MODELING THE PRESSURE DISTRIBUTION IN A SPATIALLY AVERAGED CEREBRAL CAPILLARY NETWORK

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Abstract. A boundary value problem for the Poisson's equation with unknown intensities of sources is studied in context of mathematical modeling the pressure distribution in cerebral capillary networks. The problem is formulated as an inverse problem with finite-dimensional overdetermination. The unique solvability of the problem is proven. A numerical algorithm is proposed and implemented.

1. Introduction. Promising perspectives in modeling of various processes in brain are related to the so-called continuum models that result from spatial homogenization of original ones based on capillary networks embedded in brain tissue. For example, homogenization of models of oxygen transport in the cerebral capillary network and surrounding brain tissue results in two-compartments models where the tissue and blood fractions occupy the same continuum domain [11, 12]. This approach allows for proving the unique solvability of the corresponding nonlinear initial-boundary and boundary value problems [6, 7] and the convergence of numerical algorithms [8, 9]. It should be noted that the implementation of numerical algorithms for oxygen transport problem requires the determination of blood velocity field in the continuum (spatially averaged) domain, which can be iteratively done using Darcy’s law and the blood pressure distribution.

The objective of current article is to study a model describing the distribution of blood pressure in the continuum domain representing a homogenized (spatially averaged) cerebral capillary network. The investigation includes the following parts: statement of a boundary value problem in the continuum domain, reformulation of the problem as an inverse problem with finite-dimensional overdetermination, theoretical analysis of the inverse problem, construction of a numerical algorithm, and its implementation.

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2. Capillary networks. First consider the steady-state pressure distribution in the brain capillary network. The capillary network may preliminary be considered to have the cubic topology. This means that each internal node of the graph has six adjacent nodes. Fig. 1 shows the stencil corresponding to the cubic topology with 7 nodes and 6 edges (capillaries). The notations \( u_{i\pm1,j\pm1,k\pm1} \) stand for pressures in the corresponding nodes. The symbols \( R_{i\pm\frac{1}{2},j\pm\frac{1}{2},k\pm\frac{1}{2}} \) denote resistances of the corresponding edges. In the capillary network considered, all edges have the same length, and information about the length of capillaries is included in the capillary resistances (see, e.g., [2]).

![Figure 1. Stencil corresponding to the cubic topology.](image)

According to Kirchhoff’s circuit laws, the following relations hold for all interior nodes \((i, j, k)\):

\[
\frac{u_{i+1,j,k} - u_{i,j,k}}{R_{i+\frac{1}{2},j,k}} - \frac{u_{i,j,k} - u_{i-1,j,k}}{R_{i-\frac{1}{2},j,k}} + \frac{u_{i,j,k+1} - u_{i,j,k}}{R_{i,j,k+\frac{1}{2}}} - \frac{u_{i,j,k} - u_{i,j,k-1}}{R_{i,j,k-\frac{1}{2}}} = 0. \tag{1}
\]

The difference of the first and second fractions in the left-hand side of formula (1) describes the flow change along the \(i\)-axis. The flow changes along the \(j\)- and \(k\)-axes are described by the subsequent differences in the left-hand side of (1). Thus, Kirchhoff’s law (1) expresses the fluid conservation principle at the node \((i, j, k)\). Obviously, the corresponding relations for non-interior nodes contain less terms.

Notice that some nodes corresponding to the ends of the arterioles are considered as inlets so that the pressure is prescribed for these nodes. Similarly, the pressure is prescribed for some nodes that are considered as outlets corresponding to the ends of the venules. Let \(M_+\) and \(M_-\) denote the sets of multi-indices corresponding to inlets and outlets, respectively. The system (1) is supplied with the following conditions:

\[
u_{i,j,k} = u^+, (i, j, k) \in M_+; \quad u_{i,j,k} = u^-, (i, j, k) \in M_-.
\tag{2}
where \( u^+ \) and \( u^- \), \( u^+ > u^- \), are given values of the pressure at the inlets and outlets, respectively. Thus, the relations (1) and (2) define a system of linear equations to determine the pressure distribution under given resistances of the capillaries and given pressures for inlets (cf. \( M^+ \)) and outlets (cf. \( M^- \)). In [2, 3], the numerical simulations based on system (1), (2) were conducted for large capillary networks.

3. Passage to continuum model. In [12], a continuum analogue of the problem (1), (2) is proposed on the base of Darcy’s flow equation assuming the capillary-perfused tissue as a porous medium with isotropic and homogeneous flow pathways. The continuum model gives a good approximation of the blood circulation in large enough capillary networks. The conception of porous medium for modeling the blood flow in the capillary-perfused tissue is also used in [1, 5, 13].

Let us consider the homogenization of the problem (1), (2). Let \( \Omega \subset \mathbb{R}^3 \) be a bounded Lipschitz domain comprising the capillary network and \( \Omega_j \subset \Omega \), \( j = 1, \ldots, m \), be disjoint Lipschitz domains which are some neighborhoods of the points belonging to the sets of flow inlets \( (M^+) \) and outlets \( (M^-) \). The continuum analogue of the equation (1) has the form:

\[
\text{div} (a \nabla u) = 0 \quad \text{in} \quad \Omega_0 := \Omega \setminus \bigcup_{j=1}^{m} \Omega_j,
\]

where \( a(x) = R_0^{-1}(x) \), and \( R_0(x) \) is the specific hydraulic resistance at point \( x \), defined as \( R_0(x) = \lim_{y \to x} [R(x,y)||x-y||^{-1}] \). Here \( R(x,y) \) is the hydraulic resistance between the points \( x \) and \( y \) (it is assumed that \( R \) depends only on \( |x-y| \) and does not depend on the direction).

Denote \( \Gamma = \partial \Omega \) and \( \Gamma_j = \partial \Omega_j \), \( j = 1, \ldots, m \). The pressure values \( u^+ \) and \( u^- \) from (2) can be interpreted in continuum setting as values of \( u \) on the boundaries \( \Gamma_j \) of the neighborhoods \( \Omega_j \), \( j = 1, \ldots, m \). Additionally, conditions on the boundary of the domain \( \Omega \) are required. By analogy with [12], zero pressure change in the normal direction (no flux conditions) on the boundary \( \Gamma \) may be supposed. Thus, we supply the equation (3) by the following conditions on the boundaries \( \Gamma \) and \( \Gamma_j \), \( j = 1, \ldots, m \):

\[
\partial_n u|_{\Gamma} = 0,
\]

\[
u|_{\Gamma_j} = \begin{cases} u^+, & \text{if } \Omega_j \cap M^+ \neq \emptyset, \\ u^-, & \text{if } \Omega_j \cap M^- \neq \emptyset, \end{cases}
\]

where \( \partial_n \) denotes the derivative in the direction of outward normal \( n \) to the boundary \( \Gamma \).

In the next section, the continuum model will be rewritten into that without holes \( \Omega_j \), \( j = 1, \ldots, m \), but with a source term in the right-hand side of (3). This allows to reduce the boundary value problem (3)-(5) in the perforated domain \( \Omega_0 \) to an inverse problem of finding unknown sources intensities and pressure field in the whole domain \( \Omega \) from the mean values of \( u \) in \( \Omega_j \), \( j = 1, \ldots, m \).

4. Formulation of an inverse problem. In the domain \( \Omega \), consider the following boundary value problem:

\[
-\text{div} (a \nabla u) = \sum_{j=1}^{m} \alpha_j f_j \quad \text{in} \quad \Omega, \quad \partial_n u = 0 \quad \text{on} \quad \Gamma.
\]
Here, $\alpha = (\alpha_1, \alpha_2, \ldots, \alpha_m) \in \mathbb{R}^m$ and

$$f_j(x) = \begin{cases} 1, & \text{if } x \in \Omega_j, \\ 0, & \text{if } x \in \Omega \setminus \Omega_j. \end{cases}$$

We suppose that the function $a \in L^\infty(\Omega)$ satisfies the condition $a \geq a_0 > 0$, where $a_0$ is a positive constant.

Since the intensities $\alpha_j$, $j = 1, \ldots, m$, are unknown, the problem of finding the pressure field $u$ will be formulated as an inverse problem. The inverse problem is to find a vector $\alpha \in \mathbb{R}^m$ and a function $u$ satisfying (6) and the following additional conditions:

$$\int_{\Omega_j} u(x) dx = q_j, \quad j = 1, 2, \ldots, m. \quad (7)$$

where the values $q_j$, $j = 1, 2, \ldots, m$, are prescribed. In particular, they can be set as follows:

$$q_j = \begin{cases} \text{mes}(\Omega_j) u^+, & \text{if } \Omega_j \cap M^+ \neq \emptyset, \\ \text{mes}(\Omega_j) u^-, & \text{if } \Omega_j \cap M^- \neq \emptyset, \end{cases}$$

$u^+$ and $u^-$ are prescribed (averaged) values of the function $u$ on the inlet and outlet domains, respectively.

Thus, the problem of finding the pressure distribution in a cerebral capillary network is reduced to a boundary value problem for Poisson’s equation with unknown intensities of sources and prescribed mean values of the solution. This problem can also be considered as an inverse problem with finite-dimensional overdetermination.

In [12], the continuum model of the form (6) was implemented for a simple case of cubic domain containing two inlets and two outlets. To compute the unknown intensities of the inlets and outlets, a numerical simulation of the pressure and blood flow distribution was performed for a randomly generated capillary network containing 1300 nodes. It was conducted, to compare between the continuum and network models. Obviously, except for comparison between the two models, this approach of determining the intensities of the inlets and outlets does not make sense from a practical point of view, since it requires preliminary solving the problem (1), (2) for the capillary network model. In [1], a simple case of the boundary value problem without the source function is considered, where the inflow and outflow conditions are specified only on the external part of the boundary. A continuum blood flow model in a perfused biological tissue accounting for the anisotropic properties of the media and a hierarchical structure of vessels is proposed in [13]. The model does not use the source function. The boundary conditions are set at the terminal parts of the vessel network.

Thus, the formulated inverse problem is quite new. In the following sections, the unique solvability of the problem is proved and a method for finding its solution is proposed.

5. Existence and uniqueness of a weak solution. Let $H = L^2(\Omega)$ be the Lebesgue space and $V = W^2_0(\Omega)$ be the Sobolev space. Denote by $\| \cdot \|$ and $\| \cdot \|_V$ the norms in the spaces $H$ and $V$, respectively, and by $(u, v)$ the inner product in $H$, that is

$$(u, v) = \int_{\Omega} uv dx, \quad \|u\|^2 = (u, u), \quad \|u\|^2_V = \|u\|^2 + \|\nabla u\|^2.$$
Definition 5.1. A pair \( \{ \alpha, u \} \in \mathbb{R}^m \times V \) is a weak solution of the problem \( (6), (7) \) if
\[
(a \nabla u, \nabla v) = \sum_{j=1}^{m} \alpha_j (f_j, v) \quad \forall v \in V, \quad \text{and} \quad (f_j, u) = q_j, \quad j = 1, 2, \ldots, m. \tag{8}
\]

Lemma 5.2. There is a constant \( C > 0 \) depending only on \( \Omega, \Omega_1 \) such that
\[
\|v\|_V^2 \leq C(\|\nabla v\|^2 + (f_1, v)^2) \quad \forall v \in V. \tag{9}
\]

Proof. Assuming the opposite, we find the sequence \( v_j \in V, \|v_j\| = 1 \) and wherein
\[
\|\nabla v_j\|^2 + (f_1, v_j)^2 \to 0 \quad \text{as} \quad j \to \infty.
\]
This sequence is bounded in \( V \) (cf. \( \|\nabla v_j\|^2 + \|v_j\|^2 \)), and therefore, up to a subsequence, \( v_j \to v \) weakly in \( V \) and strongly in \( H \). Then, \( \nabla v = 0 \) and \( (f_1, v) = 0 \), which implies that \( v = 0 \). This contradicts the condition \( \|v\| = 1 \). \( \Box \)

Theorem 5.3. For any \( q = (q_1, q_2, \ldots, q_m) \in \mathbb{R}^m \), a weak solution of the problem \( (6), (7) \) exists and is unique.

Proof of Theorem 5.3. As a preliminary, consider the following \( \varepsilon \)-problem:
\[
J_\varepsilon(u) = \frac{1}{2}(a \nabla u, \nabla u) + \frac{1}{2\varepsilon} \sum_{j=1}^{m} [(f_j, u) - q_j]^2 \to \inf, \quad u \in V. \tag{10}
\]

Note that
\[
J_\varepsilon(u) \geq \frac{a_0}{2} \|\nabla u\|^2 + \frac{1}{2\varepsilon} [(f_1, u) - q_1]^2 \geq C_1 (\|\nabla u\|^2 + (f_1, u)^2) - C_2 q_1^2,
\]
where \( C_1 \) and \( C_2 \) are independent on \( u \) constants. Then, by Lemma 5.2, the functional \( J_\varepsilon \) is coercive on \( V \), that is \( J_\varepsilon(u) \to +\infty \) if \( \|u\|_V \to +\infty \). Note that the second Gateaux differential of this functional is determined by the expression:
\[
J''_\varepsilon(u, \varphi, \varphi) = (a \nabla \varphi, \nabla \varphi) + \frac{1}{\varepsilon} \sum_{j=1}^{m} (f_j, \varphi)^2 > 0 \quad \text{if} \quad \varphi \neq 0.
\]
Therefore, \( J_\varepsilon \) is strictly convex and weakly lower semicontinuous. Thus, there is a unique solution \( u_\varepsilon \in V \) of the problem \( (10) \), satisfying the following optimal condition:
\[
(a \nabla u_\varepsilon, \nabla v) = \sum_{j=1}^{m} \alpha_{\varepsilon j} (f_j, v) \quad \forall v \in V, \quad \alpha_{\varepsilon j} = \frac{1}{\varepsilon} (q_j - (f_j, u_\varepsilon)). \tag{11}
\]

Let \( \{w_j\}_1^m \subset V \) be a system dual to \( \{f_j\}_1^m \), that is \( (f_i, w_j) = \delta_{ij} \). Denote
\[
w = \sum_{j=1}^{m} q_j w_j.
\]
The inequality
\[
J_\varepsilon(u_\varepsilon) \leq J_\varepsilon(w) = \frac{1}{2}(a \nabla w, \nabla w)
\]
gives the estimate
\[
(a \nabla u_\varepsilon, \nabla u_\varepsilon) + \frac{1}{\varepsilon} \sum_{j=1}^{m} [(f_j, u_\varepsilon) - q_j]^2 \leq (a \nabla w, \nabla w).
\]
From this estimate, with accounting for (9), it follows the existence of a function \( \hat{u} \in V \) such that
\[
\begin{align*}
    u_\varepsilon &\to \hat{u} \text{ weakly in } V \\
    (f_j, u_\varepsilon) &\to (f_j, \hat{u}) = q_j \text{ as } \varepsilon \to 0, \quad j = 1, 2, \ldots, m.
\end{align*}
\]
Moreover,
\[
\alpha_{\varepsilon j} = (a\nabla u_\varepsilon, \nabla w_j) \to (a\nabla \hat{u}, \nabla w_j) := \alpha_j.
\]
Passing to the limit in (11) as \( \varepsilon \to 0 \), we conclude that the function \( \hat{u} \) satisfies the conditions (8), that is, it is a weak solution of the problem (6), (7).

To prove the uniqueness, it is enough to set \( q = 0 \) and \( v = u \) in (8). Then \((f_j, u) = 0, \nabla u = 0\), and therefore \( u = 0 \), that means the uniqueness of the problem. \( \square \)

**Remark 1.** If \( v = 1 \) is set in the definition of weak solution (8), then the following equality holds:
\[
\sum_{j=1}^{m} \alpha_j \omega_j = 0,  \tag{12}
\]
where \( \omega_j = (f_j, 1) \) is the volume of the subdomain \( \Omega_j \).

6. **Method for solving the problem (6), (7).** In the proof of Theorem 5.3, an optimization algorithm for finding an approximate solution of the problem (6), (7) was proposed. However, its direct application to numerical solving the nonlocal boundary value problem (11) is difficult if the volumes of the domains \( \Omega_j \) are small.

Below, another algorithm for solving the problem (6), (7) is proposed, based on reducing the problem to solving a system of linear algebraic equations for unknown intensities of sources \( \alpha_1, \alpha_2, \ldots, \alpha_m \).

First note that the equation (12) implies the formula
\[
\alpha_m = -\frac{1}{\omega_m} \sum_{j=1}^{m-1} \alpha_j \omega_j.
\]
Therefore, the right-hand side of equation (6) assumes the form:
\[
\sum_{j=1}^{m} \alpha_j f_j = \sum_{j=1}^{m-1} \alpha_j f_j - \frac{1}{\omega_m} \sum_{j=1}^{m-1} \alpha_j \omega_j f_m = \sum_{j=1}^{m-1} \alpha_j g_j,
\]
where \( g_j = f_j - f_m \omega_j/\omega_m \), and obviously \((g_j, 1) = 0\).

Thus, the solution of the boundary value problem (6) has the following structure:
\[
    u(x) = \sum_{j=1}^{m-1} \alpha_j u_j(x) + C, \quad x \in \Omega.
\]
where \( C \) is a constant, and the functions \( u_j \in V, \ j = 1, \ldots, m - 1 \), are solutions of the following boundary value problems:
\[
    -\text{div} (a\nabla u_j) = g_j \text{ in } \Omega, \quad \partial_n u_j = 0 \text{ on } \Gamma, \quad (f_m, u_j) = 0.
\]
Then the non-local condition (7) assumes the form
\[
(f_k, \sum_{j=1}^{m-1} \alpha_j u_j(x) + C) = q_k, \quad k = 1, 2, \ldots, m.
\]
The last equation, with \( k = m \), implies that \( C = q_m/\omega_m \). Hence, the coefficients \( \alpha_1, \alpha_2, \ldots, \alpha_{m-1} \) are solutions of the following system of linear algebraic equations:

\[
\sum_{j=1}^{m-1} (f_k, u_j) \alpha_j = q_k - \frac{\omega_k}{\omega_m} q_m, \quad k = 1, \ldots, m - 1. \tag{13}
\]

**Theorem 6.1.** For any \( q = (q_1, q_2, \ldots, q_m) \in \mathbb{R}^m \), the system (13) is uniquely solvable.

**Proof of Theorem 6.1.** It is sufficient to verify that the corresponding homogeneous system has only the trivial solution. Thus, consider the system

\[
\sum_{j=1}^{m-1} (f_k, u_j) \alpha_j = 0, \quad k = 1, \ldots, m - 1. \tag{14}
\]

Denote

\[
g = \sum_{j=1}^{m-1} \alpha_k g_k, \quad w = \sum_{j=1}^{m-1} \alpha_j u_j.
\]

These functions satisfy the following conditions:

\[-\text{div} (a \nabla w) = g \text{ in } \Omega, \quad \partial_n w = 0 \text{ on } \Gamma, \quad (f_m, w) = 0, \tag{15}\]

which imply that \( (a \nabla w, \nabla u) = (g, w) \). Moreover, it is easily to see that

\[
(f_k, u_j) = (f_k - \frac{\omega_k}{\omega_m} f_m, u_j) = (g_k, u_j). \tag{16}
\]

Now, multiplying (14) with \( \alpha_k \), summing the result over \( k \), and accounting for (16) yield the equality \( (g, w) = 0 \). Therefore, \( w = 0 \) and \( g = 0 \) due to (15). Hence,

\[
0 = \sum_{j=1}^{m-1} \alpha_k g_k = \sum_{j=1}^{m-1} \alpha_k (f_k - \frac{\omega_k}{\omega_m} f_m) = \sum_{j=1}^{m} \alpha_k f_k,
\]

where

\[
\alpha_m = -\frac{1}{\omega_m} \sum_{j=1}^{m-1} \alpha_j \omega_j.
\]

The linear independence of functions \( f_1, \ldots, f_m \) implies that all coefficients \( \alpha_k \) are equal to zero, which proves the theorem.

**Remark 2.** The algorithm for solving the problem (6), (7) involves solving Neumann problems for Poisson’s equations

\[-\text{div} (a \nabla u_j) = g_j \text{ in } \Omega, \quad \partial_n u_j = 0 \text{ on } \Gamma, \quad (f_m, u_j) = 0, \quad j = 1, \ldots, m - 1.\]

Next, the coefficients \( \alpha_1, \ldots, \alpha_{m-1} \) should be found as solutions of the system (13). The resulting solution \( u \) and the coefficient \( \alpha_m \) are defined by the formulas

\[
u(x) = \sum_{j=1}^{m-1} \alpha_j u_j(x) + \frac{q_m}{\omega_m}, \quad x \in \Omega, \quad \alpha_m = -\frac{1}{\omega_m} \sum_{j=1}^{m-1} \alpha_j \omega_j.
\]

**Remark 3.** The values of the intensities \( \alpha_j \) depend on the spatial location of inlets and outlets and are generally different for different \( j \).
7. Numerical experiment. In numerical simulations, a two-dimensional square domain with the edge of 1.8 mm is considered, and 64 circular subdomains $\Omega_j$ (32 inlets and 32 outlets) with the radius of 0.02 mm are set. Such a choice provides the physiologically relevant density of inlets and outlets, e.g., as it is reported in [10]. Assuming that the medium is homogeneous, we take $a = 1$.

To build a computational mesh, each edge of the square domain is divided into 180 segments. The inlets and outlets are uniformly distributed in the computational domain. The numerical algorithm is implemented using the Finite Elements package FreeFEM++ [4], wherein $P_1$ finite elements are used.

To set values of the average pressure at the inlets and outlets, we estimate the pressure drop in the capillary network (pressure difference between inlets and outlets). For the estimation, the cerebral flow rate and total resistance of the capillary network are required. According to [14], the cerebral blood flow rate $Q = 600$ ml/min is a realistic value for an adult brain. Moreover, a cerebral vessels model from [10] yields the total resistance, $R_T$, of the capillary level to be equal to $0.1 \text{Pa} \cdot \text{s}/\text{mm}^3$, which gives the pressure drop to be equal to 1000 Pa (computed as $Q \cdot R_T$). Since only relative pressure values are important, the blood pressure of 1000 Pa is set at the inlets, and 0 Pa is set at the outlets in the numerical experiment. The computed pressure distribution is shown in Fig. 2.

![Figure 2. The pressure distribution.](image)

Using the pressure distribution and Darcy’s law, it is easy to obtain the velocity field $v$ in the model domain with the exception for subdomains $\Omega_j$, $j = 1, \ldots, m$:

$$v = -\frac{k}{\mu \sigma} \nabla u,$$
where $\sigma$ is the porosity, $\kappa$ the permeability, and $\mu$ the blood viscosity. Following [12], the values $\sigma = 0.016$, $\kappa = 3.6 \cdot 10^{-9}$ mm$^2$, and $\mu = 3.6 \cdot 10^{-3}$ Pa·s can be chosen. The corresponding distribution of the absolute velocity is shown in Fig. 3.

Figure 3. The absolute velocity distribution.

8. Conclusion. A new method for solving boundary value problems for Poisson's equation with unknown intensities of sources and prescribed averaged (over subdomains) values of solutions is proposed. The unique solvability is proven. An algorithm for finding a solution is proposed. This approach can be applied to finding pressure distributions and velocity fields in continuum domains interpreted as spatially averaged capillary networks, which is crucial for the treatment of continuum models of oxygen transport in brain (see [6, 7, 8, 9]).

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