# MODELLING AND SIMULATION OF ISCHEMIC PROCESS THAT FOLLOWING THE CLAMPING OF CEREBRAL ARTERIES

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**Abstract.** In this paper is developed a dynamic mathematical model for the concentration profiles of oxyhemoglobin and oxygen in cerebral tissue and cerebral blood capillaries, since the beginning of the capillaries until the consumption of the oxygen by the cellular metabolism. The model is applied to the study of ischemic processes that occur in the brain tissue due to the decrease in the local blood flow, causing a reduction in the concentration of oxygen in the nearby regions. This consequence of this deficit may be the die of the tissue. The resulting system is solved by the Method of Lines, with spatial discretization by Finite Differences. The understanding of the phenomenon associated to the lack of oxygen that follows a course of ischemia is crucially important to prevent the brain region evolving into a stroke. The phenomenological mathematical models supported by the conservation laws are predictive and allow a comparison to experimental data. The results of a cerebral arterial clamping simulation are presented and discussed.

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**Keywords:** ischemia, tissue oxidation, Brain blood flow.

## 1. Introduction

In order to maintain a homeostasis in the human body, the oxygen supply has to be enough to fulfill the tissue's metabolic needs. The $O_2$ is transported by the blood flow to the tissue, where it is consumed by the cellular metabolic process. Amongst the physical and chemical mechanisms involved are convection, diffusion and reaction between the oxygen and the hemoglobin, in the capillary and, in the tissue the diffusion and the metabolic reaction. Besides that, between the blood in the capillary and the tissue, the oxygen needs to cross a hemato-encephalic barrier. On the other hand, there is only a small fraction of oxygen as free oxygen, dissolved in the plasma. The biggest part, around 97%, is combined with the hemoglobin in the erythrocytes, forming the oxyhemoglobin. The relation between the oxygen dissolved in the plasma and the oxygen associated with the hemoglobin is considered to be the blood oxygenation capacity. Through out the capillary the red blood cells release oxygen, that spreads out to the plasma and then in to the tissue. Figure 1 shows a scheme of the blood micro-circulation..

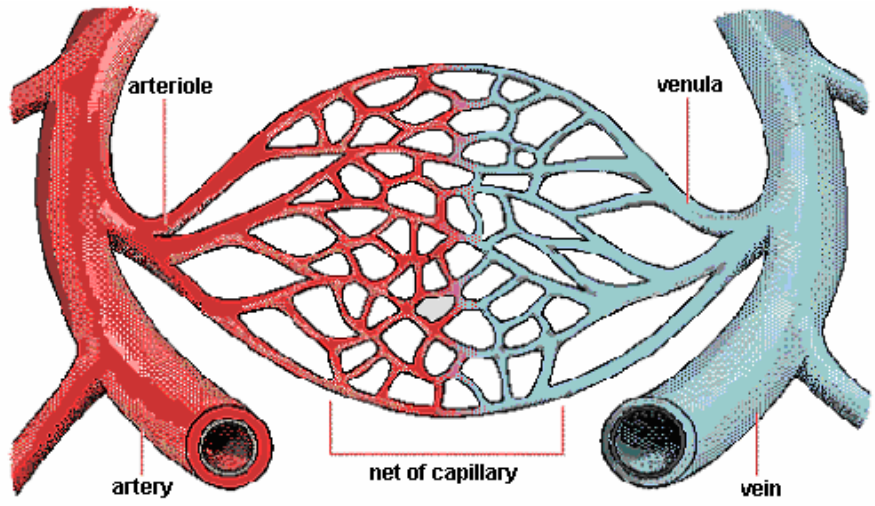


**Fig. 1.** Scheme of the blood micro-circulation geometry

The mathematical modeling of the tissues oxygenation produces a better understanding of the phenomenon associated to the cellular metabolism. Research groups in several areas have proposed phenomenological interpretations, which are utilized to fundament mathematical models of several levels of complexity. The mathematical complexity can be reduced using a capillary network simplified geometry and by disregarding part of the associated phenomenon. Still as a simplification, many mathematical models involve only the stationary state.

A more complex model for the transient state was proposed by Andreazza (2003). The model considers in the capillary, axial convection and diffusion, for both oxygen and oxyhemoglobin, and in the tissue, diffusion of oxygen in a normal direction to the capillary. The model also considers the hemato-encephalic barrier and both reaction, hemoglobin-oxygen in the capillary, and in the tissue, metabolic consumption of oxygen. The last reaction is considered a first order reaction of the oxygen concentration. There are then three variables, the concentrations of oxyhemoglobin and free oxygen in the capillary, and oxygen in the tissue, respectively $C_{HbO_2}$, $C^c_{O_2}$ and $C^t_{O_2}$. To describe the kinetic term of the reaction between the hemoglobin and the oxygen, a formulation supported on experimental data existent in the literature was applied. The present paper uses this mathematical model to study the tissues oxygenation in adverse condition, like in the case of a process of hypoxia-ischemic brain injury.

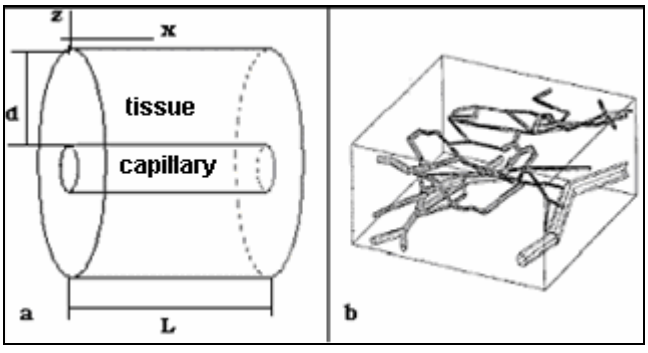


**Fig. 2** – (a) cylinder of Krogh; (b) 3D configuration of capillary geometry

An important question for the tissue oxygenation modeling is the form in which the capillaries are spatially organized. A simplified representation was proposed by Krogh

in 1919, considering an even distribution, as represented on figure 2a. In this conception, each capillary oxygenates a surrounding cylindrical region. The first mathematical model adapted for this geometry was proposed by Erlang. The so called Krogh-Erlang model considers only the radial diffusion in the tissue (Schubert and Zhang, 1997). Actually the capillary organization is not homogeneous, like the spatial organization proposed by Secomb et. al. (1999). See figure 2b.

This work utilizes a cylindrical geometry to represent the capillaries. Figure 3 shows two parallel, cylindrical capillaries, L long, separated by a 2d distance. In the beginning of the capillary enters an $O_2$ enriched blood, which is in equilibrium with the arterial hemoglobin. The oxygen supplying to the tissue occurs through the capillaries lateral surfaces, called the hemato-encephalic barrier. The oxygen concentration gradient existent between both sides of the blood brain barrier causes the flux to the tissue, where it enters the cellular metabolic route for the organism's energy supplying. This spatial representation is a simplification of the complex network of cerebral blood capillaries. However, a comparison between the results obtained and the literature data confirms its validation.

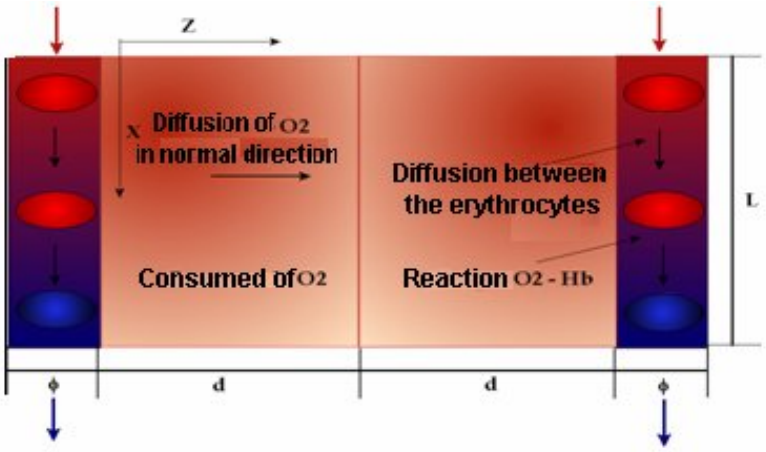


**Fig. 3.** Spatial organization of the system capillary-tissue used in this work.

## 2. Mathematical modeling

The mathematical model proposed for the blood capillary considers only the axial profiles of concentration for both, free oxygen and oxyhemoglobin. As a consequence

the functional dependences of the variables in the capillary, concentration of $O_2$ and $HbO_2$ are respectively, $C^C_{O_2} = C^C_{O_2}(x,t)$ and $C_{HbO_2} = C_{HbO_2}(x,t)$. In the tissue the oxygen concentration varies axially, parallel to the blood flow in the capillary, and normal to the capillary, or in mathematical terms $C^t_{O_2} = C^t_{O_2}(x,z,t)$. Both x and z direction represent respectively, the axial direction in the capillary and the normal direction to the capillary, in the tissue. The reaction between the $O_2$ and the Hb occurs inside the erythrocytes. Almost all of the oxygen is initially associated to the hemoglobin. As the blood moves on thru the capillary, the oxygen migrates to the tissue, where it is consumed by the cellular metabolism, and the $HbO_2$ concentration keeps dropping, until it reaches the common value in the vein vessels, approximately $1.65 \times 10^{-5}$ $mol_{HbO2}/ml_{blood}$.

The application of the mass conservation law in the capillaries creates two differential partial equations, for oxyhemoglobin and for free oxygen, equations (1) and (2). The equation for the oxyhemoglobin considers convection and diffusion in axial direction, and reaction with the free oxygen. The oxygen equation includes the term that represents the interface capillary-tissue, here described by the diffusion of the oxygen in the tissue, normal to the capillary:

$$\frac{\partial C_{HbO_2}}{\partial t} + v.\frac{\partial C_{HbO_2}}{\partial x} = D_{HbO_2}.\frac{\partial^2 C_{HbO_2}}{\partial x^2} + T \tag{1}$$

$$\frac{\partial C^C_{O_2}}{\partial t} + v.\frac{\partial C^C_{O_2}}{\partial x} = D^C_{O_2}.\frac{\partial^2 C^C_{O_2}}{\partial x^2} + \frac{4D^t_{O_2}}{\varphi}.\left.\frac{\partial C^t_{O_2}}{\partial z}\right|_{z=0} - T \tag{2}$$

Where T represents the Hb-O2 reaction, in $mol/s.ml_{blood}$.

The reaction between hemoglobin and oxygen is reversible and takes place in four stages, with different constants for each one. In the literature it is commonly treated as a single stage reversible reaction, like presented on equation (3). The order of the reaction is considered to be dependant on the hemoglobinic saturation fraction. This reaction also depends on the $CO_2$ concentration in the blood, the pH, and the temperature. These fac-

tors put together make the proposal of an equation that describes its kinetics in all the capillary very hard.

$$T = k_a.C^c_{O_2}.C_{Hb} - k_b.C_{HbO_2} \quad (3)$$

Where $C^c_{O_2}, C_{Hb}$ *and* $C_{HbO_2}$ are respectively the concentrations of, free $O_2$, hemoglobin and oxyhemoglobin, and $k_a$ and $k_b$ are respectively the association and dissociation coefficients. If $k_a$ and $k_b$ were constants the consideration of just one stage in the reaction would not reproduce the balance curve between the hemoglobin and the oxygen. For this reason, in this paper $k_a$ and $k_b$ are a function of the hemoglobinic saturation, through kinetics presented by Andreazza (2003), which are supported by experimental data from the literature.

The equation for the concentration of oxygen in the tissue, equation (4), includes a diffusive term, normal to the capillary, and the metabolic reaction term. The axial diffusion is despised in comparison with the convective flow in the capillary.

$$\frac{\partial C^t_{O_2}}{\partial t} = D^t_{O_2}.\frac{\partial^2 C^t_{O_2}}{\partial z^2} - k.C^t_{O_2} \quad (4)$$

Where k is the reaction constant of the oxygen consumption in the brain tissue ($s^{-1}$).

**Boundary Conditions**

In the entrance to the capillary, x = 0, boundary conditions of the first type are adopted, equations 5 and 6, associated to the arterial concentrations:

$$C^C_{O_2}(0,t) = C^{art}_{O_2} \quad (5)$$

$$C_{HbO_2}(0,t) = C^{art}_{HbO_2} \quad (6)$$

In the exit of the capillary, the blood meets the venule, where each capillary individually, little contributes to its concentration, which is homogeneous. The hemoglobin and oxygen concentrations meet another equilibrium point, which results in boundary conditions of the second type, equations 7 and 8:

$$\left.\frac{\partial C_{HbO_2}}{\partial x}\right|_{x=L} = 0 \tag{7}$$

$$\left.\frac{\partial C^{C}_{O_2}}{\partial x}\right|_{x=L} = 0 \tag{8}$$

For the capillary-tissue interface it is considered that the passage of the breathing gasses ($O_2$ e $CO_2$) through the hemato-encephalic barrier occurs by free diffusion. To discard the resistance to the oxygen transfer in the interface is considered conditions of continuity for the partial pressure, or:

$$P^{t}_{O_2}(x,0,t) = P^{C}_{O_2}(x,t) \tag{9}$$

According to Henry's law, the oxygen concentration can be obtained by multiplying the partial oxygen pressure by its solubility coefficient. Being so $C^{t*}_{O_2}(x,0,t) = \frac{\alpha^{t}_{O_2}}{\alpha^{c}_{O_2}} C^{c}_{O_2}(x,t)$ , where $C^{t*}_{O_2}$ is the concentration of equilibrium between the oxygen in the tissue and in the blood, and $\alpha$ is the coefficient of solubility.

Finally, in the mean part of the tissue, z = d, the condition of symmetry is used, equation 10:

$$\left.\frac{\partial C^{t}_{O_2}}{\partial z}\right|_{z=d} = 0 \tag{10}$$

## 2.2. Numerical resolution

The finite differences method was used for the spatial discretization of the equations in the mathematical model. For the convective term a regressive discretization was utilized. The spatial discretization transforms the three partial differential equations of the mathematical model in an ordinary differential equations system, solved by the method of lines. The system of equations was solved with a fourth order Runge-Kutta method, proposed by Gear (1971). As initial conditions was used the normal values for the arterial and venal concentrations of oxyhemoglobin, respectively $2.134x10^{-5}$ and $1.65x10^{-5}$ $mol_{HbO2}/ml_{blood}$. A linear profile was constructed for the concentration of oxyhemoglobin in the capillary. The profile of oxygen concentration was result of the equation 3 applied in equilibrium conditions.

## 3. Results

Some parameters that satisfy the physiologic relationships, used to solve the proposed mathematical model, and their respective numeric values, are presented in the Table 1. The numbers of the last column, refer to the bibliographical sources. The only one free parameter, for adjustment of the mathematical model is the constant of speed of reaction of the consumption of oxygen in the tissue, k.

**Table 1** – Parameters values for the mathematical model.

| Symbol | Definition | Value | Units | Ref. |
|---|---|---|---|---|
| k | constant of speed for consumption of $O_2$ in the cerebral tissue | 7,2 | $s^{-1}$ | Estimated |
| d | thickness of the tissue | $30,0.10^{-4}$ | cm | 1 |
| L | length of the capillary | 0,05 | cm | 2 |
| v | speed of the blood | 0,033 | cm / s | 2 |
| φ | thickness of the capillary | $8,0.10^{-4}$ | cm | 2 |
| $C^{art}_{O_2}$ | Concentration of $O_2$ in the artery | $1,45.10^{-7}$ | $molO_2/mlblood$ | 3 |
| $C^{art}_{HbO_2}$ | Concentration of $HbO_2$ in the artery | 2,134.10 | $molHbO_2/ml$ | 2 |

(1) Sharan & Selvakumar, 1992. (2) Guyton & Hall, 1997. (3) Sheth & ellums,1980.

The results of the mathematical model are compared to the experimental data of Bock Field and Adair (1923) for the $HbO_2$ dissociation curve. In figure 4 this comparison is shown only in the region of interest. The mathematical model presents the same behavior of the experimental results, independent of the $P_{O_2}$ value.

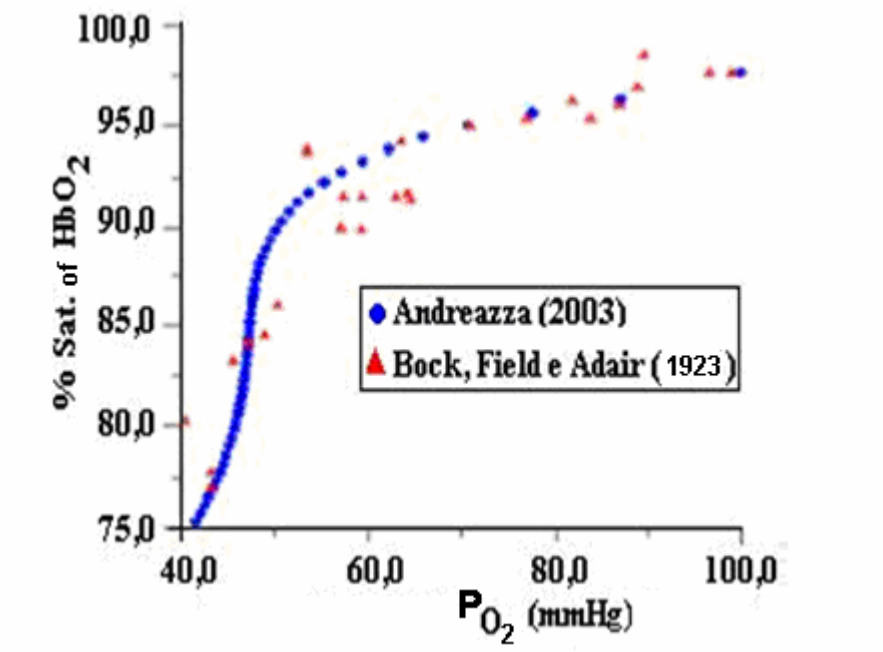


**Fig.4.** Comparison between the dissociation curve of $HbO_2$ from Andreazza (2003) and from Bock, Field e Adair (1923)

The mathematical model proposed allows the simulation of the tissue's oxygenation for several pathologies. One of those is the occlusion of an artery. In this situation a sudden and almost immediate stop occurs in the arterial blood flow. In the tissue two kinds of situation emerge: a) stroke zone – Complete stop of blood perfusion resulting low oxygen concentration and causing cellular death by hypoxia; b) ischemia zone – A significant perfusion stop, capable of interrupting the cellular work, tough not enough to

cause cellular death by hypoxia. These areas begin to form close to the end of the capillary and in the region of the tissue boundary conditions of symmetry.

The mathematical model is used to simulate a sudden and complete occlusion of the cerebral blood flow, CBF, by the clamping of a cerebral artery. In the tissue an ischemia occurs causing a reduction in the $O_2$ concentrations.

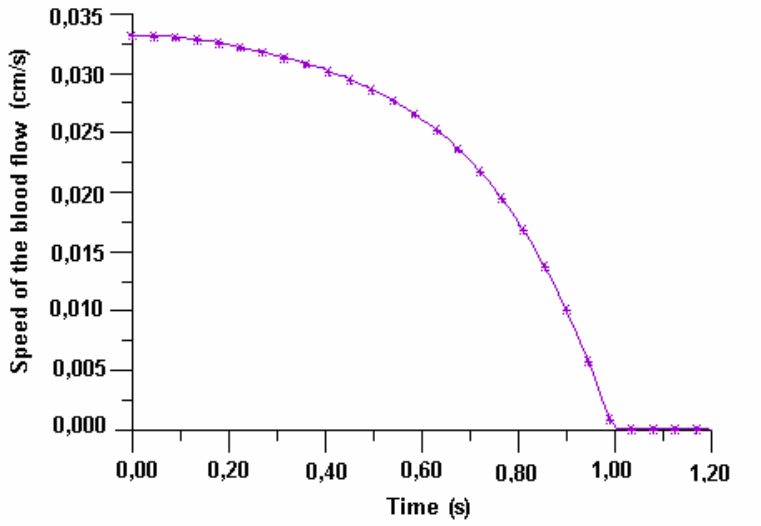


**Fig. 5.** Reduction of CBF used in the simulation of an arterial occlusion

For the simulation of one arterial clamping was used the function represented in figure 5, where the speed drops from 0,033cm/s to zero in one second. Once the blood flow is interrupted the cerebral metabolic process consumes the existing oxygen, reducing significantly its concentration in the tissue and in the capillaries. As a consequence the oxyhemoglobin concentration and the partial oxygen pressure, $C_{HbO_2}$ and $P^c_{O_2}$ evolve to zero in the capillary, like shown in figures 6 and 7.

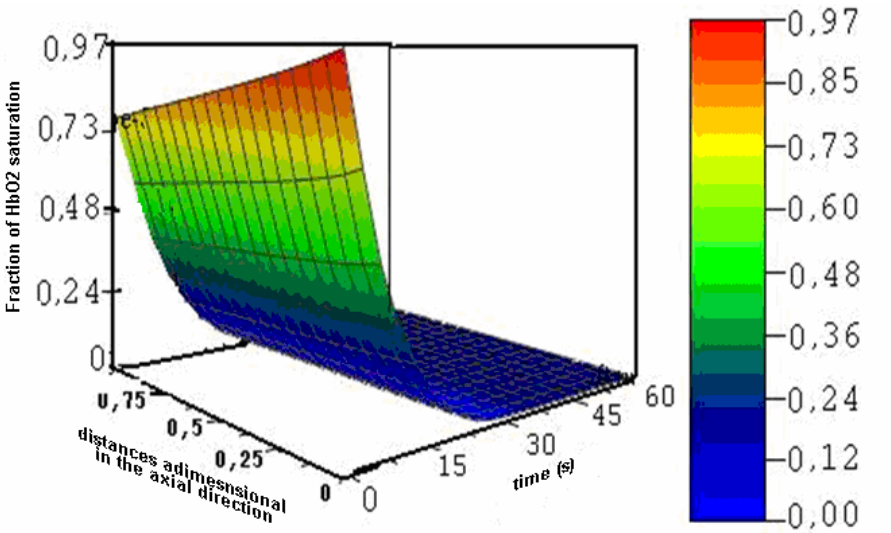


**Fig. 6.** Temporal evolution of HbO2 concentration in the capillary.

The mean oxygen pressure in the tissue initially has a value of 27,25 mmHg, reaching 5 mmHg in 11,25 s and zero in 45s. The unconscious state happens in an interval of 5s to 10s and the nervous tissue starts dying close to 45s, figure 8. These results agree with Sangrey and Levy (2005), where the authors show that the loss of consciousness may occur in 7s due to the stop in the blood flow to the brain.

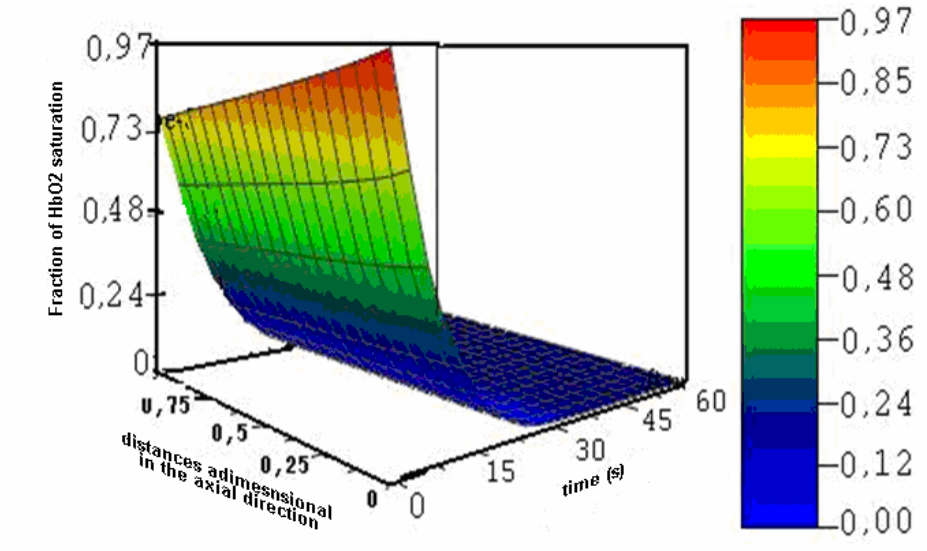


**Fig. 7.** Temporal evolution of $O_2$ concentration in the capillary.

The regions of the tissue affected by the decrease of oxygen and nutrients supplying by the blood flow are: the "stroke zone where the tissue wound takes place by the complete stop of the blood flow and the oxygenation and the "darkness zone" or ischemic where the accentuated reduction of the blood flow and oxygenation prevents proper cell functioning. Therefore, when the supplying is compromised, the hypoxia or anoxia may start in that region. Persisting this blood flow interruption scheme by these vessels the largest part of the nervous tissue perishes by malnutrition, resulting in the destruction of a grate part of the brain itself.

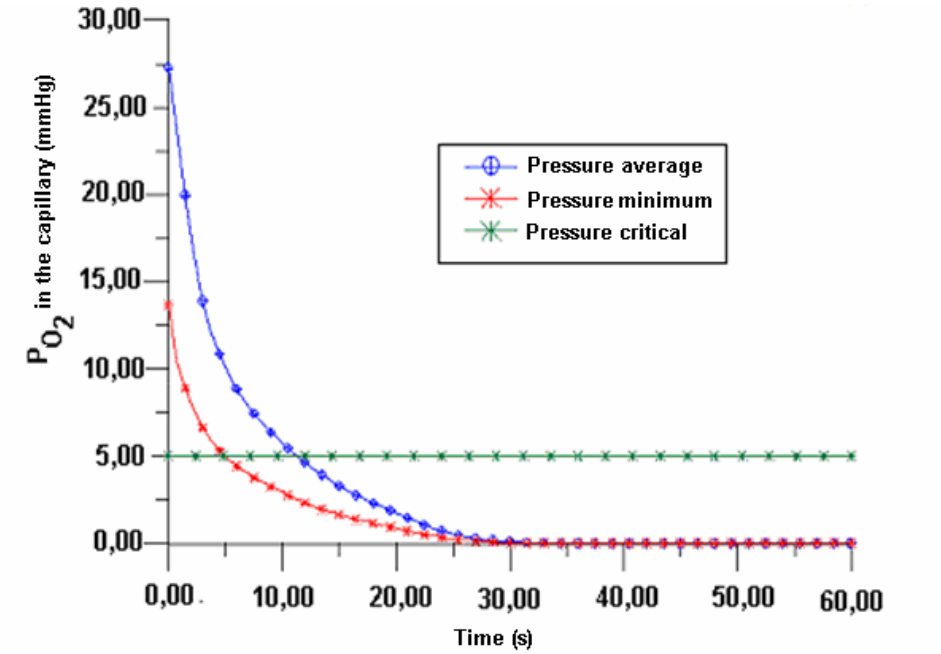


**Fig. 8.** Profiles of the average, minimum and critical pressures of $O_2$ in the tissue.

The brain is not capable of maintaining a significant level of anaerobic metabolism. One of the reasons for this is the high metabolic rate of the neurons, in a way that much more energy is needed for each brain cell then in most other tissues.

An additional reason is that the amount glycogenic present doesn't supply enough energy. The oxygen reserves in the cerebral tissue are also small, therefore, the biggest par of the neuron activity depends on the supplying, at each second, of glucose and oxygen thru the blood. Adding these factors, one can understand why a sudden stop in the

blood flow or quick drop in the oxygenation of the blood may cause unconsciousness in 5s to 10s (Guyton e Hall, 1997). If the situation persists it causes the activation of the inner cell mechanism of cellular destruction.

## 4. Conclusion

The mathematical model was tested by a common hypoxia physiologic situation, characterized by a sudden blood interruption, in the present paper called the "clamping of a cerebral artery". For the case of stroke and ischemia, the lack of oxygen supplying unbalances the kinetic reaction between the hemoglobin and the oxygen in the capillary, favoring the dissociation stage. The free oxygen spreads out to the nervous tissue, in a way that it can maintain the cellular metabolism for as long as possible. The regions affected by the lack of oxygenation are called "stroke zones", where a tissue wound occurs caused by the complete stop of the perfusão and the oxygenation. On the other hand, in the so called "darkness zone" or ischemic there is just an accentuated reduction in the blood flow and the oxygen supplying.

## 5. Symbols and units

$C_{HbO_2}$ - Concentration of oxyhemoglobin ($mol_{HbO2}/cm^3$)

$D_{HbO_2}$ - Diffusive axial oxyhemoglobin coefficient ($cm^2/s$)

$C^{art}_{HbO_2}$ - Concentration of $HbO_2$ in the artery ($mol_{HbO2}/cm^3$)

$C^{t}_{O_2}$ - Concentration of $O_2$ in tissue ($mol_{O2}/cm^3$)

$C^{c}_{O_2}$ - Concentration of $O_2$ in the capillary ($mol_{O2}/cm^3$)

$C^{art}_{O_2}$ - Concentration of $O_2$ free in the artery ($mol_{O2}/cm^3$)

$D^{t}_{O_2}$ - Coefficient normal difusivo to the capillary of $O_2$ in the tissue ($cm^2/s$)

$D^{c}_{O_2}$ - Coefficient axial difusivo of $O_2$ in the capillary ($cm^2/s$)

$P^{t}_{O_2}$ - Partial pressure of $O_2$ in the tissue (mmHg)

$P^c_{O_2}$ - Partial pressure of $O_2$ in the capillary (mmHg)

T - Hb-$O_2$ reaction (mol/min.$ml_{blood}$)

v - Speed of the blood (cm/s)

L - Length of the capillary (cm)

$\phi$ - thickness of the capillary (cm)

k - Constant of speed for consumption of $O_2$ in the cerebral tissue ($s^{-1}$)

x - Axial distance of the capillary (cm)

z - Distance in the normal tissue to the capillary (cm)

d - Thickness of the tissue (cm)

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