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Fluid Physics in Circulatory Systems – Problems, Analogies and Methods

Writing a useful research-oriented book on biofluids modeling is extremely challenging. Some expertise in mathematics, at the differential equation level or higher, is often presumed. Software proficiency is presumed. At the same time, a background in fluid mechanics is taken for granted, as is a year's preparation in biology. Yet, if our potential audience strictly interpreted and followed these requirements, there would be limited numbers of qualified readers – the simple but powerful ideas we propose would remain unknown and unlikely to benefit practitioners. How then do we proceed?

Presentation philosophy. To appeal to the broadest audience, from undergraduates, to clinicians, to medical researchers, and to engineers and scientists interested in learning about an expanding and evolving discipline – and to deliver our work assuming a basic academic preparation, between the covers of a four-hundred page book, within the constraints of a year's study time, at most – the authors have adopted a rapidly paced tutorial style that is rigorous yet understandable, focused yet encompassing, and academically oriented yet interesting. Portions of our work have been tested over time with diverse audiences, e.g., from Texas's Aldine Independent School Districts' "Education for the Energy Industry" (EEI) program in fluid mechanics, to China's Beijing No. 55 International School's biology students, and to the University of Houston's (Open Admissions) process engineering group department in pipe flow analysis. Finally, seminars at two recent Houston conferences and several engineering universities in China have proven very fruitful.

For example, we will start arterial flow discussions by citing the well known Hagen-Poiseuille equation (together with its assumptions, limitations and strengths) without the usual formalism drawing on continuum mechanics and tensor analysis. Modern science cannot evolve without strong mathematical foundations and that means partial differential equations – a broad subject area that easily consumes years of study. But for practical purposes, it is not possible to present even a watered-down course syllabus, e.g., equation types (elliptic, parabolic, hyperbolic), solution methods (separation of variables, Laplace transforms, Fourier series and integrals), numerical methods (implicit, explicit, relaxation, finite element methods, and so on) and similarly broad topics. And in biology, where major discoveries are made on a daily basis in microscopic exchange processes, advanced imaging methods, tissue engineering and blood rheology, it is difficult to review any particular paper let alone entire research disciplines.

But none of the above will limit the purpose of this volume – and that is to develop and understandably communicate new methods and tools that clinicians and medical researchers need in order to provide the information they want. In short, we will present specific math methods only when they are required in specific biological applications. For example, with the Hagen-Poiseuille law as a starting discussion point for *conduit* flows (assuming Newtonian flow in large diameter vessels), we develop bifurcation models that describe branching effects – first for double and multiple branched systems, then extensions to non-Newtonian fluids, and finally, generalizations for non-circular flow conduits with geometrically complicated cross-sectional clogs.

Or consider the use of Darcy flow modeling in *porous flow* tissue analysis. While published models are limited in breadth, we will explain why pressure transients that are measurable during syringe injections are affected by compressibility, permeability, anisotropy and porosity – and importantly give methods demonstrating how these parameters can be predicted during drug delivery. We also expand upon conventional Darcy flow analyses with comprehensive models showing how blood flows from arteries, through complex organs, and then to veins; how volume flow rates are calculated together with pressure drops; and finally, how damage or decreased functionality in any subsystem can affect the entire system. Finally, an interesting example uses an oilfield Darcy flow simulator to describe the effect of arterial flow through tissues in our "Flatman" prototype for whole-body pressure modeling.

1.1 Basic Biological Notions and Fluid-Dynamical Ideas.

In this chapter, we introduce basic fluid flow modeling concepts as they apply to principal parts of the circulatory system. As mentioned earlier, our aim is not an exhaustive (or even limited) literature review. By "circulatory system," we refer *macroscopically* to arteries, capillaries and veins" and surrounding tissues, and by necessity, do not focus on the very complicated *microscopic* biological, cellular and chemical processes that are ongoing throughout the body. Our literature search and cited figures are limited in this respect – our reviews focus only on what medical researchers and clinicians need and how we can provide better information using available knowledge and accessible data.

Similarly, our fluid-dynamics discussions and modeling methods support only those biological problems that we have introduced. However several math methods are new to the literature, for example, one developed to support general clogged flow analyses in straight and curved blood vessels in Chapters 5 and 6, and the second to support interpretation algorithms behind the "intelligent syringes" of Chapter 7. In these areas, not covered in the usual numerical analysis and engineering publications, we will present details. And so, our coverage is complete in the sense that standard topics, where external references are available, are not substantially reviewed here, while new approaches are explained to a high but understandable level for specialists.

***Conduit flow* examples.** Again, in this book we will focus on the "circulatory system," which refers *macroscopically* to arteries, capillaries and veins" and surrounding tissues, and out of necessity, do not consider the very complicated *microscopic* biological, cellular and chemical processes ongoing throughout the body. Within this framework, studies can be separated into two categories, "distinct conduit flows" and then "continuum descriptions." The former mainly refers to arteries and veins functioning independently of the tissue environment – we are mainly concerned with the effects of fluid rheology and geometric flow cross-section on pressure drop and volume flow rate, and note that the corresponding math models are largely algebraic in nature. By contrast, the latter refers to the surrounding tissue, that is, how fluids flow through permeable and porous media like sponges, sands and soils, how heterogeneities and anisotropy appear in continuum models, and how these (together with the former conduit models) affect heart pumping efficiency (that is, volume flow rate and pressure drop). These continuum models require the solution of partial differential equations.

Flows in arteries and veins are very complicated and extensively researched in the medical literature. For our purposes, they serve only as conduits whose flows require mathematical description that address blood heterogeneity and vessel geometry. Basically, blood flow emerges from the heart into arteries and ultimately returns through veins. An Internet image search leads to numerous excellent examples, as shown in Figures 1-1a and 1-1b, where typically "red" represents arteries and "blue" denotes veins.

Figure 1-1a. Arteries and veins. Credit: rxlist.com.

Figure 1-1b. Arteries and veins. Credit: focusedcollection.com.

A closer look at Figures 1-1a and 1-1b shows that single blood vessels will bifurcate, or branch, into two or more vessels, with the process repeating itself, as highlighted in Figures 1-2a, 1-2b and 1-2c. What geometric and rheological properties connect inlet and outlet flows? How are these calculated? These questions seem obvious, but the literature offers conflicting explanations and solutions at times.

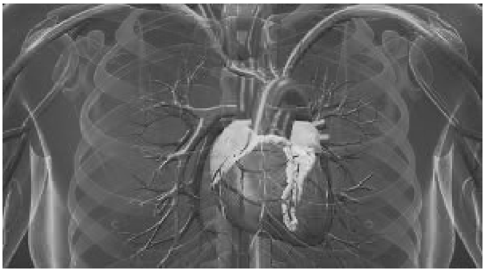


Figure 1-2a. Bifurcation example. Credit: indianaexpress.com.

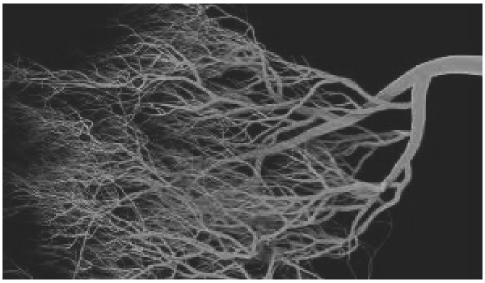


Figure 1-2b. Bifurcation example. Credit: medicalnewstoday.com.

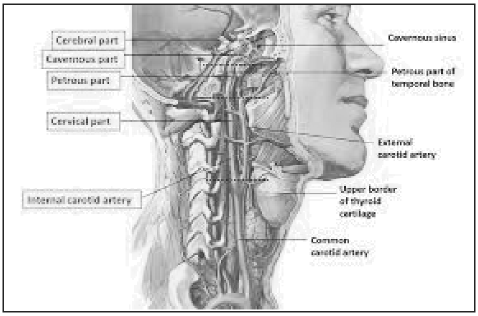


Figure 1-2c. Bifurcation example. Credit: anatomyqa.com.

For example, Chegg.com, a well known tutorial site, assumes conservation of total energy at flow junctions for simplicity, an idealistic modeling assumption that is unrealistic – fluid flow is inherently lossy. On the other hand, software used to design piping networks in process plants makes extensive use of "head loss" coefficients, e.g., empirical loss factors inferred from operations, and lab experiments for pipe roughness, inlet changes, fittings effects, pipe turns, contractions and expansions. And then, there are finite element methods, e.g., as shown in Figure 1-3, which suggest high degrees of accuracy through impressive color displays – graphics which de-emphasize grid effects related to shape and size on solution integrity. We instead present physically and mathematically rigorous methods useful in parametric analysis which are rapid, simple to use and which require minimal computational resources.

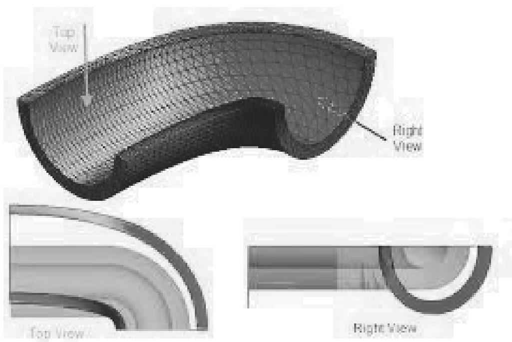


Figure 1-3. Finite element fluid flow analysis. Credit: pveng.com.

Basic *continuous flow* concepts. Having introduced *conduit* flows and their extensions, we now turn to elementary notions in continuous fluid flow modeling. Figures 1-4a and 1-4b illustrate two of the earliest flows that have yielded to analytical solution. The top diagram describes classical Couette flow and shows two parallel plates, with the upper surface moving relative to a lower stationary surface at a constant speed U_H. The plate separation is H. A velocity profile exists which is linear, the result of fluid particles adhering to solid surfaces, a property known as the "no-slip condition." The straight line velocity profile shown satisfies $U(y) = (y/H)\ U_H$, which reduces to $U = 0$ when $y = 0$ and $U = U_H$ when $y = H$. The slope $dU(y)/dy$ is known as the "shear rate," a purely geometric or kinematic property which does not reflect the force needed to propel the upper plate to the right.

Since the sliding motion of the top plate (or any layer) shears the fluid layer beneath it, the viscous stress (or "pulling force" divided by the surface area) associated with it is known as the "shear stress" denoted by τ. Physical intuition suggests that greater forces are required for more viscous fluids. Newton was first to suggest how this might follow the simple multiplicative relation $\tau = \mu$ dU/(y)/dy where μ is the constant "viscosity" of the fluid. In other words, "stress is viscosity times shear rate" while the equation itself represents a "constitutive" or "stress-strain" relation. Strain, in fluid-dynamics, describes relative deformation in shape and size of elastic, plastic or fluid materials under applied force.

Figure 1-4b illustrates flow in a circular tube, that is, the situation in Figure 1-4a when the upper and lower plates are rolled to form a circular cylinder. The velocity profile U(r) now depends on the radial coordinate r as opposed to the vertical coordinate y. As before, the shear rate dU(r)/dr is purely geometric or kinematic although for tubular flows it is variable. Here, the shear stress analogously defined as $\tau = \mu$ dU/(r)/dr. In both examples, viscous stresses are taken in "viscosity times shear rate" form, an assumption that greatly simplifies the governing momentum equations – fluids such as water and air, which satisfy this elementary model, are known as Newtonian fluids. For circular tubes, symmetry conditions at the centerline r = 0 are used to solve the governing viscous Navier-Stokes equations for Newtonian flow. But how are general ducts as shown in Figure 1-4c modeled? Where is the centerline? And if we arbitrarily defined a center, what flow properties actually apply there? This problem is rigorously solved in Chapter 5.

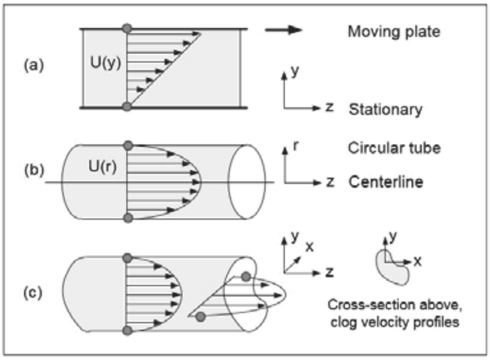


Figure 1-4a,b,c. Basic Couette (top) and Poiseuille (middle) flows (non-porous flow examples highlighting stress and strain concepts).

The Navier-Stokes equations, or the Newtonian flow equations studied in fluid mechanics incorporating the prior stress-strain relations, are structurally complicated, e.g., Figure 8-14 for two-dimensional Cartesian flows (steady) and Figure 6-17c for radial cylindrical flows (transient and steady) and difficult to solve. Their mathematical forms should be compared to Laplaces's equation $\partial^2 T/\partial x^2 + \partial^2 T/\partial y^2 + \partial^2 T/\partial z^2 = 0$ or the diffusion (heat) equation $\partial^2 T/\partial x^2 + \partial^2 T/\partial y^2 + \partial^2 T/\partial z^2 = \alpha\ \partial T/\partial t$ studied in partial differential equations which are already challenging. Despite their apparent generality, the equations shown are applicable only to narrow subsets of fluid-dynamical problems. For instance, they do not allow compressibilities, variable densities or body forces. And, as written, Figure 8-14 is useful only in problems whose boundaries are amenable to rectangular coordinate description; similarly, Figure 6-17c applies only when circular cylindrical coordinates are useful.

Perhaps the greatest limiting factor is fluid rheology. In the above discussion on Couette and Poiseuille flow, the stress was taken in the multiplicative form $\tau = \mu\ dU(y)/dy$ or $\mu\ dU(r)/dr$ where μ represents a constant viscosity and the first derivative term denotes shear rate. An increase in either will increase stress. This applies only to Newtonian fluids like air and water, and fortunately, blood in the larger diameter aorta. For industrial and food processing applications – and smaller sized blood vessels – more complicated constitutive "stress-strain" equations apply. One popular alternative is the Power Law model, in the simplest case described by $\tau = k\ (dU/dy)^n$ where n and k are the so-called Power Law coefficients. This model reduces to Newtonian form if $k = \mu$ and $n = 1$. Other laws of greater complexity are possible. The reader might consider the dynamics in pushing a box along a rough floor. The box does not respond to the first push – only when the force exerted exceeds a certain threshold does the box begin to move. This phenomenon is described in mechanics books and is associated with static and dynamic friction effects. This threshold effect also appears in fluid flow problems, in which case, the fluid does not initiate movement until a given local "yield stress" τ_{yield} is exceeded. A Newtonian flow model combined with yield stress effects is known as a Bingham Plastic, whereas a Power Law model with yield stress is classified as a Herschel-Bulkley model. These three *rheological* models result in generalized Navier-Stokes formulations far more difficult to solve than the equations cited above. In fact, the governing equations become nonlinear instead of linear, and so, are extremely challenging to solve.

Bear in mind that we have only described our formulations in terms of simple flow concepts. In three-dimensional problems, our stress-strain descriptions require more formal tensor-based mathematics. This is usually developed in continuum mechanics books, but fortunately, most conduit flows in blood vessel flow analyses are one-dimensional or pseudo-one-dimensional in nature. Flows in highly curved arteries and veins, for example, can be modeled using multiple straight tubes with local corrections for centrifugal effects (as will be done in Chapter 6).

The circular conduit in Figure 1-4b deserves special comment. When the cross-section is circular and its walls are rigid and smooth, and when the conduit is long, an exact analytical steady pipe flow solution to the cylindrical Navier-Stokes equations in Figure 6-17c is available and is known as the Hagen-Poiseuille equation. This applies strictly to Newtonian flows, which in the biofluids context, refers to flows in the larger main aorta. Flows in small blood vessels and bifurcations generally require non-Newtonian rheological descriptions – specialized related subjects are considered in Chapters 4-6.

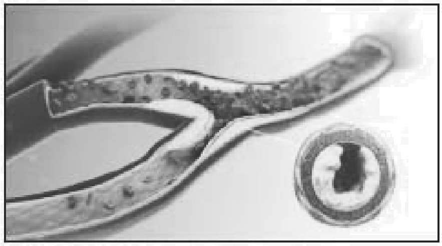
As suggested earlier, it is not our intention nor is it possible to present a comprehensive treatment of fluid mechanics. The field is extremely broad, and already, specialized biology problems have been successfully described using very well developed models. In what follows, we will cite key terminology (and likely applications) to familiarize and guide readers seeking additional information. Our own presentations will later focus on difficult problems which have so far been successfully addressed in our own research.

Eulerian versus Lagrangian descriptions. Beginning fluid mechanics books distinguish between the two descriptive modeling approaches for fluid flow. The former describes events at given points in space, e.g., the Couette velocity profile $U(y) = (y/H)\ U_H$ states that $U(H) = U_H$ and $U(H/2) = ½\ U_H$. The shear rate at $y = H$ is a constant having $dU(y)/dy = U_H /H$ while the shear stress is $\mu\ U_H /H$. On the other hand, Lagrangian flow descriptions follow particles in space, for instance, to determine the trajectories and destinations of airborne contaminants. On the biological front, an Eulerian model may be used to predict the viscous stress at the point where arterial plaque is located, that is, to determine the likelihood that it may be removed and transported elsewhere to inflict damage. A Lagrangian model, on the other hand, would calculate where clog debris is likely to move and remain, thus providing a danger assessment from a different perspective.

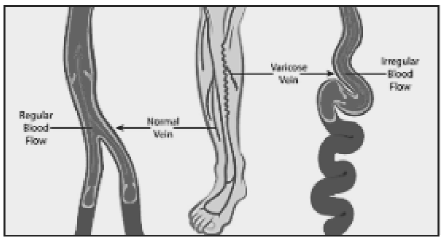
Steady versus transient models. The differences between these two categories describing time dependency appear obvious, but in reality, may involve several degrees of subtlety. This is best illustrated by example. Consider a tuning fork operating in a vacuum. Depending on how it is struck, the vibrations are found as solutions to the unsteady elastic equations. However, because it is vibrating in a vacuum, sound is not created. In order to understand sound propagation, acoustic coupling effects of compressible air movements must be considered.

A second example is also relevant to the subject of this book. Steady state fluid velocities and stresses can be calculated in rigid wall arteries using the Hagen-Poiseuille law or its non-Newtonian extensions. If the transient effects of wall elasticity are to be modeled, additional transient terms must be retained in the general formulation to account for mechanical wall deformations. Waves traveling at the interface and in the elastic medium may arise, but these transients are not to be confused with acoustic echoes that propagate through blood vessels – effects that must be modeled by coupling to compressible fluid flow equations. The consequences may surprise non-experts. An acoustic fluid signal will reflect with the same pressure sign at closed line terminations, but with a negative sign (or polarity) at opened ends. Thus, depending on the wavelength, a propagating pulse may double in signal or completely cancel depending on where the pressure measurement is taken. In formulating physical models, it is imperative to define the objectives and to pose the initial-boundary value problem correctly.

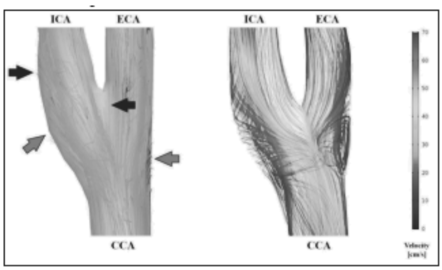
Newtonian versus non-Newtonian flows. It is fortunate that Newtonian flow models, the earliest and simplest formulations developed in the literature, also provided the greatest utility early on in modern engineering – that is, models dealing with air, water and certain oils. Such models, as shown in Chapter 3, are importantly *linear* in nature; for example, in Hagen-Poiseuille flow, doubling pressure drop doubles the volume flow rate. Predictable behavior is the case even for more complicated geometries. On the other hand, non-Newtonian fluid models are *nonlinear*. Unless an analytical solution is explicitly available for a given geometry, it is impossible to predict, for example, the flow rate outcome when the applied pressure drop doubles. For smaller blood vessels – that is, the great majority of the blood vessels found in the human body – the flows are non-Newtonian. The relationships between volume flow rate, pressure drop, local viscous stress and geometry are uncertain. This is considered in our modeling.



(d) Clogged area cross-sections in single vessels and bifurcations. Credit: scientificanimations.com.



(e) Curved flows in varicose veins. Credit: rshaheenvascular.com.



(f) Local secondary flows at junctions. Credit: Ngo et al. (2019).

Figure 1-4d,e,f. More realistic flowfields.

The flows in Figures 1-4a,b are idealized, but real flows contain arbitrary geometries as in (d), curved paths as in (e), and "secondary flows" at junctions as in (f). The former two are considered here, but the local swirling in (f) is not. While finite difference or element models can be used, claimed accuracies are illusory, as extensive "calibrations" with lab results are typically necessary. Our approaches in Chapters 3 and 4 do predict viscous wall losses, but these do not include minor local effects due to secondary motions.

Porous media continuum flow models. Historically, conduit flow solutions (applicable to the problems illustrated above) were developed first out of practical necessity – pipe flows, for example, deliver water to households, fluids in manufacturing facilities, and sewage to urban plants. But analytical solutions to the Navier-Stokes equations and their extensions, even to this day, are few. The remarkable Hagen-Poiseuille equation for Newtonian flow through a pipe sparked a wave of optimism in the nineteenth century. Scientists thought that the solution could be adapted to the crevice spaces of porous flow media – that is, to problems related to dam construction, agricultural irrigation, and so on, to provide improved predictive models relating pressure drops, velocities and cumulative flow rates. Diagrams such as those in Figure 1-5a supported interest in this area, but progress toward semi-analytical models was impeded by realities such as the packing and size heterogeneities illustrated in Figure 1-5b and 1-5c. The ultimate "nail in the coffin" came with the realization that real-world porous media are complicated as shown in Figure 1-5d. At small scales, flow elements vary in size, shape and connectivity to neighboring elements. Statistical approaches were similarly overwhelmed – broad assumptions must be made and simpler modeling strategies providing solvable equations were lacking. For porous media flows, conduit flow analogies, despite their apparent utility in smaller pipe applications, would provide little in value.

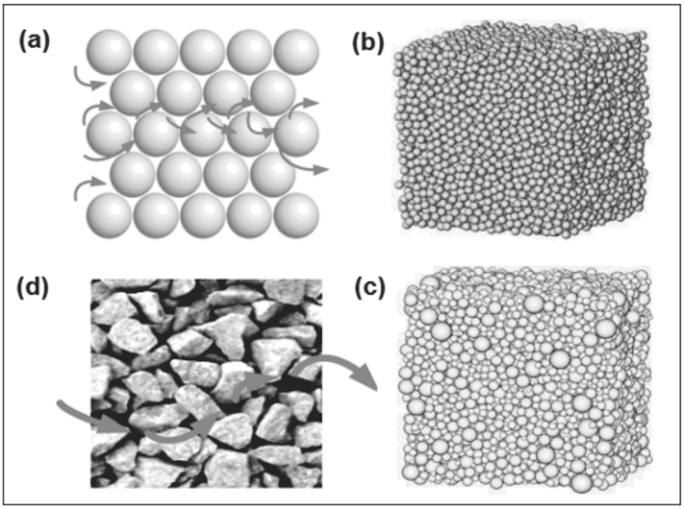


Figure 1-5. Porous media flow hierarchies.

An alternative modeling strategy different from Navier-Stokes was proposed by French engineer Henri Darcy in the nineteenth century. Rather than studying the smaller-scale physical problem suggested in Figures 1-5a,d, Darcy re-considered sand and soil media flows from a macroscopic perspective. He postulated that local Eulerian velocities would take the form "$\mathbf{q} = - (k/\mu)\ \nabla P$," or in Cartesian rectangular coordinates, $u = - (k/\mu)\ \partial P/\partial x$, $v = - (k/\mu)\ \partial P/\partial y$ and $w = - (k/\mu)\ \partial P/\partial z$. In other words, *if* the pressure field $P(x,y,z,t)$ were known, then the velocities u, v and w could be calculated from the x, y and z derivatives shown. The proportionality constant k/μ is known as the "mobility." Again, μ represents the fluid viscosity or the resistance to motion offered by the fluid. The parameter k here defines the permeability of the medium and provides a measure of flow resistance offered by the underlying sand or rock – the higher the permeability, the lower the resistance. It is clear that the net resistance depends on the lumped quantity k/μ, and that the use of k and μ individualy provides a sound conceptual framework for the separate contributions of rock and fluid.

The postulate "$\mathbf{q} = - (k/\mu)\ \nabla P$" alone is only partially useful – the pressure must be separately determined by solving a pressure equation. In so-called Darcy flows, which apply to low inertia motions (relative to those in conventional fluid mechanics), the required equation is obtained from mass conservation considerations. The general vector expression $\nabla \bullet q = 0$, which applies to steady incompressible flow, together with the momentum approximation "$\mathbf{q} = - (k/\mu)\ \nabla P$" yields $P_{xx} + P_{yy} + P_{zz} = 0$. For simplicity, we have given the steady result for the case where a single constant k applies to all three directions, that is, the medium is isotropic – in transient limit, we have instead $P_{xx} + P_{yy} + P_{zz} = (\phi\mu c/k)\ P_t$ where c is the compressibility and ϕ represents the porosity. When the underlying medium is anisotropic and heterogeneous, the empirically measured permeabilities $k_x(x,y,z)$, $k_y(x,y.z)$ and $k_z(x,y,z)$ must be used, together with $c(x,y,z,t)$ and $\phi(x,y,z,t)$. The corresponding differential equations and solutions are more complicated. These are discussed later in general steady and transient limits. It is important to note that solution properties to $P_{xx} + P_{yy} + P_{zz} = 0$ and $P_{xx} + P_{yy} + P_{zz} = (\phi\mu c/k)\ P_t$ are well understood in the mathematics literature, and that analytical and numerical solution methods are available. Darcy's approach is significant because permeability functions provide a simple macroscopic continuum view that is amenable to practical solution techniques.

Darcy flows in human and animal tissue. In the past decade, medical researchers have increasingly accepted Darcy flow modeling in studying blood movements through tissue. We concur with these approaches. But many of the published techniques are not yet mature, at least by comparison to steady and transient methods used in petroleum exploration and production. The case for Darcy flow analysis is practical and also strong. The structures evident from Figure 1-6a point to distributed heterogeneities and anisotropies suggesting that macroscopic flow models are very useful. Similarly, Figures 1-6b,c show how capillary networks, many more than are actually shown and embedded within background tissue media, will provide massive numbers of blood flow paths from arteries to veins. This large intervening medium clearly serves as a continuous porous transport medium populated with mixed tissue and microscopic capillaries and characterized by permeability functions defined conveniently over larger spatial scales.

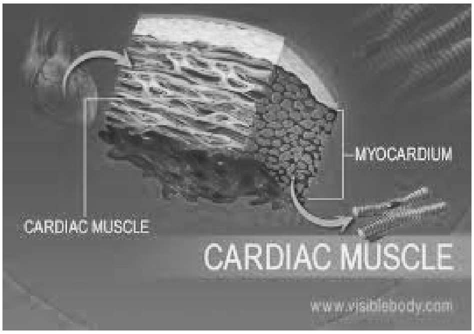


Figure 1-6a. Complicated cardiac muscle. Credit: visiblebody.com

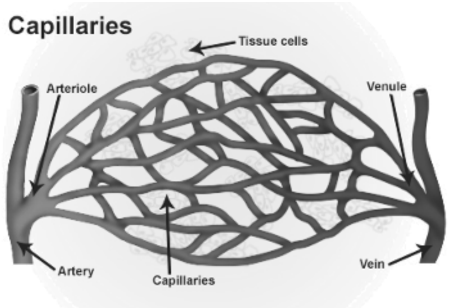


Figure 1-6b. Capillary and integrated tissue cell system.
Credit:https://training.seer.cancer.gov/anatomy/cardiovascular/blood/classification.html.

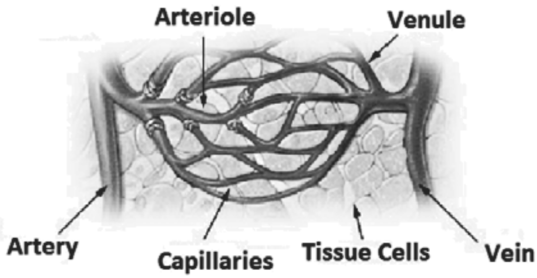


Figure 1-6c. Capillaries and background tissue cell system.
Credit: "COVID-19-associated vasculitis and vasculopathy," R.C. Becker, *Journal of Thrombosis and Thrombolysis*, Volume 50, pp. 499–511, 22 July 2020.

Objectives in conduit and Darcy flow modeling. Ultimately in biofluids, we wish to determine the mechanism by which oxygen and nutrients are delivered to tissue. In this sense, the flow modeling in arteries and veins provides "infrastructure" support – it is comparable to understanding the highway system traversed by a fleet of delivery trucks. Where are the bottle-necks? How much effort is required to do the job? In other words, what are the pressure drops along blood vessel paths? What effects induce dangerous burst pressures? Will wall shear stresses prevent clog formation? Or, if clogs already exist, will stresses dangerously thrust them downstream to impact organs like the heart, the brain or the lungs? Many activities, e.g., microscopic biological and chemical exchanges, are performed between entrance and exit ramps along the highway. The heart pumps blood through arteries which ultimately return through veins. At any particular highway stop are congested networks of smaller roads, and trucks loading or off-loading their goods. This activity is so intense that it is difficult to account for every transaction. Thus, we treat the intervening media in Figures 1-6b,c as continuous – or, more precisely, a Darcy medium as suggested. With this simplification, we can formulate "simple questions" related to its macroscopic properties. In Chapter 7, we will show how, using an "intelligent syringe," flowline pressure transients recorded during blood removal or drug delivery can be interrogated using mathematical interpretation models to predict properties like compressibility, permeability and anisotropy, which are useful to clinicians, engineers and researchers. Finally, in Chapters 8 and 9, we explore approximate ways to model artery, vein and tissue interactions three-dimensionally, using a reservoir flow simulator originally developed for oil and gas movements through porous underground sands.

1.2 Quantitative Modeling Perspectives.

1.2.1 Rheology considerations in *conduit* flows.

Not all biofluid flows are Darcy flows, but flows in porous continuous media are, and they are "fed" by systems of arteries and veins – that is, straight and tortuous conduit or pipe-like blood vessels that function as highly networked highways that transport nutrients and oxygen. Earlier, we introduced the Navier-Stokes equations, which apply to both Darcy and non-Darcy applications. We noted that few analytical solutions have been uncovered in the past two hundred years. One useful solution, when the formulation is rewritten in circular cylindrical coordinates, is the Hagen-Poiseuille solution for flow in a pipe (this is available in most fluid mechanics books and is not rederived here). This is not a porous medium solution, but to the contrary, one also describing Newtonian flow through *circular* blood vessels such as the main aorta. The equation is simple and elegant, with a volume flow rate "$Q = \pi R^4(P_i - P_o)/(8\mu L)$," applicable to the idealized geometry and paraboloidal velocity profile shown in Figure 1-7.

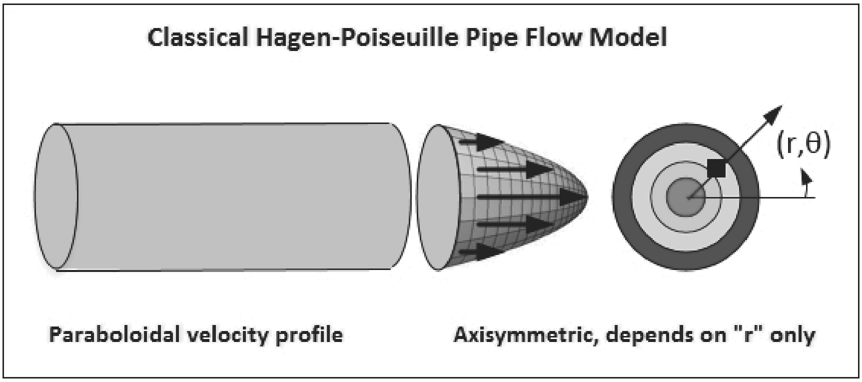


Figure 1-7. Axisymmetric pipe flow in circular (r,θ) coordinates.

Despite its popularity in engineering classroom studies and numerous citations in the hematology and related medical literature, its practical restrictions are numerous. Again, the flow cross-section must be circular and axial changes in area are not permitted. Here, R is the radius, P_i and P_o are inlet and outlet pressures, and L is the length of the conduit. The steady formula assumes smooth walls, laminar flow and does not apply to turbulent conditions. The latter is not a significant restriction in biofluids, but the assumption of Newtonian flow is. The viscosity μ is constant and the shear stress, which describes wear and tear against vessel walls, is $\tau = \mu \, dU/dr$ ("r" is the radial coordinate and "dU/dr" is the shear rate describing geometric deformation). Only when these conditions are satisfied does the Hagen-Poiseuille formula apply.

Before we discuss the limitations behind this model, we summarize its usefulness. Again, $Q = \pi R^4(P_i - P_o) /(8\mu L)$. This formula shows the role played by the "pressure gradient" $(P_i - P_o) /L$ – the flow rate is directly or linearly proportional to $(P_i - P_o) /L$. Simply said, "double the pressure drop, you'll double the flow rate." For a given pressure gradient, Q varies like the fourth power of R. This clearly illustrates the disastrous effects of clogged blood vessels – a 5% radius reduction implies a 19% drop in flow rate. For the heart to deliver blood at a given flow rate, a small reduction in R means that the pressure gradient must increase significantly – this pressure compensation means that the heart must work that much harder, and so, would be subject to more wear and tear. Higher resulting pressures may also damage blood vessels and higher stresses will induce additional wear and tear. The formula also states that Q is inversely proportional to μ. Thus, the higher the viscosity, the lower the flow rate with all other parameters fixed. Viscosity reducing medications are often needed and prescribed. The formula estimates the reduction needed to overcome the pressure effects of clogging. These math conclusions have served the engineering – and medical – communities well because they are qualitatively useful.

Better arterial flow models needed. In this book, we refer to flows in arteries, capillaries and veins as arterial for convenience. The engineering community has long recognized the limitations behind the Hagen-Poiseuille law. In practice, this equation does not describe many physical events accurately, if at all – thus, the field of "rheology" has evolved to fill this vacuum, with the first author contributing significantly to "computational rheology." There are many restrictions, discuss qualitatively below, that are considered, modeled and solved in Chapter 3. We will discuss these limitations next.

- If Hagen-Poiseulle's rule is applied to blood flows in vessels with different diameters, the simple inverse dependency on viscosity would degrade as diameters decrease in size because complicated non-Newtonian effects take over. This arises because blood is heterogeneous and not the "simple red liquid" most laymen assume. Microscopic analysis shows that blood is complicated and its constituent parts are subjects of active research. In fact, blood is a non-Newtonian fluid that does *not* satisfy $\tau = \mu$ dU/dr. Generally, the viscosity is non-constant but depends on shear rate with an algebraic dependence. When the new governing equation is solved, we find that an "apparent viscosity" will vary with flow rate, pressure gradient, vessel radius and position within the blood vessel. Thus, lab tests that predict blood viscosity are limited in value because they actually relate to the flow resistance imparted to a special moving component in the particular viscometer. The simplifications offered by the classical formula are lost. Flows in the main aorta are an exception – they are Newtonian but geometric irregularities like clogs render the formula of limited utility.

- As if the algebraic dependence were not bad enough, blood flows are often subject to yield stress limitations. A simple analogy is possible. Imagine dragging a box on a rough floor. The box does not immediately move, but motion commences only when a threshold force is exceeded. The friction acting on the bottom surface prior to motion is known in mechanical engineering as "static friction," while the friction acting once movements begin is known as "dynamic friction." In fluid mechanics, "yield stress" is the analogue to the foregoing threshold. Put simply, this renders the mathematics very difficult and actual pressures more unpredictable.

- Even with the fluid effects in the above two paragraphs solved, geometric irregularities introduce additional complications. For one, blood flow conduits are rarely straight. They may be long, short and generally nonplanar. And more often than not, they "split" or "bifurcate" into additional branches, with each branch bifurcating into still more branches. Because these branches are smaller in diameter, the flows they host will be more non-Newtonian, making solutions difficult to obtain. In civil engineering, pipe flows are simulated instead using "lumped coefficient, head loss" methods – purely empirical models for rough pipes, pipes with fittings, conduits with bends, contractions and expansions. By contrast, the sole "exact" network model in the literature, typically used in classroom discussion, assumes "ideal flow" in which total energy is completely conserved throughout – this is never the case in reality. Furthermore, the problem of bifurcated flow for non-Newtonian fluids, with or without yield stress, does not appear to have been addressed at all. This is considered in Chapter 4.

- Furthermore, real blood vessels are rarely circular. Their geometric cross-sections may be deformed, squeezed, stretched, or blocked by clogs with every conceivable geometric deformity. What are the flow consequences of such clogs? How do they affect pressure drops in the flow direction? What are the effects of viscous shear stresses on long term vessel wall wear and tear? And worse, what are the effects of non-circular clogs in bifurcations, as shown in our Figure 1-4d? Rigorous models are developed and solved in Chapter 5.
- Finally, for convenience only, we lump other real-world effects under this last single-bulleted item. (1) Simple but useful models are required to handle distributed clogs and blood vessels with axially varying areas. (2) Transient pulsatile effects are also important to study unsteady and acoustic loadings; further, how is wall elasticity in unsteady applications, handled? (3) Centrifugal effects, for instance, associated with varicose veins, can adversely affect blood flow. Finally, (4) How are models for all these modified to describe non-Newtonian fluids with cross-sectional geometric irregularities?

1.2.2 Darcy flow model in *continuous* media.

The "grand-daddy" to our porous flow discussions arises from heat transfer modeling, in particular, the "heat" or "diffusion equation" discovered over a century ago. Fourier's law states that heat transfer occurs only when temperature differences (or "gradients") exist. For example, when physical systems remain at equilibrium, nothing interesting happens. In a steady one-dimensional system, the heat transfer rate per unit area satisfies $q = - K\, dT/dx$. Here, the temperature is $T(x)$, and in "$- dT/dx$", the minus sign defines how heat $q > 0$ moves from regions of high temperature to low when $dT/dx < 0$. Here, "d/dx" is an "ordinary derivative." In transient applications, the "d/dx" is replaced a partial derivative $\partial/\partial x$. A time derivative term also appears as $\partial T/\partial t$.

Temperature diffusion. Energy conservation requires that timewise increases given by "$c\rho A\, \Delta x\, T(x,t+\Delta t) - c\rho A\, \Delta x\, T(x,t)$," where c is specific heat, ρ is lineal mass density, A is cross-sectional area, T is temperature, x is the spatial direction and t is time, with Δ denoting increments, must balance the heat entering at the left and leaving at the right, that is, $\Delta t\, A\, (- K\, \partial T/\partial x)_x - \Delta t\, A\, (- K\, \partial T/\partial x)_{x+\Delta x}$. In other words, $\{T(x,t+\Delta t) - T(x,t)\}/\Delta t = \{K/(\rho c)\}\{ (\partial T/\partial x)_{x+\Delta x} - \partial T/\partial x)_x\}/\Delta x$, where K is the thermal conductivity (all properties are constant in this derivation).

As Δx and Δt approach zero, we have $\partial T/\partial t = \{K/(\rho c)\}\ \partial^2 T/\partial x^2$ where $K/(\rho c)$ is known as the "heat diffusivity." This represents the so-called "heat equation" or "diffusion equation." It is important to understand what this equation physically describes. Imagine a metal rod that is heated at one end. The rise in temperature slowly moves or "diffuses" into the right and the rod temperature eventually rises throughout. The transport mechanism is not a "forest fire" nor is it an "explosion" – it simply diffuses, slowly but surely. In two dimensions, the derivation yields $\partial T/\partial t = \{K_x/(\rho c)\}\ \partial^2 T/\partial x^2 + \{K_y/(\rho c)\}\ \partial^2 T/\partial y^2$ while in three we have $\partial T/\partial t = \{K_x/(\rho c)\}\ \partial^2 T/\partial x^2 + \{K_y/(\rho c)\}\ \partial^2 T/\partial y^2 + \{K_z/(\rho c)\}\ \partial^2 T/\partial z^2$. The subscripts indicate "anisotropic" behavior, that is, the medium behaves differently in different directions.

Analogous results are possible in other coordinate systems. While "x, y, z" variables are natural in describing rectangular plates and solids, circular coordinates "r, θ, z" are preferable for cylindrical geometries. One can perform derivations similar to that given earlier in general coordinates. For circular applications, the geometric relations $x = r \cos \theta$ and $y = r \sin \theta$ can be used to transform the Cartesian or rectangular result, for instance, assuming an isotropic value of K, to a more general $\partial T/\partial t = \{K/(\rho c)\}\ (\partial^2 T/\partial r^2 + 1/r\ \partial T/\partial r + 1/r^2\ \partial^2 T/\partial \theta^2 + \partial^2 T/\partial z^2)$. In transient spherically symmetric problems, we find the deceptively simple equation $\partial T/\partial t = \{K/(\rho c)\}\ (\partial^2 T/\partial r^2 + 2/r\ \partial T/\partial r)$, where "r" is now the spherical radius – its anisotropic pressure analogy provides the basis for the "intelligent syringe" methods of Chapter 7. Various extensions are possible, e.g., situations with spatially variable or time-dependent properties, which we leave as exercises for the interested reader.

Darcy flow pressure diffusion. We introduced temperature diffusion above because it is an everyday phenomenon familiar to all. Furthermore, numerous mathematical, analytical and computational techniques for solution are available in textbooks and other published works. In this monograph, "pressure diffusion" in porous media plays a prominent role. Fluid mechanics covers numerous applications in modern engineering and science. Understanding its many limits requires years of study, in each of its many sub-specialties alone. We will give a brief, non-exhaustive, but accurate summary here. The exposition helps readers navigate through other fluid mechanics books, as we will introduce terminology useful in reducing the confusion that invariably arises when newcomers to the field sort through the literature.

At its foundation, the general "Navier-Stokes equations" developed two centuries ago apply. In Cartesian or rectangular coordinates, we have $\rho\ (\partial u/\partial t + u\ \partial u/\partial x + v\ \partial u/\partial y) = -\ \partial P/\partial x + \mu\ (\partial^2 u/\partial x^2 + \partial^2 u/\partial y^2)$ and $\rho\ (\partial v/\partial t + u\ \partial v/\partial x + v\ \partial v/\partial y) = -\ \partial P/\partial y + \mu\ (\partial^2 v/\partial x^2 + \partial^2 v/\partial y^2)$ which are x and y momentum equations (we consider two dimensions for simplicity). Here u(x,y,t) and v(x,y,t) are horizontal and vertical velocities measured at a fixed point (x,y) in space, P(x,y,t) is the local pressure, ρ is a constant mass density and μ is the constant laminar viscosity. Viscosity describes the "stickiness" or resistance that a fluid offers to motion. It is a subtle effect whose consequences will be discussed extensively later. Three unknowns are seen, namely, u, v and P, so that a third equation describing mass conservation is needed to provide answers. This takes the form $\partial u/\partial x + \partial v/\partial y = 0$. To be sure, these are complicated and we will not directly solve them here – only seven closed form analytical solutions have been discovered and practical solutions are generally obtained using numerical methods.

But how general is the above formulation? *Not very.* It applies only in two dimensions, and then, to problems describable in rectangular coordinates. The properties ρ and μ are constant. When the viscosity μ vanishes identically, it is possible to derive the well known "Bernoulli equation," that is, the "$P + ½\ (u^2 + v^2) = \text{constant}$" used in many inviscid (that is, non-viscous) flow applications such as ideal airfoil design. But Bernoulli's integral does not describe frictional effects in aerodynamics. Nor is it applicable to the arterial and porous flows considered in this book. Further, an added limiting assumption is the dependence of "viscous shear stresses" τ in the form $\tau_x = \mu\ \partial u/\partial x$ and $\tau_y = \mu\ \partial v/\partial y$, where the "shear rates" $\partial u/\partial x$ and $\partial v/\partial y$ describe geometric distortions of fluid elements as they move. This dependence defines "Newtonian fluids." Water and air, mainstays of aerospace and ocean engineering, are fortunately Newtonian. As shown in Chapter 3, such flows are relatively easy to model. However, flows of ketchup, mayonnaise or baby cereal in food processing plants, are not – and neither, for the most part, are blood flows in arterial or porous biofluid media. Finally, the Navier-Stokes equations shown do not apply when fluid compressibility is important – and human tissues applications are compressible. Aside from these limitations, extensions to the Navier-Stokes equations do exist and can be solved with effort. However, a porous continuum approach is more useful and rapid in practice. Importantly, we will later show how it yields important insights to "intelligent syringe" data interpretation.

Important porous media approach. The Navier-Stokes equations do not bode well for porous biofluids modeling – the equations are too complicated for practical engineering use. About a century ago, the French civil engineer Henry Darcy noted that in flows through porous media, at low speeds or, more precisely, at "low Reynolds numbers," the Navier-Stokes equations are equivalent to the so-called Darcy's equations. The Eulerian velocities u and v are here given by $u(x,y,t) = -(k/\mu)\,\partial P/\partial x$ and $v(x,y,t) = -(k/\mu)\,\partial P/\partial y$. The "k" represents the permeability of the sand or matrix rock media, written here for isotropic problems, while μ again denotes Newtonian viscosity. The two constants are used to separately book-keep the effects of fluid resistance. For instance, a high value of k describes the low resistance of a beach sand, while a low value would represent the resistance offered by fine cement. A high value of μ describes a thick liquid, applicable to certain "heavy oils," while a low value would describe water or air. The ratio k/μ is the "mobility," which describes the net effect of the fluid and its host medium. This quantity is important to Darcy flow in the same way that the lumped thermal diffusivity coefficient is relevant to heat transfer. A differential equation is needed for pressure. But instead of energy conservation, mass conservation now produces $k_x\,\partial^2P/\partial x^2 + k_y\,\partial^2P/\partial y^2 + k_z\,\partial^2P/\partial z^2 = \phi\mu c\,\partial P/\partial t$ assuming constant $\phi\mu c$ and directional anisotropic permeabilities, where ϕ is porosity and where c now denotes the net compressibility of the medium. Because Darcy's and Fourier's final differential equations are identical in form, analogous physical conclusions would apply to analogous applications. One can essentially understand Darcy pressure fields by considering temperature analogies.

Relevance of Darcy flows to biofluids. Darcy flows in underground rock formations are determined by properties like permeability, porosity, net compressibility and fluid viscosity. The efficiency offered by the rock formation in oil and gas extraction affects the economic viability of a commercial project. Now, it is clear that the principles applicable to flows in matrix rock apply to porous flows in the human body. Such flows are generally found in different tissue types, for example, brain tissue, muscles, tumors, bone marrow, cancerous masses, and so on. Each application is marked by parameters in different ranges, typical parametric attributes being relatable to "lean versus obese," "male versus female," or "elderly versus youthful." Needless to say, applications are not restricted to humans. Our methods apply to farm animals and also to certain agricultural problems for plants.

When a practitioner needs to deliver drugs, say through syringe injections, several fluid-dynamic questions arise. What are the flow properties of bodily and syringe liquids? What is the total volume? Where is the optimal injection site? How rapidly should the drug be placed? Will the drug diffuse smoothly as intended? Will the drug stay in place, and if not, in which direction is it transported? Will it hurt the patient and introduce discomfort? But these are not the only questions Darcy flow analyses address. Such models play a greater role in "the big picture." Taken as a whole, the human body represents a massive Darcy flow medium where oxygen and nutrients are delivered via arteries that emerge from the heart, then flow through smaller capillary systems situated in intervening organs and tissue, and return through systems of veins to the heart where the process begins anew.

Flow resistance, which depends on tissue permeability and porosity, as well as blood viscosity, affects heart pumping efficiency. If the "pressure drop" in the complete flow circuit is large, the heart works harder and health issues arise. The physician might prescribe viscosity reducing medications, or perhaps, recommend longer term life-style changes like exercise, that will affect mechanical tissue properties. While all of us have experienced undesirable shots or jabs at one time or another, these delivery instruments are not all bad – "intelligent syringes" can be designed to characterize parameters like permeability, anisotropy, porosity and compressibility at different target points in the body. This possibility, in which measured flowline pressure transients are interrogated using smart mathematical algorithms, is afforded by Darcy and not Navier-Stokes formulations. The theoretical basis and validation behind intelligent syringe principles and hardware design contribute to an important and integral part of this book.

While we will focus on Darcy flows in Chapters 7, 8 and 9, it is worthwhile at this point to cite recent survey papers relevant to porous media biological applications. These are

- Grillo, A., Carfagna, M. and Federico, "The Darcy-Forchheimer Law for Modelling Fluid Flow in Biological Tissues," *Theoret. Appl. Mech.*, Vol.41, No.4, pp. 283–322, Belgrade 2014.
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- Ray, L.A. and Heys, J.J., "Fluid Flow and Mass Transport in Brain Tissue – review paper," *Fluids* 2019, 4, 196; weblink, doi:10.3390/fluids4040196 www.mdpi.com/journal/fluids.
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1.3 Preview of Complicated but Simple Boundary Value Problem Solutions.

By now, the reader has been introduced to steady-state equations like $\partial^2 P/\partial x^2 + \partial^2 P/\partial y^2 = 0$ for Darcy *field* pressure and $\partial^2 T/\partial x^2 + \partial^2 T/\partial y^2 = 0$ for temperature *field* modeling, useful when temperature effects couple with local pressures. As we will learn, other important physical models take on similar mathematical expression. For instance, the axial velocity U(x,y) in a non-circular *duct* or *conduit* in x-y coordinates satisfies $\partial^2 U/\partial x^2 + \partial^2 U/\partial y^2 = (\ .\ .\ .\ )$. This importantly extends the Newtonian Hagen-Poiseuille formula to problems with arbitrary cross-sectional geometries having straight flow axes.

A more important application arises in studying non-ideal geometries, e.g., duct flows in general clogged cross-sections and porous media flows through irregular domains like distributed capillary networks. We assume that the relevant geometries are specified in rectangular x and y coordinates. As will be shown from Equations 6.20 and 6.21 in Chapter 6 (and in original detail in Chapter 2), the topology transforms given by coupled equations $(\ .\ .\ .\ )\, x_{\xi\xi} + (\ .\ .\ .)\, x_{\eta\eta} = (\ .\ .\ .\ )$ and $(\ .\ .\ .\ )\, y_{\xi\xi} + (\ .\ .\ .\ )\, y_{\eta\eta} = (\ .\ .\ .\ )$ assist in "mapping" general irregular domains into simpler rectangular ones (in a computational (ξ,η) space) where flow properties are conveniently solved. For instance, the axial velocity *U* in a duct of arbitrary cross-section is shown in Chapters 5 and 6 to satisfy an equation of the form $(\ .\ .\ .\ )\, U_{\xi\xi} + (\ .\ .\ .\ )\, U_{\eta\eta} = (\ .\ .\ .\ )$.

For brevity, the (. . .) expressions, which vary from application to application, are not written out in complete form. What is apparent, from the examples given, however, is the prominent role assumed by elliptic operators like "$(\ )\, \partial^2/\partial x^2 + (\ )\, \partial^2/\partial y^2$" and "$(\ )\, \partial^2/\partial \xi^2 + (\ )\, \partial^2/\partial \eta^2$." For this reason, Chapter 2 devotes considerable attention to solutions in rectangular (x,y) spaces but only for simplicity. And why, one might ask, why rectangular is our focus when the majority of problems appear in irregular geometric domains? The reason follows from our solutions to partial differential equations: the topology equations are first solved in an rectangular (ξ,η) space, followed by a solution of the physical problem in that same (ξ,η) rectangular space. The details of an irregular domain are fully retained, but gone are the computational limitations associated with highly irregular meshes and cumbersome interpolations.

The exact details of the different solutions will be presented as the specific applications are discussed. However, we cannot under-emphasize the generality and extreme simplicity of the method employed. For example, the equation "$\partial^2u/\partial x^2 + \partial^2u/\partial y^2 = (1/\mu)\ dp/dz$" holds for Newtonian flow in a general duct where μ is the viscosity and dp/dz is the axial pressure gradient. Straightforward finite difference methods derived in Chapter 2 show that `U(I,J) = (U(I-1,J) + U(I+1,J) + U(I,J-1) + U(I,J+1))/4. - DEL**2 * DPDZ/(4.*VISC)` where `DEL` is a uniform grid spacing. Consider the "human calculator laboratory" in Figure 1-8 and suppose that `U(I,J)` is initialized to *any* starting guess. The student at the center of the "computational molecule" carries out the indicated arithmetic operations for `U(I,J)`. His results are then transferred to surrounding students.

All of their `U(I,J)` values are immediately updated once new values are available. In time, the edge boundary values of U will have diffused throughout the flow domain; with sufficient iterations, the calculations will converge. This simple procedure provides the required answer. Suppose we wish to solve instead "$\partial^2P/\partial x^2 + \partial^2P/\partial y^2 = 0$." The same algorithm and code can be used again with obvious modifications. Finally, consider the topology models (. . .) $x_{\xi\xi}$ + (. . .) $x_{\eta\eta}$ = (. . .) and (. . .) $y_{\xi\xi}$ + (. . .) $y_{\eta\eta}$ = (. . .), and then the analogous equation for $U(\xi,\eta)$. The same baseline rectangular code again applies, provided we re-interpret the meanings for independent and dependent variables. This process is applied to the geometrically challenging problem in Chapter 5.

The iterative process itself, known as a "relaxation method," is not new. It is rapid, at least for modern digital computers, and converges irrespective of any initial guess – even those completely devoid of physical reality. It was invented in the nineteenth century for the solution of problems in elasticity before computers were available, and was later programmed for use at the Massachusetts Institute of Technology for Whirlwind computer applications in the 1940s (see Figure 1-9).

However, our application to topology inversions is new, additionally employing internal complex variables transforms that facilitate rapid and stable solutions. In short, the coupled $x(\xi,\eta)$ and $y(\xi,\eta)$ equations cited are further replaced by the complex variable $z = x + i\, y$ and its conjugate $z^* = x - i\, y$ and solved in an unconditionally numerical stable scheme (e.g., see Chapter 2).

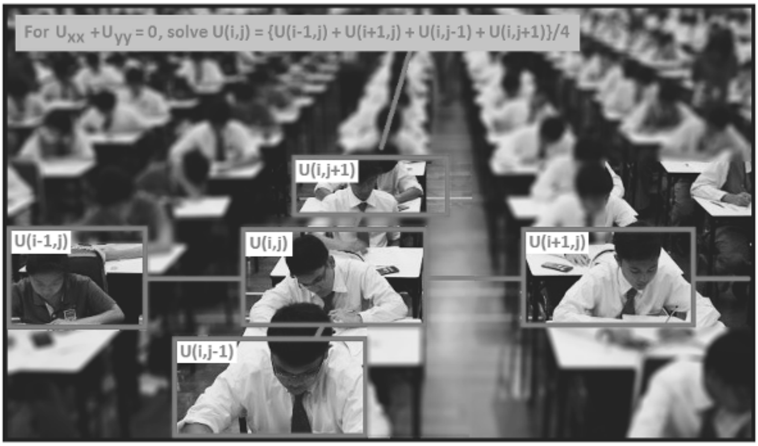

Figure 1-8. Human calculator solution to finite difference models (see discussions leading to Equation 6.19 for simple iterative methods).

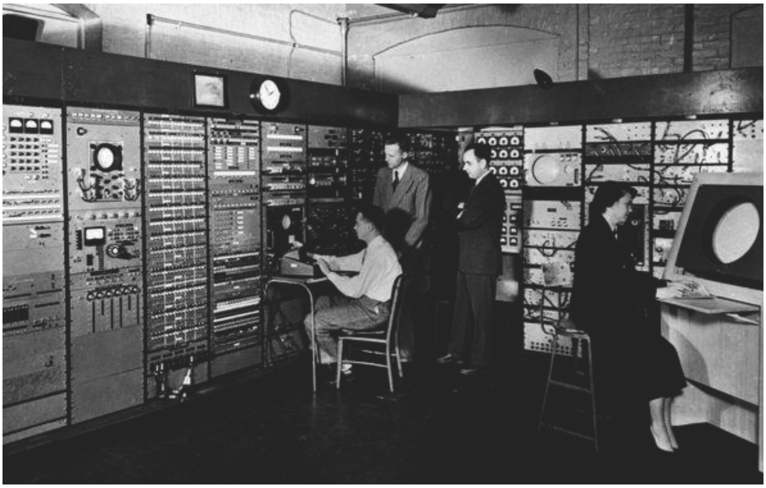

Figure 1-9. MIT Whirlwind computer, Credit: www.mit.edu.

Closing remarks. Again, many of the methods in this book, from boundary-conforming grid generation, to clog flow analysis, to flowline bifurcations, to “intelligent syringe” and whole-body porous flow analyses, and so on, were originally developed by the authors in the context of petroleum engineering and geoscience applications. We have taken care in this book to explain petroleum technologies because many more results are available from the acoustic, electromagnetic and nuclear magnetic resonance logging literature which may potentially be useful to biofluids modeling and diagnostics. It is the authors’ hope that readers will research this literature to explore physical analogies shared between the two similar disciplines. For those interested in results only, the mathematically oriented exposition in Chapter 2 may be omitted without loss of continuity. However, the specialized techniques described there should be invaluable to researchers, software designers and programmers. Many of the methods in this book have been thoroughly tested and can be used as is. Our more complicated models are available for collaborative research and other developmental efforts.

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