Multiscale analysis of simultaneous uptake of two reactive gases in the human lungs and its application to methemoglobin anemia

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ABSTRACT

We present a novel multiscale modeling and simulation methodology for quantifying the simultaneous uptake of two reactive gases in the human lungs, and apply it to predict pulmonary hypoxemia in patients suffering from methemoglobin anemia (resulting from excess inhaled nitric oxide (NO)). We start with the convection–diffusion–reaction equations at each scale of the lung and apply a spatial averaging technique (based on Liapunov–Schmidt method of the classical bifurcation theory) to obtain low-dimensional multiscale models. Our simulations for methemoglobin anemia show that while breathing in room air, the O2 saturation in the patient’s hemoglobin falls to below 94% at 50 ppm NO, and above 203 ppm NO causes severe hypoxemia by reducing the O2 saturation to below its critical value of 88%. We predict that patients respond to O2 therapy up to inhaled NO levels of 271 ppm, above which they are candidates for methylene blue therapy.

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1. Introduction

Human respiration is a multiscale process involving disparate time and length scales. These scales are extensively coupled to each other, through the processes of convection, diffusion and chemical reaction. The reaction kinetics involving the participating gaseous components in respiration are particularly nonlinear and hence the coupling between the scales displays extreme non-linearity as well. Thus, the processes at lower length scales significantly affect those at the higher scales. These disparate length scales can be characterized by three representative ones, namely, micro, meso and macro, which are hierarchically embedded within one another. The micro scale is at the level of the red blood cells (∼10⁻⁶ m) and is dominated by diffusion and chemical reaction. The next higher level is the meso-scale (∼10⁻⁴ m) that constitutes capillary transport mostly by convection, and at the top of the hierarchy is the macro-scale that represents the level of the organ, in this case, the lung.

The existing literature on multiscale pulmonary transport and reaction show two different approaches: the top-down and the bottom-up schemes. The top-down approach (Flummerfelt & Crandall, 1968; Forster & Crandall, 1976) considers independence of governing equations at each of the scales, neglecting any communication between the different scales. While this enables analytical solutions of the model equations, it suffers from oversimplification and lack of scale-coupling. On the other hand, the bottom-up approach (Groebbe & Thews, 1989; Huang & Hellums, 1994; Hellums, Nair, Huang, & Oshima, 1996) consists of direct and precise numerical simulation of detailed three-dimensional convection–diffusion–reaction (CDR) equations. However, this method can prove to be computationally expensive and the detailed solutions thus obtained require coarse-graining to obtain a measurable macro-scale quantity of engineering or physiological interest (such as the oxygen saturation in the venous blood or the partial pressure of the exhaled gas).

In this paper, we present an alternate method of modeling pulmonary gas uptake. It is called the “averaging method”, which combines the simplicity of the top-down approach with the mathematical rigor of the bottom-up approach, but is free from the ad-hoc assumptions present in the former. It may also be noted that unlike conventional averaging schemes, this method preserves information about the physics at the smaller length scales of the system, and thus effectively retains all the qualitative features of the full CDR model by retaining all its essential parameters. It consists of averaging or homogenizing the complete CDR equations over shorter length scales to obtain models of lower dimensionality. The averaging of the CDR equations using the Liapunov–Schmidt (LS) method of the classical bifurcation theory (Chakraborty & Balakotaiyah, 2002) results in easier-to-solve low dimensional models that are characterized by two or more modes
(the number of modes depends on the number of length scales involved). These modes are representative of the averaged variables of interest at different length scales and their interaction reflects the coupling between the scales. Fig. 1 shows the three approaches discussed above. These L–S averaged models reduce the computational efforts required in the bottom-up approach drastically, while they are also free from the a priori assumptions made in the top-down approach. We have shown that our spatially averaged low-dimensional models retain all the parameters and thus, most of the qualitative features of the full three-dimensional convection–diffusion–reaction equation (Chakraborty & Balakotaiah, 2002). We have also shown that the process of homogenization is rigorous and can be done exactly to any order of desired accuracy, and even when truncated at lower orders, has, on regularization, a fairly large region of validity (Chakraborty & Balakotaiah, 2005). Thus, this averaging technique combines the rigor of the bottom-up CFD methods with the elegance and simplicity of the averaging methods.

It may be mentioned with reference to our present investigation that LS-averaging based spatially averaged models for diffusion-reaction dominated transport of oxygen in the red blood cell (RBC) has been studied by Chakraborty, Balakotaiah, and Bidani (2004), while multiscale modeling of hypoxemia in hepatopulmonary syndrome (HPS) was performed by Chakraborty, Balakotaiah, and Bidani (2007). However, in both the above cases, only single component systems have been dealt with, in particular, oxygen (O2).

In this paper, we develop a multi-scale model of a two-component system i.e., where two reactive gaseous components are involved. It is intuitively obvious that the interaction due to simultaneous uptake of the constituent gaseous components, along with the difference in their reactivities at the micro-scale (RBC) will introduce additional complexity in the system dynamics other than that already present due to the scale-coupling. Here, we develop a multiscale model for simultaneous uptake of two reactive gases in the human lung, and apply it to the specific case, in which the two components are oxygen (O2) and nitric oxide (NO). NO reacts with hemoglobin much faster than O2 does, and hence, the presence of even small quantities of NO in the inhaled air can heavily interfere with pulmonary oxygen uptake causing a disease called methemoglobinemia. It is mostly acquired in nature, from external sources of NO, such as contaminated water and industrial fumes, and is characterized by the presence of above-normal levels of methemoglobin (MetHb) formed from NO’s reaction with hemoglobin. Higher concentrations of MetHb impart a brown pigmentation to arterial blood, thus producing a bluish tinge in skin color. MetHb is incapable of binding with O2, and hence O2 transport is impeded, causing moderate to severe hypoxemia. This disease occurs essentially at the micro-scale (RBC) but the hypoxemia is symptomatic even at the macro-scale (lung). So we apply our multiscale model to quantify the hypoxemia in NO-induced methemoglobinemia.

This paper is organized as follows: the fundamental multiscale transport-reaction equations are written. The scale-coupled model is subjected to spatial averaging using the LS method to obtain the low-dimensional multiscale model. Finally, the generic model is applied to the specific case of methemoglobinemia, where we perform simulations of disease conditions as well as of standard therapeutic procedures.
The two therapeutic strategies usually adopted are the supply of $O_2$ at high partial pressure (oxygen therapy) and the administration of methylene blue that inhibits MetHb formation to increase $O_2$ uptake by $Hb$. Here, we look quantify the former and briefly discuss the latter.

2. Generic multiscale model

In this section, we first develop our general multiscale model for describing simultaneous uptake of two gases in the human lung, and later present the more specific case of its application to NO induced methemoglobinemia. The model essentially consists of developing the convection–diffusion–reaction (CDR) equations at the micro (RBC) scale and meso (capillary) scales and modeling the macro (lung) scale as a continuous stirred tank. The equations at each of the three scales are then suitably coupled. Throughout this section, we shall use the subscript $i$ to refer to the $i$th gaseous component ($i = 1, 2$) and $j$ ($j = 1, 2, 3, 4$) to represent saturation of species. The development of the model is presented at each of the three length scales, the micro, meso and the macro separately.

2.1. Micro-scale: RBC

Transport of gas (such as oxygen) from the alveolus (where partial pressure of gas is denoted by $P_{i,A}$) to the RBC occurs across the membranes (alveolar epithelium and capillary endothelium) and the plasma. Human erythrocytes are biconcave discs with average dimensions of 8 $\mu$m diameter and 1.6 $\mu$m thickness. Fig. 2 presents a schematic representation of gas uptake in pulmonary capillaries. The convection–diffusion–reaction equations in Lagrangian coordinates for a single RBC of any arbitrary shape with volume $\Omega$ and external surface area $\partial \Omega$ are given as

$$\frac{d}{dt} \frac{\partial P_i}{\partial t} = D_i \frac{\partial^2 P_i}{\partial x^2} - \frac{r_i}{P_i} \left( P_i - P_{i,A} \right),$$  \hspace{1cm} (1)

$$\frac{d}{dt} \frac{\partial [Hi]}{\partial t} = D_{Hi} \frac{\partial^2 [Hi]}{\partial x^2} + \frac{r_i}{P_i} \left( [Hi] - [Hi]_i \right),$$  \hspace{1cm} (2)

where $D_i/\partial t$ is the substantial derivative and $\nabla^2$ is the three-dimensional Laplacian operator. $P_{i,rbc}$ is the partial pressure of the $i$th gaseous component dissolved in the RBC, $S_j$ is the (fractional) saturation of the $j$th species, $D_i$ and $D_{Hi}$ are the diffusion coefficients of the gaseous component $i$ and Hemoglobin inside the erythrocyte, respectively, $[Hi]_i$ is the total intra-cellular hemoglobin concentration and $\alpha_i$ is the solubility of the corresponding gaseous component in the RBC. The rates of reaction $r_i$ of the component gases with the hemoglobin in the RBC are functions of both partial pressure and saturation. The appropriate boundary conditions for these equations, under the assumption of a symmetric geometry are given by:

$$P_{i,rbc} \text{ and } S_j \text{ are finite at the center of the RBC},$$  \hspace{1cm} (3)

$$\left( D_i \alpha_i \nabla P_{i,rbc} \right) \cdot n = \eta_i \left( \langle P_{i,pl} \rangle - P_{i,rbc} \right) \text{ on } \partial \Omega \text{ (on the surface of the RBC)},$$  \hspace{1cm} (4)

$$\left( \nabla S_j \right) \cdot n = 0 \text{ on } \partial \Omega \text{ (on the surface of the RBC)},$$  \hspace{1cm} (5)

Eqs. (1) and (2) are also subject to initial conditions given by

$$P_{i,rbc}(t = 0) = P_{i,i},$$  \hspace{1cm} (6)

$$S_j(t = 0) = 0,$$  \hspace{1cm} (7)

where $n$ is the outward unit normal to the surface, $P_{i,v}$ is the mixed venous partial pressure and $\langle P_{i,pl} \rangle$ is the spatially averaged partial pressure of gas $i$. It has been shown (Kagawa & Mochizuki, 1982) that a thin unstirred plasma layer is formed around the surface of the red
cell and hinders mass transfer from the plasma. \( \eta_i \) in Eq. (4) represents the mass transfer coefficient in the unstirred layer, which quantifies the mass transfer resistance between the RBC and the plasma. Solving the coupled CDR equation of the RBC with the unstirred (boundary) layer surrounding it (Chakraborty et al., 2004) gives

\[
\eta_i \left( \frac{D_{i,bl} \Theta_{i,bl}}{\delta} \right),
\]

where \( \delta \) is the thickness of the boundary layer, \( \alpha_{i,bl} \) and \( D_{i,bl} \) are the solubility and the diffusion coefficients of the corresponding component in the stagnant layer, respectively. The objective of this modeling exercise in the micro scale would to be to carefully manipulate the system of equations (1) and (2), to eliminate the reaction terms and then spatially average it to cast it in the form,

\[
\frac{DP_{i,pl}}{Dt} = \Theta \Delta P,
\]

where \( P_{i,pl} = \left( \langle P_{1,pl} \rangle - \langle P_{2,pl} \rangle \right) \). \( \Theta = \left( \begin{array}{cc} \Theta_{11} & \Theta_{12} \\ \Theta_{21} & \Theta_{22} \end{array} \right) \) and \( \Delta P = \left( \langle P_{1,pl} \rangle - \langle P_{1,pl} \rangle, \langle P_{2,pl} \rangle - \langle P_{2,pl} \rangle \right) \). In this form the equations appear as simple gradient relations preceded by a transfer coefficient \( \Theta \). Eq. (9) is in terms of spatially averaged quantities and is considerably simpler to solve than the PDEs in Eqs (1) and (2). It can be shown that \( \Theta \) depends on \( \beta \), where \( \beta \) is a \( 2 \times 2 \) matrix, whose elements are given by

\[
\beta_{ij} = \frac{\partial \Theta_{ij}}{\partial P_{i,pl}},
\]

i.e., the slope of the equilibrium saturation curve of the \( i \)th component. The quantities \( \Theta_{ij} \) are called “diffusing capacities”, which shall be discussed in detail later.

2.2. Meso scale: capillary

A pulmonary capillary consists of a continuous plasma phase in which the RBCs are suspended. Our meso-scale model assumes the plasma phase to be a continuum in which suspended RBCs behave like sources/sinks of gaseous components that react with Hemoglobin. The general meso-scale model equation is given by

\[
(1 - h) \left[ \frac{\partial C_{i,pl}}{\partial t} + v_{pl}(r, x) \frac{\partial C_{i,pl}}{\partial x} + R_{i,pl}(C_{i,pl}) \right] + \mu = (1 - h)D_{i,pl} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_{i,pl}}{\partial r} \right) + \frac{\partial^2 C_{i,pl}}{\partial x^2} \right],
\]

where \( h \) is the hematocrit, i.e., volume fraction of RBC in the blood, \( C_{i,pl} \) is the concentration of gas \( i \) \((i = 1, 2)\) in the plasma phase expressed in L(STPD) of gas per L blood, \( D_{i,pl} \) is the effective diffusivity of gas in the plasma (effective diffusivity is used instead of molecular diffusivity, since it is known that the red cell rotation and other motions in the shear field tend to promote radial transport), and \( C_{i,pl} \) and \( P_{i,pl} \) are related linearly as

\[
C_{i,pl} = \alpha_{i,pl} P_{i,pl},
\]

where \( \alpha_{i,pl} \) is the solubility of gas \( i \) in the plasma.

\[
\mu = \frac{D_{i,pl}}{\partial P_{i,pl}}
\]

represents the flux contribution from the micro-scale and is obtained by solving Eq. (9). On substituting the value of \( \mu \) in Eq. (11), the complete general meso-scale equation takes the form

\[
(1 - h) \left[ \frac{\partial C_{i,pl}}{\partial t} + v_{pl}(r, x) \frac{\partial C_{i,pl}}{\partial x} + R_{i,pl}(C_{i,pl}) \right] + h(\Theta_{11}(\langle P_{1,pl} \rangle - \langle P_{1,pl} \rangle) + \Theta_{12}(\langle P_{2,pl} \rangle - \langle P_{2,pl} \rangle))
\]

\[
= (1 - h)D_{i,pl} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_{i,pl}}{\partial r} \right) + \frac{\partial^2 C_{i,pl}}{\partial x^2} \right],
\]

with the boundary conditions,

\[
- \frac{2}{a} (1 - h)D_{i,pl} \left. \frac{\partial C_{i,pl}}{\partial r} \right|_{r = a} = \frac{D_{M,i} \left( P_{A,i} - P_{i,pl} \right)}{V_C} \text{ at } r = a,
\]

\[
\left. \frac{\partial C_{i,pl}}{\partial r} \right|_{r = 0} = 0,
\]

where \( P_{A,i} \) is the alveolar partial pressure, \( D_{M,i} \) is the membrane diffusing capacity of the \( i \)th component under consideration and has units of L(STPD) of gas/\( mHg s \), \( a \) is the capillary radius and \( V_C \) is the total capillary bed volume. Eq. (14) accounts for mass transfer across the membrane using the concept of membrane diffusing capacity, and also couples the transport inside the capillary with that in the macro scale, while Eq. (15) is essentially a statement of centerline symmetry.

It must be pointed out that \( v_{pl}(r, x) \) is not equal to the velocity at which the red cells are carried along by the plasma, and there exists slip between the RBC and the plasma phase. The velocity of the red cells \( v_{rbc} \) and the plasma \( v_{pl} \) are not constants but are given by (Nair et al., 1989, Huang & Hellums, 1994)

\[
v_{rbc}(r) = 2(1 - \text{slip}) v_p(x) \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right], \quad r \in [0, r_c],
\]

\[
v_{pl}(x) = \frac{D_{M,i} \left( P_{A,i} - P_{i,pl} \right)}{V_C} \text{ at } r = a,
\]
\[
\nu_p(r) = \begin{cases} 
2\nu_{D}(x) \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right], & r \in [0, r_c] \\
2\nu_{A}(x) \left[ 1 - B \left( \frac{r}{r_c} \right)^2 \right], & r \in [r_c, r_t]
\end{cases}
\]  
(17)

while the hematocrit, i.e., the volume fraction of the RBC at any radius, is expressed as (Huang & Hellums, 1994; Nair, Hellums, & Olson, 1989)

\[
h = \begin{cases} 
2h_m \left[ 1 - \left( \frac{r}{r_t} \right)^m \right], & r \in [0, r_t] \\
0, & r \in [r_t, r_c]
\end{cases}
\]  
(18)

where \( r_t \) = radius of the RBC rich region, \( r_c \) = radius of the capillary, \( B \) = Blunting factor that represents deviation from parabolic flow profile \( B \in [0,1] \), and slip = relative slip between plasma and RBC \( \text{slip} \in [0,1] \). In this analysis, we consider the hematocrit profile to be constant along the transverse direction (=h) and also assume a fully developed parabolic velocity profile for the plasma, given by

\[
\nu_p(r) = 2\nu_{pl} \left[ 1 - \left( \frac{r}{a} \right)^2 \right],
\]  
(19)

and a constant velocity profile for the RBC which retains the effect of slippage and is given by

\[
\nu_{rbc}(r) = (1 - \text{slip})\nu_{pl},
\]  
(20)

where \( \nu_{pl} \) = average velocity of plasma in the capillary. Lastly, since all reactions are confined to the RBC and none occur in the plasma phase, the reaction term \( R_{p,pl}(C_{pl}) = 0 \) in Eq. (13) (for \( i = 1, 2 \)).

We proceed to non-dimensionalize the meso-scale governing equation and its boundary conditions, in order to compare the magnitude of the various time scales involved in the transport process, and accordingly simplify the governing equations. The non-dimensional forms of the different variables are

\[
t = \frac{t}{\tau}, \quad \zeta = \frac{r}{a}, \quad \xi = \frac{x}{L}, \quad i_{pl} = \frac{\nu_{pl}}{\nu_{pl}}, \quad u_{rbc} = \frac{\nu_{rbc}}{\nu_{pl}} = (1 - \text{slip}),
\]

\[
p_{i,pl} = \frac{P_{i,pl}}{P_{A,1}}, \quad C_{i,pl} = \frac{C_{i,pl}}{C_{A,1}}, \quad p_{i,rbc} = \frac{P_{i,rbc}}{P_{A,1}},
\]

while the different dimensionless numbers are given by

\[
Pe_{T,i} = \frac{a^2\nu_{pl}}{LD_{i,pl}}, \quad Pe_{l} = \frac{L\nu_{pl}}{D_{l,pl}} = \frac{t_x}{\tau},
\]

\[
\Theta_{rbc,ij} = \frac{\nu_{pl} \alpha_{ij}}{v_p \Theta_{ij}}, \quad \Theta_{l,m} = \frac{LD_{M,i}}{v_p \alpha_{ij} \Theta_{ij}} = \frac{r}{t_{m,pl}},
\]

and the constituent time scales are given by

\[
\tau = \frac{L}{v_{pl}}, \quad t_0 = \frac{a^2}{D_{pl}}, \quad t_x = \frac{L^2}{D_{pl}}, \quad t_{rbc-pl} = \frac{\alpha_{ij}}{\Theta_{ij}}, \quad t_{m-pl} = \frac{V_{pl} \alpha_{ij}}{D_{pl}}.
\]

The above expressions show that the dimensionless numbers are ratios of different time-scales in the system, e.g. \( Pe_{ij} \), is the ratio of radial diffusion time to transit time of blood in the capillary (\( \tau \)) for gas \( i \), \( Pe_{l} \) is the ratio of axial diffusion time to capillary transit time, \( \Theta_{rbc,ij} \) is the ratio of capillary transit time to mass transfer time between RBC and plasma (in effect, it is the non-dimensional form of the diffusing capacity and hence incorporates the net effect that gas \( i \) has on gas \( j \), due to both mass transfer and reaction), and \( \Theta_{l,m} \) is the ratio of blood transit time to mass transfer time across the alveolar membrane for gas \( i \). It may also be noted that all partial pressures in the system have been made dimensionless with respect to alveolar pressure of any one of the gases \( (P_{A,1}) \) (preferably the one with the larger partial pressure). The non-dimensional form of Eq. (13), therefore, becomes

\[
\frac{1}{\ell^2} \frac{d}{d\zeta} \left( \frac{\zeta \partial p_{i,pl}}{\partial \zeta} \right) = Pe_{T,i} \left\{ (1 - h) \left( \frac{\partial p_{i,pl}}{\partial \zeta} + u_{pl} \frac{\partial p_{i,pl}}{\partial \xi} - \frac{1}{Pe_{l}} \frac{\partial^2 p_{i,pl}}{\partial \xi^2} \right) + h \Theta_{ij} \left( \langle p_{1,pl} \rangle - \langle p_{1,rbc} \rangle \right) + h \Theta_{i2} \left( \langle p_{2,pl} \rangle - p_{2,rbc} \right) \right\}
\]  
(21)

with boundary conditions given by

\[
\frac{\partial p_{i,pl}}{\partial \zeta} \bigg|_{\zeta=1} = Pe_{T,i} \Theta_{1,m} \left( k_i - p_{i,pl} \right),
\]  
(22)

\[
\frac{\partial p_{i,pl}}{\partial \zeta} \bigg|_{\zeta=0} = 0,
\]  
(23)

where the parameter \( k_i \) is the non-dimensional alveolar partial pressure of the gas \( (k_1 = 1 \text{ and } k_2 = P_{A,2}/P_{A,1} = k \text{ (say)}) \). An order of magnitude analysis reveals axial diffusion to be much slower than convection (i.e. \( Pe_i \) is very large \( \sim 10^3 \)). So, we may neglect the axial diffusion term.
in this model. Further, the low value ($\sim 10^{-4}$) of the transverse Peclet number ($Per$) allows us to perform the radial/transverse averaging of the above model without losing much of the quantitative accuracy of the full CDR model.

Subsequently, the non-dimensional meso-scale governing equations are subjected to spatial averaging. The detailed process of the transverse averaging of the meso-scale model has been presented in Appendix A, and here we directly present the averaged meso-scale model equations, represented by three modes, namely the averaged partial pressure of gas in the blood plasma ($p_{i,pl}$), the cup-mixing partial pressure of the gas, $p_{i,pm}$ (which is the velocity-weighted average of the partial pressure), and the pressure inside the RBC, ($p_{i,rbc}$) – the micro-scale variable that affects the meso-scale due to scale-coupling. Post-averaging, we obtain a set of ODEs, consisting of a global evolution equation, given by

$$\langle 1 - h \rangle \frac{dp_{i,m}}{dz} = \Theta_{i,m} (k_i - p_{i,s}) - h \Theta_{i,v,bc,i} \langle (p_{1,pl}) - \langle p_{1,rbc} \rangle \rangle - h \Theta_{i,v,bc,2} \langle (p_{2,pl}) - \langle p_{2,rbc} \rangle \rangle,$$

(24)

and two local equations, given by

$$p_{i,m} = \langle p_{i,pl} \rangle - Per_i \left[ \Theta_{i,m} \left( k_i - p_{i,s} \right) + \frac{(1 - h)}{48} \langle \frac{dp_{i,m}}{dz} \rangle \right],$$

(25)

$$p_{i,s} = \langle p_{i,pl} \rangle + Per_i \left[ 3 \Theta_{i,m} (k_i - p_{i,s}) + (1 - h) \langle \frac{dp_{i,m}}{dz} \rangle \right],$$

(26)

where $p_{i,s}$ is the steady-state partial pressure at the capillary-membrane interface. The above system must be solved in conjunction with the non-dimensional Eulerian forms of the micro scale Eq. (9), which shall be explored in greater detail when we look at the specific case of simultaneous uptake of $O_2$ and $NO$ in Section 3.

2.3. Macro scale: lung

In this section, we develop the relations governing gas ventilation $(V)$ and blood perfusion $(Q)$ in the whole lung. The ratio of these two quantities, known as the ventilation to perfusion ratio $(V/Q)$, controls the alveolar partial pressure $(P_A)$, that, in turn, affects the meso and micro scales through scale coupling. For an “ideal” lung, this ratio is known to be 1 but in a “normal” lung, it varies spatially across the different lung compartments, from 0.3 to 3.3 (West, 1977). In addition, we also consider intrapulmonary right to left shunts $(V/Q = 0)$, constituting 3–5% of the blood flow. The spatial variation of ventilation and perfusion rates at the macro scale (i.e., lung) is accounted for by using a compartment model, which is illustrated in Fig. 3. As may be noted from the figure, compartment 1 of our six compartment model corresponds to the space in the lung between ribs “Top” and rib number 2, compartment 2 corresponds to that between ribs 2 and 3, and so on, for the first five compartments. The fraction of blood flow through the sixth compartment corresponds to the shunt fraction $f_{shunt}$. An intra-pulmonary shunt is a region of zero gas-blood interaction and usually occupies about 5% of the total lung. By allocating a separate compartment for the shunt, we essentially lump all such regions of no blood-gas interaction together. For a “normal lung”, the distribution of the ventilation to perfusion ratio with rib position has been obtained by fitting polynomials to data reported by West (1977) (Fig. 6A in Chakraborty et al., 2007), which is given as

$$\frac{V}{Q} = 0.3 + 3.24y - 7.19y^2 + 16.72y^3 - 21.54y^4 + 11.77y^5,$$

(27)

where $y$ is the normalized distance along the ribs ($y \in [0, 1]$), given by

$$y = \frac{N_{rib, total} - N_{rib}}{N_{rib, total} - 1},$$

(28)
where \( y = 0 \) at the bottom of the lungs and \( y = 1 \) at the top, \( N_{\text{rib}} \) has been described in Fig. 3 and \( N_{\text{rib,total}} = 6 \). For the sixth compartment (i.e., the shunt), the gaseous components are absent and hence, \( V/Q = 0 \), while the blood flow i.e., the perfusion rate is given by \( Q_s = Q_{\text{total,shunt}} \).

The remaining volume of blood flow is distributed across the other five compartments following a log-normal distribution, given by

\[
\frac{Q_{N_{\text{rib}}}}{Q_{\text{total}}(1 - J_{\text{shunt}})} = \Phi(N_{\text{rib}} = N_{c}) - \Phi(N_{\text{rib}} = N_{c} + 1),
\]

where \( N_{c} = 1, 2, 3, 4, 5 \) is the compartment number and \( \Phi \) is the cumulative distribution function of log-normal distribution, given by

\[
\Phi(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{x} \exp \left(-\frac{x^2}{2}\right) dx,
\]

and

\[
x = \frac{1}{\sigma} \left[ \ln \left( \frac{V}{Q_{\text{rib}}} \right)_{N_{\text{rib}}} - \mu \right].
\]

As mentioned before, the alveolar partial pressure (\( P_A \)) is different for each compartment and is determined by the local \( V/Q \) ratio of that compartment. The relationship between \( P_A \) and the venous partial pressure (\( P_V \)) of the corresponding gas has been fitted as a sigmoidal function of \( V/Q \) to the data presented by West (1977), which is given by

\[
P_A = P_V + c_1 \left( \frac{(V/Q)^{f_2}}{1 + (V/Q)^{f_2}} \right).
\]

For a “normal lung” breathing in room air, \( P_V \approx 40 \text{ mmHg} \), \( c_1 = 122.5 \text{ mmHg} \) and \( c_2 = 1.28 \). It may be mentioned here that the \( V/Q \) value used in Eq. (32) is an average value in that particular compartment obtained from integrating Eq. (27) as

\[
\left< \frac{V}{Q} \right>_{N_{c}} = \int \left< \frac{V}{Q} \right> (y) dy / \int dy,
\]

where the integral is taken over the whole compartment \( N_{c} \). On writing out the appropriate limits, the above quantity becomes

\[
\left< \frac{V}{Q} \right>_{N_{c}} = \left( \frac{N_{\text{rib,total}} - N_{c}}{N_{\text{rib,total}} - N_{c} - 1} \right) \left( \frac{N_{\text{rib,total}} - N_{c}}{N_{\text{rib,total}} - N_{c} - 1} \right) \left( \frac{V}{Q} \right) (y) dy.
\]

For the sixth compartment, as mentioned earlier the ventilation-perfusion ratio is zero. Using the values of \( P_A \) and \( V/Q \) for each compartment obtained by the above method, we calculate the partial pressure of the gas \( i \) and the saturation of blood exiting each compartment \( \left( S_{n,N_c,i} \right) \) using the steady-state form of the meso-scale model (Eqs. (24)–(26)). The blood leaving the six compartments is allowed to mix in the pulmonary vein, and this mixing process is modeled as one in a perfectly stirred tank. The final gas saturation of the mixed blood in the pulmonary vein \( \left( S_{n,1} \right) \) determines the total amount of uptake of the gaseous component \( i \) in the lung, which can be expressed as

\[
S_{n,1} = S_{n,\text{shunt}} + \left( \frac{1}{Q_{\text{total}}} \right) \sum_{N_{c}=1}^{5} Q_{N_{c}} S_{n,N_c,i}.
\]

where \( S_{n,1} \) is the saturation of the gas in the venous blood. Thus, we have established a hierarchy of scales where the macro scale embeds the meso and the meso scale embeds the micro scale, and the entire system must be solved simultaneously (and not sequentially) to capture the effect of the transport-reaction coupling across the scales.

### 3. Application of the model to methemoglobinemia

In this section, we discuss specific details of how our model can be applied to explain methemoglobinemia. Methemoglobinemia is a disorder characterized by the presence of above-normal levels of methemoglobin (MetHb) in the red blood cell (RBC) produced by irreversible NO-induced oxidation of the \( O_2 \) carrying ferrous iron \((Fe^{2+})\) in the heme group of the hemoglobin (Hb) molecule to its non-oxygen binding ferric state \((Fe^{3+})\). The reduced oxygen uptake produces a functional anemia, and causes symptoms such as chocolate coloration of blood leading to bluish pigmentation of the skin. The chief agent of this disease, methemoglobin is not entirely alien to the human body, and often arises from oxidant stresses continually undergone by the RBCs, and thus is continuously produced (Lee & Ferguson, 2011). The coupled reactions of \( O_2 \) and NO with hemoglobin in the red blood cell are given by

\[
\text{Hb} + \text{O}_2 = \text{Hb(O}_2)n, \tag{36}
\]

\[
\text{HbO}_2 + \text{NO} = \text{MetHb} + \text{NO}_3^- \tag{37}
\]

\[
\text{Hb} + \text{NO} = \text{HbNO}. \tag{38}
\]

Eq. (36) assumes \( O_2–\text{Hb} \) equilibrium to follow the Hill equation, with \( n \) being the Hill constant (\( =2.34 \)), and the equilibrium rate constant \( (K_1) \) being given by

\[
K_1 = \left( \frac{H}{P_{50}} \right)^n. \tag{39}
\]
where \( H = 7.4 \times 10^5 \) Torr and \( P_{SO} = 26 \) Torr (Fournier, 1998). Thus, we see that methemoglobin anemia involves physical processes of gaseous exchange at the lung alveoli, diffusion and convection of dissolved gases in the alveolar capillaries and simultaneous reaction and diffusion inside the RBCs. Evidently, the phenomenon spans across largely different length scales and can be termed as a multiscale disease.

### 3.1. Detailed model equations

The system of governing equations that describe simultaneous uptake of \( O_2 \) and \( NO \) at each scale under conditions of methemoglobinemia is a simple extension of the general model developed in Section 2. We introduce \( O_2 \) as the 1st \((i=1)\) and \( NO \) as the 2nd \((i=2)\) gaseous component in the micro and meso scale equations. Thus, writing micro-scale Eqs. (1) and (2) separately for each gas and each species formed out of reaction and employing the kinetics presented in Eqs. (36)–(38), we get the following set of diffusion-reaction equations:

\[
\frac{\partial \alpha \rho_{O_2}}{\partial t} = \frac{\partial}{\partial x} \left( D_{O_2} \frac{\partial \alpha \rho_{O_2}}{\partial x} \right) - R_1,
\]

\[
\frac{\partial \alpha \rho_{NO}}{\partial t} = \frac{\partial}{\partial x} \left( D_{NO} \frac{\partial \alpha \rho_{NO}}{\partial x} \right) - (R_2 + R_3),
\]

\[
\frac{\partial \alpha \rho_{Hb}}{\partial t} = \frac{\partial}{\partial x} \left( D_{Hb} \frac{\partial \alpha \rho_{Hb}}{\partial x} \right) + \alpha_1 \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) + \alpha_2 \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right) + R_1 - R_2.
\]

with appropriate initial and boundary conditions given by Eqs. (3)–(7). These equations are then converted to coupled diffusion equations (by eliminating the reaction rate terms through algebraic manipulation (as shown in Eq. (9))) and subjected to spatial averaging over the volume of the RBC using LS method. The details of the mathematical procedures involved as well as the process of spatial averaging at the micro-scale have been shown in Appendix B. Here, we present the spatially averaged forms of the equations, which are given by

\[
(\alpha_1 + [Hb]_r \beta_{11}) \frac{D \langle p_{1,rbc} \rangle}{Dt} = \Theta_{11} \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) + \Theta_{12} \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right),
\]

\[
(\alpha + [Hb]_r \beta_{22} + \beta_{32}) \frac{D \langle p_{2,rbc} \rangle}{Dt} = \Theta_{21} \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) + \Theta_{22} \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right).
\]

The above equations have been written in Lagrangian coordinates. We now express them in Eulerian coordinates for steady-state conditions and non-dimensionalise the system using dimensionless variables introduced in Section 2.2 to obtain

\[
\frac{\alpha_1 + |Hb|_r \beta_{11}}{\tau} u_{rbc} \frac{d \langle p_{1,rbc} \rangle}{dz} = \Theta_{11} \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) + \Theta_{12} \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right),
\]

\[
\frac{\alpha_2 + [Hb]_r \beta_{22} + \beta_{32}}{\tau} u_{rbc} \frac{d \langle p_{2,rbc} \rangle}{dz} = \Theta_{21} \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) + \Theta_{22} \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right).
\]

The diffusing capacities \( \Theta_{ij} \) are expressed as (please refer to Appendix B for detailed derivations)

\[
\Theta_{11} = \frac{\alpha_1 + \beta_{11}|Hb|_r}{b(\alpha_1 D_1 / \eta_1) + (b / S_{Hb})} G_{11},
\]

\[
\Theta_{12} = \frac{\alpha_1 + \beta_{11}|Hb|_r}{b(\alpha_2 D_2 / \eta_2) + (b / S_{Hb})} G_{12},
\]

\[
\Theta_{21} = \frac{\alpha_1 + \beta_{22} + \beta_{32}|Hb|_r}{b(\alpha_1 D_1 / \eta_1) + (b / S_{Hb})} G_{21},
\]

\[
\Theta_{22} = \frac{\alpha_2 + \beta_{22} + \beta_{32}|Hb|_r}{b(\alpha_2 D_2 / \eta_2) + (b / S_{Hb})} G_{22},
\]

where \( G_{ij} \)s are functions of \( \beta_{ij} \), i.e., the slope of the equilibrium saturation curve, as introduced in Eq. (10).

Next, we present the detailed form of the meso-scale equations, in terms of partial pressures of \( O_2 \) and \( NO \), the derivation of which has already been discussed in Section 2, and here, we directly write the spatially averaged forms. Since we write for two gases, the complete meso-scale model will now have two global equations, given by

\[
(1 - h) \frac{dp_{1,m}}{dz} = \Theta_{1,m}(1 - p_{1,s}) - h \Theta_{1bc,11} \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) - h \Theta_{1bc,12} \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right),
\]

\[
(1 - h) \frac{dp_{2,m}}{dz} = \Theta_{2,m}(1 - p_{2,s}) - h \Theta_{2bc,21} \left( \langle P_{1,pl} \rangle - \langle P_{1,rbc} \rangle \right) - h \Theta_{2bc,22} \left( \langle P_{2,pl} \rangle - \langle P_{2,rbc} \rangle \right),
\]
and four local equations, given by

\[ p_{1,m} = \left( p_{1,pl} - PeT,1 \right) + \frac{(1 - h) \, dp_{1,m}}{48 \, dz}, \]

\[ p_{2,m} = \left( p_{2,pl} - PeT,2 \right) + \frac{(1 - h) \, dp_{2,m}}{48 \, dz}, \]

\[ p_{1,s} = \left( p_{1,pl} + PeT,1 \right) + \frac{3 \, (1 - h) \, dp_{1,m}}{24}, \]

\[ p_{2,s} = \left( p_{2,pl} + PeT,2 \right) + \frac{3 \, (1 - h) \, dp_{2,m}}{24}. \]

(52–55)

As stated above, \( k \) is the ratio between the alveolar partial pressures of \( O_2 \) and \( NO \), whose value is \( \sim 10^{-6} \) in this analysis. It may be mentioned that the effects of scale-coupling between the micro and the meso levels are manifested in the equations through the magnitude of \( k \). Eqs. (47–55) constitute the coupled micro-meso model. The complete model is constructed by further coupling it with the macro-scale (Eqs. (27–35)).

### 3.2. Solution of the coupled scale model

The macro scale compartmental model when coupled with the micro and meso scale models results in a system of coupled ODEs. It turns out that numerical solution of this system in its present form results in an ill-conditioned mass matrix that is hard to handle, even with standard tools such as MATLAB. So, we exploit the linear interdependency of the modes in the meso-scale local equations (Eqs. (52–55)) to transform this set of ODEs into a form more suitable for numerical computation. The macro scale algebraic equations supply the compartmental alveolar partial pressure (Eq. (32)) as a boundary condition to this transformed system. The entire algorithm is presented in the form of an information flow diagram in Fig. 4. It may be mentioned that only macro-scale quantities are physiologically measurable and thus, we report all our final results in terms of macro-scale quantities. Before we proceed to simulate, we recast our multiscale steady state model equations into the following form

\[ \sum_{i=1}^{n} a_i(x_1, x_2, \ldots, x_n) \frac{df(x_1, x_2, \ldots, x_n)}{dx_i} = b_i(x_1, x_2, \ldots, x_n), \]

(56)

which can easily be handled by standard ODE solver algorithms in software such as MATLAB. This produces a “4-ODE” system for our case, which is of the form

\[ \frac{dp_{1,m}}{dz} + Y_1 \frac{dp_{2,m}}{dz} = Z_1, \]

\[ \frac{dp_{1,m}}{dz} + Y_2 \frac{dp_{2,m}}{dz} = Z_2. \]

(57–58)

---

![Fig. 4.](image-url) Outline of the simulation algorithm, showing the interaction between the different length scales.
\[
X_1 \frac{dp_{1,m}}{dz} + \psi_1 \frac{dp_{2,m}}{dz} = \bar{Z}_1, \\
X_2 \frac{dp_{1,m}}{dz} + \psi_2 \frac{dp_{2,m}}{dz} = \bar{Z}_2,
\]
where the coefficients are suitably grouped terms from Eqs. (47)–(55) and can be computed by elementary algebra as

\[
X_1 = 1 + \frac{3P e_{T,1} + \theta_{1,m}h e_{bc,11} + \theta_{1,m}P e_{T,1}}{8B_1} - \frac{\theta_{1,m}P e_{T,1}}{192B_1}, \\
Y_1 = h e_{bc,12} \left( \frac{P e_{T,2}}{8B_2} + \frac{\theta_{2,m}P e_{T,2}}{192B_2} \right),
\]

\[
Z_1 = \frac{\theta_{1,m}}{1 - h} \left( 1 - \frac{6P_{1,m} + \theta_{1,m}P e_{T,1}}{B_1} \right) - \theta_{bc,11} \left( \frac{3P_{1,m} + \theta_{1,m}P e_{T,1}}{4B_1} - \theta_{1,m}P e_{T,1} \right) + \theta_{bc,12} \left( \frac{3P_{2,m} + \theta_{2,m}P e_{T,2}}{4D_2} - \theta_{2,m}P e_{T,2} \right),
\]

\[
X_2 = h e_{bc,21} \left( \frac{P e_{T,1}}{8B_1} + \frac{\theta_{1,m}P e_{T,1}}{192B_1} \right), \\
Y_2 = 1 + \frac{3P e_{T,2} + \theta_{2,m}h e_{bc,22} + \theta_{2,m}P e_{T,2}}{8B_2} - \frac{\theta_{2,m}P e_{T,2}}{192B_2},
\]

\[
Z_2 = \frac{\theta_{2,m}}{1 - h} \left( k - \frac{6P_{2,m} + \theta_{2,m}P e_{T,2}}{B_2} \right) - \theta_{bc,21} \left( \frac{3P_{2,m} + \theta_{2,m}P e_{T,2}}{4B_2} - \theta_{1,m}P e_{T,1} \right) + \theta_{bc,22} \left( \frac{3P_{2,m} + \theta_{2,m}P e_{T,2}}{4D_2} - \theta_{2,m}P e_{T,2} \right).
\]

4. Results and discussions

We simulate the multiscale model presented above to calculate the O₂ and NO saturation (in hemoglobin) profiles that quantify the simultaneous gaseous uptake in methemoglobinemia as well as the effects of different parameters (including NO concentration) on the onset of the disease. Table 1 lists the standard data set used for our simulation. The reaction rate constant (k₂) for NO-induced oxidation of oxyhemoglobin to MetHb was calculated by Eich et al. [1996], while Scheele et al. [1999] reported the reaction rate constant (k₃) for the reaction between NO and deoxyhemoglobin as 2 × 10³ M⁻¹ s⁻¹, and also measured the dissociation rate of nitrosylhemoglobin. The dissociation rate constant of MetHb (k⁻) is obtained to be 2.47 × 10⁻³ s⁻¹ from Power et al. [2007]. Here, we use deoxygenated blood with an O₂ partial pressure of 40 Torr and Sₒ₂ = 75% as the initial conditions for our simulation.

Fig. 5 compares the profiles of saturation and partial pressure of O₂ in the RBC for different values of alveolar pressure of NO. It can be seen that O₂ saturation is much more sensitive to changes in the ambient NO environment, and hence shows significantly more variation than the partial pressure of O₂ (Sanyal & Chakraborty, 2011). This implies that the diagnosis of hypoxemia in methemoglobinemia can be done more effectively by measuring the oxygen saturation in the patient’s erythrocyte (which is commonly done using pulse oximetry) than by measuring the oxygen partial pressures in the patient’s pulmonary vein.

Fig. 6 shows the variation of the micro-scale diffusing capacities with the O₂ partial pressure in the RBC where the NO concentration is a parameter. The diffusing capacity is a representation of the reaction-enhanced diffusion coefficient of one gas in the presence of another. Hence, it effectively captures the net interaction between the two gases. Fig. 6(a) presents the biphasic nature of the diffusing capacity of O₂, which maximizes at around 25 Torr. From Fig. 6(b) and (c), we see that θ₁₂ and θ₂₁ are nearly equal in magnitude. This implies that the changes O₂ and NO enforce upon the dynamics of each other are almost quantitatively similar. However, in Fig. 6(d), θ₂₂ is several orders of magnitude higher than the rest of the diffusing capacities, suggesting that NO is so potent that it can lead to the onset of the disease even when present in small quantities.

Fig. 7 presents the complete solution of our multi-scale model in which the quantities of interest are reported in terms of measurable macro-scale variables. O₂ saturation falls from 96% at 0 ppm NO to 94% at around 50 ppm. It may be noted that the changes in NO saturation are negligible compared to the change of O₂ saturation for different shunt fractions. This suggests that with its increasing level, NO plays...
Fig. 5. Comparison of spatial profiles of (a) partial pressure and (b) fractional saturation of O₂ in the RBC.

Fig. 6. Variation of diffusing capacities in the RBC with O₂ partial pressure in the RBC for various alveolar partial pressures of NO.
Table 1
Data used in simulation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_1$</td>
<td>$2.648 \times 10^{10}$ Torr$^{-1}$</td>
</tr>
<tr>
<td>$K_2$</td>
<td>$2.1 \times 10^{9}$ Torr$^{-1}$</td>
</tr>
<tr>
<td>$K_3$</td>
<td>$3.4 \times 10^{9}$ Torr$^{-1}$</td>
</tr>
<tr>
<td>$n$</td>
<td>2.34</td>
</tr>
<tr>
<td>$\alpha_{O_2,\text{rh}}$</td>
<td>$1.56 \times 10^{-6}$ mol/L.mmHg</td>
</tr>
<tr>
<td>$\alpha_{NO,\text{rh}}$</td>
<td>$2.58 \times 10^{-6}$ mol/L.mmHg</td>
</tr>
<tr>
<td>$\alpha_{O_2,\text{pl}}$</td>
<td>$1.3 \times 10^{-6}$ mol/L.mmHg</td>
</tr>
<tr>
<td>$\alpha_{NO,\text{pl}}$</td>
<td>$2.15 \times 10^{-6}$ mol/L.mmHg</td>
</tr>
<tr>
<td>$D_{O_2}$</td>
<td>$9.5 \times 10^{-6}$ cm$^2$/s</td>
</tr>
<tr>
<td>$D_{NO_2}$</td>
<td>$3.5 \times 10^{-5}$ cm$^2$/s</td>
</tr>
<tr>
<td>$D_{O_2,\text{pl}}$</td>
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</tr>
<tr>
<td>$D_{NO_2,\text{pl}}$</td>
<td>$4.79 \times 10^{-5}$ cm$^2$/s</td>
</tr>
<tr>
<td>$D_{O_2,\text{membrane}}$</td>
<td>$0.727 \times 10^{-5}$ cm$^2$/s</td>
</tr>
<tr>
<td>$D_{NO_2,\text{membrane}}$</td>
<td>$0.4 \times 10^{-5}$ cm$^2$/s</td>
</tr>
<tr>
<td>$V_c$</td>
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</tr>
<tr>
<td>$D_{O_2,\text{DHb}}$</td>
<td>$40$ Torr$^{-1}$ min$^{-1}$</td>
</tr>
<tr>
<td>$D_{NO_2,\text{DHb}}$</td>
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</tr>
<tr>
<td>$P_{r,O_2}$</td>
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</tr>
<tr>
<td>$Hb_T$</td>
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</tr>
<tr>
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</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>$b$</td>
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</tr>
<tr>
<td>$Sh_i$</td>
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</tr>
<tr>
<td>$L$</td>
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</tr>
<tr>
<td>Slip</td>
<td>0.1</td>
</tr>
<tr>
<td>$\tau$</td>
<td>1 s</td>
</tr>
<tr>
<td>$\mu$</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>1.28</td>
</tr>
<tr>
<td>$N_{\text{sh, total}}$</td>
<td>6</td>
</tr>
</tbody>
</table>

a dominant role leading to a significant decrease in the O$_2$ saturation. Fig. 7 also shows that at a NO level of 203 ppm, O$_2$ saturation dips below 88%, which is the critical value below which a patient should be given long term oxygen therapy (LTOT) (ATS standards for LTOT 2005).

Fig. 8 presents a simulation of the oxygen therapy, in which the patient is given 100% pure O$_2$ so that all compartments in the lungs receive the same level of O$_2$ at 650 mm Hg. Supplemental O$_2$ is expected to increase the driving force for mass transfer even at the micro-scale (through scale coupling), thus compensating for its inhibited uptake. This represents the first line of therapy commonly used in methemoglobinemia. The results presented for a zero shunt and a standard 5% shunt show that for NO levels above 271 ppm, O$_2$ saturation will still dip below the critical value of 88% (ATS standards, 2005), despite supplying 100% pure O$_2$. This helps us to stratify

![Fig. 7. Saturation profiles for O$_2$ and NO in the lung (macro-scale) for various intrapulmonary shunt fractions.](image-url)
methemoglobinemia patients into two categories: those having NO levels below 271 ppm will respond to \( \text{O}_2 \) therapy, while those above 271 ppm NO will not and would, therefore, be candidates for antidotal therapy such as administration of methylene blue.

Methylene blue helps in reducing the MetHb back to normal hemoglobin thus facilitating its binding with \( \text{O}_2 \) and increasing \( \text{O}_2 \) uptake. The reaction can be schematically represented as:

\[
\text{MetHb} + \text{Meth-blue(reduced form)} \rightarrow \text{Hb} + \text{meth-blue(oxidised form)}.
\]

A quantitative modeling of methylene blue therapy would have to consider the above reaction in conjunction with Eqs. (36)–(38) and solve the resultant multi-scale model. However, the therapy reaction time-scale (\( \sim \)1 h) is several orders of magnitude higher than that of the binding of NO with Hb (\( \sim \)1 s). Hence, it increases the level of complexity of this multi-scale problem by introducing a further time-scale separation at the lowest (micro) length scale. Thus, the model formulation would be different in several ways from the treatment shown here, and shall be pursued in our future publications.

5. Conclusions

This paper presents a general formulation of a novel multiscale model for simultaneous uptake of two reactive gases in the human lung. We start with the fundamental convection-diffusion-reaction equations for species conservation at each of the three constituent length scales and spatially average these governing equations using the Liapunov–Schmidt method of the classical bifurcation theory to derive low-dimensional multiscale models for pulmonary uptake of two reactive gases. We use our model to quantify hypoxemia in NO induced methemoglobinemia, where the participating gaseous components are \( \text{O}_2 \) and NO.

Our model simulations show how the NO dynamics dominate over \( \text{O}_2 \) uptake at only moderately high levels of NO in the lung due to the faster reaction kinetics of NO with hemoglobin. We find that the \( \text{O}_2 \) saturation in the red blood cell is more sensitive to changes in NO level, and is, therefore, a better metric of the severity of the disease than the \( \text{O}_2 \) partial pressure in the pulmonary vein. Our multiscale simulations of methemoglobinemia and well as that of its \( \text{O}_2 \) therapy enable us to stratify methemoglobinemia patients in three different groups based on their inhaled NO concentration. As shown in Fig. 9, (a) patients with NO levels above 203 ppm suffer from severe fatal hypoxemia, (b) patients with inhaled NO levels below 271 ppm will respond to \( \text{O}_2 \) therapy, (c) patients with above 271 ppm NO will
not respond to O₂ therapy and would, therefore, be candidates for methylene blue therapy. We hope that this work shall help us evolve multiscale methodologies for quantifying other multiscale pulmonary disorders as well as their therapeutic strategies.

Appendix A. Spatial averaging of CDR equations in the meso scale

Here, we present a brief outline of the Liapunov–Schmidt (LS) reduction of the CDR equations of the meso-scale. From Eq. (21), for the ith gaseous component, we have

\[ \frac{1}{\xi} \frac{d}{d\xi} \left( \frac{\xi \partial p_i}{\partial \xi} \right) = Pe_{T,i} \left\{ (1 - h) \left( \frac{\partial p_i}{\partial t} + u \frac{\partial p_i}{\partial z} - \frac{1}{Pe_i} \frac{\partial^2 p_i}{\partial z^2} \right) + h \Theta_{Tbc,i} \left( \left\langle p_i \right\rangle - \left\langle p_{1,Tbc} \right\rangle \right) + h \Theta_{Tbc,i}(p_2 - \left\langle p_{2,Tbc} \right\rangle) \right\} \]

along with boundary conditions,

\[ \left. \frac{\partial p_i}{\partial \xi} \right|_{\xi=1} = Pe_{T,i} \frac{\Theta_{Tbc,m}}{2} (k_i - p_{1,s}), \]

\[ \left. \frac{\partial p_i}{\partial \xi} \right|_{\xi=0} = 0, \]

where \( p_{1,s} = p_{1,Tbc} \). We introduce the following definitions of average partial pressure and cup-mixing partial pressure, given by

\[ \left\langle p_i \right\rangle (z, t) = \frac{\int_0^1 p_i(z, \xi, t) 2\xi d\xi}{\int_0^1 2\xi d\xi}, \] (A.1)

\[ p_{i,m} = \frac{\int_0^1 p_i(z, \xi, t) u(\xi) 2\xi d\xi}{\int_0^1 u(\xi) 2\xi d\xi}, \] (A.2)

respectively, where the non-dimensional velocity has the usual parabolic profile for fully developed flow, as mentioned in Eq. (19). We write both pressure and velocity in terms of these newly defined quantities, as

\[ p_{i,pl} = \left\langle p_i \right\rangle (z, t) + p_i'(\xi, z, t), \] (A.3)

\[ u = \langle u \rangle + u'(\xi), \] (A.4)

where \( \left\langle p_i \right\rangle \) and \( \langle u \rangle \) are transverse averages and \( p_i' \) and \( u' \) are fluctuations about the average. The fluctuations satisfy the solvability criterion given by

\[ \int_0^1 p_i' 2\xi d\xi = 0, \] (A.5)

\[ \int_0^1 u' 2\xi d\xi = 0. \] (A.6)

Plugging these into Eq. (A.2), and using the solvability criterion gives

\[ p_{i,m} = \left\langle p_i \right\rangle (\langle u \rangle + \langle p_i' u' \rangle). \] (A.7)

We note that \( \langle u \rangle = 1 \), and then proceed to spatially average Eq. (21) over the cross section of the capillary, which gives

\[ Pe_{T,i} \Theta_{Tbc,m}(k_i - p_{1,s}) = Pe_{T,i} \left\{ (1 - h) \left( \frac{d}{dt} \left\langle p_i \right\rangle + d_{p_i,m} \frac{dp_i}{dz} - \frac{1}{Pe_i} \frac{d^2 p_i}{dz^2} \right) + h \Theta_{Tbc,i1} \left( \left\langle p_i \right\rangle - \left\langle p_{1,Tbc} \right\rangle \right) + h \Theta_{Tbc,i2} \left( \left\langle p_{2} \right\rangle - \left\langle p_{2,Tbc} \right\rangle \right) \right\}. \] (A.8)

Using Eqs. (A.3)–(A.6) in Eq. (21), and subtracting the result from Eq. (A.8), we obtain

\[ \frac{1}{\xi} \frac{d}{d\xi} \left( \xi \frac{\partial p_i}{\partial \xi} \right) = Pe_{T,i} \left[ \Theta_{Tbc,m}(k_i - p_{1,s}) - (1 - h) \left( \frac{dp_{i,m}}{dz} \frac{dp_i}{dz} - \frac{dp_i}{dz} \frac{d\xi}{dz} \right) + \frac{1}{Pe_i} \frac{d^2 p_i}{dz^2} \right] \]

\[ + h \Theta_{Tbc,i1} \left( \left\langle p_i \right\rangle - \left\langle p_{1,Tbc} \right\rangle \right) + h \Theta_{Tbc,i2} \left( \left\langle p_{2} \right\rangle - \left\langle p_{2,Tbc} \right\rangle \right). \] (A.9)

Assuming steady state and considerably high axial Peclet number \( Pe_T \approx 10^4 \), please refer to Section 2.2) allows us to neglect the axial diffusion terms and further simplify Eqs. (A.8) and (A.9). The simplified form of Eq. (A.8) is given by

\[ (1 - h) \frac{dp_{i,m}}{dz} = \Theta_{Tbc,m}(k_i - p_{1,s}) - h \Theta_{Tbc,i1} \left( \left\langle p_i \right\rangle - \left\langle p_{1,Tbc} \right\rangle \right) - h \Theta_{Tbc,i2} \left( \left\langle p_{2} \right\rangle - \left\langle p_{2,Tbc} \right\rangle \right), \]
which was introduced as the global evolution equation in Eq. (24), while the simplified form of Eq. (A.9) is given as

$$\frac{1}{\zeta} \frac{d}{dz} \left( \frac{\nu p_{m}}{\zeta} \right) = Pe_{T,i} \left[ \Theta_{i,m}(k_{i} - p_{i,s}) - (1 - h) \left( \frac{dp_{i,m}}{dz} - w(t) \frac{dp_{i,z}}{dz} \right) \right] + h \Theta_{i,2}(p_{1} - \langle p_{1,1} \rangle) + h \Theta_{i,1}(p_{2} - \langle p_{2,1} \rangle).$$

(A.10)

The Liapunov–Schmidt technique consists of solving Eq. (A.10) for $p_{i}^{\prime}(\zeta, z, t)$ by expanding it in powers of the transverse Peclet Number $Pe_{T,i}$, as

$$p_{i}^{\prime} = \sum_{j=1}^{\infty} (Pe_{T,i})^{j}C_{j},$$

(A.11)

and retaining only the first order terms, which have been shown to be sufficient for qualitative and quantitative accuracy for small values of $Pe_{T}$ (Chakraborty & Balakotaiah, 2002) [For this system, $Pe_{T} \sim 10^{-4}$]. Once we calculate $p_{i}^{\prime}$, we make use of Eq. (A.7) to obtain the relationship between the modes as

$$p_{i,m} = \langle p_{1} \rangle - Pe_{T,i} \left[ \frac{\Theta_{i,m}(k_{i} - p_{i,s}) + (1 - h) \frac{dp_{i,m}}{dz}}{24} \right],$$

which is Eq. (22). Similarly, using Eq. (22), we can solve for $p_{i,s}$. The equations thus obtained are called the local equations. A more thorough discussion of this process may be found in Chakraborty and Balakotaiah (2002, 2005).

**Appendix B. Diffusing capacities and spatial averaging in the micro-scale**

In this section, we present the detailed derivation for the expressions for the diffusing capacities presented in Section 3.1. We develop the expressions directly for the particular reaction kinetics of O2 and NO binding with Hb. To simplify the notation, we use the subscripts 1, 2 and 3 to denote saturations of species HbO2, MetHb and HbNO, respectively, and $p_{1}$ and $p_{2}$ to denote $p_{1,1}$ and $p_{2,1}$, respectively. Assuming that the reactions presented in Eqs. (36)–(38) are elementary, the equilibrium relations in terms of fractional saturations can be written as

$$K_{1} = \frac{S_{1}}{S_{1}b_{1}a^{m}_{1}},$$

(B.1)

$$K_{2} = \frac{S_{2}}{S_{2}b_{2}a^{m}_{2}},$$

(B.2)

$$K_{3} = \frac{S_{3}}{S_{3}b_{3}a^{m}_{3}}.$$

(B.3)

Using the constraint equation that says that the total Hemoglobin in the system (free + bound) is constant, we have

$$S_{1} + S_{2} + S_{3} + S_{ib} = 1.$$  

(B.4)

Solving these above equations, we have the fractional saturations as

$$S_{1} = \frac{K_{1}a^{m}_{1}p_{1}^{n}}{1 + K_{1}a^{m}_{1}p_{1}^{n} + K_{2}a^{m}_{2}p_{1}^{n} + K_{3}a^{m}_{3}p_{1}^{n} + K_{3}a_{2}p_{2}},$$

(B.5)

$$S_{2} = \frac{K_{1}K_{2}a_{2}p_{2}}{1 + K_{1}a^{m}_{1}p_{1}^{n} + K_{2}a_{2}p_{1}^{n} + K_{3}a_{2}p_{2}},$$

(B.6)

$$S_{3} = \frac{K_{3}a_{2}p_{2}^{n}}{1 + K_{1}a_{2}p_{1}^{n} + K_{1}K_{2}a_{2}p_{1}^{n} + K_{3}a_{2}p_{2}},$$

(B.7)

The dissociation constants, as mentioned in Section 2.1, represent the slopes of the equilibrium saturation curves and are obtained by differentiation as

$$\beta_{11} = \frac{\partial S_{1}}{\partial p_{1}^{\prime}} = \frac{K_{1}a^{m}_{1}(1 + K_{3}a_{2}p_{2})p_{1}^{n-1}}{(1 + K_{1}a^{m}_{1}p_{1}^{n} + K_{2}a^{m}_{2}p_{1}^{n} + K_{3}a_{2}p_{2})},$$

(B.8)

$$\beta_{12} = \frac{\partial S_{1}}{\partial p_{2}^{\prime}} = \frac{-K_{1}a^{m}_{1}(K_{3}a_{2} + K_{1}K_{2}a_{2}p_{2})p_{1}^{n-1}}{(1 + K_{1}a^{m}_{1}p_{1}^{n} + K_{2}a^{m}_{2}p_{1}^{n} + K_{3}a_{2}p_{2})^{2}},$$

(B.9)

$$\beta_{21} = \frac{\partial S_{2}}{\partial p_{1}^{\prime}} = \frac{K_{1}K_{2}a^{m}_{1}p_{1}^{n}p_{2}^{n-1}}{(1 + K_{1}a^{m}_{1}p_{1}^{n} + K_{2}a^{m}_{2}p_{1}^{n} + K_{3}a_{2}p_{2})},$$

(B.10)

$$\beta_{22} = \frac{\partial S_{2}}{\partial p_{2}^{\prime}} = \frac{K_{1}K_{2}a^{m}_{1}(1 + K_{3}a_{2}p_{2})p_{1}^{n-1}}{(1 + K_{1}a^{m}_{1}p_{1}^{n} + K_{2}a^{m}_{2}p_{1}^{n} + K_{3}a_{2}p_{2})^{2}},$$

(B.11)
\[
\beta_{31} = \frac{\partial S_1}{\partial P_2} = -\frac{K_3 \alpha_3 \beta_3 (K_1 \alpha_1^2 + K_1 K_2 \alpha_2 \beta_2 + \eta P_n^{n-1})}{(1 + K_1 \alpha_1^2 P_n^{n-1} + K_1 K_2 \alpha_2 \alpha_1^2 \beta_2 + K_1 \alpha_2\beta_2)^2},
\]

(B.12)

\[
\beta_{32} = \frac{\partial S_1}{\partial P_2} = \frac{K_3 \alpha_3 (1 + K_1 \alpha_1^2 P_n^{n-1})}{(1 + K_1 \alpha_1^2 P_n^{n-1} + K_1 K_2 \alpha_2 \alpha_1^2 \beta_2 + K_1 \alpha_2\beta_2)^2}.
\]

(B.13)

Thus, time derivatives in Eqs. (40)–(44) can be written in terms of \(\beta_{ij}\) as

\[
\frac{dS_1}{dt} = \frac{\partial S_1}{\partial P_{1,\text{rbc}}} \frac{dP_1}{dt} + \frac{\partial S_1}{\partial P_{2,\text{rbc}}} \frac{dP_2}{dt} = \beta_{11} \frac{dP_{1,\text{rbc}}}{dt} + \beta_{12} \frac{dP_{2,\text{rbc}}}{dt},
\]

(B.14)

and then the reaction rate terms are eliminated from Eqs. (40)–(44) to obtain

\[
\frac{dP_1}{dt} = G_{11} \nabla^2 P_1 + G_{12} \nabla^2 P_2,
\]

(B.15)

\[
\frac{dP_2}{dt} = G_{21} \nabla^2 P_1 + G_{22} \nabla^2 P_2,
\]

(B.16)

where the coefficients \(G_{11}, G_{12}, G_{21}\) and \(G_{22}\) are given as

\[
\begin{align*}
G_{11} &= D_{11} \alpha_1 \beta_2 + [\text{Hb}]/\alpha_1 [\beta_1, \beta_1, \beta_1, \beta_1] + D_{80} \alpha_1 \beta_1, \\
G_{12} &= [\text{Hb}]/\alpha_1 [\beta_2, \beta_2, \beta_2], \\
G_{21} &= D_{21} \alpha_1 \beta_2 + [\text{Hb}]/\alpha_1 [\beta_1, \beta_1, \beta_1, \beta_1] + D_{80} [\text{Hb}]/\alpha_2 [\beta_1, \beta_2, \beta_2, \beta_2, \beta_2, \beta_2, \beta_2, \beta_2], \\
G_{22} &= D_{22} \alpha_1 \beta_2 + \alpha_1 [\text{Hb}]/\alpha_2 [\beta_1, \beta_2, \beta_2, \beta_2, \beta_2, \beta_2, \beta_2, \beta_2].
\end{align*}
\]

(Eqs. (B.15) and (B.16) are spatially averaged over the volume of the RBC, following the method outlined in Appendix C of Chakraborty et al. (2004), to obtain the averaged equations in the form

\[
\frac{dP_1}{dt} = W_{11} (\langle P_{1,\text{rbc}} \rangle - \langle P_1 \rangle) + W_{12} (\langle P_{2,\text{rbc}} \rangle - \langle P_2 \rangle),
\]

(B.18)

\[
\frac{dP_2}{dt} = W_{21} (\langle P_{1,\text{rbc}} \rangle - \langle P_1 \rangle) + W_{22} (\langle P_{2,\text{rbc}} \rangle - \langle P_2 \rangle),
\]

(B.19)

where the coefficients \(W_{ij}\) are given as

\[
\begin{align*}
W_{11} &= \frac{\eta G_{11}}{\beta(\alpha_1 D_1)(\eta B/S_{H_1})}, \\
W_{12} &= \frac{\eta G_{11}}{\beta(\alpha_2 D_2)(\eta B/S_{H_1})}, \\
W_{21} &= \frac{\eta G_{21}}{\beta(\alpha_1 D_1)(\eta B/S_{H_1})}, \\
W_{22} &= \frac{\eta G_{22}}{\beta(\alpha_2 D_2)(\eta B/S_{H_1})}.
\end{align*}
\]

(B.20)

Multiplying both sides of Eq. (B.18) by \((\alpha_1 + [\text{Hb}]/\beta_1)\) and those of Eq. (B.19) by \(\langle \alpha_2 + [\text{Hb}]/\beta_2, \beta_2 \rangle\) we obtain the final form of the spatially averaged forms as in Eqs. (45) and (46), where the diffusing capacities are given by

\[
\begin{align*}
\Theta_{11} &= (\alpha_1 + [\text{Hb}]/\beta_1) W_{11}, \\
\Theta_{12} &= (\alpha_1 + [\text{Hb}]/\beta_1) W_{12}, \\
\Theta_{21} &= (\alpha_1 + [\text{Hb}]/\beta_2 + \beta_2) W_{21}, \\
\Theta_{22} &= (\alpha_1 + [\text{Hb}]/\beta_2 + \beta_2) W_{22}.
\end{align*}
\]

(B.21)

Plugging in the expressions for \(W_{ij}\)s and \(D_{ij}\)s into the above equation system gives the final expressions for the diffusing capacities.

References


