BLOOD PRESSURE AND FLOW VALUES IN SMALL VESSELS ANGIOARCHITECTURES: APPLICATION FOR DIABETIC RETINOPATHY

LUMINIȚA MORARU1,*, CRISTIAN DRAGOS OBREJA2, SIMONA MOLDOVANU1,2, ANTOANETA ENE1, ANJAN BISWAS3,4

1Dunarea de Jos University of Galati, Faculty of Sciences and Environment, Department of Chemistry, Physics and Environment, 47 Domneasca St., 800008 Galati, Romania
2Dumitru Moțoc High School, 15 Milcov St., 800509, Galați, Romania
3Department of Mathematical Sciences, Delaware State University, Dover, DE 19901-2277, USA
4Department of Mathematics, Faculty of Science, King Abdulaziz University, Jeddah-21589, Saudi Arabia

*Corresponding author: luminita.moraru@ugal.ro

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This paper aims to study the blood pressure and flow at any site (or node) based on the branching asymmetry, the number of nodes and elements of a branching tree in the real retinal vascular structures. The analysis of blood flow in the circulatory system is based on Navier-Stokes equation, Poiseuille flow and an asymmetry parameter in order to gather information on the pressure field distribution as well as flow profile. Two retinal vessel geometries were investigated, i.e. normal human eye and diabetic retinopathy. The measured branching asymmetry is 0.4. Only two exceptions were established for diabetic retinopathy images. For the analyzed structures, the pressure gradient have almost similar profiles indicating that the overall behavior of pressure drop in all the vessels remains very much unaltered. Changes in the blood flow profiles were highlighted for diabetic retinopathy pathology (p < 0.001). This study is a first step in a right direction toward personalized medicine for pathologies related to the dynamics of blood flow.

Key words: Retinal vascular tree; Branching asymmetry; Hemodynamics; Blood pressure; Blood flow.

1. INTRODUCTION

The geometry of the vessel influences blood flow pattern and has a decisive influence on health and disease. Certain pathologies such as diabetic retinopathy, stroke, hemorrhage lesions, traumatic brain injury and vascular dementias are closely related to the dynamics of blood flow [1–3]. It is very difficult to predict and to obtain results on pressure and flow at any site in the vascular system. Generally, reported studies are accounting either for the blood pressure or for the velocity field, failing to focus on blood pressure and flow at the same time.

Branching symmetry and asymmetry have been intensively studied as an optimization operation, consistent with vascular adaptation or various diseases [4–6]. In [6], a model that correlates fractal perfusion heterogeneities with the scaling of vessel resistance, in a branching asymmetry approach, is reported. The branching asymmetry parameter in their model varies between 0.1 and 0.5. The models that addressed the asymmetrical branching distribution are mostly dedicated to air flow through the tracheobronchial tree [7, 8]. Local hemodynamics is involved in vascular diseases associated with flow at bifurcations such as atherosclerosis aneurysms and diabetic retinopathy. In the case of diabetic retinopathy, most of the previous researches focused only on the detection of retinal blood vessels and of neovascularization architecture [9, 10]. Pemp et al. [11] investigated retinal blood flow in diabetic patients during normalized glucose levels. Their results are related to the insulin administration moment.

Due to a large number of parameters required to describe such a complex vascular tree system, development of a general applied model is very difficult. In an attempt to simplify this analysis and to predict the diameters of branching vessels in the cardiovascular system, Murray [12] derived an equation based on the principle of minimum energy. Murray’s law states that the power required to operate a cylindrical vessel network via Poiseuille flow is proportional to the cube of the vessel diameter. For a parent vessel diameter \(D_1\) and their daughter diameters \(D_2\) and \(D_3\), power is minimized if the branching exponent \(z\) is in the following relationship:

\[
(D_1)^3 = (D_2)^3 + (D_3)^3.
\]

Here, it is assumed that \(z = 3\) at each bifurcation point and for all trees whose internal flows obey laminar conditions. Murray’s law is not applicable to the aorta, pulmonary artery and the smallest capillaries [13]. It works well for the human coronary arteries, the larger airways of lung [14], in other fluid transport systems in zoology [15] or in industry (network of pipes). Later, Uylings [16] demonstrated that the branching exponent varies in the range of 2.33–3.0 depending on whether the flow is turbulent (2.33) or laminar (3.0).

A method for quantifying the blood pressure and flow profiles in each node of a branching tree structure is presented in this paper. To our knowledge, there is no hemodynamics study which predicts the blood pressure and flow values at each node of a retinal vascular tree. The model is relatively simple and is based on the assumption that the branching tree is asymmetrical, defined as the relative blood volume fraction passing through the branch of a vessel bifurcation. In order to validate the proposed model, two sets of retinal images containing vascular structures of a normal human retina and diabetic retinopathy were utilized.

The goals of our research are as follows: i) to explore the impact of various vascular geometries on the hemodynamics of small vessels. A new and direct application of our research consists of finding the numerical values of the blood
pressure and flow distribution at each node into the vascular tree having various vascular geometries; ii) to quantify the resistance of the branching trees for a chosen branching pattern.

We believe that this study could have important functional implications.

2. EXPERIMENTAL

2.1. VASCULAR GEOMETRY

The proposed model takes into consideration both the arterial and venous flows. The flow proceeds from a single inlet arteriole vessel, passes through many small vessels and the outlet terminal is a venule. The capillary bed is neglected as it doesn’t obey the physical laws of fluid flow. We treated the vessels as the thin ones assuming that the internal and external radii have nearly the same size. According to Takahashi et al. [17], the retinal arterioles and venules form a regular dichotomic network. The measured asymmetry parameter has the value 0.4. The inertia effect of flow has been neglected according to data reported in [18]. Also, we neglected the precise geometric form of the bifurcations and junctions. In order to compute the flow, the total resistance of the structure is estimated. The blood viscosity is assumed to be constant.

2.2. POISEUILLE’S LAW AND PRESSURE GRADIENT

The blood flow in the circulatory system is described based on the Navier–Stokes equations. Usually, the blood motion into the circulatory system is assumed to be a steady, laminar flow with constant viscosity and Poiseuille’s law is largely usable. The vascular geometry is cylindrical and the resistance of flow

\[ R_{\text{eff}} = \frac{8\mu L}{\pi r^4} \]

is independent of the vessel location being dependent of the size (length \( L \) and radius \( r \)) of the vessels and blood dynamic viscosity \( \mu \). The pressure gradients \( \Delta P = P_{\text{inlet}} - P_{\text{outlet}} \) of the system obey Poiseuille’s law [19]. \( P_{\text{inlet}} \) refers to the blood pressure in arterioles and \( P_{\text{outlet}} \) to the blood pressure in venules. In order to ensure the continuity of the pressure and conservation of flow, for a parent vessel \((D_1)\) and their daughter \((D_2 \text{ and } D_3)\), the following conditions are imposed, at each bifurcation:

\[ p|_{D_1} = p|_{D_2} = p|_{D_3} \quad \text{and} \quad Q|_{D_1} = Q|_{D_2} + Q|_{D_3}. \]

Kirchhoff’s law has been used to calculate the resistance of flow as

\[ R_{\text{series}} = R_x + R_y \quad \text{or} \quad R_{\text{parallel}} = (R_x R_y)/(R_x + R_y), \]

depending on the local geometry. The effective resistance \( R_{\text{eff}} \) has been computed following the same laws of
physics. \( R_{\text{eff}} \) allows the computation of pressure variation and flow with the aid of Matlab (The MathWorks Inc., Natick, Massachusetts, USA). The input data for our algorithm is as follows: the length and diameter of vessel, and the inlet and outlet pressure. Also, information about the number of nodes, number of branches (or edges) and blood viscosity is required. The outlet pressure, namely the pressure in the venule vessel, is the known parameter of the system. The inlet pressure has been computed for each vascular system taking into account the value of \( R_{\text{eff}} \), blood flow and geometrical data of branches.

2.3. CLINICAL DATABASE

The experimental results are performed on the patient’s clinical images from two publicly available datasets containing human retinal images. The DRIVE retinal image database has been used to test the developed approach [20]. It provides two sets of hand labeled images segmented by two human experts as ground truth. The experiments were conducted on 40 manually segmented binary images collected from the DRIVE database that were made available by [21]. This retinal vessel reference dataset allows an accurate assessment of the vessel width and length. 20 clinical images of normal human eye and 20 of diabetic retinopathy were used (Fig. 1). In order to reduce the computation efforts we decided to focus on the limited regions. Two different vascular architectures were selected; one shows less complicated branches geometry and the other has a more complex structure. The number of the used blood vessels varied between 3 and 12, depending on the individual retinal angioarchitecture.

![Fig. 1 – Examples of hand-segmented and binarized image from the DRIVE database.](image1.png)
a) Normal human retina (NHR); b) diabetic retinopathy (DR). The retinal vessels appear white. The analyzed ROIs are in the red rectangles.

![Fig. 2 – Hand-labeled images with the information about the artery and vein provided by STARE database.](image2.png)
a) Normal; b) Diabetic retinopathy.

The information regarding the artery and vein labeling done by the experts were gathered from STARE database, for both analyzed pathologies (Fig. 2) [22]. The hand-labeling was done by an ophthalmologist. The following convention was
followed for the labeling: ‘A’ if the vessel was artery; ‘V’ if the vessel was vein; and ‘white dot’ if the labeling was questionable.

In the case of diabetic retinopathy, the vessels become thin with fragile walls, and the new development of retinal vessel patterns due to extensive lack of oxygen occurs. The fundamental question is if the pathological vascular architecture insures an adequately perfusion for all areas of the tissue. A reliable patient-specific blood flow analysis will be strongly influenced by the geometric accuracy of the patient-specific vascular model and by some parameters such as inflow blood speed and blood viscosity. The first issue is overcome by the use of segmented retinal images provided by DRIVE database. The second issue is partly overcome by using the same blood viscosity and outlet pressure values while the inlet pressure varies according to the studied vascular architecture.

3. RESULTS

In this section we present the pressure gradient and flow rate profiles between nodes. All measurements were based on the same set of parameters. Blood was considered as an incompressible Newtonian fluid with blood density \( \rho = 1060 \text{ kg m}^{-3} \) and blood viscosity \( \mu = 3.5 \times 10^{-3} \text{ Pa s} \). The outlet pressure is the known parameter of the system and had the same values for all experiments.

Statistical analysis was performed with SPSS 17.0. Data are presented as means ± SD. An unpaired t test and a level of significance \( p < 0.001 \) were used to assess differences between NHR and DR.

Patient-specific vessel geometry represents the base for performing hemodynamic analysis in order to assess the performance of the proposed model. Figure 3 presents examples of the cropped areas from retinal images. Depending on the vascular architecture, a variable number of points were defined to establish the blood pressure and flow. Tables 1 and 2 show the parameters of the regions of interest of vascular trees, for each branch and \( \delta = 0.4 \). Only two exceptions have been determined for image DR1: at node N1 the asymmetry parameter is 0.3 and at node N5 (with three daughter vessels) there are two values of 0.3 and one value of 0.4. The algorithm considered the same value of 0.4 for all these trees.

The retinal vessels have the diameter range 250–650 \( \mu \text{m} \) and length range 1400–14000 \( \mu \text{m} \). According to the data in Tables 1 and 2, changes to the blood vessels exist (differences in vessel size and abnormal new blood vessels grow on the surface of the retina).

The magnitudes of change of blood pressure as a function of average vessel diameter for NHR and DR samples are shown in Fig. 4. Figures 5 and 6 provide samples of the profile of blood pressure and flow field in selected NHR and DR areas.
Fig. 3 – Selected vascular architecture of a normal human retina (NHR) and diabetic retinopathy (DR).

Table 1
The parameters of the region of interest of vascular trees for each branch and for asymmetry parameter $\delta = 0.4$ for two normal human retina ROIs

<table>
<thead>
<tr>
<th>Vessel segment</th>
<th>Diameter [μm]</th>
<th>Length [μm]</th>
<th>Vessel segment</th>
<th>Diameter [μm]</th>
<th>Length [μm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHR1</td>
<td></td>
<td></td>
<td>NHR2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>577</td>
<td>2106</td>
<td>A</td>
<td>604</td>
<td>8152</td>
</tr>
<tr>
<td>B</td>
<td>331</td>
<td>13660</td>
<td>B</td>
<td>509</td>
<td>4242</td>
</tr>
<tr>
<td>C</td>
<td>447</td>
<td>7131</td>
<td>C</td>
<td>350</td>
<td>7749</td>
</tr>
<tr>
<td>D</td>
<td>262</td>
<td>4282</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>345</td>
<td>4457</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$R_{eff}$ [kg mm$^{-4}$ s$^{-1}$] 0.629

Inlet pressure [Pa] (mm Hg)

3764 (31.9)

Table 2
The parameters of the region of interest of vascular trees for each branch and for asymmetry parameter $\delta = 0.4$ for two diabetic retinopathy ROIs

<table>
<thead>
<tr>
<th>Vessel segment</th>
<th>Diameter [μm]</th>
<th>Length [μm]</th>
<th>Vessel segment</th>
<th>Diameter [μm]</th>
<th>Length [μm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR1</td>
<td></td>
<td></td>
<td>DR2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>610</td>
<td>4012</td>
<td>A</td>
<td>327</td>
<td>5859</td>
</tr>
<tr>
<td>B</td>
<td>257</td>
<td>3901</td>
<td>B</td>
<td>241</td>
<td>4243</td>
</tr>
<tr>
<td>C</td>
<td>557</td>
<td>4160</td>
<td>C</td>
<td>370</td>
<td>6917</td>
</tr>
<tr>
<td>D</td>
<td>274</td>
<td>6251</td>
<td>$R_{eff}$ [kg mm$^{-4}$ s$^{-1}$] 0.310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>407</td>
<td>1046</td>
<td>Inlet pressure [Pa] (mm Hg) 3116 (23.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>408</td>
<td>7918</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>284</td>
<td>1432</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>246</td>
<td>3063</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 7 shows the experimental values of blood flow as a function of vessel diameter values for arterioles and venules, for both NHR1 and DR1 samples. The threshold of significance is $p < 0.001$.
Fig. 5 (continued) – The pressure gradients between nodes and flow profiles along the branches of vascular tree for NHR1 and DR1 images.

Fig. 6 – The pressure gradients between nodes and flow profiles along the branches of vascular tree for NHR2 and DR2 images.
4. DISCUSSION

The main contribution of this study is the quantification of the blood pressure gradients and the blood flow heterogeneity related to the vascular architecture and branching asymmetry of retinal vascular trees. We observed a decrease in both retinal blood flow and pressure for patients with DR. In the DR, abnormal new blood vessels (neovascularisation) are formed at the back of the eye; they can burst and bleed and blur the vision because these new blood vessels are fragile. For all the analyzed images the vessel diameters are smaller in DR than in NHR. Similarly, blood pressure as well as flow values tended to be decreased in patients with DR and clear differences in the blood flow profiles exist between NHR and DR images. Pressure and flow patterns were calculated and compared in all bifurcation sites, as shown in Figs. 5 and 6. The blood pressure gradient ranged from 32 mmHg to 15 mmHg between nodes for NHR, and from 24 mmHg to 16 mmHg between nodes for DR. The blood flow in NHR retinal arterioles and
venules varied from 54 ± 5.39 to 216 ± 7.23 [μL min⁻¹] and from 68 ± 2.64 to 212 ± 2.08 [μL min⁻¹], respectively. The blood flow in DR arterioles and venules ranged from 14 ± 2.01 to 205 ± 3.40 [μL min⁻¹] and from 20 ± 1.4 to 206 ± 3.94 [μL min⁻¹], respectively. The pathological state changes the branch where the volume of blood is stagnant from arterioles to venules. These branches with almost zero flow indicate a high pressure in parent vessel (e.g. branches 2-3 and 4-5 in DR2) and an inadequate perfusion of the tissue. They present blood stagnation, and as a result several areas of the retina are deprived of their blood supply. As a consequence, this extensive lack of oxygen leads to new development of retinal vessel patterns. Also, the $R_{eff}$ shows a large variation between the analyzed architectures due to the existing differences between the number of branches and nodes and due to the patient-specific geometry, as well.

According to data depicted in Figs. 5–7, the retinal angioarchitecture specific to DR dramatically changes the blood flow profile. Abnormal blood flow distribution for both arterial and venous segments of smaller diameters is clearly showed. This indicates retinal alterations and the occurrence of neovascularization architecture. Results explain the crucial role of arterioles in the regulation of the local blood flow. Arterioles are known as resistance vessels. They prevent damaging the microcirculation. By variation of the arteriolar radius, arterioles control the distribution of blood to different tissues. Thus, small changes to arteriolar radius can exert large effects in resistance and therefore in blood flow to an organ. On the contrary, venous resistance is relatively low. Despite this, there are no direct methods for measuring vascular resistance.

To the best of our knowledge, Langham’s study [23] has been the first attempt to assess the average ophtalmic arterial pressure and the ocular pulsatile blood flow for healthy and diabetic patients. They reported that for healthy patients a mean ophtalmic arterial pressure of 83 ± 2.4 mmHg and an ocular pulsatile blood flow of 648 ± 42 [μL min⁻¹] respectively. For DR, a pulsatile blood flow of 210 ± 37 [μL min⁻¹] and a low ophtalmic arterial pressure were found. These values were measured in large retinal vessels. The arterial and venous retinal blood pressure and flow distribution in each node of the vascular tree have not been measured in patients with diabetes thus far. Later, Olufsen’s study [24] predicted only the pressure drop across the systemic and pulmonary arterial vascular beds using a tree model with no reference to any flow profile between the nodes of the vascular tree. On the other hand, results reported in [11] apparently contradict our finding and instead show an increase of retinal blood flow and a reduction of retinal blood velocities during a euglycemic clamp. It is important to note that this study assessed the total volumetric retinal blood flow rate and that the glucose and
insulin plasma levels have a considerable influence on retinal blood flow. Cybulska-Heinrich et al. [25] reported an increase in retinal venous pressure values for DR patients until the value of 33.8 ± 10.1 mmHg but this result was significantly age dependent.

Our data is in agreement with previous studies [23, 24], indicating decreased retinal blood pressure and flow in diabetic retinopathy. Compared with these previous studies our method provides local information about the measured quantities, i.e. at each node of vessel tree. However, this wide range of experimental results clearly indicates that this topic remains very challenging.

It has to be noted that individual blood flow analysis is subject to the limitations of time and facilities because the most demanding step is the effective computation of the $R_{eff}$. Thus, the proposed model contains the following limitations: (i) it does not take into account the local geometry at the vessel bifurcations; (ii) it does not incorporate the elastic properties of the arteriole walls; (iii) the geometry of the eye could affect the experimental determination of the pressure and flow values, and (iv) the wall friction in the vessel was neglected. Moreover, we recognize that although the asymmetry of the vascular tree is an important factor for flow distribution, there are other determinant factors in this process. But, the proposed model balances some possible geometric and hemodynamic inaccurate data with its simplicity.

5. CONCLUSIONS

The purpose of this study was to analyze the blood flow profiles and pressure gradients in small vessels of retinal images. Clinical images of normal human eye and diabetic retinopathy were used. Blood pressure as well as flow values tended to be decreased in patients with DR and clear differences in the blood flow profiles exist between NHR and DR images. The blood pressure and flow profiles for an asymmetry parameter of 0.4 indicate in the cases of NHR1 and DR2 that the pathological state changes the branch where volume of blood is stagnant from arterioles to venules.

This study is a first step in a right direction toward personalized medicine for pathologies related to the dynamics of blood flow. A further research direction to be explored is concerned with the vision loss present in diabetic edema. These results can be extrapolated by specifying changes in retinal vascular characteristics.

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