Blood Vessel Branching: Beyond the Standard Calculus Problem

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As one who is very thankful to have survived a heart attack in 1996, I have more than a passing interest in the vascular system. Perhaps this is due to the following statement by my cardiologist: "Your left anterior descending coronary artery is 99.9% blocked." While that might have been an exaggeration, the sight of my artery narrowing to a thread on the angiogram was certainly a cause for concern.

The *vascular system* is the collection of all arteries, veins, and capillaries that permit the flow of blood from the heart, around the body, and back to the heart again. A combination of fluid flow and diffusion brings every cell in a healthy body within reach of the nutrients and gases it needs. The combined length of all this plumbing is rather large: Indeed, in 1967 the mathematical biologist Robert Rosen [5] made the claim that the total length of the vascular system in large mammals is of the order of 50,000 miles!

The purpose of this article is to describe a significant application of mathematics to the understanding of the vascular system. Over a century ago, in 1878, Wilhelm Roux [6] described the relationships among the angles and radii of bifurcating blood vessels, showing how they arise from some simple principles of optimality. Our goals here are to rederive Roux's results for the benefit of a wider audience, to examine their implications, and to establish how relevant they may be to the human vascular system. To accomplish this, we first study the equations for the flow of fluid in a pipe and establish a fundamental result, which is standard fare (or once was) in most engineering-style calculus books. We then present a sequence of increasingly faithful models of blood-vessel branching. In these models, we judge optimality using a succession of so-called *cost functionals*.

Our treatment is based on some rather obscure material, referred to in passing by Thompson [9], and in somewhat more detail by Rosen [5], but expanded considerably here.

At the outset we acknowledge some simplifying assumptions.

The first concerns the nature of fluids. Newton modeled the simplest kind of fluids by imagining them to consist of thin layers that slide past one another, developing a resistance to the flow. An important factor of proportionality—the ratio of "drag" to the velocity gradient perpendicular to the direction of flow—is called *viscosity*. A fluid with the property that the viscosity is independent of the forces applied to it, is called a *Newtonian fluid*. Naturally enough, if the viscosity does depend on the applied force, then the fluid is called *non-Newtonian*.

In this paper we model blood as a Newtonian fluid. This proves to be a reasonable approximation except when blood cells are forced through the tiniest capillaries, which are barely as large as the blood cells themselves. In these capillaries, it is not reasonable to think of layers of fluid sliding past each other, so our models do not apply.

Furthermore, the pressure driving the whole system is far from constant; there are short time lags between the high pressure and the peak blood flow because of the

inertia of the blood. In addition, the blood vessels are flexible, not rigid (though of course, hardening of the arteries occurs with age). Cumulatively, this can modify the blood dynamics, as do the surface waves along the vessel walls, induced by the changes in pressure and flow generated by the heart. Such waves can be reflected at various points in the arterial tree: at branching junctions, or where the vessel diameter changes significantly. By contrast, we always assume time-independence and a constant shape for the blood vessels.

Having acknowledged these realities, we proceed to build our first model.

Viscous fluid flow

We begin by describing the flow of a fluid, such as blood, through a cylindrical pipe, such as a large blood vessel. We will derive equations for the velocity of the fluid (which varies with location in the pipe) and for the amount of fluid that passes through the pipe per unit time.

Our model is ultimately based on the *Navier-Stokes equations*. These equations arise from applying Newton's second law of motion to viscous fluids, which we imagine to consist of thin layers, each small element of which must obey conservation of momentum. In simplest form, the force on each element of fluid is the sum of a pressure-gradient term and a viscous term. For an incompressible Newtonian fluid, the viscous term, mathematically, is proportional to the Laplacian of the velocity field. This is important because it implies that momentum is diffused in the same way heat diffuses; indeed in the simplest example of unidirectional time-dependent flow, the Navier-Stokes equations reduce to the heat (or diffusion) equation.

Now consider the flow of a fluid in a uniform circular cylindrical pipe of radius a. The fluid is assumed to be incompressible and independent of time, and subject to a fluid pressure that decreases along the pipe in the positive direction. The flow is described by a velocity field $\mathbf{u}$, which is a vector field, giving the velocity of the fluid at each point inside the pipe. Under these circumstances the velocity field $\mathbf{u}$ is in the axial direction only, which means that, in cylindrical coordinates, $\mathbf{u} = \langle 0, 0, u(r) \rangle$, $0 \le r \le a$. In the presence of a uniform pressure gradient P_x along the pipe, the fluid velocity $u(r)$ satisfies the differential equation

$$\frac{1}{r} \frac{d}{dr} \left(r \frac{du}{dr} \right) = \frac{P_x}{\mu}, \tag{1}$$

where μ is the coefficient of viscosity. (You can find a derivation of this equation in any standard text on fluid dynamics [3].) Note that the left-hand side of equation (1) is just the radial part of the Laplacian in cylindrical coordinates. Integrating the equation twice, we find that

$$u = u(r) = \frac{P_x r^2}{4\mu} + B \ln r + C,$$

where B and C are constants to be determined. If $u(0)$ is to be well defined then $B \equiv 0$ of course, and because of friction, the velocity is zero at the inner surface of the pipe, so $u(a) = 0$, and this implies that $C = -P_x a^2 / 4\mu$. Therefore the velocity profile is a parabolic one, moving the direction opposite the pressure gradient:

$$u(r) = \frac{-P_x}{4\mu} (a^2 - r^2). \tag{2}$$

We can use (2) to compute the rate at which volume flows through the vessel. The technical term for volume flow rate is the *volume flux* per unit time through any cross section (as in FIGURE 1). It is given by the integral

$$V(a) = \int_0^a 2\pi r u(r)\, dr,$$

where V is expressed in units of volume/time. The *mass flux* is determined by multiplying this expression by the (constant) fluid density ρ.
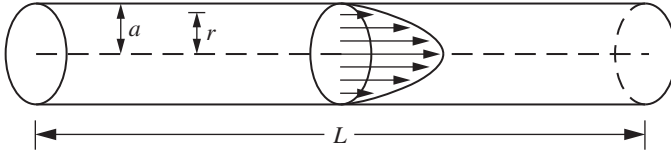
Figure 1   Fluid flow in a cylindrical pipe

Substituting the above expression for u,

$$V(a) = \frac{-\pi P_x}{2\mu} \int_0^a r\left(a^2 - r^2\right) dr = \frac{-\pi P_x a^4}{8\mu}. \tag{3}$$

This result is known as *Poiseuille's law*. Since P_x is the constant negative pressure gradient, we may write it in terms of the pressure difference, ΔP, over the length L of the pipe, that is, $P_x = -\Delta P/L$, so the volume flux (or equivalently, the how much blood flows per unit time) is

$$V(a) = \frac{\pi \Delta P a^4}{8\mu L} \propto a^4 L^{-1}.$$

The fourth power makes volume flux very sensitive to the radius of the pipe, which has significant implications for vascular disease in particular. Halving the radius of the tube results in a volume flux *one sixteenth* of the original, and even a reduction in radius of about 16% will *halve* the volume flow rate!

The reciprocal of V has units of time/volume and can be taken as a measure of the frictional resistance. Given a fixed pressure drop, the frictional resistance is directly proportional to the length of the pipe. The dependence of the resistance on a^{-4} is perhaps harder to visualize, but a standard analogy may prove helpful. Poiseuille's law is effectively a hydraulic metaphor for *Ohm's law* in electrical circuits. This law states that the voltage E in the circuit is equal to the product of the current I and the resistance R: that is, $E = IR$. In fluid flow, the pressure drop ΔP is the analog of the voltage, and the volume flux V is equivalent to the current. Thus the hydraulic resistance can be expressed as

$$\frac{\Delta P}{V} = \frac{8\mu L}{\pi a^4} \propto a^{-4} L. \tag{4}$$

The idea, then, is that the resistance to the flow of a fluid through a pipe, or a system of pipes, measures the amount of work required to pump the fluid through the system. The lower the resistance, the more efficient the system will be. Our first method to find the best angle of branching (and hence the location) of a smaller vessel is to minimize resistance along the branching path. Thus, our first cost functional is based on the total hydraulic resistance of the system to the flow.

The standard calculus model

We consider the case of a smaller vessel branching off from a larger one. For the time being, we consider the larger vessel to be straight. FIGURE 2 shows the basic configuration: The main blood vessel of radius r_1 has a narrower vessel of radius r_2 ($< r_1$) branching at an angle θ to the axis of the former.

We consider the points A, B, and C to be fixed, with BC perpendicular to AC and with distances denoted by $c = |AC|$ and $b = |CB|$. The choice of θ determines the location of the point O along with the distances $L_1 = |AO| = c - b \cot \theta$ and $L_2 = |OB| = b \csc \theta$.
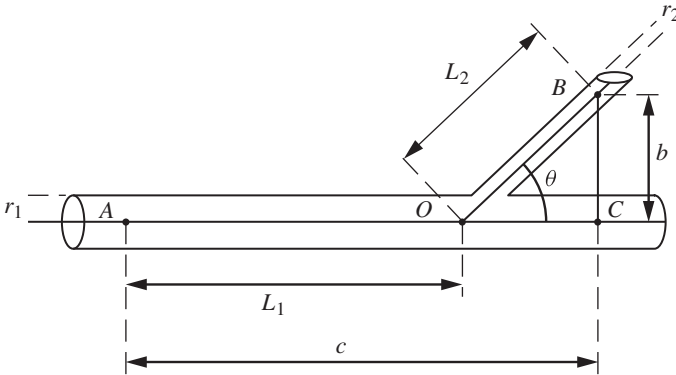
Figure 2   Blood vessel branching from an artery

The first cost functional we examine is one found in many elementary calculus books [**8**]. We use (4) to calculate the minimum total hydraulic resistance along the path AOB.

Since we have established that the hydraulic resistance, according to Poiseuille's law, is proportional to length and inversely proportional to the fourth power of the radius for each component of the system, we may express the total resistance $\mathcal{L}_1$ as

$$\mathcal{L}_1 = k \left[\frac{L_1}{r_1^4} + \frac{L_2}{r_2^4} \right]$$
$$= k \left[\frac{c - b \cot \theta}{r_1^4} + \frac{b \csc \theta}{r_2^4} \right].$$

The constant k will be significant later. To minimize resistance as a function of θ, set

$$\frac{d\mathcal{L}_1}{d\theta} = \frac{kb}{r_2^4} \csc^2 \theta \left[\left(\frac{r_2}{r_1} \right)^4 - \cos \theta \right] = 0.$$

Then the only critical value is

$$\theta_m = \cos^{-1} \left(\frac{r_2}{r_1} \right)^4,$$

and a quick verification shows that $\mathcal{L}_1$ assumes an absolute minimum on the interval $(0, \pi/2)$ at θ_m. We substitute some relative values for the radii to test our model: If $r_2 = 0.5r_1$, then $\theta \approx 86°$; and if $r_2 = 0.8r_1$, then $\theta \approx 66°$.

The first angle is almost a right angle. Is our model sound enough to justify such an extreme prediction? One concern is that the cost functional relates only to the path *AOB*; the implied assumption is that the effect of θ on the path *AOC* can be neglected. We will address that issue soon; but first, we consider variations of the cost functional.

Varying the cost functional

In addition to minimizing the total resistance to flow, Roux and Rosen consider minimizing the cost of *maintaining* the structure. It seems reasonable to suppose that the maintenance cost should be proportional to the *volume* of the system. The volume along the path *AOB* is given by

$$\mathcal{L}_2 = K \left(L_1 r_1^2 + L_2 r_2^2 \right)$$

where K is another constant. This is minimized when

$$\theta = \cos^{-1} \left(\frac{r_1}{r_2} \right)^2,$$

which is *not* the same as the value θ_m that minimizes the previous functional $\mathcal{L}_1$.

We can also combine these functionals. Our next cost functional includes a term proportional to resistance and a term proportional to volume:

$$\begin{aligned}
\mathcal{L} &= \mathcal{L}_1 + \mathcal{L}_2 \\
&= k \left(\frac{L_1}{r_1^4} + \frac{L_2}{r_2^4} \right) + K \left(L_1 r_1^2 + L_2 r_2^2 \right) \\
&= L_1 \left(\frac{k}{r_1^4} + K r_1^2 \right) + L_2 \left(\frac{k}{r_2^4} + K r_2^2 \right) \\
&\equiv L_1 A_1 + L_2 A_2,
\end{aligned} \tag{5}$$

where k and K are constants of proportionality. Proceeding in the same manner as before, we find that

$$\frac{d\mathcal{L}}{d\theta} = A_2 b \csc^2 \theta \left[\frac{A_1}{A_2} - \cos \theta \right]$$

which is zero when

$$\theta = \cos^{-1} \left[\frac{A_1}{A_2} \right] = \cos^{-1} \left[\left(\frac{r_2}{r_1} \right)^4 \left(\frac{k + K r_1^6}{k + K r_2^6} \right) \right].$$

This result depends on the relative values of k and K. For any positive values of the constants, it agrees with the original minimizer θ_m only in the two limiting situations: (i) $r_2 \to r_1$ and (ii) $r_1 \to 0$.

Observations

How can we choose a cost functional? More generally, how can we choose a good model? One test is how well its predictions match observations.

Roux gave a set of empirical observations about about vascular branching (cited separately by Thompson [9] and Rosen [5]). In paraphrased form, they are:

(1) *If an artery bifurcates into two equal branches, they deviate at equal angles from the main stem.*

(2) *If the branches do not have the same radius, then the larger branch (i.e., the continuation of the main artery) makes a smaller angle with the original direction than does the smaller branch.*

(3) *Branches that are so narrow that they do not significantly diminish the flow in the main stem branch off at large angles (typically between $70°$ and $90°$).*

Considering units

One way to understand the combined functional (5) is as a measure of the *power dissipated* by the flow. Power is defined as work done per unit time, in this case by the flow, and work has the dimensions of force times distance. To make this clear, we need to understand the units of the constants k and K.

In *dimensional analysis*, use is often made of the units of mass, length, and time (denoted by $[M]$, $[L]$, and $[T]$, respectively). These define the dimensions of particular physical quantities, and are called *fundamental units*. They are analogous to basis vectors for a vector space, such as the unit vectors $\{\mathbf{i}, \mathbf{j}, \mathbf{k}\}$ for the space $\mathcal{R}^3$. Thus, the dimension of force being mass $\times$ length$/$time^2 is denoted $[M][L][T]^{-2}$. (Other choices of fundamental units are possible; for example, mass, length, and force could have been used just as well. The author has written elsewhere about this and the valuable Buckingham Pi Theorem [1].)

Considering our combined functional (5), we see that the first parenthetical expression has units $[L]^{-3}$. But from the definition above, power has units

$$\left([M][L][T]^{-2}\right)[L][T]^{-1} = [M][L]^2[T]^{-3}.$$

Therefore, for the term itself to be in units of power, the constant k must have units of

$$[M][L]^5[T]^{-3}.$$

By the same token, the second parenthetical expression has units $[L]^{+3}$, so the constant K must have units

$$[M][L]^{-1}[T]^{-3}.$$

These considerations would be the starting point for any serious inquiry into what determines the values of the constants k and K.

Optimizing a single vessel

Next, we consider the contribution to $\mathcal{L}$ from a single unbranched vessel of radius r and length L:

$$\mathcal{L} = kLr^{-4} + KLr^2. \tag{6}$$

Biologically, this means that the vessel's contribution to the total cost is determined by two competing factors: the power required to maintain the volume of blood needed to fill the vessel, and the power required to pump blood through that same vessel. The first is proportional to the inverse fourth power of the radius, and for optimality this requires that the radius be as large as possible; the second is proportional to the square of the radius, and so the radius should be as small as possible [11].

If we expect that the branching configuration minimizes the functional, then we should expect that the radius of each single vessel should minimize it as well. From equation (6),

$$\frac{d\mathcal{L}}{dr} = (-4kr^{-5} + 2Kr)L$$

which is zero when $k = Kr^6/2$. Since $\mathcal{L}''(r) > 0$, this is a minimum. For the optimal value of r we have

$$\mathcal{L} = \beta L r^2, \tag{7}$$

where $\beta = 3K/2$ is another constant.

Branching versus bifurcation

Thus far the cost functionals used have referred to a smaller vessel branching off a larger one, not bifurcation. This will now be amended.

From this point forward we consider all three branches in FIGURE 3. We consider the points A, B, and C fixed. The choice of the point O (in the same plane) determines the branching angles ϕ and θ.

The radii and lengths of the vessels AO, OB, and OC are denoted respectively by r_0, L_0, r_1, L_1, and r_2, L_2.
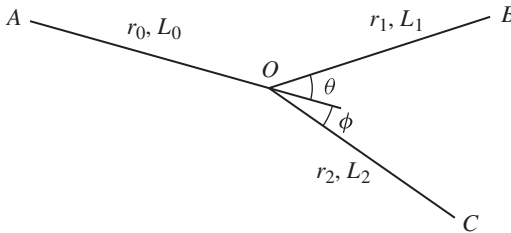

Figure 3   Bifurcation

Optimizing the configuration

The important relation (7) will be used in connection with the three diagrams in FIGURE 4. In each diagram we consider a small change in the location of the bifurcation point O to a new point O'. In each case, the distance from O to O' is δ, which is small compared with the distances AO, OB, and OC.

Now from the theorem from the calculus of variations known as the Principle of Minimum Work [**7**], we know that a small *first-order* change in the minimal configuration results in a *second-order* change in the cost functional, so to the first order, the value of the functional is unchanged. In each part of FIGURE 4, this means that the change in $\mathcal{L}$, summed over the three vessels in the configuration, must be zero (to first order in δ). We will see what this implies in each diagram.

Using the law of cosines for FIGURE 4(a), we have

$$(O'B)^2 = L_1^2 + \delta^2 - 2\delta L_1 \cos\theta \approx L_1^2 \left(1 - \frac{2\delta}{L_1}\cos\theta\right).$$
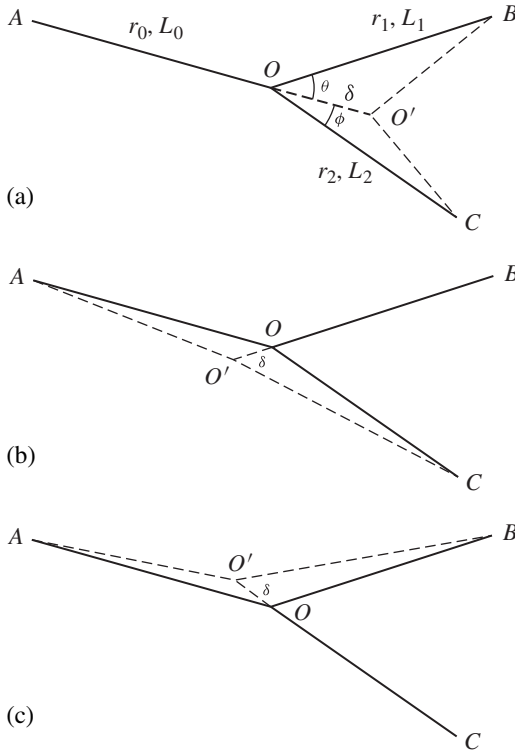
Figure 4   First-order changes to the configuration

Therefore

$$O'B \approx L_1 \left(1 - \frac{\delta}{L_1} \cos \theta \right) = L_1 - \delta \cos \theta,$$

so the path OB has been shortened by approximately $\delta \cos \theta$. Similarly, the path OC is shortened by $\delta \cos \phi$, and of course, the path AO has been increased by the amount δ. Now we apply the result $\mathcal{L} = \beta L r^2$ for each branch. The total increment in cost is zero, and this is equal to the sum of these cost increments. After canceling the common factors β and δ, we find that

$$r_0^2 = r_1^2 \cos \theta + r_2^2 \cos \phi.$$

In FIGURE 4(b), the length of OB is increased by δ. It is readily shown using the law of cosines that AO is reduced by approximately $\delta \cos \theta$, OC is increased by approximately $\delta \cos(\theta + \phi)$, and once again, the cost increments sum to zero, so that

$$r_1^2 = r_0^2 \cos \theta - r_2^2 \cos(\theta + \phi). \tag{8}$$

The result corresponding to FIGURE 4(c) is most easily accomplished by interchanging r_1 and r_2 and θ and ϕ in the result (8):

$$r_2^2 = r_0^2 \cos \phi - r_1^2 \cos(\theta + \phi).$$

From these three equations we can solve for the three angles to obtain

$$\cos \theta = \frac{r_0^4 + r_1^4 - r_2^4}{2r_0^2 r_1^2}; \quad \cos \phi = \frac{r_0^4 + r_2^4 - r_1^4}{2r_0^2 r_2^2}; \quad \cos(\theta + \phi) = \frac{r_0^4 - r_1^4 - r_2^4}{2r_1^2 r_2^2}. \tag{9}$$

These results can be taken further. For optimal flow in a single vessel, the flow rate f (for a given value of L) turns out to be proportional to the cube of the radius. When vessels branch the flow must split into two parts, which means that $f_0 = f_1 + f_2$ and

$$r_0^3 = r_1^3 + r_2^3. \tag{10}$$

(This equation might appear to contradict Poiseuille's law (3), which might suggest that $r_0^4 = r_1^4 + r_2^4$. But applying Poiseuille's law in this case would require identical pressure gradients P_x in all three branches, which is not the case in general.)

Eliminating the superfluous radius in each case we obtain

$$\cos\theta = \frac{r_0^4 + r_1^4 - \left(r_0^3 - r_1^3\right)^{4/3}}{2r_0^2 r_1^2}; \quad \cos\phi = \frac{r_0^4 + r_2^4 - \left(r_0^3 - r_2^3\right)^{4/3}}{2r_0^2 r_2^2}, \tag{11}$$

and a similar equation for $\cos(\theta + \phi)$.

To examine some consequences of this newest cost functional, let $r_1 = r_2$, corresponding to equal branchings from the primary vessel. According to (11), this implies that $\theta = \phi$: *Vessels with equal radii branch off at equal angles to the main stem.* This is exactly the first empirical law of Roux.

Next let $r_2 = \alpha r_1$ with $0 < \alpha < 1$. The formulas in (9) imply that

$$\cos\theta = \frac{r_0^4 + r_1^4(1 - \alpha^4)}{2r_0^2 r_1^2}; \quad \cos\phi = \frac{r_0^4 - r_1^4(1 - \alpha^4)}{2\alpha^2 r_0^2 r_1^2}.$$

Is it possible to determine from these equations which of the two angles θ or ϕ is the larger? For angles in $(0, \pi/2)$, the equation $\cos(\theta) > \cos(\phi)$ is equivalent to

$$\left(1 + \alpha^2\right)^2 r_1^4 > r_0^4.$$

But $r_0^3 = r_1^3 + r_2^3$ leads to $r_0^4 = (1 + \alpha^3)^{4/3} r_1^4$. This and the easily verified inequality

$$\left(1 + \alpha^2\right)^2 > \left(1 + \alpha^3\right)^{4/3}$$

show that for $\theta, \phi \in (0, \pi/2)$, $\theta < \phi$. Thus *the larger vessel branches off at a smaller angle than the narrower vessel.* This is the second empirical law of Roux.

Now suppose that $r_2 \ll r_1$ (so that $\alpha \ll 1$). This also implies that $r_1 \lesssim r_0$. Then using the results

$$\cos\phi = \frac{r_0^4 - r_1^4(1 - \alpha^4)}{2\alpha^2 r_0^2 r_1^2} \quad \text{and} \quad r_0^4 = \left(1 + \alpha^3\right)^{4/3} r_1^4,$$

we may write

$$\cos\phi = \frac{\left(1 + \alpha^3\right)^{4/3} - 1 + \alpha^4}{2\alpha^2 \left(1 + \alpha^3\right)^{2/3}}.$$

For a branching angle $\phi = 70°$, this gives $\alpha \approx 0.34$; and if $\phi = 80°$, then $\alpha \approx 0.17$, clearly indicating that *the branching angle steepens as the vessel radius narrows.* Retaining only the leading terms in α we obtain

$$\alpha \to 0 \text{ as } \alpha \to 0,$$

so $\phi \to \pi/2$ as $\alpha \to 0$, that is, the branching angle approaches 90° as the vessel radius tends to zero. These statements are the third empirical law of Roux. Thus with the cost

functional (5) all three empirical laws have been verified, leading one to conclude that the model may well be fairly realistic for many animal vasculatures, particularly for the smaller vessels.

Calculating total length

We now apply these ideas to examine the statement of Rosen, quoted at the beginning of the article, regarding the total length of the (large) mammalian vascular system. Suppose for simplicity that the primary branch (aorta) bifurcates into two vessels with equal radii: if $r_1 = r_2$ the statement $r_0^3 = r_1^3 + r_2^3$ is equivalent to $r_1 = 2^{-1/3} r_0 \approx 0.794 r_0$. Suppose further that every vessel in a generic vascular system arises from an equal bifurcation of the immediately preceding larger vessel. In mammals, a typical capillary radius is about 5 microns, and it is of interest to calculate how many bifurcations from a given primary vessel are required to reach this radius. Therefore the number n of bifurcations from an aorta of radius r_0 that will result in such a capillary must satisfy the equation

$$(0.794)^n r_0 = 5 \times 10^{-6} \text{ m}.$$

For an animal such as a dog, $r_0 \approx 0.5$ cm $= 5 \times 10^{-3}$ m, so

$$(0.794)^n = 10^{-3}, \text{ and } n = \frac{-3}{\log_{10}(0.794)} \approx 30. \tag{12}$$

It follows from this that the number of vessels in the system resulting from the final bifurcation is $2^{30} \approx 1.07 \times 10^9$, which is close to the estimate of 1.2×10^9 given by Rashevsky [4] and Zamir [11]. As pointed out by Rosen [5], the agreement becomes even closer when one realizes that observationally, it is probably difficult to distinguish vessels in the final bifurcation from those arising from several preceding ones (the 29th or even 28th bifurcation).

Now we try to estimate of the total *length* of the vascular system. In the absence of much physiological information (but see below), and in the spirit of a back-of-the-envelope calculation, we suppose that the primary vessel, the aorta, has length L_0, and that each bifurcation k produces twice as many vessels, each of length $L_k = \eta L_{k-1}$, where it is assumed that $0 < \eta < 1$. Then the total length of the system after n bifurcations is

$$\begin{aligned} L_n &= L_0 + 2\eta L_0 + 2^2 \eta L_1 + 2^3 \eta L_2 + \cdots + 2^n \eta L_{n-1} \\ &= L_0 \left(1 + 2\eta + (2\eta)^2 + (2\eta)^3 + \cdots + (2\eta)^n\right) \\ &= L_0 \frac{\left[(2\eta)^{n+1} - 1\right]}{2\eta - 1}, \quad \eta \neq \frac{1}{2}. \end{aligned} \tag{13}$$

For discussion purposes, based on the table below, we suppose that $L_0 = 40$ cm, and take various values for $\eta > 1/2$. For $\eta = 2/3$,

$$L_{30} = 0.4 \frac{\left[(4/3)^{31} - 1\right]}{1/3} \text{ m} \approx 9 \times 10^3 \text{ m} \approx 10 \text{ km};$$

whereas if $\eta = 7/8$, then

$$L_{30} = 0.4 \frac{\left[(7/4^{31} - 1\right]}{3/4} \text{ m} \approx 2 \times 10^7 \text{ m} = 2 \times 10^4 \text{ km}.$$

If $\eta > 1$ (a given bifurcation is longer than the immediately preceding one), the length explosion is even more rapid: $\eta = 6/5$ results in $L_{30} \approx 6 \times 10^7$ km! If Rosen's estimate of 50,000 km for the total length of the vascular system in large mammals is accurate, then we would on average expect η to be slightly less than 15/16 on the basis of this approach. It would appear that since real vascular systems are unlikely to have this degree of predictability, our version of Rosen's estimate is at best an educated guess!

The table below, adapted from that in Zamir [11], is based on the so-called "classical model," wherein the arterial tree was thought of as being highly ordered on a global scale. It remains essentially unmodified today apart from some numerical changes, but the main difficulty, according to Zamir, is not its numerical accuracy, but its central premise, namely that all these vessels have a well defined beginning, end, length, and diameter. Such conceptual considerations, while interesting, would take us too far afield in this paper. Nevertheless, the approximate length of the arterial tree (of the dog) is obtained from level nine of the classical model, yielding about 10^8 cm or 1000 km, again, considerably lower than Rosen's estimate.

TABLE 1: Hierarchical structure of the arterial tree

Level	Vessel Description	No. of Vessels	Length (cm)	Diameter (mm)
1	aorta	1	40	10
2	large arteries	40	20	3
3	main branches	600	10	1
4	secondary branches	1.8×10^3	4	0.6
5	tertiary branches	7.6×10^4	1.4	0.14
6	terminal arteries	10^6	0.1	0.05
7	terminal branches	1.3×10^7	0.15	0.03
8	arterioles	4×10^7	0.2	0.02
9	capillaries	1.2×10^9	0.1	0.008

Finally, we summarize the appropriateness of the fundamental result (10), which is really the basis for both the estimate for the number of bifurcations in the vascular system of large mammals, and the derivation of Roux's empirical laws. According to Zamir, in his discussion of the branching structure of arterial trees, "A consideral amount of data from the cardiovascular systems of man and animals has been shown to support these results, though with a considerable scatter in some cases." [11] Such a cube law is also consistent with there being a constant shear force throughout the arterial network, a conclusion reached by several authors. (Zamir's papers give details.[10, 11])

Regarding the number of bifurcations in the arterial tree, Zamir also writes "If the global structure of the tree were purely ad hoc, the number of branching sites along certain paths could, simply by chance, be very large, perhaps of the order of thousands. Yet it is usually found to be surprisingly small, of the order of 30 or so." Furthermore, the average increase in cross-sectional area at an arterial bifurcation, that is, the ratio

$$A = \frac{r_1^2 + r_2^2}{r_0^2},$$

is found to be about 1.26 for symmetrical bifurcations, and somewhat lower for non-symmetrical ones. As is easily shown from equation (10), used in conjunction with the additional statement (used above) that $r_2 = \alpha r_1$, $0 < \alpha < 1$,

$$A = \frac{1 + \alpha^2}{(1 + \alpha^3)^{2/3}}.$$

For $\alpha = 1$, $A = 2^{1/3} \approx 1.26$; for $\alpha = 0.7$, $A \approx 1.22$, and for $\alpha = 0.5$, $A \approx 1.16$. Indeed, the function $A(\alpha)$ is readily seen to possess a single maximum at $(1, 2^{1/3})$ on any interval $[0, b]$, where $b > 1$. Recall that the reciprocal of this maximum value, $2^{-1/3}$, arises naturally in the corresponding bifurcation problem discussed above. It is also noteworthy that the accepted value for the increase in cross-section area from the aorta to the capillary beds is about 1000 [2]. Since we have identified the likely bifurcation number in this system as $n = 30$, the definition of A requires that

$$A^{30} = 1000, \quad \text{so that} \quad A = 10^{0.1} \approx 1.26.$$

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Summary   Calculating the optimal angle for blood vessel branching is a standard calculus problem. However, optimality in that setting is judged by a *cost functional* that turns out not to give realistic results. We study a sequence of improvements to the cost functional, finally arriving at one that passes an important modeling test: From this last functional, we derive three empirical laws of blood vessel branching, originally proposed by German zoologist Wilhelm Roux.

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