Micro- and Meso-Scale Analyses for Quantifying Hypoxemia in Methemoglobinemia

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Abstract— Methemoglobinemia is a disease that results from abnormally high levels of methemoglobin (MetHb) in the red blood cell (RBC) caused by simultaneous uptake of oxygen ($O_2$) and nitric oxide (NO) in the human lungs. MetHb is produced in the RBC by irreversible NO-induced oxidation of the oxygen carrying ferrous ion ($Fe^{2+}$) in the heme group of the hemoglobin (Hb) molecule to its non-oxygen binding ferric state ($Fe^{3+}$). In this paper, we study the role of NO in the pathophysiology of methemoglobinemia by performing a multiscale quantitative analysis of the relation between levels of NO inhaled by the patient and the hypoxemia resulting from the disease. Reactions of NO occurring in the RBC with both Hb and oxyhemoglobin are considered in conjunction with the usual reaction between oxygen and Hb to form oxyhemoglobin. Our dynamic simulations of NO and $O_2$ uptake in the RBC and in the plasma in pulmonary capillaries under continuous, simultaneous exposure to both gases reveal that at the end of the pulmonary transit time of 1 s, the oxygen saturation in the RBC equilibrates at 97% in absence of NO but it shows a steady decline to 95% as the concentration of NO increases to 50 ppm. We further show that NO levels of 150 ppm or higher while breathing in room air may be considered to be fatal for methemoglobinemia patients since it causes severe hypoxemia by decreasing the oxygen saturation to below its critical value of 90%. Our analysis shows that the diagnosis of hypoxemia in methemoglobinemia cannot be done by measuring oxygen partial pressures in the patient’s pulmonary artery, but by estimating the oxygen saturation in the patient’s erythrocyte using a standard procedure such as pulse oximetry.

Index Terms—nitric oxide, red blood cells, capillary, methemoglobin anemia, hypoxemia

I. INTRODUCTION

Methemoglobinemia is a disorder characterized by the presence of above-normal levels of methemoglobin (MetHb) in the blood. Methemoglobin is a compound formed from hemoglobin (Hb) by oxidation of iron atom from ferrous to ferric state. MetHb lacks the electron needed to form a bond with oxygen, and hence, is incapable of oxygen transport. Generally, red blood cells (RBCs) are continuously exposed to various oxidant stresses and so MetHb is continually produced in humans. Typically, less than 1 percent of the total circulating hemoglobin in a healthy adult is present in the form of MetHb. However, injury or toxic agents convert a larger proportion of hemoglobin into MetHb. In healthy children, the ferric iron in MetHb is readily reduced to the ferrous state through the action of the cytochrome b5 oxidase enzyme (also referred to as methemoglobin reductase), which is present in erythrocytes and other cells.

In this paper, we focus on micro- and meso-scale modeling of Methemoglobinemia. Our analysis comprises of a rigorous formulation and quantification of the variation of the partial pressure and saturation (in RBC) profiles of $O_2$ and NO caused by convective-diffusive transport in the capillary plasma coupled with diffusive-reactive uptake in the RBC. Continuous exposure of the patient to NO allows the reactions to attain equilibrium, as a result of which the transport of NO through the lung becomes transport-limited. We perform spatial averaging over the volume of the RBC at the micro-scale and over the cross section of the alveolar capillary at the meso-scale using the Liapunov-Schmidt technique of the classical bifurcation theory. The spatially averaged low-dimensional model we obtain is used to quantify the increased Methemoglobin levels inside the RBC, which causes Methemoglobinemia. We also estimate the levels of inhaled NO that could be fatal.

The reactions that occur inside the human RBC in presence of NO and $O_2$ are given by

$$Hb + O_2 \Leftrightarrow Hb(O_2)_n \quad (1)$$

$$HbO_2 + NO \Leftrightarrow MetHb + NO_3^- \quad (2)$$

$$Hb + NO \Leftrightarrow HbNO \quad (3)$$

In eqn. 1, the Oxygen-Hb equilibrium is assumed to follow the Hill equation, where $n$ is the Hill coefficient (=2.37) and the equilibrium rate constant ($K_1$) is given by

$$K_1 = \left( \frac{H}{P_{50}} \right)^n, \quad (4)$$

where $H= 7.4 \times 10^5$ Torr and $P_{50}= 26$ Torr. The reaction rate constant for NO induced oxidation of oxyhemoglobin to MetHb (given by eqn. 2) was calculated by Eich and coworkers [1]. Sheele et al. [2] reported the reaction rate constant for the reaction between NO and deoxyhemoglobin (eqn. 3) as $2 \times 10^7$ M$^{-1}$s$^{-1}$, and also measured the dissociation rate of Nitrosylhemoglobin. The dissociation rate constant of MetHb (in eqn. 2) is obtained to be $2.47 \times 10^5$ s$^{-1}$ [3, 4].

In normal RBCs, MetHb is maintained at a level of less than 1% of total hemoglobin through two MetHb-reducing pathways [5, 6]. One of these systems is the redox cycle consisting of cytochrome b5 (cyt$b5$) and cytochrome b5-metHb reductase (b5R), which uses NADH for electron transfer to cyt$b5$ (“cyt$b5$-NADH system”). The other
pathway uses flavin as an electron carrier for the reduction of MetHb coupled with NADPH oxidation, catalyzed by NADPH-dependent flavin reductase (FR) (“flavin-NADPH system”).

II. MATHEMATICAL MODELING

A. Micro Scale

The 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 by \[7, 8\]

\[
\alpha_2 \frac{\partial P_{O_2,RBC}}{\partial t} = D_2 \alpha_2 \nabla^2 P_{O_2,RBC} - R_1, \quad (5)
\]

\[
[Hb]_T \frac{\partial S_{O_2}}{\partial t} = D_{nb}[Hb]_T \nabla^2 S_{O_2} + R_1 - R_2, \quad (6)
\]

\[
\alpha_{NO} \frac{\partial P_{NO,RBC}}{\partial t} = D_{NO} \alpha_{NO} \nabla^2 P_{NO,RBC} - (R_2 + R_3), \quad (7)
\]

\[
[Hb]_T \frac{\partial S_{MetHb}}{\partial t} = D_{nb}[Hb]_T \nabla^2 S_{MetHb} + R_2, \quad (8)
\]

\[
[Hb]_T \frac{\partial S_{HbNO}}{\partial t} = D_{nb}[Hb]_T \nabla^2 S_{HbNO} + R_3, \quad (9)
\]

where $P_{O_2,rbc}$ is the partial pressure of the physically dissolved gas ‘$i$’ (NO or O2) in the RBC, $S_i$ is the fractional saturation of ‘$j$’ (HbO2, MetHb, or HbNO) in the hemoglobin, $\nabla^2$ is the three dimensional Laplacian in the local coordinate in the RBC, $D_i$ and $D_{nb}$ are the diffusion coefficients of gases ‘$i$’ and hemoglobin, respectively, inside the RBC, $R_i$ is the net rate of conversion for corresponding reaction for the compound ‘$j$’, $[Hb]_T$ is the total intracellular hemoglobin (free + bound), and $a_i$ is the solubility of gas ‘$i$’ in the RBC. The uptake rate of oxygen depends on the alveolar partial pressure of oxygen, $P_{A,O_2}$, which is typically around 100-110 Torr at STP.

We perform spatial averaging of the above equations over the volume of a single RBC using the Liapunov-Schmidt based spatial-averaging method $[7, 8]$. Due to space constraints, we skip the detailed derivation and presentation of the final models we obtained for the micro- and meso-scales. Post-spatial averaging, the micro-scale model for simultaneous reactive uptake of O2 and NO in RBC is obtained as

\[
(\alpha_1 + [Hb]_T \beta_1) \frac{\partial P_{O_2}}{\partial t} = \Theta_{11}[P_{i,O_2} - P_{RBc,O2}] + \Theta_{12}[P_{i,NO} - P_{RBc,NO}], \quad (10)
\]

\[
(\alpha_2 + [Hb]_T (\beta_2 + \beta_3)) \frac{\partial P_{NO}}{\partial t} = \Theta_{21}[P_{i,O_2} - P_{RBc,O2}] + \Theta_{22}[P_{i,NO} - P_{RBc,NO}], \quad (11)
\]

where $\beta_j = \frac{\partial S_j}{\partial P_{j,rbc}}$, $a_i$ is the solubility of gas ‘$i$’ in the RBC, and $P_{i,RBC}$ and $P_{i,pl}$ are the spatially averaged partial pressures of gas ‘$i$’ in the RBC and the plasma, respectively. The quantity $\Theta_i$ is called ‘Diffusing Capacity’ $[7]$, which represents the reaction-altered mass transport coefficient of gas ‘$i$’ under the driving force of gas ‘$j$’ in the presence of simultaneous reaction and molecular diffusion.

The expressions for $\Theta_i (i=1,2)$ have been derived to be

\[
\Theta_{11} = \frac{(a_1 + \beta_1)[Hb]_T}{b(a_2 D_{/\eta_1} + b/b_{/\eta_1})} G_{11}, \quad (12)
\]

\[
\Theta_{12} = \frac{(a_1 + \beta_1)[Hb]_T}{b(a_2 D_{/\eta_1} + b/b_{/\eta_1})} G_{12}, \quad (13)
\]

\[
\Theta_{21} = \frac{(a_2 + \beta_2 + \beta_3)[Hb]_T}{b(a_2 D_{/\eta_1} + b/b_{/\eta_1})} G_{21}, \quad (14)
\]

\[
\Theta_{22} = \frac{(a_2 + \beta_2 + \beta_3)[Hb]_T}{b(a_2 D_{/\eta_2} + b/b_{/\eta_2})} G_{22}, \quad (15)
\]

where $\eta_i$ is a mass transfer coefficient of gas ‘$i$’ in the plasma boundary layer surrounding the RBC $[7]$ and $G_j$ is a function of $\beta_j$ (slope of the saturation curve).

B. Meso Scale

Our meso-scale analysis is essentially a study of O2 and NO profiles along a representative pulmonary capillary. The mass transport in the capillary is governed 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, $P_{pl,i}$, 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. The overall global convection-diffusion-reaction (CDR) equations for gas transport in the plasma are given by

For O2:

\[
(1-h) \left( \frac{\partial C_{pl,O_2}}{\partial t} + v_{pl}(r,x) \frac{\partial C_{pl,O_2}}{\partial x} + R_p C_{pl,O_2} \right) + h \Theta_{11} \left( P_{pl,O_2} - P_{RBc,O2} \right) + h \Theta_{12} \left( P_{pl,NO} - P_{RBc,NO} \right) = (1-h) D_{pl,O_2} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_{pl,O_2}}{\partial r} \right) + \frac{\partial^2 C_{pl,O_2}}{\partial x^2} \right], \quad (16)
\]

For NO:

\[
(1-h) \left( \frac{\partial C_{pl,NO}}{\partial t} + v_{pl}(r,x) \frac{\partial C_{pl,NO}}{\partial x} + R_p C_{pl,NO} \right) + h \Theta_{21} \left( P_{pl,O_2} - P_{RBc,O2} \right) + h \Theta_{22} \left( P_{pl,NO} - P_{RBc,NO} \right) = (1-h) D_{pl,NO} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial C_{pl,NO}}{\partial r} \right) + \frac{\partial^2 C_{pl,NO}}{\partial x^2} \right], \quad (17)
\]

where $h$ is the hematocrit (volume fraction of RBC in blood), $C_{pl,i}$ and $D_{pl,i}$ are the concentration and effective diffusivity, respectively, of the gas $i$ in plasma phase and $v_{pl}$ is the velocity profile of blood in the capillary. The above model is subject to the following boundary conditions:
\[
\frac{2}{a} (1-h) \frac{\partial C_{pl,i}}{\partial r} = \frac{D_{M,i}}{V_e} (P_{A,i} - P_{pl,i} |_{r=a}),
\]
\[
\frac{\partial C_{pl,i}}{\partial r} = 0,
\]
where \(D_{M,i}\) is the membrane diffusive capacity of gas \(i\), \(V_e\) is the capillary bed volume and \(a\) is the capillary radius. The meso-scale CDR equations (eqns. 17-19) are subjected to Liapunov-Schmidt spatial averaging over the radius of the pulmonary capillary in order to reduce the dimensionality of the model and the computational effort required to solve it. Subsequently, we employ the assumptions of no reaction occurring in the plasma, and a parabolic laminar velocity profile within the capillary, and non-dimensionalize the spatially-averaged steady-state equation system. On doing so, we obtain two global equations given by eqn. (20a) (which are ODEs) and four local equations (two for each gas) given by eqn. (20b) (which are algebraic in nature). Thus, the meso-scale model given by eqn. (20) is a set of Differential Algebraic Equations (DAEs), which must be solved in conjunction with the Eulerian form of the dimensional micro-scale equations (eqn. 21).

**Meso-scale Global Equations:**

\[
(1-h) \frac{dp_{1,m}}{dz} = \Theta_{1,m} (1-p_{1,s}) - h \Theta_{rbc,11} (p_{1,pl} - p_{1,rbc}),
\]
\[
- h \Theta_{rbc,12} (p_{2,pl} - p_{2,rbc}),
\]
\[
(1-h) \frac{dp_{2,m}}{dz} = \Theta_{2,m} (k-p_{2,s}) - h \Theta_{rbc,21} (p_{2,pl} - p_{2,rbc}),
\]
\[
- h \Theta_{rbc,22} (p_{2,pl} - p_{2,rbc}),
\]

**Meso-scale Local Equations:**

\[
p_{1,m} = p_1 - Pe_{T,1} \left\{ \Theta_{1,m} (1-p_{1,s}) + \frac{(1-h) dp_{1,m}}{48} \right\},
\]
\[
p_{2,m} = p_2 - Pe_{T,2} \left\{ \Theta_{2,m} (k-p_{2,s}) + \frac{(1-h) dp_{2,m}}{48} \right\},
\]
\[
p_{1,s} = p_1 + \frac{Pe_{T,1}}{24} \left\{ 3 \Theta_{1,m} (1-p_{1,s}) + (1-h) \frac{dp_{1,m}}{dz} \right\},
\]
\[
p_{2,s} = p_2 + \frac{Pe_{T,2}}{24} \left\{ 3 \Theta_{2,m} (k-p_{2,s}) + (1-h) \frac{dp_{2,m}}{dz} \right\},
\]

**Micro-scale Equations:**

\[
\left( \frac{\alpha_1 + [Hb]_f \beta_1}{\tau} \right) \frac{dp_{rbc,1}}{dz} \frac{\partial p_{rbc,1}}{\partial r} = \Theta_{12} \left\{ \frac{p_1 - p_{rbc,1}}{\partial r} \right\},
\]
\[
\left\{ \alpha_2 + [Hb]_f (\beta_2 + \beta_{32}) \right\} \frac{dp_{rbc,2}}{dz} \frac{\partial p_{rbc,2}}{\partial r} = \Theta_{21} \left\{ \frac{p_1 - p_{rbc,1}}{\partial r} \right\} + \Theta_{22} \left\{ \frac{p_1 - p_{rbc,1}}{\partial r} \right\},
\]

where \(p_{1,s}\) is the cup-mixing partial pressure, \(p_{1,s}\) is the steady-state pressure at the capillary-membrane interface, \(p_{1,pl}\) and \(p_{1,rbc}\) are the spatially averaged dimensionless partial pressures of gas ‘\(i\)’ in the RBC and the plasma, respectively. The quantities \(\Theta_{12}\) and \(\Theta_{21}\) are the non-dimensional diffusion capacities of the micro-scale and the capillary membrane, respectively, while \(Pe_T\) is the transverse Peclet Number in the pulmonary capillary. \(Pe_T\) usually has a value \(\sim 10^4\), which justifies the use of a low-dimensional description, both qualitatively and quantitatively [8]. The parameter \(k\) is the ratio between the alveolar partial pressures of Oxygen and Nitric Oxide, and is of the order of \(10^6\) in this analysis.

**C. Solution of Coupled Micro and Meso Scale**

The coupled two-scale DAE system results in an ill-conditioned matrix that is hard to handle, even with standard tools such as MATLAB. So, we exploit the linear independency of the modes in the meso-scale local equations (eqn. 20b) to convert the system of DAEs into a system of 4 coupled ODEs that describe the coupled two-scale process in terms of partial pressure in the RBC (which is representative of the micro-scale) and cup-mixing partial pressure in the plasma (which is representative of the meso-scale). This set of coupled ODEs is given by

\[
X_1 \frac{dp_{1,m}}{dz} + Y_1 \frac{dp_{2,m}}{dz} = Z_1,
\]
\[
X_2 \frac{dp_{1,m}}{dz} + Y_2 \frac{dp_{2,m}}{dz} = Z_2,
\]

where

\[
X_1 = 1 + \frac{3Pe_{T,1}}{8B_1} \Theta_{1,m} + h \Theta_{rbc,11} \left\{ \frac{Pe_{T,1}}{8B_1} \Theta_{1,m} + \frac{\Theta_{1,m} Pe_{T,1}^2}{192B_1} \right\},
\]
\[
Y_1 = h \Theta_{rbc,12} \left\{ \frac{Pe_{T,2} + \Theta_{1,m} Pe_{T,1}^2}{8B_2} + \frac{192B_1}{192B_1} \right\},
\]
\[
Z_1 = \Theta_{1,m} \left\{ \frac{6 p_{1,m} + \Theta_{1,m} Pe_{T,1}}{B_1} \right\} - \Theta_{rbc,11} \left\{ \frac{3 p_{1,m} (8 + \Theta_{1,m} Pe_{T,1}) + \Theta_{1,m} Pe_{T,1}^2 - p_{rbc,1}}{4B_1} \right\} + \Theta_{rbc,12} \left\{ \frac{3 p_{2,m} (8 + \Theta_{1,m} Pe_{T,1}) + k \Theta_{2,m} Pe_{T,1}^2 - p_{rbc,2}}{4B_1} \right\},
\]
\[
X_2 = h \Theta_{rbc,11} \left\{ \frac{Pe_{T,1}^2 + \Theta_{1,m} Pe_{T,1}^2}{8B_1} + \frac{192B_1}{192B_1} \right\},
\]
\[
Y_2 = 1 + \frac{3Pe_{T,2}}{8B_1} \Theta_{2,m} + h \Theta_{rbc,12} \left\{ \frac{Pe_{T,2} + \Theta_{1,m} Pe_{T,1}^2}{8B_2} + \frac{192B_1}{192B_1} \right\},
\]

where

\[
B_1 = (6 + Pe_{T,1}\Theta_{1,m}) \text{ and } B_2 = (6 + Pe_{T,2}\Theta_{1,m}),
\]
and the presence of the small parameter \(k\) (=10^6) (as well as in the
The axial diffusion time \( \tau = 1 \text{ s} \) introduces a large difference of magnitude between the micro- and meso scales.

The solution of the system of ODEs (eqn. 22-26) was performed using MATLAB. The mass matrix being extremely stiff and ill-conditioned due to the large difference in variable values at the two scales, appropriate stiff solvers were employed.

The value of \( K_1 = 3.4 \times 10^9 \text{ s}^{-1} \), and that for NO has been found to be \( \alpha \approx 10^{-7} \text{ cm}^2 \text{ s}^{-1} \).

We use deoxygenated blood with an oxygen partial pressure of 40 Torr in the RBC, 42 Torr in the plasma and \( S_{\text{HbO}_2} = 75\% \text{ as initial conditions for our simulation. Figure } 1 \text{ shows the profile for the total NO saturation in the RBC, } S_{\text{NO}} = S_{\text{MetHb}} + S_{\text{SHbNO}} \text{ along the length of the pulmonary capillary. The steady state is attained at 20\% of the total capillary length.}

Figures 2(a) and 2(b) show the individual saturations (along the capillary) of the two components of reacted NO in the hemoglobin, namely Nitrosylhemoglobin (\( \text{HbNO} \)) and Methemoglobin (\( \text{MetHb} \)), respectively. As discussed before, the level of \( \text{MetHb} \) in normal hemoglobin is known to be 1\%. However, it may observed from Fig. 2(b) that as the concentration of NO in the RBC increases, \( \text{MetHb} \) saturation increases significantly to about 6\% (in the critical case), leading to the onset of methemoglobinemia.

The value of \( D_{\text{MetHb}} \) is based on literature [7].

The value for the diffusivity of oxygen in membranes has been found to be \( 0.727 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1} \) and that for NO has been estimated at \( 0.4 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1} \) [14].

We may note that the differences at the capillary and RBC levels are related more to the disparity in characteristic time scales rather than that of the length scales. All the three reactions are extremely fast (as indicated by the reaction rate constants provided below). Next to reaction, radial diffusion has the shortest time scale (approximately 1000 s) is significantly larger than the rest of the time scales. All the three reacti ons are extremely fast (as indicated by the reaction rate constants provided below).
Fig. 1. Profiles of (a) $S_{HbO_2}$ and (b) $S_{NO}$ inside RBC (along the capillary length) for different values of alveolar NO concentration ($P_{A,NO}$).

Fig. 2. Profiles of (a) $S_{HbNO}$ and (b) $S_{MetHb}$ inside RBC along the capillary length for different values of alveolar NO concentration ($P_{A,NO}$).

Figures 3(a) and 3(b) present the variation of the partial pressures of Oxygen in the RBC and the plasma, respectively, along the capillary length for different values of alveolar NO concentration. We note that for both the micro- and meso-scales, steady states are attained at around 20% of the capillary distance for an alveolar pressure of 110 mmHg. Thus, the oxygen partial pressure in the RBC and plasma are not significantly affected by changes in alveolar concentration of NO but oxygen saturation is strongly dependent on it, as is evident from Fig. 1(a). It may also be noted that the partial pressure of Oxygen inside the RBC always remains slightly lower than that inside the plasma so that a diffusional gradient exists until equilibrium is attained. Though intuitively obvious, we shall soon see that this does not hold true for Nitric Oxide.

Figures 4(a) and 4(b) show the profiles of the partial pressures of Nitric Oxide at the meso (capillary) and micro (RBC) scale. A close look at the magnitudes at which equilibration occurs shows that the pressure inside the RBC, though initially lower steadies at a slightly higher value than that in the plasma. This could be attributed to the interesting dynamics of convection, diffusion and reaction that the two scales with widely differing time-scales are locked into.

The system of equations that were obtained and solved takes into account the three reactions (1), (2) and (3) that describe the kinetic interaction of Nitric Oxide and Oxygen with Hemoglobin in the RBC. For NO concentration above 150 ppm, the patient needs to be treated with methylene blue, which works as a cofactor for the enzyme NADPH-hemoglobin reductase that helps in rapid conversion of MetHb back to Hb. In that case, the kinetic model would include one more reaction (in addition to eqns. 1-3) given by

$$\text{MetHb} + \text{MetHb} - \text{reductase(red.)} \rightleftharpoons \text{Hb} + \text{MetHb(ox.)},$$

and the CDR model (eqn. 5-9) and the subsequent spatially-averaged low-dimensional analyses would have to be
modified accordingly. The dynamics of the therapy of methemoglobinemia using a similar multiscale approach shall be examined in our future publications.

IV. CONCLUSIONS

In order to quantify hypoxemia in methemoglobinemia, we start with the fundamental convection-diffusion-reaction equations and derive a coupled two (micro-meso) scale model for coupled reactive transport of nitric oxide and oxygen in the red blood cell and the pulmonary capillary. The rate equations for reactions of NO with oxy- and deoxy-hemoglobin are developed and incorporated in the diffusion-reaction model. The three-dimensional model equations both at the micro and at the meso scales are spatially averaged using the Liapunov-Schmidt technique of the classical bifurcation theory to obtain low-dimensional models that include analytical expressions for O₂ and NO diffusing capacities in the RBC for the case of continuous exposure to these gases.

The numerical solution of our coupled two-scale model shows that for NO concentration above 150 ppm, oxygen saturation falls below the critical limit of 90% required for the human body to function. Thus, we find that an alveolar NO concentration of 150ppm or higher in methemoglobinemia patients would be fatal, if not provided with immediate therapy. We also find that while oxygen partial pressures in both the RBC and plasma are seen to be extremely weak functions of the alveolar NO levels, the oxygen saturation is significantly and often fatally affected. Thus, our model simulations reveal that the diagnosis of hypoxemia in methemoglobinemia cannot be done by measuring oxygen partial pressures in the patient’s pulmonary artery but by measuring the oxygen saturation in the patient’s erythrocyte using pulse oximetry. Further, we briefly discuss the commonly-used therapeutic approach for methemoglobinemia and outline the changes that need to be incorporated in our kinetic and transport models to quantify the dynamics of the therapeutic process using this multiscale analysis.

Fig.4. Profiles of (a) P_{RBC,NO}(inside RBC) and (b) P_{PA,NO} along the capillary for different values of alveolar NO concentration (P_{ALVEOLAR}).

REFERENCES