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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 Lückner
 - 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

Most oxygen required to support the energy needs of vertebrate tissues is delivered by diffusion from microvessels. The presence of red 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 transport cannot fully capture the consequences of complex hemodynamic effects on tissue oxygenation, and are often not suitable for studying unsteady phenomena. With our new approach based on moving RBCs, the impact of blood flow heterogeneity on oxygen partial pressure (PO_2) in the tissue can be quantified. Oxygen transport was simulated using parachute-shaped solid RBCs flowing through a capillary. Using a conical tissue domain with radii $19\ \mu\text{m}$ and $13\ \mu\text{m}$ respectively, our computations indicate that PO_2 at the RBC membrane exceeds PO_2 between RBCs by 30 mmHg on average, and that the mean plasma PO_2 decreases by 9 mmHg over $50\ \mu\text{m}$. These results reproduce well recent intravascular PO_2 measurements in the rodent brain. We also demonstrate that instantaneous variations of capillary hematocrit cause associated fluctuations of tissue PO_2 . Further, our results suggest that homogeneous tissue oxygenation requires capillary networks to be denser on venular side than on arteriolar side. Our new model for oxygen transport will make it possible to quantify in detail the effects of blood flow heterogeneity on tissue oxygenation in realistic capillary networks.

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

29 **1 Introduction**

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

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

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

64 Models for oxygen transport in the microcirculation were reviewed by
65 Goldman (8). Current models for oxygen transport from capillaries to tissue
66 generally employ two distinct approaches. The first class of models focuses
67 on the tissue and does not represent individual RBCs. Instead, they employ a
68 boundary condition at the capillary wall that accounts for oxygen transport
69 from the capillary. While the original Krogh model assumed a constant
70 oxygen tension at the capillary wall, more recent models often use a mass
71 transfer coefficient (MTC) that relates the PO_2 drop from the RBC to the
72 oxygen flux across the capillary wall ($j = k\Delta P$). Since these MTCs depend
73 on hematocrit (15, 5), this approach captures the influence of RBC flow on
74 tissue oxygenation. Besides, these models have the advantage that they do

75 not resolve the complex intravascular PO_2 field with individual RBCs, which
76 makes them applicable to capillary networks (9, 29, 10, 35). However, this
77 first class of models is dependent on other models that compute the oxygen
78 flux out of capillaries.

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

94 Although the models for intravascular oxygen transport described above
95 are convenient for numerical computations and useful for estimating MTCs,
96 they suffer from limitations that restrict their scope. In the RBC frame of
97 reference, the boundary condition at the distal end of the tissue cylinder has
98 a considerable effect on tissue PO_2 since the PO_2 value at that boundary is
99 advected backwards by the apparent tissue motion. Therefore, models that

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

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

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

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

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

153 Although we apply this new model to an axially symmetric geometry,
154 our algorithm is formulated in a general way and can be applied to arbitrary 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**

163 **2.1 Mathematical model**

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

171 Dissolved oxygen can be quantified by its concentration C [$\text{mlO}_2 \text{ cm}^{-3}$]

172 and partial pressure $P = \text{PO}_2$ [mmHg], which are related by Henry's law as

$$C = \alpha P, \quad (1)$$

173 where α is the solubility coefficient in $\text{mlO}_2 \text{ cm}^{-3} (\text{mmHg})^{-1}$. The formu-
 174 lation of the conservation equation for oxygen in terms of $C = \alpha P$ is most
 175 convenient for our purposes. Hemoglobin is expressed using the saturation
 176 S , which is the concentration ratio of oxyhemoglobin to total hemoglobin.

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

$$S = \frac{P^n}{P_{50}^n + P^n} \quad (2)$$

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

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

186 where k_- is the dissociation rate. This function satisfies $f = 0$ when oxygen
 187 and hemoglobin are in equilibrium (Eq. (2)). Since no hemoglobin is present

188 in healthy blood plasma, the reaction term $f(P, S)$ was only used within
 189 RBCs.

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

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

192 where M_0 is the maximal metabolic rate of oxygen consumption in $\text{mlO}_2 \text{ cm}^{-3} \text{ s}^{-1}$
 193 and P_{crit} is the oxygen level at which consumption is half of M_0 . Since we
 194 compared our results with measurements performed in the rodent brain where
 195 no muscles are present, we did not consider myoglobin-facilitated diffusion of
 196 oxygen inside the tissue.

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

$$\frac{\partial \alpha P}{\partial t} + \mathbf{v} \cdot \nabla(\alpha P) = \nabla \cdot (D \alpha \nabla P) + c f(P, S) - M(P), \quad (5)$$

199 where D is the diffusion coefficient and $\mathbf{v}$ the advection velocity. The factor
 200 c is given by $c = N_{\text{Hb}} V_{\text{mol}, \text{O}_2}$, where N_{Hb} is the molar density of heme groups
 201 and $V_{\text{mol}, \text{O}_2}$ is the molar volume of oxygen. Hemoglobin saturation is governed
 202 by the equation

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

203 where D_{Hb} is the diffusivity of hemoglobin in RBCs.

204 At interfaces between regions with different solubility or diffusion coef-

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

$$D_w \alpha_w \frac{\partial P}{\partial n} = D_t \alpha_t \frac{\partial P}{\partial n}, \quad (\gamma)$$

208 where the subscripts refer to the wall and the tissue, respectively.

209 The choice of boundary conditions depends on the computational domain.
 210 In this study, we considered representative domains with $\partial P / \partial n = 0$ at the
 211 tissue boundary. At the capillary entrance, a PO_2 value is required since
 212 oxygen is convected into the domain by the blood flow. When a RBC overlaps
 213 with the domain boundary, the oxygen tension is interpolated from this RBC
 214 to the capillary entrance. When plasma is flowing in, a constant PO_2 value
 215 $P_{p,\text{in}}$ was used. At the capillary outlet, the boundary condition $\partial P / \partial n = 0$
 216 was applied.

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

223 The entry of RBCs into the capillary plays a crucial role, since it deter-
 224 mines the amount of oxygen in bound form that enters the domain. The
 225 oxygen tension in entering erythrocytes was set to a constant value $P_{\text{rbc},\text{in}}$.
 226 The simplest model for capillary spacing is a constant distance between each
 227 RBC pair. However, Chaigneau et al. (2) observed large instantaneous fluc-

228 tuations of the RBC linear density. Moreover, they showed that variations
 229 of RBC flow were primarily caused by fluctuations of linear density, whereas
 230 instantaneous RBC velocity fluctuations were 2.5 times lower. Therefore,
 231 we treated RBC spacings as a random variable and modeled it using a log-
 232 normal random variable with independent values for each RBC pair. The
 233 parameters were chosen to match experimentally measured mean μ_{LD} and
 234 standard deviation σ_{LD} of linear density.

235 The initial PO_2 field in RBCs was set to $P_{\text{rbc},\text{in}}$ and hemoglobin saturation
 236 was set to equilibrium with oxygen. Outside RBCs, the initial PO_2 was set
 237 to $P_{\text{p},\text{in}}$ in the plasma and to 22 mmHg in the tissue.

238 **2.2 Discretization**

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

248 The fixed frame of reference motivated above is problematic when solv-
 249 ing Eq. (6). Hemoglobin is a large protein that cannot cross erythrocyte
 250 membranes. However, the discretization of the advection term would cre-

ate 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
the tissue, denoted by Ω , as well as a moving domain for each RBC, denoted
by Ω_{rbc} (Fig. 1). Each domain is covered by its own computational mesh.
This overlapping mesh approach was adapted from the overset grid method
(26), which has been applied to aerodynamic problems with moving objects.
We will also refer to Ω as Eulerian domain and to Ω_{rbc} as Lagrangian domain.
To simplify the notation, we omit RBC indices. Since RBCs are entering and
leaving Ω , the Lagrangian domain Ω_{rbc} may be completely or partly inside
 Ω .

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

Equation (5) for oxygen was solved in the Eulerian domain Ω , whereas
the hemoglobin equation (6) was solved in the Lagrangian domain Ω_{rbc} .

276 Since Ω_{rbc} moves with the velocity $\mathbf{v}_{\text{rbc}}$, the coordinate transformation $\mathbf{x}' =$
 277 $\mathbf{x} + \mathbf{v}_{\text{rbc}}t$ cancels the advection term and yields

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

278 Since this equation is discretized in Ω_{rbc} , the oxygen partial pressure is also
 279 needed in that domain. This field, denoted by P_{rbc} , is obtained by inter-
 280 polation from Ω to Ω_{rbc} . Likewise, since Eq. (5) is solved in Ω , values of
 281 S in the Eulerian domain, denoted by S_{Euler} , have to be interpolated from
 282 Ω_{rbc} (Fig. 1). The interpolation method may considerably affect simulation
 283 results, since most oxygen in the blood is bound to hemoglobin. Thus, in-
 284 terpolation errors that cause inaccurate values of S_{Euler} may have a large
 285 effect on the resulting PO_2 . A conservative interpolation scheme is therefore
 286 crucial.

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

$$w_{I,J}^{\text{rbc}} = \frac{|V_I \cap V_{\text{rbc},J}|}{|V_{\text{rbc},J}|} \quad (9)$$

291 and

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

292 The interpolation formulas for P_{rbc} and S_{Euler} are then given by

$$P_{\text{rbc},J} = \sum_I w_{I,J}^{\text{rbc}} P_I \quad (11)$$

293 and

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

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

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

$$= \sum_{k=1}^m \sum_J |V_{I_k}| \frac{|V_{I_k} \cap V_{\text{rbc},J}|}{|V_{I_k}|} S_J \quad (14)$$

$$= \sum_J \sum_{k=1}^m |V_{I_k} \cap V_{\text{rbc},J}| S_J \quad (15)$$

$$= \sum_J |\Omega' \cap V_{\text{rbc},J}| S_J \quad (16)$$

$$= \int_{\Omega'} S dV. \quad (17)$$

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

300 Grid cells in Ω that overlap with the RBC border require special care. If
 301 the intersection of a grid cell V_I with Ω_{rbc} occupies a small volume, $S_{\text{Euler},I}$
 302 will be also small. This fact has to be accounted for in the discretization of

303 the reaction term $f(P, S)$. We introduce the RBC volume fraction

$$\gamma_I = \frac{|V_I \cap \Omega_{\text{rbc}}|}{|V_I|}. \quad (18)$$

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

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

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

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

317 The governing equations were discretized using a finite-volume method
 318 with the central scheme for the divergence operator. For the Laplace oper-
 319 ator, Gauss integration, centered differences for the surface normal gradient
 320 and harmonic interpolation for the diffusion coefficient were used. Time step-

ping 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.

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, Ω can be represented by a two-
dimensional domain. As shown in Figure 2, Ω 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 $10.8 \mu\text{m}$ (20). In a hexagonal array of Krogh cylinders
with a capillary diameter of $4 \mu\text{m}$, this corresponds to a radius of $16 \mu\text{m}$.
Therefore, unless stated otherwise, the radii on the arteriolar and venular
sides were set to $r_{t,a} = 19 \mu\text{m}$ and $r_{t,v} = 13 \mu\text{m}$, respectively. The length of
the capillary was set to $100 \mu\text{m}$.

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

344 by Chaigneau et al. (2).

345 The cerebral metabolic rate of oxygen consumption (CMRO_2) is an es-
346 sential model parameter. To our knowledge, no measurement of CMRO_2 in
347 the olfactory glomerulus has been performed. Therefore, we chose the value
348 $\text{CMRO}_2 = 197 \mu\text{M s}^{-1}$ to obtain PO_2 values in the tissue between 15 and 20
349 mmHg approximately (using the perfect gas law at 36.9°C , this corresponds
350 to $M_0 = 5 \cdot 10^{-3} \text{ mlO}_2 \text{ cm}^{-3} \text{ s}^{-1}$). The resulting values of PO_2 in the plasma
351 agree well with the results of Parpaleix et al. (24).

352 **3 Results**

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

364 Using the parameters listed in Table 1, we obtained an averaged EAT
365 amplitude of 29.7 mmHg (RBC $\text{PO}_2 = 50.8$ mmHg, inter-RBC $\text{PO}_2 = 21.1$
366 mmHg, mean $\text{PO}_2 = 27.4$ mmHg). These values were obtained by sampling

367 PO_2 on the capillary centerline at nine evenly spaced longitudinal locations
 368 (between $x = 10 \mu\text{m}$ and $90 \mu\text{m}$). The maximal PO_2 in the plasma was
 369 attained on the rear side of the RBC membrane. Parpaleix et al. (24) also
 370 observed significant differences between these quantities ($\text{RBC } \text{PO}_2 = 57.1 \pm$
 371 1.3 mmHg (mean $\pm$ s.e.m.), inter-RBC $\text{PO}_2 = 23.6 \pm 0.7 \text{ mmHg}$, mean PO_2
 372 $= 30.8 \pm 0.9 \text{ mmHg}$). Since they performed 241 measurements, the results for
 373 our sample capillary differ from these average values by less than one third
 374 of a standard deviation.

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

389 We then investigated longitudinal variations of PO_2 along our sample
 390 capillary. Figure 4 shows time-averaged oxygen partial pressures for the
 391 cone-shaped geometry (Fig. 2) and for a cylinder with equal tissue volume.

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

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

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

430 Since linear density affects tissue PO_2 , we investigated the influence of
 431 the standard deviation σ_{LD} of linear density on tissue PO_2 . Figure 6 shows
 432 tissue PO_2 at $10\ \mu\text{m}$ from the capillary wall and $x = 50\ \mu\text{m}$ for two different
 433 values of σ_{LD} . The same random numbers were used and the parameters
 434 of the log-normal distribution for RBC spacings were adjusted to obtain an
 435 average linear density of 0.28 over four seconds and the desired standard
 436 deviation. Only the last second of the simulation is shown. Random fluc-
 437 tuations of linear density led to large PO_2 oscillations. For $\sigma_{LD} = 0.08$, the
 438 difference between minimal and maximal PO_2 was 5.7 mmHg, and for higher
 439 fluctuations ($\sigma_{LD} = 0.16$), it increased to 10.9 mmHg. This is a consequence
 440 of RBC groups that are close to or far away from each other. Occasionally, a
 441 large RBC spacing resulted in a sudden drop of tissue PO_2 by several mmHg.

Therefore, if linear density fluctuations as reported by Chaigneau et al. (2) are present, PO_2 in the tissue cannot be considered to be constant.

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

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

$$\text{Nu} = \frac{j d_p}{D_p \alpha_p (P^* - P_w)}, \quad (21)$$

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 $3.6 \mu\text{m}$ and a tube hematocrit of 0.28, Secomb and Hsu (28) calculated $\text{Nu} = 1.22$ using a solid cylinder model. Our computed value for this tube hematocrit is 1.17. Therefore, our model reproduces oxygen fluxes from previous studies

464 in steady state situations.

465 4 Discussion

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

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

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

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

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

512 in the brain. This finding may imply that capillary density increases along
 513 RBC paths through capillary networks. In other words, we suggest that an
 514 evenly distributed tissue PO_2 requires denser capillary networks on venular
 515 side. However, one should examine whether these simulation results hold in
 516 realistic networks, where capillary interactions and tortuosity are present.

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

537 remains above this level. Since the geometry of complex capillary networks
538 affects tissue PO_2 , it will be essential to further study the influence of linear
539 density fluctuations.

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

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

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

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

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

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

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

609 Appendix A Time integration

610 Generation of PO_2 maps in realistic capillary network may require simulations
611 with at least hundreds of red blood cells during several seconds. The ability
612 to use large time steps is therefore crucial to keep the computational time
613 sufficiently low. Special care is required to achieve this within our frame-
614 work based on overlapping meshes. The nonlinear reaction term $f(P, S)$
615 (Eq. (3)) combined with RBC displacements prevents from using an explicit
616 scheme. As observed by Clark et al. (3), the boundary layer inside erythro-
617 cytes is a region of chemical nonequilibrium, such that large explicit time
618 steps inevitably cause overshooting. Another requirement is that the cou-
619 pling between hemoglobin and oxygen equations conserves the total of free
620 and bound oxygen.

621 To achieve this, we use Godunov splitting for Eq. (5) and linearization of
622 the reaction and consumption terms using Picard's method. While the equa-
623 tion for oxygen can be integrated without Godunov splitting, this unsplit
624 approach would severely limit the maximal stable time step, since the lin-
625 earization of the reaction term requires PO_2 values in Ω to vary moderately.
626 If RBCs undergo large displacements during one time step, the resulting large
627 PO_2 variations would lead to instabilities.

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

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

631 Here, the solubility α^* corresponds to RBC positions after their displace-
 632 ment. The reaction term $f(P, S)$ and the consumption term $M(P)$ were
 633 both linearized and their linear part is treated implicitly as

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

634 and

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

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

642 The moving meshes Ω_{rbc} are displaced during each time step by the incre-
 643 ment $\mathbf{v}_{\text{rbc}} \Delta t$. When a RBC leaves the domain Ω and no longer overlaps it,
 644 the corresponding mesh is moved to the front of the RBC queue and placed
 645 at a distance to the next RBC, which is randomly generated based on a
 646 log-normal distribution. In the plasma, the coefficients α and D have to be

647 updated to reflect RBC motion. In a grid cell V_I , the discretized coefficients
 648 are given by

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

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

649 where the subscripts “rbc” and “p” refer to values in the RBCs and in the
 650 plasma. The algorithm is summarized in Table 3.

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

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

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

667 The accuracy of the algorithm with a coarser Eulerian grid and larger

time steps was also examined. Table 4 shows absolute and relative errors on the capillary centerline and in the tissue against a baseline case with $\Delta t = 0.1$ ms and $\Delta x = \Delta y = 0.1$ μ m in the capillary. The relative error was normalized by the maximum PO₂ value in the considered longitudinal profile. When multiplying the grid spacing and the time step by three, the relative error stays below 2.5%. With a 50 times larger timestep ($\Delta t = 5$ ms), the absolute error in the tissue is still smaller than 1 mmHg, while the computational time is divided by 10. This is an indication that our numerical algorithm is very robust in terms of time step size and grid spacing. This property will allow for simulations of oxygen transport in larger capillary networks.

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The authors declare no conflict of interest.

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Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Table 1: Model parameters

Parameter	Description	Value	Units	Reference
α_{rbc}	O ₂ solubility in RBCs	$3.38 \cdot 10^{-5}$	mlO ₂ mmHg ⁻¹ cm ⁻³	(5)
α_{p}	O ₂ solubility in the plasma	$2.82 \cdot 10^{-5}$	mlO ₂ mmHg ⁻¹ cm ⁻³	(5)
α_{w}	O ₂ solubility in the capillary wall	$3.89 \cdot 10^{-5}$	mlO ₂ mmHg ⁻¹ cm ⁻³	(5)
α_{t}	O ₂ solubility in the tissue	$3.89 \cdot 10^{-5}$	mlO ₂ mmHg ⁻¹ cm ⁻³	(5)
D_{rbc}	O ₂ diffusivity in RBCs	$9.5 \cdot 10^{-6}$	cm ² s ⁻¹	(5)
D_{p}	O ₂ diffusivity in the plasma	$2.18 \cdot 10^{-5}$	cm ² s ⁻¹	(5)
D_{w}	O ₂ diffusivity in the capillary wall	$8.73 \cdot 10^{-6}$	cm ² s ⁻¹	(5)
D_{t}	O ₂ diffusivity in the tissue	$2.41 \cdot 10^{-5}$	cm ² s ⁻¹	(5)
D_{Hb}	hemoglobin diffusivity in RBCs	$1.44 \cdot 10^{-7}$	cm ² s ⁻¹	(5)
k_{-}	dissociation rate constant	44	s ⁻¹	(5)
L_{rbc}	RBC length	7.27	μm	based on (30), (32)
M_0	maximal O ₂ consumption rate	$5 \cdot 10^{-3}$	mlO ₂ cm ⁻³ s ⁻¹	fitted
μ_{LD}	mean linear density	0.36	–	(24)
n	Hill exponent	2.64	–	fitted from (38)
N_{Hb}	total heme density	$2.03 \cdot 10^{-5}$	mol cm ⁻³	(5)
P_{50}	PO ₂ at hemoglobin half-saturation	47.9	mmHg	fitted from (38)
P_{crit}	critical PO ₂ in the tissue	1.0	mmHg	(8)
$P_{\text{p,in}}$	plasma PO ₂ at the capillary entrance	40	mmHg	based on (24)
$P_{\text{rbc,in}}$	RBC PO ₂ at the capillary entrance	90	mmHg	based on (24)
σ_{LD}	standard deviation of linear density	0.1	–	based on (2)
r_{p}	radius of capillary lumen	2.0	μm	(34)
$r_{\text{w}} - r_{\text{p}}$	capillary wall thickness	0.6	μm	(1)
$r_{\text{t,a}}$	tissue radius on arteriolar side	19	μm	based on (20)
$r_{\text{t,v}}$	tissue radius on venular side	13	μm	based on (20)
v_{rbc}	RBC velocity	$5.7 \cdot 10^{-2}$	cm s ⁻¹	(2)
$V_{\text{mol,O}_2}$	O ₂ molar volume at 36.9°C	$2.54 \cdot 10^4$	mlO ₂ mol ⁻¹	ideal gas law
V_{rbc}	RBC volume	59.0	μm^3	(32)

Table 2: Longitudinal variation of capillary PO_2

	cone		cylinder		experiment (24)
	art.	ven.	art.	ven.	
$\Delta\text{RBC PO}_2$	25.7	14.3	25.6	16.4	14.1 ± 9.2
$\Delta\text{mean PO}_2$	12.0	6.4	16.9	12.4	4.6 ± 2.4
$\Delta\text{inter-RBC PO}_2$	8.0	4.3	14.4	11.3	3.0 ± 2.7

Longitudinal variation of time-averaged PO_2 over $50 \mu\text{m}$ in the cone and cylinder geometries, compared with experimental data. The columns with the heading “art.” (“ven.”) show the averaged PO_2 variation between $x = 10 \mu\text{m}$ ($x = 40 \mu\text{m}$) and $x = 60 \mu\text{m}$ ($x = 90 \mu\text{m}$). Last column: mean $\pm$ s.e.m.

Table 3: Time integration algorithm

```

1: move all RBCs by  $\mathbf{v}_{\text{rbc}}\Delta t$ 
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  $R^{(\nu)} > \text{tol}$  do
9:   for all RBCs that overlap  $\Omega$  do
10:     interpolate  $P^{(\nu)}$  to  $P_{\text{rbc}}^{(\nu)}$  using Eq. (11)
11:     interpolate  $S^{(\nu)}$  to  $S_{\text{Euler}}^{(\nu)}$  using Eq. (12)
12:   end for
13:   solve for  $P^{(\nu+1)}$  (Eq. (23))
14:    $R^{(\nu+1)} \leftarrow$  initial residual of Eq. (23)
15:   for all RBCs that overlap  $\Omega$  do
16:     solve for  $S^{(\nu+1)}$  (Eq. (24))
17:   end for
18:    $\nu \leftarrow \nu + 1$ 
19: end while

```

Time integration of oxygen and hemoglobin equations for one time step Δt

Table 4: Convergence study

Parameters		Centerline		Tissue (10 μm)	
Δt	Δx	abs. L^∞	rel. L^∞	abs. L^∞	rel. L^∞
0.3 ms	0.3 μm	1.65	2.00 %	0.431	2.11%
5 ms	0.3 μm	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 $\Delta x = \Delta y = 0.1$ μm in the capillary.