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Direct modeling of blood flow through the vascular network of the germinal matrix

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ABSTRACT

A premature birth, before completion of the 32nd pregnancy week, increases the risk of cerebral hemorrhage. The cause of brain bleeding is very often the germinal matrix of the immature brain. The germinal matrix consists of richly vascularized neuroepithelial cells and is located over the lower part of the head of the caudate nucleus. By 32-36 gestation weeks, the germinal matrix essentially disappears so that its hemorrhage is a disease of premature infants.

The aim of this paper consists in developing a model of the brain vascular network and computing the pressure distribution in the germinal matrix, particularly near arterioles and venules, where cerebral hemorrhage may occur. Capillary networks consisting of several millions of vessels are directly simulated in the present study.

1. Introduction

Advances in neonatal care have increased survival of preterm infants, but the occurrence of complications in postnatal development remains high. One of the most frequent (around 15–20% [1,2]) complications in infants born before 32 weeks gestation is intracerebral hemorrhage, which can lead to lifelong impairments such as cerebral palsy [3]. Most hemorrhages originate from the subependymal germinal matrix [4], a specific region in the immature brain between thalamus and caudate nucleus with high vascularity and a fragile capillary network [5]. The germinal matrix reaches its maximum size at 22 weeks gestation, then rapidly shrinks and disappears by 34 weeks [6]. Electron-microscope observations [7–9] show that vessels in the germinal matrix have a larger diameter than in the cortex, having thereby, according to Laplace's law, a larger wall tension and, consequently, higher probability of vessel rupture [8].

During recent years, numerical simulations clarifying influence factors and consequences of intracerebral hemorrhage in preterm infants have been performed [10,11]. These simulations, however, do not take into account the presence of the germinal matrix in the preterm brain. The aim of the present study is the development of a mathematical model for computing pressure fields in the germinal matrix. The study is a part of the project "Mathematical simulations towards preventing cerebral hemorrhage in premature infants" supported by the Klaus Tschira Stiftung. In the current stage, data necessary for the simulations are taken from the literature. Nevertheless, the implementation of the project assumes collection of clinical data for different gestation ages of patients.

An important part of the simulation of cerebral blood flow is the statement of a vascular model that includes a capillary network. There are different approaches to modeling brain capillary networks. Publication [12] contains an overview of some recent results concerned with microvascular simulations. Various methods have been developed to generate anatomically consistent capillary networks (see e.g. Refs. [13–19]). In Ref. [14], numerical simulations are conducted for an anatomically accurate human intra-cortical vascular network consisting of about 10 thousand of vessels. Sets of model data used there have been obtained in Ref. [13] on the base of Duvernoy's collection of brain slices, see Ref. [20]. Using flow balance models yielding systems of linear equations, the authors calculate important characteristics of blood circulation in small parts of human brain. Particularly, the mean pressure drop and the pressure distribution in microvascular networks considered are computed. Similar to [14], a mathematical model aiming at the simulation of capillary blood circulation is considered in Ref. [16]. In the last paper, the consideration is restricted to two-dimensional networks to

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avoid limitations when using experimental images. Numerical simulations are conducted for capillary networks containing several dozen of capillaries. In Ref. [18], an algorithm for the creation of capillary networks from X-ray microscopic images is proposed to calculate pressure and flow distributions. In Ref. [19], four methods for artificial network creation to simulate the real cerebral microvasculature have been proposed and numerically compared. The methods are based on the random generation of nodes and edges of the capillary network. The number of edges corresponding to one node does not exceed 3. The main criterion of adequacy of the generated network is the obtained vessel length distribution in comparison with data from Ref. [13]. The microvascular flow and oxygen transport are analyzed using the constructed networks. It should be noted that only small networks, consisting of several hundreds of capillaries, can be simulated in such a way.

On the other hand, our experience shows that a precise recovery of the geometric structure of capillary networks is not too much important for estimating its hydraulic resistance. The more essential thing is the topology of the network, i.e. the number of incident capillaries for each capillary junction. Moreover, there is experimental evidence that the number of incident capillaries varies essentially from node to node. By analogy with electric circuits (cf. [21]), taking into account that capillary vessels are very short and do not interact one with another, topologically equivalent capillary networks with different geometries give similar outcomes. The model proposed in the present paper implements random net-like capillary topologies with variable numbers of incident edges. The creation of such networks is relatively simple and allows us to simulate regions with jammed or corrupted vessels. Our algorithm is able to treat networks containing up to 800 million capillaries, which corresponds to the capillary network of the complete adult human brain (see Ref. [22]). Thus, the algorithm proposed is well suited for some applications that deal with large vascular networks [18].

Another important question in modeling capillary network flow is the computation of hydraulic resistances of capillaries. In this connection, there is a popular approach considering the propagation of red blood cells (RBCs) and plasma as Poiseuille's flow of a homogeneous fluid with the so-called apparent viscosity, see e.g. Refs. [14] and [23]. The direct role of RBCs in the dynamics of microcirculation has been considered in numerous publications (see e.g. Refs. [21,24–29]). It is shown that the local concentration of RBCs has a strong impact on the local flow resistance, which influences the pressure and flow fields in the whole network. Particularly, the importance of considering the capillary perfusion as two-phase flow of RBCs and plasma is indicated in Ref. [21]. The specific of our approach is that the flow is considered as the motion of a fluid with variable viscosity: Very viscous central part corresponds to RBCs, and a lubrication plasma layer between the capillary wall and RBCs reduces the friction.

The present paper is organized as follows. In section 2, a hydrodynamical description of the propagation of red cells in capillaries is developed. This allows us to compute the hydraulic resistance of a single capillary, depending on its radius and length. An explicit formula derived here is important for the simulation of large capillary networks considered in the next sections. In sections 3 and 4, a method of computing total resistance of the germinal matrix and the rest part of the brain is proposed. It is assumed that capillaries are connected in a network according to some variable topology, i.e., for each node, a random number of incident edges are generated. The topology is characterized by the average number of incident edges for each node. It is supposed that the length and radius of capillaries are random values distributed according to data reported in the literature. Moreover, the network contains blood sources and sinks (inlets and outlets) distributed over the network. They are associated with the arteriolar and venular endpoints, respectively. The calculation of the total resistance is being performed by the direct computation of the total blood flux through the capillary network by analogy with electric circuits, i.e. using Kirchhoff's law and solving a large sparse system of linear algebraic equations. Section 5 concerns with computing the pressure distribution in the germinal matrix. First, the total hydraulic resistance of the germinal matrix and the rest part of the brain are computed. Second, using a modified model from Ref. [22], the pressure drop in the germinal matrix is determined. Finally, solving large sparse systems of linear algebraic equations resulting from Kirchhoff's law, the pressure distribution inside the germinal matrix is calculated. Thus, the pressure value in each capillary becomes available, which allows us to catch dangerous pressure gradients near inlets or outlets. This seems to be important because some authors consider germinal matrix hemorrhage as the result of venous rupture (cf. [30]), and other authors claim that the hemorrhage is caused by rupture during arterial hypertension (cf. [8]).

2. Blood flow through capillaries

Red cells move one by one in capillaries using the blood plasma as lubrication, see Fig. 1 and [29]. This motion can be modeled as the flow of a continuous fluid with the variable viscosity as sketched in the above mentioned figure. The idea of modeling the cell/plasma mixture as a fluid with variable viscosity is based on the results obtained in Ref. [31]. It is proven there that the motion of a rigid body in a fluid can be described by replacing the body with another viscose fluid whose viscosity tends to infinity. The neglection of gaps between the red cells is motivated by the following results. First, data of capillary imaging, see e.g. Refs. [32] and [33], indicate very small gaps between the red cells. Second, the results of [34] and [35], where the authors have proven that a very strongly oscillating structure, even with excluded volume, does not allow the liquid to penetrate inside it. The same do relatively quickly moving (hundreds of diameters per second) red cells. Therefore, in a first approximation, the resistance of a capillary can be considered to be independent on small variations of gaps between red cells, i.e., on small variations of the haematocrit. Thus, in our opinion, the blood flow model proposed in the present paper is more reliable compared with the popular model of Poiseuille flow with the so-called apparent viscosity, see e.g. Refs. [14] and [23].

To describe the blood flow in a capillary, consider the velocity field, $\mathbf{u}$, in the cylindrical coordinates (see Fig. 2). Conventionally, neglect the radial and angular components of the velocity ($u_r = u_\theta = 0$) and assume that its vertical component depends on the radial variable only ($u_z = u_z(r)$). Moreover, assume the stationarity of the velocity, incompressibility of the fluid ($\nabla\cdot\mathbf{u} = 0$), absence of external forces, and radial variability of the viscosity ($\mu = \mu(r)$).

With these assumptions and the notation $v = u_z$, for brevity, the Navier-Stokes equations of motion is reduced to the following ordinary

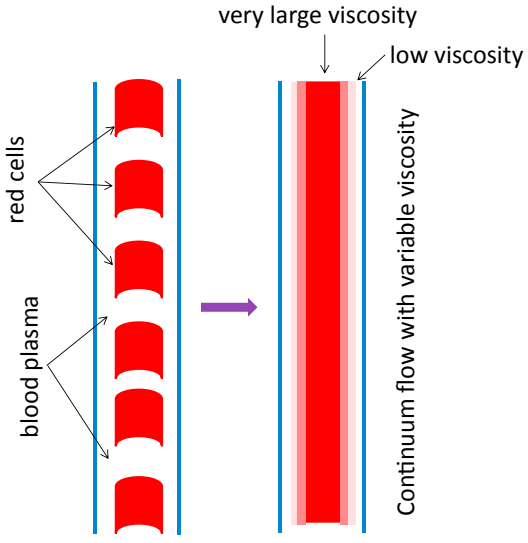

Fig. 1. Modeling the motion of red cells.

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