Mathematical Biology: Modeling and Analysis

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Preface

Mathematical biology is a fast growing field which is concerned with problems that arise in biology. The aim is to address biological questions using mathematics. The mathematical models that are used to address these questions depend in the specific biological context. They include dynamical systems, probability, statistics and discrete mathematics. The approach in addressing a biological question is to develop a mathematical model that represents the biological background needed in order to address the question, show that simulations of the model are in agreement with known biological facts, and, finally, provide a solution to the original question. This approach to mathematical biology was carried out in two recent books: "Introduction to Mathematical Biology", by C-S Chou and A. Friedman (Springer-2016) and "Mathematical Modeling of Biological Processes" by A. Friedman and C-Y Kao (Springer-2014). Each of these books was based on a one semester course (the first one for undergraduate students and the second for Master's students) taught over several years at The Ohio State University in Columbus, Ohio. Each of the books included MATLAB simulations and exercises. The present monograph considers biological processes which are described by systems of partial differential equations (PDEs). It focuses on modeling such processes, not on numerical methods and simulations. On the other hand it also includes results in mathematical analysis of the mathematical models, or of their simplified versions, as well as many open problems.

The monograph is addressed primarily to students and researchers in the mathematical sciences who do not necessarily have any background in biology, and may have had only little exposure to PDEs. We have included in an Appendix a 'short course' in PDEs in order to familiarize the reader with the mathematical aspects of the models which appear in the book. The first chapter introduces the basic biology that will be used in the book. The second chapter introduces the basic blocks in building models, for example how to express the fact that a ligand activates an immune cell. The third chapter gives several simple examples of models on population dynamics. The fourth chapter develops two models of cancer. The choice of parameters in the cancer models, as in all other PDE models, is critically important if the models are to have a predictive value. In Chapter 5, we illustrate how to estimate the parameters of the first cancer models of Chapter 4 using both experimental data and some 'reasonable' assumptions.

Chapter 6 describes mathematical results inspired by cancer models, including stability of spherical tumors and symmetry breaking bifurcations, and it also suggests many open problems.

Chapter 7 addresses the question of the risk of atherosclerosis associated with cholesterol levels. The model develops a system of PDEs that describe the growth of a plaque in the artery. Chapter 8 describes mathematical results and open problems for a simplified model of plaque growth. Chapters 9 and 10 follow the format of Chapters 7 and 8: Chapter 9 develops a model of wound healing, and Chapter 10 describes mathematical results and open problems associated with this model.

Almost all the PDE models introduced in this book are free boundary problems, that is, the domain where each PDE system holds is unknown in advance, and its boundary has to be determined together with the solution to the PDE system.

It is our hope that this monograph will demonstrate to the reader the challenges and excitement, and the opportunities for research at the interface of mathematics and biology.

It is finally my pleasure to express my thanks and appreciation to Dr. Xiulan Lai for typing the manuscript and drawing all the figures.

Contents

Mathematical Biology: Modeling and Analysis

Description of Lectures

Professor Avner Friedman will give 10 lectures on Mathematical Biology. Modeling and Analysis. The 10 lectures are aimed at mathematics graduate students and faculty members with basic background in ordinary and partial differential equations (ODEs and PDEs): no previous knowledge of biology is required. The aim of the 10 lectures is to introduce the attending participants and students to basic concepts and knowledge of biology, and to demonstrate by examples how to formulate interesting biological research questions, and how to address these questions using mathematics.

The first two lectures will introduce the biological background and the biological expressions of biological interactions that will be used in the remaining eight lectures. In the subsequent lectures, we shall present biological research questions and develop mathematical models to address these questions. We shall also describe rigorous mathematical results inspired by the models, and present open research problems.

Lecture 1. Introductory Biology

Description of the structure of a cells, the different types of cells, what is the functions of cells and how they perform their tasks. In particular, we focus on cells of the immune system. Concepts such as proteins, cytokines, chemotaxis, receptors, etc. will be explained.

Lecture 2: Building blocks of mathematical models

A mathematical model is developed in order to address a biological question. The model should include all the biological species which are needed to address the biological question, but otherwise it, should be minimal. The relations among these species are based on physical and biochemical laws.

We shall explain the concept of enzyme dynamics, derive the Michaelis-Menten and Hill laws. We shall show how to express mathematically the fact that "a cell X produces cytokine Y," or that "a cytokine Z inhibits the production of Y by X." the concepts of "logistic growth" and "chemo attractive force" will be defined, and advection-diffusion equations will be introduced.

Lecture 3: Models of population dynamics

Many biological processes are concerned with populations of cells, but not with what happens within the cells. An example is the harvesting of bacteria a chemostat. The chamber of the chemostat contains bacteria and nutrients, and the bacteria feed on the nutrients and keep multiplying. At one side of the chamber there is influx of nutrients and at the opposite side there is outflow of mixture of bacteria and unused nutrients. A mathematical model will address the following question: How do we adjust the rate of inflow/outflow in order to maximize the bacteria output?

Epidemiology is the study of patterns, causes, and effects of health and disease in a population. Of particular interest is the spread of infectious diseases in a population. The simplest example is the SIR model of susceptible, infected, and recovered populations. We shall develop a mathematical model of SIR and use it to determine whether an initial infection in a population will spread or die out.

Another completely different biological question arises when two species compete for resources or space. For example, consider cancer cells and normal healthy cells in a tumor region. The cancer cells proliferate faster than normal cells, but they are partially killed by immune cells. The question is whether the tumor will grow or shrink, and this will be formulated as a mathematical model.

Lecture 4: Mathematical models of cancer

A solid tumor, or cancer, is an abnormal new growth of tissue that has no physiological function. Cancer initiates when normal healthy cells undergo mutation and they begin to divide abnormally fast. There are different types of cancer, depending on the location of origin. Cancer treatment includes surgery, radiation and drugs (chemotherapy). Here, we focus on a specific drug.

We shall develop a mathematical model of cancer by a system of PDEs which includes enough variables (cells and cytokines) in order to determine how effective the drug is.

Lecture 5: How to estimate model parameters
In Lecture 4, we encountered systems of PDEs, but in order to simulate the models, we need to determine all the parameters, which appear in the equations.

In this lecture we shall illustrate how to estimate all the parameters which appeared in the tumor model of Lecture 4. Several methods will be used and several underlying assumptions will be made.

Lecture 6. Mathematical analysis inspired by cancer models
Mathematical models of biological processes include simulations. But we would also like to develop rigorous mathematical analysis for the models. However, typically we can do it only for simplified models. In this lecture we consider a very special case of spherical tumor and state theorems on the stability of the spherical tumor, and on the existence of non-spherical branches of tumors which bifurcate from the spherical tumor.

Many open problems will be described.

Lecture 7: A mathematical model of atherosclerosis and the risk of high cholesterol
Atherosclerosis is a disease in which a plaque grows inside an artery that may eventually cause a heart attack or a stroke. It is the leading cause of death in the United States. Cholesterol is a protein that lines up the membrane of cells; these proteins are produced in the liver, packaged by lipoproteins, and then shipped to the cells through the blood circulation. There are low density lipoproteins (LDL) and high density lipoproteins (HDL). If the inner layer of an artery incurs a damage, the cholesterols enter into the inner layer of the artery and become oxidized, initiating the process of plaque growth.

In this lecture we develop a mathematical model of plaque formation, and use it to develop a color "risk map" in the (L_0, H_0)-plane, where L_0 and H_0 are the LDL and HDL levels in the blood, and the color shows the growth (or decrease) of a small plaque once formed in the artery.

Lecture 8: Mathematical analysis inspired by the atherosclerosis model
We develop a simplified model of plaque formation consisting of only 4 variables: LDL, HDL, macrophages and foam cells ('obese' macrophages). We prove mathematically that there exists small stable plaques, and determine their stability.

However, the geometry of the artery is highly simplified, and many mathematical questions are open.

Lecture 9: Mathematical models of chronic wounds
Chronic wounds represent a major public health problem. Ischemia, primarily caused by damage to the capillary system, presents a major complication in cutaneous would healing. One of the approaches to treat ischemic wounds is to surround the wound with oxygen rich environment, so that cells which move into the wound microenvironment in order to heal the wound receive the oxygen they need for their survival and function. In order to determine optimal schedules for the oxygen treatment (how often and at what pressure) we develop a mathematical model

The model variables satisfy a system of PDEs in the healing tissue. The model predictions agree with experimental results, and the model can be used to determine the state of healing for different oxygen treatments.

Lecture 10: Mathematical analysis inspired by the chronic wound model
We first consider a flat symmetric wound. We shall show that if the flux of oxygen into the wound is too small, the wound will not heal, and its radius will not decrease after some time. The interesting open problem, mathematically, is to prove that, if treated with enough oxygen, the wound will heal. (This has been shown in simulations.)

We also consider a 3-d wound and the question: would the wound start to heal for at least a small time? This is also an open mathematical question.

Appendix: Introduction to PDEs

A.1. Elliptic equations

The **Laplace operator** in $\mathbb{R}^n$ in defined as follows:

$$\nabla^2 = \triangle = \sum_{j=1}^{n} \frac{\partial^2}{\partial x_j^2}.$$

Consider the following **boundary value problem** (BVP) for a function $u(x)$ in a bounded domain Ω with boundary $\partial\Omega$:

$$\triangle u = f(x) \quad \text{in } \Omega, \tag{A.1}$$

$$\beta \frac{\partial u}{\partial n} + (1-\beta) u = g(x) \quad \text{on } \partial\Omega \tag{A.2}$$

where $0 \leq \beta \leq 1$, $\partial/\partial n$ is the derivative in the direction of the outward normal $\vec{n}$, and f and g are given functions. We refer to the system (A.1)-(A.2) with the boundary conditions $\beta = 0$, $\beta = 1$ and $0 < \beta < 1$ as the **Dirichlet problem**, the **Neumann problem** and the **Robin problem**, respectively, or as the first, second and third BVPs, respectively.

If $0 \leq \beta < 1$ then the system (A.1)-(A.2) cannot have more than one solution. Indeed, if u_1 and u_2 are two solutions then their difference $v = u_1 - u_2$ satisfies the homogeneous system

$$\triangle v = 0 \text{ in } \Omega, \quad \beta \frac{\partial v}{\partial n} + (1-\beta) v = 0 \text{ on } \partial\Omega.$$

By integration by parts,

$$\begin{aligned} 0 = \int_\Omega v \triangle v = \int_\Omega v \nabla \cdot \nabla v = \int_\Omega (\nabla \cdot v \nabla v - \nabla v \cdot \nabla v) \\ = \int_{\partial\Omega} v \nabla v \cdot \vec{n} - \int_\Omega |\nabla v|^2 \end{aligned} \tag{A.3}$$

and

$$\nabla v \cdot \vec{n} = \frac{\partial v}{\partial n} = -\frac{1-\beta}{\beta} v \quad \text{if } 0 < \beta < 1.$$

Hence

$$\frac{1-\beta}{\beta} \int_{\partial\Omega} v^2 + \int_{\Omega} |\nabla v|^2 = 0$$

so that $v \equiv 0$ in Ω if $0 < \beta < 1$. If $\beta = 0$ then $v = 0$ on $\partial\Omega$, and, by (A.3),

$$\int_{\Omega} |\nabla v|^2 = 0,$$

and again $v \equiv 0$ in Ω. We conclude that $u_1 \equiv u_2$.

In case $\beta = 0$ (the Neumann problem) we can only conclude from (A.3) that $v \equiv$ constant, so that the solution is unique up to an additive constant.

An **elliptic operator** of the second order has the form

$$L = \sum_{i,j=1}^{n} a_{ij}(x) \frac{\partial^2}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_i(x) \frac{\partial}{\partial x_i} + c(x) \tag{A.4}$$

where $a_{ij}(x) = a_{ji}(x)$ and $(a_{ij}(x))$ is a uniformly positive definite matrix,

$$\sum_{i,j=1}^{n} a_{ij}(x)\xi_i\xi_j \geq \gamma|\xi|^2 \quad \text{for all } x \in \Omega,\ \xi = (\xi_1, ..., \xi_n) \in \mathbb{R}^n \tag{A.5}$$

where γ is a positive constant. Similarly to the BVP (A.1)-(A.2) we define the BVP for the elliptic operator L by the equation

$$Lu(x) = f(x) \quad \text{in } \Omega \tag{A.6}$$

and the boundary condition

$$\beta \frac{\partial u}{\partial N} + (1-\beta)u = g \quad \text{on } \partial\Omega, \tag{A.7}$$

where

$$\frac{\partial u}{\partial N} = \sum_{i,j=1}^{n} a_{ij}(x) n_i \frac{\partial u}{\partial x_j}$$

and $\vec{n} = (n_1, n_2, ..., n_n)$ is the outward normal to $\partial\Omega(t)$. Note that $\frac{\partial}{\partial N}$ is a derivative in an outward direction, and $\partial u/\partial N = \partial u/\partial n$ when $L = \triangle$.

To prove uniqueness of the solution we shall use the following **maximum principle**.

Theorem A.1. *Assume that the coefficients $a_{ij}(x)$, $b_i(x)$, $c(x)$ are bounded functions, that (A.5) holds, and that $c(x) \leq 0$ for $x \in \Omega$. If $v(x)$ is a continuous function in $\overline{\Omega}$,*

$$v(x) \not\equiv \text{constant}, \quad \text{and} \quad -Lv(x) \leq 0 \text{ in } \Omega$$

then $v(x)$ cannot take a positive maximum in $\overline{\Omega}$ at any point x_0 of Ω; furthermore, if the positive maximum is attained at a point $x_0 \in \partial\Omega$, then

$$\frac{\partial u(x_0)}{\partial N} > 0.$$

To prove the first assertion, we assume that

$$\max_{x \in \overline{\Omega}} v(x) = v(x_0) > 0 \quad \text{for some } x_0 \in \Omega.$$

Then

$$\frac{\partial v}{\partial x_i}(x_0) = 0 \quad \text{and} \quad \sum_{i,j=1}^{n} a_{ij}(x_0) \frac{\partial^2 v(x_0)}{\partial x_i \partial x_j} \leq 0,$$

so that

$$-Lv(x_0) \geq -c(x_0)v(x_0) > 0 \quad \text{if } c(x_0) < 0,$$

which contradicts the assumption that $-Lv(x) \leq 0$ in Ω. If however $c(x_0) = 0$ then there is no contradiction, and in this case a much deeper argument (for details see, for instance, [8]) shows that $v \equiv$ constant in Ω, which is a contradiction to the assumption that $v \not\equiv$ constant.

The second assertion of the maximum principle, with the strict inequality $\frac{\partial u(x_0)}{\partial N} > 0$, requires the same type of argument used in the case where $c(x_0) = 0$ [8].

Theorem A.2. *If the coefficients of the elliptic operator (A.4) are bounded functions and $c(x) \leq 0$ in Ω, then the BVP (A.6)-(A.7) has at most one solution if $0 \leq \beta < 1$; if $\beta = 1$ then a solution is unique up to an additive constant.*

Proof. If u_1, u_2 are two solutions, then the difference $v = u_1 - u_2$ satisfies the homogeneous equation $Lv = 0$ in Ω, and the boundary condition

$$\beta \frac{\partial v}{\partial N} + (1 - \beta)v = 0 \quad \text{on } \partial\Omega. \tag{A.8}$$

Suppose $v \not\equiv$ constant. Then by the maximum principle, if v takes positive values in $\overline{\Omega}$ then its positive maximum can be attained only at boundary points. At one such point x_0, $\frac{\partial v}{\partial N}(x_0) > 0$ so that

$$\beta \frac{\partial v}{\partial N}(x_0) + (1-\beta)v(x_0) > 0,$$

which is a contradiction to Eq. (A.8). Hence if $v \not\equiv$ constant, then $v \leq 0$, and similarly $-v \leq 0$, so that $v \equiv 0$, a contradiction. We conclude that $v \equiv$ constant and then, from Eq. (A.8) it follows that $v \equiv 0$ if $0 \leq \beta < 1$.

We now turn to the question of existence. We begin with some definitions.

A function $w(x)$ is said to be **Hölder continuous** with exponent α $(0 < \alpha < 1)$ in a domain Ω if

$$H_{\alpha,\Omega}(w) \equiv \sup_{\substack{x,y\in\Omega \\ x\neq y}} \frac{|w(x)-w(y)|}{|x-y|^\alpha} < \infty.$$

We introduce the following norms:

$$|w|_{C^\alpha(\Omega)} = |w|_{L^\infty(\Omega)} + H_{\alpha,\Omega}(w),$$

and, more generally,

$$|w|_{C^{m+\alpha}(\Omega)} = \sum_{k=0}^{m} |D^k w|_{L^\infty(\Omega)} + H_{\alpha,\Omega}(D^m w),$$

where $D^k w$ is the vector whose components are all the partial derivatives of order k of w. We denote by $C^{m+\alpha}(\Omega)$ the Banach space of functions w with norm $|w|_{C^{m+\alpha}(\Omega)}$.

We make the following assumptions:

$$a_{ij}, b_i, c \text{ and } f \text{ belong to } C^\alpha(\Omega),\ (A.5) \text{ holds, and } c(x) \leq 0 \text{ in } \Omega; \tag{A.9}$$

$$\begin{aligned}&\text{the boundary } \partial\Omega \text{ can be represented locally by functions}\\ &x_j = \Phi_j(x_1, .., x_{j-1}, x_{j+1}, ..., x_n) \text{ (for some } j) \text{ which belong}\\ &\text{to } C^{2+\alpha}, \text{ and } g(x) \text{ is in } C^{2+\alpha} \text{ in these local coordinates.}\end{aligned} \tag{A.10}$$

Theorem A.3. *If the assumptions (A.9), (A.10) hold and $0 \leq \beta < 1$ then there exists a unique solution u of the BVP (A.6), (A.7), which belongs to $C^{2+\alpha}(\Omega)$.*

One can prove the theorem first for the special case of the Laplace operator, and then use a method of continuity to prove the theorem for

$$L_\theta = (1-\theta)\triangle + \theta L, \quad 0 \le \theta \le 1,$$

starting from $\theta = 0$ and ending at $\theta = 1$. The tool to accomplish this procedure relies on $C^{2+\alpha}$ *a priori* estimates for elliptic equations; for details see [8].

In the case of the Neumann BVP ($\beta = 1$) f and g must satisfy a specific condition in order for a solution u to exist. For example, when $L = \triangle$, then by integration,

$$\int_\Omega f = \int_\Omega \triangle u = \int_{\partial\Omega} \frac{\partial u}{\partial n} = \int_{\partial\Omega} g,$$

so that $\int_{\partial\Omega} g$ must be equal to $\int_\Omega f$.

A.2 Parabolic equations

We introduce a **parabolic operator** $\frac{\partial}{\partial t} - L$ in a domain $\Omega_T = \{(x,t); x \in \Omega(t),\ 0 < t < T\}$, where

$$L = \sum_{i,j=1}^{n} a_{ij}(x,t)\frac{\partial^2}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_i(x,t)\frac{\partial}{\partial x_i} + c(x,t), \tag{A.11}$$

$$\sum_{i,j=1}^{n} a_{ij}(x,t)\xi_i\xi_j \ge \gamma|\xi|^2 \quad \text{for all } (x,t) \in \Omega_T \text{ and } \xi \in \mathbb{R}^n, \tag{A.12}$$

where $\gamma > 0$ and $a_{ij} = a_{ji}$. We consider the **initial-boundary value problem** (IBVP) for a function $u(x,t)$:

$$\frac{\partial u}{\partial t} - Lu = f(x,t) \quad \text{in } \Omega_T, \tag{A.13}$$

$$\beta\frac{\partial u}{\partial N} + (1-\beta)u = g(x,t) \quad \text{on lateral boundary } \partial_0\Omega_T = \{(x,t);\ x \in \partial\Omega(t),\ 0 < t < T\}, \tag{A.14}$$

$$u(x,0) = h(x) \quad \text{on } \Omega(0) \tag{A.15}$$

where $0 < T \le \infty$, $0 \le \beta \le 1$,

$$\frac{\partial u}{\partial N} = \sum_{i,j=1}^{n} a_{ij}(x,t)n_j\frac{\partial u}{\partial x_i},$$

and $\vec{n} = (n_1, ..., n_n)$ is the outward normal to the boundary $\partial\Omega(t)$ of $\Omega(t)$. Eq. (A.13) is also called a **diffusion equation**.

Analogously, to Theorem A.1, the maximum principle for parabolic equations asserts the following:

Theorem A.4 *Assume that the coefficient a_{ij}, b_i, c are bounded in Ω_T, $T < \infty$, that (A.13) holds, and that $c(x,t) \leq 0$ in Ω_T. If*

$$\frac{\partial u}{\partial t} - Lu \leq 0 \quad \text{in } \Omega_T,$$

and if u takes its positive maximum in $\overline{\Omega_{t_0}}$ at some point (x_0, t_0) where $x_0 \in \Omega(t_0)$, $0 < t_0 \leq T$, then $u(x,t) \equiv u(x_0,t_0)$ for all points (x,t) for which there is a curve $(\xi(\tau),\tau)$ with $t \leq \tau \leq t_0$ such that

$$\xi(\tau) \in \Omega(\tau) \quad \text{for } \; t \leq \tau < t_0, \quad \text{and } \; \xi(t) = x, \quad \xi(t_0) = x_0.$$

If, on the other hand, $x_0 \in \partial\Omega(t_0)$ and $\frac{\partial u}{\partial N}(x_0,t_0) = 0$ then the same assertion holds.

This theorem can be used to prove uniqueness of the IBVP. We note that the condition $c \leq 0$ is not needed for the proof of uniqueness. Indeed, if we set $u = e^{\lambda t} w$ then the parabolic problem for u becomes a parabolic problem for w with different f and g, and with $c(x,t)$ replaced by $c(x,t) - \lambda$, and we simply choose λ such that $c(x,t) - \lambda \leq 0$ in Ω_T. From Theorem A.4 with u replaced by $-u$ we conclude the following:

Theorem A.5. *Consider the IBVP (A.13)-(A.15). If $f \geq 0$ in Ω_T, $g \geq 0$ in $\partial_0\Omega_T$ and $h \geq 0$ in $\Omega(0)$, then $u \geq 0$ in Ω_T.*

We introduce the following notation.

$$H_{\alpha,\Omega_T}(w) = \sup_{\substack{(x,t),(y,s)\in\Omega_T \\ (x,t)\neq(y,s)}} \frac{|w(x,t) - w(y,s)|}{|x-y|^\alpha + |t-s|^{\alpha/2}},$$

$$|w|_{C^{\alpha,\alpha/2}}(\Omega_T) = |w|_{L^\infty(\Omega_T)} + H_{\alpha,\Omega_T}(w),$$

$$|w|_{C^{2+\alpha,1+\alpha/2}}(\Omega_T) = |w|_{L^\infty(\Omega_T)} + \sum_{j=1}^{2} |D_x^j w|_{C^{\alpha,\alpha/2}(\Omega_T)} + |w_t|_{C^{\alpha,\alpha/2}(\Omega_T)}$$

where $D_x^j w$ is the vector whose components are all the j-th order derivatives of w with respect to the variables $x_1, ..., x_n$.

To prove existence of solutions of the IBVP we need to make assumptions similar to (A.9),(A.10):

$$a_{ij}, b_i, c \text{ and } f \text{ belong to } C^{\alpha,\alpha/2}(\Omega_T); \tag{A.16}$$

the lateral boundary $\partial_0\Omega_T$ can be represented in local coordinates by

functions $x_i = \Phi_j(x_1, ..., x_{j-1}, x_{j+1}, ..., x_n, t)$ which belong to $C^{2+\alpha,1+\alpha/2}$, (A.17)

and $g(x,t)$ belongs to $C^{2+\alpha,1+\alpha/2}$ in these local coordinates;

$h(x)$ belongs to $C^{2+\alpha}(\Omega(0))$ and satisfies the following compatability condition:

There exists a $C^{2+\alpha,1+\alpha/2}(\Omega(t_0))$ function, for some $t_0 > 0$, which statisfies (A.18)

(A.14) on $\partial_0\Omega_{t_0}$ and coincides with h in an $\Omega(0)$-neighborhood of $\partial\Omega(0)$.

Theorem A.6. [8] *If the assumptions (A.12) and (A.16)-(A.18) hold then there exists a unique solution of the IBVP (A.13)-(A.15) which belongs to* $C^{2+\alpha,1+\alpha/2}(\Omega_T)$.

A.3. Nonlinear equations and systems

Consider the case where in the BVP (A.6),(A.7) f is a nonlinear function of u and Du:

$$f = f(x, u, Du). \tag{A.19}$$

To prove uniqueness we take the difference $v = u_1 - u_2$ between two solutions u_1, u_2 and derive for v a linear equation with coefficients which involve $u_i(x)$, $Du_i(x)$ $(i = 1, 2)$, and then apply the maximum principle. To prove existence we use an iteration method, or a fixed point theorem:

We take any function $\tilde{u}$ in $C^{2+\alpha}(\Omega)$, set

$$f(x) = f(x, \tilde{u}, D\tilde{u}),$$

and define u as the solution of (A.6),(A.7) for this $f(x)$. We then consider the mapping $W : \tilde{u} \to u$ in an appropriate closed subset of $C^{2+\alpha}(\Omega)$ and prove that it is a contraction mapping and hence has a unique fixed point, which is then the solution of (A.6),(A.7) for the function f given by (A.19). The proof that W is a contraction mapping can be carried out under some assumptions on f; for example, if $f(x, u, w)$ and its first derivatives are in C^α, and

$$|f(x, y, w)| \le A + \varepsilon(|u| + |w|)$$

where A, ε are positive constants and ε is sufficiently small.

The same procedures for uniqueness and existence apply to a parabolic IBVP with

$$f = f(x, t, u, D_x u);$$

in particular, one can prove that if f is any smooth function in all its variables then there exists a unique smooth solution in a small t-interval [8].

In models that arise in biology we do not have just one but several parabolic equations:

$$\frac{\partial u_k}{\partial t} - \sum_{i,j=1}^{n} a_{k,ij}(x,t)\frac{\partial^2 u_k}{\partial x_i \partial x_j} + \sum_{i=1}^{n} b_{k,i}(x,t)\frac{\partial u_k}{\partial x_i} + c_k(x,t)u_k = f_k(x,t,\vec{u}, D_x\vec{u}) \quad \text{in } \Omega_T, \tag{A.20}$$

with boundary and initial conditions

$$\beta_k \frac{\partial u_k}{\partial N_k} + (1-\beta_k)u_k = g_k(x,t) \quad \text{on } \partial_0\Omega_T, \tag{A.21}$$

$$u_k = h_k \quad \text{on } \Omega(0), \tag{A.22}$$

where $\frac{\partial u_k}{\partial N_k} = \sum_{i,j=1}^{n} a_{k,ij}(x,t) n_i \frac{\partial u_k}{\partial x_j}$, $0 \le \beta_k \le 1$, $k = 1, 2, ..., m$, and $\vec{u} = (u_1, ..., u_m)$; notice that the equations are coupled through the functions $f_k(x, t, \vec{u}, D_x\vec{u})$.

As in the case of one equation, existence and uniqueness can be proved for a small time interval.

In order to extend the solution to all of Ω_T, we need to establish *a priori* estimates of the following type:

If a solution $\vec{u} \in C^{2+\alpha, 1+\alpha/2}(\Omega_\tau)$ exists for some $0 < \tau < T$, then

$$|f_k(x,t,\vec{u}(x,t), D_x\vec{u}(x,t))|_{C^{\alpha,\alpha/2}(\Omega_\tau)} \le \Psi(\tau)$$

where $\Psi(\tau)$ is a bounded function in any interval $0 \le \tau \le T - \varepsilon$, $\varepsilon > 0$.

Since in biological models the u_k represent concentrations of species, it is important to establish that the u_k are positive, or at least non-negative, functions. This is the case under the following assumption:

$$f_k(x,t,\vec{u},D\vec{u}) = f_k^0(x,t,\vec{u},D\vec{u})u_k + f_k^1(x,t,\vec{u},D\vec{u})$$
$$\text{where } f_k^1(x,t,\vec{u},D\vec{u}) \geq 0 \text{ for any } \vec{u}, D\vec{u}, \;\; 1 \leq k \leq m. \tag{A.23}$$

Indeed, we can then join f_k^0 to c_k to obtain a system with $c_k - f_k^0$ instead of c_k, and then use the transformation

$$u_k = e^{\lambda t} w_k \quad \text{with } \lambda > c_k - f_k^0$$

for all k, as in the case of Theorem A.5. We thus have the following result:

Theorem A.7. *Let $\vec{u}$ be a solution in $C^{2+\alpha}(\Omega_T)$ of (A.20)-(A.22) such that (A.23) holds in Ω_T. If $g_k \geq 0$ on $\partial_0\Omega_T$ and $h_k \geq 0$ on $\Omega(0)$ for $k = 1, 2, ..., m$, then $u_k \geq 0$ in Ω_T for all $k = 1, ..., m$.*

In the mathematical models that we encounter in this book the parabolic systems have the following form:

$$\frac{\partial u_k}{\partial t} + \theta_k \nabla \cdot (\vec{V}_k u_k) - A_k \nabla^2 u_k = F_k(\vec{u}, D\vec{u}), \;\; 1 \leq k \leq m, \tag{A.24}$$

where $\vec{u} = (u_1, ..., u_m)$, $\theta_k \geq 0$, A_k are positive constants, and $\vec{V}_k$ is the velocity of species u_k. Equations of this form are called **advection-diffusion** equations. Such equations are based on the mass conservation law plus diffusion. The velocity $\vec{V}_k$ arise form internal pressure among the species, but they can also include chemotaxis.

As a result of this pressure the lateral boundary of Ω_T varies in time with velocity $\vec{V}$, that is, the velocity in the direction of the outward normal $\vec{n}$ is $\vec{V} \cdot \vec{n}$. Then the boundary conditions, dictated by both diffusion and conservation of mass, take the form

$$\beta_k \left(A_k \frac{\partial u_k}{\partial n} + \theta_k (\vec{V}_k - V) \cdot \vec{n} u_k \right) + (1 - \beta_k)(u_k - u_k^0) = 0 \tag{A.25}$$

where u_k^0 is the density of u_k from outside the boundary.

A.4. Free boundary problems

Most of the problems in this book are **free boundary problems**, where the PDE system needs to be solved in a domain whose boundary, or a portion of it, is not known. A very simple example of a free boundary problem is the **Stefan problem** which represents the melting of a thin block of ice, as shown in Fig. A.1.

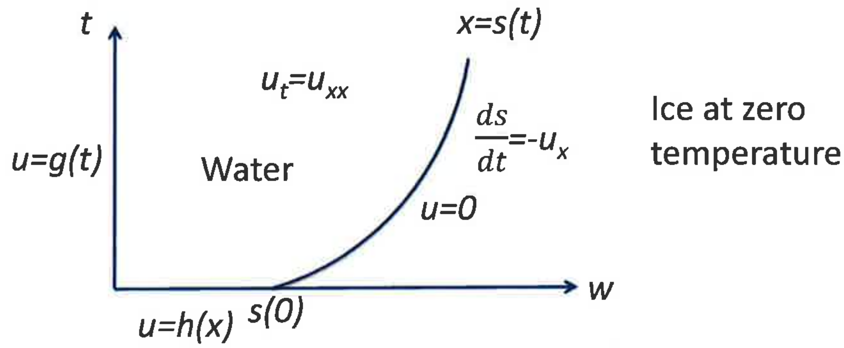

Fig. A.1. Melting of ice at zero temperature; $g(t) > 0$ for $t > 0$, $h(x) > 0$ for $0 < x < s(0)$. The ice occupies the interval $s(t) < x < \infty$.

By the maximum principle, $u > 0$ in the water region $\Omega_T = \{(x,t),\, 0 \le x < s(t),\, 0 < t < T\}$ and $u_x(s(t),t) < 0$, so that

$$\frac{ds(t)}{dt} > 0;$$

hence the free boundary $x = s(t)$ is strictly monotone increasing.

There are different methods to prove existence and uniqueness for the Stefan problem. One method uses a change variables,

$$y = \frac{x}{s(t)}, \quad v(y,t) = u(x,t)$$

to obtain a parabolic problem in a fixed domain:

$$\begin{aligned} &v_t - \frac{1}{s^2}v_{yy} + \frac{y\dot{s}}{s}v_y \quad \text{for } 0 < y < 1,\ t > 0, \\ &v(0,t) = g(t), \quad v(1,t) = 0 \quad \text{for } t > 0, \\ &v(y,0) = h(ys(0)) \quad \text{for } 0 < y < 1 \end{aligned} \tag{A.26}$$

where $\dot{s} = ds/dt$, together with

$$s(t)\dot{s}(t) = -v_y(1,t) \quad \text{for } t > 0, \\ s|_{t=0} = s(0). \tag{A.27}$$

We can then use a fixed point argument: Given any function $s(t)$ in $C^{1+\alpha}$ we solve the system (A.26) and define a new function $\tilde{s}(t)$ by

$$s(t)\frac{d\tilde{s}}{dt} = -v_y(1,t) \quad \text{and} \quad \tilde{s}(0) = s(0).$$

One can show that the mapping $s \to \tilde{s}$ is a contraction, in some subset of $C^{1+\alpha}(0, t_0)$, provided t_0 is small, and its fixed point is then the unique solution to the Stefan problem for $0 \leq t \leq t_0$.

To extend the solution to all $t > 0$ we need to establish an *a priori* bound on ds/dt and then proceed step-by-step to extend the local solution; details can be found in [8].

The above method extends to parabolic systems (as in A.24) where all the variables are radially symmetric, and the free boundary $r = R(t)$ is given by a law of the following form:

$$\frac{dR}{dt} = G(R, \vec{u}, D\vec{u})|_{r=R(t)}. \tag{A.28}$$

Here we make a change of variables

$$\bar{r} = \frac{r}{R(t)}, \quad v_k(\bar{r}, t) = u_k(r, t)$$

and derive a parabolic system for the v_k in the fixed domain $0 \leq \bar{r} < 1$, $0 < t < T$. For any function $R(t)$ we solve the system for the v_k and define a new function $\tilde{R}(t)$ by

$$\frac{d\tilde{R}}{dt} = G(R, \vec{v}, D\vec{v})|_{\bar{r}=1}, \quad \tilde{R}(0) = R(0).$$

One then shows that the mapping $R \to \tilde{R}$ has a unique fixed point. Simple numerical examples with MATLAB-based codes are given in [48].

Quite often the parabolic equations that occur in models of biological processes which involve cells and cytokines are based on conservation of mass, and the cells are moving with a common velocity $\vec{V}$, while also subject to diffusion. In such cases we assume that the free boundary is moving with the velocity $\vec{V}$ of the cells. The density ρ of the extracellular tissue where the cells are moving satisfies a conservation of mass equation,

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{V}) = f_\rho$$

with some function f_ρ. We do not prescribe boundary conditions for ρ since the free boundary is a characteristic surface, so that the values of ρ on the free boundary are determined from the values of ρ at $t = 0$ by solving an ODE for ρ along characteristic curves; see [48] for details.

We finally mention a special but a very important free boundary problem for a function u:

$$\Delta u = f(x, t) \quad \text{in } \Omega_T, \tag{A.29}$$

$$u = \gamma\kappa \quad \text{on } \partial_0 \Omega_T \ (\gamma > 0) \tag{A.30}$$

where κ is the mean curvature ($\kappa > 0$ when Ω is a sphere),

$$\Omega(t)|_{t=0} = \Omega(0) \text{ is prescribed,} \tag{A.31}$$

$$V_n = -\frac{\partial u}{\partial n} \tag{A.32}$$

where V_n is the velocity of the boundary points in the direction of the outward normal. The case $f \equiv 0$ is known as the **Hele-Shaw problem**. In this case the stationary solutions (i.e., solution with $V_n \equiv 0$) are spheres, since the equations

$$\Delta u = 0 \text{ in } \Omega \text{ and } \frac{\partial u}{\partial n} = 0 \text{ on } \partial\Omega$$

imply that $u \equiv$ constant, so that $\kappa \equiv$ constant, and therefore Ω is necessarily a sphere.

It is known that if $\Omega(0)$ is a smooth function, then there exists a smooth solution to the free boundary problem (A.29)-(A.32) for some interval $0 \leq t < t_0$, but the solution may not exists for all $t > 0$, even in the case where $f \equiv 0$. On the other hand, when $f \equiv 0$ and the boundary $\partial\Omega(0)$ is 'very close' to a sphere $r = R$, then there exists a unique solution for all $t > 0$ and its free boundary converges to a sphere $r = R_1$ as $t \to \infty$.