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Interactive Software for Simulation of Oxygen Transport from Capillaries to Brain Tissue of Preterm Infants

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Abstract

The paper presents a description of a computational algorithm and applied software designed to find the partial pressure of oxygen in a model domain known as the Krogh cylinder. The algorithm is implemented using the finite element method in the FreeFEM package, the graphical interface is made using Python language. The developed software is adapted for calculating partial pressure of oxygen in the brain tissue of preterm infants.

1 Introduction

Mathematical modeling of oxygen transport in brain tissue is important for assessing the influence of various physiological characteristics on the risk of hypoxia. Models of oxygen transport in the brain can be divided into two main groups: two-compartment and continuum models. The two-compartment models include a capillary network filled with blood and surrounded by tissue. The transfer of oxygen in the blood is described by a nonlinear first-order ODE, and the transfer of oxygen in tissues by a nonlinear diffusion-type PDE. Currently, there are quite a lot of works on numerical modeling of oxygen transfer based on the two-compartment model [11,16,17]. Despite the realism of the two-compartment models, the diameter of the computational domain in their implementation is not large and does not exceed 1 mm. Another group are continuum models of oxygen transport [8,20], which are the result of homogenization of the model domain. Continuous models allow us to describe oxygen transport for fairly large areas of the brain, up to the entire brain [2].

Of particular interest to researchers is a simplified model proposed by A. Krogh in 1919 [9]. The model domain is a cylinder whose axis determines the position of a single capillary, the remaining part is filled with tissue. The use of this model allows for analytical and numerical assessments of the influence of model parameters on the distribution of oxygen at different distances from the capillary [12–14]. In the article [7], a non-linear model of oxygen transport from capillary to tissue is considered, where a Krogh cylinder is taken as a computational domain. The model takes into account the convection of oxygen in the blood, its diffusion transfer through the capillary wall, and the diffusion and consumption of oxygen in tissue. A boundary value problem for the oxygen transport model is studied. The existence theorem is

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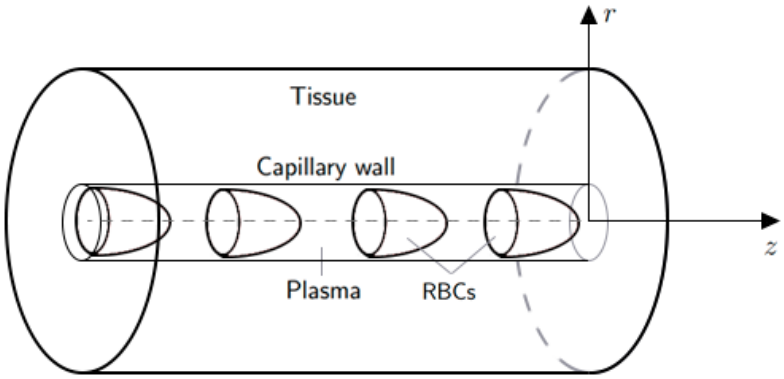

Figure 1: The computational domain taken in the form of a Krogh cylinder.

proved and a numerical algorithm is constructed and implemented. The numerical experiments studying the effect of low hematocrit and reduced blood flow rate on cerebral hypoxia in preterm infants are conducted.

This article presents a description of the applied software that implements the solving the boundary value problem for the oxygen transport model in the Krogh cylinder formulated in [7]. The developed software is adapted for calculating partial pressure of oxygen in the brain tissue of preterm infants. An algorithm for computing partial pressure of oxygen (pO_2) is combined with a procedure for calculation of cerebral blood flow (CBF) and the rate of blood flow in a capillary based on the patient's clinical data. The calculations are carried out using the finite element method and the FreeFEM package [6]. The proposed software allows users to find the pO_2 distribution corresponding to the clinical data of the patient. In addition, the pO_2 distribution for the input parameters corresponding to the boundaries of physiological range of pO_2 is computed.

2 Mathematical model

The computational domain is shown in Fig. 1. The domain filled with tissue is denoted by Ω, the boundary between blood and tissue (the capillary wall) is Γ_1, the rest part of the boundary of the domain Ω is Γ_2. The height of the cylinder is denoted by L.

Let us consider the following oxygen transport model [7]:

$$-\kappa\Delta p + M(p) = 0, \quad x \in \Omega, \tag{1}$$

$$p|_{\Gamma_1} = p_c(z) - \gamma q(z), \quad z \in (0, L); \quad \partial_n p|_{\Gamma_2} = 0. \tag{2}$$

Here, p and p_c describe the partial pressure of oxygen in the tissue and capillary, respectively; the term $M = M_0 p/(p + p_0)$ describes the oxygen consumption rate on the base of the Michaelis–Menten equation; κ, M_0, p_0, γ are given positive constants; M_0 is the rate of oxygen consumption when oxygen supply is not limited, p_0 is the partial pressure of oxygen at half-maximal consumption, γ is the intravascular resistance to the radial oxygen diffusion. The

symbol ∂_n denotes the derivative in the direction of the outward normal $\mathbf{n}$ to the domain Ω. The function

$$q(z) = \kappa r_c \int_0^{2\pi} \partial_n p|_{\Gamma_1} d\theta \tag{3}$$

is interpreted as the diffusive oxygen flux entering the domain Ω from the capillary, where θ is the polar angle on a circle, r_c the radius of the capillary.

The function p_c is determined from the following initial value problem:

$$-\frac{df(p_c(z))}{dz} = q(z), \quad p_c(0) = p_+, \tag{4}$$
$$f(p_c) = ap_c + \frac{bp_c^n}{p_c^n + c},$$

where $f(p_c)$ is the rate of convective oxygen transport along a vessel segment; $a = \alpha Q$, where α is the effective solubility of oxygen in the blood, Q is the rate of blood flow; $b = C_0 H_D Q$, where C_0 is the concentration of hemoglobin-bound oxygen in a fully saturated red blood cell, H_D is the discharge hematocrit; c is the partial oxygen pressure at 50% saturation; n is the Hill coefficient. Values of the basic parameters of the model and their physical units are presented in Table 1.

Name	Description	Value	Physical Units
α	Effective O_2 solubility in blood	3.1×10^{-5}	$\frac{\text{cm}^3\text{O}_2}{\text{cm}^3\,\text{mmHg}}$
M_0	O_2 consumption rate when oxygen supply is not limiting	2.3×10^{-3}	$\frac{\text{cm}^3\text{O}_2}{\text{cm}^3\,\text{s}}$
κ	Diffusion coefficient	6×10^{-10}	$\frac{\text{cm}^3\text{O}_2}{\text{cm}\cdot\text{s}\cdot\text{mmHg}}$
C_0	Concentration of hemoglobin-bound O_2 in a fully saturated red blood cell	0.5	$\frac{\text{cm}^3\text{O}_2}{\text{cm}^3}$
γ	Intravascular resistance to radial O_2 diffusion	2.5×10^8	$\frac{\text{cm}\cdot\text{s}\cdot\text{mmHg}}{\text{cm}^3\text{O}_2}$
c	pO_2 at 50% saturation	38	mmHg
p_0	pO_2 at half-maximal consumption	1	mmHg
n	Hill coefficient	3	–

Table 1: Problem parameters [16,17].

The system (1) – (4) can be considered as a boundary value problem in the domain Ω for the nonlinear diffusion equation (1). At the part of the boundary Γ_2, the Neumann boundary conditions are set, at the part of the boundary Γ_1 coinciding with the capillary wall, the tissue pO_2 depends on a solution of the nonlinear Cauchy problem (4) describing the oxygen transport in the blood. Thus, the equalities (2) and (4) represent nonlinear boundary conditions for equation (1). Due to the specific nonlinear boundary conditions (2) and (4), the considered problem is not a standard boundary value problem for an elliptic equation. In the work [7], the solvability of the boundary value problem (1) – (4) was established and an iterative algorithm to find its solution was constructed and implemented.

3 Numerical algorithm

To find the solution of the problem (1) – (4) in the weak formulation constructed in [7], the finite element method is used. The following iterative algorithm is applied to find the partial oxygen pressure distribution in the capillary and surrounding tissue.

Iterative algorithm

1: Input a patient clinical data.

2: Compute the CBF and the rate of blood flow Q.

3: Set a relative accuracy of calculation δ.

4: Set the initial approximation $p^{(0)}$ of the tissue pO_2

5: Initialize the counter: $m \leftarrow 0$.

6: Find an approximation $q^{(m)}(z)$ from (3)

7: Find a solution $p_c^{(m)}(z)$ of the problem (4).

8: Find a solution $p^{(m+1)}(z)$ of the problem (1), (2).

9: **if** $\|(p^{(m+1)} - p^{(m)})/p^{(m+1)}\| < \delta$ **then** Stop.

10: **else** $m \leftarrow m + 1$; Go to 6.

The value of the parameter δ is chosen to ensure a balance between the convergence rate of the iterative algorithm and the stability of the computational process.

The implementation of the iterative algorithm was conducted using the FreeFEM package [6]. To find tissue pO_2 distribution, we first need to find the rate of blood flow Q in the capillary. We calculate Q using the cerebral vascular model which was proposed by S. Piechnik in 2008 for calculation of CBF in adult brain [15] and then modified for immature brain of preterm infants [3,4,10,18,19]. The advantage of this approach is that it estimates CBF from 6 medical parameters, namely the gestational age, birth weight, hematocrit, pO_2, pCO_2, and mean arterial pressure (MAP) (last 4 measured on a particular day of life). The model of the brain vessels consists of 19 sequentially connected levels of vessels with parallel topology: 9 levels of arterioles (with number from 1 to 9), a level of capillaries (with number of 10), and 9 levels of venules (with number from 11 to 19). At each level, the number of vessels, their length and diameter are scaled according to the gestational age and weight of the newborn [18]. In more detail, to adapt the modified vascular model to a preterm infant with brain weight w (units in grams), for each i-th level, the numbers of vessels, their lengths, and their diameters are reduced by dividing the values from [15] over

$$1200/w - (1200/w - 1)\,|i - 10|/9, \quad i \neq 10,$$

$$1 + 0.1(1200/w - 1)\,|i - 10|/9,$$

$$1 + 0.1(1200/w - 1)\,|i - 10|/9,$$

respectively (see [18]). The weight of the infant brain w is calculated by its gestational age A (in weeks) using the following approximation [5]:

$$w = 255.25 - 35.44\,A + 1.52\,A^2 - 0.01A^3.$$

The value of 1200 (grams) corresponds to the approximate weight of the adult brain [15]. The coefficient 0.1 is used to scale the vessel length and diameter to the experimental measurements [1, 21].

In addition, the effect of hematocrit on blood viscosity is taken into account when calculating CBF [4, 19] Furthermore, autoregulatory activity of cerebral vessels is modeled by increasing and decreasing vessel diameter according to the values of MAP, pCO_2, and pO_2 [10, 18].

Following the modified vascular model [3], capillary level of preterm infants consists of two parallel parts, related to the germinal matrix and the rest of the brain. The number of capillaries in the germinal matrix and the rest of the brain is

$$1.5\,N\,g\,w/1200 \quad \text{and} \quad N\,(1-g)\,w/1200, \tag{5}$$

respectively, where N is the number of capillaries in an adult brain, $N = 7.56\text{e+}08$ [15], and g is the fraction of the germinal matrix with respect to the entire infant brain. To find the rate of blood flow Q in a capillary of the germinal matrix or the rest of the brain, the obtained value of the CBF must be divided by the number of capillaries in the germinal matrix or the rest of the brain, respectively, obtained by (5).

4 Graphical user interface

The graphical user interface (GUI) has been implemented in Python language using the Tkinter graphics library. To construct the GUI, the following widgets were used:
Frame widget that contains all the visual components;
Canvas widget which is necessary for drawing various objects, graphs, etc;
Button widget that, when pressed, executes a specified command;
Radiobutton is a switch which allows us to select one value from those offered;
Combobox is a drop-down list from which the user can select one item;
Label is a text label which displays text without the ability to edit;
Entry is a text input field.

We use the *Button* widget to save the data entered in the *Entry* widgets, and the selected values in the *Combobox* and *Radiobutton* widgets to a separate file which is then used by the calculation module developed in the FreeFem package. When the calculations are completed, the computed pO_2 data is saved to an output file which is then used to visualize the obtained results in the GUI. To plot figures on *Canvas* widget, the Matplotlib data visualization library is used. Graphs are built by the *plot* method, and to plot the space distribution of pO_2, the *imshow* and *pcolormesh* methods are used.

Let us describe the GUI in more detail. The patient's clinical data, namely gestational age, weight, hematocrit, pO_2, pCO_2, MAP, and number of days of life are entered into the text fields (*Entry* widgets) of the GUI, see, Fig. 2. Also, through the *Radiobutton* widget, it is indicated which part of the newborn's brain is of interest for modeling: the germinal matrix or the rest of the brain. These areas differ in the density of vessels and their sizes. Based on the entered data, cerebral blood flow is calculated for the selected part of the brain.

The computational domain in the cylindrical coordinate system with angular symmetry is shown in Fig. 3. Here, the blue lines mark the horizontal and vertical cross-sections of

the computational domain in which the pO_2 behavior is studied. Cross-section positions are set via the *Combobox* widgets (units in μm). When the user selects horizontal and vertical cross-section positions in the *Combobox* widgets, the corresponding lines on the *Canvas* widget are automatically redrawn. After computing pO_2 and following change only the cross-section positions, the graphs on *Canvas* widget are redrawn without additional running the FreeFEM module, based on the already completed calculations.

As an example, we consider a newborn with a gestational age of 25 weeks and a weight of 765 grams, which have the values of hematocrit, pO_2, pCO_2, and MAP shown in Table 2. The table also contains the values of these parameters corresponding to low ("Data –") and high ("Data +") pO_2 levels for a given gestational age and weight. The pO_2 distributions in the selected cross-sections, corresponding to the patient's data and also "Data –" and "Data +", are shown in two upper figures of the GUI (see Fig. 2) or in better quality in Figs. 4 and 5. The blue solid lines correspond to the patient's data, the dashed lines correspond to the clinical data leading to low or high level of pO_2.

The two lower figures in the GUI (see Fig. 2) show the pO_2 distributions corresponding to the patient's clinical data. The middle bottom figure shows the pO_2 distribution in the entire computational domain and right bottom figure shows the pO_2 distribution in selected vertical cross-section. The calculated values of the CBF and blood flow rate in the capillary corresponding to patient's data are shown in the lower left corner.

The *Combobox* widget in the upper right corner of the GUI allows us to select a color map for two lower figures. The following color maps can be selected: HSV, BWR, Coolwarm, Rainbow, and Cool.

Input parameter	Patient data	Data –	Data +
Hematocrit, %	40	30	45
pO_2, mmHg	60	50	80
pCO_2, mmHg	50	40	60
MAP, mmHg	35	30	40

Table 2: Input parametrs for numerical example.

5 Conclusion

The paper presents a description of a computational algorithm and an applied software designed to find the partial pressure of oxygen in a model domain known as the Krogh cylinder. The algorithm is implemented using the finite element method in the FreeFEM package, the graphical interface is developed using the Python language. The developed software can be used to monitor oxygen levels in the brains of preterm infants and help to prevent hypoxia.

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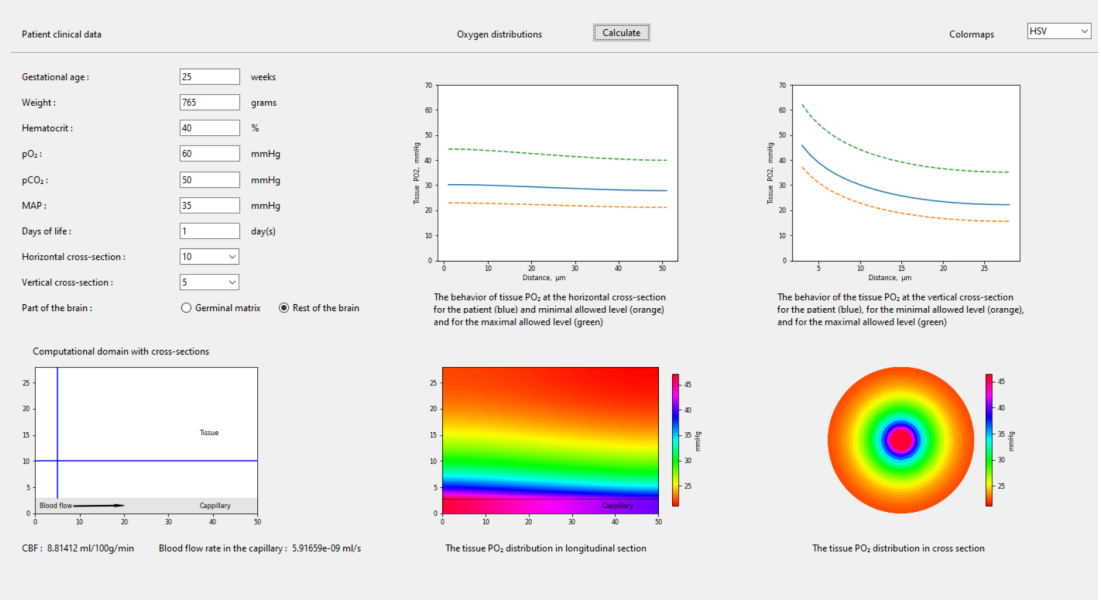

Figure 2: Graphical user interface for the calculation of pO_2 in brain tissue of preterm infants.

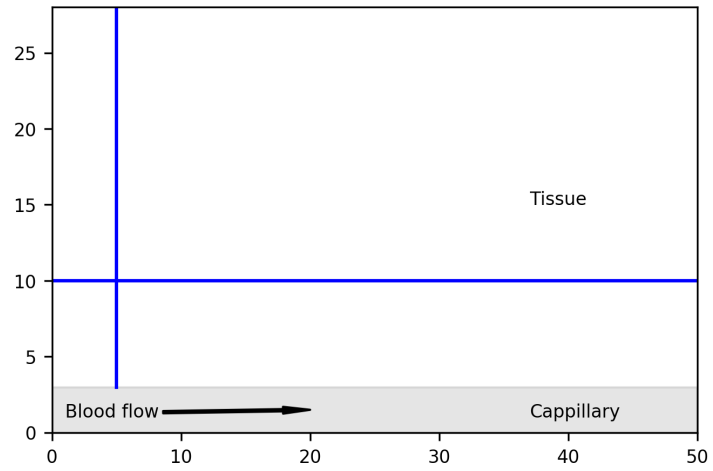

Figure 3: Computational domain presented in the GUI. Linear dimensions are given in μm. Blue lines mark cross-sections in which the pO_2 behavior is studied.

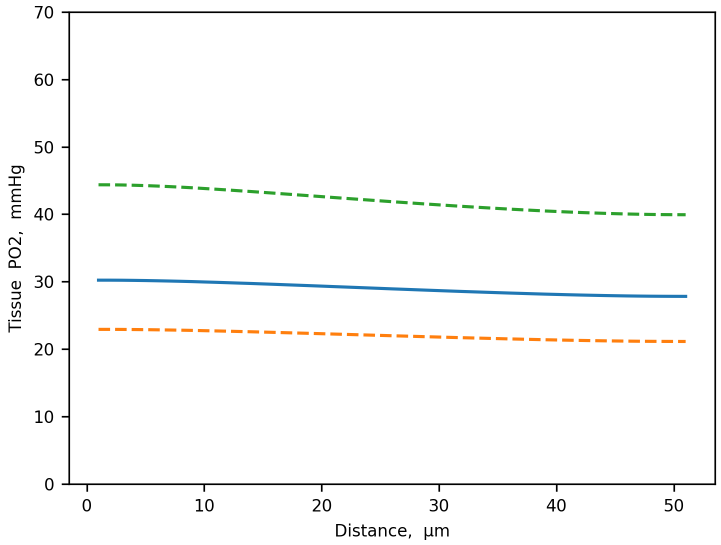

Figure 4: pO_2 distribution in horizontal cross-section:
patient (blue), lower boundary (orange dashed line), higher boundary (green dashed line).

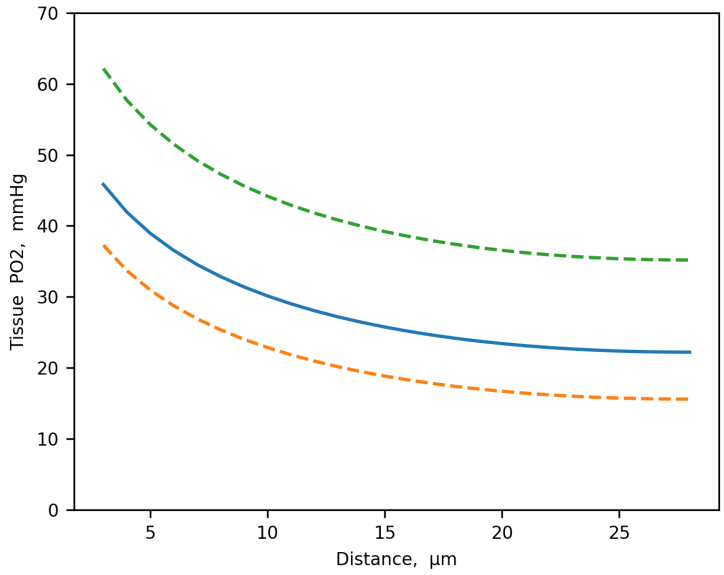

Figure 5: pO_2 distribution in vertical cross-section:
patient (blue), lower boundary (orange dashed line), higher boundary (green dashed line).

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