

# A COMPARISON BETWEEN ANALYTICAL AND NUMERICAL SOLUTION OF THE KROGH'S TISSUE CYLINDER MODEL FOR HUMAN BONE MARROW

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## Abstract

*The Danish physiologist, August Krogh is the founder of the theory of oxygen transport to tissues. It was his famous tissue cylinder model developed for skeletal muscle, together with his colleague mathematician Erlang that laid down the foundation of the mathematical modeling of oxygen transport to tissues. Here an analytical solution of the Krogh's model has been presented based on justifiable assumptions in order to validate the numerical approach used to solve more realistic oxygen transport models. The numerical solution of Krogh's model is performed using computational fluid dynamics (CFD) software CFX 4.4. From the analytical solution, it is demonstrated that variation from the numerical result is less than 0.2% which in turn justifies the use of computer software in developing mathematical model for such physiological systems like BM.*

## Introduction

The mathematical modeling of oxygen transport processes in the human bone marrow (BM) is a very important arena of biological systems modeling that offers numerous clinical or medical applications. The BM is the sole site for effective hematopoiesis or blood cell production in the adult human being and oxygen is the principal nutrient for differentiation and proliferation of BM hematopoietic cells. So it is very important to have a better understanding of oxygen tension/concentration ( $pO_2$ ) levels in the BM.

At present, direct *in vivo* measurements of  $pO_2$  are practically impossible in BM and so, detailed modeling is the only available means to provide reasonable estimates. August Krogh's pioneering work of tissue cylinder model is the cornerstone of such mathematical modeling. Due to the physical inaccessibility of the BM, no major study has been undertaken to-date that investigates the effect of oxygen and its distribution within the BM microenvironment. However, several sophisticated models have been developed for other tissues including the brain, muscle, skin and kidney. Although Krogh's model has been the starting point, in general, for all these models, in which the tissue is approximated as a cylinder with a single capillary at its centre, mathematical modeling of  $pO_2$  distribution in the human BM is very different and more challenging to that of other tissues due to the complexity of the vascular structure and the heterogeneity of the tissue region.

The use of numerical method necessitates the verification of the solution obtained and typically the

validation is via experimental results. However, as stated previously, the physical inaccessibility of the human bone marrow has hindered any detailed analysis through experimental methods. Using simplifying, but reasonable assumptions, an analytical solution to the oxygen transport model has been presented here. This in turn has been compared to the numerical solution obtained for the Kroghian model from the CFD software CFX 4.4. The geometry for the Kroghian system is presented in Figure 2, utilized to obtain a numerical solution.

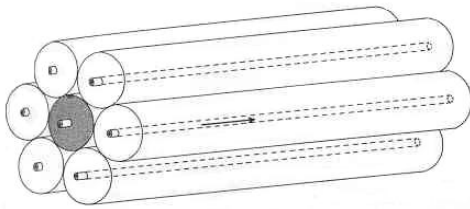
## Krogh's Tissue Cylinder Model

The foundation of the theory of "oxygen transport to tissue" was established by August Krogh, a Danish physiologist, who provided the first insights into the role of the smallest micro vessels in the supply of oxygen to striated or skeletal muscle. Together with his colleague, mathematician Erlang in 1918, Krogh developed the famous mathematical model named 'Krogh's cylinder model', which described how oxygen is delivered by a single capillary of a uniform array of capillaries to a surrounding tissue cylinder<sup>2</sup>. He theorized that the rate of transport is dependent upon the number and distribution of capillaries. In addition, he presumed that the capillaries are the sole supplier of oxygen to blood and each one obtained all of its oxygen by convection (bulk flow) from the terminal arterioles. Each capillary, in turn, served as an independent diffusive source delivering oxygen to a single distinct volume of tissue with homogenous oxygen consumption. Thus, Krogh's model predicted a linear decrease in hemoglobin oxygen content along each capillary<sup>3</sup>. The model also captures the

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longitudinal and radial  $O_2$  gradients within the capillary and surrounding tissue, further providing significant insights into the dynamics of oxygen delivery to the tissues<sup>2</sup>.

The essence of Krogh's model lies in the assumption that the tissue can be subdivided into circular cylindrical units, each of which has a capillary oriented along the axis and the units do not exchange oxygen with each other (Figure 1). In formulating this geometrical model, Krogh had in mind the capillary geometry in skeletal muscle where muscle fibers have a preferential direction and capillaries tend to be oriented along the fibers.



**Fig 1. Geometry of the Krogh's tissue cylinder model<sup>5</sup>.**

The assumptions for formulating an equation governing tissue oxygen transport, are, 1)  $pO_2$  distribution in the tissue cylinder is axisymmetric, 2) the permeability of tissue to oxygen or the Krogh diffusion coefficient,  $K=D\alpha_t$  is independent of spatial position; 3)  $O_2$  in the tissue is not bound to a carrier. Under these assumptions, the equation governing oxygen transport in the tissue can be written in the form<sup>4</sup>

$$\alpha_t \frac{\partial P_t}{\partial t} = K \left[ \frac{1}{r} \frac{\partial}{\partial r} r \frac{\partial P_t}{\partial r} + \frac{\partial^2 P_t}{\partial z^2} \right] - M \quad (1)$$

At the outer boundary of the tissue cylinder the flux of oxygen is zero in accordance with the assumption that adjacent units do not exchange oxygen. Hence

$$\frac{\partial P_t}{\partial r} = 0 \quad \text{at} \quad r = R \quad (2)$$

Krogh further assumed that, 4) a steady state condition (the term  $\partial P_t / \partial t$  in equation 1 is zero), 5) a constant oxygen consumption rate, 6) negligible axial diffusion (the term  $\partial^2 P_t / \partial z^2$  is small)

He did not consider the transport of oxygen in the capillary; rather the  $pO_2$  at the capillary wall was specified:

$$P_t = P_w \quad \text{at} \quad r = R_c \quad (3)$$

The solution of equation 1 with boundary conditions 2 to 3 is

$$P_t = P_w(z) + \frac{M}{4K} (r^2 - R_c^2) - \frac{MR^2}{2K} \ln \frac{r}{R_c} \quad (4)$$

This equation gives the radial distribution of tissue  $pO_2$  in terms of capillary and tissue cylinder radii and tissue permeability. In particular, it permits the calculation of the minimum tissue  $pO_2$ , which occurs at the outer rim of the tissue cylinder, i. e. at  $r=R$ .

### The Oxygen Transport Equation

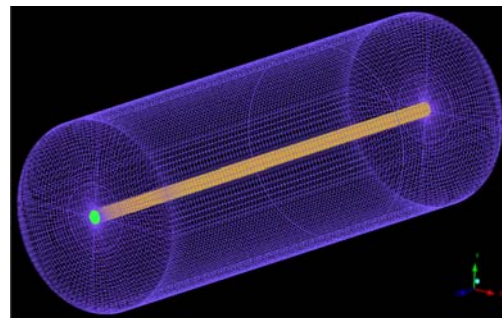
Substance diffusion is an equilibration process in which substance molecules are transferred from loci of higher concentration to ones of lower concentration and this is the basis of oxygen transport in blood. The basic law that is applicable in this study is Fick's second law of diffusion and the Henry-Dalton law, and its application yields the following equation:

$$\alpha \frac{\partial p}{\partial t} = K \cdot \nabla^2 p \quad (5)$$

where  $\alpha$  is the  $O_2$  solubility,  $\partial p / \partial t$  is the change in  $pO_2$  with time and  $\nabla^2$  is the Laplace operator.

In addition to the diffusion processes there are other mechanisms that exert their influence on the local oxygen distribution; these include<sup>1</sup>:

1. Physiological oxygen sink; which may vary with local  $pO_2$  (Michaelis-menten kinetics).
2. Presence of  $O_2$  carrier, hemoglobin (Hb) implies the release or binding of oxygen.
3. This carrier bound  $O_2$  (Hb- $O_2$ ) represents a second oxygen species. The exchange between carrier-bound and free  $O_2$  is quantified via the release rate  $R$ ; which constitutes the link between these equations.
4. Facilitated diffusion enhances free  $O_2$  diffusive transport.
5. Local convection displaces free and Hb- $O_2$  at a rate depending on the velocity vector ( $\mathbf{v}$ ). The change in local  $O_2$  and Hb- $O_2$  concentrations is proportional to the magnitudes of  $\mathbf{v}$  and the concentration gradients.



**Fig 2. Krogh's tissue cylinder.**

Taking into account the above factors, the O<sub>2</sub> transport equation can be written as<sup>1,4</sup>:

$$\alpha_b \left[ \frac{\partial p_b}{\partial t} + \vec{v} \cdot \nabla p_b \right] = \nabla \cdot [K_b \nabla p_b] - R \quad (6)$$

$$H_T \left[ \frac{\partial \gamma}{\partial t} + \vec{v} \cdot \nabla \gamma \right] = \nabla \cdot [H_T D_H \nabla \gamma] + R \quad (7)$$

where R represents the net rate of carrier O<sub>2</sub> release. Under most conditions, it is further possible to reduce the above set of equations to form a single equation under the assumption that the reaction rate described is extremely fast and thus the two states are always in equilibrium. Accordingly, the hemoglobin saturation ( $\gamma$ ) solely depends on the partial pressure (pO<sub>2</sub>). Thus equations 6 and 7 can be reduced to:

$$\alpha_b \left[ \frac{\partial p_b}{\partial t} + \vec{v} \cdot \nabla p_b \right] + H_T \left[ \frac{\partial \gamma}{\partial t} + \vec{v} \cdot \nabla \gamma \right] = \nabla \cdot [K_b \nabla p_b] + \nabla \cdot [H_T D_H \nabla \gamma] \quad (8)$$

Applying the following chain rule, the above equation can be written as

$$\frac{\partial \gamma}{\partial t} = \frac{\partial \gamma}{\partial p_b} \cdot \frac{\partial p_b}{\partial t} = \gamma'(p) \frac{\partial p_b}{\partial t}, \nabla \gamma = \gamma'(p) \nabla p \quad (9)$$

$$\alpha_b \left[ \frac{\partial p_b}{\partial t} + \vec{v} \cdot \nabla p_b \right] + H_T \left[ \gamma'(p) \frac{\partial p_b}{\partial t} + \vec{v} \cdot \gamma'(p) \nabla p_b \right] = \nabla \cdot [K_b \nabla p_b] + \nabla \cdot [H_T D_H \gamma'(p) \nabla p_b] \quad (10)$$

Simplification of the above equation gives

$$\alpha_b \left[ 1 + \frac{H_T}{\alpha_b} \gamma'(p) \right] \left[ \frac{\partial p_b}{\partial t} + \vec{v} \cdot \nabla p_b \right] = \nabla \cdot K_b \left[ 1 + \frac{H_T}{K_b} D_H \gamma'(p) \right] \nabla p_b \quad (11)$$

$$\Rightarrow \alpha_b (1+m) \left[ \frac{\partial p_b}{\partial t} + \vec{v} \cdot \nabla p_b \right] = \nabla \cdot K_b \left[ 1 + \frac{H_T}{K_b} D_H \gamma'(p) \right] \nabla p_b \quad (12)$$

where  $m = \frac{H_T}{\alpha_b} \gamma'(p)$  and  $\gamma'(p)$  is the first derivative

$$\text{of } \gamma(p) = \frac{\left( \frac{p}{p_{50}} \right)^n}{1 + \left( \frac{p}{p_{50}} \right)^n}$$

The term  $K_b (1+m)$  is referred to as effective conductivity  $K_{eff}$ . Hence, the oxygen transport equation for the blood region becomes

$$\alpha_b (1+m) \left[ \frac{\partial p_b}{\partial t} + \vec{v} \cdot \nabla p_b \right] = \nabla \cdot [K_{eff} \nabla p_b] \quad (13)$$

In cylindrical co-ordinates, the above equation can be written as,

$$\alpha_b (1+m) \left[ \frac{\partial p_b}{\partial t} + v \frac{\partial p_b}{\partial z} \right] = K_{eff} \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial p_b}{\partial r} \right) + \frac{\partial^2 p_b}{\partial z^2} \right] \quad (14)$$

Replacing  $K_{eff}$  by  $\alpha_b D_b$  and dividing by  $\alpha_b$ ,

$$(1+m) \left[ \frac{\partial p_b}{\partial t} + v \frac{\partial p_b}{\partial z} \right] = D_b \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial p_b}{\partial r} \right) + \frac{\partial^2 p_b}{\partial z^2} \right] \quad (15)$$

For the tissue region, the O<sub>2</sub> transport eq<sup>n</sup> can be written as

$$\alpha_t \left[ \frac{\partial p_t}{\partial t} \right] = K_t \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial p_t}{\partial r} \right) + \frac{\partial^2 p_t}{\partial z^2} \right] - m_0 \quad (16)$$

where  $m_0$  is the volumetric metabolic oxygen consumption rate of tissue (assumed constant).

After dividing both sides by  $\alpha_b$

$$\left( \frac{\alpha_t}{\alpha_b} \right) \left[ \frac{\partial p_t}{\partial t} \right] = \left( \frac{\alpha_t}{\alpha_b} \right) D_t \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial p_t}{\partial r} \right) + \frac{\partial^2 p_t}{\partial z^2} \right] - \left( \frac{m_0}{\alpha_t} \right) \quad (17)$$

### Boundary Conditions

The boundary conditions needed to solve equations 15 and 16 are as follows:

$$\text{Blood region: } 0 \leq z \leq L \text{ and } 0 \leq r \leq r_c \quad (18)$$

BC 1:  $z=0, p_b = p_b(t)$

BC 2:  $z=L, \partial p_b / \partial z = 0$

BC 3:  $r=0, \partial p_b / \partial r = 0$

$$\text{BC 4: } r = r_c, p_b = p_t \text{ and } D_b \frac{\partial p_b}{\partial r} = \left( \frac{\alpha_t}{\alpha_b} \right) D_t \frac{\partial p_t}{\partial r}$$

$$\text{Tissue region: } 0 \leq z \leq L \text{ and } r_c \leq r \leq r_t \quad (19)$$

BC 5:  $z=0, \partial p_t / \partial z = 0$

BC 6:  $z=L, \partial p_t / \partial z = 0$

BC 7:  $r=r_t, \partial p_t / \partial z = 0$

These two boundary conditions state that oxygen cannot leave the tissue region at either end by axial diffusion.

### Analytical Solution

Solution of the above equations for the oxygen concentrations within the blood and tissue regions is a formidable problem which can be accomplished numerically with the help of computational techniques but, a reasonable analytical solution can be obtained with some simplifications and this was explored by Fournier<sup>6</sup>.

The basic assumptions include, 1) steady-state condition, 2)  $m$  is constant, 3) negligible axial diffusion within the tissue region, 4) within the

capillary, negligible axial diffusion in comparison to axial convection.

Applying these assumptions in equation 15 gives

$$(1+m)v \frac{\partial p_b}{\partial z} = D_b \left( \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial p_b}{\partial r} \right) \right) \quad (20)$$

Radial averaging of the above equation gives

$$2\pi \int_0^{r_c} (1+m)v \frac{\partial p_b}{\partial z} r dr = 2\pi D_b \int_0^{r_c} \frac{1}{r} \left( \frac{\partial}{\partial r} \left( r \frac{\partial p_b}{\partial r} \right) \right) r dr \quad (21)$$

$$\Rightarrow 2\pi(1+m)v \frac{d}{dz} \int_0^{r_c} p_b r dr = 2\pi D_b r_c \left. \frac{\partial p_b}{\partial r} \right|_{r_c} \quad (22)$$

The radially averaged pO<sub>2</sub> level in the blood,  $\langle p_b \rangle$  can be defined as

$$\langle p_b \rangle \pi r_c^2 = 2\pi \int_0^{r_c} p_b r dr \quad (23)$$

This allows equation 22 to be written as

$$(1+m) \frac{\partial \langle p_b \rangle}{\partial z} = \frac{2D_b}{r_c v} \left. \frac{dp_b}{dr} \right|_{r_c} \quad (24)$$

Applying BC 4 in the above equation, we have

$$(1+m) \frac{\partial \langle p_b \rangle}{\partial z} = \frac{2D_t \alpha_t}{r_c v \alpha_b} \left. \frac{dp_t}{dr} \right|_{r_c} \quad (25)$$

The basic assumptions simplifies equation 17 to the following form

$$\frac{d}{dr} \left( r \frac{dp_t}{dr} \right) = \frac{m_0}{\alpha_t D_t} r \quad (26)$$

Integration of the above equation two times followed by application of the boundary conditions 4 and 7 in equations 18 and 19 gives the following result.

$$p_t(r,z) = \langle p_b(z) \rangle - \frac{r_c^2 m_0}{4\alpha_t D_t} \left[ 1 - \left( \frac{r}{r_c} \right)^2 \right] - \frac{r_t^2}{2\alpha_t D_t} \ln \left( \frac{r}{r_c} \right) \quad (27)$$

Equation 27 is the analytical solution of the oxygen concentration equation in the tissue region.

Differentiation of Equation 27 with respect to r at r = r<sub>c</sub> gives the following equation

$$\left. \frac{dp_t}{dr} \right|_{r_c} = \frac{r_c m_0}{2\alpha_t D_t} - \frac{r_t^2 m_0}{2\alpha_t D_t r_c} \quad (28)$$

Using this result in equation 26 gives

$$(1+m) \frac{\partial \langle p_b \rangle}{\partial z} = \frac{2D_t \alpha_t}{r_c v \alpha_b} \left( \frac{r_c m_0}{2\alpha_t D_t} - \frac{r_t^2 m_0}{2\alpha_t D_t r_c} \right) \quad (29)$$

$$\Rightarrow \frac{d \langle p_b \rangle}{dz} = - \frac{m_0}{(1+m)(\alpha_b v)} \left[ \left( \frac{r_t}{r_c} \right)^2 - 1 \right] \quad (30)$$

This equation may be integrated to give the following result,

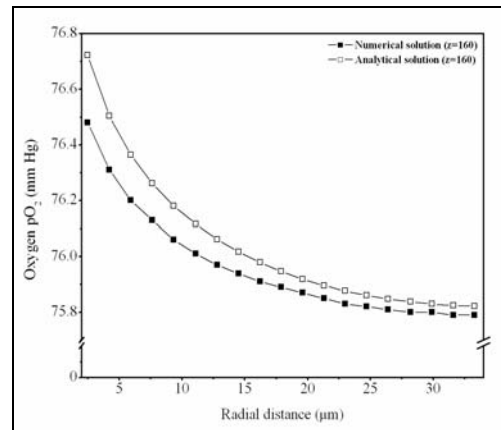
$$\langle p_b(z) \rangle = \langle p_b \rangle_{in} - \frac{m_0}{(1+m)(\alpha_b v)} \left[ \left( \frac{r_t}{r_c} \right)^2 - 1 \right] z \quad (31)$$

Equation 31 is the analytical solution of the oxygen concentration equation in the capillary region.

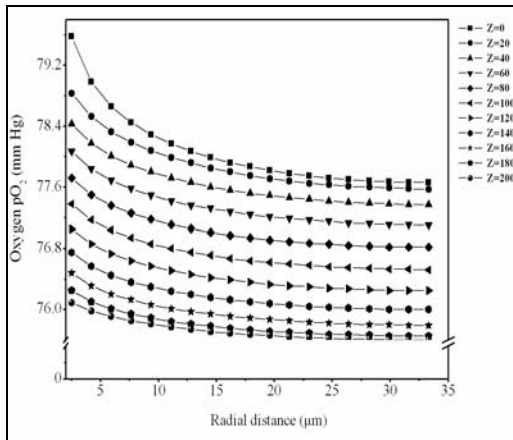
## Results and Analyses

The results obtained by using CFD software CFX 4.4 for the numerical solution of the Kroghian model have been compared with the results of the aforementioned analytical solutions in a view to justify the use of CFX 4.4 for developing more realistic mathematical model of bone marrow<sup>7</sup>.

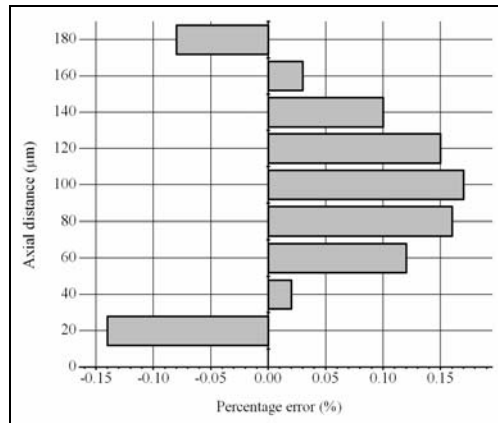
Figure 3 depicts the comparison between analytical and numerical solution for the tissue region at an input oxygen partial pressure of 80 mm Hg and a radial distance of 160 μm in the capillary region. It clearly demonstrates that the oxygen partial pressure gradually decreases with the increase of radial distance in the tissue region, which signifies that the oxygen concentration distant from the supplying region experiences lower oxygen content. This in turn can affect the cellular functions residing in this region, such as granulopoietic cells. The small variation in the partial pressure of oxygen is due to the choice of the lowest consumption rate for the cells (granulocytes).



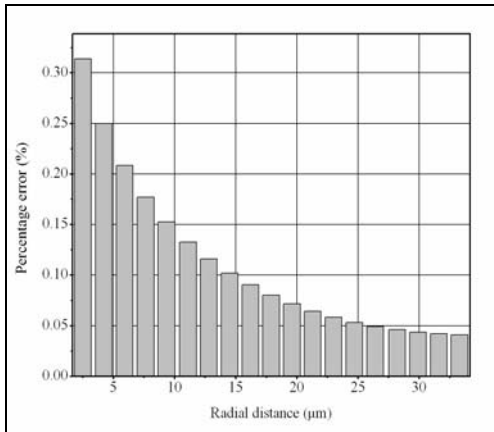
**Fig 3. Plot of numerical vs. analytical solution for tissue region at pO<sub>2</sub> = 80 mm Hg and Z = 160 μm.**



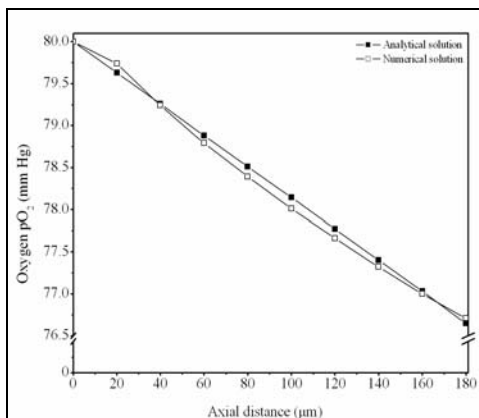
**Fig 4. Plot of numerical solutions in different capillary distances for the tissue region at  $pO_2 = 80$  mm Hg.**



**Fig 7. Percentage error between numerical and analytical solution for the capillary region at  $pO_2 = 80$  mm Hg.**



**Fig 5. Percentage error in between numerical and analytical solution for the tissue region at  $pO_2 = 80$  mm Hg.**



**Fig 6. Comparison between numerical and analytical solution for the capillary region at  $pO_2 = 80$  mm Hg.**

Figure 4 illustrates the varying oxygen tension with radial distance in the BM microenvironment, at different axial distances in the capillary region. The main objective of this section is to highlight the minimal error between the numerical solutions obtained from CFX when compared to an analytical solution, and in Figure 5 the error between analytical and numerical solution is between (0.05-0.35) %; which is within the acceptable margin of error (1%). Furthermore, the error decreases exponentially as the radial distance increases.

Figure 6 is the comparison of analytical and numerical solutions for the capillary region, while Figure 7 is the error of the solutions for the capillary. The only notable difference from the solutions for the tissue region is that for capillary, the trend of decreasing oxygen partial pressure is linear which demonstrates the homogeneity of the capillary region. Hence, the error is also much lower than the capillary region and in some instances the error almost diminishes.

## Conclusion

Given the small error between the expected and the simulated data, the numerical method utilized within this work is assumed to be predictive, with a high level of confidence. This in turn validates the use of CFX 4.4 to develop more realistic mathematical models for normal as well as pathological BM with potential clinical applications.

## Acknowledgement

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### Nomenclature

$D_b$	Diffusion coefficient of blood in tissue	$\text{cm}^2\text{s}^{-1}$
$D_t$	Diffusion coefficient of oxygen in tissue	$\text{cm}^2\text{s}^{-1}$
$H_T$	Volume fraction of hemoglobin in blood	%
$M$	Modified Hill Constant for $\text{CO}_2$	1/mmHg
$m_0$	Volumetric oxygen consumption rate	$\text{mol O}_2 \text{cm}^{-3}\text{s}^{-1}$
$K_{\text{eff}}$	Effective Krogh coefficient	$\text{mol O}_2 \text{cm}^{-3}\text{s}^{-1} \text{mmHg}^{-1}$
$K$	Oxygen permeability	$\text{mol O}_2 \text{cm}^{-3}\text{s}^{-1} \text{mmHg}^{-1}$
$K_b$	Oxygen permeability-blood	$\text{mol O}_2 \text{cm}^{-3}\text{s}^{-1} \text{mmHg}^{-1}$
$K_t$	Oxygen permeability-tissue	$\text{mol O}_2 \text{cm}^{-3}\text{s}^{-1} \text{mmHg}^{-1}$
$p\text{O}_2$	Oxygen tension (Partial pressure)	mm Hg
$p_t$	Oxygen Tension in tissue	mm Hg
$p_b$	Oxygen Tension in blood	mm Hg
$r_t$	Radius of the tissue cylinder	$\mu\text{m}$
$r_c$	Radius of the sinus	$\mu\text{m}$

### Greek Symbols

$\alpha_b$	Oxygen solubility-blood	$\text{mol O}_2 \text{cm}^{-3} \text{mm Hg}^{-1}$
$\alpha_t$	Oxygen solubility-tissue	$\text{mol O}_2 \text{cm}^{-3} \text{mm Hg}^{-1}$
$\gamma$	Oxygen saturation function	-

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