_2$ diffusivity in RBCs	$9.5\cdot10^{-6}$	$\mathrm{cm}^2\mathrm{s}^{-1}$	(5)
$D_{\mathrm{p}}$	$O_2$ diffusivity in the plasma	$2.18\cdot10^{-5}$	$\mathrm{cm}^2\mathrm{s}^{-1}$	(5)
$D_{\rm w}$	$O_2$ diffusivity in the capillary wall	$8.73 \cdot 10^{-6}$	$\mathrm{cm}^2\mathrm{s}^{-1}$	(5)
$D_{\mathrm{t}}$	$O_2$ diffusivity in the tissue	$2.41 \cdot 10^{-5}$	$\mathrm{cm}^2\mathrm{s}^{-1}$	(5)
$D_{ m Hb}$	hemoglobin diffusivity in RBCs	$1.44 \cdot 10^{-7}$	$\mathrm{cm}^2\mathrm{s}^{-1}$	(5)
$k_{-}$	dissociation rate constant	44	$s^{-1}$	(5)
$L_{ m rbc}$	RBC length	7.27	$\mu { m m}$	based on $(30), (32)$
$M_0$	maximal $O_2$ consumption rate	$5 \cdot 10^{-3}$	$mlO_2  cm^{-3}  s^{-1}$	fitted
$\mu_{LD}$	mean linear density	0.36	_	(24)
n	Hill exponent	2.64	_	fitted from $(38)$
$N_{ m Hb}$	total heme density	$2.03 \cdot 10^{-5}$	$ m molcm^{-3}$	(5)
$P_{50}$	$Po_2$ at hemoglobin half-saturation	47.9	m mmHg	fitted from $(38)$
$P_{\mathrm{crit}}$	critical $PO_2$ in the tissue	1.0	m mmHg	(8)
$P_{ m p,in}$	plasma $PO_2$ at the capillary entrance	40	m mmHg	based on $(24)$
$P_{\rm rbc,in}$	RBC $Po_2$ at the capillary entrance	90	$\rm mmHg$	based on $(24)$
$\sigma_{LD}$	standard deviation of linear density	0.1	_	based on $(2)$
$r_{ m p}$	radius of capillary lumen	2.0	$\mu\mathrm{m}$	(34)
$r_{ m w}-r_{ m p}$	capillary wall thickness	0.6	$\mu\mathrm{m}$	(1)
$r_{ m t,a}$	tissue radius on arteriolar side	19	$\mu\mathrm{m}$	based on $(20)$
$r_{ m t,v}$	tissue radius on venular side	13	$\mu\mathrm{m}$	based on $(20)$
$v_{ m rbc}$	RBC velocity	$5.7 \cdot 10^{-2}$	$\mathrm{cm}\mathrm{s}^{-1}$	(2)
$V_{\rm mol,O_2}$	$O_2$ molar volume at $36.9^{\circ}C$	$2.54\cdot 10^4$	$mlO_2 mol^{-1}$	ideal gas law
$V_{ m rbc}$	RBC volume	59.0	$\mu \mathrm{m}^3$	(32)

Table 1: Model parameters

	cone		cylinder		experiment $(24)$
	art.	ven.	art.	ven.	
$\Delta RBC PO_2$	25.7	14.3	25.6	16.4	$14.1 \pm 9.2$
$\Delta mean Po_2$	12.0	6.4	16.9	12.4	$4.6 \pm 2.4$
$\Delta$ inter-RBC PO <sub>2</sub>	8.0	4.3	14.4	11.3	$3.0\pm2.7$

Table 2: Longitudinal variation of capillary PO<sub>2</sub>

Longitudinal variation of time-averaged PO<sub>2</sub> over 50  $\mu$ m in the cone and cylinder geometries, compared with experimental data. The columns with the heading "art." ("ven.") show the averaged PO<sub>2</sub> variation between  $x = 10 \ \mu$ m ( $x = 40 \ \mu$ m) and  $x = 60 \ \mu$ m ( $x = 90 \ \mu$ m). Last column: mean  $\pm$  s.e.m.

Table 3: Time integration algorithm

1: move all RBCs by  $\boldsymbol{v}_{\rm rbc}\Delta t$ 2: update interpolation coefficients (Eq. (9) and (10)) 3: update D and  $\alpha$  (Eq. (25) and (26)) 4: solve advection equation for  $P^*$  (Eq. (22)) 5:  $P^{(0)} \leftarrow P^*, S^{(0)} \leftarrow S^k$ 6:  $R^{(0)} \leftarrow \infty$ 7:  $\nu \leftarrow 0$ 8: while  $R^{(\nu)} > \text{tol } \mathbf{do}$ for all RBCs that overlap  $\Omega$  do interpolate  $P^{(\nu)}$  to  $P^{(\nu)}_{\rm rbc}$  using Eq. (11) interpolate  $S^{(\nu)}$  to  $S^{(\nu)}_{\rm Euler}$  using Eq. (12) 9: 10:11: end for 12:solve for  $P^{(\nu+1)}$  (Eq. (23)) 13: $R^{(\nu+1)} \leftarrow \text{initial residual of Eq. (23)}$ 14: for all RBCs that overlap  $\Omega$  do 15:solve for  $S^{(\nu+1)}$  (Eq. (24)) 16:end for 17: $\nu \leftarrow \nu + 1$ 18: 19: end while

Time integration of oxygen and hemoglobin equations for one time step  $\Delta t$ 

 Table 4: Convergence study

Parar	neters	Cente	erline	Tissue (10 $\mu$ m)		
$\Delta t$	$\Delta x$	abs. $L^{\infty}$	rel. $L^\infty$	abs. $L^{\infty}$	rel. $L^\infty$	
0.3 ms	$0.3 \ \mu \mathrm{m}$	1.65	2.00~%	0.431	2.11%	
$5 \mathrm{ms}$	$0.3~\mu{ m m}$	3.51	4.26~%	0.717	3.51%	

Algorithm accuracy with coarse time steps and grid cells. The grid cell size is given in the capillary, where  $\Delta x = \Delta y$ . The errors were measured against longitudinal profiles computed with  $\Delta t = 0.1$  ms and  $\Delta x = \Delta y = 0.1 \ \mu$ m in the capillary.