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978-0-521-11924-5 - An Introduction to Modeling of Transport Processes: Applications to Biomedical Systems
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Excerpt
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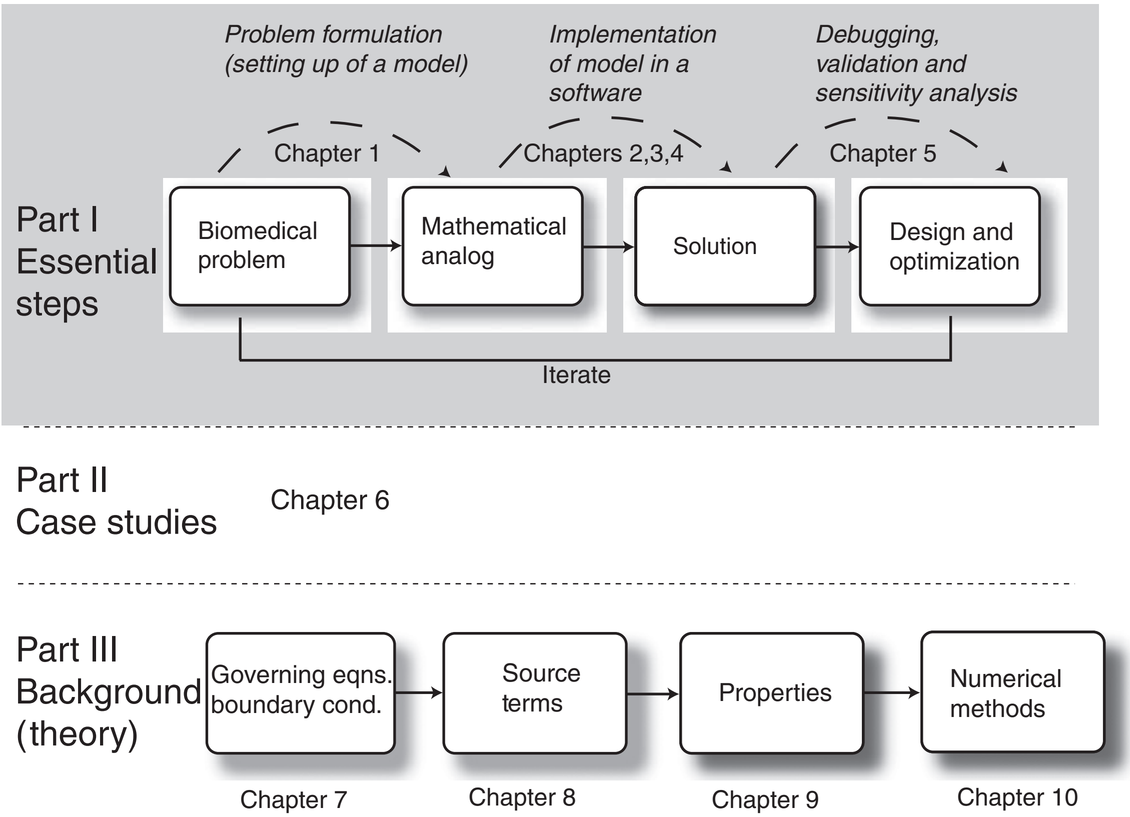
Essential steps



1 Problem formulation
From reality to realistic computer representation

In this chapter we will learn about problem formulation, which is the first step in developing a mathematical model of a physical (such as a biomedical) process, as illustrated in Figure 1.1. In problem formulation, we take reality, make assumptions thereby simplifying it, and apply universal physical laws to generate the equations (*the model*) which describe the real physical process. It is critical to see that everything we will learn from our model depends on how we have formulated the problem. This chapter provides the big picture of problem formulation, with additional details available in theory chapters (7–9). As shown in Figure 1.1, problem formulation in this chapter will be followed by subsequent chapters on the solution process.

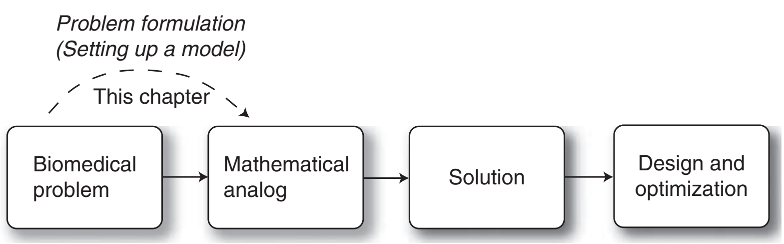


Figure 1.1

Problem formulation as the first step in modeling.

1.1 Context: biomedical transport processes

Transport processes, that is fluid flow, heat transfer and mass transfer, often underlie a biomedical process, perhaps the most common examples being drug delivery and thermal therapy. The relevance of heat and mass transfer to biomedical processes is now introduced.

1.1.1 Heat transfer and thermal therapy

Heat transfer refers to movement of thermal energy due to conduction, convection or radiation. Thermal therapy is any treatment or technique that elevates or decreases cell/tissue temperature for some length of time with an ultimate therapeutic goal. Thermal therapy can include hyperthermia, tissue coagulation and ablation as well as ultrasonic, laser, radiofrequency and microwave heating to destroy tissue, plus cryosurgery, burn therapy, bone growth stimulation, wound healing and thermally mediated gene therapy. Clinical applications include deep heating for various musculoskeletal diseases (rheumatoid arthritis, osteoarthritis, fibrositis and myositis), deep heating for many neuromuscular disorders (muscular dystrophy, progressive muscular atrophy), treatment of various eye disorders (iritis, postoperative uveitis), dental problems (swelling and trismus following extractions, toothache), elevating body temperature following hypothermia surgery and cancer therapy using hyperthermia (40–50 °C). Thus, modeling of thermal therapy would require modeling of heat transfer.

1.1.2 Mass transfer and drug delivery

Mass transfer refers to movement of a material due to diffusion and convection. Drug delivery can be described as the process of delivering a drug to the site of action. Drug transport, i.e., drug diffusion or flow, is intimately related to drug delivery. Even traditional drug delivery processes, such as oral intake, require mass transfer questions to be answered. For example, how do we design a tablet that releases the active drug material at a rate that is nearly constant? Newer methods of drug delivery, such as through skin as in the case of a patch placed over the skin, often require somewhat greater understanding of mass transfer through skin and other materials. In a critical process such as drug delivery in the brain, a mass transfer model that includes diffusion and elimination of drug can provide valuable insight into the complex process. Thus, modeling of drug delivery processes would require modeling of mass transfer.

1.1.3 Quantification of goals in a biomedical process

The goals of a thermal therapy or a drug delivery process need to be stated quantitatively. Examples of quantitative measures of several biomedical processes are shown in Table 1.1.

Table 1.1 Examples of quantitative measures of success in various biomedical processes.

Process	Design goal in quantitative terms
Radiofrequency heating of tumorous tissue	Reach temperatures in the tumorous tissue in the region of 43–45 °C.
Laser ablation	Reach temperatures in the region to be ablated above 300 °C.
Cancer therapy	Cumulative number of equivalent minutes of heating at 43 °C, defined by Eqn. 8.39, needs to reach a certain value.
Cryosurgery	Tissue to be destroyed needs to reach below −45 °C.
Drug delivery (design of a coated tablet, design of a patch)	Rate of drug release over time has to meet certain criteria such as a minimum dose; rate needs to stay near constant over time; release needs to be over a certain time period.
Drug delivery (placement in tissue, as in a brain tumor)	Penetration distance into the tissue (area of coverage) has to meet certain criteria. Additional criteria can be from those listed under tablet and patch.

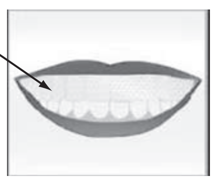
1.2 What is problem formulation?

Problem formulation is creating an equivalent mathematical formulation of a physical problem, i.e., coming up with equations which describe the physical process or processes that constitute the problem (and therefore virtually replace such a process or processes). It is the first step in modeling. Consider, for example, the whitening strip in Figure 1.2 which is placed over teeth to remove unwanted stains. Hydrogen peroxide from the strip diffuses into the teeth and reacts with the stain (an organic material), thus removing the stain and whitening the teeth. We would like to know the rate of diffusion of the hydrogen peroxide into the teeth over time which will provide the time needed to whiten them. This is the problem in the physical world, as shown on the left side of the figure. In order to simulate this physical problem on the computer, we need to describe the physical process in terms of mathematical equations (i.e., develop a problem formulation).

The right side of Figure 1.2 shows the mathematical equivalent, or analog, that is achieved after many simplifications of the real process. The mathematical analog consists of a geometry (computational domain), governing equation, boundary

A biomedical process → **Problem formulation** → Its simplified mathematical equivalent

A plastic strip with a film containing hydrogen peroxide is placed on the teeth to whiten them (see Figure 1.22 for a section of a tooth).



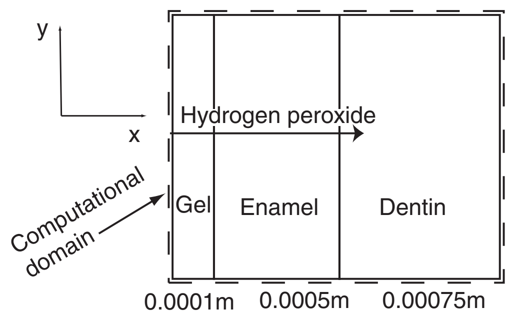
Goal

To find out how far into the teeth the whitening progresses and how that changes with time

Goal

To find the concentration of hydrogen peroxide in the teeth as it varies with position and time

Schematic



Governing equation

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} + r_A$$

Boundary conditions

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = 0 \quad c(x=l) = 0 \quad \left.\frac{\partial c}{\partial y}\right|_{y=0} = 0 \quad \left.\frac{\partial c}{\partial x}\right|_{y=h} = 0$$

Initial condition

$$c = \begin{cases} 2.8 \times 10^{-5} \text{ g/liter in gel} \\ 0 \text{ elsewhere} \end{cases}$$

Properties and Parameters

$$\text{Diffusivity} = \begin{cases} 1.3 \times 10^{-9}\ \text{m}^2\text{/s (gel)} \\ 7.8 \times 10^{-11}\ \text{m}^2\text{/s (enamel)} \\ 7.8 \times 10^{-11}\ \text{m}^2\text{/s (dentin)} \end{cases}$$

$$r_A = 1.871 \times 10^3\ \text{g/s}$$

Figure 1.2

Illustration of problem formulation where a real process (whitening of teeth) is transformed into its computational model consisting of a goal, a computational domain, governing equation, boundary conditions, initial condition and material properties. Properties data taken from Bermudez *et al.* (2004).

conditions, material properties and other parameters that define the real process. The computational domain is the region over which computations will be performed. The governing equation represents the conservation of mass species, H_2O_2 in this case. Boundary conditions are the conditions imposed by the surroundings on the computational domain. In this figure, the first condition, $\partial c/\partial x = 0$ at $x = 0$, implies that H_2O_2 cannot escape into the air, while the second condition, $c(x = L) = 0$, means that H_2O_2 cannot penetrate very far into the teeth and therefore, at a far away place given by $x = l$, the concentration stays at $c = 0$. This mathematical analog can now be used in a computer to simulate the problem in the physical world. For the purpose of understanding and optimizing of the physical process, the mathematical analog can now be a substitute.

Where does this mathematical analog come from? A mathematical analog uses the fundamental laws of the physical world in a mathematical form. The fundamental physical laws that are used in the problems of interest to us are: (1) conservation of total mass (continuity equation); (2) conservation of a mass species (mass transfer equation); (3) conservation of momentum (fluid flow or Navier–Stokes equations); and (4) conservation of thermal energy (heat transfer equation). These are called the governing equations – they are presented in Section 1.7 and are derived in Chapter 7.

1.3 Steps in problem formulation

Problem formulation is perhaps the most critical activity in modeling a process. On the one hand, this step can be made overly complex by retaining a lot of unnecessary details in the model that will increase the computational complexities greatly. On the other hand, if simplification is not done carefully, the main physics of the process can be lost, leading to a worthless model for the purpose of simulating the physical process of interest. For these reasons, all of the steps in problem formulation require simplification, based on understanding of the process in terms of the fundamental physics, such as fluid flow, heat transfer or mass transfer. Problem formulation is also critical because the results we will obtain simply reflect how the model has been set up.

Depending on how we proceed in problem formulation, we can end up with different sets of governing equations and boundary conditions to solve. Analytical solutions to these equations, of the kind found in first courses in transport processes, are possible only for simpler forms of these equations which force a more drastic simplification of the physics. As numerical solutions, the kind that will be used in this book are considerably more flexible than analytical solutions, many more details of the physical process can be included, making the formulated

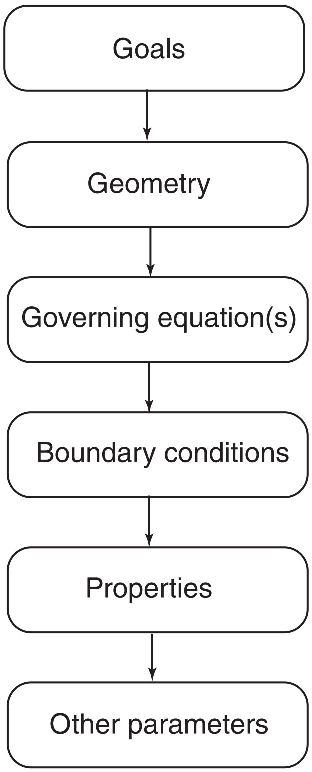


Figure 1.3

Steps in problem formulation. Each of the steps requires some simplification, as discussed throughout this chapter. For an example, see Figure 1.2.

mathematical problem considerably more realistic, i.e., closer to the actual physical situation. As we go through the various steps of problem formulation, we can always consider more realistic alternatives.

An example of problem formulation is shown in Figure 1.2. The process of arriving at the mathematical formulation can be divided into several steps, as shown in Figure 1.3. We first decide on the eventual goal of the simulation – this sets the stage for approaching the steps that follow. Next, we decide on the geometry or the region over which simulation will take place. This is followed by the choice of the governing equations and boundary conditions that will describe the process. To actually solve these equations for specific cases, we need the material properties and parameters corresponding to the situation.

Guidelines on performing the primary steps of problem formulation (geometry, governing equations, boundary conditions and properties) are provided in this chapter, Chapters 7–9 on theory and various software implementations in Chapters 2, 3 and 6. This interrelationship between chapters is illustrated in

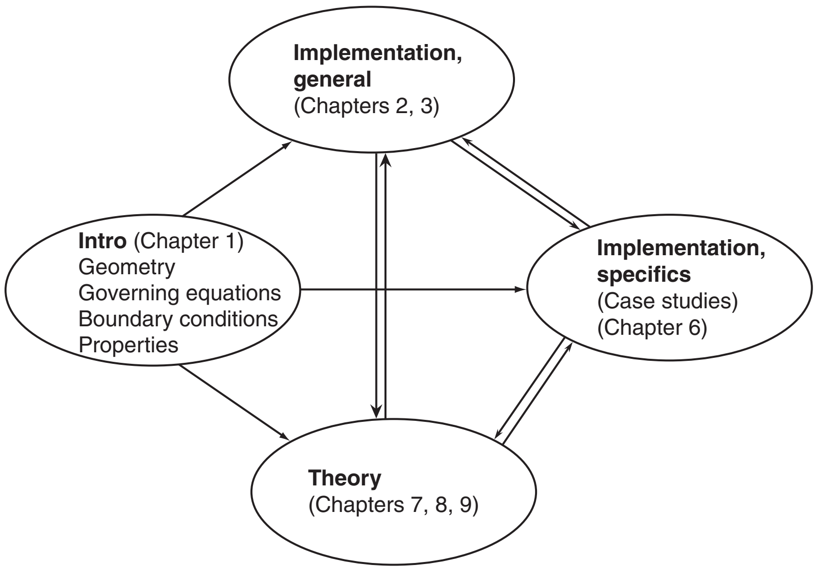


Figure 1.4

Relationship between the components of problem formulation and their software implementation, as presented in various chapters. Cross-references between chapters on a topic are highlighted throughout the chapters. For example, boundary conditions are introduced in Chapter 1, its general implementation in COMSOL is discussed in Chapter 2, more specific implementations discussed in Case studies in Chapter 6 and its theoretical description is provided in Chapter 7.

Figure 1.4 and is highlighted through cross-referencing in the individual chapters. Chapters 4 and 5 provide ways to visualize and further analyze the results.

1.4 Defining goals for problem formulation

Although the general goal of modeling is to improve understanding and facilitate optimization, it is critical to define the specific goals of a problem formulation clearly at the outset, as the formulated problem very much depends on what exactly we want to achieve from it. For example, Figure 1.5 shows two different formulations for the physical situation of drug delivery through skin, using a patch. In the first formulation the primary goal is to look at the effect of penetration enhancers on diffusion through skin. Details of the patch construction are probably unnecessary for this goal.

The second has the goal of finding the effect of using three different materials for the microporous membrane (with correspondingly varying diffusivities) on the rate of drug delivery. Obviously, the details of the membrane would have to

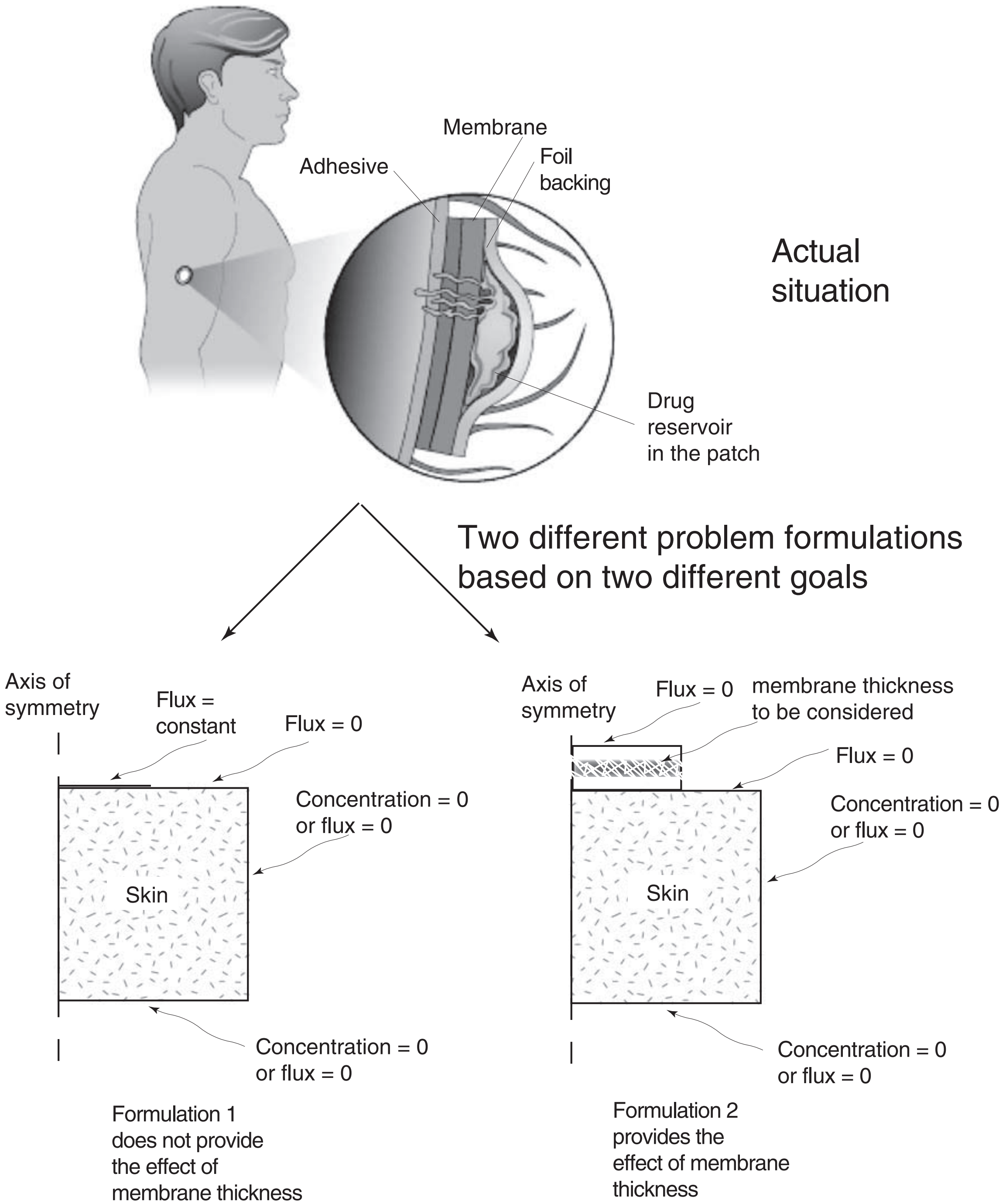


Figure 1.5

Two different goals lead to two different problem formulations for approximately the same physical problem. In Formulation 1, the goal is to study the drug transport primarily in the skin region. In Formulation 2, the goal is to study the drug transport inside the patch as well as in the skin.

be included in this problem formulation. A list of possible goals in biomedical problem formulation is shown in Table 1.1.

1.5 Simplify, simplify, simplify

We always simplify to achieve the least complex problem formulation possible, keeping in mind the important phrase "as simple as possible, but no simpler." Sometimes we simplify because the software cannot handle the required complexity. We simplify at other times to be within the limits of computing resources (memory and cpu speed) available. Even if we need to eventually solve the more complex problem, it is often instructive to solve a simpler problem first as simplification enhances our own understanding of the problem. By dissecting the problem into distinct processes, we can focus on a very specific goal within the more complex physics. Starting simple also makes it easier to debug. Some possible simplifications are: (1) starting with a 2D instead of a 3D geometry, or a 1D instead of a 2D geometry; (2) starting with no heat transfer (isothermal formulation) even though the physical situation is non-isothermal and therefore heat transfer will eventually need to be added; (3) starting with constant properties instead of properties varying with temperature or concentration, etc.

1.6 Geometry: setting the computational domain

The computational domain is the chosen region of the physical domain (actual geometry) where computations will be performed. Generally speaking, the larger the computational domain, the more computation is required. Thus, deciding on the computational domain is a very critical step in problem formulation. Although today's numerical methods can handle various shapes and sizes, and computers have significant speed and memory, prudent choices must be made in simplifying the actual geometry; otherwise meshing can be difficult or we can run into cpu speed and/or memory limitations.

In the example given in Figure 1.2, the geometry can have several possibilities, as shown in Figure 1.6. Depending on the geometry chosen, the amount of computation increases dramatically, but the question we have to answer is: are we learning anything new as we move from 1D to 3D? If we think of the 3D geometry in terms of r, θ and z directions, it seems reasonable to assume that most of the diffusion of H_2O_2 will be in the r direction (since the boundary concentration is uniform in the θ and z directions, respectively). Thus, a 1D computation, as shown in Figure 1.6(c), should suffice. Sometimes, however, the software does not allow a 1D geometry. In this case, the 2D geometry can be made to represent a 1D physics