To my family and friends, without whom I would have never gotten this far
ACKNOWLEDGMENTS

I would like to thank my advisor Professor Greg Sawyer for allowing me to pursue this research and for sharing his resources, time and thoughts in helping me during the past two years. I would also like to thank Dr. Dan Dickrell for helping me conquer the obstacles of this project over many cups of coffee.

I would also like to extend my appreciation to all the members of the University of Florida Tribology Lab for their support and encouragement throughout my graduate career.
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<td>asymmetry ratio</td>
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<tr>
<td>$\beta$</td>
<td>area ratio</td>
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<td>fluid dynamic viscosity</td>
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<td>$\theta$</td>
<td>bifurcation angle</td>
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<td>power loss through vessel</td>
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<td>$L, l$</td>
<td>length of segment</td>
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<td>power loss per unit volume of blood</td>
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<td>pressure drop across a segment</td>
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<td>$r$</td>
<td>vessel radius</td>
</tr>
<tr>
<td>$t$</td>
<td>drag force per unit length</td>
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<tr>
<td>$\vec{u}$</td>
<td>vessel directional unit vector</td>
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<tr>
<td>$x$</td>
<td>junction exponent</td>
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Abstract of Thesis Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Master of Science

ANALYSIS OF ARTERIAL BIFURCATIONS IN THE HUMAN RETINA

By

Richard Dean Clark III

May 2013

Chair: Wallace Gregory Sawyer
Major: Mechanical Engineering

The bifurcating nature of the human vascular system has been of scientific and medical interest for over a century. The morphological growth of arteries has been attributed to various theories of optimization while changes in morphology and deviations from normal geometries have been suggested to be the result of pathological conditions.

Because of the noninvasive nature of observing the retinal vasculature, fundus photographs present a means of easily viewing and recording an arterial network. If the morphology can then be quantified, it could be a useful tool for diagnosing ocular or systemic diseases.

A program was developed which analyzed the bifurcation angles, area ratios, asymmetry ratios and junction exponents of 13 healthy retinal arterial networks and compared the results against various theories of optimization including the principles of minimum work, minimum drag force, minimum volume and minimum surface area. The results conformed to different theories to various degrees depending on the parameter measured, leading to the conclusion that not one theory alone can be assumed if an optimum model is to be developed.
Anatomy of the Human Retina

The human retina is a complex layer of tissue that lies on the anterior inner surface of the eye. It is an extension of the central nervous system and is responsible for the nerve impulses that create vision through the collection of light. It lies between the vitreous, the clear liquid in the center of the eye, and the choroid, a vascular layer of the eye [1].

The main components of the retina are the tissues layers, which are responsible for the chemical and electrical processes that interpret light and create vision; the optic disc, a small oval portion through which the retinal blood flow enters and exits; the macula, a small yellow spot at the center of the back of the eye which contains a depression known as the fovea, responsible for sharp, high resolution vision; and the vasculature, responsible for supplying oxygen and nutrients to the retinal tissue. The typical anatomy of the eye is seen in Figure 1-1.

The retinal vasculature begins with the central retinal artery that branches from the ophthalmic artery (Figure 1-2), pierces the optic nerve behind the eye and transports blood into the retina through the optic disc. This artery then branches into smaller arterioles which ultimately branch down into capillaries through which oxygen and nutrients are dispersed into and collected from the retinal tissue. The collected blood is then funneled through venules which merge into larger veins and ultimately the central retinal vein which exits through the optic disc.
**Fundus Photography**

Due to the requirement for light, the retina contains the only vasculature of the human body that can be observed noninvasively [2]. This fact has led to a wide variety of examinations and devices that focus on looking through the pupil and analyzing the retina in order to check for possible disease. Because these images generally only capture the fundus, or inner back surface, of the eye, this practice is known as fundus photography.

Originally, fundus images were taken on film, but with the development of the charge-coupled device for capturing light, the practice has moved into the digital realm. The ability for a clinician to accurately diagnose a fundus image has been determined to be equal for film and digital images [3]. A typical fundus camera can be seen in Figure 1-3.

Fundus cameras can vary in field of view and magnification of the produced images. Some cameras also vary on their need of dilation (non-mydriatic cameras do not need the patient to be dilated). Additionally, some cameras produce red-free images as the red layer of an RGB image sometimes contributes to the ambiguity in discerning objects from the image [4].

Typically, fundus images (Figure 1-4) are fovea-centered, contain a 30° to 50° field of view and display the optic disc as well as the arteries and veins at a magnification of 2.5. Initially, the arteries and veins seem indistinguishable, but due to their function and anatomy they are generally able to be discerned from each other based on diameter, brightness, tortuosity and connectivity.
Diagnostic Methods and Morphology of the Retinal Vasculature

The current method of practice involves a technician taking the image and then the image being surveyed by either a medical doctor or a specialized reader. This is a highly manual process that requires the viewer to pick out abnormalities or lesions in the retina, which has been found to be slow, laborious and prone to human errors [5]. The automation of diagnoses has mostly focuses on detection of microaneurisms, cotton wool spots, exudates, or hemorrhages [6,7], most of which are used as markers for diabetic retinopathy, a disease that has been rapidly growing across the world and results in an approximate 30-fold chance of blindness over someone without the disease [8].

In recent years interest has grown in the morphology of the retinal vasculature [9,10]. The interesting shape has led many to try to classify the morphology for use of diagnosis [11]. While the resulting shapes are interesting, but the underlying causes and principles of that geometry, and the geometry of the vascular system as a whole, have also interested scientists and doctors for almost a century. In particular, scientists and doctors have observed the diameters and angles of blood vessels at bifurcations to determine what underlying principles might contribute to the formation of, or deviation from, an efficient method of blood transport [12].

This study collects the information from bifurcations in the arterial vasculature of a set of healthy eyes and compares this information to that of various proposed optimization theories.
Figure 1-1. A cross-sectional drawing of the typical anatomy of the human eye including a description of the various layers of retinal tissue. (Source: http://www.intechopen.com/source/html/26714/media/image1.png. Last accessed March, 2013).
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Figure 1-3. A non-mydriotic Topcon digital fundus camera. (Source: http://upload.wikimedia.org/wikipedia/commons/thumb/5/5e/Retinal_camera.jpg/1280px-Retinal_camera.jpg).

Figure 1-4. Example red-free fundus image with main components labeled.
Origins of Biological Design

Some of the first work on optimal vascular branching was done by during the 1920’s by Cecil Murray [13]. Murray claimed that physiological systems not only adapt to changes in order to maintain an “optimum” performance, but also that there are underlying mathematical and scientific laws that govern the geometric growth of these systems. These laws are based in physiologically independent fields such as thermodynamics and fluid mechanics.

Murray cited the first ideas of “theoretical physiology” to come from Galileo, who is credited with the idea of the principle of similitude, in which he remarks upon the scaling laws between the cross sectional area of bone and its strength as well as between the volume of bone and its weight. This gave insight into the “design” of animal sizes and a departure from the idea of randomness in biological structures.

While also citing Darwin for the idea of macroscopic biological adaptation, Murray focused primarily on the concept of internal organization of physiological systems. As with the design of bones, intended to support animal weights and bear various other forces effectively, the design of the vascular system must also perform its function effectively. Murray argued that this design is not only effective, but optimal.

Murray and the Principal of Minimum Work

Two competing factors contribute to the development of the vascular system – cost and function. It is the optimization of these two parameters, Murray states, that leads to an optimized overall design that should resemble the structure of our vascular
network. Discrepancies between a theoretical optimization and the observed network must be attributed to an unknown factor.

The primary purpose of the arterial vascular system, Murray claimed, is to distribute oxygen to various organs in the body, and this is the focus of his work. He attempts to balance the functionality of the system – delivering oxygen via capillaries in tissue – with the costs of the system. Murray identified two costs associated with blood transport – the cost of friction and the cost of volume.

In order to estimate the friction loss and volumetric loss, Murray assumed that a blood vessel is a cylinder with a constant radius \( r \) and length \( l \). He also assumed that the volumetric flow rate is laminar at a rate of \( f \) and constant dynamic viscosity of \( \eta \). With these assumptions it was possible to use the Hagen-Poiseuille equation (Equation 2-1) to find the pressure drop, \( p \), along the length of the vessel due to friction.

\[
p = \frac{fl8\eta}{\pi r^4} \tag{2-1}
\]

By multiplying each side of Equation 2-1 by the volumetric flow rate, \( f \), Equation 2-2 is found, which describes the power loss due to friction.

\[
pf = \frac{f^2l8\eta}{\pi r^4} \tag{2-2}
\]

In order to estimate the volumetric power loss of blood, Murray multiplied the volume of blood in a vessel by a constant \( b \), representing the power cost per unit volume of blood, as seen in Equation 2-3.
This encompasses various contributing costs such as the metabolism of the blood and vessel walls, the cost of comprising elements of the blood such as hemoglobin and the actual weight of the blood. For the sake of simplicity, Murray attributed these factors into a single parameter.

The total power cost was thus estimated by the following equation:

\[ E = pf + bV = \frac{f^2 l8\eta}{\pi r^4} + bl\pi r^2 \]  

(2-4)

Murray determined the optimized economy to exist when the total power cost is at a minimum. By this logic, he differentiated Equation 2-4 with regard to the radius and equated the result to zero (Equation 2-5).

\[ \frac{dE}{dr} = -\frac{4f^2 l8\eta}{\pi r^5} + 2bl\pi r = 0 \]  

(2-5)

This allowed b to be solved in terms of the flow rate, viscosity and radius:

\[ b = \frac{2f^2 8\eta}{\pi^2 r^6} \]  

(2-6)

The equation can then be solved for f to yield

\[ f = \frac{r^6\pi^2 b}{\sqrt{16\eta}} = r^3 \frac{\pi^2 b}{\sqrt{16\eta}} \]  

(2-7)

Since b and \( \eta \) are both treated as constants, a new constant k can be used to encompass both terms and express the flow rate with a simple expression.
\[ k = \sqrt{\frac{\pi^2 b}{16\eta}} \]  

(2-8)

\[ f = kr^3 \]  

(2-9)

Equation 2-9 states that the flow rate through any vessel is proportional to the cube of the radius of that vessel and has been referred to as “Murray’s Law”.

By applying the principle of conservation of mass, a relationship between the three vessels at a bifurcation can be described with Equation 2-12.

\[ f_0 = f_1 + f_2 \]  

(2-10)

\[ kr_0^3 = kr_1^3 + kr_2^3 \]  

(2-11)

\[ r_0^3 = r_1^3 + r_2^3 \]  

(2-12)

This relationship states that the sum of the cubes of the child radii, \( r_1 \) and \( r_2 \), is equal to the cube of the parent radius, \( r_0 \), at a bifurcation (Figure 2-1). This can also be stated using diameters:

\[ D_0^3 = D_1^3 + D_2^3 \]  

(2-13)

Murray also investigated the effects that bifurcation angles have on minimum work [14]. He demonstrated that a change in length of any of the three connecting vessels leads to known changes in bifurcation angles. Using Equation 2-4, he determined the effects these length changes had on the power cost of each vessel,
which, for minimum work, must yield a total change of zero. This led to relationships for \( \theta_1 \) and \( \theta_2 \), the deviation angles of the first and second child vessels, respectively:

\[
\cos \theta_1 = \frac{r_0^4 + r_1^4 - r_2^4}{2 r_0^2 r_1^2} \quad (2-14)
\]

\[
\cos \theta_2 = \frac{r_0^4 + r_2^4 - r_1^4}{2 r_0^2 r_2^2} \quad (2-15)
\]

Substituting Equation 2-12 into Equations 2-14 and 2-15, he yielded his final result of

\[
\cos \theta_1 = \frac{r_0^4 + r_1^4 - (r_0^3 - r_1^3)^{4/3}}{2 r_0^2 r_1^2} \quad (2-16)
\]

\[
\cos \theta_2 = \frac{r_0^4 + r_2^4 - (r_0^3 - r_2^3)^{4/3}}{2 r_0^2 r_2^2} \quad (2-17)
\]

If the child branches are equal in diameter, each angle can be represented by Equation 2-18.

\[
\cos \theta_{1,2} = \frac{r_0^2 - (r_0^3 - 2 r_1^3)^{2/3}}{2 r_1^2} \quad (2-18)
\]

**Principle of Minimum Volume**

Horsfield and Cumming [15] focused on the bronchial tree morphology to determine an optimum branching pattern, but the principles of fluid transport remain similar. The optimization problem of interest involved maximizing the alveolar surface area and cross-sectional area of the air passageways in order to facilitate oxygen transport from the alveolar sacs to the pulmonary capillaries. A concurrent goal exists that strives for efficient use of volume within the lungs, which requires small cross-
sectional areas for the passageways, leading to investigations of how these parameters influence the morphology.

Assuming a symmetric dichotomous style of branching, Horsfield determined the optimum diameter of a child vessel, \( r_{(w+1)} \), to be a constant fraction of the parent vessel, \( r_w \). This relationship is expressed by Equation 2-19

\[
r_{(w+1)} = r_w \cdot 2^{-1/3} = 0.794 \cdot r_w
\]  

(2-19)

which correlates with Murray's law if \( r_1 = r_2 \).

He then focused on the principle of minimum volume, using a similar technique to Murray. By changing the length of each vessel (\( L_1, L_2, \) and \( L_3 \)), and assuming that the point of bifurcation is already at an optimum minimum volume position, a change in volume in the parent vessel is equal to the total change in volume of the child branches.

\[
\Delta L_0 \pi r_0^2 = \Delta L_1 \pi r_1^2 + \Delta L_2 \pi r_2^2
\]

(2-20)

The changes in length were related to the deviation angles of the child branches, which ultimately led to a relationship between the area ratios and the deviation angles:

\[
\frac{r_0^2}{r_1^2} = P \quad \frac{r_1^2}{r_2^2} = Q \quad \frac{r_2^2}{r_0^2} = R
\]

(2-21)

\[
\cos \theta_1 = \frac{1}{2} \left( P + \frac{1}{P} - \frac{R}{Q} \right)
\]

(2-22)

\[
\cos \theta_2 = \frac{1}{2} \left( R + \frac{1}{R} - \frac{Q}{P} \right)
\]

(2-23)
This relationship is mathematically viable only when the total cross-sectional area of the child vessels is not less than that of the parent vessel. For these special cases, a separate relationship was derived while holding the parent vessel length constant.

\[
\frac{\sin \theta_2}{\sin \theta_1} = \frac{r_1^2}{r_2^2}
\] (2-24)

Kamiya and Togawa also attempted to optimize the branching of the vascular network by volume minimization, citing the inverse relationship between volume and transmission time of information as well as the increased metabolic needs maintaining greater amounts of blood until it is actually used at the capillary level. [16].

**Principle of Minimum Shear Stress**

Zamir argued that the two principles discussed thus far – minimum power and minimum volume – either require the blood vessels to “sense” the volume or power, which he immediately discards, or that these patterns are genetically embedded. The latter, he argues, is improbable because of the natural variations witnessed in the vascular network.

Through power and volume management, Zamir stated that there is no mechanism by which the vessels may try to optimize. That is, there is no feedback system governing the formation of these vessels. Instead of a global principle governing the geometry of vessels, he proposed that vessels grow according to local factors, which he believed to be local shear stresses [17].

Zamir defined the shear stress on the inner wall tangential to the vessel and parallel to flow as
\[ \tau = \frac{4\eta f}{\pi r^3} \]  

(2-25)

The viscosity, volumetric flow rate and radius are represented by \( \eta \), \( f \), and \( r \), respectively. The total force in the vessel, \( T \), is found by multiplying the shear stress by the inner surface area of the vessel, \( 2\pi rl \), where \( l \) is the length of the vessel. The force per unit length, \( t \), is found by dividing the force by the length of the vessel.

\[ T = 2\pi rl\tau = \frac{8\eta fl}{r^2} \]  

(2-26)

\[ t = \frac{T}{l} = \frac{8\eta f}{r^2} \]  

(2-27)

After asserting that the total tension in the three vessels involved at a bifurcation is equal to the sum of the tensions of each individual vessel, Zamir attempted to minimize this total tension by moving the point of bifurcation in an x-y coordinate system (Figure 2-2), in a manner very similar to Murray’s method of minimum power and Horsfield’s method of minimum volume.

\( T_0 \), \( T_1 \), and \( T_2 \) are the total drag force in the parent vessel, larger-diameter child vessel and smaller-diameter child vessel, respectively. This can be represented with drag per unit length.

\[ T = T_0 + T_1 + T_2 \]  

(2-28)
\[ T = t_0 l_0 + t_1 l_1 + t_2 l_2 \]  

(2-29)

When this equation is differentiated by \( x \) and \( y \) and set to zero, the bifurcation angles for minimum total drag are obtained, seen in Equations 2-30 and 2-31.

\[ \cos \theta_1 = \frac{t_0^2 + t_1^2 - t_2^2}{2t_0 t_2} \]  

(2-30)

\[ \cos \theta_2 = \frac{t_0^2 + t_2^2 - t_1^2}{2t_0 t_1} \]  

(2-31)

The solution is only dependent on the drag per length, which, as seen in Equation 2-27, is a function of vessel flow and radius.

**Zamir’s Summary of Optimization Theories**

Zamir later summarized four different optimization principles, all of which involve the minimization of a single factor [18], as seen in Equations 2-32 through 2-40.

For minimum lumen surface area:

\[ \cos \theta_1 = \frac{r_0^2 + r_1^2 - r_2^2}{2r_0 r_1} \]  

(2-32)

\[ \cos \theta_2 = \frac{r_0^2 + r_2^2 - r_1^2}{2r_0 r_2} \]  

(2-33)

\[ \cos (\theta_1 + \theta_1) = \frac{r_0^2 - r_1^2 - r_2^2}{2r_1 r_2} \]  

(2-34)
For minimum lumen volume:

\[
\cos \theta_1 = \frac{r_0^4 + r_1^4 - r_2^4}{2r_0^2 r_1^2} \tag{2-35}
\]

\[
\cos \theta_2 = \frac{r_0^4 + r_2^4 - r_1^4}{2r_0^2 r_2^2} \tag{2-36}
\]

For minimum power:

\[
\cos \theta_1 = \frac{\left(\frac{f_0^4}{r_0^8}\right) + \left(\frac{f_1^4}{r_1^8}\right) - \left(\frac{f_2^4}{r_2^8}\right)}{2\left(\frac{f_0^2 f_1^2}{r_0^4 r_1^4}\right)} \tag{2-37}
\]

\[
\cos \theta_2 = \frac{\left(\frac{f_0^4}{r_0^8}\right) + \left(\frac{f_2^4}{r_2^8}\right) - \left(\frac{f_1^4}{r_1^8}\right)}{2\left(\frac{f_0^2 f_2^2}{r_0^4 r_2^4}\right)} \tag{2-38}
\]

For minimum drag:

\[
\cos \theta_1 = \frac{\left(\frac{f_0^2}{r_0^4}\right) + \left(\frac{f_1^2}{r_1^4}\right) - \left(\frac{f_2^2}{r_2^4}\right)}{2\left(\frac{f_0 f_1}{r_0^2 r_1^2}\right)} \tag{2-39}
\]

\[
\cos \theta_2 = \frac{\left(\frac{f_0^2}{r_0^4}\right) + \left(\frac{f_2^2}{r_2^4}\right) - \left(\frac{f_1^2}{r_1^4}\right)}{2\left(\frac{f_0 f_2}{r_0^2 r_2^2}\right)} \tag{2-40}
\]

Zamir then introduced two new terms to simplify these relationships [19] – the asymmetry ratio, \( \alpha \), and the area ratio, \( \beta \), seen in Equations 2-41 and 2-42.
\[ \alpha = \frac{r_2^2}{r_1^2} \]  
\[ \beta = \frac{r_1^2 + r_2^2}{r_0^2} \]  

In these equations \( r_0 \), \( r_1 \), and \( r_2 \) are the parent vessel radius, larger child vessel radius and smaller child vessel radius, respectively. By combining Equations 2-41 and 2-42 with Equation 2-12, the following relationship was derived.

\[ \beta = \frac{1 + \alpha}{(1 + \alpha^{3/2})^{2/3}} \]  

Combining Equations 2-41 and 2-9 into Equations 2-32 through 2-40, Zamir arrived at simple equations defining the bifurcation angles [20], seen in Equations 2-44 through 2-47. The equations for minimum work mirrored those for minimum volume, while the equation for minimum drag mirrored those for minimum surface area.

For minimum power and lumen volume:

\[ \cos \theta_1 = \frac{(1 + \alpha^{3/2})^{4/3} + 1 - \alpha^2}{2(1 + \alpha^{3/2})^{2/3}} \]  
\[ \cos \theta_2 = \frac{(1 + \alpha^{3/2})^{4/3} + \alpha^2 - 1}{2\alpha(1 + \alpha^{3/2})^{2/3}} \]

For minimum drag and lumen surface area:

\[ \cos \theta_1 = \frac{(1 + \alpha^{3/2})^{2/3} + 1 - \alpha}{2(1 + \alpha^{3/2})^{1/3}} \]
\[
\cos \theta_2 = \frac{(1 + \alpha^{3/2})^{2/3} + \alpha - 1}{2\alpha^{1/2}(1 + \alpha^{3/2})^{1/3}}
\] (2-47)

**Generalization of Optimization Theories for Varying Exponents**

While the optimization for minimum lumen surface and lumen volume do not require the relationship stated by Murray, the equations for minimum power and drag rely on the fact that the flow is proportional to the cube of the radius. Uylings [21] argued that the possibility for turbulent flow exists in the vasculature, and derived an equation for the relationship of flow to the radius that encompasses both types of flow.

\[
f = kr^{(j+2)/(j-2)}
\]

(2-48)

For laminar flow the value of \( j \) is 4.0 and for turbulent flow \( j \) is equal to 5.0. The power to which the radius is raised is represented by Equation 2-49. The principle of conservation of mass can be applied to determine the relationship between flow rates in Equation 2-50, in which the \( x \) is referred to as the junction exponent. According to Uylings, laminar flow optimization requires a junction exponent of 3.0 while turbulent flow requires a junction exponent 2.33.

\[
x = \frac{(j + 2)}{(j - 2)}
\]

(2-49)

\[
r_0^x = r_1^x + r_2^x
\]

(2-50)
By replacing Murray’s constant of 3.0 with \( x \), Roy and Woldenberg [22] derived more general versions of the relationships previously defined by Zamir, seen in Equations 2-51 through 2-59.

\[
\beta = \frac{1 + \alpha^2}{(1 + \alpha^x)^{2/x}} \tag{2-51}
\]

Minimum power:

\[
\cos \theta_1 = \frac{(1 + \alpha^x)^{4-8/x} + 1 - \alpha^{4x-8}}{2(1 + \alpha^x)^{2-4/x}} \tag{2-52}
\]

\[
\cos \theta_2 = \frac{(1 + \alpha^x)^{4-8x} - 1 + \alpha^{4x-8}}{2(1 + \alpha^x)^{2-4/x} \alpha^{2x-4}} \tag{2-53}
\]

Minimum drag:

\[
\cos \theta_1 = \frac{(1 + \alpha^x)^{2-4/x} + 1 - \alpha^{2x-4}}{2(1 + \alpha^x)^{1-2/x}} \tag{2-54}
\]

\[
\cos \theta_2 = \frac{(1 + \alpha^x)^{2-4x} - 1 + \alpha^{2x-4}}{2(1 + \alpha^x)^{1-2/x} \alpha^{x-2}} \tag{2-55}
\]

Minimum volume:

\[
\cos \theta_1 = \frac{(1 + \alpha^x)^{4/x} + 1 - \alpha^4}{2(1 + \alpha^x)^{2/x}} \tag{2-56}
\]

\[
\cos \theta_2 = \frac{(1 + \alpha^x)^{4/x} - 1 + \alpha^4}{2(1 + \alpha^x)^{2/x} \alpha^2} \tag{2-57}
\]
Minimum surface area:

\[ \cos \theta_1 = \frac{(1 + \alpha^x)^{2/x} + 1 - \alpha^2}{2(1 + \alpha^x)^{1/x}} \] (2-58)

\[ \cos \theta_2 = \frac{(1 + \alpha^x)^{2/x} - 1 + \alpha^2}{2(1 + \alpha^x)^{1/x} \alpha} \] (2-59)

Relationship to Presented Work

In the following work, the distribution of junction exponents are analyzed to understand if the retinal arterial network truly conforms to Murray’s Law. Additionally, the theories presented by Zamir (Equations 2-43 through 2-47) and Roy (Equations 2-51 through 2-59) are tested against the measured data.
Figure 2-1. Drawing of an arterial bifurcation with labelled flow rates, radii and bifurcation angles.
Figure 2-2. An arterial bifurcation positioned on a rectangular coordinate system along with its labeled lengths, endpoints and angles.
CHAPTER 3
METHODS

Image Dataset Description

The images used in this study come from the Gold Standard Database for Evaluation of Fundus Image Segmentation Algorithms. This database is maintained by the Department of Computer Science at University of Erlangen-Nuremberg in Bavaria, Germany [23]. The database contains three categories: healthy, diabetic and glaucomatous. For each category there exist fifteen fundus images accompanied by a corresponding binary image of segmented blood vessels (Figure 3-1).

All fundus images are fovea-centered with the optic disc to either the left or right side of the image, depending on whether the image of the patient’s right eye (oculus dexter) or left eye (oculus sinister). Each image has dimensions of 2336 x 3504 pixels with a red, green and blue color layer. The fundus can be observed in a trimmed circle with a radius of approximately 1600 pixels at the center of the image.

The corresponding segmented image contains an array of logical values the same size as the original fundus images, with ones signifying the presence of vasculature. These images were produced through the collaboration of image processing experts, ophthalmologists, and ophthalmologic clinicians in order to create a “ground truth” to which segmentation algorithms can be compared. Manual segmentation was used for this dataset to ensure accuracy.

Network Separation

The segmented images contain information on the locations of retinal vasculature, but no information is given on the classification of vasculature as arterial or venous. In order to analyze each network separately, two images were created from the
segmented images: an arterial segmented image and a venous segmented image (Figure 3-2).

Adobe Photoshop (Adobe, 2012) was used to modify the segmented image to create the arterial and venous networks. In order to create the arterial network, the veins were identified and deleted from the image. A set of vessel categorization rules was developed, most of which relate to the appearance of the vessel. Veins tend to be wider, darker and more tortuous than arteries at the same radial distance from the optic disc [24]. Through adherence to these criteria, it was possible to distinguish arteries from veins and delete the appropriate vessels (Figure 3-3).

At crossover points, where arteries and veins meet, great care must be taken to ensure the right vessels are retained by observing the vessel properties such as diameter, orientation and intensity, and must also strive to retain a smooth vessel profile at points where a crossover vessel is deleted. This method introduces a small level of uncertainty in the geometry of the vessel through deletion errors (Figure 3-4).

Due to the nature of the connectivity algorithms later implemented, no loops can exist in the image, defined by areas of isolated black pixels. These loops tend to form more often in diabetic eyes that experience neovascularization (Figure 3-5). If these loops are encountered, the vessels are deleted “upstream” until no loops exist.

**Network Skeletonization**

The separated image, whether arterial or venous, was imported into MATLAB (The Mathworks, 2012) and converted to binary using a native MATLAB threshold function. The image was then treated as a logical array and subjected to a MATLAB-
native thinning algorithm [25] to create a single pixel-wide network defining the skeleton of the network (Figure 3-6).

In order to disregard any network fragments entering from the boundaries of the image as well as possible floating artifacts, each area of connected white pixels was labeled and its comprising pixels counted. The region containing the most connected white pixels, i.e. the network to be analyzed, was retained while all others were deleted. Often, sometimes due to the nature of separating the arterial and venous networks, small skeletal endpoint segments may exist called “stubs” (Figure 3-7). These stubs were deleted by isolating only endpoint segments and deleting any of those segments that fell below a certain pixel length filter.

The skeletal image was then checked for loops by inverting the image and counting the number of 4-neighbor-pixel connected regions. If this number exceeded one, loops were detected and analysis ceased. This required modification of the separated image file and starting the analysis again.

Arterial Source Selection

After the skeletal network was defined, the source of arterial flow (or destination of venous flow) was manually chosen by drawing an ellipse around a set of pixels within the optic disc (Figure 3-8). This is the area inside which the central retinal artery and central retinal vein enter and exit the optic disc. This characteristic set of pixels was later used in determining the connectivity of the network.

Identification of Endpoints and Junctions

Endpoints are defined as skeletal pixels with only one neighbor (Figure 3-9). MATLAB contains a native function for finding these endpoints, but sometimes
attributes non-white pixels as endpoints. Additionally, any endpoints within the source area are not to be considered. In order to identify only the endpoints that are wanted, the native MATLAB function was first used. Any endpoints that were black pixels were then neglected, as well as any endpoints lying within the source area.

A junction is defined as a skeletal pixel that connects three separate lengths of pixels (Figure 3-10). Unlike intra-segment pixels, these pixels have three neighbors not adjacent to each other. While the criterion of having three neighbors should suffice, an extra precaution is taken to avoid interpreting "kinks" in the skeletal network as junctions. The process of thinning should inherently remove these kinks, but the additional criterion neighbor pixels not being adjacent did not hinder the discovery of these points.

**Determination of Connectivity and Junctions**

With the endpoints, junctions and source area defined, the network connectivity was able to be determined. The connectivity was defined by assigning the term “node” to endpoints, junctions and the source area while assigning the term “segment” to all skeletal pixels between and including the two containing nodes (Figure 3-11). By defining which nodes connected to which segments, and vice versa, the connectivity of the entire network was able to be defined.

In order to actually determine the connections between nodes and segments, a systematic “walking” method was implemented. For a local node, every length of pixels connected at that node was traced until another node was reached, at which point that length of pixels is defined as a segment with its respective bounding nodes. This
process is repeated until all pixels are accounted for, with every segment having two containing nodes. The generation of a segment is determined by how many bifurcations exist between the segment and the arterial origin. Segments emanating from the source were given the generation number of “1” and increase with each bifurcation (Figure 3-12). By knowing the generation of each segment meeting at a junction, it was possible to determine which segment was the parent segment and which were the children segments of the bifurcation (Figure 3-13).

**Calculation of Segment Geometry and Bifurcation Angles**

The skeletal segments are an estimation of the centerline of a vessel segment. Using this information, it is possible to estimate the width based on the location of the nearest non-segment pixel. Since the projection of a portion of a vessel resembled a rectangle, and the skeletal pixels represent a line that equally divides the area of the rectangle and runs parallel to the vessel walls, it can be assumed that the shortest distance to a point outside of the vessel represents the approximate radius of a vessel. By inverting the segmented image, thus making vessel pixels black, the MATLAB function ‘bwdist’ could be applied, applying a zero value to all non-vessel pixels and distance values to all vessel pixels. This distance value increases with distance from a vessel wall (Figure 3-14). By using the distance value from the points on which the skeletal pixels lie, a radius for the segment is determined and doubled to arrive at a diameter at that point.
This width has a fair amount of uncertainty due to two factors: the skeletal pixel may not lie exactly on the centerline of the vessel, and the line connecting the skeletal pixel to the nearest non-vessel pixel may not be perpendicular to the vessel walls. In larger vessels, this is less worrisome because the uncertainty does not scale with vessel size.

After widths were determined for every skeletal pixel of a segment, the mean was calculated and this value was assigned as a “segment width”. This value is used in lieu of a value immediately next to a bifurcation because of the difficulty in obtaining an accurate measurement at that point.

In order to determine the bifurcation angles of the child segments, it was required to attribute a directional unit vector to each segment. For each segment, two vectors were calculated, one at each end directed inwards along the segment (Figure 3-15). These were calculated by finding the unit vectors from one end of the segment to each of up to 50 pixels into the segment. These unit vectors were then averaged to find a unit vector for that end of the segment. This process was repeated for the other end of the segment to determine another unit vector.

\[
\vec{u}_i = \frac{(x_i - x_1) \mathbf{i} + (y_i - y_1) \mathbf{j}}{\sqrt{(x_i - x_1)^2 + (y_i - y_1)^2}} \quad (3-1)
\]

\[
\vec{u}_{a,b} = \frac{1}{N} \left( \sum_{i=1}^{N} \vec{u}_i \right) \quad (3-2)
\]

With the unit vectors of the parent segment and children segments defined at each bifurcation, the bifurcation angles (\(\theta_1, \theta_2\)) were calculated including the deviation angles for each child segment (Figure 3-16).
\[ \theta_1 = \cos^{-1}(-\vec{u}_0 \cdot \vec{u}_1) \quad (3-3) \]

\[ \theta_2 = \cos^{-1}(-\vec{u}_0 \cdot \vec{u}_2) \quad (3-4) \]

**Calculation of Junction Exponents**

The junction exponent can be found through Equation 3-5, with the parent segment diameter for \( D_0 \), the smaller diameter of the children segments for \( D_1 \) and the larger for \( D_2 \) (Figure 3-17). Because there is not a closed-form solution for \( x \), the exponent was solved numerically using MATLAB’s native solving capabilities. If a solution could not be found numerically, the bifurcation was excluded from analysis.

\[ D_0^x = D_1^x + D_2^x \quad (3-5) \]
Figure 3-1. An illustration of the vascular segmentation process. A.) original fundus image, B.) binary segmented image
Figure 3-2. Illustration depicting the separation of the original binary network into arterial and venous binary networks. A.) Binary network, B.) Color-coded network, C.) separated arterial network, D.) separated venous network
Figure 3-3. Example of a vein next to an artery in a fundus image.

Figure 3-4. Illustration showing the separation process of arteries and veins.
Figure 3-5. An example of neovascularization.
Figure 3-6. Illustration of the skeletonization process. A.) binary section, B.) skeletonized section
Figure 3-7. Illustration of stub removal.

Figure 3-8. Manual selection of the source of arterial flow.
Figure 3-9. Skeletal network section with endpoints identified.

Figure 3-10. Skeletal network section with junctions identified.
Figure 3-11. Skeletal network section with a node and respective segments labeled.

Figure 3-12. Skeletal network section with segment generation labels.
Figure 3-13. Example node with parent and children segments labeled.

Figure 3-14. Method of nearest non-vessel pixel method of width calculation.
Figure 3-15. Sample skeletal segment with directional unit vectors labeled.

Figure 3-16. Sample node with bifurcation angles labeled.
Figure 3-17. Sample node with branch diameters labeled.
CHAPTER 4
RESULTS AND DISCUSSION

The methods described in the previous chapter were used to calculate various parameters from 13 healthy arterial retinal vascular networks. Before the data was analyzed and represented graphically, it was filtered through a set of criteria. The first criterion was that the junction exponent was actually found through an iterative solving method. The second restriction was that the junction exponent was positive. The third was that the junction exponent was valid according to Chauvenet’s Theorem of outliers [26]. The fourth restriction was that both bifurcation angles must be positive.

The distribution of junction exponents was represented in a histogram (Figure 4-1) to determine if Murray’s law was an obvious outcome.

With a distribution mean of 1.97 and a standard deviation of 0.59, the result did not verify Murray’s law but instead suggested that a range of junction exponents exists in the retinal vasculature.

The relationship between the asymmetry ratio, α, and the area ratio, β, was then investigated. In Figure 4-2 the measured values of α and β are represented along with the predictions of Zamir (Equation 2-43) and Roy (Equation 2-51). The theoretical line representing Zamir’s prediction (black) is independent of the measured junction exponent. The other theoretical lines represent Roy’s prediction with several different junction exponents.

In order to understand the distribution of the measured values better Figure 4-3 displays the same theories and data averaged over evenly spaced bins of the asymmetry ratio. The data seems very random and does not seem to conform to Zamir’s prediction.
Figures 4-4 through 4-6 show a comparison of measured data and theoretical prediction of Roy based on a junction exponent of 1.5, 2.5 and 3.0, respectively. These plots give insight into the exponent-reliant relationship of $\alpha$ and $\beta$. The measured data seems to follow these predictions much more closely than that of Zamir's.

Figures 4-7 and 4-10 display the measured values for $\theta_1$ and $\theta_2$ against the measured asymmetry ratio, $\alpha$. Additionally, the theoretical predictions of Zamir (Equations 2-44 through 2-47) are also shown. The data seems to have a fairly wide distribution, but when averaged into evenly spaced bins of $\alpha$, it can be seen that the means of the bins fit fairly well between the two theories.

Figures 4-11 through 4-16 display theoretical relationships between the measured bifurcation angles and the asymmetry ratio as predicted by Roy (Equations 2-52 through 2-59). Each figure is isolated to a junction exponent of either 1.5, 2.5 or 3.0 and within each figure various theories of optimization are compared. For some plots the theoretical relationship was not applicable (e.g. a junction exponent of 1.5 in Equation 2-56 yields imaginary results, therefore the relationship for volume is not shown in Figures 4-11 and 4-12).

In each figure the data follows at least one trend that aligns with a theory. For a junction exponent of 1.5 the data only seems to follow the principle of minimizing surface area, while with other junction exponents it could be argued that the data could follow any of the four optimization principle predictions.
Figure 4-1. Histogram of junction exponents.
Figure 4-2. Scattered data of area ratios vs. asymmetry ratios along with theoretical predictions.
Figure 4-3. Binned data of area ratios vs. asymmetry ratios along with theoretical predictions.
Figure 4-4. Measured area ratios versus asymmetry ratios along with theoretical predictions with a junction exponent of 1.5.
Figure 4-5. Measured area ratios versus asymmetry ratios along with theoretical predictions with a junction exponent of 2.5.
Figure 4-6. Measured area ratios versus asymmetry ratios along with theoretical predictions with a junction exponent of 3.0.
Figure 4-7. Scattered larger-diameter bifurcation angles versus asymmetry ratios along with Zamir’s theoretical predictions for minimum power/volume and drag/surface area.
Figure 4-8. Binned larger-diameter bifurcation angles versus asymmetry ratios along with Zamir’s theoretical predictions for minimum power/volume and drag/surface area.
Figure 4-9. Scattered smaller-diameter bifurcation angles versus asymmetry ratios along with Zamir's theoretical predictions for minimum power/volume and drag/surface area.
Figure 4-10. Binned smaller-diameter bifurcation angles versus asymmetry ratios along with Zamir’s theoretical predictions for minimum power/volume and drag/surface area.
Figure 4-11. Scattered larger-diameter bifurcation angles versus asymmetry ratios along with Roy’s theoretical predictions for minimum power, drag and surface area for a junction exponent of 1.5.
Figure 4-12. Scattered smaller-diameter bifurcation angles versus asymmetry ratios along with Roy's theoretical predictions for minimum power, drag and surface area for a junction exponent of 1.5.
Figure 4-13. Scattered larger-diameter bifurcation angles versus asymmetry ratios along with Roy’s theoretical predictions for minimum power, drag and surface area for a junction exponent of 2.5.
Figure 4-14. Scattered smaller-diameter bifurcation angles versus asymmetry ratios along with Roy’s theoretical predictions for minimum power, drag and surface area for a junction exponent of 2.5.
Figure 4-15. Scattered larger-diameter bifurcation angles versus asymmetry ratios along with Roy’s theoretical predictions for minimum power, drag and surface area for a junction exponent of 3.0.
Figure 4-16. Scattered smaller-diameter bifurcation angles versus asymmetry ratios along with Roy’s theoretical predictions for minimum power, drag and surface area for a junction exponent of 3.0.
CHAPTER 5
CONCLUSIONS

Overall the program seemed proficient at collecting information about retinal arterial bifurcations. Occasionally the junction exponent could not be defined or angles could not be calculated, but this is probably due to either the methods of segmentation, methods of separation, or errors in the calculation of segment diameters or directional unit vectors. For the use of comparison to theory, it also provided some additional insight.

The distribution of the junction exponents seemed to indicate that Murray’s law, i.e. that the junction exponent is always equal to 3.0, was not a valid assumption to make. This could be due to a multitude of factors ranging from the assumptions of laminar flow the possibilities of other principles of optimization outside of minimum work.

In predicting the relationship between area ratio and the asymmetry ratio, the inclusion of a junction exponent seemed to follow theory more closely than a junction-independent method. When Murray’s law was assumed and Zamir’s calculations were used, there seemed to be no discernable conformity to the predicted values.

When predicting bifurcation angles, however, the theories supposed by Zamir seemed to encompass the data much more closely than those of Roy with various exponents. The inconsistencies between various theory predictions may suggest that vascular growth is based on multiple theories, or relies on factors outside of this analysis.

Future work should investigate possible additional relationships based on flow-based factors, such as flow rate, pressure gradients or fluid resistances. As Zamir suggested, vascular growth may rely on local factors instead of a full-network
optimization principle. The distribution of junction exponents should also be investigated to determine if there is a reliance on a known factor, such as parent diameter or distance from the optic disc. Additionally, as bifurcation information may be useful as a diagnostic tool, these methods should be tested on eyes with known pathologies such as diabetic retinopathy or glaucoma.
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Richard Clark was born in 1988 in Orlando, Florida. He attended Winter Springs High School in Winter Springs, FL and continued his education at the University of Florida, majoring in mechanical engineering. During his undergraduate career he held various leadership positions including president of the Sigma Omicron branch of Pi Tau Sigma, an honor society for mechanical engineers. After graduating magna cum laude in 2006 with his Bachelor of Science degree he continued his studies under Professor W. Gregory Sawyer in the University of Florida Tribology Laboratory. While researching the vasculature of retinal fundus images, he also held a mentoring position in the Engineering Freshman Transition Program and led weekly lectures in the undergraduate statics course. He graduated in the spring of 2013 with his Master of Science degree in mechanical engineering.