

Convection-Diffusion Model Based on Variational Finite Element Method for the Estimation of Oxygen Transport in Biological Tissues

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Abstract: A mathematical model has been established to study O_2 transport in the biological tissues. The formulation of the model is based on transient convection-diffusion oxygen transport uptake and the variational finite element method has been employed to analyse the role of O_2 diffusion process in the tissues. From the estimation, it has been observed that the counter-current flow of oxygen occurs near the arteriole end and venule end of a capillary and convection-diffusion process plays a greater effect in tissue surrounding the middle of the capillary. The results obtained may be helpful in understanding the problems associated with oxygen distribution in the biological systems.

Keywords: *Oxygen; diffusion; microcirculation, pore pressure.* **AMS Classification** (2010): *92Bxx;92B05;97Mxx;92C50*

Introduction

It has been observed that many tumour diseases in animal species develop due to the abnormality in the transport of oxygen at microcirculation level. Mathematical models can help in knowing the oxygen distribution behaviour to such type of solid tumours. The mechanism of oxygen transport can be well understood through the theoretical models and is extremely difficult at the empirical level as it has to be carried out at a micron level.

The study of various theoretical, experimental and numerical studies of oxygen transport have been proposed during the last few decades. The main emphasis of these studies is to simulate the oxygen transport models for better clinical results. But, it is extremely difficult to propose such a model as it would involve more parameters to make it difficult for realistic outcomes.

In this direction Krogh's model [1] was a first attempt to study the oxygen transport to the tissues through the microcirculation. With the advent of this model, more realistic models began to study the role of oxygen transport to the tissues [2, 3].

A one dimensional spherical type of models have been fairly discussed by Crank[28]. Spherical symmetric form of the steady state diffusion equation has been employed

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for modelling oxygen concentration in ovarian follicles by Godsen et al [25]. Sharan et al [29] claimed that oxygen transport to the tissues is mainly transported through radial diffusion process. They further analysed that oxygen accumulation in tissues is more with first order metabolic rate. Sharan et al [19] have considered a two layer model for studying the effect of plasma layer on the delivery of oxygen to a tissue. The prediction of oxygen consumption under the conditions of high oxygen demand in skeletal muscles has been studied by Mcguire et al [7]. They studied oxygen transport from capillaries to exercising tissue muscles by Krogh type cylindrical model. Simpson [23] has considered a similar type of formulation with Michaelis-Menten type oxygen uptake. Khanday and his co-workers [8, 9, 20, 30] also studied the diffusion of heat and mass in the biological tissues particularly in dermal regions and in multi-layered human head. The most recent works in this area have been studied by Khanday et al [26, 27, 31] by using Variational Finite Element Methods.

Different numerical models have been developed in the last few decades to effectively study the oxygen transport by incorporating more and more realistic parameters [4, 5, 6, 10]. The effect of fibre size and type on the heterogeneity of oxygen distribution was studied by Liu [11]. Sharma and Jain [12] have studied time dependent model for oxygen transport to the peripheral nerves. The role of arterioles and venules in the transport of oxygen to the tissues have also been studied to understand how they carry and liberate oxygen to the surrounding tissues [13, 15]. From the literature survey, we can say that the oxygen has the ability to move from capillary to the tissues under the influence of oxygen tension gradient [17, 18, 21]

The present study deals with a mathematical coupled model with convection-diffusion, molecular diffusion and pore pressure for the transport of oxygen to the tissues. A suitable approach (FEM) for the solution of the coupled model has been discussed in this study.

General assumptions and Mathematical formulation

A mathematical formulation for studying the oxygen transport mechanism from capillaries to tissues is based on the following general assumptions:

General assumptions

- The domain of study (capillary bed surrounded by tissues) is assumed to be isotropic and uniform.
- The fluid seepage obeys Darcy's law.

- Mass diffusion (convection diffusion and molecular diffusion) obeys Fick's laws.
- The circulatory system is assumed to be thermodynamically homeostatic.
- The oxygen diffused to plasma is instantaneously replenished by dissociation of oxygen from RBC's.
- RBC's membrane act as a negligible barrier to the transport of oxygen to the plasma.
- Hb concentration remains constant throughout the diffusion of oxygen to the tissues.

Figure 1: Schematic diagram showing different layers along with nodal points and concentrations

The mass conservation of oxygen in microcirculation is given by [16, 28]

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial r} \left(D \frac{\partial C}{\partial r} \right) - \frac{\partial}{\partial r} (CV) + S \quad (1)$$

where the first term on the right side of equation (1) represents oxygen uptake based on diffusion and second term represents oxygen uptake by convection, V is seepage velocity ($V = k \frac{\partial P}{\partial r}$), $C(r, t)$ concentration of oxygen, D is the diffusion coefficient and S is the source or sink of oxygen.

Also, the governing equation for fluid seepage is given by [16] $\frac{\partial}{\partial r} \left(K \frac{\partial P}{\partial r} \right) = \beta n \frac{\partial P}{\partial t} + W \quad (2)$

where, W is source or sink of a fluid, n is porosity, K is permeability constant, βn is the compressibility coefficient of tissue fluid and P is the pore pressure.

Hb Saturation

Oxygen in blood is carried mainly by haemoglobin molecules and a little percentage in dissolved form. The governing relationship between oxygen partial pressure and fractional saturation of Hb solution with oxygen (S_{O_2}) is given by Hill's equation [16] as

$$S_{O_2} = \frac{(P_{O_2}/P_{50})^m}{1 + (P_{O_2}/P_{50})^m} \quad (3) \text{ where } P_{O_2} \text{ is the partial pressure of oxygen, } P_{50} = 27.2 \text{ mmHg is the partial}$$

pressure of oxygen when the solution is half saturated and m is the Hill's exponent. The average difference between the partial pressure at the arteriole end and the venule end of a capillary is about 55 mmHg . Therefore, the concentration of oxygen in the capillary can be estimated at any time with the help of following relationship

$$C = 1.39S_{O_2}\phi\chi + \alpha(1-\phi)P_{O_2} \quad (4)$$

where $\phi = 0.45$ is the volume concentration of RBC's, $\chi = 0.25$ is the volume concentration of Hb in an RBC and α is the solubility of oxygen in plasma.

Oxygen exchange

The oxygen molecules bound to Hb diffuse into the plasma through the RBC membrane which then passes through the capillary wall into the tissues. The difference in the O_2 concentrations in plasma and tissues drives the oxygen molecules towards the tissues. Therefore, the oxygen concentration can be calculated at any time through the following process .

Assume that oxygen concentration decreases at a rate of $\delta C(r, t_0)$, where t_0 is the initial time, therefore, at time $t = t_1$,

$$C(r, t_1) = C(r, t_0) - \delta C(r, t_0) \quad (5)$$

During this time, we assume that partial pressure decreases from $P_{O_2}(r, t_0)$ to $P_{O_2}(r, t_1)$. Therefore, by equation (4), we have

$$C(r, t_1) = 1.39S_{O_2}P_{O_2}(r, t_0)\phi\chi + \alpha(1-\phi)P_{O_2}(r, t_1) \quad (6)$$

From the general assumptions (5) and (6), the oxygen partial pressure at t_1 rebalances instantaneously and let it be $P'_{O_2}(r, t_0)$. Therefore, we also have

$$C(r, t_1) = 1.39S_{O_2}P'_{O_2}(r, t_0)\phi\chi + \alpha(1-\phi)P'_{O_2}(r, t_1) \quad (7)$$

Combining equations (5) and (6), we can find the value of $P'_{O_2}(r, t_1)$.

Source and sink of oxygen

The source and sink of oxygen is essential in the analysis of oxygen transport models. The density and oxygen consumption rate are two important factors. The normal consumption rate of oxygen in tissues is taken as $5.38 \times 10^{-5} \text{ mlO}_2 \text{ ml}^{-1} \text{ tissues}^{-1}$ [34]. For example, the consumption rate of oxygen in a tumor cell tissue having density $6.7 \times 10^7 \text{ cells ml}^{-1}$ is $9.38 \times 10^{-5} \text{ mlO}_2 \text{ ml}^{-1} \text{ tissues}^{-1}$ [34].

Solution of the Model

The O_2 distribution and pore pressure along the radial direction in the biological tissues described in the introductory part of the paper can be established by solving equations (1) and (2) using variational finite element method.

Oxygen Distribution

Because of the intricate structure of tissues, the metabolic oxygen requirements are spatially varied and highly heterogeneous. Due to the complex structure and irregular geometry of the tissues, we employ a method that is suitable for such structures. Keeping in view, the flexibility and the position dependent properties of the parameters, it is meaningful to use finite element method (FEM). This method gives better approximations of continuous domains to solve partial differential equations. The governing partial differential equations (1) has been transferred into the variational integrals described in Myers [24] and Khanday and Saxena [20].

The variational integral

$$I = \int F(C, C', r) dr \quad (8)$$

in optimum form is equivalent to the Euler-Lagrange differential equation

$$\frac{\partial F}{\partial C} - \frac{d}{dr} \left(\frac{\partial F}{\partial C'} \right) = 0, C' = \frac{\partial C}{\partial r} \quad (9)$$

On comparing equation (1) with differential equation (9), we arrive at the following variational integral

$$I = \frac{1}{2} \int_{l_0}^{l_2} \left(D \left(\frac{\partial C}{\partial r} \right)^2 + \frac{\partial}{\partial t} C^2 + V \frac{\partial}{\partial r} C^2 + \frac{\partial^2}{\partial r^2} (KP) - 2SC \right) dr \quad (10)$$

Let I_1 and I_2 be the variational integrals of the oxygen concentration over the sub-domains from l_0 to l_1 and l_1 to l_2 respectively. Then the total variation of oxygen concentration in the whole domain is given by

$$I = \sum_{i=1}^2 I_i = I_1 + I_2 \quad (11)$$

The solution $C(r, t)$ of the problem can be approximated by polynomial functions of higher degrees. Since the distances between the layers is of minute length, the use of higher degree shape functions

may not contribute a significant change in the mass diffusion as described by Khanday and Saxena [22, 30]. Therefore, we assume $C^i(r) = Q_i + R_i r$; $i = 0, 1, 2$. (12)

where C^i represents oxygen concentration across the elements formed by the nodal concentrations C_0 , C_1 and C_2 . Optimising equation (11) w.r.t. nodal concentrations and using equation (12), we obtain the optimal values of integrals given by

$$I_1 = \frac{D_1 (C_1 - C_0)^2}{2(l_1 - l_0)} + \dot{C}_1 l_0 \frac{C_1 l_0 - C_0 l_1}{(l_1 - l_0)^2} + \frac{\dot{C}_1 (l_1^2 + l_1 l_0 + l_0^2)(C_1 - C_0)}{3(l_1 - l_0)} \\ + \frac{\dot{C}_1 (l_0 + l_1)(C_0(l_0 + l_1) - 2C_1 l_0)}{2(l_1 - l_0)} + S \frac{(C_1 + C_0)(l_0 - l_1)}{2} \\ + \frac{K_1(P_1 - P_0)(C_1 - C_0)}{2(l_1 - l_0)} \left(\frac{l_1 + l_0}{2} + \frac{C_0 l_1 - C_1 l_0}{l_1 - l_0} \right) \quad (13)$$

$$I_2 = \frac{D_2 (C_2 - C_1)^2}{2(l_2 - l_1)} + \dot{C}_2 l_1 \frac{C_2 l_1 - C_1 l_2}{(l_2 - l_1)^2} + \frac{\dot{C}_2 (l_2^2 + l_1 l_2 + l_1^2)(C_2 - C_1)}{3(l_2 - l_1)} \\ + \frac{\dot{C}_2 (l_1 + l_2)(C_1(l_2 + l_1) - 2C_2 l_1)}{2(l_2 - l_1)} + S \frac{(C_1 + C_2)(l_1 - l_2)}{2} \\ + \frac{K_2(P_2 - P_1)(C_2 - C_1)}{2(l_2 - l_1)} \left(\frac{l_2 + l_1}{2} + \frac{C_1 l_2 - C_2 l_1}{l_2 - l_1} \right) \quad (14)$$

where dot(·) represents the derivative of C with respect to t.

Rearranging the terms of equations (13) and (14), we obtain the following system of algebraic equations $A_1 C_1 + A_2 \dot{C}_1 + A_3 C_2 + A_4 \dot{C}_2 = A_0$ (15) $B_1 C_1 + B_2 C_2 + B_3 \dot{C}_2 = B_0$ (16)

where the coefficients are given in Appendix. Taking the Laplace transform on both sides of equations (15) and (16), we obtain

$$\bar{C}_1 = \frac{A_0 B_2 + \{A_0 B_3 + B_2 A_2 C_0 + B_2 A_4 C_0\}s + \{B_3 A_2 + B_3 A_4\}C_0 s^2}{s\{A_1 B_2 - B_1 A_3 + (A_1 B_3 + B_2 A_2 + B_3 A_4)s + B_3 A_2 s^2\}} \quad (17)$$

$$\bar{C}_2 = \frac{B_0}{s(B_2 + sB_3)} - \frac{B_1}{B_2 + sB_3} \bar{C}_1 \quad (18)$$

Pore Pressure Distribution

The pore pressure at different locations is obtained by transforming the model equation (2) into the variational form. The transformed variational form of the model equation (2) is

$$J = \frac{1}{2} \int_{l_0}^{l_2} \left(K \left(\frac{\partial P}{\partial r} \right)^2 + \beta n \frac{\partial P^2}{\partial t} + 2WP \right) dr \quad (19)$$

The total variation of pore variation at the nodal points is given by

$$J = J_1 + J_2 \quad (20)$$

where J_1 and J_2 represent the variational integral J over the sub-domains l_0 to l_1 and l_1 to l_2 respectively. Optimising the equation (20) over the different layers of the domain of study and assuming the linear variation of the pore pressure across these layers, we obtain the following algebraic equations

$$J_1 = \frac{K_1 (P_1 - P_0)^2}{2 (l_1 - l_0)} + \frac{\beta n}{2} \dot{P}_1 l_0 \frac{P_1 l_0 - P_0 l_1}{(l_1 - l_0)^2} + \frac{\beta n}{2} \frac{\dot{P}_1 (l_1^2 + l_1 l_0 + l_0^2) (P_1 - P_0)}{3(l_1 - l_0)} + \frac{W}{2} (P_0 l_1 - P_1 l_0 + P_1 l_1 - P_0 l_0) \quad (21)$$

$$J_2 = \frac{K_2 (P_2 - P_1)^2}{2 (l_2 - l_1)} + \frac{\beta n}{2} \dot{P}_2 l_1 \frac{P_2 l_1 - P_1 l_2}{(l_2 - l_1)^2} + \frac{\beta n}{2} \frac{\dot{P}_2 (l_2^2 + l_1 l_2 + l_1^2) (P_2 - P_1)}{3(l_2 - l_1)} + \frac{W}{2} (P_1 l_2 - P_2 l_1 + P_2 l_2 - P_1 l_1) \quad (22)$$

Rearranging equations (21) and (22), we get

$$E_1 P_1 + E_2 \dot{P}_1 + E_3 P_2 + E_4 \dot{P}_2 = P_0 \quad (23)$$

$$F_1 C_1 + F_2 P_2 + F_3 \dot{P}_2 = F_0 \quad (24)$$

where the coefficients are given in Appendix. Taking Laplace transform on both sides of equations (23) and (24), we have

$$\bar{P}_1 = \frac{(E_0 F_2 - F_0 F_3) + E_2 F_2 P_1(0)s}{s \{E_1 F_2 - F_1 E_3 + E_2 F_2 s\}} \quad (25)$$

$$\bar{P}_2 = \frac{F_0}{s F_2} - \frac{F_1}{F_2} \bar{P}_1 \quad (26)$$

From equations (17)-(18) and similarly from (25)-(26), the nodal values of O_2 concentration and pore pressure can be estimated by using Laplace inversion formula.

Numerical Solution

The value of initial concentration of oxygen in plasma C_0 is obtained from equation (4). To obtain the values of the oxygen concentrations at the located points, we first solve the equations (25) and (26) for pore pressure. After obtaining the values of P_1 and P_2 , we solve equations (17) and (18) for C_1 and C_2 . Taking the inverse Laplace transform of equations (25) and (26), and using the values of the coefficients, we obtain $P_1 = 0.2643 Ncm^{-2}$ and $P_2 = 0.2473 Ncm^{-2}$. We used Heaviside's method to solve equations (17)-(18), and with the help of inverse Laplace transform and the physiological parameters given in Table-1, the nodal oxygen concentrations obtained are

$$C_1 = -0.007 - 0.012e^{-2.69t} + 0.016e^{0.14t}; t > 0 \quad (27)$$

$$C_2 = \left(-0.0032e^{-0.36t} - 0.0055e^{-3.05t} + 0.007e^{-0.22t} \right) \left(\frac{e^{0.36t} - 1}{0.36} \right); t > 0 \quad (28)$$

Discussion and Conclusion

The diffusion of O_2 in the biological tissues is the main purpose in the formulation of this model. The oxygen transport from the capillaries to the tissues is studied by using Krogh-type of cylindrical model. The goal of the study is to predict the oxygen consumption under the influence of convection-diffusion, molecular diffusion and pore pressure variations. From the numerically calculated values of pore pressure, it seems evident that the pore pressure gradient decreases from capillaries to tissues. The pore pressure also decreases in the direction of blood flow from arteriole to venule side of a capillary as shown in Figure-3. The pore pressure in the tissues surrounding the middle part of the capillaries also decreases. The counter-current flow of oxygen occurs near the arteriole and the venule end of a capillary. To the cells that are far away from the arteriole end, a part of oxygen must return back to the capillary at the arteriole end. During this time there is an abrupt change in the pore pressure gradient and hence the oxygen partly returns back to the capillary through convection-diffusion. The less oxygenated blood in the capillaries is then carried towards the venule end. At this site, tissue has a relatively higher oxygen concentration and thus the oxygen has to partly return to the capillary to be supplied to the tissues farther from the arteriole end.

The tissue oxygen concentration has a little variation in the middle of a capillary. To estimate the change in oxygen concentration in the direction of blood flow, the one dimensional equation (1) in

cartesian coordinates representing the direction of blood flow also has been solved numerically. Figure-4 shows the change in oxygen concentration in the direction of blood flow in the capillary and tissue regions. It is clear from the graph that oxygen concentration reduces abruptly near the arteriole end and almost remains constant thereafter. This is because when the oxygen reaches a capillary bed, it is immediately transported to the tissue and is then supplied to the individual cells uniformly. Figure-2 shows that oxygen concentration in a capillary initially increases and then becomes almost constant within a very short time which may be due to the fact that the oxygen concentration in a capillary is replenished by the break down of oxygen from the haemoglobin in the plasma which closely follows the standard oxygen dissociation curve. Figure-3 shows that oxygen to the tissues is immediately supplied and continuously dependent on the oxygen concentration in the capillary.

Comparison of our model with the previous models

Many researchers have neglected the convection-diffusion of oxygen within both capillaries and tissues [11, 17, 33]. Schuff et al [32] have taken convection diffusion of oxygen within capillaries and neglected it in tissues and have taken fluid seepage velocity in tissues as zero. In the present study, we have taken the fluid seepage in the capillaries as well as in tissues and the results in our case seems to be more realistic than other models. To see the effect of convection diffusion on the oxygen uptake in the radial direction, we have solved the model equation (1) without the convection term and then plotted its graph as shown in Figure-5. It is clear from the graph that uptake of oxygen in presence of convection diffusion is more as compared with the simple molecular diffusion.

The present model leads to the following conclusions

- That convection diffusion is an important factor in the uptake of the oxygen by the tissues.
- The increase in permeability coefficient may have a more convection effect on the transport of the oxygen.
- The oxygen concentration is more by the proposed coupled model than a simple molecular diffusion model.
- The pore pressure gradient decreases along the radial direction and the obvious change occurs at the two ends of a capillary.

The study can be improved further by taking into account conditions like hypoxia, physiological disorders, the role of reversible CO_2 supply and other factors. Further, metabolic rate, non linear oxygen dissociation and other factors may help other researchers to carry out the problems

based on this model. It may also help in understanding the phenomena of oxygen transport in the growth and metastasis of certain tumours.

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Figure 2: Oxygen concentration along the radial direction in the capillary

Figure 3: Oxygen concentration along the radial direction in the tissue

Figure 4: Average oxygen concentration along the direction of blood flow in the capillary and tissue

Figure 5: Variation of mean oxygen concentration along the radial direction in presence and absence of convection diffusion term

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Appendix

$$A_1 = \frac{D_1}{l_1 - l_0} + \frac{D_2}{l_2 - l_1} - \frac{2K_c(P_1 - P_0)l_0}{(l_1 - l_0)^2} - \frac{2K_t(P_2 - P_1)l_2}{(l_2 - l_1)^2} \quad A_2 = \frac{l_0^2}{(l_1 - l_0)^2} + \frac{l_1^2 + l_1l_0 + l_0^2}{3(l_1 - l_0)^2} - \frac{l_0(l_0 + l_1)}{l_1 - l_0}$$

$$A_3 = \frac{D_2}{l_2 - l_1} + \frac{2K_t(P_2 - P_1)(l_2 + l_1)}{(l_2 - l_1)^2}; \quad E_1 = \frac{K_c}{l_1 - l_0} + \frac{K_t}{l_2 - l_1} \quad A_4 = -\frac{l_1l_2}{(l_2 - l_1)^2} - \frac{l_2^2 + l_1l_2 + l_1^2}{3(l_2 - l_1)^2} + \frac{(l_2 + l_1)}{2(l_2 - l_1)}$$

$$A_0 = \frac{DC_0}{l_1 - l_0} - \frac{K_c(P_1 - P_0)}{l_1 - l_0} \left\{ \frac{l_1 + l_0}{2} + \frac{C_0(l_1 + l_0)}{l_1 - l_0} \right\} + \frac{K_t(P_2 - P_1)(l_2 + l_1)}{2(l_2 - l_1)} - \frac{S(l_0 - l_2)}{2} \quad B_1 = A_3; \quad B_2 = \frac{D_2}{l_2 - l_1} - \frac{2K_t(P_2 - P_1)l_1}{(l_2 - l_1)^2}; \quad E_3 = -\frac{K_t}{l_2 - l_1}; \quad F_0 = \frac{W(l_1 - l_2)}{2}$$

$$B_3 = \frac{l_1^2}{(l_2 - l_1)^2} + \frac{l_2^2 + l_1l_2 + l_1^2}{3(l_2 - l_1)^2} - \frac{l_1(l_1 + l_2)}{l_2 - l_1}; \quad F_1 = E_3; \quad F_2 = -E_3$$

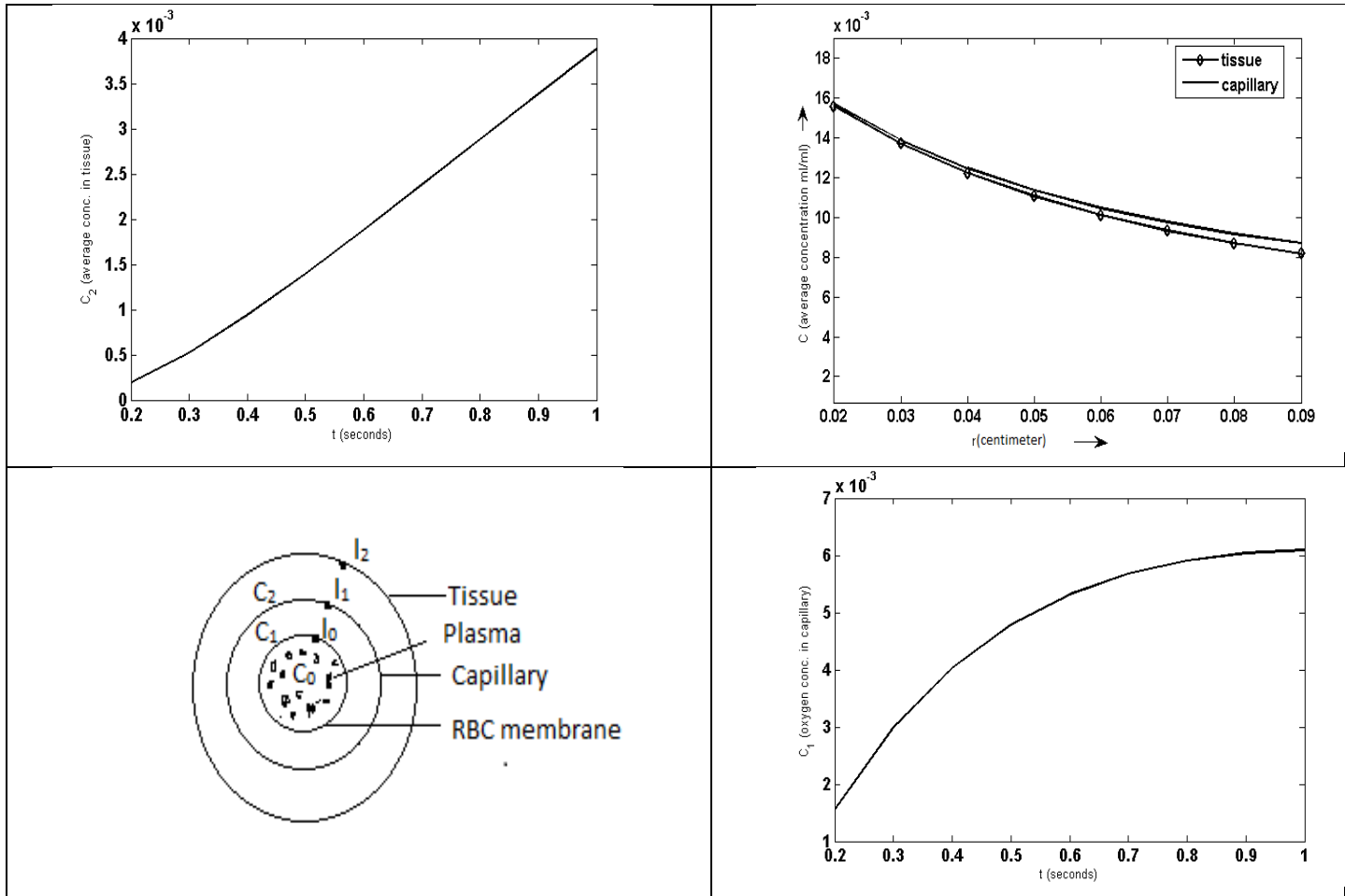
$$B_0 = \frac{K_t(P_2 - P_1)(l_2 + l_1)}{2(l_2 - l_1)} - \frac{S(l_2 - l_1)}{2}; \quad E_2 = \frac{\beta n}{2} \left(\frac{l_0^2}{(l_1 - l_0)^2} + \frac{l_1^2 + l_1l_0 + l_0^2}{3(l_1 - l_0)^2} \right) \quad E_4 = \frac{\beta n}{2} \left(\frac{l_1l_2}{(l_2 - l_1)^2} - \frac{l_2^2 + l_1l_2 + l_1^2}{3(l_2 - l_1)^2} \right); \quad E_0 = \frac{K_cP_0}{l_1 - l_0} + \frac{W(l_0 - l_2)}{2}$$

$$F_3 = \frac{\beta n}{2} \left(\frac{l_1^2}{(l_2 - l_1)^2} + \frac{l_2^2 + l_1l_2 + l_1^2}{3(l_2 - l_1)^2} \right)$$

Parameter	Unit	Value
Diffusion coefficient in capillary (D_1) ^{zi}	cm^2sec^{-1}	.0003
Diffusion coefficient in tissue (D_2) ^{zi}	cm^2sec^{-1}	2×10^{-5}
Permeability coefficient in capillary	$cmsec^{-1}$	.005

$(K_c)^{zi}$		
Permeability coefficient in tissue $(K_t)^{zi}$	$cmsec^{-1}$	8×10^{-6}
Initial pore pressure $(P_0)^{zi}$	Ncm^{-2}	0.26
Compressibility coefficient of tissue fluid $(\beta n)^{zi}$	dimensionless	10^{-7}
Radius of capillary $(l_1)^{sha}$	cm	3.25×10^{-4}
Radius of tissue $(l_2)^{sha}$	cm	3.25×10^{-3}
Exponent in Hill's equation $(m)^{ms}$	dimensionless	2.7
Oxygen solubility of blood at 37^0 , 1 atm $(\alpha)^{zi}$	$mlml^{-1}(atm)^{-1}$	0.023
Initial oxygen concentration (C_0)	ml/ml	0.0016

Table 1: Physiological parameters and their values used in this study



Figures: 2,3,4,5.