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MATHEMATICAL STUDY OF PULMONARY AND INTRAVENOUS ADMINISTRATION OF OXYGEN IN BIOLOGICAL TISSUES UNDER HYPOXIA CONDITIONS

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Abstract: Mathematical modelling of oxygen transport in biological tissues played a great role and provides optimal results for advanced biomedical and biophysical research. Conventionally, oxygen is administered to hypoxic patients through pulmonary route. A mathematical model has been proposed to establish an alternative route for oxygen supply, whereby oxygen is administered directly into the target tissue bypassing the lung compartment. Our study aims at evaluating the feasibility of the novel approach using compartment modelling. The model is represented by a system of first order ordinary differential equations and their solution by Cramer's rule and Laplace transform method. The concentration profiles of oxygen through pulmonary and intravenous routes were estimated in the arterial blood and tissue compartments at different flow rates; and with respect to initial oxygen concentration in the lung compartment and in the injected solution. Our results are in agreement with those arrived at by Lin Gui and Jing Liu (2006) [4]. The method offers a promising alternative to the conventional approach for clinical rescue of hypoxic patients, more so in emergency situations.

Keywords and Phrases: Compartment model, Hypoxia, Laplace transform, Pulmonary Administration, Intravenous Administration.

2020 Mathematics Subject Classification: 92-10, 92BXX, 92CXX.

1. Introduction

Oxygen is indispensable for survival of cell and essential for all human beings. The deficiency of oxygen in tissues, called hypoxia, can cause illness not only to the respiratory system but also can disturb the whole physiological set-up of the body. Being aerobic, humans and other animals fundamentally rely upon oxygen consumption for survival [17]. In association with this fact several abnormalities may emerge putting the life of an individual at stake. The noteworthy of those conditions is *hypoxia* - the state of oxygen deficiency in the tissues [5, 9, 10, 15, 18]. Aerobic respiration, involving oxygen as the final electron acceptor, is extremely efficient than anaerobic respiration. The later, when takes place in the body cells under hypoxia conditions, results in the production of lactic acid which renders the environment too acidic for cells to function properly. Therefore, the survival of hypoxic patients is contingent upon the timely availability of oxygen to the tissues [19]. The most common approach adopted in clinical emergencies for this purpose is to supply supplemental oxygen via breathing (pulmonary) route. However, this approach is beset with many complications especially the delayed delivery of the oxygen to the important organs like brain etc. This provides scope for an alternative efficient route i.e., direct supply of oxygen to the target tissues and organs.

The direct delivery of oxygen to the target tissues and organs may prove to be very effective in those organs and tissues that are highly sensitive to low oxygen levels, such as nervous system (brain and neurons). The prolonged inadequate supply of oxygen to neurons is manifest in several complications, including reduction in the level or complete halting of metabolism in neurons, gradual accumulation of poisonous intermediates in brain and even death of the patient [12, 13]. In view of these serious complications arising in face of oxygen deficiency, the timely supply and maintenance of adequate levels of oxygen in the target tissues is of prime importance for the clinical rescue of the patient. One novel technical route proposed for direct supply of oxygen to the target tissues involves direct injection of a solution with high oxygen content [4]. The proposers of this technique developed a simulated model to check the feasibility of the approach. They devised oxygen transport model equation in line with Pennes bio-heat equation to evaluate the feasibility of the proposed approach of oxygen delivery and used finite difference method to solve the model equations.

Oxygen is known to play an important role in cellular respiration. Both oxidation and other forms of energy production depend on a continuous supply of oxygen to the cells. It has been verified by Nunn [15] that a human being consumes about 260 millilitre of oxygen per minute under normal conditions. Oxygen is transported from the atmospheric air into the lungs, and carried by the arterial blood through

circulation to the tissues, where it is utilized mainly within the mitochondria [5, 7, 8, 18]. Tissue is considered metabolically very active and is sensitive to hypoxia conditions. In view of that, the subject assumes considerable importance in order to understand the intricacies proper supply of oxygen to the living tissues for research and other clinical purposes. Our study aims at employing compartment modelling for the evaluation of the above mentioned approach of oxygen delivery to the tissues, whereby oxygen is administered directly into the target tissue bypassing the lung compartment. The model is represented by a system of first order ordinary differential equations (ODEs) and their solution by Cramer's rule and Laplace transform method.

2. Mathematical Model and Solution

A mathematical model has been formulated with the help of three physiologically meaningful compartments. The first compartment corresponds to lungs, the second is identified with the arterial blood and the third compartment describes the ultimate processing compartment, the tissue. The three compartments are interconnected and, the distribution of oxygen is assumed to take place between the compartments.

In the present study, we considers two routes through which oxygen can be administered into the biological tissue of the human body and hence, the tissues where its utilization takes place. One, oxygen normally reaches the tissues via pulmonary route i.e., from lungs via arterial blood into the tissues. Second, oxygen can be administered into the target tissue through intravenous injection bypassing the first compartment, the lungs. The schematic representation of the compartment model is shown in Figure 1.

2.1. Pulmonary Administration (*p.a*)

The mathematical form of the compartment model describing pulmonary administration of oxygen is given by the following system of ordinary differential equations of first order:

$$\frac{dC_1(t)}{dt} = a_{31}C_3(t) - a_{12}C_1(t); \qquad C_1(0) = \mu \tag{1}$$

$$\frac{dC_2(t)}{dt} = a_{12}C_1(t) - S; \qquad C_2(0) = \rho \tag{2}$$

$$\frac{dC_3(t)}{dt} = -a_{31}C_3(t) + S; \qquad C_3(0) = p_0 \tag{3}$$

Equations (1), (2) and (3) describes, respectively, the arterial blood compartment, the tissue compartment and the lung compartment in case of pulmonary administration. The parameters a_{31} and a_{12} denotes, respectively, the flow rate of O_2 from

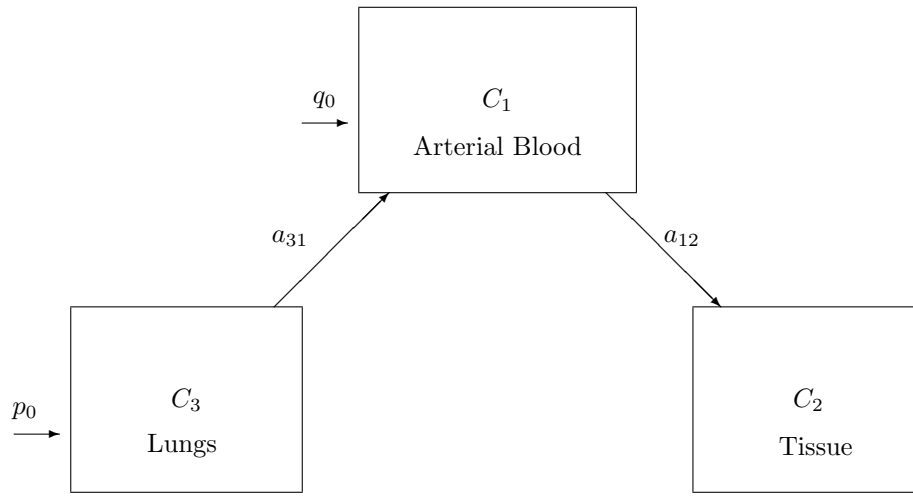

Figure 1: General scheme of the compartment model.

lung compartment to arterial blood compartment and from arterial blood compartment to tissue compartment and $C_3(0) = p_0$ is the initial oxygen concentration in the lungs. The parameter S represents the source term or sink term. It represents source term with plus sign i.e., $+S$ and sink term with minus sign i.e., $-S$. The source and sink are assumed to be constant. The constants μ and ρ are oxygen concentrations in the blood and tissue compartments at $t = 0$, respectively.

The solution to any initial value problem can be obtained using standard methods such as algebraic transformation of the equation, separation of variables, eigenvalue method, Laplace transform, Fourier transform etc. [1, 3, 11, 16]. We use Laplace transform method to solve the model Equations (1)- (3). The pulmonary and intravenous administration model equations have a solution on $[0, \infty)$ that is well behaved (i.e., bounded at any finite time and continuous for $t > 0$) and unique [1, 3, 16].

Re-write Equations (1) - (3) in matrix form as:

$$P'(t) = \frac{dP(t)}{dt} = MP(t) + b(t), \qquad P(0) = P_0 \tag{4}$$

where $M = \begin{bmatrix} -a_{12} & 0 & a_{31} \\ a_{12} & 0 & 0 \\ 0 & 0 & -a_{31} \end{bmatrix}$, $P(t) = \begin{bmatrix} C_1(t) \\ C_2(t) \\ C_3(t) \end{bmatrix}$, $b(t) = b = \begin{bmatrix} 0 \\ -S \\ S \end{bmatrix}$ and $P_0 = \begin{bmatrix} \mu \\ \rho \\ p_0 \end{bmatrix}$

Applying Laplace transform to Equation (4):

$$\mathscr{L}\{P'(t)\} = \mathscr{L}\{MP(t) + b\} \;\Leftrightarrow\; s\mathscr{L}\{P(t)\} - P(0) = M\mathscr{L}\{P(t)\} + \mathscr{L}\{b\}$$
$$\Leftrightarrow \quad (sI - M)\mathscr{L}\{P(t)\} = P(0) + \frac{1}{s}b \qquad \Leftrightarrow \quad A(s)\mathscr{L}\{P(t)\} = X(s) \tag{5}$$

$$\text{where} \quad A(s) = (sI - M) = \begin{bmatrix} s + a_{12} & 0 & -a_{31} \\ -a_{12} & s & 0 \\ 0 & 0 & s + a_{31} \end{bmatrix}, \text{ and } \; X(s) = \begin{bmatrix} \mu \\ -\frac{S}{s} + \rho \\ \frac{S}{s} + p_0 \end{bmatrix}$$

On solving system of Equations (5) by *Cramer's rule* [2], we have

$$\det\big(A(s)\big) = s(s + a_{12})(s + a_{31}) \tag{6}$$

Since $a_{12},\ a_{31}$ are positive real numbers. Therefore, $\det\big(A(s)\big) > 0$ for all $s > 0$.

To find the solution of the lung compartment $C_3(t)$, arterial blood compartment $C_1(t)$ and tissue compartment $C_2(t)$ in case of pulmonary administration, we replace the kth column of the matrix $A(s)$ by the entries of the column matrix

$$X(s) = \begin{bmatrix} \mu \\ -\frac{S}{s} + \rho \\ \frac{S}{s} + p_0 \end{bmatrix}$$

and denote the resulting matrices by $A_k(s),\ k = 1, 2, 3$.

Therefore, we have

$$\begin{aligned}
\mathscr{L}\{C_1(t)\} &= \frac{det\{A_1(s)\}}{det\{A(s)\}} = \frac{(S + sp_0)a_{31}}{s(s + a_{12})(s + a_{31})} + \frac{\mu}{(s + a_{12})} \\
\mathscr{L}\{C_2(t)\} &= \frac{det\{A_2(s)\}}{det\{A(s)\}} = \frac{(S + sp_0)a_{31}a_{12} - S(s + a_{12})(s + a_{31})}{s^2(s + a_{12})(s + a_{31})} + \frac{\mu a_{12}}{s(s + a_{12})} + \frac{\rho}{s} \\
\mathscr{L}\{C_3(t)\} &= \frac{det\{A_3(s)\}}{det\{A(s)\}} = \frac{(S + sp_0)}{s(s + a_{31})}
\end{aligned} \tag{7}$$

Applying inverse Laplace transform to Equations (7) and using *Heaviside's Theorem* [14] which says if P(s) and Q(s) are polynomials where P(s) has degree

less than that of Q(s) and Q(s) has n distinct zeros $\alpha_k,\ k = 1, 2, ...n$, then

$$\mathscr{L}^{-1}\Big\{\frac{P(s)}{Q(s)}\Big\} = \sum_{k=1}^{n} \frac{P(\alpha_k)}{Q'(\alpha_k)} e^{\alpha_k t} \tag{8}$$

We obtain the solution for the arterial blood compartment $C_1(t)$, tissue compartment $C_2(t)$ and lung compartment $C_3(t)$ in case of pulmonary administration $(p.a)$:

$$\begin{aligned} C_1^{p.a}(t) &= \frac{a_{31}}{a_{12}-a_{31}}\Big\{\alpha e^{-a_{12}t} + \beta e^{-a_{31}t}\Big\} + \mu e^{-a_{12}t} + \frac{S}{a_{12}} \\ C_2^{p.a}(t) &= \frac{1}{a_{12}-a_{31}}\Big\{a_{12}\beta(e^{-a_{31}t}-1) - a_{31}\alpha(e^{-a_{12}t}-1)\Big\} \\ &\quad - \mu e^{-a_{12}t} + \rho + \mu \\ C_3^{p.a}(t) &= \frac{S}{a_{31}} - \beta e^{-a_{31}t} \end{aligned} \tag{9}$$

where $\alpha = \dfrac{S - a_{12}p_0}{a_{12}}$ and $\beta = \dfrac{S - a_{31}p_0}{a_{31}}$.

2.2. Intravenous Administration $(i.a)$

In intravenous administration, solution with oxygen content is injected directly into the bloodstream for delivery into the target tissues. This route bypasses the lung compartment of the three-compartment model, which now, therefore, consists of only two compartments: blood and tissue. Therefore, the mathematical form of the compartment model describing an intravenous administration of oxygen is given by the following system of ordinary differential equations of first order:

$$\frac{dC_1(t)}{dt} = -a_{12}C_1(t) + S; \qquad C_1(0) = q_0 \tag{10}$$

$$\frac{dC_2(t)}{dt} = a_{12}C_1(t) - S; \qquad C_2(0) = \rho \tag{11}$$

where $C_1(0) = q_0$ is the initial oxygen concentration of the injected solution.

We write Equations (10)- (11) in matrix form:

$$Q'(t) = M^*Q(t) + b^*(t), \qquad Q(0) = Q_0 \tag{12}$$

where $M^* = \begin{bmatrix} -a_{12} & 0 \\ a_{12} & 0 \end{bmatrix}$, $Q(t) = \begin{bmatrix} C_1(t) \\ C_2(t) \end{bmatrix}$, $b^*(t) = b^* = \begin{bmatrix} S \\ -S \end{bmatrix}$ and $Q_0 = \begin{bmatrix} q_0 \\ \rho \end{bmatrix}$

Applying Laplace transform to Equation (12):

$$A^*(s)\mathscr{L}\{Q(t)\} = Y(s) \tag{13}$$

where $A^*(s) = (sI - M^*) = \begin{bmatrix} s + a_{12} & 0 \\ -a_{12} & s \end{bmatrix}$, and $Y(s) = \begin{bmatrix} \frac{S}{s} + q_0 \\ -\frac{S}{s} + \rho \end{bmatrix}$

Now, $\det\big(A^*(s)\big) = s(s + a_{12}) > 0$ for all $s > 0$. Hence, by similar procedure as we did above in case of pulmonary administration, we obtain by *Cramer's rule* [2]

$$\begin{aligned} \mathscr{L}\{C_1(t)\} &= \frac{det\{A_1^*(s)\}}{det\{A^*(s)\}} = \frac{(S + sq_0)}{s(s + a_{12})} \\ \mathscr{L}\{C_2(t)\} &= \frac{det\{A_2^*(s)\}}{det\{A^*(s)\}} = \frac{(S + sq_0)a_{12} - S(s + a_{12})}{s^2(s + a_{12})} + \frac{\rho}{s} \end{aligned} \tag{14}$$

where $A_1^*(s)$ and $A_2^*(s)$ are, respectively, the matrices obtained by replacing the 1st column of $A^*(s)$ and the 2nd column of $A^*(s)$ by the entries of the column matrix

$$Y(s) = \begin{bmatrix} \frac{S}{s} + q_0 \\ -\frac{S}{s} + \rho \end{bmatrix}$$

Applying inverse Laplace transform to Equations (14) and using *Heaviside's Theorem* [14], we obtain the solution for the blood compartment $C_1(t)$ and tissue compartment $C_2(t)$ in case of an intravenous administration $(i.a)$:

$$\begin{aligned} C_1^{i.a}(t) &= \frac{S}{a_{12}} - \gamma e^{-a_{12}t} \\ C_2^{i.a}(t) &= \gamma(e^{=a_{12}t} - 1) + \rho \end{aligned} \tag{15}$$

where $\gamma = \dfrac{S - a_{12}q_0}{a_{12}}$.

3. Results and Discussion

Respiration has an indispensable role in the growth and survival of an organism. Oxygen is one of the fundamental components employed in the process of respiration; it acts as terminal electron acceptor in the process of ATP synthesis. Human body receives oxygen from the atmosphere through respiratory system

composed chiefly of a pair of lungs. Oxygen enters the alveoli (air sacs) of the lungs through inspiration, from where it diffuses into the bloodstream across the wall of the pulmonary capillaries apposed to the alveolar membrane. The oxygen is then carried by hemoglobin in the bloodstream and finally delivered to tissues for use in respiratory metabolism. Humans are obligatory aerobic, thus, making the tissues sensitive to low supply of oxygen.

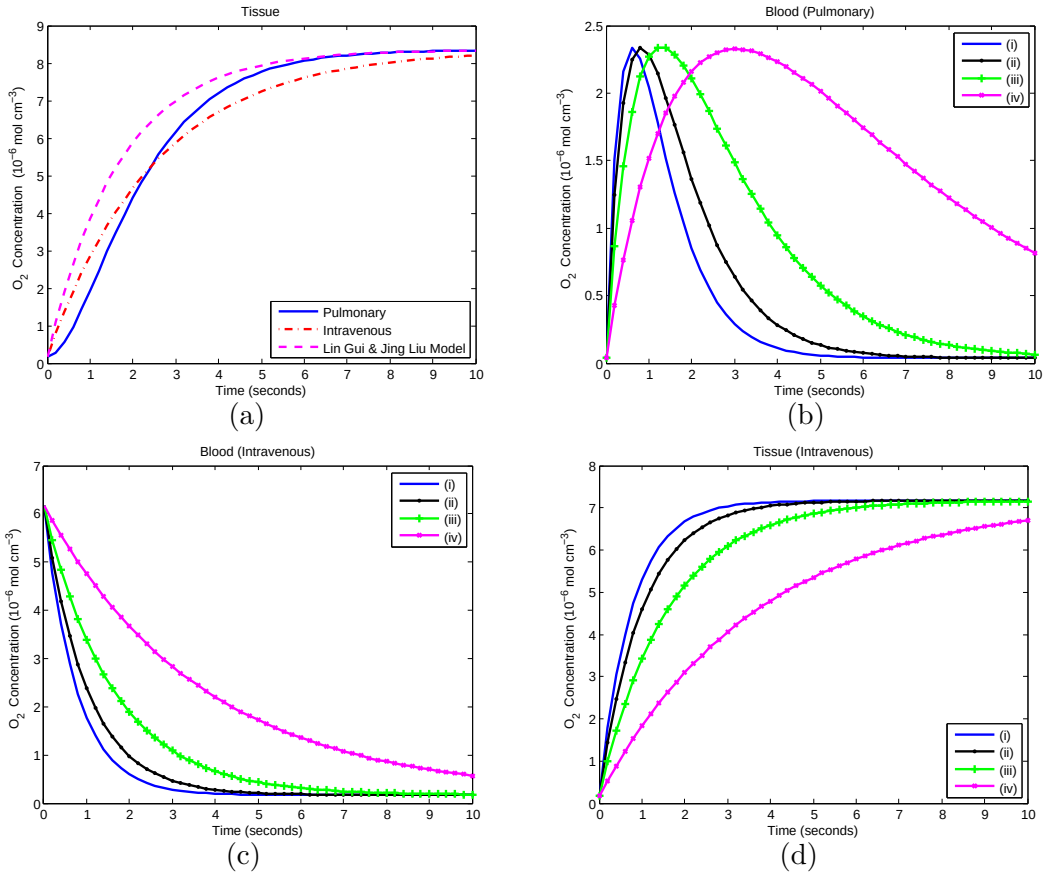

Figure 2: (a) Comparison of oxygen concentration in the tissue compartment, (b) Temporal variation of pulmonary administration of oxygen concentration in the arterial blood compartment, (c) Temporal variation of intravenous administration of oxygen concentration in the arterial blood compartment, (d) Temporal variation of intravenous administration of oxygen concentration in the Tissue compartment at rates $/sec : (i) = \{a_{31} = 1.98,\ a_{12} = 1.32\},\ (ii) = \{a_{31} = 1.5,\ a_{12} = 1.0\},\ (iii) = \{a_{31} = 0.975,\ a_{12} = 0.625\}$ and $(iv) = \{a_{31} = 0.4,\ a_{12} = 0.27\}$ with $p_0 = q_0 = 5 \times 10^{-6}\ mol\ cm^{-3}$.

In view of the fundamental role played by oxygen in human body, it is important to understand the factors and processes governing the transport and supply of oxygen in the body. The conditions that alter the supply of oxygen in the tissues, especially hypoxia, therefore, assumes considerable attention. In the present study, compartment model has been established in order to evaluate the feasibility of the direct oxygen delivery method in rescue operations of hypoxic patients. The results of the study are depicted in the graphs shown in Figure 2. The numerical value of the parameter S is taken to be $3.8 \times 10^{-4} cm^3\ O_2/cm^3/sec$ [6].

A comparison is shown in Figure 2a between the pulmonary and intravenous administration of oxygen in the tissue compartment. In Figure 2a, the feasibility of intravenous administration of O_2 in relation to its pulmonary administration is portrayed. The cross comparison of the two methods of O_2 administration showed different results at same rates. Intravenous administration yielded steep rise in O_2 concentration in tissues compared to pulmonary administration of oxygen. The results attest to the feasibility of intravenous administration of O_2 in situations of clinical emergency when immediate supply of O_2 to the tissues is required.

Figure 2b represents the usual pulmonary administration of oxygen to the hypoxia patient. The resulting bell-shaped curve shows a steep rise in O_2 concentration inside the arterial blood compartment followed by its steep decline. The former trend relates to the delivery of oxygen from lungs into the arterial blood, while the latter corresponds to the combination of free oxygen with hemoglobin forming oxy-hemoglobin, which carries the oxygen to the target tissue, hence resulting in decline of O_2 concentration in the arterial blood compartment.

Figure 2c represents the newly proposed approach of direct injection of solution with high O_2 content into the target tissue, thereby omitting the lung compartment. As a result of direct injection, O_2 concentration rapidly builds up inside the arterial blood compartment which then delivers oxygen into the target tissue as oxy-hemoglobin, thus resulting in steep decline in the O_2 content in the arterial blood compartment. Corresponding to decline in the O_2 concentration in the arterial blood compartment, the tissue compartment (target tissue under hypoxic condition) shows gradual increase in the oxygen concentration, as depicted in Figure 2d. The graph is in conformation with the results arrived at by Lin Gui and Jing Liu (2006) [4], attesting to the credibility of our results. Our model does not consider the effect of temperature of the injected solution on the results. However, it has been estimated that the results show variation in response to difference in the temperatures of the oxygen-loaded solution [4]. It has been found that the use of cooling solution is more effective in decreasing O_2 consumption rate thereby ensuring prolonged availability of O_2 in the tissues [4].

Further, the results depicted in the graphs (Figure 2) highlight the effect of flow rates on the outcome of the oxygen delivery. It is clear that higher the value of flow rates, more rapid is the delivery of oxygen to the target tissues, and hence greater chances of clinical rescue of the patient.

4. Conclusion

A three-compartment model of oxygen transport in biological tissues under hypoxia conditions was developed. The aim of this study was to evaluate the feasibility of oxygen delivery to the tissues of the hypoxic patients. The model was represented by a system of first order ordinary differential equations and their solution by Cramer's rule and Laplace transform method. From the above discussion,, it follows that the direct delivery of oxygen (oxygen in solution) provides a viable alternative route to the conventional oxygen supply to the hypoxic patients. The method may be more effective in emergency situations whereby timely availability of oxygen to the tissues under stress is essentially important. The study finds prospects in biomedical engineering and other sciences to deal with respiratory aliments faced by the people living at high altitudes.

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References

[1] Britton N. F., Reactions-diffusion Equations and their Applications to Biology, Academic Press, London, 1986.

[2] David C. Lay, Linear Algebra and its Applications, Pearson Education, Inc., 4th ed. 2012.

[3] Farlow S. J., Partial Differential Equations for Scientists and Engineers, Dover, New York, 1993.

[4] Gui Lin, Liu Jing, Simulation of delivering oxygen directly to the target tissues by injection, International Journal of Thermal Sciences, 45 (2006), 528-535.

[5] Guyton A. C., Hall J. E., Text Book of Medical Physiology, W. B. Saunders, 12th ed., 2011.

[6] Hsu R., Secomb T. W., A green's function method for analysis of oxygen delivery to tissue by microvascular networks, Math. Biosci., 96 (1989), 61-78.

[7] Khanday M. A., Najar A. A., Maclaurin's series approach for the analytical solution of oxygen transport to the biological tissues through capillary bed, Journal of Medical Imaging and Health Informatics, 5, (5) (2015), 959-963.

[8] Khanday M. A., Najar A. A., Mathematical model for the transport of oxygen in the living tissue through capillary bed, Journal of Mechanics in Medicine and Biology, 15, (4) (2015), 1550055.

[9] Lone A. U. H., Khanday M. A., Mathematical analysis of oxygen and carbon dioxide exchange in the human capillary and tissue system, Computer Methods in Biomechanics and Biomedical Engineering, Taylor & Francis: https://doi.org/10.1080/10255842.2022.2053115.

[10] Lone A. U. H., Khanday M. A., Mubarak Saqib, Explicit finite difference method to estimate oxygen concentration in biological tissues under variable oxygen tension in capillaries, Comp and Math Methods, Wiley, 3 (2), e1128 (2021).

[11] Lone A. U. H., Khanday M. A., Mubarak Saqib, A four-compartment model to estimate oxygen and carbon dioxide exchange concentrations via blood using eigenvalue approach, South East Asian J. of Mathematics and Mathematical Sciences, 17 (2), 367-384.

[12] Lv Y. G., Liu J., Effect of dendritic cell structure on enhancing oxygen transport in neuron, Forschung im Ingenieurwesen-Engineering Research, 68 (2004), 155-168.

[13] Michenfelder M. D., Milde J. H., The relationship among canine brain temperature, metabolism, and function during hypothermia, Anesthesiology, 75 (1991), 130-136.

[14] Murray R. Spiegel, Theory and Problems of Laplace Transform, McGraw-Hill, Inc., Ist ed., 1965.

[15] Nunn J. F., Applied Respiratory Physiology, Butterworths, 3rd ed., 2013.

[16] Pinsky M. A., Partial Differential Equations and Boundary-Value Problems with Applications, McGraw-Hill, New York, 1991.

[17] Popel A. S., Theory of oxygen transport to tissue, Crit. Rev. Biomed. Engrg., 17 (1989), 257-321.

[18] Tortora G. J., Derrickson B., Principles of Anattomy and Physiology, John Wiley & Sons, Inc., 13th ed., 2012.

[19] Ye G. F., Jaron D., Buerk D. G., Oxygen-hemoglobin reaction kinetics and the Fahraeus effect during stagnant, hypoxic, and anemic supply deficit, Ann. Biomed. Engrg., 26 (1998), 60-75.