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Blood flow regulation and oxygen transport in a heterogeneous model of the mouse retina

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Abstract

Elevated intraocular pressure is the primary risk factor for glaucoma, yet vascular health and ocular hemodynamics have also been established as important risk factors for the disease. The precise physiological mechanisms and processes by which flow impairment and reduced tissue oxygenation relate to retinal ganglion cell death are not fully known. Mathematical modeling has emerged as a useful tool to help decipher the role of hemodynamic alterations in glaucoma. Several previous models of the retinal microvasculature and tissue have investigated the individual impact of spatial heterogeneity, flow regulation, and oxygen transport on the system. This study combines all three of these components into a heterogeneous mathematical model of retinal arterioles that includes oxygen transport and acute flow regulation in response to changes in pressure, shear stress, and oxygen demand. The metabolic signal (S_j) is implemented as a wall-derived signal that reflects the oxygen deficit along the network, and three cases of conduction are considered: no conduction, a constant signal, and a flow-weighted signal. The model shows that the heterogeneity of the downstream signal serves to regulate flow better than a constant conducted response. In fact, the increases in average tissue PO_2 due to a flow-weighted signal are often more significant than if the entire level of signal is increased. Such theoretical work supports the importance of the non-uniform structure of the retinal vasculature when assessing the capability and/or dysfunction of blood flow regulation in the retinal microcirculation.

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Keywords

Mathematical model; blood flow regulation; oxygen transport; retina; heterogeneous vascular network

1. Introduction

Primary open angle glaucoma (OAG) is the second-leading cause of blindness worldwide and is characterized by progressive retinal ganglion cell death and irreversible loss of vision. Glaucoma is a heterogeneous disease that differentially affects groups by age, race, and gender, and has high individual variation in associated risk factors [1]. While reduction of intraocular pressure (IOP) remains the only approved therapeutic option, many individuals will develop OAG and/or continue to have disease progression despite low and/or medically lowered IOP. Vascular health and ocular hemodynamics have been well-established as risk variables in many patients [2], yet we do not have a full understanding of retinal blood flow, structure, and ganglion cell health in glaucoma. Previous experimental studies have established relationships between retinal structure and function, while other clinical studies have shown a very significant correlation between retinal function and blood flow/hemodynamics [3, 4]. While there is evidence indicating that glaucomatous damage precedes structural changes, the exact physiological mechanisms and order of events related to ganglion cell death remain poorly understood.

The eye is highly complex, and many ocular tissues and their physiological interactions are difficult to image and observe *in vivo*. Theoretical modeling has emerged as a valuable tool [1, 5-12] to identify the specific mechanisms that combine to impair retinal blood flow and influence the course of glaucomatous disease. Previous mathematical models of the retinal microvasculature and tissue have been developed that account for some of the factors that influence retinal blood flow and oxygenation (Figure 1). The vessel network supplying the tissue is heterogeneous, with wide variations in vessel size, spacing, density, and path length. The vessel network structure, capacity for flow regulation, and transport processes of oxygen are key factors that affect perfusion and oxygenation of the retina. Some models have considered all of these factors in the context of longer-term structural adaptation in the developing retinal microvasculature [11, 12]. However, acute time frame mathematical models of the retina have included some of these factors, but not all. For example, some modeling studies have accounted for blood flow regulation in the retinal microcirculation [5, 13]; however, these have assumed a uniform structure to the vascular network. Studies that have included a more complex network and tissue structure and/or realistic description of oxygen transport have not accounted for flow regulation [8-10]. The current study models oxygen transport and acute flow regulation in an explicit representation of a retinal network obtained from confocal microscopy images.

Previous modeling work [14, 15] demonstrated that mechanisms of flow regulation are inherently different in a heterogeneous vascular network than in a uniform network representation. The present study establishes a framework to investigate blood flow regulation and oxygenation in a non-uniform retinal microvasculature. Thus, this model fills

a major void by providing an accurate depiction of oxygen delivery to retinal tissue based on flow regulation principles in a realistic network structure.

The model also predicts the role and relative importance of myogenic, shear-dependent, and metabolic response mechanisms in maintaining adequate oxygenation under a range of metabolic and flow regulation conditions. Specifically, for a range of varying levels of tissue oxygen demand, the impact of the myogenic response is examined, and the effectiveness of a range of metabolic responses is explored. Ultimately, by demonstrating the importance of various flow regulation mechanisms in maintaining tissue oxygenation in a realistic, retinal microvascular network with non-uniform structure, this model will have important translational applications in a mechanistic understanding of the origins of flow impairments, structural changes, and glaucomatous vision loss.

2. Material and Methods

2.1 Network description

A previous study [9] established a heterogeneous vascular network model of the mouse retina. The positions, diameter, lengths, and connections of the retinal arterioles and venules were based on confocal microscopy images obtained by Ganesan et al. [16]. A capillary network was also defined (as in Ganesan et al. [17]) based on capillary density measurements in retinal tissue. The confocal microscopy images revealed that the retinal arteriolar network of the mouse contains 6 main branches fed by the central retinal artery, and that each of these branches feeds a non-uniform distribution of 4-5 orders of downstream arterioles of various lengths and diameters before reaching a terminal arteriole (Figure 2).

The present study adds a flow regulation component to the heterogeneous arteriolar network model of oxygen transport described in Fry et al. [9]. Diameters, lengths, and positions of vessels in the arteriolar network are taken directly from Fry et al. [9]; all values are reproduced in Table 1 and correspond to reference (control) state conditions. Because the capillary network in [9] was generated with averaged parameters, it produced a large homogeneous network structure that vastly increased computation time and lacked the realistic heterogeneity obtained from the confocal images that produced the arteriolar network. Thus, the capillary network was not included in this study, to focus on the effects of the explicit heterogeneous structure of the arteriolar network on flow regulation.

2.2 Blood flow

The vascular network is represented as a directed graph where each edge corresponds to a blood vessel segment with a specific diameter and length. Flow through each vessel is driven by pressure and follows Poiseuille's Law: $Q = \Delta P \frac{\pi D^4}{128 \mu L}$, where Q is the flow rate in an individual vessel, ΔP is the pressure drop along the vessel, D is the vessel diameter, L is the length of the vessel, and μ is the apparent viscosity, which is assumed to depend on vessel diameter and hematocrit (H_D), as described in [18, 19]:

$$\mu = \left[1 + (\mu_{0.45} - 1) \frac{(1 - H_D)^C - 1}{(1 - 0.45)^C - 1} \left(\frac{D}{D - 1.1} \right)^2 \right] \left(\frac{D}{D - 1.1} \right)^2 \quad (1)$$

where

$$\mu_{0.45} = 6e^{-0.085D} + 3.2 - 2.44e^{-0.06D^{0.645}}$$

and

$$C = (0.8 + e^{-0.075D}) \left(-1 + \frac{1}{1 + 10^{-11}D^{12}} \right) + \frac{1}{1 + 10^{-11}D^{12}}$$

Flows, pressures, hematocrits, and apparent viscosities are calculated for each vessel segment of the network using an iterative scheme of two parts (described in detail in Fry et al. [9]): (1) Inflow and outflow pressure for the network are specified (inflow pressure is 40 mmHg and outflow pressure is 24 mmHg), and the conservation of flow yields a system of linear equations where the unknowns are the pressures at each node; the system is solved using successive over-relaxation to obtain pressures at each node, and flows are also calculated (assuming constant viscosity); (2) Hematocrit and apparent viscosity are calculated in each segment using the flows and pressures found in part (1) and assuming conservation of red blood cell flow rate and plasma flow rate at each node. The two schemes are alternately applied until convergence. These blood flow rates and pressures are calculated throughout the network initially using the measured vessel diameters from Table 1. Subsequently, they are re-calculated throughout the flow regulation procedure (see Section 2.4) every time a vessel diameter is changed.

2.3 Green's function model (O₂ transport)

In a heterogeneous network, oxygen is delivered to tissue via multiple vessels, and thus a simplified oxygen transport model (such as a Krogh-cylinder model) may not adequately describe the distribution of tissue partial pressure of oxygen (PO₂). In particular, simplified models have been shown to underestimate the degree of hypoxia in a tissue bed [20, 21]. In this study, a more realistic transport model (called the Green's function model) is used which allows for the diffusive exchange of oxygen among the tissue and all vessels in the network.

To describe the steady-state diffusion of oxygen in the tissue, the following governing equation is used:

$$D_{diff} \alpha \nabla^2 P_{O_2} = M(P_{O_2}) \quad (2)$$

where P_{O_2} is the partial pressure of O₂, D_{diff} is the diffusion coefficient, α is the solubility of O₂ in tissue, and $M(P_{O_2})$ is the O₂ consumption rate in the tissue. The oxygen consumption rate in tissue is assumed to depend on PO₂ as follows:

$$M(P_{O_2}) = \frac{M_0 P_{O_2}}{P_0 + P_{O_2}} \quad (3)$$

where M_0 is the maximum tissue oxygen demand and P_0 is the PO_2 at which the consumption rate is half-maximal. $D_{diff}\alpha$ is set to $6 \times 10^{-10} \text{ cm}^3 \text{ O}_2/\text{cm}/\text{s}/\text{mmHg}$, and P_0 is set to 10 mmHg [22], M_0 is varied in this study between $1 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$ (baseline) and $4 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$.

To solve Equation 2, a Green's function method [20] is used where the vessels are represented as discrete oxygen sources and the tissue points are represented as discrete oxygen sinks. The tissue PO_2 is then determined as the superposition of the oxygen fields resulting from the sources and sinks. This method takes into account diffusive interactions among all tissue and vessels in the network. In addition, the method is computationally efficient, since the number of unknowns needed to compute the oxygen field in the problem is reduced compared to other approaches and much of the computation can be parallelized.

Convective oxygen transport in the blood is also simulated, including the nonlinear binding of oxygen to hemoglobin. Specifically, the convective O_2 transport rate along a vessel segment is given by

$$f(P_b) = Q(H_D C_0 S(P_b) + \alpha_b P_b) \quad (4)$$

where Q is the blood flow rate, H_D is the discharge hematocrit, C_0 is the concentration of hemoglobin-bound oxygen in a fully-saturated red blood cell, P_b is the blood PO_2 , α_b is the solubility of oxygen in blood, and $S(P_b)$ is the oxyhemoglobin saturation.

It is assumed that the oxyhemoglobin saturation is related to blood PO_2 by a Hill equation:

$$S(P_b) = \frac{P_b^n}{P_b^n + P_{50}^n} \quad (5)$$

where $P_{50} = 41.5 \text{ mmHg}$ and $n = 3.5$ for mice [23]. By conservation of oxygen, in each vessel segment,

$$\frac{df(P_b)}{ds} = -q_v(s) \quad (6)$$

where s is the distance along the segment, and $q_v(s)$ is the rate of diffusive O_2 efflux per unit vessel length. To calculate the source and sink strengths in the Green's function method, it is assumed that both the PO_2 and the O_2 flux at the blood-tissue interface are continuous. This gives

$$q_v(s) = -D_{diff}\alpha \int_0^{2\pi} \frac{\partial P_v}{\partial r} r_v d\theta \quad (7)$$

where r_v is the vessel radius, P_v is the tissue PO_2 at the interface with the blood vessel, r is the distance from the center of the vessel, and θ is the angle around the vessel circumference

[20]. To represent intravascular resistance to radial oxygen diffusion, it is assumed that $P_v(s) = P_b(s) - Kq_v(s)$, where K is a constant that depends on the vessel diameter [24, 25].

2.4 Blood flow regulation

A previous model of oxygen transport in the retina [9] is extended here to include flow regulation in response to changes in pressure, shear stress, and oxygen demand. Although the current study focuses on myogenic (pressure), shear, and metabolic responses, the model provides a framework to which additional regulatory mechanisms could be added, such as neurovascular coupling (which has been identified as an important contributor to flow regulation in the retina). The total circumferential tension (T) developed in a vessel wall to balance the transmural pressure across the vessel wall is defined via the Law of Laplace:

$$T = \frac{(P - IOP)D}{2} \quad (8)$$

As established in previous wall mechanics models [26, 27], this tension can be modeled as the sum of passive tension (T_{pass}) and active tension (AT_{act}^{max}) to yield total tension (T_{total}):

$$T_{total} = T_{pass} + AT_{act}^{max} \quad (9)$$

Passive tension (T_{pass} , Eq. 10) is generated from the structural components of the vessel wall and is modeled as an exponential function of vessel diameter (D), where D_0 represents the passive diameter of the vessels at 100 mmHg. The value of D_0 can be obtained from Eq. 10 by setting $D = D_0$ and $P = 100$ mmHg; namely, $D_0 = \frac{2C_{pass}}{P}$.

$$T_{pass} = C_{pass} \exp\left[C'_{pass} \left(\frac{D}{D_0} - 1\right)\right] \quad (10)$$

Active tension is generated from the contraction of smooth muscle cells and is modeled as the product of the maximally active tension (T_{act}^{max} , Eq. 11) that a muscle can generate (assumed to be a Gaussian function of diameter) and the vascular smooth muscle activation or tone (A).

$$T_{act}^{max} = C_{act} \exp\left[-\left(\frac{\frac{D}{D_0} - C'_{act}}{C''_{act}}\right)^2\right] \quad (11)$$

Vascular smooth muscle activation is modeled using a sigmoidal function of a stimulus function that varies between 0 and 1 (A_{total} , Eq. 12) and depends on a stimulus for tone (S_{tone} , Eq. 13), which is modeled as a linear combination of the myogenic (pressure) response, shear stress response, and conducted metabolic response.

$$A_{total} = \frac{1}{1 + \exp(-S_{tone}(T_{total}))} \quad (12)$$

$$S_{tone} = C_{myo}T(D) - C_{shear}\tau_{wall}(D, Q) - C_{meta}S_{meta}(P_{O2}) + C''_{tone} \quad (13)$$

where T is defined in Eq. 8, wall shear stress is a function of diameter and flow (Q) and is given by and $\tau_{wall} = \frac{32\mu Q}{\pi D^3}$ and S_{meta} is described below.

The myogenic response ($C_{myo}T_{total}$) is the intrinsic ability of the vasculature to constrict as pressure is increased. An increase in wall shear stress ($C_{shear}\tau_{wall}$) that results from an increase in flow (Q) causes vasodilation (decreased tone). The metabolic signal ($C_{meta}S_{meta}$) is implemented as a wall-derived signal that reflects the oxygen deficit along the network. The final term of S_{tone} is a constant (C''_{tone}) that accounts for all other mechanisms that affect smooth muscle tone but that are not explicitly modeled via mechanistic descriptions in this study. In the reference (control) state, all arteriolar diameters are given by the values obtained from the confocal microscopy images (see Table 1). Activation is assumed to be 0.5 in each vessel in the control state (i.e., 50% activation), which allows for the greatest dilation or constriction of vessels outside of control conditions. The constant C''_{tone} is chosen so that $S_{tone} = 0$ and thus activation is 0.5 in the control state. Following a simulated change in tissue oxygen demand, the steady state values of the arteriolar diameters (D_i) and activation levels (A_i) are then determined by integrating the following system of differential equations:

$$\frac{dD_i}{dt} = \frac{1}{\tau_d} \frac{D_c}{T_c} (T_i - T_{total,i}) \quad (14)$$

$$\frac{dA_i}{dt} = \frac{1}{\tau_a} (A_{total,i} - A_i) \quad (15)$$

At each time step, as the diameters change, flows, pressures, and oxygen levels are recalculated using the procedures from Section 2.2 and Section 2.3.

Parameter values for equations 1-15 are listed in Table 3 along with their source. A limitation of this study is that the parameters are taken from a variety of sources that represent multiple species and tissue types; however, several parameters are diameter dependent and thus can be applied directly to the mouse retina. Additionally, many parameters represent blood characteristics that are assumed to be similar across species. A few parameters are calculated or estimated; for example, C_{meta} is chosen in order to yield similar results from a wall-derived signal as was obtained previously for an ATP-dependent metabolic signal [5]. The notation of the parameters (e.g., the use of primes in the superscripts) is consistent with notation from the previous models upon which this study is based and simply denote different parameter names.

To compute the metabolic response (S_{meta}) in Eq. 13, an averaged value of the signal generated along the length of the vessel is used. The value of S_{meta} for a vessel results from two components: (i) the signal from the outflow node of the vessel ($S_{meta,out}$), exponentially decayed along the length of the vessel; and (ii) the local signal rate (S_{loc}) generated at every point along the vessel, and exponentially decayed along the remaining length of the vessel. Thus, S_{meta} can be computed for a particular vessel as:

$$S_{meta} = \frac{1}{L} \int_0^L S_{meta,out} e^{-x/L_0} dx + \frac{1}{L} \int_0^L \left[\int_0^x S_{loc} e^{-(x-y)/L_0} dy \right] dx \quad (16)$$

where L is the length of the vessel and L_0 is the length constant for decay (assumed here to be $L_0 = 1$ cm). The metabolic signal generated at each point along the vessel (S_{loc}) is given in Eq. 17. The signal represents the local oxygen deficit and is inversely related to the local PO_2 . As shown in Eq. 17, the signal is also proportional to the difference between the oxygen demand (M_0) and the oxygen consumption rate ($M(P_{O2})$).

$$S_{loc} = \frac{P_0}{P_0 + P_{O2}} \propto M_0 \frac{P_0}{P_0 + P_{O2}} = M_0 - M_0 \frac{P_{O2}}{P_0 + P_{O2}} \quad (17)$$

In a full microvascular network that includes the downstream capillaries and venules, metabolic responses would be generated by all vessels and conducted upstream to influence arteriolar tone. In such a network, the outflowing nodes of the full network would be assigned a metabolic response signal value ($S_{meta,out}$) of 0. However, since the outflowing nodes of the network in this study are arterioles (which in reality would be connected to downstream capillaries that generate conducted responses), the outflowing arteriolar nodes should be assigned a nonzero value of $S_{meta,out}$. Thus, the effect of assigning different values of $S_{meta,out}$ to the outflow arteriolar nodes is investigated in this study. Three cases are considered: (1) $S_{meta,out} = 0$ (i.e., no downstream conducted response); (2) $S_{meta,out} = S^*$, where S^* is a constant value (i.e., a constant downstream conducted response at each arteriolar outflowing node); and (3) $S_{meta,out} = S^* n_{bc,out} (Q_i / Q_{tot})$, where $n_{bc,out}$ is the total number of outflowing arteriolar nodes, Q_i is the flow rate in the i th outflow vessel, and Q_{tot} is the total flow rate in the network (i.e., a conducted response at each arteriolar outflowing node weighted by the flow rate in the vessel). Simulations are run for a range of tissue O_2 demand under varying blood flow regulation conditions. Blood and tissue PO_2 is predicted by the model for the arteriolar network.

3. Results

Figure 3 shows model predicted levels of tissue PO_2 for low oxygen demand ($M_0 = 1$ cm³ O_2 /100 cm³/min, panels A and D) and high oxygen demand ($M_0 = 4$ cm³ O_2 /100 cm³/min, panels B, C, E, and F). The metabolic response is absent in panels B and E and present in panels C and F. Given that the incoming blood to the arteriolar retinal circulation is assumed to be well-oxygenated, the PO_2 in some portions of the network is predicted to be relatively high; however, the average tissue PO_2 levels predicted by the model vary between 42.62 mmHg and 59.73 mmHg (depending on assumed tissue oxygen demand) and are thus in the range of experimental studies of the superficial layer of the retina [35-37]. The contour plots

in panels A-C and the histograms in panels D-F indicate that a fourfold increase in tissue oxygen demand leads to large reductions in tissue PO_2 . Panels E and F indicate that inclusion of the metabolic regulation response leads to a moderate decrease in the fraction of tissue $PO_2 < 10$ mmHg.

Figures 4A and 4B give the model-predicted average tissue PO_2 (reported as the integral mean of the predicted PO_2 over the tissue domain) and fraction of tissue < 5 mmHg, respectively, for M_0 values of 1, 2, and 4 $cm^3 O_2/100 cm^3/min$ with the following combinations of regulatory mechanisms: (i) all responses are on (All on); (ii) shear and metabolic on, but myogenic off (No Myo); (iii) myogenic on, but shear and metabolic off (Only Myo); and (iv) all responses off (All off). In general, as in Figure 3, the model predicts that an increase in tissue oxygen demand leads to a decrease in average tissue PO_2 and an increase in the fraction of tissue < 5 mmHg. A cutoff value of 5 mmHg is chosen to represent hypoxia in the arteriolar network (rather than 1 mmHg) because arterioles are fairly well-oxygenated. Since the arterioles supply downstream tissue, any pathway in the arteriolar network with PO_2 less than 5 mmHg will likely supply areas downstream at risk of hypoxia < 1 mmHg. Figure 4A indicates that for varying levels of tissue O_2 demand, the difference in average tissue PO_2 is negligible between the cases with and without blood flow regulation included. However, when $M_0 = 2 cm^3 O_2/100 cm^3/min$, the predicted average tissue PO_2 is considerably lower when only the myogenic response is on. Similarly, when $M_0 = 2 cm^3 O_2/100 cm^3/min$, the highest predicted fraction of tissue < 5 mmHg occurs when only the myogenic response is on. Figure 4B indicates that for $M_0 = 2 cm^3 O_2/100 cm^3/min$ and $M_0 = 4 cm^3 O_2/100 cm^3/min$, the lowest predicted fraction of tissue < 5 mmHg occurs when only the metabolic and shear responses are on (i.e., when the myogenic response is off).

To investigate the effect of the myogenic response on metabolic flow regulation, the weight of the metabolic response (C_{meta}) is varied in the presence or absence of the myogenic response. Figure 5 shows the predicted difference in average tissue PO_2 between the case of all responses active (i.e., myogenic, shear, and metabolic responses included, All on) and the case of an inactive myogenic response (i.e., only shear and metabolic responses included, No Myo) for two different values of C_{meta} (assuming $M_0 = 2 cm^3 O_2/100 cm^3/min$). At the baseline value of C_{meta} , the predicted difference between the two cases is negligible (0.16 mmHg); however, when the assumed contribution of the metabolic response was reduced by 90%, the difference between the two cases is much larger (3.31 mmHg), suggesting that a larger metabolic response helps to dampen a possibly negative contribution to flow regulation by the myogenic response.

As indicated in the Methods, conducted metabolic signals are produced by the vessels in the network in response to local PO_2 levels and generate a metabolic flow regulation response. The response generated by each vessel is a function of both the partial pressure of oxygen at the vessel (S_{loc}) and the signal conducted from downstream vessels ($S_{meta,out}$). To investigate the effect of downstream conducted signals on blood flow regulation in the arterioles, simulations were run for three choices of $S_{meta,out}$ to the outflowing arteriolar nodes: (1) zero at all outflows; (2) a constant value (S^*) at all outflows; and (3) a flow-weighted value at all outflows.

Figures 6A and 6B show predicted average tissue PO_2 and fraction of tissue < 5 mmHg for M_0 values of 1, 2, and $4 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$ for these three different prescribed values of downstream conducted response signal ($S_{meta,out,i}$) at outflowing vessels i : $S_{meta,out,i} = 0$ (no downstream response); $S_{meta,out,i} = S^*$ (constant downstream response in each vessel); or $S_{meta,out,i} = S^* n_{bcout} Q_i / Q_{tot}$ (flow-weighted downstream response in each vessel). For all values of M_0 the predicted average tissue PO_2 is highest (and predicted tissue hypoxic fraction is lowest) when the downstream signal at each outflowing vessel is weighted by the flow rate in the vessel.

Figures 6C and 6D show predicted average tissue PO_2 and fraction of tissue < 5 mmHg for S^* values of 0.001, 0.01, and 0.1, assuming the signal is fixed or flow-weighted. As S^* is increased, there is a moderate increase in the average tissue PO_2 and moderate decrease in tissue hypoxic fraction in all cases. Interestingly, the model predicts that it is always better to have a flow-weighted signal than a fixed signal for effective oxygenation in a heterogeneous network. Specifically, for all values of S^* , the predicted average tissue PO_2 is higher and predicted tissue hypoxic fraction is lower if a flow-weighted signal is used. For some values of S^* , it is even better to have a flow-weighted signal than a larger fixed signal; to see this more clearly, notice that when $S^* = 0.01$, there is a much greater increase in average PO_2 between the fixed and flow-weighted prediction (points (a) and (b) in Figure 6C) than for an increase in the fixed signal by a factor of ten (points (a) and (c) in Figure 6C).

4. Discussion

A critical void exists in understanding the interplay of retinal blood flow and metabolism, tissue structure, and function. This lack of knowledge has significant impact in ocular pathologies such as glaucoma where retinal homeostasis and ganglion cell preservation are intertwined. Difficulty in imaging internal eye structures has been a prohibitive obstacle to advancing disease management, and mathematical modeling represents a novel approach to revealing the mechanism(s) involved in glaucoma pathophysiology. In working to solve this enigma, the present study provides a comprehensive model of the retina that combines oxygen transport and flow regulation within a heterogeneous description of the retinal arteriolar network.

The model predicts a large spread in tissue PO_2 , and a shifted PO_2 distribution, when the tissue oxygen demand is increased (Fig. 3) both with and without blood flow regulation included. It might seem erroneous that panels E and F of Figure 3 predict only a minor change in the tissue PO_2 distribution with the inclusion of the metabolic regulation response. However, this is expected, since the current model only accounts for the arteriolar network, where all PO_2 levels are relatively high compared to the rest of the microcirculation. Since the metabolic response is assumed to be inversely related to the PO_2 , these arteriolar PO_2 levels do not elicit major metabolic regulation responses. And, it is important to note that Figure 3 is generated assuming no downstream metabolic signal ($S_{meta,out,i} = 0$). Inclusion in the model of downstream microvessels (either explicitly or implicitly, as in Figure 6) will lead to the generation of metabolic signals conducted upstream to the terminal arterioles that should elicit larger diameter and flow changes than were simulated in this study.

A useful feature of mathematical models is the ability to simulate different combinations of active or inactive blood flow regulation mechanisms. Figure 4A shows that the model predicts a lower average tissue PO_2 for moderate tissue O_2 demand ($M_0 = 2 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$) when only the myogenic response is included in the model, compared to the case when no regulation responses are included. Further, Figure 4B shows that the model predicts a lower fraction of tissue $< 5 \text{ mmHg}$ for $M_0 = 2 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$ and $M_0 = 4 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$ when the myogenic response is turned off, compared to when it is turned on. Together, Figures 4A and 4B indicate that the myogenic response may have a detrimental effect on blood flow regulation in response to changing oxygen demand.

The effects of the myogenic response on metabolic flow regulation were investigated further by simulating the cases of an active or inactive myogenic response while also varying the strength of the metabolic response. Figure 5 indicates that a smaller strength of the metabolic response (C_{meta}) leads to a larger difference between the cases with and without the myogenic response included. This prediction seems to indicate that a larger contribution from the metabolic response helps to blunt possible detrimental effects of the myogenic response. The vascular health and autoregulatory ability of a given person have been shown to vary greatly and be reduced in glaucoma patients specifically [5, 38-40]. Therefore, the ability (or lack thereof) of the metabolic response to mitigate myogenic involvement is a novel and highly impactful observation that may explain, in part, the individual variation in OAG disease susceptibility. In the future, neurovascular coupling mechanisms that mediate the functional hyperemia response in the retina [41] should be added to the model to provide an even more complete description of retinal flow regulation.

A current limitation of the model is that the full retinal microcirculation is not being represented, only the arteriolar network. In a full arteriovenous network, the outflow nodes would correspond to the end of the network. In this study, the outflow nodes correspond to terminal arterioles, with an implied downstream set of capillaries and venules. In a full network, the downstream capillaries and venules would generate a metabolic signal that propagates upstream to the arterioles. In an attempt to capture this effect in the current model construct, three different metabolic signals are simulated at the terminal arterioles. Case (1) assumes that the outflow node values of $S_{meta,out}$ are all zero. This case essentially implies that the arteriolar network exists in isolation. This is a very unlikely situation, given that the arteriolar network comprises only the beginning of a full microvascular network. However, given a lack of downstream data, this case was used as the default. Case (2) assumes that the outflow node values of $S_{meta,out}$ are all nonzero and constant. This case implies that a nonzero signal is being generated downstream and conducted upstream to the arteriolar outflows. This case is more realistic than Case (1) since it is very reasonable to assume that there should be a nonzero signal propagated upstream. However, given the lack of data on the strength of this signal, different values of $S_{meta,out}$ were simulated. Not surprisingly, as $S_{meta,out}$ was increased, moderate increases in average tissue PO_2 and decreases in tissue hypoxic fraction were predicted (Fig. 6C and 6D). Case (3) assumes that the signal is flow-dependent so that outflow vessel nodes with larger flow rates receive larger signals. The justification for this is that outflowing vessels with larger flow rates supply larger downstream areas, which should produce larger signals. Results from simulations using a flow-weighted signal value (Fig. 6) predict that a flow-weighted signal

produces higher average tissue PO_2 and lower tissue hypoxic fraction throughout the network.

Importantly, the predicted improvement in oxygenation using a flow-weighted signal instead of a constant signal is often greater than the predicted improvement in oxygenation with an increase in the value of the signal. That is, the model predicts that, for some values of S^* , the heterogeneity of the signal is at least as, if not more, important as the strength of the signal. This indicates that the heterogeneity of the downstream conducted responses serves to regulate flow better than a constant conducted response, further supporting the importance of considering the non-uniform structure of the retinal arteriolar microvasculature when trying to understand how and to what extent blood flow regulation is working in the microcirculation. This finding has significant implications for ophthalmic pathologies such as glaucoma where retinal metabolism and homeostasis are determinants of ganglion cell health and vision preservation.

A theoretical modeling approach has the significant advantage of encapsulating all retinal regions compared to singular zone assessment from traditional modalities including metabolic probes. The selective placement of probes only reveals PO_2 within a defined segment, allowing hidden pockets of hypoxia to remain unseen. Importantly, glaucomatous changes to structure and ganglion cell death occur non-uniformly, often within isolated segments while other tissue remains unaltered. This study overcomes this significant assessment limitation by providing a comprehensive model of retinal blood flow regulation and oxygen status across the entire heterogeneous retinal arteriolar circuit. Model results give insight into the spatial distribution of oxygenation at a particular depth, rather than simply an average value provided by a probe that may not capture the spread of PO_2 levels at that depth. The ability to provide oxygen status across the retina without extrapolating singular tissue assessment to the whole network is highly impactful in understanding slow moving chronic disturbances to retina homeostasis.

Ultimately, this model provides an important step in predicting oxygen transport and blood flow regulation in a heterogeneous description of the retinal microvasculature. To relate the predictions of the model more closely to outcomes in humans, the arteriolar network will be adapted to human parameters and structure (e.g., humans have 4 main branches off of the central retinal artery, compared to 6 in the mouse). In addition, inclusion of a more explicit representation of the downstream microvessels will allow for predictions of tissue PO_2 downstream of the arterioles, and, more importantly, provide more accurate predictions of downstream conducted metabolic signals (including effects of the downstream PO_2 distribution). Overall, results from this mathematical model have significant implications for ocular functionality and pathologies involving retinal hemodynamics and metabolism.

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Highlights

- Retinal flow regulation and O_2 transport are modeled in a realistic vascular network.
- Flow regulation is modeled in response to pressure, shear stress, and oxygen demand.
- Simulations predict tissue PO_2 under varying blood flow regulation conditions.
- Model predicts myogenic response has detrimental effects on metabolic flow regulation.
- Heterogeneous metabolic responses better regulate blood flow than uniform responses.

Model Reference	Oxygen Transport	Blood Flow Regulation	Vessel Heterogeneity
[8-10]			
[5, 13]			
This Study			

Figure 1.

Summary of previous mathematical models of the retina that have included some of the following hemodynamic elements: oxygen transport, acute blood flow regulation, and vessel heterogeneity. The current study combines all three in a model of the retinal microcirculation.

Figure 2.
Heterogeneous arteriolar network in the mouse retina (as defined in [9]).

Figure 3.

Contour plots and histograms of predicted PO_2 levels in the arteriolar network and surrounding tissue for low O_2 demand ($M_0 = 1 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$, panels A and D), high O_2 demand with no metabolic response ($M_0 = 4 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$, panels B and E), and high O_2 demand with the metabolic response included ($M_0 = 4 \text{ cm}^3 \text{ O}_2/100 \text{ cm}^3/\text{min}$, panels C and F).

Figure 4.

A. Average tissue PO_2 (in mmHg) vs. tissue oxygen demand (M_0 , in $cm^3\text{ O}_2/100\text{ cm}^3/\text{min}$), for the following four cases: no regulatory response (All off, purple), only the myogenic response (Only Myo, yellow), all responses except the myogenic response (No Myo, red), and all regulatory responses (All on, blue). B. Tissue hypoxic fraction vs. tissue oxygen demand for the same four cases defined in panel A.

Figure 5.

Average tissue PO₂ difference between the case of all responses active (i.e., myogenic, shear, and metabolic responses included, All on) and the case of an inactive myogenic response (i.e., only shear and metabolic responses included, No Myo). Left: metabolic response strength, C_{meta} is set to 10% of baseline. Right: C_{meta} is at the baseline level. Here, $M_0 = 2$ cm³ O₂/100 cm³/min.

Figure 6.

Panels A and B: Plots of average tissue PO₂ (in mmHg) and tissue hypoxic fraction vs. oxygen demand (in cm³ O₂/100 cm³/min), for the following three cases: no downstream metabolic signal ($S^* = 0$, blue), fixed downstream metabolic signal ($S^* = 0.01$, red), and flow-weighted downstream metabolic signal (yellow). Panels C and D: Plots of average tissue PO₂ and tissue hypoxic fraction vs. weight of downstream metabolic signal (S^*), for the fixed signal (blue) and flow-weighted signal (red) cases (with $M_0 = 4$ cm³ O₂/100 cm³/min). Points a, b, and c are labeled to illustrate the impact of a flow-weighted signal compared to an increase in signal strength (see text).

Table 1.

Order, initial (reference) diameter, and quantity of arterioles in the vascular network.

Network	Order	Diameter (μm)	Quantity
Artery 1	1	5.75	61
	2	7.71	32
	3	10.28	15
	4	14.42	6
	5	21.16	4
Artery 2	1	5.75	221
	2	7.94	75
	3	11.54	25
	4	18.86	10
	5	30.42	7
Artery 3	1	5.75	136
	2	7.87	48
	3	12.18	12
	4	17.98	9
	5	26.84	6
Artery 4	1	5.75	126
	2	7.79	39
	3	11.65	14
	4	22.91	7
Artery 5	1	5.75	102
	2	8.03	48
	3	11.47	12
	4	16.01	9
	5	24.02	6
Artery 6	1	5.75	147
	2	8.01	69
	3	11.05	13
	4	19.56	4
	5	28.48	4

Table 2.

Variable names, descriptions, and units for the model

Description	Variable	Unit	Initial value
Vessel diameter	D	μm	See Table 1
Vascular smooth muscle (VSM) activation	A	-	0.5

Table 3.Parameter values for O₂ transport, conducted metabolic response, and wall tension

Description	Parameter	Value	Unit	Reference
Oxygen capacity of RBCs	C_0	0.5	cm ³ O ₂ /cm ³	[28]
Inflow Discharge hematocrit	H_D	0.4	-	[29]
Inflow PO ₂ of blood	P_b	84.4	mmHg	[9]
Krogh diffusion coefficient	$D_{diff}a$	6×10^{-10}	cm ³ O ₂ /cm/s/mmHg	[30, 31]
Solubility of oxygen in blood	a_b	3.1×10^{-5}	cm ³ O ₂ /cm ³ /mmHg	[32]
Intravascular resistance	K	0.730-2.45	mmHg·µm·s/µm ³ O ₂	[25]
Oxygen demand	M_0	1 – 4	cm ³ O ₂ /100 cm ³ /min	varied
Michaelis constant for O ₂ consumption	P_0	10	mmHg	[22]
Constant conducted wall signal	S^*	0-0.1	-	varied
Length constant	L_0	1	cm	[5]
Time constant for diameter	τ_d	1	s	[33]
Time constant for activation	τ_a	60	s	[34]
VSM activation sensitivity	C_{myo}	$1.37/D_0$	cm/dyn	[14]
VSM shear stress sensitivity	C_{shear}	0.0258	cm ² /dyn	[5]
VSM metabolic sensitivity	C_{meta}	1000	1/µM/cm	[14]
VSM constant	C''_{tone}	0.592 – 10.5	-	calculated
Passive tension strength	C_{pass}	$5.67 \cdot D_0$	dyn/cm	[14]
Passive tension sensitivity	C'_{pass}	$-0.0270 \cdot D_0 + 12.5$	-	[14]
Max active peak tension	C_{act}	$1.30 \cdot D_0^{1.48}$	dyn/cm	[14]
Max active length dependence	C'_{act}	$-0.00146 \cdot D_0 + 1.13$	-	[14]
Max active tension range	C''_{act}	$-0.00146 \cdot D_0 + 0.308$	-	[14]
Passive reference diameter	D_0	13.2 to 41.4	µm	calculated