What is the Optimal Branching Angle of a Vascular Network?

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Abstract

Branching angles of a vascular network affect the efficiency of blood flow and associated energy cost. Minimizing this associated energy cost leads to solutions for an optimal angle. In this project, I investigated different optimization approaches that attempt to explain the branching angles of vascular networks. Specifically, I compared three different optimal angle calculations to measured branching angles from a wildtype mouse lung. The model angles were calculated under the assumptions that the network was designed to minimize (i) surface area, (ii) volume, or (iii) resistance to blood flow in the network. I determined the optimal angles and the measured angles at different branching levels in the network to see if the mean values at each level were a function of the branching level. For the mouse data, I used the software *angicart* to measure angles, and found that the measured angles were consistent with a median optimal angle of $72°$, with some deviations at the highest and lowest branching levels. Typical errors were about $\pm 10\%$. There were no clear trends with branching level for the model angle values. I found that the optimal surface area model predictions all had median values in the range $100° - 120°$ and were consistently higher than the measured angles. The predictions from the optimal volume model were more erratic with the differences between data and models being small at some levels and large at other branching levels. The minimal resistance to flow model predicted angles that were closest to the measured data, but this model also had the largest errors.

1 Introduction

The metabolic rates of mammals may be the key factor determining several biological processes [1]. The metabolic rate is a function of body mass with a 3/4 scaling exponent [2], and this relation remarkably holds over several orders of magnitude. However, it is believed that this may not be entirely accurate in predicting scaling exponents of metabolic rate because they are more complicated than a simple 3/4 power law [3], and there are several assumptions of the model that makes it inaccurate in certain scenarios [4].

The rate at which metabolism takes place is to a large degree determined by the cardiovascular network. The cardiovascular system in mammals is composed of the heart, blood, and blood vessels, and it is responsible for transporting nutrients in blood throughout the entire organism. Naturally, an organism would want nutrients to be transported in the most energy-efficient way possible. Vascular system structure controls the pathway through which nutrients are allowed to flow, which in turn affects the energy required to pump blood through the network [2]. The network itself also comes with an energy cost; energy is required to both build and maintain network structure.

Cardiovascular networks can be modeled mathematically, which allows a better understanding of their structure. Models can provide a more accurate understanding of the general principles underlying networks, and they can also be used to predict and analyze and synthesize larger amounts of data. The structure of a vascular network itself can be approximated quite well using mathematical models. Models of cardiovascular networks have been successfully used in fields such as drug delivery (researchers need to understand network structure in order to track the pathways the drug acts on) and tumor growth (tumors have drastically different structure from healthy tissue, and understanding these differences help researchers identify tumors in early stages).

One such mathematical theory based on an organism's vascular system architecture was proposed in 1997 by West, Brown, and Enquist, primarily to estimate the relationship between metabolic rate and body mass [2]. The WBE model was created by making several assumptions about vascular network structure. Each individual blood vessel is modeled as a cylinder with a fixed radius. The network composed of these vessels is hierarchical (there is a constant labeling system used from heart to capillaries) and aims to fill as much space as possible, with every level of the hierarchy composed of identical vessels. Capillaries have the same measurements within the network of an organism and across species, and they are the only places in the model where exchange of resources takes place [4].

The WBE model has since provided a framework for analyzing the underlying structure of vascular networks, but there are several parameters that it overlooks which could significantly influence network structure and by extension metabolic rate. The angle formed between two daughter vessels of the same parent, or the branching angle, is an important property of vascular networks. The branching angle is important for calculating the energy required for the network to fill a certain space. Larger angles would fill lateral space while not covering much distance (from the central organ or heart), while smaller angles would mean that vessels cover greater distance but do not transport nutrients to a wide lateral area.

In an ideal situation, blood vessels would branch at an optimal angle which would minimize the energy cost of building and maintaining the network. Optimal angle predictions have been made by using calculus to minimize the surface area or the volume of each individual vessel in the network [5]. One optimal angle prediction was made by Zamir in his book *The Physics of Coronary Blood Flow* [6], where he examined the properties of networks to estimate an optimal angle of 60 degrees.

Current models of vascular networks do not model the branching angle in detail and even when it is considered, it is assumed that branching angle remains at an optimal constant throughout the entire network [6]. However, network structure is known to change with branching level; large vessels are dominated by pulsatile flow, which is area preserving while branching [2], whereas smaller vessels have laminar or smooth flow and are governed by an energy minimization principle [7]. Therefore, it is not clear that branching angles should all have the same optimal value at all levels. This project tests this assumption and tries to determine the importance of branching angles for network structure. Branching angles as a function of the level of branching are measured from vascular network data of a healthy mouse and they are compared to optimal angle calculations made under different assumptions.

2 Methods

2.1 *angicart*

The software *angicart* was used to extract the network structure from an MRI scan of a healthy mouse lung (see Figure 1). The data was a series of 2-dimensional images of vasculature that were produced by micro-CT (high resolution computed tomography). These images can be aligned to provide a 3-dimensional map of the network structure. *angicart*

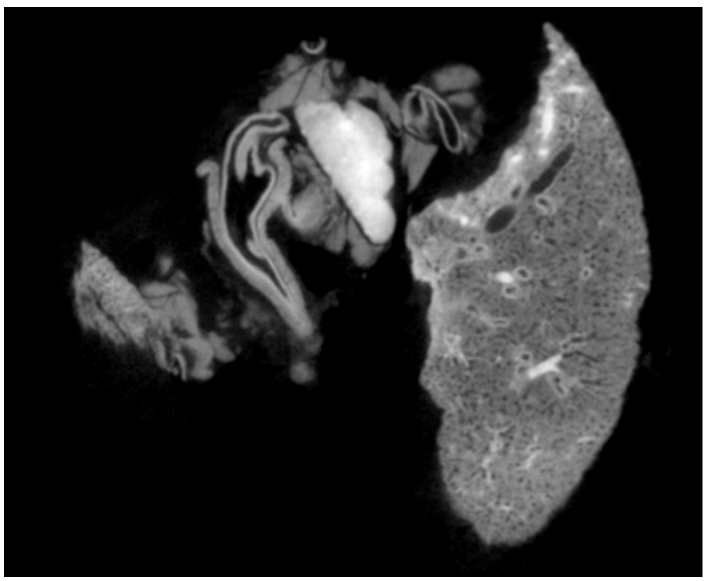

Figure 1: *An MRI scan of the lung of a wildtype mouse that was used for studying the vascular network structure.*

is a software written in the language OCaml, and can extract the network structure from imaging data [8]. MRI scans are used as input files, and this data is used to determine the 3-dimensional structure embedded in the scan. The software does this by identifying relative brightnesses of voxels (three-dimensional pixels) in the scan and then by grouping them into segments. It then finds the largest connected component of voxels that are all above a certain user-specified intensity threshold. The identified vascular regions, branching nodes and end nodes are all used to skeletonize the network. The radius and length of each vessel are also determined. *angicart* can therefore be used to efficiently extract a table of measurements of the network from an MRI scan of a region of the cardiovascular network of an organism.

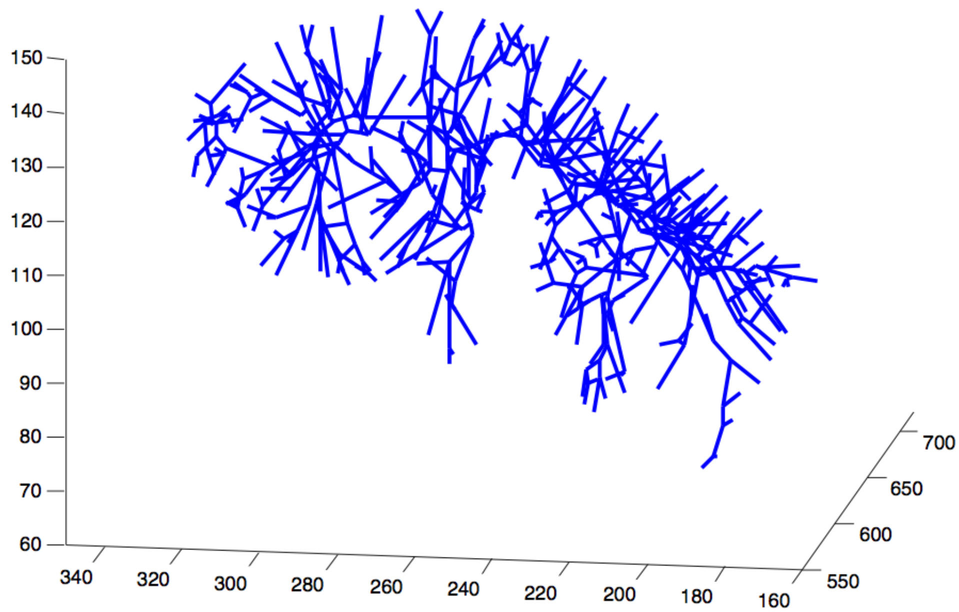

Figure 2: *This figure is a MATLAB visualization of the mouse lung network, and was generated from the skeletonized structure extracted from the data using angicart. The three axes are the voxel coordinates.*

2.2 Mouse Data Measurements

I used *angicart* as described above to analyze data from an MRI scan for a healthy mouse. A sensitivity threshold of 0.83 was used to obtain a list of the coordinate (x, y, z) values for the two ends of a vessel segment and for identifying parent and daughter branches. After processing the MRI data through *angicart*, I obtained the skeletonized mouse lung structure. I then used the list of coordinates to generate a plot of the network structure using MATLAB; this is shown in Figure 2. Measurements of the branch radii were also obtained. I developed a JAVA program (*BrAngle*) to read these values from the output file, identify the nodes and calculate the branching angle at each node. The node was determined by first identifying two vessels that shared one of the two coordinates that define each vessel segment. Assigning a 3D vector to each segment, the branching angle was then calculated by taking the vector dot product. *BrAngle* also identifies parent and daughter branches and the branching level which indicates how far this branch is from the first node (vessel with no parent) in the network. My procedure was to start with one vessel, and then repeatedly find each vessel's parent and increment the level number until the first node was reached. This method was used to generate a list of the branching angles and the branching level that each angle was measured to be at.

2.3 Calculating Model Optimal Angles

Three different theoretical models were considered; these minimized surface area, volume or resistance to flow. Minimizing the energy cost associated with constructing and maintaining the network requires minimizing the material needed, which is measured by surface area. Minimizing the energy cost required to pump blood through the network requires maximizing the capacity of each vessel, which is measured by volume. Optimizing the transport of blood through the network requires minimizing resistance to flow. The optimal angle calculated in each case is a function of the parent and daughter branch radii, which were obtained using *angicart*. Since radius changes across level, every branching level may have a different optimal angle. I added another JAVA method to *BrAngle* to calculate the expected optimal angle for every theoretical optimization. The different equations for optimal surface area and volume are:

Minimum Surface Area:

$$\cos\theta_m = \frac{r_0^2 - r_1^2 - r_2^2}{2r_1 r_2}$$

Maximum Volume:

$$\cos\theta_m = \frac{r_0^4 - r_1^4 - r_2^4}{2r_1^2 r_2^2}$$

where θ_m is the optimal angle, r_0 is the radius of the parent vessel and r_1 and r_2 are the radii of the two daughter branches [6] (see Fig. 3).

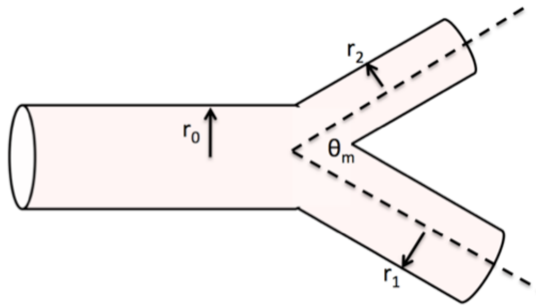

Figure 3: *A sketch of the branching node of the network, identifying the parent and daughter branch radii (r_0, r_1, r_2) and the branching angle θ_m.*

The final model assumes that the optimal angle is determined by minimizing resistance to flow in the network. Instead of minimizing surface area or volume of single vessels at a time, this model finds the optimal spatial location of the branching junction that minimizes the entire parent-daughter branching structure's resistance to flow [9]. It takes as input the points A, B, and C, where A is the starting coordinate for the parent segment and B and C are the coordinates of the terminal nodes of the daughter branches. The angle ϕ which corresponds to the angle BAC of a single junction (Fig. 4), can therefore be uniquely determined. h_0, h_1, and h_2 are the cost functions per unit length of the parent vessel and the two daughter vessels respectively. b and c are imaginary line segments connecting AC and AB, and they are also labeled in Fig. 4. The location J of the branching junction is then calculated so that the resistance to flow is minimal [9]. The optimal half-angles are then given by

$$\cos\theta_1 = \frac{(1+w)^4 h_0^2 + h_1^2 - h_2^2 w^4}{2h_0 h_1 (1+w)^2} \quad \text{and} \tag{1}$$

$$\cos\theta_2 = \frac{(1+w)^4 h_0^2 - h_1^2 + h_2^2 w^4}{2h_0 h_2 w^2 (1+w)^2}, \quad \text{where} \tag{2}$$

$$w = \frac{h_1 L_1}{h_2 L_2} = \frac{h_1 c \sin\theta_2}{h_2 b \sin\theta_1}(-\cos\phi + \sin\phi\cot(\phi + \gamma - \theta_1)) \quad \text{and} \tag{3}$$

$$\gamma = \cot^{-1}\left[\frac{\frac{c\sin\theta_2}{b\sin\theta_1} + \cos(\theta_1 + \theta_2 - \phi)}{\sin(\theta_1 + \theta_2 - \phi)}\right] \tag{4}$$

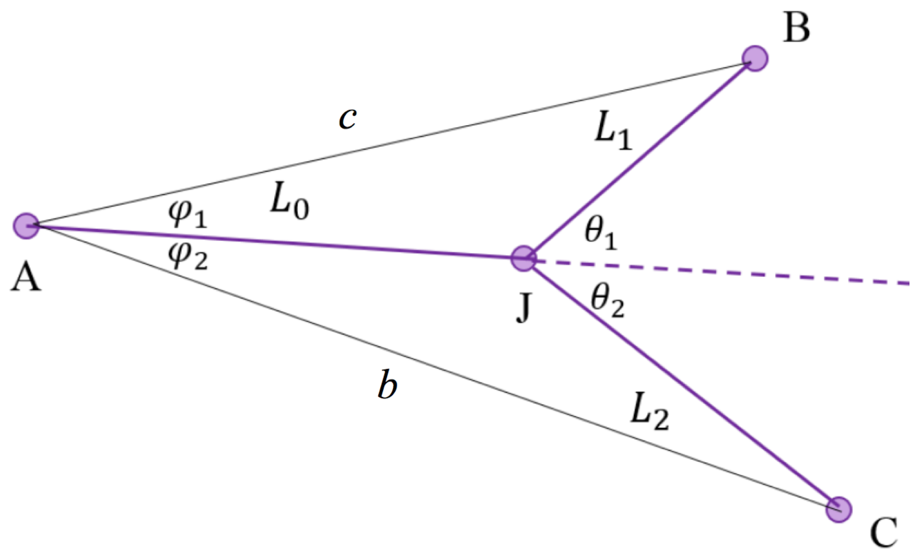

Figure 4: *A sketch of the branching node for the minimum resistance to flow calculation, with the three input points A, B and C identified. The lengths L_0, L_1 and L_2 are determined by finding the location of point J. The branching angle $(\theta_1 + \theta_2)$ is also then determined.*

I first calculated ϕ, which is the minimum branching angle for the junction since an angle $\theta_m = \theta_1 + \theta_2 = \phi$ would result in no junction at all. I attempted to find solutions to the above equations numerically. I started with an initial guess solution x and then varied x until the solutions were equal, similar to Newton's method. The other angles were obtained from graphical solutions to the equations by finding the intersection points of the curves using MATLAB [9].

Some solutions for ϕ were sometimes out of range ($\cos\phi > 1$, for example), I discovered then that *angicart*'s convention for starting and ending coordinates were not always consistent. This caused confusion because the starting coordinate A of the parent segment could sometimes be misidentified as its ending coordinate and vice versa. I then modified *BrAngle* to examine all the coordinates and label the junction coordinate as the one shared by all three vessels at a branching junction. This allowed me to properly determine A and calculate the location of J which could be compared with the actual branching junction coordinate. When the right coordinates were used, ϕ was no longer out of range.

At each level, I averaged values over all the branches so that each branching level had one measured angle and one optimal angle calculation. I first assumed that all parents split into two daughter branches, but then found this was not always true. There were some vessels that split into three branches. Such vessels were then deleted from the list of angles and the analysis repeated.

3 Results and Analysis

3.1 Results: Measured and Optimal Branching Angles

The histograms in Figure 5 show the frequency of the measured and optimal angles averaged across all branching levels. The average measured angles were consistently between 70° and 80°, while optimal angles for all three models were systematically higher and in the range 110° to 130°.

I then found the average angles across level, this is shown in Figure 6 with the level number on the x-axis (level 1 represents the largest branch) and the angle in degrees on the y-axis, and compared the model calculations with the measurements. Measured angles are represented by blue diamonds, while optimal angles are represented by red squares. I calculated the standard errors which were surprisingly low, suggesting that branching angle remains mostly constant throughout each level.

For the surface area optimization, I found that the optimal angles were consistently higher than the measured angles, with the closest match still about 10 degrees off. Error was generally low throughout, which suggests that the measurements and calculations were accurate.

The volume optimization was more erratic across branching level than the surface area optimization. Most of the errors are due to the measurement of the branch radii which

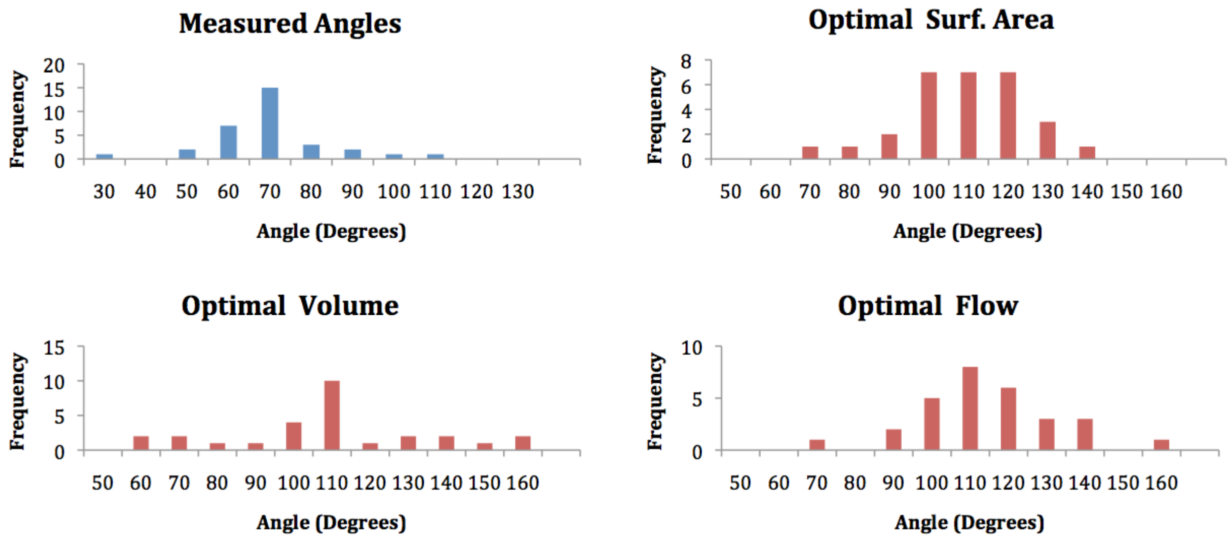

Figure 5: *Histograms of the branching angles for the data measurements and the three different models are shown in the above figure. Most of the measurements lie in the range from* $60 - 80°$. *The median of the measured angles is 72.3°. The minimum surface area optimization model gives a broad range of values from* $100 - 120°$. *The maximum volume model has a narrower distribution with a peak in the* $100 - 110°$. *The optimal flow model also peaks at* $110 - 120°$, *but gives a range of angles from* $90 - 140°$. *All the models give higher values than the measured angles.*

enters as the fourth power in this calculation. Calculations for the earlier branching levels were extremely high (140° - 160°); they averaged out at a smaller value of about 120° during the middle levels before varying more toward the end. Error was higher than that of the surface area optimization where the branch radius measurement error propagates only as radius squared.

The resistance to flow optimization had the highest error margins. It was less varied than the volume optimization but more varied than the surface area optimization, and was still on average significantly higher than the measured values. Some of the optimal angle predictions were close to the measured values, but many were much larger.

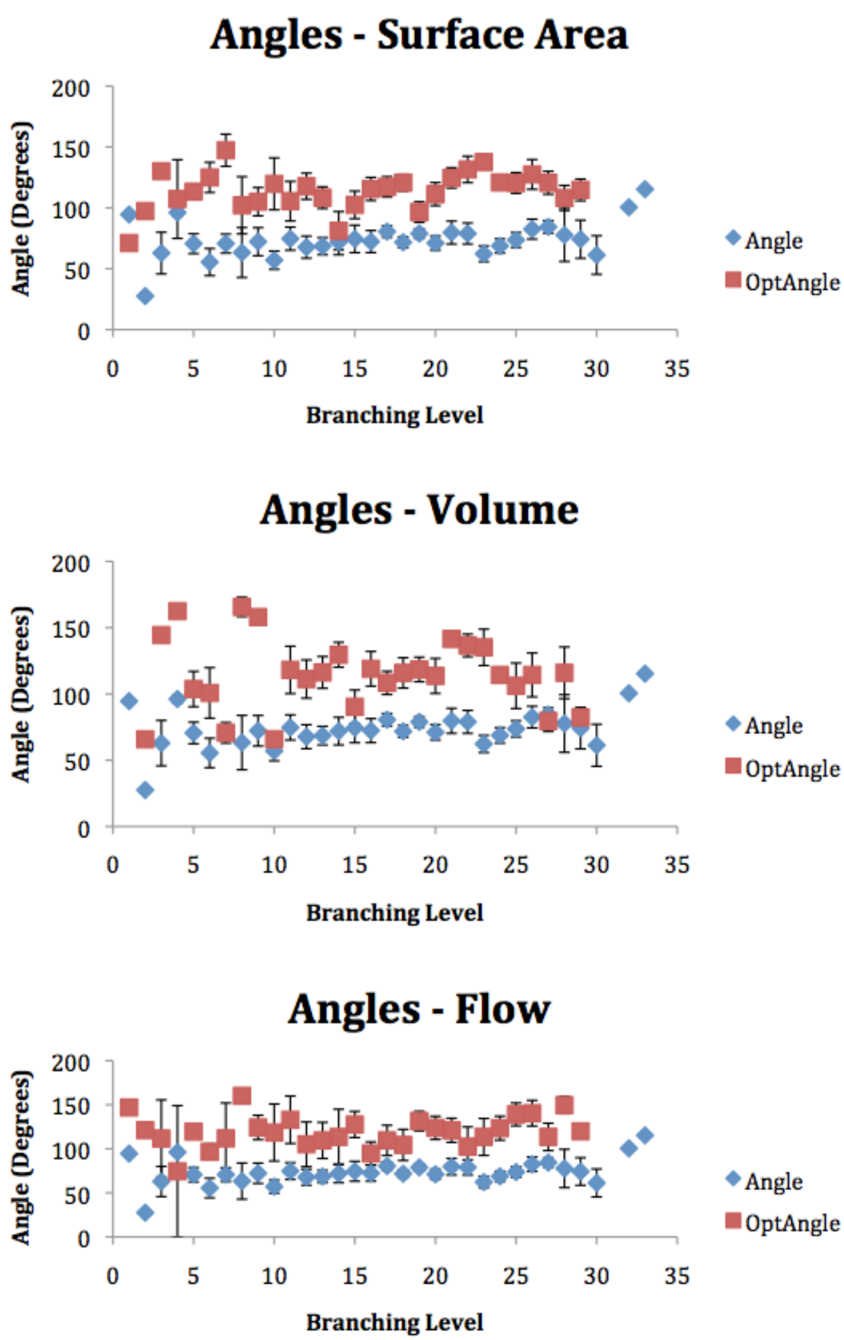

Figure 6: *The measured branching angles (blue diamonds) and shown in comparison with the three optimal angle models (red squared) as a function of branching level. Branching angles are averaged across each level number. At lower levels, there are fewer branches and the errors are higher. At the highest levels, the branch radii measurements are sometimes not very accurate and the errors can be large here as well.*

3.2 Analysis

The measured branching angles stayed almost constant across branching level and had very low error, with slight variations in both the first few and the last few levels. These variations are probably because measurements are fewer in number for the first levels (giving larger statistical errors) and radii measurements have larger errors for the small vessels at high branching levels of the network. The average angle was about 72°. Therefore, the change from pulsatile flow to smooth flow may not affect the branching angle of the network [6].

None of the three models matched the measurements particularly well, with all models giving angles higher than the measured values. The surface area model was consistently higher than the measured angles. The volume model had a few predictions which matched the measured angles near the beginning and the end of the network, but no matches near the middle. The flow model was marginally better in its agreement with data, since the mean values lie closer to the measured angles. The values are still higher in value like the surface area and volume models, and had larger errors at lower levels. The comparison of optimal angle calculations with data suggests that more precise calculations for optimal branching angle still need to be developed. The histograms reveal that almost all of the measured angle values are between 70 and 80 degrees, but most of the optimal angle values are between 110 and 120 degrees.

Since the measured radii from the mouse data were used to calculate the optimal angles, the difference in angles can also be interpreted as being due to how the daughter branch radii are related to the parent branch radius. It is possible to use the optimal angle equations and angle values to calculate β, the ratio between the daughter and parent vessels. Assuming that $r_1 = r_2 = \beta r_0$, and using the formula for volume:

$$\cos\theta_m = \frac{r_0^4 - r_1^4 - r_2^4}{2r_1^2 r_2^2} = \frac{r_0^4 - (\beta r_0)^4 - (\beta r_0)^4}{2(\beta r_0)^2(\beta r_0)^2} = \frac{1 - 2\beta^4}{2\beta^4}$$

Substituting the average measured value of $\theta_m = 72°$ gives $\beta = 0.786$. A similar calculation for optimal surface area leads to $\beta = 0.618$. Higher measured values of β will give larger values for θ. This means that the daughter branches are larger in radius compared to the radius of the parent branch than expected by the optimal surface area and volume models. This calculation is more complicated for the optimal flow model, but the higher values of the optimal angle obtained imply that the true location of the branching junction is closer to the starting point of the parent segment than the expected location.

What could account for the discrepancy between measured angles and optimal angle calculations? One possibility is that since the network is three-dimensional, the three calculations for optimal angle might be measuring the wrong angle. Instead of calculating the angle in the plane of the two daughter vessels, it could be calculating angles in different planes. To test this, I made a graph of the deviation from the optimal angle in a junction vs. the orthogonal unit vector in the same junction. I calculated this by taking the cross products of the parent with both daughters, and comparing the difference between the two cross products. This would then indicate whether or not the daughter vessels and the parent were all in the same plane. However, I found no correlation, which means that the optimal angle calculations are not affected by the fact that the vessel network is three-dimensional.

Another issue may be that optimizing one of the parameters leads to others being far from their optimal values. A more accurate optimal angle calculation could involve optimizing the total energy cost with respect to surface area, volume, and resistance to flow simultaneously.

4 Summary and future work

4.1 Summary

This project calculated branching angles from mouse cardiovascular network measurements and compared them to different models for optimal branching angle which minimized surface area, volume, and resistance to flow. The measured branching levels were found to be quite constant for all branching levels, and had a median value of 72°. I found that the optimal angle models were not in good agreement with the measured branching angle. The optimized flow model generally had the most accurate measurements, with the optimized volume model being erratic and the optimized surface area model consistently giving higher angle values.

4.2 Implications

Measuring branching angles of vascular networks and their deviations from optimal angles has several implications. Optimal angles are often assumed based on minimizing energy costs associated with the maintenance and function of the vascular network, but here I found that measured angles can be very different from these expected values. It is important to understand why these differences arise, because this knowledge has consequences for many fields. For example, it has been found that tumors have significantly different vasculature from healthy tissue. This affects the effectiveness of cancer drugs because they tend to become concentrated in certain areas of the network. Understanding the structure of branching angles of these networks would help in understanding how drugs move through a tumor network, which can lead to the design of more efficient drug delivery systems. Additionally, high blood pressure has been known to influence branching angles. Branching angles in the retina are more acute in both the elderly and people with high blood pressure. Branching angle seems to decline and branching geometry steadily worsens with age, which increases the power cost required to pump blood through the retina [10]. The causes of this decline are so far unknown. Other diseases where branching angles are of interest include peripheral artery disease and formation of cerebral aneurysms [11]. Understanding how branching angles are determined in a normal network may help in developing better treatments for many health issues related to the cardiovascular system.

4.3 Future Work

In the future, I plan to extend this project by using more data, possibly of different organisms. I have so far developed tools for efficient data analysis and can now work on improving statistics. I thus hope to gain a better understanding of the principles that determine the branching angles of networks. I will also try to develop additional models to test based on the characteristics shown by the data. For example, the surface area model had very consistent values and low error, so modifications to that simple model may yield useful results. The flow model values were, however, closer to the measured value. The branching junction appears to be located closer to the start of the parent segment than calculated, suggesting that minimizing construction costs may not be important.

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