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Multiple equilibrium states in a micro-vascular network

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ABSTRACT

We use a simple model of micro-vascular blood flow to explore conditions that give rise to multiple equilibrium states in a three-node micro-vascular network. The model accounts for two primary rheological effects: the Fåhræus–Lindqvist effect, which describes the apparent viscosity of blood in a vessel, and the plasma skimming effect, which governs the separation of red blood cells at diverging nodes. We show that multiple equilibrium states are possible, and we use our analytical and computational tools to design an experiment for validation.

1. Introduction

The microvascular system is responsible for the transfer of nutrients and waste products to and from the tissues of the body. Blood vessels in the microvascular system are less than approximately 100 μm in diameter, and include arterioles, venules, and capillaries. The ability to describe the flow of blood through microvessels could result in more efficient drug delivery. For example, Chambers and Mitragotri demonstrated that drugs engineered to attach to red blood cells (RBC) have a longer lifespan [4]. Additionally, the study of micro-vascular networks can be abstracted and applied to other, similar networks such as traffic flow, shipping routes, or other large scale networks.

Cavalcanti and Ursino showed that blood flowing through capillary networks tends to exhibit chaotic behavior [3]. This oscillation in blood velocity is often attributed to arterial vasomotion, or the change in diameter of blood vessels. Vasomotion is not necessary, however, for dynamic behavior. In 1994, Kiani et al. found oscillatory behavior in experiments using large networks and explained their results using a model containing only the rheological properties of blood [8]. In 2000, Carr and LaCoin demonstrated (using the same model) similar results in small micro-vascular networks (networks with ~10 vessels) [2].

In 2005 and 2007, Geddes et al. analyzed the dynamics of a network with just four vessels and two nodes: the two-node network [1,6]. They observed that the network could sustain multiple equilibria and that in some parameter regimes the equilibria could undergo Hopf bifurcations leading to limit cycle oscillations. They were also able to successfully simulate flow through the two-node network, showing sustained oscillations. However the conditions they found for multiple equilibria and oscillations are unlikely to be met in human microvascular beds.

We focus on the next more complicated network shown in Fig. 1—the so-called three-node network with six vessels and three nodes. While conditions for multiple equilibria are unlikely to be met in the two-node network, the three-node network could present enough complexity to exhibit such behavior in a more reasonable parameter range. In Section 2 we describe the three-node network, review the major properties of blood including the Fåhræus–Lindqvist effect, plasma skimming, and Poiseulle's Law, and determine a method for finding equilibrium. In Section 3 we explore conditions that give rise to multiple equilibria and present an experimental design that could be used for validation. Finally, in Section 4 we discuss the results and compare the three-node network to other small networks.

2. Model of micro-vascular blood flow

To describe a network of blood vessels and how it is interconnected, we borrow notation from graph theory. A single network is represented by a directed graph. Each vessel in the network is represented by an edge on the graph and the nodes, naturally, are the junctions where vessels intersect. We assume the diameter of a vessel is constant along its length and that neither length nor diameter change with time. We also assume that each node in the network forms an intersection of exactly three blood vessels.

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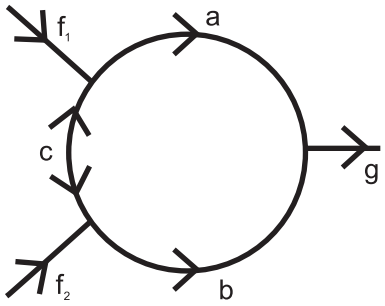

Fig. 1. A topological representation of the three-node network studied in this paper. Note that this network has three nodes, two inlets, and one outlet. Arrows indicate the direction of blood flow. Blood flow in vessel c can be in either direction.

For the three-node network (Fig. 1), blood enters the network through vessels f_1 and f_2, and exits through vessel g. Blood in vessels a and b must always flow toward vessel g, however blood in vessel c can flow either toward vessel a or vessel b. To account for this, we define flow in vessels a and b to always be positive, while we define flow in vessel c toward vessel b to be positive, and flow toward vessel a to be negative.

We use the variable Q_i to denote the blood flow, in units of nL/min, through a given vessel i. We assume that the blood flow is constant throughout a vessel, and that blood cannot accumulate in any part of the network. Conservation of blood at the nodes means that the blood flow into a node must equal the blood flow out of a node,

$$\begin{aligned} Q_a + Q_b &= Q_g, \\ Q_a + Q_c &= Q_{f_1}, \\ Q_b - Q_c &= Q_{f_2}, \end{aligned} \tag{1}$$

and that the total blood flow into the network matches the blood flow out of the network,

$$Q_{f_1} + Q_{f_2} = Q_g. \tag{2}$$

2.1. Relevant properties of blood

Blood is a suspension of cells (erythrocytes, leukocytes, or platelets) in plasma. Erythrocytes (red blood cells) are biconcave discs measuring 8 μm in diameter and 2 μm in height. RBCs account for about 45% of blood by volume; this percentage is referred to as hematocrit, and we denote this percentage with the variable H. Leukocytes (white blood cells) and platelets make up another 1% of blood, and plasma makes up the remainder [5].

Since blood is a suspension and travels through small vessels, it has some unique non-Newtonian properties which govern its flow. There are two notable effects which help to describe the flow of blood through small vessels. The first is known as plasma skimming, which predicts how RBCs will be partitioned into branching vessels. The second is the Fåhræus–Lindqvist effect which describes the relative apparent viscosity of blood as a function of hematocrit and the diameter of the vessel.

2.1.1. Plasma skimming

The term "plasma skimming" was first coined in 1921 by August Krogh [9]. Krogh observed that red blood cells tend to migrate radially toward the center of small vessels. This migration creates what Krogh called a "marginal zone" of plasma surrounding the flow of red blood cells. Furthermore, Krogh noted that when small vessels branched, there would occasionally be branches which received virtually no red blood cells but still maintained a flow. These branches were skimming plasma from the marginal zone.

The migration toward the center of a vessel is due to a lift force acting on the red blood cells [10]. Frictional forces due to the wall of the vessel create a velocity profile in which blood near the center of the vessel is flowing faster than blood near the wall of the vessel. The non-uniform velocity profile of these small vessels creates a pressure difference on opposing halves of each cell. The steepness of this velocity profile is dependent on the diameter of the vessel. For large vessels (>100 μm), the RBCs do not feel a strong lift force, and therefore they are homogeneously mixed across the vessel. As the diameter of the vessel decreases, the marginal zone of plasma increases, and the plasma skimming effect becomes relevant.

There have been numerous studies performed to determine a model for the plasma skimming effect. In this paper we use the model proposed by Pries et al. [11]. The model describes how RBC flow is partitioned when a vessel branches into two vessels. If we consider a node where a vessel f branches into vessels a and b, then the RBC flow through vessel a (H_aQ_a) normalized by the RBC flow through the feed vessel (H_fQ_f),

$$\frac{H_aQ_a}{H_fQ_f} = \begin{cases} 0, & \frac{Q_a}{Q_f} < Q_0, \\ \dfrac{e^r\left(\frac{Q_a}{Q_f} - Q_0\right)^p}{e^r\left(\frac{Q_a}{Q_f} - Q_0\right)^p + \left(1 - \frac{Q_a}{Q_f} - Q_0\right)^p}, & Q_0 \leqslant \frac{Q_a}{Q_f} \leqslant 1 - Q_0, \\ 1, & \frac{Q_a}{Q_f} > 1 - Q_0, \end{cases} \tag{3}$$

$$r = -\frac{6.96}{D_f}\ln\left(\frac{D_a}{D_b}\right),$$

$$p = 1 + 6.98\frac{1 - H_f}{D_f},$$

$$Q_0 = \frac{0.4}{D_f},$$

is dependent on the fractional flow $\frac{Q_a}{Q_f}$ through vessel a, the diameters of all three vessels (D_f,D_a,D_b) and the hematocrit of the feed (H_f). Q_0 is the minimum fractional flow required to receive any RBCs. As we see in Fig. 2, there exists marginal zones $\left(\frac{Q_a}{Q_f} < Q_0 \text{ and } \frac{Q_a}{Q_f} > 1 - Q_0\right)$

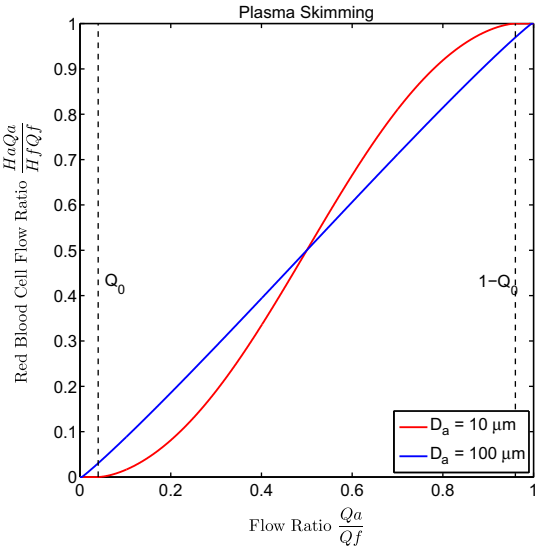

Fig. 2. Pries, Ley, and Geahtgens model of plasma skimming. Plasma skimming is most prominent at low diameters. In a vessel with a diameter of 100 μm there is virtually no plasma skimming and RBC flow ratio is proportional to flow ratio. At a diameter of 10 μm RBC flow ratio is not proportional to flow ratio—the vessel with higher flow gets even higher RBC flow. Furthermore, for $\frac{Q_a}{Q_f} < Q_0$ and $\frac{Q_a}{Q_f} > 1 - Q_0$, one of the blood vessels receives no RBC's.