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Mathematical Analysis of Some Models for Drug Delivery

by

Vo Thi Ngoc Tuoi

A PhD thesis submitted to the School of Mathematics, Statistics and Applied Mathematics, National University of Ireland, Galway

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Abstract

This thesis is concerned with the mathematical modelling of controlled drug release from a number of delivery systems. There are two major strands to the work: (i) modelling release from affinity-based systems, and, (ii) modelling release from thermoresponsive films. A model that is related to the affinity models is also considered, and used to evaluate the effect of reversible binding on drug release in vivo.

In Chapter 1, the topic is introduced by briefly discussing some commonly used drug delivery systems and the mathematical models that have been developed to describe them. In Chapters 2 and 3, two affinity-based delivery systems composed of modified fibrin matrices are analysed. The model equations are reduced, and the non-dimensional parameters governing the release rate identified. For both models, a parameter regime that minimises the passive leakage of growth factor from the system is found. In Chapter 4, a reaction-diffusion model for drug redistribution in tissue is considered, and some generic problems to evaluate drug penetration and persistence in tissue are analysed.

In Chapter 5, a model for pulsatile drug release from the thermoresponsive polymer poly(N-isopropylacrylamide) is developed. Theoretical pulsatile release profiles are compared with experimental profiles generated by colleagues working at the National Centre for Biomedical and Engineering Sciences, and the correspondence between theory and experiment is found to be good. In Chapter 6, a mathematical model is developed to evaluate the feasibility of an in vivo implanted drug delivery system based on a thermoresponsive polymer and a cooling device, and it is found that the system may be realised for realistic parameter values and materials.

Finally, in Chapter 7, an evaluation of the modelling work of the thesis is presented, and strengths and weaknesses of some of the models are identified.
Declaration

The work presented in this thesis is my own, except for Chapters 5 and 6, where the work was carried out in collaboration with experimental scientists (Ms. Rongbing Yang and Dr. Yury Rochev) at the National Centre for Biomedical Engineering Science at NUI Galway. In these chapters, I developed the mathematical models, calculated the analytical and numerical solutions, and fitted the theoretical curves to the experimental data.

The material in this thesis has not been previously submitted for another degree at a degree granting institution.


1. Introduction

1.1. Motivation

A drug is defined as any substance that brings about a change in biological functioning through its chemical reactions \[130\]. There are multiple routes of drug administration: oral (used for small-molecule drugs such as aspirin, paracetamol or ibuprofen), injections (used for larger molecule drugs such as insulin), transdermal patches (nitroglycerin patches for treating angina), or controlled release implants which allow for long-term release (for example, contraceptive devices, cancer therapy, the delivery of protein drugs) \[143\].

Drug delivery systems are designed to deliver drug at a rate determined by the needs of the body over a specified period of time. When developing a drug delivery system, it is important to control the rate at which the drug is being released; too much of the drug at once can be harmful to the body, but too little of it may limit its effectiveness. The therapy is more effective if an optimal drug dose is delivered over an appropriate time period.

Pharmacology is the study of drugs and their actions. The two main branches of pharmacology are pharmacokinetics and pharmacodynamics \[114,130\]. The former is concerned with the effect of the body on the drug. Components of pharmacokinetic studies include drug metabolism, the mechanisms of drug transport, absorption, and elimination. In contrast, the latter is concerned with the effects of drugs on the body, and encompasses the molecular mechanisms of drug activity as well as dose-response relationships \[114,130,143\].

To improve the performance of drug delivery systems, traditional delivery systems have frequently been replaced by controlled release systems \[46,69,143,158\]. Controlled release systems often lead to a reduction in dosing frequency and can help eliminate the danger of overdosing. The usual goal of controlled
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drug delivery is the maintenance of drug concentration at a desired level in target tissues or cells for a prolonged period. Most local drug delivery systems aim to maintain the drug concentration at some appropriate therapeutic level for a specified period of time, and this objective is frequently achieved using sustained release dosage forms; see Figure 1.1 [14,62,92]. However, for some drugs, an optimum therapeutic effect comes from a periodically fluctuating drug concentration [70]. To realise such behaviour, pulsed or pulsatile drug release systems, which possess a cycle with two distinct release stages: on/fast release and off/slow release, have been developed [9,25,192]. The release duration time for the fast release stage is typically much shorter than that for the slow stage, but the release rate is usually much greater.

Mathematical modelling has the potential to be an important tool in facilitating product development in the pharmaceutical industry. Modelling can greatly assist in the design, operation and evaluation of drug delivery systems [46,156,158]. Employing a modelling approach can, for example:
1.1. Motivation

- aid in the design of a drug delivery system; it can be used to help determine the geometry, dimensions and composition of a system, as well as the initial drug loading concentration that should be chosen. It can assist in identifying the key parameters that control the drug release rate, and in estimating the expected life-time of a device [192]. We shall see in Chapter 5, for example, how a modelling approach was used to evaluate drug release from thermoresponsive polymer films.

- enable a schedule to be devised for when a pulsatile drug delivery system should be switched on and off for the delivery of appropriate drug doses at appropriate time intervals; see Chapter 5.

- assist experimentalists in the design of release experiments to evaluate drug release systems. The judicious use of mathematical modelling can decrease the number of experimental studies required to optimize existing or develop new drug products, thereby saving time and money [156].

In 1961, Professor Higuchi formulated the first mathematical model for drug delivery [51,156]. A simple equation was used to describe drug release from an ointment base exhibiting a considerable initial excess of dispersed drug within an inert film. Since then, numerous mathematical models have been developed [155,156]. Siepmann [156] argues that there are a number of useful guiding principles that should always be borne in mind when developing a mathematical model for a drug delivery system. The first is that when modelling a real system, especially one that is to be deployed in vivo, it is usually not possible or even useful to incorporate all of the various biological, chemical and physical processes that may be at work in the system. An all encompassing model would inevitably be large, and would contain a correspondingly large number of parameters, many of whose values may be uncertain. It can sometimes be difficult to obtain reliable quantitative predictions from a large model, and extracting useful qualitative information from such models is frequently not possible. It is often better to incorporate only the dominant processes at work in a system. Hence, for example, if amongst a number of processes, there is a very slow rate-limiting step, it may be that only this step need be considered in the modelling.
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Siepmann further argues that theoretical calculations should always be com-
pared with experimental data. The model parameters may first be estimated
by appropriately (156) fitting the model to experimental data. Once the
model parameters have been determined, the model may then be used to make
predictions as to how the system should behave if some of its properties are
altered. By then changing the properties of the system appropriately, and
comparing the resulting experimental results with the theoretical predictions,
a strong test of the validity of the model may be obtained.

In this study, some mathematical models for controlled drug delivery systems
are developed, described and analyzed. There are two major strands to this
thesis: (i) modelling the effect of reversible binding on drug delivery (Chapters
2, 3 and 4), and (ii) modelling drug release from thermoresponsive systems
(Chapters 5 and 6); see the thesis outline in Section 1.5.

![Diagram of drug delivery systems](image)

Figure 1.2. The two main types of nondegradable polymeric drug delivery devices:
(A) reservoir devices enclose a drug suspension within a polymer mem-
brane, and, (B) monolithic devices contain uniformly dispersed drug in
a polymer matrix [36,143].
1.2. Drug delivery systems

In this section, I discuss a number of drug delivery devices that have been developed to realise the goals outlined in the previous section, placing particular emphasis on systems that are considered in this thesis.

1.2.1. Polymeric systems

Many polymeric materials have been used in the construction of controlled drug delivery systems [141,143]. Polymers are particularly attractive materials for use in drug delivery because their technology is highly developed and chemists can synthesise polymers with desired properties [142]. The polymers that have been used in the fabrication of drug release devices to date have been variously degradable, nondegradable, swellable, nonswellable, and pulsatile [36,44,66,141,142,150,158]. The rate, pattern and duration of drug release for a specific therapeutic agent can frequently be controlled by selecting an appropriately designed polymer.

1.2.1.1. Nondegradable polymers

There are two broad classes of nondegradable polymer systems: reservoir systems and monolithic systems; see Figure 1.2 [36,143]. In a reservoir system, the drug is dissolved in a fluid suspension that is enclosed by a polymer membrane. In such systems, the release behaviour is controlled by the concentration of the enclosed drug and the transport properties of the drug molecules in the polymer membrane [156]. I shall discuss a simple mathematical model for such a system in Section 1.4.

Silicone elastomers and poly(ethylene-co-vinyl acetate) (EVAc) are the two most commonly used non-degradable polymers. Silicone elastomers were used to design the first controlled release polymeric systems. In 1964, researchers discovered that low molecular weight compounds could diffuse through the walls of silicone tubing at a controlled rate [142,143]. Reservoir drug delivery systems were developed as a result of this observation. When a hollow silicone tube is filled with a liquid suspension containing the drug of interest and
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then immersed in water, the drug is released from the system through the silicone wall via diffusion. Norplant® silicone-based devices, which provide reliable contraception for five years after implantation into the forearm, are one commercial example of the use of this technology. It was approved for use in the United States in 1990 after extensive testing in women around the world [49,142,143]. The Progestasert® intrauterine device, which has a controlled release EVAc coating, directly delivers contraceptive hormones to the female reproductive tract [49,142,143]. EVAc was also used in Ocusert® devices to deliver the drug pilocarpine to the surface of the eye in the treatment of glaucoma [142,143,158].

In a monolithic (or matrix) system, the drug molecules are dispersed throughout a polymeric material, and the drug molecules must diffuse through the polymer to the surface of the device in order to be released. Potent drugs are frequently delivered using such systems because even if the polymeric material fails (breaks), there will not be an ensuing rapid and dangerous release of drug.

A particularly important and interesting example of the use of nondegradable polymers in drug release is provided by drug-eluting stents (DES), and I discuss these in more detail now. Two first generation commercially available DESs are the Cypher® stent (reservoir) and the TAXUS Express® stent (monolithic) [17,89].

**Drug-eluting stents**

A stent is a small, lattice-shaped, metal tube that is typically placed in a diseased coronary artery to hold it open. Coronary arteries can become constricted due to a build up of atherosclerotic plaque. The stent is inserted into the constricted area on a balloon catheter, which is expanded and then removed, leaving the stent in place [17,89,93]. However, the insertion of the stent tends to cause injury to the artery wall, resulting in smooth muscle cell proliferation over the wall and re-blockage of the artery. This process is known as restenosis [15,17,78,89,93].
A drug-eluting stent (DES) is a standard stent that is coated with a polymer containing a drug that diffuses into its surroundings subsequent to deployment. The drug, which is usually an anti-proliferant, helps to prevent re-blockage of the artery due to restenosis. A DES has three principal components: a stent platform, a polymer coating and a drug. The drug is contained within the polymer coating and then diffuses into the arterial wall from the polymer source. In Figure 1.3, the deployment of a stent in a diseased coronary artery is schematically represented. The use of DESs for the prevention of restenosis after corrective surgery is now widespread [17,53,78,89]. The first DESs were designed with nondegradable polymer coatings; however, some of the newer DESs are manufactured with biodegradable polymer coatings [17,89].

### 1.2.1.2. Biodegradable polymers

Delivery systems composed of nondegradable polymers usually have to be surgically removed from the patient at the end of the therapy. Biodegradable polymers, however, are designed to slowly dissolve following implantation and surgery is not required. In biodegradable polymeric devices, the drug is released by the degradation and dissolution of the polymer matrix, or by the
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Figure 1.4. Biodegradable polymeric drug delivery devices: drug can be released by (A) erosion or degradation of the polymer matrix, or, by (B) cleavage of a covalent bond that binds the drug within the polymer matrix [143].

cleavage of a covalent bond that binds the drug within the polymer matrix; see Figure 1.4. Degradable systems have been shown to be capable of releasing drug at an approximately constant rate for an extended period. In pendant-chain systems, the drug molecules are bound to the main polymer chain via degradable covalent linkages. These linkages break down to release the drug as the polymer is exposed to water or chemical environments.

Many biodegradable polymers have been developed for use as materials in biomedical devices, examples being poly(lactide-co-glycolide) (pLGA), polyanhydrides, poly(orthoesters), and polyphosphazenes [142,143,158]. Biodegradable polymers used in drug delivery must induce no undesirable or harmful tissue responses, and the degradation products must be nontoxic [143,158]. To control the release of drugs from a degrading polymeric matrix, the degradation process must occur in a reproducible controlled manner. Small biodegradable polymeric microspheres can be manufactured as injectable delivery systems [143,158]. For example, Lupron Depot® devices contain injectable pLGA microspheres loaded with the drug leuprolide, and have been used for the
treatment of prostate cancer in humans. GLIADEL® wafers are made from a biodegradable polyanhydride polymer containing the chemotherapy drug carmustine, and they are commonly used to treat brain tumors in humans.

1.2.1.3. Swellable polymers

Figure 1.5. Hydrogels can undergo dramatic changes in conformation in response to external stimuli, such as a change in the temperature or pH of their environment. In the above, a polymer in an aqueous solution swells/collapses as its temperature or pH is varied across a critical value.

Swellable polymers are lightly cross-linked polymers that have been specifically designed to swell when exposed to water. They have been used as biomaterials in numerous biomedical applications. Hydrogels are swellable polymeric materials that can absorb large volumes of water. They are capable of exhibiting dramatic changes in their swelling behaviour, network structure, permeability or mechanical strength in response to external stimuli, such as a change in the temperature or pH of their environment; see Figure 1.5. Examples of hydrogels are poly(2-hydroxyethylmethacrylate) (pHEMA), poly(ethylene glycol) (PEG), poly(acrylic acid) and poly(vinyl alcohol). In a swellable drug delivery system, drug release is activated by the swelling action of the water which increases the rate of release; see Figure 1.6.
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![Swelling-controlled drug delivery systems](image)

Figure 1.6. Swelling-controlled devices incorporate drugs in a hydrophilic polymer that is condensed or glassy when dry, but swells and releases drug when exposed to water.

Thermoresponsive polymers (TRP) are members of a family of environment-sensitive hydrogels which undergo dramatic changes in conformation in response to a small change in temperature \[66,82\]. They can undergo temperature dependent phase transitions between an open porous hydrophilic state and a condensed, collapsed hydrophobic state. The temperature at which this transition occurs is known as the lower critical solution temperature (LCST). As the temperature rises above the LCST, hydrophobic interactions increase, leading to a collapse of the polymer and a loss of water solubility. Below the LCST, the polymer swells and absorbs water \[66\]. By exploiting this special property, thermoresponsive hydrogels have been used to obtain on-off drug release profiles in response to temperature changes \[9,25,192\].

Poly(N-isopropylacrylamide) (pNIPAm) is by far the best known thermoresponsive polymer, and it has been extensively studied \[81,82,196\]. PNIPAm-based polymers possess a LCST in aqueous solution near physiological temperature (37°C) \[50,195\], below which they are hydrophilic and absorb water to become swollen, and above which they are hydrophobic and expel water to become dense and dry \[66\]. Their LCST can be varied by copolymerization with an appropriate amount of hydrophilic or hydrophobic monomer \[66,82,108\].

In this thesis, a mathematical model has been developed for the first time to describe pulsatile drug release from thin pNIPAm films; see Chapter 5.
1.2.2. Affinity-based delivery systems

Affinity-based delivery systems immobilize drugs within a matrix via non-covalent interactions, and allow for the release rate to be controlled by both binding and diffusion mechanisms \[90, 137, 168, 178, 185, 188, 189\]. An early example of an affinity system is provided by the heparin-based delivery system developed by Edelman \[33\]. In this system, basic fibroblast growth factor (bFGF) binds electrostatically to heparin molecules that coat sepharose beads. The heparin molecules protect the growth factor from denaturation and proteolytic degradation, and regulate their rate of release.

Microcapsule-based delivery systems provide another example of an affinity-based system. They were developed by Wissink \[187\] using heparinized collagen matrices. In this system, bFGF was immobilized within the collagen matrices to enhance endothelial cell proliferation and reduce the minimum cell seeding density required for proliferation.

Benoit \[13\] have developed a system in which heparin was copolymerized with dimethacrylated poly(ethylene glycol) (PEG) to produce hydrogels that can localize bFGF. Pike \[121\] have described a system in which heparin was modified with thiol groups and then cross-linked with hyaluronan, gelatin, and poly (ethylene glycol) diacrylate (PEGDA) to yield hydrogels that can sequester bFGF or vascular endothelial growth factor (VEGF). Heparin-based affinity systems have also been used to stabilize growth factors within collagen matrices \[148\]. Such systems have been shown to help prevent loss of growth factor activity both \textit{in vitro} and \textit{in vivo}.

In this study, a heparin-based delivery system developed by Sakiyama-Elbert & Hubbel \[137\] is analyzed in detail. This system consists of four components: fibrin, synthetic linker peptide, heparin and heparin-binding growth factor; see Figure 1.7. The peptide contains a domain which covalently cross-links to the fibrin matrix and a domain that can bind to heparin. Heparin bound in this way can in turn bind to heparin-binding growth factor. Hence, the growth factor is sequestered within the fibrin matrix via heparin-binding affinity. The system has been used to deliver several growth factors, including basic fibroblast growth factor (bFGF), nerve growth factor (NGF), neurotrophin-3
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Figure 1.7. A schematic representation of a fibrin matrix containing the six species of the model considered in Chapter 2.

(NT-3), and glial-derived neurotrophic factor (GDNF) [137,168,185,188,189].

However, heparin-based delivery systems are not optimal for controlled release of growth factors that have a weak binding affinity for heparin. This limits the proteins that can be delivered using these systems. Willerth et al. [184] have developed a growth factor delivery system that exploits the ability of some peptides to bind directly with growth factors with high affinity. The growth factor is immobilized within the fibrin matrix via direct binding to peptide which has been covalently cross-linked to the matrix. This system is analyzed in detail in Chapter 3.

1.3. Modelling drug redistribution

In this section, I shall briefly sketch how some important mechanisms for drug redistribution in materials (fluids, tissues, polymers, for example) are modelled mathematically. The models described here, and throughout this thesis, are continuous and usually consist of a single partial differential equation, or a system of partial differential equations. This is quite a large topic, and it is not feasible to discuss it fully here; more detailed and comprehensive treatments of these issues can be found in [141,156]. I shall focus instead here on those aspects of the modelling that are particularly relevant to the work.
of this thesis. The emphasis in this section will be on general principles and mechanisms, rather than on particular drug delivery systems. In the next section, successful mathematical models for some specific drug delivery systems will be described. I begin by considering a single species model that tracks the evolution of the concentration of a drug in space and time.

1.3.1. A scalar convection-reaction-diffusion equation

I denote by \( c(r, t) \) the concentration of drug in a material at location \( r \) and time \( t \). Consider a fixed volume \( \Omega \) of the medium enclosed by a (sufficiently smooth) boundary \( \partial \Omega \). We denote by \( J(r, t) \) the flux of drug per unit area per unit time at \( (r, t) \), and by \( \psi(r, t) \) the amount of drug produced (sources) or eliminated (sinks) at \( (r, t) \) per unit volume per unit time. Conservation of drug mass then implies that:

\[
\frac{d}{dt} \int_\Omega c dV = - \int_{\partial \Omega} J \cdot n da + \int_\Omega \psi dV, \quad (1.1)
\]

where \( dV \) is a volume element of \( V \), \( da \) is a surface area element of \( \partial \Omega \), and \( n \) is an outward unit normal to \( \partial \Omega \). Applying the divergence theorem to the first term on the right hand side of (1.1) leads to:

\[
\int_\Omega \left( \frac{\partial c}{\partial t} + \nabla \cdot J - \psi \right) dV = 0,
\]

and since \( \Omega \) was arbitrarily chosen (apart from \( \partial \Omega \) being sufficiently smooth for
1. Introduction

the divergence theorem to apply), we arrive at the following partial differential equation:

$$\frac{\partial c}{\partial t} + \nabla \cdot \mathbf{J} = \psi. \quad (1.2)$$

In many applications involving drug delivery, \( \mathbf{J} \) may be decomposed into two components:

$$\mathbf{J} = \mathbf{J}_{\text{diff}} + \mathbf{J}_{\text{con}}, \quad (1.3)$$

where \( \mathbf{J}_{\text{diff}} \) is the diffusive flux, which models the motion of drug molecules due to gradients in their drug concentration profile, and \( \mathbf{J}_{\text{con}} \) is the convective flux, which accounts for the movement of drug due to bulk motion of the carrying medium. The convective contribution for dilute drug concentrations is given simply by:

$$\mathbf{J}_{\text{con}} = \mathbf{v}c, \quad (1.4)$$

where \( \mathbf{v} \) is the velocity of the carrying medium. In some circumstances, \( \mathbf{v} \) may need to be solved for as part of the solution to a problem, although this does not arise in the work of this thesis.

The form for \( \mathbf{J}_{\text{diff}} \) depends on the character of the medium in which the drug molecules are diffusing. The simplest possible case is that of a homogeneous isotropic medium. For such materials, \( \mathbf{J}_{\text{diff}} \) may frequently be adequately described by a constitutive law of the form:

$$\mathbf{J}_{\text{diff}} = -D \nabla c, \quad (1.5)$$

where \( D \) is a constant called the diffusivity of the material. This equation is sometimes referred to as Fick’s first law [26]. For inhomogeneous isotropic materials, \( D \) depends on location, so that \( D = D(r) \). For inhomogeneous anisotropic materials, \( D \) must be replaced by a \( 3 \times 3 \) diffusion tensor whose elements depend on position, so that:

$$\mathbf{D} = (D_{ij}(r)), \quad i, j = 1, 2, 3.$$  

Substituting (1.3), (1.4) and (1.5) in (1.2) now yields:

$$\frac{\partial c}{\partial t} + \nabla \cdot (c\mathbf{v}) = D \nabla^2 c + \psi, \quad (1.6)$$
1.3. Modelling drug redistribution

where I am assuming here that the material is homogeneous and isotropic. If it is further assumed that the material is incompressible, then $\nabla \cdot \mathbf{v} = 0$, and equation (1.6) may be written as:

$$\frac{\partial c}{\partial t} + \mathbf{v} \cdot \nabla c = D \nabla^2 c + \psi,$$

which is a convection-reaction-diffusion for the evolution of the drug concentration.

As mentioned above, the function $\psi$ is used to model the presence of a drug source or sink in the medium. For example, if drug is eliminated from a tissue, with the rate of elimination being first order, then the appropriate form for $\psi$ is:

$$\psi(c) = -kc,$$

where $k$ is a rate constant [141].

If in a particular problem, $L^*, c^*, v^*$ give a representative length scale, drug concentration scale, and velocity scale, respectively, then we may define non-dimensional variables as follows:

$$\bar{r} = \frac{r}{L^*}, \quad \bar{t} = \frac{t}{L^*^2/D}, \quad \bar{v} = \frac{v}{v^*}, \quad \bar{c} = \frac{c}{c^*},$$

to obtain the following non-dimensional form for (1.7) with $\psi = 0$:

$$\frac{\partial \bar{c}}{\partial \bar{t}} + Pe(\bar{v} \cdot \nabla \bar{c}) = \nabla^2 \bar{c},$$

where I have immediately dropped the overbars, and where:

$$Pe = \frac{v^* L^*}{D}$$

is a dimensionless parameter called the Péclet number, which measures the relative importance of convection compared to diffusion for mass transport in a system. Convection is the dominant mode of transport for systems with $Pe \gg 1$, and diffusion is dominant for systems with $Pe \ll 1$. 
1. Introduction

1.3.2. A system of convection-reaction-diffusion equations

When modelling drug delivery systems, it is sometimes necessary to keep track of the concentration of more than one species. For example, it may be required to distinguish between the extracellular and intracellular concentrations of drug, or between the concentrations of bound and unbound drug. The various species in a model may be able to diffuse, interact with each other via chemical reactions, or be transported by their host medium via convection. I now suppose that there are \( N \) distinct species in the system, and that their concentrations at location \( \mathbf{r} \) and time \( t \) are given by \( c_i(\mathbf{r}, t), i = 1, 2, ..., N \). If the concentrations of the various species in the host medium are dilute, then the governing equations frequently take the general form:

\[
\frac{\partial c_i}{\partial t} + \mathbf{v} \cdot \nabla c_i = D_i \nabla^2 c_i + \psi_i(c), \quad i = 1, 2, ..., N,
\]

where \( \mathbf{v} \) is the velocity of the medium, \( D_i \) is the diffusivity of species \( i \), \( \psi_i \) models the production/elimination of species \( i \), and \( c = (c_1, c_2, ..., c_N) \). It should be emphasized here that \( \psi_i \) may contain terms that model chemical reactions between species \( i \) and the other species of the system.

I shall discuss models of this kind in Chapters 2, 3 and 4 of this thesis.

1.4. Some elementary illustrative models for controlled drug release

In the previous section, the mathematical modelling of some important mechanisms for drug redistribution in materials was discussed in general terms, with particular emphasis being placed on convective and diffusive processes. In this section, I shall briefly consider a few illustrative models for specific drug delivery systems. The intention here is to introduce some of the important concepts of drug delivery in an elementary setting, and to give some examples of modelling approaches that have proved to be particularly successful in the past. I shall not consider models that are extensively discussed in later chapters of this thesis.
1.4. Some elementary illustrative models for controlled drug release

1.4.1. A barrier release model

1.4.1.1. Below solubility

A general discussion of some polymeric drug delivery devices was presented in Section 1.2.1 and barrier release systems were amongst the devices that were briefly considered there. In a barrier release system, the drug is initially enclosed in an aqueous medium by a polymeric membrane barrier; see (A) in Figure 1.2. In these systems, the rate limiting step is the speed at which the drug molecules penetrate the barrier membrane; I shall make this notion more precise below. At time $t$, the concentration of drug inside and outside of the medium is denoted by $c_i(t)$ and $c_o(t)$, respectively. If it is assumed that Fick’s first law of diffusion governs the motion of the drug molecules through the barrier membrane, then the flux of drug molecules from the inside to the outside through the membrane per unit time is:

$$j(t) = -KAD \left( \frac{c_o(t) - c_i(t)}{h} \right), \quad (1.8)$$

where $K$ is the partition coefficient of the drug between the reservoir and the membrane, $A$ is the total surface area of the membrane, $D$ is the (constant) diffusivity of the drug in the membrane, and $h$ is the (uniform) thickness of the membrane [156].

Denoting by $M(t)$ the total amount of drug released into the surrounding medium from the reservoir by time $t$, it is clear that:

$$M(t) = V_i(c_i(0) - c_i(t)) = V_o c_o(t), \quad (1.9)$$

where $V_i, V_o$ denote the volumes of the regions interior and exterior to the barrier, respectively, and from which it follows immediately that:

$$c_o(t) = \frac{V_i}{V_o} (c_i(0) - c_i(t)). \quad (1.10)$$

Also, conservation of drug mass implies that:

$$\frac{dM(t)}{dt} = j(t),$$
1. Introduction

and substituting (1.8), (1.9), (1.10) into this expression yields:

\[
\frac{dc_i}{dt} + \frac{KAD}{hV_i} \left( 1 + \frac{V_i}{V_o} \right) c_i = \frac{KAD}{hV_o} c_i(0), \quad t > 0,
\]

\[c_i = c_i(0), \quad t = 0.
\]

Solving this initial value problem yields:

\[
c_i(t) = \frac{c_i(0)}{V_i + V_o} \left( V_i + V_o e^{-t/\tau} \right),
\]

(1.11)

where:

\[
\tau = \frac{hV_i}{KAD(1 + V_i/V_o)}
\]

(1.12)
determines the time scale over which drug penetrates the barrier. It is noteworthy that:

\[
c_i(t) \to \frac{V_i c_i(0)}{V_i + V_o} \quad \text{as} \; t \to \infty,
\]

as would be expected. It also follows that:

\[
\frac{M(t)}{M(\infty)} = 1 - e^{-t/\tau},
\]

(1.13)
is the fraction of drug that has released from the system by time \(t\).

Implicit in the above analysis is the assumption that the drug inside and outside of the barrier is well mixed, as this is what enabled the drug concentrations to be modelled as function of time only. It is not difficult to establish a sufficient criterion for this assumption to be valid. If the geometrical aspect ratios of the regions inside and outside of the medium are all \(O(1)\), then \(V_i^{1/3}, V_o^{1/3}\) may be used as representative length scales for them. Assuming, as is often the case in drug delivery, that the region outside of the barrier membrane is also water dominated, then \(V_i^{2/3}/D_w, V_o^{2/3}/D_w\) determine the drug diffusion time scales inside and outside of the barrier, respectively, where \(D_w\) is the diffusivity of the drug in water. Hence, a sufficient condition for the drug to be well mixed is that:

\[
\frac{V_i^{2/3}}{D_w}, \frac{V_o^{2/3}}{D_w} \ll \tau = \frac{hV_i}{KAD(1 + V_i/V_o)},
\]

(1.14)
In many applications, \( V_i \ll V_o \), and equations (1.11), (1.12) may then be simplified to:

\[
c_i(i) \approx c_i(0)e^{-t/\tau}, \quad \tau \approx \frac{hV_i}{KAD},
\]

and the criterion (1.14) then reduces to:

\[
\frac{D}{D_w} \ll \frac{hV_i}{KA V_o^{2/3}}.
\]

1.4.1.2. Above solubility

Figure 1.9. Plot of the release profile (1.15), with \( T = 1 \) day and \( \tau = 2 \) days.

The solubility of a drug in a fluid is defined to be the maximum concentration of drug the fluid can sustain. If the initial drug concentration exceeds the drug solubility in the reservoir, then some of the drug will be in the form of amorphous aggregates or crystals in the solution. As the drug leaves the device, it is replaced by the dissolution of undissolved drug, and provided the dissolution rate is much faster than the rate at which the drug diffuses through the barrier, the concentration of drug in the device may be taken to be at its solubility, \( c_s \), say. This situation will persist until such time all of the drug in the reservoir has dissolved. Once the drug has fully dissolved, the subsequent release may be described by the equations displayed in the
1. Introduction

preceding subsection. However, while undissolved drug remains, the analysis must be modified.

I shall restrict my attention here to the case where \( V_i/V_o \to 0 \) so that the drug concentration outside of the membrane may be neglected. Then the formula (1.8) is modified to:

\[
\frac{dM(t)}{dt} = \frac{KADc_s}{h}, \quad \text{so that } M(t) = \frac{KADc_s t}{h} \quad \text{for } 0 \leq t < T,
\]

where \( T \) is the time it takes for all of the drug in the reservoir to dissolve. We thus have:

\[
c_i(t) = \begin{cases} 
  c_s & \text{for } 0 \leq t < T, \\
  c_s e^{-(t-T)/\tau} & \text{for } t \geq T,
\end{cases}
\]

where \( \tau = \frac{hV_i}{KAD} \) here, and:

\[
\frac{M(t)}{M(\infty)} = \begin{cases} 
  \frac{t}{T+\tau} & \text{for } 0 \leq t < T, \\
  1 - \frac{\tau}{T+\tau} e^{-(t-T)/\tau} & \text{for } t \geq T,
\end{cases}
\]

(1.15)

so that we have a two stage release profile: linear release while the drug concentration is above solubility in the reservoir, followed by an exponential decay in the release rate once all of the drug has dissolved [156]. A release profile of this kind can be found in Figure 1.9. In Figure 1.10 I have fitted the theoretical profile (1.15) to experimental release data taken from [59] for a reservoir system.

1.4.2. Drug release from monolithic devices

In a monolithic device, the drug is dispersed throughout a solid polymeric matrix, and drug molecules must diffuse through the bulk of the polymer and arrive at a surface before they can be released. Monolithic devices are safe systems for delivering potent drugs, such as cancer drugs (carmustine and paclitaxel [41], for example), because even if the polymeric matrix suffers a breakage, there will not be an ensuing dangerous rapid release of drug. Contrast this with the situation for a barrier release system where there could
1.4. Some elementary illustrative models for controlled drug release

Figure 1.10. A comparison between the theoretical release curve (1.15) and experimental release data for a reservoir system taken from [59]. Here, $\tau$ and $T$ have been used as fitting parameters, and in the figure, the values $\tau = 10$ hours and $T = 32$ hours are used.

be a rapid burst of drug if the enclosing membrane was to fail.

Figure 1.11. A side view of a polymer film loaded with drug.

I shall consider a planar thin polymer film, and neglect edge effects. The film occupies $-L < x < L$ as shown in Figure 1.11, and I denote by $c(x,t)$ the total (dissolved plus undissolved) concentration of drug at penetration $x$ in the film and at time $t$. It is supposed that the solubility of the drug in the polymer is given by the constant concentration $c_s$. If $c < c_s$, all of the drug is dissolved in the polymer, and I suppose that its diffusion through the polymer can then be characterised by a constant diffusivity $D$. However, in those regions of the polymer where the drug concentration is above solubility, the undissolved component is immobile, while the dissolved component has
1. Introduction

zero diffusive flux since its concentration is at the constant value \(c_s\). This situation can be described by setting the diffusivity of the drug to be zero for \(c > c_s\). Hence, the diffusive behaviour of the drug in the polymer can be modelled by the following concentration dependent diffusivity:

\[
D(c) = \begin{cases} 
D & \text{for } c < c_s, \\
0 & \text{for } c > c_s,
\end{cases}
\]  

(1.16)

or \(D(c) = DH(c_s - c)\) where \(H\) is the Heaviside step function.

If \(c_0\) is the uniform initial concentration of drug in the polymer, and we choose perfect sink boundary conditions for the top and bottom faces of the film, then we arrive at the following (potentially) nonlinear initial boundary value problem for the total drug concentration:

\[
\begin{align*}
\frac{\partial c}{\partial t} &= \frac{\partial}{\partial x} \left( D(c) \frac{\partial c}{\partial x} \right), \quad -L < x < L, t > 0, \\
c(x, 0) &= c_0 \quad \text{for } -L < x < L, \\
c(\pm L, t) &= 0 \quad \text{for } t \geq 0.
\end{align*}
\]  

(1.17)

Perfect sink boundary conditions are justified if the volume and drug diffusivity for the release medium are much greater than those for the polymer, and this is often the case in drug delivery applications. The cases \(c_0 < c_s\) and \(c_0 > c_s\) now need to be considered separately.

1.4.2.1. Initial concentration below solubility: \(c_0 < c_s\)

We now have \(D(c) = D\) at all locations in the polymer, and equation \(1.17\) reduces to the linear heat equation. The problem \(1.17\) is now readily solved by separating variables \(26\), and the following expression is obtained:

\[
c(x, t) = \frac{4c_0}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{2n-1} \exp \left( -\frac{(2n-1)^2 \pi^2 D t}{4L^2} \right) \cos \left( \frac{(2n-1) \pi x}{2L} \right),
\]  

(1.18)

The total amount of growth factor released from the system by time \(t\), \(M(t)\), is given by:

\[
M(t) = A \left( 2Lc_0 - \int_{-L}^{+L} c(x, t) \, dx \right).
\]
1.4. Some elementary illustrative models for controlled drug release

Using (1.18), the fraction to the total drug released from the film by time \( t \) is now readily calculated:

\[
\frac{M(t)}{M(\infty)} = 1 - \frac{8}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \exp \left( - \frac{(2n-1)^2 \pi^2Dt}{4L^2} \right). \tag{1.19}
\]

Equation (1.19) is frequently replaced by a much simpler formula for the early stages of release. If \( t \ll L^2/D \), the thickness of the polymer may be taken to be effectively infinite, and writing \( y = L - x \), drug out-diffusion from the top face of the polymer may be described approximately by the following initial boundary value problem:

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial y^2}, \quad -\infty < y < 0, \quad t > 0,
\]

\[
c(0, t) = 0 \quad \text{for } t \geq 0, \tag{1.20}
\]

\[
c(y, 0) = c_0 \quad \text{for } -\infty < y < 0,
\]

\[
c(y, t) \to c_0 \quad \text{as } y \to -\infty, \quad t \geq 0,
\]

and solving this yields:

\[
c = -c_0 \text{erf} \left( \frac{y}{2\sqrt{Dt}} \right).
\]

The drug released from the top face of the polymer by time \( t \) is thus given by:

\[
A \int_{-\infty}^{0} (c_0 - c) \, dy = A c_0 \int_{-\infty}^{0} \left( 1 + \text{erf} \left( \frac{y}{2\sqrt{Dt}} \right) \right) \, dy = 2A c_0 \sqrt{\frac{Dt}{\pi}},
\]

where \( A \) is the surface area of the film. The total drug released from the system by time \( t \), \( M(t) \), is twice this, so that:

\[
M(t) \approx 4A c_0 \sqrt{\frac{Dt}{\pi}} \quad \text{for } t \ll L^2/D,
\]

and:

\[
\frac{M(t)}{M(\infty)} \approx 2 \sqrt{\frac{Dt}{L^2\pi}} \quad \text{for } t \ll L^2/D. \tag{1.21}
\]

In Figure 1.12 I plot the release profiles (1.19) and (1.21) as functions of \( t/(L^2/D) \) on the same graph; it is noted that the short time approximation
1. Introduction

![Figure 1.12. Plots of the release profiles (1.19) (blue) and (1.21) (red) as functions of \( t/(L^2/D) \).](image)

(1.21) is adequate for \( t < 0.4L^2/D \), or \( M(t)/M(\infty) < 0.7 \).

The model discussed above has been used to describe the release of drug from numerous experimental systems. In [139], the model was successfully used to characterise the release of bovine serum albumin (BSA) protein from EVAc matrices. The model has also been successfully used to describe the release of rhodamine B from thin cross-linked pNIPAm films [192]. In Figure 1.13, I display experimental release data drawn from this study, together with a theoretical curve based on (1.19) that was used to fit it.

1.4.2.2. Initial concentration above solubility: \( c_0 > c_s \)

The analysis of this case is considerably more subtle than that of the \( c_0 < c_s \) case because the drug concentration now crosses the solubility concentration twice in the domain. A problem of this kind was first considered by Higuchi [51], and the results given here are similar to, but somewhat more general than, those of Higuchi. The approach taken here is based on the work of [115][116].

It is clear that the problem is symmetric about the centreline \( x = 0 \), and so only \( 0 < x < L \) need be considered here. Because of the perfect sink boundary
1.4. Some elementary illustrative models for controlled drug release

Figure 1.13. Experimental release data taken from [192], together with a corresponding theoretical curve based on [1,19].

condition $c = 0$ on $x = L$, there is a region in the film adjacent to this surface where the drug concentration is below solubility. At sufficient penetrations into the film, there is a region where the drug concentration is above solubility with $c = c_0 > c_s$. These two regions are separated by a moving boundary, $x = s(t)$ (say), which tracks from the surface of the film towards its centre. In physical problems, moving boundaries often denote the location of a change in phase of a material [27]. In the current context, the moving boundary separates a region where the drug is completely dissolved in the polymer from a region where the drug is above solubility and aggregates/crystals of drug may be present.

The governing equations are now:

\[ c(x, t) = c_0 \quad \text{for } 0 < x < s(t), \]

and:

\[ \frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}, \quad s(t) < x < L, \ t > 0, \]

\[ c(s(t), t) = c_s \quad \text{for } t > 0, \]

\[ c(L, t) = 0 \quad \text{for } t > 0, \quad (1.22) \]
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\[ s(0) = L. \]

In (1.22), the moving boundary is unknown and must be solved for as part of the solution to the problem. A boundary condition of Stefan type is required to determine it, and I now derive this using conservation of drug mass. At time \( t \), the mass of drug in the system is \( m(t) = 2A \int_0^\infty c(x,t)dx \). Clearly \( \frac{dm(t)}{dt} = 0 \), so that:

\[
0 = \frac{d}{dt} \int_0^\infty c(x,t)dx = \frac{d}{dt} \left\{ \int_0^{s(t)} cdx + \int_{s(t)}^L cdx + \int_L^\infty cdx \right\}
\]

\[
= \frac{ds}{dt} c(s^-,t) + \left[ D \frac{\partial c}{\partial x} \right]_{s^+}^{L^-} - \frac{ds}{dt} c(s^+,t) + \left[ D_w \frac{\partial c}{\partial x} \right]_{L^-}^{\infty}
\]

\[
= \frac{ds}{dt} (c_0 - c_s) - \left( D \frac{\partial c}{\partial x} \right)_{x=s^+}^0 + \left( D \frac{\partial c}{\partial x} \right)_{x=L^-}^0 - \left( D_w \frac{\partial c}{\partial x} \right)_{x=L^-}^0 ,
\]

(1.23)

where \( D_w \) is the drug diffusivity in the surrounding aqueous medium. If continuity of drug flux is now imposed across \( x = L \), so that:

\[- \left( \frac{D}{\partial x} \right)_{x=L^-} = \left( D_w \frac{\partial c}{\partial x} \right)_{x=L^+} ;
\]

equation (1.23) reduces to:

\[- \left( D \frac{\partial c}{\partial x} \right)_{x=L^-} = \frac{ds}{dt} (c_s - c_0) ,
\]

(1.24)

and this provides the final condition required to close the problem. Equations (1.22), (1.24) may now be solved for \( c(x,t), s(t) \) by noting that the problem has the similarity structure:

\[ c(x,t) = F(\xi), \ s(t) = L - \theta \sqrt{t}, \ \xi = \frac{L-x}{\sqrt{t}} , \]

where \( \theta \) is a constant to be determined. In the similarity variable \( \xi \), the problem (1.22), (1.24) reduces to the ordinary differential equation problem:

\[ D \frac{d^2 F}{d\xi^2} = -\frac{\xi}{2} \frac{dF}{d\xi} , \ 0 < \xi < \theta , \]
1.4. Some elementary illustrative models for controlled drug release

\[ F = 0 \text{ on } \xi = 0, \quad \text{(1.25)} \]
\[ F = c_s, \quad D \frac{dF}{d\xi} = \frac{\theta}{2} (c_0 - c_s) \quad \text{on } \xi = \theta. \]

Equations (1.25) are readily solved by separating variables to yield:

\[ F(\xi) = c_s \frac{\text{erf}(\frac{\xi}{2\sqrt{D}})}{\text{erf}(\frac{\theta}{2\sqrt{D}})}, \]

where \( \theta \) is determined by solving the algebraic equation:

\[ \theta \text{erf} \left( \frac{\theta}{2\sqrt{D}} \right) \exp \left( \frac{\theta^2}{4D} \right) = 2 \sqrt{\frac{D}{\pi}} \frac{c_s}{c_0 - c_s} \text{ with } c_0 > c_s. \]

In the original variables, the solution is now given by:

\[ c = c_s \frac{\text{erf}(\frac{L-x}{2\sqrt{D}})}{\text{erf}(\frac{\theta}{2\sqrt{D}})} \text{ for } s(t) < x < L. \quad \text{(1.26)} \]

The total amount of drug released from the system by time \( t \) is given by:

\[
M(t) = 2A \left\{ (L - s(t))c_0 - \int_{s(t)}^{L} c(x, t)dx \right\} \\
= 2A\sqrt{t} \left\{ \theta c_0 - \int_0^\theta F(\xi)d\xi \right\} \\
= 2A\sqrt{t} \left\{ \theta(c_0 - c_s) + \frac{2c_s\sqrt{D} \left[ 1 - \exp \left( -\frac{\theta^2}{4D} \right) \right]}{\sqrt{\pi} \text{erf} \left( \frac{\theta}{2\sqrt{D}} \right)} \right\},
\]

so that \( M(t) \propto \sqrt{t} \) prior to the two moving boundaries meeting at \( x = 0 \). A plot of the solution \( c(x, t) \) and \( s(t) \) for successive times can be found in Figure 1.14.

For \( c_0 \gg c_s \), we have \( \theta \ll 1 \) and:

\[ \theta \approx \sqrt{\frac{2Dc_s}{c_0 - c_s}} \text{ so that } s(t) \approx L - \sqrt{\frac{2Dc_st}{c_0 - c_s}}, \]

and:
1. Introduction

\[ M(t) \approx A \sqrt{2Dc_s t \frac{(2c_0 - c_s)^2}{c_0 - c_s}} \quad \text{for } c_0 \gg c_s, \]

which is close to the following form derived by Higuchi [51] for \( c_0 \gg c_s \):

\[ M(t) = 2A \sqrt{Dc_s t (2c_0 - c_s)}. \]

Figure 1.14. Plots of the similarity solution (1.26) for the drug concentration for various times \( t \), and with \( D = 10^{-2} \text{ mm}^2/\text{h} \), \( c_0 = 1 \), \( c_s = 0.5 \), and \( L = 1 \text{ mm} \). Here \( x = 0 \) corresponds to the surface of the polymer and \( x = 1 \) is its centreline.

1.4.2.3. Initial drug concentration above solubility: a two-dimensional problem

I now briefly discuss a two-dimensional generalisation of the problem considered in the previous subsection. The polymer is taken to occupy a bounded region \( \Omega(0) \) of the \((x, y)\) plane, with the remainder of the plane being occupied by an aqueous medium. I denoted by \( c(x, y, t) \) the concentration of drug at location \((x, y)\) in the polymer and time \( t \), and I suppose that:

\[ c(x, y, t = 0) = c_0 > c_s \quad \text{for all } (x, y) \in \Omega(0). \]
1.4. Some elementary illustrative models for controlled drug release

Figure 1.15. A two-dimensional problem for the drug concentration in a polymer occupying a region $\Omega(0)$ in the plane. In the region $\Omega(t)$ of the polymer, the drug concentration is at the constant concentration $c_0 > c_s$.

For $t > 0$, there will be a shrinking region in the core of the polymer where $c(x, y, t) = c_0$, and which I shall denote by $\Omega(t)$. This region is bounded by an inward moving curve $\partial \Omega(t)$ which needs to be determined as part of the solution to the problem; see Figure 1.15.

The problem that governs the concentration $c(x, y, t)$ in $\Omega(0) \setminus \Omega(t)$ is given by:

\[
\frac{\partial c}{\partial t} = D \left( \frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} \right) \quad \text{for } (x, y) \in \Omega(0) \setminus \Omega(t), \quad t > 0,
\]

\[
c(x, y, 0) = c_0 \quad \text{for } (x, y) \in \Omega(0),
\]

\[
c(x, y, t) = c_s, -D \frac{\partial c}{\partial n} = (c_s - c_0)V_n \quad \text{on } \partial \Omega(t), \quad t \geq 0,
\]

where $\partial c/\partial n = \nabla c \cdot n$, with $n$ being the unit normal of $\partial \Omega(t)$ pointing towards $\Omega(t)$, and $V_n$ the normal velocity of $\partial \Omega(t)$.

In Figures 1.16 and 1.17 I display some numerical solutions to (1.27) for various times. These solutions were calculated by explicitly time-stepping (1.27) for the drug concentration on a uniform grid in the usual way. The moving curve $\partial \Omega(t)$ was tracked using a level set method for Stefan problems. This method was first proposed in [22], and a detailed description of it can be found there. A good general reference for level set methods is [113].
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Figure 1.16. Plots of the moving boundary in two dimensions for various times $t$ arising in the solution of the initial boundary value problem (1.27) with $D = 1$, $c_0 = 1$, $c_s = 0.6$, and $\Omega(0) = \{(x, y)|\sqrt{x^2 + y^2} < 0.1\}$.

1.5. Thesis outline

This project is concerned with the mathematical modelling of drug release from a variety of delivery systems. A significant proportion of the work (Chapter 5 and 6) was carried out in collaboration with experimentalists working in this area at the National Centre for Biomedical and Engineering Science (NCBES); there were four in all in the team, two mathematicians and two experimentalists. Much of the mathematical work was focused on modelling the experimental data generated by our colleagues, or on data available in the literature. Mathematical modelling was also used to aid in the design of drug release experiments.

In Chapter 1, the subject area is introduced by discussing the role of controlled drug release in modern medicine, and by describing some commonly used delivery systems. We mathematically describe diffusive and convective mechanisms arising in drug delivery, and discuss the role modelling can play in realising the goal of controlled release. Some introductory mathematical mod-
Figure 1.17. Numerical surface plots of solutions for the drug concentration \( c(x, y, t) \) of the initial boundary value problem (1.27), with \( D = 1, c_0 = 1, c_s = 0.6, \) and \( \Omega(0) = \{(x, y) | \sqrt{x^2 + y^2} < 0.1\} \).
1. Introduction

eels that have been successfully employed previously are presented to illustrate
our points.

In Chapter 2, a mathematical model that describes the release of heparin-
binding growth factors from a heparin-based delivery system is considered. In
this system, heparin binds to peptide which has been covalently cross-linked
to a fibrin matrix. Growth factor in turn binds to the heparin, and growth
factor release is governed by binding and diffusion mechanisms. The governing
nondimensional parameters that can be varied to tune the growth factor release
rate are identified, and a parameter regime that ensures that the passive release
of growth factor is slow is found. Also, for the first time, in vitro experimental
release data is directly compared with theoretical release profiles, and our
predictions for the conditions that ensure slow release are confirmed.

In Chapter 3, a mathematical model that incorporates free peptide in an
affinity-based delivery system containing no heparin is described. In this sys-
tem, a peptide molecule binds directly to the growth factor, and there is no
intermediary heparin molecule. Unlike the model considered in Chapter 2, this
model takes account of the effect of free peptide on the release behaviour . A
parameter regime that ensures that the release of growth factor will be slow is
again identified, and the theoretical profiles are found to match corresponding
experimental data well.

In Chapter 4, a reaction-diffusion model that has been used to describe drug
re-distribution in coronary artery tissue from a drug-eluting stent source is
analysed. Some generic problems to evaluate drug penetration and persistence
in tissue are formulated and analysed. In particular, the model is used to
investigate tissue loading and residence times for strongly retained drugs, and
it is found that if the drug is presented to the tissue at a sufficiently high
concentration, it will be deposited over a short diffusion time scale, but will
clear the system over a long time scale determined by diffusion and binding
parameters.

In Chapter 5, a model for pulsatile drug release from a thermoresponsive
polymer poly(N-isopropylacrylamide) is developed. Our experimental col-
leagues conducted drug release experiments from this polymer using the model
drug rhodamine B. The polymer possesses a lower critical solution temperature
(LCST), below which it absorbs water to become swollen, and above which it expels water to become dense and dry. Drug release is rapid in the swollen state, but slow in the condensed state, so that varying the release medium temperature across the LCST effectively switches drug release on or off. The model was used to design pulsatile release experiments with a uniform drug dose being delivered in each release cycle.

In Chapter 6, a mathematical model is developed to evaluate the feasibility of an \textit{in vivo} implanted drug delivery system. The proposed delivery device consists of a cooling material coated by a drug-loaded thermoresponsive polymer film. In the thin polymer film limit, the model provides an upper bound for the temperature the cooling material must be dropped to for drug delivery to be initiated. The independent non-dimensional parameters governing the behaviour of the system are also identified. It is found that the system may be realised for realistic parameter values and materials.

Finally, in Chapter 7, the discussion chapter, a critical evaluation of the modelling work of the thesis is presented, and strengths and weaknesses of some of the models are identified. Some preliminary work to address the weaknesses of the modelling is also presented. In particular, a large model for a heparin-based affinity system that incorporates the effect of free peptide is briefly considered. Also, a more sophisticated model for pulsatile release that tracks the motion of swelling and erosion fronts in a thermoresponsive polymer is formulated, and some numerical solutions displayed.
2. Minimizing the passive release of heparin-binding growth factors from an affinity-based delivery system

In this chapter, a mathematical model that describes the leakage of heparin-binding growth factors from an affinity-based delivery system is considered. In the delivery system, heparin binds to a peptide which has been covalently cross-linked to a fibrin matrix. Growth factor in turn binds to the heparin, and growth factor release is governed by both binding and diffusion mechanisms, the purpose of the binding being to slow growth factor release. The governing mathematical model, which in its original formulation consists of six partial differential equations, is reduced to a system of just two equations. It is usually desirable that there be no passive release of growth factor from a device, with all of the growth factor being held in place via binding until such time as it is actively released by invading cells. However, there will inevitably be some passive release, and so it is of interest to identify conditions that will make this release as slow as possible. In particular, I shall identify a parameter regime that ensures that at least a fraction of the growth factor will release slowly. It is found that slow release is assured if the matrix is prepared with the concentration of cross-linked peptide greatly exceeding the dissociation constant of heparin from the peptide, and with the concentration of heparin greatly exceeding the dissociation constant of the growth factor from heparin. Also, for the first time, in vitro experimental release data is directly compared with theoretical release profiles generated by the model. I propose that the
two stage release behaviour frequently seen in experiments is due to an initial rapid out-diffusion of free growth factor over a diffusion time scale (typically days), followed by a much slower release of the bound fraction over a time scale depending on both diffusion and binding parameters (frequently months).

2. Minimizing the passive release of heparin-binding growth factors

2.1. Heparin-based delivery systems

2.1.1. Background

In vertebrates, the extracellular matrix is a complex mixture of carbohydrates, proteins, and possibly minerals, that surrounds the cells that form tissues [4]. The extracellular matrix helps cells to bind together, and regulates a number of cellular functions, such as differentiation, proliferation, migration, and adhesion [166]. The matrix can achieve such regulation via the appropriate release of growth factors, for which it can act as a depot. Macromolecules within the structure of the matrix can bind growth factors with high affinity, enabling the matrix to serve as a growth factor reservoir. In response to changes in local physiological conditions (such as the occurrence of a wound, for example), cells may secrete enzymes that can release such growth factor depots from the matrix [149,166]. This natural growth factor release mechanism has inspired the design of affinity-based drug delivery systems that mimic the retentive and protective properties of the extracellular matrix for growth factor [56]. Sakiyama-Elbert & Hubbel [137] have developed a mathematical model that describes passive growth factor release from a system of this kind. In this chapter, I shall analyze this mathematical model and use it to make recommendations for how the delivery system should be prepared to prevent excessive loss of growth factor from passive release. Also, the predictions of the model are compared directly with experimental data for the first time.

The extracellular matrix consists predominantly of two classes of macromolecules: glycosaminoglycans, and fibrous proteins, such as collagen and fibronectin [4]. Glycosaminoglycans are polysaccharide polymers that typically have a repeating unit consisting of two sugars. Heparin is glycosaminoglycan of the matrix that is known to bind with a number growth factors in vivo via elec-
2.1. Heparin-based delivery systems

trostatic interactions, examples being basic fibroblast growth factor (bFGF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and vascular endothelial growth factor (VEGF) [166]; some discussion of growth factors is given in the next subsecion. Heparin is only one of a number of molecules to which growth factors can bind in the matrix, other important examples being heparan sulfate and chondroitin sulfate. The binding helps regulate the bioavailability of the growth factors, and protects them from proteolytic degradation. Some growth factors are known to be active in the bound state, while others only become fully active subsequent to being released from the matrix by enzymes secreted from neighbouring cells [56].

2.1.2. Heparin-binding growth factors

Growth factors are normally proteins or steroid hormones that are capable of stimulating cellular growth, proliferation and cellular differentiation. They play a significant role in the regulation of a variety of cellular processes, especially in regeneration, both naturally and therapeutically [95]. Below, I list some heparin-binding growth factors have been used in affinity-based delivery systems:

- Neurotrophins are a family of growth factors which includes Nerve Growth Factor (NGF), Neurotrophin-3 (NT-3), Brain-Derived Neurotrophic Factor (BDNF), and Neurotrophin-4/5 (NT-4/5). They play a critical role in regulating the differentiation, growth, and survival of peripheral and central nervous system neurons. They have been used in treatment of several types of neurodegenerative disease, cancers of the nervous system, spinal cord injury, and peripheral neuropathy [34,101,138,160,168,188].

- Fibroblast Growth Factors (FGFs) are a family of heparin-binding growth factors that are involved in angiogenesis, wound healing, and embryonic development. FGFs also play an important role in regulating cell proliferation, migration and differentiation, and have the potential to enhance peripheral nerve regeneration [111,123,137].

- Glial-Derived Neurotrophic Factor (GDNF) is a small protein which pro-
2. Minimizing the passive release of heparin-binding growth factors

...notes the survival of several types of neurons and neurite outgrowth. It plays a significant role in neural migration and differentiation, and has been implicated in the treatment of peripheral nerve injuries [1,144,189].

- Platelet-Derived Growth Factor (PDGF) is a protein that helps regulate cell growth and division. It plays a significant role in the wound healing, cell proliferation and migration, and angiogenesis [8,126,185].

2.1.3. A heparin-based delivery system

Sakiyama-Elbert & Hubbel [137] have developed a growth factor delivery system for wound healing that exploits heparin’s ability to bind electrostatically with growth factors. The various elements of their system are depicted schematically in Figure 2.1. The natural blood clotting matrix, fibrin, was chosen as the base material. Three dimensional fibrin hydrogel scaffolds were fabricated, into which invading cells could infiltrate, and release (via enzymatic processes) growth factor attached to the fibrin matrix. The growth factor attaches to the matrix via a bi-domain peptide bound to heparin, in a manner that is now explained. The peptide contains a domain which covalently cross-links to the fibrin matrix. However, the peptide also contains a domain that can bind to heparin, and such bound heparin can in turn bind to heparin-binding growth factor. Hence, growth factor attachment to the matrix is dependent on three distinct interactions, which can be crudely represented by: (fibrin)–(peptide)–(heparin)–(growth factor).

The peptide is susceptible to cleavage by enzymes released from invading cells. Cells infiltrate the scaffold and release growth factor by secreting enzymes that degrade the peptide [4,90,164]. In these systems, it is desirable that the growth factor be retained by the matrix until such time as it is actively released by cells. However, there inevitably will be some passive release, whereby free growth factor diffuses out of the system before cells have had the opportunity to actively release it. Growth factor binding to heparin is reversible, and growth factor will not be permanently fixed to the matrix even in the absence of cells. The passive release of growth factor is usually undesirable, and in this study I shall use a mathematical model proposed by [137] to help identify conditions...
2.1. Heparin-based delivery systems

Figure 2.1. A schematic representation of the fibrin matrix containing all six species of the model. In the figure, the peptide (P) is attached directly to the fibrin matrix. Some of this peptide is bound with heparin to form heparin-peptide complexes (HP), and some of these complexes are in turn bound with growth factor to form growth factor-heparin-peptide complexes (GHP). The three species that are not attached to the fibrin matrix are also depicted, these being: free growth factor (G), free heparin (H), and free growth factor-heparin complexes (GH).

In [137], the system was used to deliver the high affinity heparin-binding growth factor bFGF. The purpose of their experiments was to evaluate the effect of the delivery system on neurite extension from the dorsal root ganglia of chickens. Their results demonstrated that the delivery system could enhance neurite extension by up to about 100% relative to unmodified fibrin. In subsequent studies, the system has been used to deliver lower affinity heparin-binding growth factors, such as NGF [138, 188, 190], NT-3 [168, 185], glial-derived neurotrophic growth factor (GDNF) [189, 190], platelet-derived growth factor (PDGF) [185], and sonic hedgehog [185]. Wood et al. [190] investigated the repair of a 13 mm gap in a rat sciatic nerve using a silicone nerve guidance conduit containing the delivery system loaded with GDNF; see Figure 2.2. It was found that systems that contained the delivery system resulted in a higher frequency of nerve regeneration compared to control groups without the delivery system.
2. Minimizing the passive release of heparin-binding growth factors

![Diagram of a nerve conduit with fibrin matrix, peptide, heparin, and growth factor]

**Figure 2.2.** A schematic depiction of a device that uses an affinity-based delivery system to promote nerve regeneration [190]. In the figure, a nerve guidance conduit is shown bridging the gap between the two ends of a severed nerve. The delivery system in the conduit contains neurotrophic factors that promote the survival and growth of neurons.

### 2.1.4. Fibrin matrix preparation

I now briefly sketch how the fibrin matrices in the experimental studies referred to above were prepared. The more technical details can be found in [137], and are not given here. Fibrinogen is purified from blood and mixed with appropriate amounts of the following quantities to obtain a polymerization mixture: calcium ions, growth factor, thrombin, peptide, the transglutaminase zymogen factor XIII (this crosslinks fibrin), and heparin. This polymerization mixture is then placed in a 24-well tissue culture plate and incubated under appropriate conditions for an hour [137].

It is clear from this description that the concentrations of peptide, heparin and growth factor in the polymerization mixture are readily varied. However, a distinction needs to be made between the peptide that cross-links to the fibrin matrix and the peptide that remains unbound in the gel since it is the cross-linked peptide only that forms part of the delivery system. In [136] and [147], a procedure for quantifying the amount of peptide that cross-links to the matrix is described. If the unbound peptide interacts significantly with the other free components of the system, then account must be taken of this in the mathematical modelling, and in [188] a quite large mathematical model incorporating such effects is described. However, I do not incorporate free peptide in the model considered here for reasons I shall discuss in Section 2.3.
2.1. Heparin-based delivery systems

2.1.5. Experimental setup

Figure 2.3. A schematic depiction of the experimental setup for the release of growth factor from the fibrin matrix. The matrix containing the growth factor is in the base of a tissue culture plate well. Dissolution medium is added to the well and growth factor releases into the medium from the matrix via diffusion. In the experimental work discussed in this chapter, the thickness of the fibrin matrix is approximately 0.2 cm and the height of the fluid medium above the matrix is approximately 0.5 cm. The dissolution medium is replaced five times in the first day of release, and once a day thereafter.

I now describe the setup for the growth factor release experiments of [137, 168, 184, 185, 188, 189]. The release system used in these studies is depicted schematically in Figure 2.3. The fibrin matrix containing the growth factor is in the base of a tissue culture plate well. 1 ml of aqueous dissolution medium is added to the well, and the growth factor releases into the medium from the matrix via diffusion. The thickness of the matrix is approximately 0.2 cm and its diameter is approximately 1.5 cm. The height of the fluid medium above the matrix is 0.5 cm. The dissolution medium is replaced five times in the first day of release, and once a day thereafter. The quantity measured in the experiments is the fraction of total growth factor released from the matrix as a function of time.

The growth factor, heparin and peptide are uniformly distributed throughout the fibrin matrix initially. This, combined with the simple geometry of
the enclosing impenetrable walls, implies that the only spatial dimension that
need be considered in the modelling is the vertical depth through the matrix.

2.1.6. Preview

A mathematical model has been developed by Sakiyama-Elbert & Hubbel
[137] to determine optimal conditions for slow passive release of heparin-
binding growth factors from affinity-based delivery systems. However, Lin
& Metters [82] comments that the modelling approach adopted by [137] is
complicated by the relatively large number of parameters appearing in their
equations. The model is described in detail in the next section, and we shall
see there that it has three diffusivities and four rate constants. The model
in its original formulation contains six differential equations, three of which
contain diffusion terms. A major goal of the analysis developed in this chapter
is to simplify the governing mathematical model. I shall show that under typ-
ical experimental conditions, the model can be reduced to a standard system
of just two coupled partial differential equation governing the evolution of the
concentrations of the total growth factor and total heparin. I shall further show
that for typical experiments, the release behaviour is dominated by the val-
ues of just two non-dimensional parameters: the ratio of the concentration of
cross-linked peptide to the dissociation constant of heparin from peptide, and
the ratio of the initial concentration of heparin to the dissociation constant of
the growth factor from heparin. Lin further comments that theoretical profiles
generated by the model had yet to be directly compared with experimental
data. This issue is addressed in Section 2.4.

2.2. The model

2.2.1. Model equations

The mathematical model which we shall now describe was first developed
by Sakiyama-Elbert & Hubbell [137]. There are six species in all in the model
and, following [137], I use the following notation:
2.2. The model

P is an immobile peptide covalently fixed to the fibrin matrix;
H is a mobile free heparin molecule that can diffuse through the fibrin matrix;
G is a mobile free growth factor molecule that can diffuse through the matrix;
GH is a mobile growth factor-heparin complex that can diffuse through the matrix;
HP is an immobile heparin-peptide complex fixed to the matrix;
GHP is an immobile heparin-peptide-growth factor complex fixed to the matrix.

In Figure 2.1, all six species are schematically represented in the fibrin matrix. The possible interactions between these various species are described by the following four chemical reactions:

\[
\begin{align*}
G + H & \xrightarrow{k_f} GH \\
H + P & \xrightarrow{K_P} HP
\end{align*}
\]

and

\[
\begin{align*}
H + P & \xrightarrow{K_L} GH \\
G + HP & \xrightarrow{k_r} GHP
\end{align*}
\]

(2.1)

where \(k_f, k_r, K_P, K_L\) are the rate constants as shown. The first reaction, for example, represents the reversible binding of a free growth factor molecule to a free heparin molecule, with association and dissociation rate constants \(k_f\) and \(k_r\), respectively. The other three reactions are similarly interpreted; see Figure 2.1. It is noteworthy that the rate constants for the first and second reactions above are assumed to be the same, and similarly for the third and fourth reactions. This implies that we are assuming that the association/dissociation behaviour of growth factor for heparin does not depend on whether the heparin is free or bound to peptide; a similar comment applies to the binding heparin to peptide.

The problems that are considered in this chapter are one-dimensional, and throughout I shall denote the spatial variable by \(x\) and the time variable by \(t\). Following the notation of [137], I denote by \(c_G(x,t)\) the concentration of free growth factor G at location \(x\) and time \(t\); the notation for the concentrations of the other five species follows in an obvious fashion. In view of the chemical reactions (2.1), and our assumptions regarding the mobility of the various species, the governing equations for the six concentrations take the form:
2. Minimizing the passive release of heparin-binding growth factors

\[
\begin{align*}
\frac{\partial c_G}{\partial t} &= D_G \frac{\partial^2 c_G}{\partial x^2} - k_f c_G c_H + k_r c_G c_{HP} + k_r c_{GHP}, \\
\frac{\partial c_H}{\partial t} &= D_H \frac{\partial^2 c_H}{\partial x^2} - k_f c_G c_H + k_r c_G c_P + k_r c_{HP} + k_r c_{GHP}, \\
\frac{\partial c_{GH}}{\partial t} &= D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2} + k_f c_G c_H - k_r c_G c_{GH} + k_r c_{GH} c_P + k_r c_{GHP}, \\
\frac{\partial c_P}{\partial t} &= -k_r c_H c_P + k_r c_{HP} + k_r c_{GHP}, \\
\frac{\partial c_{HP}}{\partial t} &= -k_f c_G c_{HP} + k_r c_{GHP} + k_r c_{GHP} c_P - k_r c_{HP}, \\
\frac{\partial c_{GHP}}{\partial t} &= k_f c_G c_{GHP} - k_r c_{GHP} + k_r c_{GHP} c_P - k_r c_{GHP},
\end{align*}
\] (2.2)

where \(D_G\), \(D_H\) and \(D_{GH}\) are the diffusivities for the free growth factor, free heparin, and free growth factor-heparin complex, respectively; the species \(P\), \(HP\) and \(GHP\) are taken to be immobile since the peptide is assumed to be fixed covalently to the fibrin matrix, and consequently the equations for their concentrations do not contain diffusion terms.

2.2.2. Boundary and initial conditions

Simple boundary conditions are chosen for (2.2) that allow direct comparison with available experimental and theoretical results for growth factor release from the delivery system. It is supposed that the fibrin matrix occupies \(0 \leq x \leq L\), with \(x = 0\) giving the base of the container, and \(x = L\) denoting the interface between the matrix and an external medium into which growth factor releases; see Figure 2.3. At the base of the container, no-flux conditions for the mobile species are imposed, so that:

\[
\begin{align*}
\frac{\partial c_G}{\partial x}(0, t) &= 0, \quad \frac{\partial c_H}{\partial x}(0, t) = 0, \quad \frac{\partial c_{GH}}{\partial x}(0, t) = 0 \quad \text{for } t \geq 0. \quad (2.3)
\end{align*}
\]

At the interface between the matrix and the external medium, perfect sink conditions for the mobile species are imposed:

\[
\begin{align*}
c_G(L, t) &= 0, \quad c_H(L, t) = 0, \quad c_{GH}(L, t) = 0 \quad \text{for } t \geq 0. \quad (2.4)
\end{align*}
\]
Perfect sink boundary conditions are justified by recalling that the release medium is typically replaced several times during the first day of release, and once a day thereafter. The concentration of growth factor in the medium is reset to zero each time it is replaced. Also, the volume of the release medium is typically more than twice that of the fibrin matrix, and the growth factors have a larger diffusivity in water than in the fibrin gel. It is noteworthy that the boundary conditions (2.3), (2.4) could also model \textit{in vitro} growth factor release from a nerve guide tube \cite{137} occupying $-L \leq x \leq L$, with $x = \pm L$ giving the location of the ends of the tube; see Figure 2.2. In this context, (2.3) are interpreted as symmetry conditions on the centre-line of the tube.

Equations (2.2) are solved subject to the following initial conditions:

$$
c_G(x,0) = c_0^G, \quad c_H(x,0) = c_0^H, \quad c_{GH}(x,0) = 0, \quad c_P(x,0) = c_0^P, \quad c_{HP}(x,0) = 0, \quad c_{GHP}(x,0) = 0$$

for $0 < x < L$, (2.5)

where $c_0^G, c_0^H, c_0^P$ denote the initial concentrations of growth factor, heparin, and peptide, respectively, in the polymerization mixture. In the model, I make the simplifying assumption that all of the peptide in the polymerization mixture crosslinks covalently to the fibrin matrix. This is not likely to occur in practice, but I shall show in Section 2.3 how the results may be modified to take account of the presence of free peptide in the matrix. It should also be noted that free peptide will typically clear the system over a period of a few days.

The mathematical model is now complete, and consists of equations (2.2), (2.3), (2.4), (2.5).

2.2.3. Model reduction

I now show how, under typical experimental conditions, the model may be reduced to a coupled pair of partial differential equations.

2.2.3.1. Non-dimensionalisation

Before giving the non-dimensionalisation, it is first noted that (2.2) may be written in the following equivalent form:
2. Minimizing the passive release of heparin-binding growth factors

\[
\frac{\partial}{\partial t} (c_G + c_{GH} + c_{GHP}) = D_G \frac{\partial^2 c_G}{\partial x^2} + D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2},
\]

\[
\frac{\partial}{\partial t} (c_H + c_{GH} + c_{HP} + c_{GHP}) = D_H \frac{\partial^2 c_H}{\partial x^2} + D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2},
\]

\[
\frac{\partial}{\partial t} (c_{GH} + c_{GHP}) = D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2} + k_f c_G (c_H + c_{HP}) - k_r (c_{GH} + c_{GHP}),
\]

\[
\frac{\partial}{\partial t} (c_{HP} + c_{GHP}) = K_F c_P (c_H + c_{GH}) - K_R (c_{HP} + c_{GHP}),
\]

\[
\frac{\partial c_{GHP}}{\partial t} = k_f c_G c_{HP} + K_F c_{GH} c_P - (k_r + K_R) c_{GHP},
\]

\[
c_p + c_{HP} + c_{GHP} = c_0^p,
\]

where, for example, equation (2.6) is obtained by forming (2.2) \(^4 + (2.2)\) \(^5 + (2.2)\) \(^6\). I denote the total concentrations of growth factor and heparin in the matrix at location \(x\) and time \(t\) by \(c_T^G(x,t)\) and \(c_T^H(x,t)\), respectively, so that:

\[
c_T^G(x,t) = c_G(x,t) + c_{GH}(x,t) + c_{GHP}(x,t),
\]

\[
c_T^H(x,t) = c_H(x,t) + c_{GH}(x,t) + c_{HP}(x,t) + c_{GHP}(x,t).
\]

Equations (2.6) \(^1\) and (2.6) \(^2\) give the evolution equations for the total growth factor and heparin, and may be written in conservation form as:

\[
\frac{\partial c_T^G}{\partial t} + \frac{\partial j_T^G}{\partial x} = 0, \quad \frac{\partial c_T^H}{\partial t} + \frac{\partial j_T^H}{\partial x} = 0,
\]

where:

\[
j_T^G = -D_G \frac{\partial c_G}{\partial x} - D_{GH} \frac{\partial c_{GH}}{\partial x}, \quad j_T^H = -D_H \frac{\partial c_H}{\partial x} - D_{GH} \frac{\partial c_{GH}}{\partial x},
\]

give the total flux of growth factor and heparin, respectively.

Non-dimensional variables are introduced as follows:

\[
\bar{x} = \frac{x}{L}, \quad \bar{t} = \frac{t}{(L^2/D_{GH})}, \quad \bar{c}_G = \frac{c_G}{c_0^G}, \quad \bar{c}_H = \frac{c_H}{c_0^H}, \quad \bar{c}_P = \frac{c_P}{c_0^P}, \quad \bar{c}_{GH} = \frac{c_{GH}}{c_0^G}, \quad \bar{c}_{HP} = \frac{c_{HP}}{c_0^H},
\]

\[
\bar{c}_{GHP} = \frac{c_{GHP}}{c_0^G}, \quad \bar{c}_p^T = \frac{c_p^T}{c_0^G}, \quad \bar{c}_H^T = \frac{c_H^T}{c_0^H}, \quad \bar{j}_G^T = \frac{j_G^T}{(D_{GH}c_0^G/L)}, \quad \bar{j}_H^T = \frac{j_H^T}{(D_{GH}c_0^H/L)}.
\]

to obtain the following non-dimensional form for the governing initial boundary value problem (upon dropping over-bars):
2.2. The model

\[ \frac{\partial}{\partial t} (c_G + c_{GH} + c_{GHP}) = D^*_G \frac{\partial^2 c_G}{\partial x^2} + 2 \frac{\partial^2 c_{GH}}{\partial x^2} + \frac{\partial^2 c_{GHP}}{\partial x^2}, \]

\[ \frac{\partial}{\partial t} (c_H + c_{HP} + (c_{GH} + c_{GHP})/\eta_{H/G}) = D^*_H \frac{\partial^2 c_H}{\partial x^2} + 2 \frac{\partial^2 c_{GH}}{\partial x^2}, \]

\[ \delta_G \frac{\partial}{\partial t} (c_{GH} + c_{GHP}) = \delta_G \frac{\partial^2 c_{GH}}{\partial x^2} + K_{bh} c_G (c_H + c_{HP}) - (c_{GH} + c_{GHP}), \]

\[ \delta_H \frac{\partial}{\partial t} (\eta_{H/G} c_{GH} + c_{GHP}) = K_{bp} c_P (\eta_{H/G} c_H + c_{GH}) - (\eta_{H/G} c_{HP} + c_{GHP}), \]

\[ \delta_G \delta_H \frac{\partial c_{GHP}}{\partial t} = \delta_H (K_{bh} c_G c_{HP} - c_{GHP}) + \delta_G (K_{bp} c_G c_P - c_{GHP}), \quad \text{(2.10)} \]

\[ c_P + \eta_{H/P} c_{HP} + \eta_{H/G} c_{GHP} = 1, \]

\[ \frac{\partial c_G}{\partial x}(0,t) = 0, \quad \frac{\partial c_H}{\partial x}(0,t) = 0, \quad \frac{\partial c_{GH}}{\partial x}(0,t) = 0 \quad \text{for} \ t \geq 0, \]

\[ c_G(1,t) = 0, \quad c_H(1,t) = 0, \quad c_{GH}(1,t) = 0 \quad \text{for} \ t \geq 0, \]

\[ c_G(x,0) = 1, \quad c_H(x,0) = 1, \quad c_{GH}(x,0) = 0 \quad \text{for} \ 0 < x < 1, \]

\[ c_P(x,0) = 1, \quad c_{HP}(x,0) = 0, \quad c_{GHP}(x,0) = 0 \quad \text{for} \ 0 < x < 1, \]

where:

\[ D^*_G = \frac{D_G}{D_{GH}}, \quad D^*_H = \frac{D_H}{D_{GH}}, \quad \eta_{H/G} = \frac{c_H^0}{c_G^0}, \quad \eta_{H/P} = \frac{c_H^0}{c_P^0}, \]

\[ \delta_G = \frac{D_{GH}}{k_r L^2}, \quad \delta_H = \frac{D_{GH}}{k_r L^2}, \quad K_{bh} = \frac{k_f c_H^0}{k_r}, \quad K_{bp} = \frac{k_p c_P^0}{k_r}, \quad \text{(2.11)} \]

are the governing non-dimensional parameters. The quantities \( K_{bh}, K_{bp} \) give a non-dimensional measure of the strength of retention of growth factor by the heparin, and of heparin by the peptide, respectively. I denote by

\[ K_{G-H}^D = \frac{k_r}{k_f}, \quad K_{H-P}^D = \frac{k_r}{k_p}, \]

the dissociation constants of growth factor from heparin, and of heparin from peptide, respectively, so that:

\[ K_{bh} = \frac{c_H^0}{K_{G-H}^D}, \quad K_{bp} = \frac{c_P^0}{K_{H-P}^D}. \quad \text{(2.12)} \]

It is noteworthy that \( K_{bh} \) involves both the concentration of available binding
2. Minimizing the passive release of heparin-binding growth factors

sites for the growth factor and the dissociation constant of growth factor from heparin. The case \( K_{bh} \gg 1 \) corresponds to the growth factor being strongly retained by the heparin. Conversely, \( K_{bh} \ll 1 \) corresponds to weak retention of growth factor by the heparin. The parameter \( K_{hp} \) is similarly interpreted in the context of heparin retention by the peptide.

The non-dimensional form for the total growth factor and heparin and their fluxes are given by:

\[
\begin{align*}
    c_T^G(x,t) &= c_G(x,t) + c_{GH}(x,t) + c_{GHP}(x,t), \\
    c_T^H(x,t) &= c_H(x,t) + c_{HP}(x,t) + \left( c_{GH}(x,t) + c_{GHP}(x,t) \right) / \eta_{H/G}, \\
    j_T^G &= -D^*_G \frac{\partial c_G}{\partial x} - \frac{\partial c_{GH}}{\partial x}, \quad j_T^H = -D^*_H \frac{\partial c_H}{\partial x} - \frac{1}{\eta_{H/G}} \frac{\partial c_{GH}}{\partial x}.
\end{align*}
\]

The quantity that is most frequently measured in release experiments is the fraction of the total growth factor that has released from the fibrin matrix by a given time. For the system being modelled here, this fraction is given in non-dimensional form by:

\[
\frac{M(t)}{M(\infty)} = 1 - \int_0^1 c_T^G(x,t) \, dx,
\]

where \( M(t) \) is the total amount of growth factor released from the fibrin by time \( t \).

2.2.3.2. Parameter values

In \[137,168,184,185,188,189\], the fibrin gels were prepared by placing 400 \( \mu l \) of polymerization mixture in the wells of a 24-well plate. The diameter of each well in such a plate is 1.56 cm, from which it follows that the thickness of the gels was \( L \approx 0.2 \) cm. In \[137\], the growth factor considered was bFGF, and the values used for the diffusivities were based on the work of Saltzman et al. \[140\] and Gaigalas et al. \[42\]. These values can be found in Table 2.1 and all have order of magnitude \( 10^{-5} \) cm\(^2\)min\(^{-1}\). In Taylor et al. \[168\], where the growth factor considered was NT-3, the diffusivities used were again of order \( 10^{-5} \) cm\(^2\)min\(^{-1}\); see Table 2.2. Taking \( D = 3.0 \times 10^{-5} \) cm\(^2\)min\(^{-1}\) as a representative diffusivity for a free species in the matrix and \( L = 0.2 \) cm,
Table 2.1. A listing of some of the parameter values referred to in Section 2.2.3.2. The growth factor here is bFGF.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value</th>
<th>Parameter description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_G$</td>
<td>$6.0 \times 10^{-5}\text{cm}^2\text{min}^{-1}$</td>
<td>Diffusivity of bFGF [140]</td>
</tr>
<tr>
<td>$D_H$</td>
<td>$3.0 \times 10^{-5}\text{cm}^2\text{min}^{-1}$</td>
<td>Diffusivity of heparin [42]</td>
</tr>
<tr>
<td>$D_{GH}$</td>
<td>$1.0 \times 10^{-5}\text{cm}^2\text{min}^{-1}$</td>
<td>Diffusivity of bFGF-heparin complex [140]</td>
</tr>
<tr>
<td>$k_f$</td>
<td>$0.9 \times 10^8\text{ M}^{-1}\text{min}^{-1}$</td>
<td>Association rate constant for bFGF/heparin [107]</td>
</tr>
<tr>
<td>$k_r$</td>
<td>$0.68\text{ min}^{-1}$</td>
<td>Dissociation rate constant for bFGF/heparin [107]</td>
</tr>
<tr>
<td>$\kappa_f$</td>
<td>$9.0 \times 10^8\text{ M}^{-1}\text{min}^{-1}$</td>
<td>Association rate constant for heparin/peptide (ATIII) [74,172,173]</td>
</tr>
<tr>
<td>$\kappa_R$</td>
<td>$78\text{ min}^{-1}$</td>
<td>Dissociation rate constant for heparin/peptide (ATIII) [110]</td>
</tr>
<tr>
<td>$c^0_P$</td>
<td>$2.5 \times 10^{-4}\text{M}$</td>
<td>Initial total concentration of peptide [137]</td>
</tr>
<tr>
<td>$c^0_H$</td>
<td>$62.5 \times 10^{-6}\text{M}$</td>
<td>Initial total concentration of heparin [137]</td>
</tr>
<tr>
<td>$K_{D,G-H}^P$</td>
<td>$7.5 \times 10^{-8}\text{M}$</td>
<td>Dissociation constant of bFGF from heparin (using above data)</td>
</tr>
<tr>
<td>$K_{H,P}^D$</td>
<td>$8.67 \times 10^{-8}\text{M}$</td>
<td>Dissociation constant of heparin from peptide (using above data)</td>
</tr>
<tr>
<td>$K_{bh}$</td>
<td>$8.2 \times 10^3$</td>
<td>Binding constant for bFGF binding to heparin (using above data)</td>
</tr>
<tr>
<td>$K_{bp}$</td>
<td>$3.0 \times 10^3$</td>
<td>Binding constant for heparin binding to peptide (using above data)</td>
</tr>
</tbody>
</table>
2. Minimizing the passive release of heparin-binding growth factors

we calculate a typical diffusion time scale for the system to be $L^2/D \approx 1$ day. Hence, in a release experiment where the diffusivities are of order $10^{-5}$ $\text{cm}^2\text{min}^{-1}$, we would typically expect the unbound components to clear the system over a period of some days, and this is consistent with the experimental results of [168,188,189].

There are also time scales associated with the rate constants for the chemical reactions (2.1), namely, $1/k_r$, $1/(k_f c_0^H)$, $1/\kappa_R$, and $1/(\kappa_F c_0^P)$. In [137] and [168], the values of the rate constants for the binding of heparin to the peptide were taken to be $\kappa_R \approx 80$ $\text{min}^{-1}$ and $\kappa_F \approx 10^9$ $\text{M}^{-1}\text{min}^{-1}$, and $c_0^P$ was of order $10^{-4}$ M. For these values, it is found that $1/\kappa_R \approx 1$ s, $1/(\kappa_F c_0^P) = 10^{-5}$ s, and it is noted that these times are negligible compared to the typical time scales associated with diffusion (days), and furthermore, would remain so even if we made $c_0^P$ orders of magnitude smaller. For the binding of growth factor to heparin, the rate constants will depend on the nature of the growth factor, and data is unfortunately frequently lacking. For bFGF, [137] use parameter values corresponding to $1/k_r = 1$ min and $1/(k_f c_0^H) \approx 10^{-2}$ s, and these times are also small compared to the diffusion time scales.

For NT-3, the $k_f$ and $k_r$ values are unknown, but [168] gives the approximation $K_D^{G-H} \approx 10^{-6}$ M for the dissociation constant, which would imply that NT-3 has a low affinity for the heparin binding site. By contrast, bFGF has a relatively high affinity for the heparin binding site, with dissociation constant $K_D^{G-H} \approx 10^{-8}$ M. However, it is shown in this chapter that, provided the governing mathematical model is appropriate, the passive release of growth factor can be made slow even for low affinity binding of growth factor to heparin.

2.2.3.3. Reduction to a pair of coupled partial differential equations

It is concluded from the above remarks concerning parameters that for many experimental release systems, the time scales for the association and dissociation rates in the chemical reactions (2.1) are typically much shorter than the diffusion time scales, so that we frequently have:

$$\frac{L^2}{D_{GH}} \gg \frac{1}{k_r}, \frac{1}{k_f c_0^H}, \frac{1}{\kappa_R}, \frac{1}{\kappa_F c_0^P}.$$
2.2. The model

In such cases, diffusion is rate limiting since it is the slowest process. I shall restrict my attention to such systems in the current analysis. In terms of the dimensionless parameters \((2.11)\), the conditions above imply that \(\delta_c \ll \min(K_{bh}, 1)\) and \(\delta_h \ll \min(K_{hp}, 1)\), and so the differential equations \((2.10)_3, (2.10)_4\) and \((2.10)_5\) are replaced by the algebraic expressions:

\[
\begin{align*}
K_{bh}c_G(c_H + c_{GHP}) &= c_{GH} + c_{GHP}, \\
K_{hp}c_P(\eta_{h/c}c_{HG} + c_{GHP}) &= \eta_{h/c}c_{HP} + c_{GHP}, \\
\theta (K_{bh}c_Gc_HP - c_{GHP}) + K_{hp}c_Gc_PH - c_{GHP} &= 0, \tag{2.15}
\end{align*}
\]

where \(\theta = \delta_h/\delta_c = k_p/k_R\). The first two equations in \((2.15)\) correspond to the equilibrium forms for the binding of growth factor to heparin, and of heparin to peptide, respectively. It should be recalled here that neglecting small parameters in differential equations is not always justified because of the possible presence of boundary layers, for example. However, the simplified model I shall derive produces results that match experimental data well, and this in my view justifies my decision here to neglect terms involving \(\delta_c\) or \(\delta_h\).

The concentrations of the six species \(c_G, c_H, c_{GH}, c_P, c_{HP}, c_{GHP}\) can be written in terms of the total concentration of growth factor, \(c_G^G(x, t)\), and heparin, \(c_H^H(x, t)\), by solving the six algebraic expressions \((2.10)_6, (2.13)_1, (2.13)_2\) and \((2.15)\) to obtain:

\[
\begin{align*}
c_G(c_G^T, c_H^T) &= c_G^T - \eta_{h/c}c_H^T - \frac{\eta_{h/c}}{K_{GH}} + \frac{\sqrt{(c_G^T - \eta_{h/c}c_H^T - \frac{\eta_{h/c}}{K_{GH}})^2 + \frac{4\eta_{h/c}c_G^T}{K_{GH}}}}{2}, \\
c_P(c_G^T, c_H^T) &= \frac{1 - \frac{1}{K_{MP}} - \frac{(c_H^T - \eta_{h/c}c_H^T)}{\eta_{h/c}c_H^T}}{\frac{1}{2} + \frac{\eta_{h/c}c_H^T}{K_{MP}}}, \\
c_{GH}(c_G^T, c_H^T) &= c_{GH}^T - c_H - \frac{\eta_{h/c}}{\eta_{h/p}} \left(1 - c_P\left(c_H^T\right)\right) \left(\frac{\theta_{K_{MHCG}}(c_G^T, c_H^T)}{\eta_{h/c}(1+\theta) + \theta_{K_{MHCG}}(c_G^T, c_H^T)}\right), \\
c_{HP}(c_G^T, c_H^T) &= \frac{1 - c_P\left(c_H^T\right) - K_{MP}c_{GH}(c_G^T, c_H^T)c_P\left(c_H^T\right)}{\frac{\eta_{h/p}}{\eta_{h/c}(1+\theta)}}, \\
c_{GHP}(c_G^T, c_H^T) &= c_G^T - c_G(c_G^T, c_H^T) - c_{GH}(c_G^T, c_H^T), \\
c_{H}(c_G^T, c_H^T) &= c_H^T - c_{HP}(c_G^T, c_H^T) - (c_{GH}(c_G^T, c_H^T) + c_{GHP}(c_G^T, c_H^T))/\eta_{h/c}.
\end{align*}
\]
It is noted that these formulae can be used to calculate the equilibrium concentrations for the various species prior to release since both $c_T^G$ and $c_T^H$ are known at $t = 0$. A numerical calculation is not required to obtain such quantities. I also note that it is sufficient to solve for $c_T^G$ and $c_T^H$ as the concentrations for $c_G$, $c_H$, $c_{GH}$, $c_P$, $c_{HP}$, $c_{GHP}$ then follow immediately from (2.16). This implies that we can replace the problem containing five differential equations given by (2.10) by the following problem containing just two coupled partial differential equations:

$$
\begin{align*}
\frac{\partial c_T^G}{\partial t} + \frac{\partial}{\partial x} j_G^T(c_T^G, c_T^H, c_{Gx}, c_{Hx}) &= 0, \\
\frac{\partial c_T^H}{\partial t} + \frac{\partial}{\partial x} j_H^T(c_T^G, c_T^H, c_{Gx}, c_{Hx}) &= 0, \\
\frac{\partial c_T^G}{\partial x}(0, t) &= 0, \quad \frac{\partial c_T^H}{\partial x}(0, t) = 0 \quad \text{for } t \geq 0, \\
c_T^G(1, t) &= 0, \quad c_T^H(1, t) = 0 \quad \text{for } t \geq 0, \\
c_T^G(x, 0) &= 1, \quad c_T^H(x, 0) = 1 \quad \text{for } 0 < x < 1,
\end{align*}
$$

where:

$$
\begin{align*}
&j_G^T(c_T^G, c_T^H, c_{Gx}, c_{Hx}) = -D_G^* \frac{\partial}{\partial x} c_G(c_T^G, c_T^H) - \frac{\partial}{\partial x} c_{GH}(c_T^G, c_T^H), \\
&j_H^T(c_T^G, c_T^H, c_{Gx}, c_{Hx}) = -D_H^* \frac{\partial}{\partial x} c_H(c_T^G, c_T^H) - \frac{1}{\eta_{h/G}} \frac{\partial}{\partial x} c_{GH}(c_T^G, c_T^H),
\end{align*}
$$

and the expressions for $c_G(c_T^G, c_T^H)$, $c_{GH}(c_T^G, c_T^H)$ and $c_H(c_T^G, c_T^H)$ are given in (2.16).

It is noted that (2.17) is in a standard form that can be readily given to a mathematical package such as MAPLE to solve.

It is noteworthy that the equations (2.17) and (2.17) may also be written in the form:

$$
\frac{\partial \mathbf{c}^T}{\partial t} = \frac{\partial}{\partial x} \left( \mathbf{D}(\mathbf{c}^T) \frac{\partial \mathbf{c}^T}{\partial x} \right) \quad \text{where} \quad \mathbf{c}^T = \left( \begin{array}{c} c_T^G \\ c_T^H \end{array} \right),
$$

and where $\mathbf{D}(\mathbf{c}^T)$ is a diffusion matrix for the system given by:

$$
\mathbf{D}(\mathbf{c}^T) = \left( \begin{array}{cc} D_{GG}(\mathbf{c}^T) & D_{GH}(\mathbf{c}^T) \\ D_{HG}(\mathbf{c}^T) & D_{HH}(\mathbf{c}^T) \end{array} \right),
$$

where:

$$
\begin{align*}
&j_G^T(c_T^G, c_T^H, c_{Gx}, c_{Hx}) = -D_G^* \frac{\partial}{\partial x} c_G(c_T^G, c_T^H) - \frac{\partial}{\partial x} c_{GH}(c_T^G, c_T^H), \\
&j_H^T(c_T^G, c_T^H, c_{Gx}, c_{Hx}) = -D_H^* \frac{\partial}{\partial x} c_H(c_T^G, c_T^H) - \frac{1}{\eta_{h/G}} \frac{\partial}{\partial x} c_{GH}(c_T^G, c_T^H),
\end{align*}
$$

and the expressions for $c_G(c_T^G, c_T^H)$, $c_{GH}(c_T^G, c_T^H)$ and $c_H(c_T^G, c_T^H)$ are given in (2.16).
2.3. Analysis and Results

with:

\[
D_{GG}^T (c^T) = D_G \frac{\partial c_G}{\partial c_G} (c^T) + \frac{\partial c_G}{\partial c_T} \frac{\partial c_T}{\partial c_G} (c^T),
\]

\[
D_{GH}^T (c^T) = D_G \frac{\partial c_G}{\partial c_H} (c^T) + \frac{\partial c_H}{\partial c_G} \frac{\partial c_G}{\partial c_H} (c^T),
\]

\[
D_{HG}^T (c^T) = D_H \frac{\partial c_H}{\partial c_G} (c^T) + \frac{1}{\eta_{H/G}} \frac{\partial c_G}{\partial c_H} \frac{\partial c_H}{\partial c_G} (c^T),
\]

\[
D_{HH}^T (c^T) = D_H \frac{\partial c_H}{\partial c_H} (c^T) + \frac{1}{\eta_{H/P}} \frac{\partial c_P}{\partial c_H} \frac{\partial c_H}{\partial c_P} (c^T).
\]

In this notation, the fluxes may be written as:

\[
\mathbf{j}^T = -D(c^T) \frac{\partial c^T}{\partial x} \quad \text{where} \quad \mathbf{j}^T = \begin{pmatrix} j_G^T \\ j_H^T \end{pmatrix}.
\]

2.3. Analysis and Results

2.3.1. Minimizing the passive release of growth factor: strongly retained heparin and growth factor

In a medical device such as a nerve guide tube, it is frequently required to maintain growth factor in the device until such time as it is actively released by invading cells. In such cases, the device should be designed so as to minimise passive release of growth factor via diffusion. One of the motivations of [137] in developing the model described here was to determine how the matrix should be prepared so as to minimize passive release. There are five dimensionless parameters that can in principle be independently varied in experiments to tune the system for a given growth factor, and these are:

\[
\eta_{H/G} = \frac{c^0_H}{c^0_G}, \quad \eta_{H/P} = \frac{c^0_H}{c^0_P}, \quad \theta = \frac{k_r}{\kappa_R}, \quad K_{bh} = \frac{c^0_H}{K_D^{H-G}}, \quad K_{bp} = \frac{c^0_P}{K_D^{H-P}}.
\]

It is emphasised that the parameters \( K_D^{H-P} \) and \( \kappa_R \) are in principle tunable since peptides with desired properties can be designed (see [188]). However, if the peptide is also fixed, only three dimensionless parameters can be independently varied in the experiments; one possible choice for these parameters is \( \eta_{H/G}, \eta_{H/P} \) and \( K_{bp} \). The parameters \( D_G^* \) and \( D_H^* \) cannot be changed in experiments as they are fixed for a given growth factor. The parameters \( \delta_G \) and \( \delta_H \) are neglected here since they are typically very small in release experiments.
2. Minimizing the passive release of heparin-binding growth factors

In the literature to date, the emphasis has been on experimentally varying the parameters $\eta_{H/G}$ and $\eta_{H/P}$ to determine conditions that ensure that the passive release of growth factor is slow; see [137,168,185,188,189]. In particular, experiments have been carried out for very large values of the ratio $\eta_{H/G}$, and quite small values for the ratio $\eta_{H/P}$. However, I now show that if one wishes to make passive release slow, then the key parameters to monitor are $K_{bH}$ and $K_{bP}$, rather than $\eta_{H/G}$ and $\eta_{H/P}$. More precisely, I shall show that slow release of at least a proportion of the growth factor is assured provided $K_{bH}, K_{bP} \gg 1$ (with the other parameters being $O(1)$, although there are other possibilities), or, equivalently:

$$c_0^H \gg K_{G-H}^0 \quad \text{and} \quad c_0^P \gg K_{H-P}^0.$$  \hspace{1cm} (2.19)

Recall that $K_{bH}, K_{bP} \gg 1$ corresponds to strong retention of both growth factor by the heparin, and of heparin by the peptide. Hence, if practicable, for slow release of growth factor, the matrix should usually be prepared with the initial concentration of heparin being much larger than the dissociation constant of growth factor from heparin, and the concentration of peptide covalently cross-linked to the fibrin matrix peptide being much larger than the dissociation constant of heparin from peptide. I now justify this conclusion using an asymptotic argument and by providing numerical evidence. In particular, I shall demonstrate numerically that growth factor release can be relatively fast if the conditions (2.19) are not met even with $\eta_{H/G} \gg 1$ and $\eta_{H/P} \ll 1$.

2.3.1.1. Asymptotics: $K_{bH}, K_{bP} \gg 1$

We write $K_{bH} = 1/\varepsilon$, $K_{bP} = \mu/\varepsilon$ and consider the limit $\varepsilon \to 0$ in (2.16) for fixed $O(1)$ values of $c_*^G$ and $c_*^P$, and with $\mu$ and all the remaining dimensionless parameters in (2.16) being $O(1)$. The expressions I shall display for this limit were derived with the aid of the series command in MAPLE.

The fraction of bound growth factor in the matrix, which is denoted by $f_B$, is given by:

$$f_B(x,t) = \frac{c_{\text{GHP}}(x,t)}{c_G(x,t) + c_{GH}(x,t) + c_{\text{GHP}}(x,t)} = \frac{c_{\text{GHP}}(x,t)}{c_G(x,t)};$$
some solutions for this quantity at \( t = 0 \) are displayed in Figures 2.4 and 2.5. For clarity, I revert to dimensional quantities in this section. In the limit \( \varepsilon \to 0 \), it is found that:

\[
f_B(x, t) \sim \begin{cases} 
\frac{c_H^T}{c_G^T} & \text{if } c_H^T < c_G^T \text{ and } c_H^T < c_P^0, \\
\frac{c_P^0}{c_H^T} & \text{if } c_H^T < c_G^T \text{ and } c_H^T > c_P^0, \\
\frac{c_H^0}{c_H^T} & \text{if } c_H^T > c_G^T \text{ and } c_H^T > c_P^0, \\
1 & \text{if } c_H^T > c_G^T \text{ and } c_H^T < c_P^0.
\end{cases}
\] (2.20)

There are also four narrow transition regions at the interfaces of the regimes listed above, and the detail of the behaviour in these regions is given in the Appendix. The results of (2.20) are readily interpreted. Take, for example, the case \( f_B \sim 1 \) for \( c_H^T > c_G^T \) and \( c_H^T < c_P^0 \). Since in the current limit both the growth factor and heparin are strongly retained, then provided there is enough heparin to accommodate the growth factor (\( c_H^T > c_G^T \)) and enough peptide to accommodate the heparin (\( c_H^T < c_P^0 \)), all of the growth factor in the matrix will be bound to leading order (\( f_B \sim 1 \)); see Figures 2.4 and 2.5. This is the desired regime for passive release to be slow, as I now confirm. The other cases are similarly interpreted.

To gain insight into the time it would take for the growth factor to passively release from the matrix, I now consider the two components of the diffusion matrix that arise in the total growth factor flux, namely, \( D_{GG}^T \) and \( D_{GH}^T \). It is found as \( \varepsilon \to 0 \) that:

\[
D_{GG}^T \sim \begin{cases} 
D_G & \text{if } c_H^T < c_G^T, \\
\frac{D_{GH}(c_H^T-c_P^0)}{c_H^T} & \text{if } c_H^T > c_G^T \text{ and } c_H^T > c_P^0, \\
\varepsilon \left\{ \frac{D_G c_H^0 c_H^T}{(c_G^T-c_H^T)^2} - \frac{D_{GH} c_H^0}{\mu(c_H^T-c_P^0)} \right\} & \text{if } c_H^T > c_G^T \text{ and } c_H^T < c_P^0.
\end{cases}
\] (2.21)
2. Minimizing the passive release of heparin-binding growth factors

Figure 2.4. Theoretical curves for the equilibrium bound fraction of growth factor prior to release. The curves are calculated using the formulae (2.16). In (a), $\eta_{H/P}$ is varied and the remaining non-dimensional parameters are fixed. In (b), $\eta_{H/G}$ is varied with the other parameters fixed. The parameter values used are $\eta_{H/G}/\eta_{H/P} = 2000$, $\theta = 9 \times 10^{-3}$, $K_{bp} = 3000$ and $K_{D,G,H} = 7.5 \times 10^{-9}\text{M}$ \[107\].
2.3. Analysis and Results

Figure 2.5. Plots of the fraction of bound growth factor prior to release as a function of (a) $K_{bH}$ with $K_{bP} = 3000$, and, (b) $K_{bP}$ for various values of $K_{bH}$. The other parameter values used are $\eta_{h/G} = 500$, $\eta_{h/P} = 1/4$, $K_{D,G-H} = 7.5 \times 10^{-9}$M, $K_{D,H-P} = 8.67 \times 10^{-8}$M.
2. Minimizing the passive release of heparin-binding growth factors

and,

\[
D^T_{GH} \sim \begin{cases} 
-D_G & \text{if } c^T_H < c^T_G \text{ and } c^T_G < c^0_P, \\
D_{GH} - D_G & \text{if } c^T_H < c^T_G \text{ and } c^T_G > c^0_P, \\
\frac{D_{GH} \epsilon c^T_G}{c^0_H} - \frac{D_G \epsilon c^T_G}{(c^T_G - c^0_H)^2} & \text{if } c^T_G > c^0_H \text{ and } c^T_H > c^0_P, \\
\epsilon \left( \frac{D_{GH} \epsilon c^T_G}{h(c^T_G - c^0_P)^2} - \frac{D_G \epsilon c^T_G}{(c^T_G - c^0_H)^2} \right) & \text{if } c^T_H > c^T_G \text{ and } c^T_G > c^0_P.
\end{cases}
\]  

(2.22)

Surface plots for \(D^T_{GC}(c_G^T, c_H^T)\) and \(D^T_{GH}(c_G^T, c_H^T)\) are given in Figure 2.6 for parameter values corresponding to \(\epsilon \ll 1\), and the principal asymptotic regions are indicated on the surfaces. The point to note here is that the flux of growth factor for the region (IV) \(c^T_H > c^T_G\) and \(c^T_H < c^0_P\), are \(O(\epsilon)\) smaller than those for the other regions.

In view of (2.20), (2.21) and (2.22), it is now clear that the optimal regime for the undesirable passive release of growth factor to be slow is \(c^T_H > c^T_G\) and \(c^T_H < c^0_P\), which indicates that the polymerization mixture for the matrix should have \(c^0_G < c^0_H < c^0_P\). Hence, the original recommendations for matrix preparation, (2.19), are expanded to the following:

\[
c^0_H \gg K^D_{G-H}, \quad c^0_P \gg K^D_{H-P}, \quad c^0_G < c^0_H < c^0_P.
\]  

(2.23)

We have large diffusion coefficients for the first two cases in (2.21) and the first three cases in (2.22) because for each of these regimes, there is a substantial free component of growth factor that can diffuse. For example, for the case, \(c^T_H < c^T_G\) and \(c^T_G < c^0_P\), we have \(c_G \sim c^T_G - c^T_H\). For the boundary and initial conditions of (2.17), this free drug will clear the system to leading order on the time scale \(t = O(L^2/D_{GH})\). However, once the free component has cleared, the remaining bound component in the bulk will be governed by the slow regime in (2.21) and (2.22), and this will clear the system on the long time scale \(t = O(L^2/(\epsilon D_{GH})) \gg O(L^2/D_{GH})\). Similar remarks apply to the second and third regimes in (2.22). Hence, if the matrix is prepared
2.3. Analysis and Results

Figure 2.6. Surface plots for $D_{GG}^{T}(c_{G}^{T}, c_{H}^{T})$ and $D_{GH}^{T}(c_{G}^{T}, c_{H}^{T})$ in dimensional variables. In the plots, $D_{G} = 6 \times 10^{-5}$ cm$^2$/min, $D_{GH} = 3 \times 10^{-5}$ cm$^2$/min, $c_{P}^{0} = 2.5 \times 10^{-4}$M, $c_{H}^{0} = 2c_{P}^{0}$, $K_{BH} = 8000$, and $K_{BP} = 3000$. These parameter values correspond to the asymptotic limit $\varepsilon \ll 1$ considered in Section 2.3.1.1 and on the surfaces I have indicated the asymptotic regions I, II, III and IV.
2. Minimizing the passive release of heparin-binding growth factors

with $K_{bh}, K_{bp} \gg 1$, and if the governing model is appropriate, then it is assured that at least a fraction of the growth factor will release on the slow time scale $t = O(L^2/(\varepsilon D_{GH}))$. Furthermore, we predict that almost all of the growth factor will release slowly if the matrix is prepared with $c^0_h/c^0_G > 1$ and $c^0_p/c^0_H > 1$; notice that it is not required that these fractions be large; see Figure 2.4. However, it should be cautioned that if there is a substantial component of free peptide (which is not included in the model described here), then there can still be a significant amount of free growth factor that can release on a fast diffusion time scale.

The two stage release behaviour just described has been observed in experiments (see Section 2.4), where one sometimes sees a proportion of the growth factor releasing quickly over a period of some days (which could correspond to free growth factor releasing on a diffusion time scale) followed by much slower release of the remaining fraction (which could correspond to a strongly retained bound component releasing on a longer time scale such as that described above).

### 2.3.1.2. Incorporating free peptide in the analysis

I now consider the case where a substantial fraction of the peptide remains free and competes with the covalently bound peptide for free heparin. I assume that heparin bound to free peptide has the same binding behaviour for growth factor as free heparin. The essence of my results above carry over, as I now explain. It is supposed that the conditions (2.23) hold, and that the ratio of peptide covalently attached to the fibrin, $r$, has been quantified. Then the concentration of cross-linked peptide in the system is $rc^0_p$, and since $c^0_p > c^0_H$, the initial concentration of heparin that is bound to cross-linked peptide is, to leading order, $rc^0_h$. Since in turn $c^0_H > c^0_G$, the initial concentration of growth factor trapped by the delivery system is, to leading order, $rc^0_G$. It follows that a fraction $(1 - r)$ approximately of the growth factor will diffuse out of the system over a diffusion time scale. Hence, the final recommendation, which is added to (2.23), is that $c^0_G$ should be chosen so that $rc^0_G$ is sufficiently large for the therapy to be effective.
2.3.2. Numerical results

2.3.2.1. Numerical methods

Two different procedures were used to numerically integrate the initial boundary value problem (2.17). In one method, simple explicit time-stepping was used to update the values of $c^T_G$, $c^T_H$, with the other quantities being then updated using (2.16). Centred difference approximations were used for $c_{Gxx}$, $c_{Hxx}$, $c_{GHxx}$, and the no-flux conditions on $x = 0$ were handled by introducing a fictitious line in the usual way. In the other method, the system was numerically integrated using the MAPLE command `pdsolve/numeric`, which is based on a centred implicit finite difference scheme. Good agreement was obtained between the two schemes and with known analytical results.

![Figure 2.7](image)

Figure 2.7. The fraction of bound growth factor (bFGF) as a function of position and for various times, with $D_G = 6 \times 10^{-5}$ cm$^2$/min, $D_H = 3 \times 10^{-5}$ cm$^2$/min, $D_{GH} = 1 \times 10^{-5}$ cm$^2$/min, $\eta_{H/G} = 500$, $\eta_{H/P} = 1/4$, $K_{bH} = 8200$ and $K_{bP} = 3000$. 

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2. Minimizing the passive release of heparin-binding growth factors

2.3.2.2. Results

In Figure 2.7 I have plotted the fraction of bound growth factor as a function of penetration through the matrix for parameter values corresponding to when the conditions (2.23) are satisfied; the parameter values used are shown in Table 2.1. The results of this simulation predict that about 90% of the growth factor remains bound in the fibrin matrix and is available to be released by cell-mediated mechanisms after 14 days.

![Figure 2.8. Numerical solutions of the initial boundary value problem (2.17). The predicted fraction of total growth factor released (see equation (2.14)) is displayed over a two week period. The parameter values chosen are $D^*_G = 6$, $D^*_H = 3$, $\theta = 9 \times 10^{-3}$, $K_{bh} = 8000$, $K_{bp} = 3000$, and with various $\eta_{H/G}$, $\eta_{H/P}$ values indicated on the curves.](image)

In Figure 2.8 - 2.9 I display numerical profiles for the fraction of total growth factor (see equation (2.14)) that has released from the system as a function of time over a period of a fortnight. Four of the five release profiles displayed in Figure 2.8 correspond to the case $K_{bh}, K_{bp} \gg 1$, the regime is recommended for matrix preparation. The other parameter values are all $O(1)$, and can be found either on the figure or in its caption. The fifth profile, the
2.3. Analysis and Results

Figure 2.9. Numerical solutions of the initial boundary value problem (2.17). The predicted fraction of total growth factor released (see equation (2.14)) is displayed over a two week period. The parameter values chosen are $D^*_G = 6$, $D^*_H = 3$, $\theta = 9 \times 10^{-3}$ throughout. In (a), $K_{bH} = 3000$, $\eta_{H/G} = 1000$, $\eta_{H/P} = 1/40$, with various $K_{bH}$ values indicated on the curves. In (b), $K_{bH} = 8000$, $\eta_{H/G} = 2$, $\eta_{H/P} = 1/2$, with various values for $K_{bP}$ indicated on the curves.
top curve in the figure, corresponds to the case of no drug delivery system, and has been included for comparison. In this case, all of the growth factor is free in the gel, and its concentration is governed by the linear diffusion equation (see Section 2.5.1). The other four curves correspond to the four asymptotic regimes identified in Section 2.3.1. It is observed for these that the growth factor release rate becomes slow after a period of approximately a day, and this is easily interpreted. The fast initial release phase corresponds to the rapid out-diffusion of free growth factor on a diffusion time scale; notice that this period coincides (tellingly) with the period over which the growth factor releases when there is no delivery system. Once the free component has substantially exited the system, the remaining bound fraction releases slowly over a long time scale, as previously explained.

Consider, for example, the curve in Figure 2.8 that has \( \eta_{H/G} = \frac{1}{3}, \eta_{H/P} = \frac{1}{2} \). These parameter values correspond to \( c_0^G = 3c_0^H, c_0^P = 2c_0^H \), so that for \( \varepsilon \ll 1 \), all of the heparin is bound to the peptide, but only one third of the growth factor is bound to the heparin at leading order. Hence we expect two thirds of the growth factor approximately to have left the system after a period of a few days; this is confirmed by the numerical results displayed in Figure 2.8, where we see that \( M(1 \text{ day})/M(\infty) \sim 2/3 \) for \( \eta_{H/G} = 1/3 \) and \( \eta_{H/P} = 1/2 \). In all cases, the numerical results displayed in Figure 2.8 are consistent with asymptotic predictions of this kind.

In Figure 2.9 (a), numerical solutions to (2.17) are displayed for \( K_{bp}, \eta_{H/G} \gg 1 \), and for various values of \( K_{bl} \). These parameters correspond to the heparin being strongly retained by the peptide, and the initial concentration of heparin greatly exceeding that of the growth factor. However, we see from the figure that this is not sufficient to guarantee slow release of growth factor. For values \( K_{bl} = O(1) \), which correspond to moderate retention of growth factor, the growth factor will release over a period of some days. This compares unfavourably with the results displayed in Figure 2.8 where both \( K_{bp} \) and \( K_{bl} \) are large and we have slow release in all cases even though the values for \( \eta_{H/G} \) there are only \( O(1) \). In Figure 2.9 (b), numerical solutions to (2.17) are displayed for \( K_{bl} \gg 1, \eta_{H/G} = O(1) \), and for various values of \( K_{bp} \). When the growth factor is strongly retained by the heparin, the release rate for the growth factor
is only slow for $K_{	ext{pp}} \gg 1$.

2.4. Comparison with experimental data

I now compare the theoretical release profiles generated by the model with in vitro experimental release data. For experimental data where there is no delivery system or no heparin, the comparison with the model is made for all times using the analytical expression (2.25). However, for experimental data where the full delivery system is present, I do not attempt to compare the model results with experimental data in the first two days of release since free peptide may play a significant role in this period, and the model does not track the concentration of this species. In fact, to incorporate the effect of free peptide would require the inclusion of three more species in the model: free peptide, free peptide-heparin complex, and free peptide-heparin-growth factor complex; see [188]. This would add three reaction-diffusion equations to the governing mathematical model, and would complicate the analysis considerably. However, after a period of some days, all of these species should have substantially diffused out of the system since there is no mechanism to replenish them (the covalently bound peptide does not dissociate), and the species that then remain do form part of the model described here. It should be said that it is not difficult to fit the model results with complete release profiles that include the first few days, but this would require the selection of parameters in the model that are not compatible with the experimental conditions. The numerical solutions displayed in Figure 2.8 do have the qualitative character of many experimental profiles; see the experimental results displayed in Figure 2.10 for example.

In selecting parameter values for the model, I use wherever possible the values used in the experiments. I always use the same heparin to growth factor ratio $\eta_{H/G}$ and heparin to peptide ratio $\eta_{H/P}$ as used in the experiments. Where estimates for the diffusivities can be found, either in the experimental paper in question, or elsewhere, I use them. Where a value for $D_G$ is not available, I estimate it by fitting an experimental profile for no delivery system to the corresponding theoretical release profile (2.25). For $D_{GH}$, I then select
2. Minimizing the passive release of heparin-binding growth factors

Figure 2.10. Comparison of experimental and theoretical release profiles (see equation (2.14)). The curves are theoretical and the symbols are experimental. In the figure, (a) has data for NT-3 taken from [168], (b) has data for NGF taken from [188], and (c) has data for GDNF taken from [189]. The values of $K_{bh}$ used to generate the theoretical curves are given on them and the remaining parameters used can be found in Table 2.2. In (a), two approximate $K_{bh}$ values for experimental data are also given.
2.4. Comparison with experimental data

A value which has order of magnitude $10^{-5}$ cm$^2$/min, and which is such that $D_{GH} < D_G, D_H$. The values for $K_{bp} = c_0^G/K_{H,P}^{D_G}$ are calculated using the given values for $c_0^G$ and $K_{H,P}^{D_G} = 8.67 \times 10^{-8}$ M. This is probably an over-estimate since I am beginning my simulation after day two and unbound peptide will have been lost, reducing the value for $c_0^G$. A similar remark applies to the values of $c_0^H$ and $c_0^H$. However, the values for $K_{bp}$ are of the order of thousands, and adjusting them by a factor of two or so has very little effect on the resulting profiles. The selection of appropriate values for $K_{bH} = c_0^H/K_{G,H}^{D_H}$ is a more delicate issue though because its values can vary over orders of magnitude in the experiments and consequently the behaviour can be strongly dependent on it. Unfortunately, both numbers involved in the calculation of $K_{bH}$ are uncertain here since the available value for $c_0^H$ is probably an overestimate as explained above and only order of magnitude estimates are available for $K_{G,H}^{D_H}$. Hence, I use $K_{bH}$ as a fitting parameter, but insist that it has the same order of magnitude as $c_0^H/K_{G,H}^{D_H}$, where $c_0^H$ is the value given in the experiment and $K_{G,H}^{D_H}$ is the order of magnitude estimate for this dissociation constant.

I have chosen to compare the model results with experimental data drawn from three studies: (a) [168], (b) [188], and (c) [189]; we shall subsequently refer to these as (a), (b), (c), and this labelling has also been used in Figure 2.10 where the comparison between the model and the experimental data is given. In (a), (b), (c) the growth factors used are NT-3, NGF and GDNF, respectively. The setup for these experiments is as described in the introduction of this chapter, and in each case, the quantity measured is the fraction of total growth factor released as a function of time. Most of the data displayed is for the full delivery system, although some results for experiments in which elements of the delivery system have been omitted are also shown. In Figure 2.10 I also display in each case the solution (2.25) with the appropriate value for $D_G$, which is the theoretical prediction when there is no delivery system or no heparin. In Figure 2.10 (a), I display experimental data with $K_{bH} \sim 1$ and $K_{bH} \sim 5$, but I do not attempt to fit this data other than to comment that it follows quite closely the behaviour of the solution (2.25).

It is noted that the correspondence between the model and experimental data is satisfactory in all cases. It is clear that for $K_{bH} \gg 1$, the experimental
release rates become slow after a few days, which is consistent with the theoretical prediction. For $O(1)$ values of $K_{bh}$ (Figure 2.10 (a)), the experimental release rates are comparable to that for no delivery system. The experimental release profiles for data corresponding to no delivery system or no heparin are adequately described by (2.25).

Table 2.2. The data used to generate the theoretical curves in Figure 2.10. Unmarked data is taken from the paper referred to in its column. The markings on the remaining data are explained below the table.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Figure 2.10 (a)</th>
<th>Figure 2.10 (b)</th>
<th>Figure 2.10 (c)</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_G$</td>
<td>$2.5 \times 10^{-5(a)}$</td>
<td>$9.7 \times 10^{-5}$</td>
<td>$2.0 \times 10^{-5(a)}$</td>
<td>cm$^2$/min</td>
</tr>
<tr>
<td>$D_H$</td>
<td>$3.0 \times 10^{-5(b)}$</td>
<td>$9.1 \times 10^{-5}$</td>
<td>$3.0 \times 10^{-5(b)}$</td>
<td>cm$^2$/min</td>
</tr>
<tr>
<td>$D_{GH}$</td>
<td>$1.0 \times 10^{-5(c)}$</td>
<td>$7.5 \times 10^{-5}$</td>
<td>$1.5 \times 10^{-5(a)}$</td>
<td>cm$^2$/min</td>
</tr>
<tr>
<td>$c_0$</td>
<td>$2.3 \times 10^{-4}$</td>
<td>$2.5 \times 10^{-4}$</td>
<td>$2.5 \times 10^{-4}$</td>
<td>M</td>
</tr>
<tr>
<td>$c_0^{G}$</td>
<td>$7.4 \times 10^{-9}$</td>
<td>$7.4 \times 10^{-9}$</td>
<td>$3.1 \times 10^{-9}$</td>
<td>M</td>
</tr>
<tr>
<td>$K_{D,G,H}$</td>
<td>$1.5 \times 10^{-7(a)}$</td>
<td>$0.33 \times 10^{-7(a)}$</td>
<td>$1.25 \times 10^{-7(a)}$</td>
<td>M</td>
</tr>
<tr>
<td>$K_{D,H,P}^D$</td>
<td>$8.67 \times 10^{-8(d)}$</td>
<td>$8.67 \times 10^{-8(d)}$</td>
<td>$8.67 \times 10^{-8(d)}$</td>
<td>M</td>
</tr>
</tbody>
</table>

(a) Estimated from data in [168,188,189].
(b) [42].
(c) [140].
(d) $\kappa_R = 78$ min$^{-1}$ ([110]) and $\kappa_p = 9.0 \times 10^8$ M$^{-1}$min$^{-1}$ ([74,172,173]).

2.5. Some special cases

The appropriateness of the proposed governing mathematical model may be assessed experimentally for a particular system by simply omitting components from the polymerization mixture when preparing the fibrin gels. The governing mathematical model may then reduce considerably, making it easier to compare its predictions with experimental data and enabling parameter estimation. It is suggested that such simpler systems should be assessed experimentally as a preliminary to consideration of the complete release system. I consider four such cases, and then make a brief remark concerning the full system.
2.5. Some special cases

2.5.1. No heparin

If in the preparation of the fibrin matrices, no heparin is added to the fibrinogen solution, then in dimensional variables:

\[ c_u(x, t) = c_{GH}(x, t) = c_{HP}(x, t) = c_{GHP}(x, t) = 0 \]

for all \( 0 \leq x \leq L \) and \( t \geq 0 \), and the governing equations reduce to:

\[
\frac{\partial c_G}{\partial t} = D_G \frac{\partial^2 c_G}{\partial x^2},
\]

\[
\frac{\partial c_G}{\partial x}(0, t) = 0 \quad \text{for } t \geq 0,
\]

\[ c_G(L, t) = 0 \quad \text{for } t \geq 0, \]

\[ c_G(x, 0) = c_G^0 \quad \text{for } 0 < x < L. \]

This is easily solved by separating variables \([26]\) to obtain:

\[ c_G(x, t) = \frac{4c_G^0}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^n + 1}{2n-1} \exp \left( -\frac{(2n-1)^2\pi^2 D_G t}{4L^2} \right) \cos \left( \frac{(2n-1)\pi x}{2L} \right), \]

from which it follows that the fraction of the available growth factor released by time \( t \) is (see \((2.14)\)):

\[ \frac{M(t)}{M(\infty)} = 1 - \frac{8}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \exp \left( -\frac{(2n-1)^2\pi^2 D_G t}{4L^2} \right). \]

This expression contains only one unknown parameter, \( D_G \), and it predicts that the growth factor should release on the time scale \( t = O(L^2/D_G) \), which for the matrices described here and typical growth factors corresponds to a period of some days. I suggest a four day release experiment and at least three data points per day for the fraction of growth factor released. If the correspondence between theory and experiment is good, then the growth factor diffusivity \( D_G \) is estimated. The four day release period is suggested here because it is typically found in release experiments with no heparin that the growth factor has effectively exited the system after four days; see, for example, the experimental data displayed in Figure \([2.10]\).
2. Minimizing the passive release of heparin-binding growth factors

2.5.2. No growth factor and peptide

If both growth factor and peptide are omitted from the polymerization mixture, then:

\[ c_G(x, t) = c_P(x, t) = c_{GH}(x, t) = c_{HP}(x, t) = c_{GHP}(x, t) = 0, \]

for all \( 0 \leq x \leq L \) and \( t \geq 0 \). The only surviving species in the model is free heparin, and its concentration is governed by an initial boundary value problem identical in structure to (2.24); simply substitute G with H in (2.24) and (2.25). I now suggest a four day release experiment for the heparin with at least three data points per day for the fraction of heparin released. The experimental and theoretical release results may then be compared, providing a second test of the validity of the model. If the correspondence between theory and experiment is good, then the heparin diffusivity \( D_H \) is estimated (of course the value obtained must be consistent with previous estimates; it must have the correct order of magnitude).

2.5.3. No peptide

If no peptide is added to the fibrinogen solution in the preparation of the fibrin matrices, then:

\[ c_P(x, t) = c_{HP}(x, t) = c_{GHP}(x, t) = 0 \]

for all \( 0 \leq x \leq L \) and \( t \geq 0 \).

The dimensional form for the governing equations then reduces to:

\[
\begin{align*}
\frac{\partial}{\partial t}(c_G + c_{GH}) &= D_G \frac{\partial^2 c_G}{\partial x^2} + D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2}, \\
\frac{\partial}{\partial t}(c_H + c_{GH}) &= D_H \frac{\partial^2 c_H}{\partial x^2} + D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2}, \\
k_f c_G c_H &= k_r c_{GH}, \\
\frac{\partial c_G}{\partial x}(0, t) &= 0, \quad \frac{\partial c_H}{\partial x}(0, t) = 0, \quad \frac{\partial c_{GH}}{\partial x}(0, t) = 0 \quad \text{for } t \geq 0, \\
c_G(L, t) &= 0, \quad c_H(L, t) = 0, \quad c_{GH}(L, t) = 0 \quad \text{for } t \geq 0, \\
c_G(x, 0) &= c_G^0; \quad c_H(x, 0) = c_H^0; \quad c_{GH}(x, 0) = 0 \quad \text{for } 0 < x < L.
\end{align*}
\]
2.5. Some special cases

If $D_G$ and $D_H$ have been estimated using the procedures described in the previous two subsections, then the only unknown parameters in (2.26) are $D_{GH}$ and $K_{G-H}^0 = k_r/k_f$. If the value of $K_{G-H}^0$ is known for a given growth factor and heparin, then $D_{GH}$ may be estimated by comparing theoretical release profiles generated by (2.25) with experimental data.

2.5.4. No growth factor

If no growth factor is added to the fibrinogen solution, then:

$$c_G(x, t) = c_{GH}(x, t) = c_{GHP}(x, t) = 0 \text{ for all } 0 \leq x \leq L \text{ and } t \geq 0.$$  

The dimensional governing equations then reduce to:

$$\frac{\partial}{\partial t} (c_H + c_{HP}) = D_H \frac{\partial^2 c_H}{\partial x^2},$$

$$\kappa_F c_H c_P = \kappa_R c_{HP}, \quad c_{HP} + c_P = c_P^0,$$

$$\frac{\partial c_H}{\partial x}(0, t) = 0, \quad \text{for } t \geq 0,$$

$$c_H(L, t) = 0, \quad \text{for } t \geq 0,$$

$$c_H(x, 0) = c_H^0, \quad c_P(x, 0) = c_P^0 \quad \text{for } 0 < x < L.$$  

(2.27)

If $D_H$ has been estimated as described above, then it is in principle possible to estimate the remaining unknown parameter $K_{H-P}^0 = \kappa_R/\kappa_F$ by fitting to experimental data.

The model given by (2.27) has an identical mathematical structure to a model for drug redistribution in tissue that I shall describe and analyse in some detail in Chapter 4. In the drug model, the heparin in (2.27) corresponds to the drug, and the peptide corresponds to the specific binding sites for the drug. The solutions developed in Chapter 4 are relevant to the current analysis.

2.5.5. The full system

If the model passes the tests set for it in the preceding subsections, one may proceed to preparing the matrix with all components included. If the
matrix is prepared in accordance with the recommendations \cite{2.23}, one should experimentally observe that the growth factor release rates become slow after a period of a few days if the model is valid.

### 2.6. Discussion

It has been shown that for typical experimental systems, the governing mathematical model may be reduced to a system of just two partial differential equations, and that the release behaviour is frequently dominated by the values of two non-dimensional parameters. If the model is valid for a particular system, then the passive release of at least a fraction of the growth factor will be slow if the fibrin matrices are prepared with the concentration of crosslinked peptide greatly exceeding the dissociation constant of heparin from peptide, and the concentration of heparin greatly exceeding the dissociation constant of growth factor from heparin. It is noteworthy that these criteria do not preclude slow release for growth factors that bind heparin with low affinity. I also note the value of having reliable estimates for the two dissociation constants in the system.

It is experimentally convenient to vary the ratios of heparin to growth factor and of heparin to peptide in the polymerisation mixture for the gels to determine the optimal conditions for passive release to be slow. However, these ratios are not usually the key parameters, and where this strategy does result in slow release, it has been found that it is because the binding constants have strayed into the regime referred to in the paragraph immediately above. My results indicate that the ratios of heparin to growth factor and of heparin to peptide in the polymerisation mixture need neither be large nor small for passive release to be slow.

For the first time, theoretical release profiles generated by the model are compared directly with \textit{in vitro} experimental data. It is found that once the free components have cleared the system, the correspondence between experimental and theoretical results is satisfactory. In particular, my predictions concerning conditions that will give rise to slow passive release are confirmed.

It may be possible to partially unpick the system experimentally by simply
omitting components in the polymerization mixture for the fibrin gels. For example, if heparin is omitted from the polymerization mixture, the governing mathematical model reduces to a standard linear diffusion equation for the growth factor, and theoretical predictions may then be readily compared with experimental data to help validate the model and estimate a diffusivity; see Section 2.5.
3. Controlled release of growth factors from a peptide-based affinity system

3.1. Introduction

In Chapter 2, a mathematical model that describes the release of heparin-binding growth factors from an affinity-based delivery system was formulated and analyzed in some detail. However, this model takes no account of the possible presence of free peptide in the fibrin gel. In a gel where the growth factor binds strongly to heparin, the free components in the system may be effectively removed by allowing them to out-diffuse into an elution medium that is periodically replaced over a period of some days. Once the free components have exited the system, growth factor release from the fibrin matrix may then be adequately described by the model considered in Chapter 2.

However, if one wishes to describe an entire release profile that includes the first few days, then free peptide must be incorporated in the modelling. Incorporating free peptide in the model of Chapter 2 would require the consideration of three more species: free peptide, free peptide-heparin complex, and free peptide-heparin-growth factor complex. Each of these mobile species has its own governing partial differential equation containing a diffusion term, and the complete system of model equations is now formidable, containing no less than eight partial differential equations in all. These equations are listed and very briefly discussed in Chapter 7. In my view, this large and complex system does not provide a sensible starting point for evaluating the effect of
3. Controlled release of growth factors from a peptide-based affinity system

In this chapter, I shall analyze instead a considerably simpler set of equations that model an affinity-based delivery system that contains no heparin.

In the model I shall consider here, a peptide molecule binds directly to the growth factor, and there is no intermediary heparin molecule. It will be seen that this system can be modelled by a system of five partial differential equations, which compares favourably with the eight equations that are required if heparin also forms part of the delivery system.

3.1.1. Experimental studies

In the current system, the binding properties of the peptide for the target growth factor are clearly crucial since there is now no heparin in the matrix. The peptides used are bidomain. They contain a transglutaminase substrate at the N-terminus that forms a covalent bond with fibrin; this is the interaction that fixes the peptide to the fibrin matrix. They also contain a second domain that can bind with a target growth factor or drug. Systematic approaches for identifying peptides that bind target drugs with high affinity have been adopted in some studies. In Maynard & Hubbell [91], a sulfated peptide that binds to vascular endothelial growth factor (VEGF) was discovered by screening a large combinatorial library of sulfated peptides composed of four amino acids. In Maxwell et al. [90], combinatorial phage display libraries were used to identify short peptide sequences with varying affinities for heparin. In Willerth et al. [184], a phage display library was screened to select for peptide sequences that bind to NGF.

Vulic & Shoichet [177] have developed an affinity-based delivery system that consists of a hydrogel containing covalently incorporated peptides that can bind with the Src homology 3 domain of proteins. In vitro experiments were conducted using the system, and the release behaviour of human basic fibroblast growth factor was investigated. It was found that growth factor release from the modified gels was considerably slower compared to release from unmodified controls. The system was demonstrated to be tunable, and it is claimed that it is capable of delivering a number of different proteins. The re-
lease rate of protein can be controlled by using binding peptides with different affinities, or changing the concentration of the binding peptide.

Shepard et al. [151] have developed a gene delivery system by incorporating affinity peptides in hydrogels. The peptides bound to gene vectors in the hydrogels, slowing their release from the system. The increased retention of the gene vectors was shown to lead to a corresponding increase in the gene delivery.

3.1.2. The growth factor delivery system

Willerth et al. [184] have developed a growth factor delivery system that exploits peptide’s ability to bind with growth factors. Figure 2.1 displays schematically the various elements of their system. The natural blood clotting matrix, fibrin, was chosen as the base material. Three dimensional fibrin hydrogel scaffolds were fabricated, into which invading cells could infiltrate, and release growth factor attached to the fibrin matrix via enzymatic processes. The growth factor attaches to the matrix via a peptide which is covalently cross-linked to the fibrin matrix. Hence, growth factor attachment to the matrix is dependent on two distinct interactions, which may be crudely represented by: (fibrin)–(peptide)–(growth factor).

3.1.3. Matrix preparation and release experiments

Although the analysis presented in this chapter is theoretical, it is nevertheless useful to give some indication of how the fibrin matrices were prepared and how the growth factor release experiments were conducted in the experimental studies referred to in Section 3.1.1. The discussion here parallels closely corresponding descriptions given in Chapter 2 for the heparin-based system and so I shall be brief. I begin by sketching the matrix polymerization procedure. The more technical details are omitted here; these can be found in [137], for example.

Fibrinogen is purified from blood and mixed with appropriate amounts of calcium ions, thrombin, growth factor, and peptide, to obtain a polymerization mixture. This mixture is then placed in a 24-well tissue culture plate and
incubated under appropriate conditions for an hour \[137\]. It is clear from this that the concentrations of peptide and growth factor in the polymerization mixture are readily varied. In this chapter, both unbound and bound peptide are incorporated in the modelling, but the model unfortunately makes no prediction as to what fraction of the peptide binds to the fibrin matrix initially; this information must be provided separately.

The setup for the growth factor release experiments is as described in Section 2.1.5.

![Diagram of fibrin matrix with species](image)

Figure 3.1. A schematic representation of the fibrin matrix containing all five species of the model. In the figure, the bound peptide (PB) is attached directly to the fibrin matrix. Some of this peptide is bound with free growth factor to form growth factor-bound peptide complexes (GPB). The three species that are not attached to the fibrin matrix are also depicted, these being: free growth factor (G), unbound peptide (PU), and growth factor-unbound peptide complexes (GPU).

### 3.2. The model

#### 3.2.1. Model equations

The structure of the mathematical model I now consider is quite similar to that for the model described in Chapter 2, and so I shall be brief again here. The model, which was developed first by Maxwell *et al.* \[90\], considers five distinct species in the fibrin matrix. I shall denote a single molecule of each of these species as follows:
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G is an unbound growth factor molecule (mobile);
PU is an unbound peptide molecule (mobile);
PB is a bound peptide molecule (immobile);
GPU is an unbound growth factor-peptide complex (mobile);
GPB is a bound growth factor-peptide complex (immobile);

see Figure 3.1. The chemical reactions involving these species may be represented by:

\[
\begin{align*}
G + PU & \xrightarrow{k_f} GPU \\
G + PB & \xrightarrow{k_r} GPB
\end{align*}
\]

(3.1)

where \(k_f, k_r\) are association and dissociation rate constants, respectively. These reactions represent the reversible binding of a free growth factor molecule to an unbound and bound peptide molecule, respectively.

The problems considered in this chapter are one-dimensional, and I denote by \(c_G(x,t)\) the concentration of free growth factor (G) at location \(x\) and time \(t\); the notation for the concentrations of the other four species then follows in an obvious fashion. The partial differential equations governing the concentrations of the five species that incorporates (3.1) and the assumptions made about species mobility are given by:

\[
\begin{align*}
\frac{\partial c_G}{\partial t} &= D_G \frac{\partial^2 c_G}{\partial x^2} - k_f c_G (c_{PU} + c_{PB}) + k_r (c_{GPU} + c_{GPB}), \\
\frac{\partial c_{PU}}{\partial t} &= D_{PU} \frac{\partial^2 c_{PU}}{\partial x^2} - k_f c_G c_{PU} + k_r c_{GPU}, \\
\frac{\partial c_{GPU}}{\partial t} &= D_{GPU} \frac{\partial^2 c_{GPU}}{\partial x^2} + k_f c_G c_{PU} - k_r c_{GPU}, \\
\frac{\partial c_{PB}}{\partial t} &= -k_f c_G c_{PB} + k_r c_{GPB}, \\
\frac{\partial c_{GPB}}{\partial t} &= k_f c_G c_{PB} - k_r c_{GPB},
\end{align*}
\]

(3.2)

where \(D_G\), \(D_{PU}\) and \(D_{GPU}\) are the diffusivities for the free growth factor, unbound peptide, and free growth factor-unbound peptide complex, respectively.

The species PB and GPB are covalently fixed to the fibrin matrix, so that the equations for their concentrations do not contain diffusion terms.
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3.2.2. Boundary and initial conditions

The boundary and initial conditions model an experimental setup identical to the one discussed in Chapter 2; see Figure 2.3. No-flux conditions for the mobile species are imposed at the base of the container, so that:

\[
\frac{\partial c_G}{\partial x}(0, t) = 0, \quad \frac{\partial c_{PU}}{\partial x}(0, t) = 0, \quad \frac{\partial c_{GPU}}{\partial x}(0, t) = 0 \quad \text{for } t \geq 0.
\] (3.3)

Perfect sink conditions for the mobile species are imposed at the interface between the matrix and the fluid medium:

\[
c_G(L, t) = 0, \quad c_{PU}(L, t) = 0, \quad c_{GPU}(L, t) = 0 \quad \text{for } t \geq 0.
\] (3.4)

The appropriate initial conditions here are:

\[
c_G(x, 0) = c^0_G, \quad c_{PU}(x, 0) = c^0_{PU}, \quad c_{PB}(x, 0) = c^0_{PB}, \quad c_{GPU}(x, 0) = c^0_{GPU}, \quad c_{GPB}(x, 0) = c^0_{GPB} \quad \text{for } 0 < x < L,
\] (3.5)

where \(c^0_i\) denote the constant initial concentrations of species \(i\), for \(i\) being G, PU, PB, GPU or GPB. This completes the formulation of the governing mathematical model.

3.2.3. Non-dimensionalisation

By taking appropriate combinations of its equations, the system (3.2) is easily written in the following equivalent form:

\[
\frac{\partial}{\partial t}(c_G + c_{GPU} + c_{GPB}) = D_G \frac{\partial^2 c_G}{\partial x^2} + D_{GPU} \frac{\partial^2 c_{GPU}}{\partial x^2},
\]

\[
\frac{\partial}{\partial t}(c_{PU} + c_{PB} + c_{GPU} + c_{GPB}) = D_{PU} \frac{\partial^2 c_{PU}}{\partial x^2} + D_{GPU} \frac{\partial^2 c_{GPU}}{\partial x^2},
\]

\[
\frac{\partial c_{GPU}}{\partial t} = D_{GPU} \frac{\partial^2 c_{GPU}}{\partial x^2} + k_f c_G c_{PU} - k_r c_{GPU},
\] (3.6)

\[
\frac{\partial c_{GPB}}{\partial t} = k_f c_G c_{PB} - k_r c_{GPB},
\]

\[
c_{PB} + c_{GPB} = c^0_{PB} + c^0_{GPB}.
\]
3.2. The model

I denote the total concentrations of growth factor and peptide in the matrix at location \( x \) and time \( t \) by \( c_T^G(x,t) \) and \( c_T^P(x,t) \), respectively, so that:

\[
\begin{align*}
    c_T^G(x,t) &= c_G(x,t) + c_{GPU}(x,t) + c_{GPB}(x,t), \\
    c_T^P(x,t) &= c_{PU}(x,t) + c_{PB}(x,t) + c_{GPU}(x,t) + c_{GPB}(x,t).
\end{align*}
\] (3.7)

Equations (3.6)\(_1\) and (3.6)\(_2\) give the evolution equations for the total growth factor and peptide, and may be written in conservation form as:

\[
\begin{align*}
    \frac{\partial c_T^G}{\partial t} + \frac{\partial j_T^G}{\partial x} &= 0, \\
    \frac{\partial c_T^P}{\partial t} + \frac{\partial j_T^P}{\partial x} &= 0,
\end{align*}
\] (3.8)

where:

\[
\begin{align*}
    j_T^G &= -D_G \frac{\partial c_G}{\partial x} - D_{GPU} \frac{\partial c_{GPU}}{\partial x}, \\
    j_T^P &= -D_{PU} \frac{\partial c_{PU}}{\partial x} - D_{GPU} \frac{\partial c_{GPU}}{\partial x},
\end{align*}
\] (3.9)

give the total flux of growth factor and peptide, respectively.

The total initial concentrations of growth factor and peptide in the matrix are denoted by \( c_{T0}^G \) and \( c_{T0}^P \), respectively, so that:

\[
\begin{align*}
    c_{T0}^G &= c_G^0 + c_{GPU}^0 + c_{GPB}^0, \\
    c_{T0}^P &= c_{PU}^0 + c_{PB}^0 + c_{GPU}^0 + c_{GPB}^0.
\end{align*}
\] (3.10)

and non-dimensional variables are introduced as follows:

\[
\begin{align*}
    \bar{x} &= \frac{x}{L}, \quad \bar{t} = \frac{t}{(L^2/D_{GPU})}, \quad \bar{c}_G = \frac{c_G}{c_{T0}^G}, \quad \bar{c}_{GPU} = \frac{c_{GPU}}{c_{T0}^G}, \quad \bar{c}_{GPB} = \frac{c_{GPB}}{c_{T0}^G}, \quad \bar{c}_{PU} = \frac{c_{PU}}{c_{T0}^P}, \\
    \bar{c}_{PB} &= \frac{c_{PB}}{c_{T0}^P}, \quad \bar{c}_G^T = \frac{c_G^T}{c_{T0}^G}, \quad \bar{c}_{GPU}^T = \frac{c_{GPU}^T}{c_{T0}^G}, \quad \bar{c}_{GPB}^T = \frac{c_{GPB}^T}{c_{T0}^G}, \quad \bar{c}_{PU}^T = \frac{c_{PU}^T}{c_{T0}^P}, \\
    \bar{\delta}_G &= \frac{\partial c_G}{\partial t} = \frac{\partial^2 c_G}{\partial x^2}, \quad \bar{\delta}_{GPU} = \frac{\partial^2 c_{GPU}}{\partial x^2}, \quad \bar{\delta}_{GPB} = \frac{\partial^2 c_{GPB}}{\partial x^2}, \quad \bar{\delta}_{PU} = \frac{\partial^2 c_{PU}}{\partial x^2},
\end{align*}
\]

to obtain the following non-dimensional form for the governing problem (3.6) (where the over-bars are dropped immediately):

\[
\begin{align*}
    \frac{\partial}{\partial \bar{t}}(c_G + c_{GPU} + c_{GPB}) &= D_G^* \frac{\partial^2 c_G}{\partial x^2} + \frac{\partial^2 c_{GPU}}{\partial x^2}, \\
    \frac{\partial}{\partial \bar{t}} \left( c_{PU} + c_{PB} + \frac{1}{\eta_{PU/G}}(c_{GPU} + c_{GPB}) \right) &= D_{PU}^* \frac{\partial^2 c_{PU}}{\partial x^2} + \frac{1}{\eta_{PU/G}} \frac{\partial^2 c_{GPU}}{\partial x^2}, \\
    \delta_G &\frac{\partial c_{GPU}}{\partial \bar{t}} = \delta_G \frac{\partial^2 c_{GPU}}{\partial x^2} + K_{BU} c_G c_{PU} - c_{GPU},
\end{align*}
\] (3.11)

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\[
\delta_G \frac{\partial c_{GBP}}{\partial t} = K_{bp} c_G c_{PB} - c_{GBP},
\]

\[
\eta_{P/G} c_{PB} + c_{GBP} = r \eta_{P/G},
\]

where:

\[
D^* = \frac{D_G}{D_{GPU}}, \quad D^*_P = \frac{D_P}{D_{GPU}}, \quad \eta_{P/G} = \frac{c_T^0}{c_P^0},
\]

\[
r = \frac{c_{PB}^0 + c_{GBP}^0}{c_P^0}, \quad \delta_G = \frac{c_{GPU}^0}{k_r L^2}, \quad K_{bp} = \frac{k_f c_P^0}{k_r},
\]

are non-dimensional parameters. The quantity \(K_{bp}\) gives the binding constants for growth factor to peptide. We denote by \(K_{G-P}^D = k_f / k_r\) the dissociation constant of growth factor from peptide, so that:

\[
K_{bp} = \frac{c_P^0}{K_{G-P}^D}.
\]

Here \(K_{bp} \gg 1\) and \(K_{bp} \ll 1\) correspond to strong retention and weak retention, respectively, of the growth factor by the peptide. The parameter \(r\) gives the fraction of the peptide that was initially bound.

The non-dimensional form for the total growth factor and peptide and their fluxes are given by:

\[
c_T^G(x,t) = c_G(x,t) + c_{GPU}(x,t) + c_{GBP}(x,t),
\]

\[
c_T^P(x,t) = c_P^0(x,t) + c_{PB}(x,t) + \frac{1}{\eta_{P/G}} (c_{GPU}(x,t) + c_{GBP}(x,t)),
\]

\[
j_T^G = -D^*_G \frac{\partial c_G}{\partial x} - \frac{\partial c_{GPU}}{\partial x}, \quad j_T^P = -D^*_P \frac{\partial c_P}{\partial x} - \frac{1}{\eta_{P/G}} \frac{\partial c_{GPU}}{\partial x}.
\]

3.2.4. Reduction to a pair of coupled partial differential equations

Much of the analysis given here parallels that given in Chapter 2, but the results are significantly different, and so the details are recorded briefly here. The time scales for the association and dissociation rates in the chemical reactions (3.1) are usually much shorter than the diffusion time scales in the experiments [90,184], so that we frequently have:

\[
\frac{L^2}{D_{GPU}} \gg \frac{1}{k_r}, \quad \frac{1}{k_f c_P^0}.
\]
3.2. The model

In [184], for example, the growth factor studied was NGF, and its diffusivity has order of magnitude \(10^{-4} \text{ cm}^2\text{min}^{-1}\). Taking \(D = 1.0 \times 10^{-4} \text{ cm}^2\text{min}^{-1}\) as a representative diffusivity for a free species in the matrix and \(L = 0.2 \text{ cm}\), we calculate a typical diffusion time scale for the system to be \(L^2/D \approx 7 \text{ hours}\).

The values of the rate constants for the binding of growth factor (NGF) to the peptide were taken to be \(k_r = 0.6 \text{ min}^{-1}\) and \(k_f \approx 3 \times 10^5 \text{ M}^{-1} \text{ min}^{-1}\), and the total initial concentration of peptide was \(c_{p0} = 2.5 \times 10^{-4} \text{ M}\). Hence the time scales associated with binding are \(1/k_r \approx 1.7 \text{ min}\) and \(1/(k_f c_{p0}) \approx 1 \text{ s}\), and these times are clearly small compared to the diffusion time scales.

I shall restrict my attention to such systems in the analysis presented here. In terms of the dimensionless parameters (3.12), the conditions above imply that \(\delta_G \ll \min(K_{bp}, 1)\) and so the differential equations (3.11) may be replaced by the algebraic expressions:

\[
K_{bp} c_G c_{pu} = c_{gpu}, \quad K_{bp} c_G c_{pb} = c_{gpb}.
\]  

The two equations in (3.15) correspond to the equilibrium forms for the binding of growth factor to unbound peptide, and bound peptide, respectively.

The concentrations of the five species \(c_G, c_{pu}, c_{pb}, c_{gpu}, \) and \(c_{gpb}\) may be written in terms of the total concentration of growth factor, \(c_G(x, t)\), and peptide, \(c_p(x, t)\), by solving the five algebraic expressions (3.11), (3.14)\textsuperscript{1}, (3.14)\textsuperscript{2}, and (3.15), to obtain:

\[
c_G(c_G^T, c_p^T) = \frac{K_{bp} (c_G^T - \eta_{pg} c_p^T) - \eta_{pg} + \sqrt{[K_{bp} (c_G^T - \eta_{pg} c_p^T) - \eta_{pg}]^2 + 4K_{bp} \eta_{pg} c_G^T}}{2K_{bp}},
\]

\[
c_{pu}(c_G^T, c_p^T) = \frac{\eta_{pg} (c_p^T - r)}{\eta_{pg} + K_{bp} c_G(c_G^T, c_p^T)},
\]

\[
c_{gpu}(c_G^T, c_p^T) = \eta_{pg} (c_p^T - r - c_{pu}(c_G^T, c_p^T)),
\]

\[
c_{gpb}(c_G^T, c_p^T) = c_G^T - c_G(c_G^T, c_p^T) - c_{gpu}(c_G^T, c_p^T),
\]

\[
c_{pb}(c_G^T, c_p^T) = r - \frac{c_{gpb}(c_G^T, c_p^T)}{\eta_{pg}}.
\]  

Hence, it is sufficient to solve for \(c_G^T\) and \(c_p^T\) as the concentrations for \(c_G, c_{pu}, c_{pb}, c_{gpu}, \) and \(c_{gpb}\) then follow immediately from (3.16). This implies that we can replace the problem (3.11) by the following problem containing just two
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coupled partial differential equations:

\[
\frac{\partial c_T^G}{\partial t} + \frac{\partial}{\partial x} j_T^G(c_T^G, c_T^P, c_{Gx}^T, c_{Px}^T) = 0, \quad 0 < x < 1, t > 0,
\]

\[
\frac{\partial c_T^P}{\partial t} + \frac{\partial}{\partial x} j_T^P(c_T^G, c_T^P, c_{Gx}^T, c_{Px}^T) = 0, \quad 0 < x < 1, t > 0,
\]

\[
\frac{\partial c_T^G}{\partial x}(0, t) = 0, \quad \frac{\partial c_T^P}{\partial x}(0, t) = 0 \quad \text{for} \quad t \geq 0,
\]

\[
c_T^G(x, 0) = 1, \quad c_T^P(x, 0) = 1 \quad \text{for} \quad 0 < x < 1,
\]

where:

\[
j_T^G(c_T^G, c_T^P, c_{Gx}^T, c_{Px}^T) = -D_T^G \frac{\partial}{\partial x} c_T^G(c_T^G, c_T^P) - \frac{\partial}{\partial x} c_{GPU}(c_T^G, c_T^P),
\]

\[
j_T^P(c_T^G, c_T^P, c_{Gx}^T, c_{Px}^T) = -D_T^P \frac{\partial}{\partial x} c_T^P(c_T^G, c_T^P) - \frac{1}{\eta_{P/G}} \frac{\partial}{\partial x} c_{GPU}(c_T^G, c_T^P),
\]

and where the expressions for \(c_G(c_T^G, c_T^P), c_{GPU}(c_T^G, c_T^P)\) and \(c_{PU}(c_T^G, c_T^P)\) are given in (3.16).

Equations (3.17) \(_1\) and (3.17) \(_2\) may also be written in the form:

\[
\frac{\partial c_T}{\partial t} = \frac{\partial}{\partial x} \left( D(c_T) \frac{\partial c_T}{\partial x} \right) \quad \text{with} \quad c_T = \begin{pmatrix} c_T^G \\ c_T^P \end{pmatrix},
\]

where \(D(c_T)\) is a diffusion matrix for the system given by:

\[
D(c_T) = \begin{pmatrix} D_{GG}^T(c_T) & D_{GP}^T(c_T) \\ D_{PG}^T(c_T) & D_{PP}^T(c_T) \end{pmatrix},
\]

with:

\[
D_{GG}^T(c_T) = D_{G}^* \frac{\partial c_G}{\partial c_T^G}(c_T) + \frac{\partial c_{GPU}}{\partial c_T^G}(c_T),
\]

\[
D_{GP}^T(c_T) = D_{G}^* \frac{\partial c_G}{\partial c_T^P}(c_T) + \frac{\partial c_{GPU}}{\partial c_T^P}(c_T),
\]

\[
D_{PG}^T(c_T) = D_{P}^* \frac{\partial c_P}{\partial c_T^G}(c_T) + \frac{1}{\eta_{P/G}} \frac{\partial c_{GPU}}{\partial c_T^G}(c_T),
\]

\[
D_{PP}^T(c_T) = D_{P}^* \frac{\partial c_P}{\partial c_T^P}(c_T) + \frac{1}{\eta_{P/G}} \frac{\partial c_{GPU}}{\partial c_T^P}(c_T).
\]
In this notation, the fluxes may be written as:

\[ j^T = -D(c^T) \frac{\partial c^T}{\partial x} \quad \text{where} \quad j^T = \begin{pmatrix} j^T_G \\ j^T_P \end{pmatrix}. \]

### 3.2.5. Asymptotics: strong binding, \(K_{bp} \gg 1\)

I write \(K_{bp} = 1/\varepsilon\) and consider the limit \(\varepsilon \to 0\) in (3.16) for fixed \(O(1)\) values of \(c^T_G\) and \(c^T_P\), and with all the remaining dimensionless parameters in (3.16) being \(O(1)\). As in Chapter 2, the asymptotic expressions I shall display here were derived with the aid of the `series` command in MAPLE.

![Figure 3.2. The fraction of bound growth factor, \(f_B\), prior to release as a function of the binding constant, \(K_{bp}\), and for various values for the fraction of bound peptide, \(r\), with \(\eta_{P/G} = 2\).](image)

The fraction of bound growth factor in the matrix, which I denote by \(f_B\), is given by:

\[ f_B(x,t) = \frac{c_{GBP}(x,t)}{c_G(x,t) + c_{GPU}(x,t) + c_{GPB}(x,t)} = \frac{c_{GBP}(x,t)}{c_G^2(x,t)}. \]

Reverting to dimensional quantities, it is found in the limit \(\varepsilon \to 0\) that:
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\[
f_B(x,t) \sim \begin{cases} 
\frac{rc_{T0}}{c_G} & \text{for } c_G^T > c_P^T, \\
\frac{rc_{T0}}{c_P} & \text{for } c_G^T < c_P^T.
\end{cases} \tag{3.19}
\]

Figure 3.2 displays the fraction of bound growth factor at time \( t = 0 \) as a function of the binding constant, \( K_{P} \), and for various values of the initially fraction of bound peptide, \( r \), with \( \eta_{P/G} = 2 \). It is noteworthy in this figure that \( f_B \sim 1 \) for \( K_{P} \gg 1 \) and \( r = 1 \), as would be expected.

I also consider the asymptotic behaviour of the two diffusion components for the growth factor in the diffusion tensor, namely, \( D_{GG}^T \) and \( D_{GP}^T \). However, I shall only consider the behaviour for \( c_{PU} = c_{GPU} = 0 \) here since the free peptide substantially exits the system on a relatively short diffusion time scale, and the focus here is on slow release. Setting \( c_{PU} = c_{GPU} = 0 \) in \( D_{GG}^T \) and \( D_{GP}^T \), it is found as \( \varepsilon \to 0 \) that:

\[
D_{GG}^T \sim \begin{cases} 
D_G & \text{for } c_G^T > c_P^T, \\
\frac{D_G}{2} \left( 1 + \frac{\alpha}{\sqrt{\alpha^2 + 4c_P^Tc_{T0}^P}} \right) & \text{for } \alpha = O(1), c_G^T = c_P^T + \varepsilon^{1/2}\alpha, \\
\varepsilon D_Gc_{T0}^Pc_P^T \left( c_G^T - c_P^T \right)^2 & \text{for } c_G^T < c_P^T.
\end{cases} \tag{3.20}
\]

and,

\[
D_{GP}^T \sim \begin{cases} 
-D_G & \text{for } c_G^T > c_P^T, \\
-\frac{D_G}{2} \left( 1 + \frac{\alpha}{\sqrt{\alpha^2 + 4c_P^Tc_{T0}^P}} \right) & \text{for } \alpha = O(1), c_G^T = c_P^T + \varepsilon^{1/2}\alpha, \\
-\varepsilon D_Gc_{T0}^Pc_G^T \left( c_G^T - c_P^T \right)^2 & \text{for } c_G^T < c_P^T.
\end{cases} \tag{3.21}
\]

Hence, subsequent to the free peptide leaving the gel, growth factor releases slowly on the long (dimensional) time scale \( t = O(L^2/(\varepsilon D_{GPU})) \) as \( \varepsilon \to 0 \) provided \( c_G^T < c_P^T \). This suggests that the matrix should be prepared, if feasible, such that:

\[ c_{P0}^T > c_G^T, \quad c_{P0}^T \gg K_{G,P0}^D. \]

The proportion of the growth factor, \( c_G^{T0} \), that then releases slowly is, to leading order, \( re_{c_G}^{T0} \), \( 0 \leq r \leq 1 \).
### 3.2.6. Numerical results

#### 3.2.6.1. Numerical methods

Explicit time-stepping was used to numerically integrate (3.17). The values for $c^T_G$, and $c^T_P$ were first updated using (3.17), with the updates for the remaining quantities then following immediately from (3.16). The second order spatial derivatives were approximated using centred differences, and the boundary condition on $x = 0$ was handled by introducing a fictitious line in the usual way.

#### 3.2.6.2. Results

In Figures 3.3 - 3.5, numerical profiles for the fraction of total growth factor that has released from the system as a function of time are plotted. The release profiles displayed in Figure 3.3 correspond to the case of strong binding, $K_{bp} \gg 1$, which is the recommended regime for matrix preparation. The other parameter values are all $O(1)$, and can be found either on the figure or in its caption. In Figures 3.3, it is seen that the growth factor release rate becomes slow after a period of approximately a day. The fast initial release phase corresponds to the rapid out-diffusion of free growth factor and unbound growth factor-peptide complex on a short time scale. Once the unbound components have substantially exited the system, the remaining bound fraction releases slowly over a long time scale.

In Figure 3.3 (a), we have $r = 1$, so that all of the peptide is covalently fixed to the fibrin matrix. Hence, provided there is sufficient peptide to accommodate the growth factor ($\eta_{P/G} \geq 1$), all of the growth factor should release slowly, and this is confirmed by inspecting the curves in Figure 3.3 (a) with $\eta_{P/G} \geq 1$. However, the curves in Figure 3.3 (a) with $\eta_{P/G} < 1$ have a different character. Consider, for example, the curve which has $\eta_{P/G} = 0.5$. In this case, the initial concentration of growth factor is twice that for the peptide. Hence, to leading order, half of the growth factor will be initially free in the matrix, and will diffuse out of the system on a short diffusion time scale. This is confirmed by inspecting the $\eta_{P/G} = 0.5$ curve in Figure 3.3 (a), where it is seen that $M(0.5 \text{ days})/M(\infty) \approx 0.5$. 

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Figure 3.3. Numerical solutions of the initial boundary value problem (3.17). The predicted fraction of total growth factor released (see equation (2.14)) as a function of time over a period of a week is displayed. The parameter values chosen are $D_G = 1 \times 10^{-4}$ cm$^2$/min, $D_{PU} = 1.8 \times 10^{-4}$ cm$^2$/min, $D_{GPU} = 9.6 \times 10^{-5}$ cm$^2$/min, $K_{BP} = 1000$, and various values for $\eta_{P/G}$, which have been indicated on the curves. In (a), $r = 1$, and in (b), $r = 0.5$. 

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Figure 3.4. Numerical solutions of the initial boundary value problem (3.17). The predicted fraction of total growth factor released (see equation (2.14)) as a function of time over a period of a week is displayed. The parameter values chosen are $D_G = 1 \times 10^{-4}$ cm$^2$/min, $D_{PU} = 1.8 \times 10^{-4}$ cm$^2$/min, $D_{GPU} = 9.6 \times 10^{-5}$ cm$^2$/min, $\eta_{P/G} = 2$, and various values for $K_{bp}$, which have been indicated on the curves. In (a), $r = 1$, and in (b), $r = 0.5$. 

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3. Controlled release of growth factors from a peptide-based affinity system

Figure 3.5. Numerical solutions of the initial boundary value problem (3.17). The predicted fraction of total growth factor released (see equation (2.14)) as a function of time over a period of a week is displayed. The parameter values used are $D_G = 1 \times 10^{-4} \text{cm}^2/\text{min}$, $D_{PU} = 1.8 \times 10^{-4} \text{cm}^2/\text{min}$, $D_{GPU} = 9.6 \times 10^{-5} \text{cm}^2/\text{min}$, $\eta_{P/G} = 2$, and various values for $r$, which have been indicated on the curves. In (a), $K_{br} = 1000$, and in (b), $K_{br} = 100$. 

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3.2. The model

In Figure 3.3 (b), we have \( r = 0.5 \), so that only half of the peptide is covalently fixed to the matrix. Hence, for \( \eta_{p/G} \geq 1 \), we expect approximately half of the growth factor to be lost from the matrix on a short time scale. Inspecting the curve with \( \eta_{p/G} = 1 \) in Figure 3.3 (b), it is seen that \( M(0.5 \text{ days})/M(\infty) \approx 0.5 \). For \( \eta_{p/G} < 1 \), even more growth factor will leak out of the system quickly. Consider the curve in Figure 3.3 (b) which has \( \eta_{p/G} = 0.5 \). For this case, approximately half of the growth factor is initially bound to peptide, but only half of the peptide is fixed to the matrix. Hence, only approximately one quarter of the growth factor is bound to the matrix initially, with the remaining three quarters free to diffuse out of the system. For the \( \eta_{p/G} = 0.5 \) curve in Figure 3.3 (b), it is seen that \( M(0.5 \text{ days})/M(\infty) \approx 0.75 \). The key features of the curves in Figure 3.3 may be interpreted using simple asymptotic arguments in this way.

In Figure 3.4 numerical solutions to (3.17) are displayed for \( \eta_{p/G} = 2 \) and for various values of \( K_{bp} \), with \( r = 1 \) in (a) and \( r = 0.5 \) in (b). For those curves which have \( K_{bp} = O(1) \), which corresponds to moderate retention of growth factor, it is seen that the growth factor releases over a period of some days. The release rate is only slow for those curves which have \( K_{bp} \gg 1 \). However, there is always a fast initial release phase in the curves of Figure 3.4 (b) because only half of the peptide is fixed to the matrix initially.

In Figure 3.5 numerical solutions of (3.17) are displayed for \( \eta_{p/G} = 2 \) and various values of \( r \), and with \( K_{bp} = 1000 \) in (a), and \( K_{bp} = 100 \) in (b). In Figure 3.5 (a), we see as expected that a fraction \( (1 - r) \) of the growth factor is lost in the first few days, but that release thereafter is slow. In Figure 3.5 (b), where the binding is weaker by an order of magnitude, this effect is weaker, though still discernible.
3. Controlled release of growth factors from a peptide-based affinity system

3.3. Comparison with experimental data

The model results have been compared with experimental data drawn from [184]. In the experiments conducted for this study, the release of the growth factor NGF from a fibrin matrix containing NGF-binding peptides is considered. The binding affinity of the peptides for the growth factor was varied by changing the pH of the elution medium. The setup for these experiments is as described in Section 2.1.5, and the quantity measured is the fraction of total growth factor released as a function of time. The data used to generate the theoretical curves in Figure 3.6 is listed in Table 3.1. Most of this data was taken from [184]. The only values that were not drawn from [184] were for $r$ and $K_{bp}$, which were used as fitting parameters. The same value $r = 0.3$ was chosen for all three curves, so that 30% of the peptide was taken to be initially fixed to the fibrin matrix. However, three different values were chosen for $K_{bp}$ since the peptide affinity for the growth factor changes when the pH of the elution medium is changed. The correspondence between theory and experiment in Figure 3.6 is seen to be satisfactory in all cases.

Table 3.1. The data used to generate the theoretical curves in Figure 3.6. The values for $r$ and $K_{bp}$ were determined in this study, and the remaining parameter values were taken from [184].

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Figure 3.6 (a) $K_{bp} = 110$</th>
<th>Figure 3.6 (b) $K_{bp} = 130$</th>
<th>Figure 3.6 (c) $K_{bp} = 140$</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_G$</td>
<td>$1.01 \times 10^{-4}$</td>
<td>$1.01 \times 10^{-4}$</td>
<td>$1.01 \times 10^{-4}$</td>
<td>cm$^2$/min</td>
</tr>
<tr>
<td>$D_{PU}$</td>
<td>$1.84 \times 10^{-4}$</td>
<td>$1.87 \times 10^{-4}$</td>
<td>$1.82 \times 10^{-4}$</td>
<td>cm$^2$/min</td>
</tr>
<tr>
<td>$D_{GPU}$</td>
<td>$9.58 \times 10^{-5}$</td>
<td>$9.60 \times 10^{-5}$</td>
<td>$9.57 \times 10^{-5}$</td>
<td>cm$^2$/min</td>
</tr>
<tr>
<td>$c_T^{PU}$</td>
<td>$2.50 \times 10^{-4}$</td>
<td>$2.50 \times 10^{-4}$</td>
<td>$2.50 \times 10^{-4}$</td>
<td>M</td>
</tr>
<tr>
<td>$c_T^{GPU}$</td>
<td>$7.57 \times 10^{-9}$</td>
<td>$7.57 \times 10^{-9}$</td>
<td>$7.57 \times 10^{-9}$</td>
<td>M</td>
</tr>
<tr>
<td>$r$</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>6.0</td>
<td>2.8</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>
3.3. Comparison with experimental data

Figure 3.6. A comparison of experimental and theoretical release profiles for the peptide affinity system discussed in this chapter. In the figure, the curves are theoretical and the symbols are experimental. The experimental data is taken from [184], and the parameter values used to generate the theoretical curves can be found in Table 3.1.
3. Controlled release of growth factors from a peptide-based affinity system

3.4. Discussion

The governing mathematical model has been reduced to a coupled system of partial differential equations for the total concentration of growth factor and peptide. It has been demonstrated that the release behaviour is strongly dependent on the ratio of the concentration of bound peptide to the dissociation constant for the growth factor from the peptide, and that the release rate may be tuned effectively by appropriately varying the concentration of bound peptide.

The principal disadvantage of the model presented in Chapter 2 is that it can only be used subsequent to the free peptide exiting the system, so that it is incapable of describing the complete experimental release profiles. By contrast, the model presented here for a simpler system is capable of describing the release profiles for all times, including the first few days of release. Furthermore, it has been seen that the model produces results that matches published experimental data well.
4. **A reaction-diffusion model for drug redistribution in tissue**

In this chapter, I consider a model for local drug redistribution in a tissue that incorporates the effects of diffusion and reversible binding with immobile sites within the tissue. The model I shall develop here is closely related to the model discussed in Chapter 3, though the context is significantly different here in that I shall now be analyzing problems that describe the behaviour of drug *in vivo*. The model tracks the evolution of the concentration in tissue of free drug, specifically and non-specifically bound drug, and specific binding sites. I shall show that for many cases of practical interest, the model may be reduced to a scalar nonlinear convection-reaction-diffusion equation for the total drug. This equation is shown to further reduce to a nonlinear diffusion equation with a concentration dependent diffusivity for the case of the binding sites being uniformly distributed. The model is used to investigate tissue residence time for strongly bound drugs by considering a problem with uniform initial drug concentration and perfect sink boundary conditions. The rate at which the drug penetrates tissue is investigated by analyzing a surface source problem. The behaviour predicted by the model has potential implications for the design of local drug delivery systems if the drug binds strongly to its target receptors.

In the final section of this chapter, I shall use a somewhat more detailed model to provide an elementary description of drug release into artery tissue from an implanted stent.
4. A reaction-diffusion model for drug redistribution in tissue

4.1. The model

4.1.1. Some background

Many natural ligands bind to their receptors with high affinity. Receptors are most commonly found on the surface of cells (insulin receptors, for example), but can also be located in the interior of the cell, and even in the nucleus (estrogen receptors) \[4,143\]. When a ligand binds with its receptor, a complex sequence of biochemical events frequently ensues that leads to a physiological response in the cell; as an example, insulin binding transmits a signal that leads to the movement of glucose transporters to the plasma membrane, enabling the cell to take up more glucose; see Figure 4.1 \[4,143\].

![Figure 4.1](image.png)

Figure 4.1. Insulin binding transmits a signal that leads to the movement of glucose transporters to the cell membrane, enabling the cell to take up more glucose \[4,143\].

Because receptors are frequently gateways to producing physiological responses in cells, they are often the targets of drugs. When a drug, which may or may not be a natural ligand in the body, binds to its target binding site, this is referred to as specific binding. Specific binding sites are frequently saturable. When the drug binds to any other binding site, which it typically has a low affinity for, this is referred to as non-specific binding; non-specific binding sites are typically not saturable \[77,97,104\].
The concentration of molecules in a tissue can depend, among other things, on the rate at which they diffuse through the tissue and their propensity to bind with elements of the tissue [77,141]. The binding can be highly specific, as is the case for receptor-ligand interactions, or non-specific. The action of many drugs is dependent on the drug molecules binding with high affinity to specific receptors in a tissue. If the binding sites are immobile, then binding will clearly have an effect on the rate at which the molecules can move through the tissue, and in this chapter, I investigate the effect of binding on drug mobility.

4.1.2. Model equations

The model incorporates drug diffusion through the tissue and reversible binding of drug with immobile sites, both specific and non-specific, within the tissue; see Figure 4.2. I denote by \( C, B, B_n, A, A_n \) a free molecule, a specific binding site, a non-specific binding site, a drug-specific binding site complex, and a drug-non-specific binding site complex, respectively. The reversible binding reactions can then be represented by:

\[
C + B \xrightarrow{k_{on}} A \quad \text{(specific binding),} \\
C + B_n \xrightarrow{k_{on,n}} A_n \quad \text{(non-specific binding),}
\]

Figure 4.2. Schematic representation of a free drug molecule, \( C \), binding to a specific binding site, \( B \), to form a specific drug-binding site complex, \( A \), or joining a non-specific site, \( B_n \), to form a non-specific drug-binding site complex, \( A_n \); these processes are reversible.
4. A reaction-diffusion model for drug redistribution in tissue

where $k_{on}, k_{off}, k_{on,n}, k_{off,n}$ are rate constants. I denote by $c, b, a, a_n$ the concentrations of $C, B, A, A_n$, respectively, and for the problems considered here, each of these quantities can depend on time $t$ and a single spatial variable $x$. Note that I have not included a concentration for the non-specific binding sites since these are assumed to be non-saturable, so that their concentration is constant. The governing equations are:

\[
\begin{align*}
\frac{\partial a_n}{\partial t} &= k_{on,n}b^*c - k_{off,n}a_n, \\
\frac{\partial a}{\partial t} &= k_{on}bc - k_{off}a, \\
\frac{\partial b}{\partial t} &= -k_{on}bc + k_{off}a, \\
\frac{\partial c}{\partial t} &= D\frac{\partial^2 c}{\partial x^2} - k_{on}bc + k_{off}a - k_{on,n}b^*c + k_{off,n}a_n,
\end{align*}
\]

(4.1)

where the constants $D, b^*$ refer to the diffusivity of the drug and the concentration of non-specific binding sites, respectively; it is noteworthy in this model that the drug can only diffuse in its free form, and that both the binding sites and the drug-binding site complexes are immobile. From (4.1), it is clear that:

\[
\begin{align*}
\frac{\partial}{\partial t} (a + a_n + c) &= D\frac{\partial^2 c}{\partial x^2}, \\
\frac{\partial}{\partial t} (a + b) &= 0, \\
\frac{\partial a}{\partial t} &= k_{on}bc - k_{off}a, \\
\frac{\partial a_n}{\partial t} &= k_{on,n}b^*c - k_{off,n}a_n.
\end{align*}
\]

(4.2)

I denote by $c^*$ a representative free drug concentration, by $L$ a representative tissue length scale, and by $b^*$ a representative concentration for the specific binding sites. Defining the following non-dimensional variables:

\[
\tilde{t} = \frac{t}{(L^2/D)}, \quad \tilde{x} = \frac{x}{L}, \quad \tilde{a} = \frac{a}{b^*}, \quad \tilde{b} = \frac{b}{b^*}, \quad \tilde{c} = \frac{c}{c^*}, \quad \tilde{a_n} = \frac{a_n}{b^*},
\]

the following dimensionless equations are obtained (dropping overbars):

\[
\begin{align*}
\frac{\partial}{\partial \tilde{t}} (\eta a + \eta a_n + c) &= \frac{\partial^2 c}{\partial \tilde{x}^2}, \\
\delta \frac{\partial a}{\partial \tilde{t}} &= K_b bc - a, \\
\delta_n \frac{\partial a_n}{\partial \tilde{t}} &= \frac{K_{bm}}{\eta} c - a_n.
\end{align*}
\]

(4.3)
4.1. The model

where $F(x)$ gives the distribution of specific binding sites in the tissue, and:

$$\eta = \frac{b^*}{c^*}, \quad \delta = \frac{D}{k_{\text{off}} L^2}, \quad \delta_n = \frac{D}{k_{\text{off,n}} L^2}, \quad K_b = \frac{k_{\text{on}} b^*}{k_{\text{off}}}, \quad K_{bn} = \frac{k_{\text{on,n}} b_n^*}{k_{\text{off,n}}},$$

are dimensionless parameters. A possible measure for the concentration of specific binding sites is now:

$$b^* = \max_x \{F(x)\}.$$

From Chapters 2 and 3, we recognise $K_b, K_{bn}$ as the specific and non-specific binding constants, respectively, with $K_b \gg 1$ corresponding to the case of the drug molecules having a high affinity for their target binding sites. As before, note that $K_b, K_{bn}$ may be written as:

$$K_b = \frac{b^*}{K_D}, \quad K_{bn} = \frac{b_n^*}{K_{Dn}},$$

where $K_D = k_{\text{off}}/k_{\text{on}}$, $K_Dn = k_{\text{off,n}}/k_{\text{on,n}}$ are the dissociation constants for the binding of the drug to the specific and non-specific binding sites, respectively.

Similar models for drug redistribution in tissue to the one just described can be found in Lovich & Edelman [86], Sakharov et al. [135], Borghi et al. [15], and Tzafriri et al. [175].

4.1.3. Model reduction

I shall confine my discussion to cases for which the diffusion time scale is much longer than the time scales associated with the binding reactions, so that:

$$L^2/D \gg \max \left\{1/(k_{\text{on}} b^*), 1/k_{\text{off}}, 1/(k_{\text{on,n}} b_n^*), 1/k_{\text{off,n}} \right\},$$

which implies that $\delta \ll \min(K_b, 1)$ and $\delta_n \ll \min(K_{bn}, 1)$. In Tables 4.1, 4.2, 4.3 and 4.4 some values of the parameters appearing in the model are displayed for various drugs, binding sites, and tissues. The references from which this data is drawn can also be found in the tables. In Table 4.4 it is seen that for some drug/tissue systems of particular interest, the diffusion time
4. A reaction-diffusion model for drug redistribution in tissue

| Table 4.1. A listing of parameter values for some drugs and their associated specific binding sites. |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 (heterodimer)</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>T lymphocyte cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>IL-2</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>IgE Fc</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Mouse macrophage cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Interferon A549 cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Fibronectin Fibroblast cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Insulin Insulin Rat fat-cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Heparin Heparin binding site Arterial tissue</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>bFGF Heparan sulfate Basement membrane</td>
<td>10^{-8}</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>T lymphocyte cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>IL-2</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>IgE Fc</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Mouse macrophage cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Interferon A549 cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Fibronectin Fibroblast cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Insulin Insulin Rat fat-cells</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>Heparin Heparin binding site Arterial tissue</td>
<td>10^{-8}</td>
</tr>
<tr>
<td>bFGF Heparan sulfate Basement membrane</td>
<td>10^{-8}</td>
</tr>
</tbody>
</table>
4.1. The model

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Representative Thickness/Length scale, $L$ (mm)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basement membrane</td>
<td>$0.1 - 1.4 \times 10^{-3}$</td>
<td>7</td>
</tr>
<tr>
<td>Gel-immobilized oligonucleotides</td>
<td>$0.02-0.03$</td>
<td>85</td>
</tr>
<tr>
<td>Rabbit iliac artery</td>
<td>0.20</td>
<td>86</td>
</tr>
<tr>
<td>Articular cartilage</td>
<td>0.40</td>
<td>43</td>
</tr>
<tr>
<td>Porcine coronary artery</td>
<td>0.45</td>
<td>176</td>
</tr>
<tr>
<td>Calf internal carotid artery</td>
<td>0.70</td>
<td>80</td>
</tr>
<tr>
<td>Human coronary artery</td>
<td>0.75</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 4.3. Drug diffusivities, $D$, in specified tissues.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tissue</th>
<th>Diffusivity, $D$ (mm$^2$/s)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Gel-immobilized oligonucleotides</td>
<td>$1.0 \times 10^{-4}$</td>
<td>85</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>Arterial tissue</td>
<td>$2.0 \times 10^{-4}$</td>
<td>176</td>
</tr>
<tr>
<td>IGF-I</td>
<td>Articular cartilage</td>
<td>$2.6 \times 10^{-5}$</td>
<td>43</td>
</tr>
<tr>
<td>Dextran</td>
<td>Arterial tissue</td>
<td>$3.0 \times 10^{-5}$</td>
<td>80</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Arterial tissue</td>
<td>$2.6 \times 10^{-6}$</td>
<td>28, 198</td>
</tr>
<tr>
<td>Heparin</td>
<td>Arterial tissue</td>
<td>$7.7 \times 10^{-6}$</td>
<td>86</td>
</tr>
<tr>
<td>bFGF</td>
<td>Basement membrane</td>
<td>$7.0 \times 10^{-7}$</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 4.4. (A) A listing of $L^2/D$ (hours) values for various tissue length scales $L$ (mm) and drug diffusivities in the tissue $D$ (mm$^2$/s) [93]. The values for $L$ and $D$ can be found in Tables 4.2 and 4.3. (B) Specific binding parameters and time scales. The values for $k_{on}$, $k_{off}$ and $b^*$ can be found in Tables 4.1. (C) Non-specific binding parameters and time scales.

<table>
<thead>
<tr>
<th>Drug</th>
<th>$1/(k_{on}b^*)$ (hours)</th>
<th>$1/k_{off}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I</td>
<td>$1.40 \times 10^{-3}$</td>
<td>$1.39 \times 10^{-2}$</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>$1.06 \times 10^{-4}$</td>
<td>0.17</td>
</tr>
<tr>
<td>bFGF</td>
<td>$1.28 \times 10^{-5}$</td>
<td>$2.78 \times 10^{-2}$</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>$8.33 \times 10^{-6}$</td>
<td>$3.06 \times 10^{-3}$</td>
</tr>
<tr>
<td>DNA</td>
<td>$2.78 \times 10^{-6}$</td>
<td>$2.80 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>$k_{off,n}$ (s$^{-1}$)</th>
<th>$k_{on,n}$ (M$^{-1}$s$^{-1}$)</th>
<th>$b^*_n$ (M)</th>
<th>$1/(k_{on,n}b^*_n)$ (hours)</th>
<th>$1/k_{off,n}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapamycin</td>
<td>$5.2 \times 10^{-3}$</td>
<td>$2.0 \times 10^3$</td>
<td>$3.63 \times 10^{-4}$</td>
<td>0.05</td>
<td>$3.83 \times 10^{-4}$</td>
</tr>
</tbody>
</table>
4.1. The model

scale is much longer than the two time scales associated with specific binding. Neglecting the terms involving $\delta, \delta_n$ in (4.3)_3, (4.3)_4, respectively, one obtains:

$$K_{bc} = \eta a, \quad K_{nc} = \eta a_n,$$

(4.4)

which correspond to the equilibrium forms for the specific and non-specific binding reactions. The total drug concentration (bound plus free), which I shall denote by $c_T(x,t)$, is given in dimensionless terms by:

$$c_T(x,t) = \eta a(x,t) + \eta a_n(x,t) + c(x,t).$$

(4.5)

The quantities $a, a_n, b, c$ may now be written as functions of $c_T$ using the algebraic relations (4.3)_2, (4.4) and (4.5). Elementary algebra yields:

$$
\begin{align*}
a &= \frac{K_b c_T + \eta (1 + K_{bn} + K_b F) - S(c_T, F)}{2\eta K_b}, \\
a_n &= \frac{K_{bn} (K_b c_T - \eta (1 + K_{bn} + K_b F) + S(c_T, F))}{2\eta K_b (1 + K_{bn})}, \\
b &= \frac{-K_b c_T - \eta (1 + K_{bn} - K_b F) + S(c_T, F)}{2\eta K_b}, \\
c &= \frac{K_b c_T - \eta (1 + K_{bn} + K_b F) + S(c_T, F)}{2K_b (1 + K_{bn})},
\end{align*}
$$

(4.6)

where:

$$S(c_T, F) = \sqrt{(\eta (1 + K_b F + K_{bn}) - K_b c_T)^2 + 4\eta K_b (1 + K_{bn}) c_T}.$$  

(4.7)

Hence, in this model, it is sufficient to solve for $c_T$ as the concentrations for $a, a_n, b, c$ then follow immediately from (4.6). Equation (4.3)_1 now yields the following convection-reaction-diffusion equation for $c_T$:

$$
\frac{\partial c_T}{\partial t} + v_{\text{eff}}(c_T, F) \frac{\partial c_T}{\partial x} = \frac{\partial}{\partial x} \left( D_{\text{eff}}(c_T, F) \frac{\partial c_T}{\partial x} \right) + r_{\text{eff}}(c_T, F),
$$

(4.8)

where:

$$v_{\text{eff}}(c_T, F) = \frac{\eta^2 K_b (1 + K_{bn} + K_b F) + K_b c_T F'}{S(c_T, F)^3},$$

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4. A reaction-diffusion model for drug redistribution in tissue

\[
D_{\text{eff}}(c_T, F) = \frac{1}{2(1 + K_{bn})} \left( 1 + \frac{\eta(1 + K_{bn} - K_b F) + K_b c_T}{S(c_T, F)} \right), \tag{4.9}
\]

\[
r_{\text{eff}}(c_T, F) = \frac{\eta F''}{2(1 + K_{bn})} \left( -1 + \frac{\eta(1 + K_{bn} + K_b F) - K_b c_T}{S(c_T, F)} \right) + \frac{2K_b^2 \eta^3 c_T(F')^2}{S(c_T, F)^3},
\]

are the effective convective velocity, diffusivity, and reaction term, respectively. It is clear from (4.9) that \(v_{\text{eff}} > 0\) if \(F' > 0\) and \(v_{\text{eff}} < 0\) if \(F' < 0\), so that the effective convective velocity is in the direction of increasing binding site concentration, as would be expected.

In this chapter, I shall restrict my attention to the case of the distribution of binding sites being uniform, so that \(F(x) \equiv 1\). Also, for simplicity, I shall suppose that the effect of non-specific binding is negligible, and set \(K_{bn} = 0\); incorporating non-specific binding would involve only a relatively minor adjustment to the analysis given below. Under these assumptions, the convection and reaction terms in (4.8) vanish, and it reduces to the following nonlinear diffusion equation with a concentration dependent diffusivity:

\[
\frac{\partial c_T}{\partial t} = \frac{\partial}{\partial x} \left( D_{\text{eff}}(c_T) \frac{\partial c_T}{\partial x} \right), \tag{4.10}
\]

where the effective diffusivity for the total drug, \(D_{\text{eff}}(c_T)\), is now given by:

\[
D_{\text{eff}}(c_T) = \frac{1}{2} \left( 1 + \frac{\eta(1 - K_b) + K_b c_T}{\sqrt{\eta(1 + K_b) - K_b c_T}^2 + 4\eta K_b c_T} \right). \tag{4.11}
\]

This form has also been recently noted in [175]. It is easily seen that \(D_{\text{eff}}(c_T) \leq 1\) (or \(D_{\text{eff}}(c_T) \leq D\) in dimensional terms), as would be expected since \(c_T\) contains the immobile species \(a\).

**4.1.4. Strongly retained drug: \(K_b \gg 1\)**

For the case of strong binding, \(K_b \gg 1\), it is found that:

\[
D_{\text{eff}}(c_T) \sim \begin{cases} 
1 & \text{for } c_T > \eta, \quad \text{(Fast rate)} \\
\frac{1}{2} \left( 1 + c_T^* / \sqrt{c_T^*^2 + 4\eta^2} \right) & \text{for } c_T^* = O(1) \text{ where } c_T = \eta + K_b^{-1/2} c_T^*, \\
K_b^{-1/2} \eta^2 / (\eta - c_T)^2 & \text{for } c_T < \eta. \quad \text{(Slow rate)}
\end{cases}
\tag{4.12}
\]
4.1. The model

Figure 4.3. Plots of the effective diffusivity \( D_{ef}(c_T) \) with \( \eta = 1/2 \) and for various values of the binding constant \( K_b \). The three asymptotic regions indicated in (4.12) are clearly visible on those curves with \( K_b \gg 1 \).

and:

\[
\begin{align*}
  a & \sim \begin{cases} 
    1 & \text{for } c_T \geq \eta, \\
    c_T/\eta & \text{for } c_T < \eta,
  \end{cases} \\
  b & \sim \begin{cases} 
    K_b^{-1}\eta/(c_T - \eta) \ll 1 & \text{for } c_T > \eta, \\
    K_b^{-1/2}\frac{1}{2\eta}\left(\sqrt{c_T^2 + 4\eta^2} - c_T^*\right) \ll 1 & \text{for } c_T^* = O(1) \text{ where } c_T = \eta + K_b^{-1/2}c_T^*, \\
    1 - c_T/\eta & \text{for } c_T < \eta,
  \end{cases} \\
  c & \sim \begin{cases} 
    c_T - \eta & \text{for } c_T > \eta, \\
    K_b^{-1/2}\frac{1}{2}\left(\sqrt{c_T^2 + 4\eta^2} + c_T^*\right) \ll 1 & \text{for } c_T^* = O(1) \text{ where } c_T = \eta + K_b^{-1/2}c_T^*, \\
    K_b^{-1}\eta c_T/(\eta - c_T) \ll 1 & \text{for } c_T < \eta.
  \end{cases}
\end{align*}
\]

(4.13)

The result (4.12) is readily interpreted by noting that \( c_T > \eta \) corresponds in dimensional terms to \( c_T > b^* \), which implies that the total concentration of drug exceeds that of the available binding sites. In this case, we have that for strong binding and at leading order, the available binding sites are occupied
4. A reaction-diffusion model for drug redistribution in tissue

and the free drug diffuses unhindered by binding (the fast rate). For \( c_T < \eta \), which corresponds to the concentration of binding sites exceeding that of the total drug, the concentration of free drug is asymptotically low and at leading order the drug is bound (the slow rate). It should be emphasised that for very many drug/tissue systems of interest, \( K_b \) is large. In Table 4.1, it is seen that \( K_b \gg 1 \) for most of the systems displayed there; for example, in arterial tissue, \( K_b \sim 1700 \) for rapamycin, and \( K_b \sim 400 \) for paclitaxel.

In Figure 4.3, \( D_{\text{eff}}(c_T) \) is plotted as a function of \( c_T \) for \( \eta = 1/2 \) and for various values of \( K_b \). For the \( K_b = 1000 \) curve (strong binding), the three regimes indicated in (4.12) are clearly visible: for \( c_T > 1/2 \), we see that \( D_{\text{eff}}(c_T) \sim 1 \), and \( D_{\text{eff}}(c_T) \ll 1 \) for \( c_T < 1/2 \). The rapid transition near \( c_T = 1/2 \) is also evident. For the curve with \( K_b = 0.01 \) (weak binding), we have that \( D_{\text{eff}}(c_T) \sim 1 \), as expected since \( D_{\text{eff}}(c_T) = 1 \) for \( K_b = 0 \) (see (4.11)).

4.2. Drug deposition: a surface source problem

4.2.1. Boundary and initial conditions

I now indicate how the behaviour exhibited in (4.12) might be exploited in the design of drug delivery devices. The speed of tissue penetration for strongly bound drugs is evaluated by considering the following generic surface source problem for \( K_b \gg 1 \):

\[
\frac{\partial c_T}{\partial t} = \frac{\partial}{\partial x} \left( D_{\text{eff}}(c_T) \frac{\partial c_T}{\partial x} \right), \quad 0 < x < \infty, \quad t > 0, \quad (4.14)
\]

\[
c_T(0, t) = 1 \quad \text{for } t \geq 0, \quad c_T(x, t) \rightarrow 0 \quad \text{as } x \rightarrow \infty, \quad t \geq 0
\]

\[
c_T(x, 0) = 0 \quad \text{for } 0 < x < \infty.
\]

This problem could, for example, serve as a crude model for the release of drug from a drug-eluting stent, where \( x = 0 \) represents the interface between the stent and artery tissue [175]. The problem has already been discussed in [175] for the case \( K_b = \infty \) in which the diffusivity (4.12) becomes a step function.
I shall display a reasonably complete asymptotic analysis for \( K_b \gg 1 \) here, that includes a discussion of narrow layers. There are two cases to consider here: saturated specific binding sites \( (c^* > b^*, \eta > 1) \), and unsaturated specific binding sites \( (c^* < b^*, \eta < 1) \). The behaviour exhibited for the two cases differs dramatically, as I shall now demonstrate.

### 4.2.2. Rapid in-diffusion: \( \eta < 1 \)

This corresponds in dimensional terms to \( c^* > b^* \), so that in a region adjacent to the surface, there is free drug that can in-diffuse. In the tissue bulk, the drug profile falls rapidly where the drug concentration becomes comparable with the binding site concentration, since the effective diffusivity becomes asymptotically small there. This occurs at the so-called binding site barrier \[37, 45, 112, 134, 182\], which is denoted here by \( x = q(t; K_b) \); see Figure 4.4. The location of this barrier is determined as part of the solution of a moving boundary problem.

![Figure 4.4](image-url)

**Figure 4.4.** A schematic representation of the three asymptotic regions that arise in the limit \( K_b \gg 1 \) to the surface source problem (4.14). The regions have been superposed on a numerical solution to (4.14) which has \( K_b = 200 \) and \( \eta = 1/2 \). Note the sharp diffusion front in the profile; this corresponds to the binding sites barrier discussed in the text.
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4.2.2.1. Behind the binding site barrier: $0 < x < q(t; K_b)$

In this region, $c_T > \eta$ and $D_{\text{eff}}(c_T) \sim 1$, and we pose $c_T \sim c_{T_0}(x, t), q(t; K_b) \sim q_0(t)$ as $K_b \to \infty$ to obtain:

$$\frac{\partial c_{T_0}}{\partial t} = \frac{\partial^2 c_{T_0}}{\partial x^2}, \quad 0 < x < q_0(t),$$

$$c_{T_0}(0, t) = 1 \quad \text{for} \ t \geq 0,$$

$$c_{T_0}(x, t) = \eta \quad \text{on} \ x = q_0(t), t \geq 0,$$

$$q_0(t) = 0 \ at \ t = 0,$$

where $q_0(t)$ is a moving boundary that approximates the depth the drug has penetrated to by time $t$. Since $q_0(t)$ is unknown, and needs to be found as part of the solution to (4.15), another boundary condition involving $c_{T_0}, q_0$ is required. A second boundary condition on $x = q_0(t)$ may be determined using conservation of drug mass. For $K_b \gg 1$, we have:

$$\frac{d}{dt} \int_0^\infty c_T \, dx = \int_0^{q_0(t)} \frac{\partial}{\partial x} \left( D_{\text{eff}}(c_T) \frac{\partial c_T}{\partial x} \right) \, dx = - \left( D_{\text{eff}}(c_T) \frac{\partial c_T}{\partial x} \right)_{x=0} \sim - \left( \frac{\partial c_{T_0}}{\partial x} \right)_{x=0},$$

(4.16)

and also,

$$\frac{d}{dt} \int_0^\infty c_T \, dx \sim \frac{d}{dt} \int_0^{q_0(t)} c_{T_0} \, dx = \frac{dq_0(t)}{dt} c_{T_0}(q_0(t), t) + \int_0^{q_0(t)} \frac{\partial c_{T_0}}{\partial t} \, dx$$

$$= q_0(t) \eta + \int_0^{q_0(t)} \frac{\partial^2 c_{T_0}}{\partial x^2} \, dx = \dot{q}_0(t) \eta + \left( \frac{\partial c_{T_0}}{\partial x} \right)_{x=q_0(t)} - \left( \frac{\partial c_{T_0}}{\partial x} \right)_{x=0}$$

(4.17)

Comparing (4.16) with (4.17) gives:

$$\left( \frac{\partial c_{T_0}}{\partial x} \right)_{x=q_0(t)} = -\dot{q}_0(t) \eta.$$

(4.18)

Equations (4.15), (4.18) constitute a well-posed problem that can be solved explicitly by noting that it is self-similar in the Boltzmann variable $\xi = x/\sqrt{t}$. Writing $q_0(t) = \alpha \sqrt{t}$ where $\alpha$ is a constant, (4.15) and (4.18) may be replaced by the following two-point boundary value problem:
4.2. Drug deposition: a surface source problem

\[- \frac{\xi}{2} \frac{dc_{T_0}}{d\xi} = \frac{d^2 c_{T_0}}{d\xi^2}, \quad 0 < \xi < \alpha,\]

\[c_{T_0} = 1 \quad \text{on} \quad \xi = 0,\]

\[c_{T_0} = \eta, \quad \frac{dc_{T_0}}{d\xi} = -\frac{\alpha \eta}{2} \quad \text{on} \quad \xi = \alpha.\]

Solving this problem by separating variables yields:

\[c_{T_0} = 1 - (1 - \eta) \frac{\text{erf}(x/2\sqrt{t})}{\text{erf}(\alpha/2)},\]

where the constant \(\alpha\) is determined by solving the transcendental equation

\[\alpha \text{erf}(\alpha/2) \exp(\alpha^2/4) = \frac{2(1 - \eta)}{\eta \sqrt{\pi}}.\]

Notice that \(\alpha \to 0 (q_0(t) \to 0)\) as \(\eta \to 1^- (c^* \to b'^+),\) and \(\alpha \to \infty (q_0(t) \to \infty)\) as \(\eta \to 0^+ (b^* \ll c^*),\) as would be expected.

In dimensional terms then, the drug penetrates a distance \(x = O(L)\) in time \(t = O(L^2/D)\) with a speed of penetration \(q_0 = O(D/L),\) so that the drug may be deposited in the tissue on a time scale \(t = O(L^2/D);\) see Figure 4.5 (a).

From the point of view of applications, these are the important results. Nevertheless, for the sake of completeness, I now display the remaining asymptotic details.

4.2.2.2. Boundary layers near \(x = q(t; K_b)\)

Inspecting Figure 4.4, it is seen that the solution for \(c_T\) drops from \(c_T = \eta\) to \(c_T \ll 1\) over a narrow region near \(x = q(t; K_b).\) There are in fact two distinct boundary layers near \(x = q_0(t)\) for \(K_b \gg 1,\) and I shall now discuss these.

\[x^* = O(1), \quad x = q_0(t) + K_b^{-1/2} x^*.\]

This region corresponds to the shoulder of the curve in Figure 4.4. We have \(c_T = \eta + O(K_b^{-1/2})\) in \(x^*, t = O(1),\) so we write \(c_T = \eta + K_b^{-1/2} c^*_T(x^*, t)\) and pose \(c^*_T \sim c^*_{T_0}(x^*, t)\) in \(x^*, t = O(1)\) as \(K_b \to \infty,\) to obtain:

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\[
\frac{\partial}{\partial x^*} \left( D_{\text{eff}}(c_{T0}) \frac{\partial c_{T0}}{\partial x^*} \right) = 0, \quad (4.20)
\]

where:

\[
D_{\text{eff}}(c_{T0}) = \frac{1}{2} \left( 1 + \frac{c_{T0}^*}{\sqrt{c_{T0}^*} + 4\eta^2} \right), \quad (4.21)
\]

Matching requires that:

\[
\lim_{x^* \to -\infty} \left( -D_{\text{eff}}(c_{T0}^*) \frac{\partial c_{T0}^*}{\partial x^*} \right) = \lim_{x \to q_0(t)^-} \left( -\frac{\partial c_{T0}}{\partial x} \right) = \dot{q}_0(t)\eta. \quad (4.22)
\]

Integrating (4.20) subject to (4.22), one obtains:

\[
\frac{1}{2} \left( 1 + c_{T0}^*/\sqrt{c_{T0}^*} + 4\eta^2 \right) \frac{\partial c_{T0}^*}{\partial x^*} = -\dot{q}_0(t)\eta,
\]

and integrating this equation gives:

\[
\frac{1}{2} \left( c_{T0}^* + \sqrt{c_{T0}^*} + 4\eta^2 \right) = -\dot{q}_0(t)\eta (x^* - q_1(t)), \quad (4.23)
\]

where \(q_i(t)\) is a function arising from integration. From (4.23), it is clear that \(c_{T0}^* \sim -\dot{q}_0(t)\eta x^*\) as \(x^* \to -\infty\), and that:

\[
c_{T0}^* \sim \frac{\eta}{\dot{q}_0(t)} (x^* - q_1(t)) \quad \text{as} \quad x^* \to q_1(t)^-\quad (4.24)
\]

so that \(c_{T0}^* \to -\infty\) as \(x^* \to q_1(t)^-\); this gives the behaviour in Figure 4.4 where the curve begins to drop rapidly just past the shoulder. It is clear from (4.24) that we need to re-scale near \(x^* = q_1(t)\), and the region arising is discussed now.

\[
z = O(1), \quad x = q_0(t) + K^{-1/2} q_1(t) + K^{-1} z
\]

This region corresponds to the rapid fall in the curve from approximately \(\eta\) to small values just past the shoulder. As \(K \to \infty\), we pose \(c_T \sim \tilde{c}_{T0}(z,t)\) for \(z,t = O(1)\), to obtain:

\[
-\dot{q}_0(t) \frac{\partial \tilde{c}_{T0}}{\partial z} = \frac{\partial}{\partial z} \left( \frac{\eta^2}{(\eta - \tilde{c}_{T0})^2} \frac{\partial \tilde{c}_{T0}}{\partial z} \right). \quad (4.25)
\]
4.2. Drug deposition: a surface source problem

Integrating (4.25) twice and matching gives:

\[- \dot{q}_0(t) \eta z = \frac{\eta^2}{\eta - \hat{c}_{T0}} + \eta \ln \left( \frac{\eta \hat{c}_{T0}}{\eta - \hat{c}_{T0}} \right).\]  

(4.26)

It is easily seen from (4.26) that \( \hat{c}_{T0} \to \eta \) as \( z \to -\infty \), and \( \hat{c}_{T0} \sim \exp(-\dot{q}_0 z) \) as \( z \to \infty \), so that the discussion of this case is now complete.

4.2.3. Slow in-diffusion: \( \eta > 1 \)

In the case of the concentration of total drug at the surface being maintained at a value below the concentration of available binding sites (\( c^* < b^*, \eta > 1 \)), I now show that the speed of drug penetration is asymptotically slow, and that it takes an asymptotically long time for the drug to be loaded onto the tissue. In dimensional terms, it will be seen that the drug penetrates a distance \( x = O(L) \) on the long time scale \( t = O(K_b L^2 / D) \), so that in-diffusion is slow; see Figure 4.5 (b). This suggests that for drug/tissue systems where strong binding and diffusion are the dominant mechanisms, the drug should be presented to the tissue for the purpose of loading at a sufficiently high concentration (if feasible) for the fast rate discussed in the previous subsection to apply.

The above comments are justified by simply noting that for \( \eta > 1 \), the drug is confined to a narrow boundary layer at \( \hat{x} = O(1) \) for \( t = O(1) \) in the limit \( K_b \to \infty \), where \( x = K_b^{-1/2} \hat{x} \). In \( \hat{x} = O(1) \), we pose \( c_T \sim \hat{c}_{T0}(\hat{x}, t) \) as \( K_b \to \infty \) to obtain the leading order problem:

\[ \frac{\partial \hat{c}_{T0}}{\partial t} = \frac{\partial}{\partial \hat{x}} \left( \frac{\eta^2}{(\eta - \hat{c}_{T0})^2} \frac{\partial \hat{c}_{T0}}{\partial \hat{x}} \right), \quad 0 < \hat{x} < \infty, t > 0, \]
\[ \hat{c}_{T0}(0, t) = 1 \quad \text{for } t \geq 0, \]
\[ \hat{c}_{T0}(\hat{x}, t) \to 0 \quad \text{as } \hat{x} \to \infty, t \geq 0, \]
\[ \hat{c}_{T0}(\hat{x}, 0) = 0 \quad \text{for } 0 < \hat{x} < \infty. \]  

(4.27)

This nonlinear problem can in fact be solved analytically using a transformation first introduced by Fujita [38]. The construction of the analytical solution to (4.27) is admittedly somewhat peripheral to the main discussion here since
Figure 4.5. Numerical solutions to (4.14) for the total drug concentration at time \( t = L^2/D \) in dimensional terms. In (a), the parameter values are \( K_b = 200, \eta = 1/2 \) (fast in-diffusion), and in (b), \( K_b = 200, \eta = 2 \) (slow in-diffusion).
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the scalings provide the most useful information from the point of view of applications, but is nevertheless worth recording.

Writing:

$$\xi = \frac{\hat{x}}{2\sqrt{t}}, \quad \alpha = \frac{1}{\eta},$$

equation (4.27) can be reduced to the following two-point boundary value problem for an ordinary differential equation:

$$-2\xi \frac{d\hat{c}_{T0}}{d\xi} = \frac{d}{d\xi} \left( \frac{1}{1 - \alpha \hat{c}_{T0}} \frac{d\hat{c}_{T0}}{d\xi} \right),$$

$$\hat{c}_{T0}(\xi) \to 0 \text{ as } \xi \to \infty, \quad (4.28)$$

$$\hat{c}_{T0}(0) = 1.$$

Introducing the variables:

$$\theta = -\frac{d\hat{c}_{T0}}{d\xi}, \quad y = 1 - \alpha \hat{c}_{T0},$$

equation (4.28) may be rewritten as:

$$\frac{d}{dy} \left( \theta y^2 \right) = -\frac{2\xi}{\alpha}. \quad (4.30)$$

Differentiating both sides of (4.30) with respect to $y$ then gives:

$$\frac{d^2}{dy^2} \left( \theta y^2 \right) = -\frac{2}{\alpha^2 \theta}. \quad (4.31)$$

If we now let $\omega = \theta / y^3$, $z = 1/y$, equation (4.31) transforms to:

$$\frac{d^2\omega}{dz^2} = -\frac{2}{\alpha^2 \omega}. \quad (4.32)$$

Multiplying both sides of (4.32) by $dw/dz$ and integrating yields:

$$\frac{d\omega}{dz} = \pm \left( A - \frac{4}{\alpha^2} \ln(\omega) \right)^{1/2}, \quad (4.33)$$

where $A$ is an integration constant. In addition, from (4.29) and (4.30), we
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obtain:

\[
\frac{d\omega}{dz} = -y^2 \left[ \frac{1}{y} \frac{d}{dy} \left( \frac{\theta}{y^2} \right) - \frac{1}{y^2} \frac{\theta}{y^2} \right] = (1 - \alpha \hat{c}_{\tau_0}) \left( \frac{2\xi}{\alpha} - \frac{1}{(1 - \alpha \hat{c}_{\tau_0})^3} \frac{d\hat{c}_{\tau_0}}{d\xi} \right). \tag{4.34}
\]

From (4.28), we have that \( \hat{c}_{\tau_0} \to 0 \) and \( d\hat{c}_{\tau_0}/d\xi \to 0 \) as \( \xi \to \infty \), and then (4.34) implies that \( d\omega/dz \to +\infty \) as \( \xi \to \infty \). Hence, we must select the positive root in (4.33):

\[
\frac{d\omega}{dz} = \left( A - \frac{4}{\alpha^2} \ln(\omega) \right)^{1/2}. \tag{4.35}
\]

Equation (4.34) may be rewritten in the form:

\[
\frac{d\omega}{dz} = \frac{2\xi}{\alpha z} + \omega \cdot \frac{1}{z}, \tag{4.36}
\]

and setting \( \xi = 0 \) in this equation gives:

\[
\frac{d\omega}{dz} = \omega(1 - \alpha) \text{ on } z = \frac{1}{1 - \alpha}. \]

Substituting this into equation (4.35) gives:

\[
A = (1 - \alpha)^2 \mu^2 + \frac{4}{\alpha^2} \ln(\mu),
\]

where \( \mu = (\omega)_{z=\frac{1}{1-\alpha}} \) is a constant. Then equation (4.35) becomes:

\[
\frac{d\omega}{dz} = (1 - \alpha) \mu \left( 1 - 2\gamma \ln \frac{\omega}{\mu} \right)^{1/2}, \tag{4.37}
\]

where \( \gamma = 2 / [(1 - \alpha)^2 \alpha^2 \mu^2] \) is a constant. Integrating equation (4.37) subject to \( z \to 1 \) as \( \omega \to 0 \) gives:

\[
z - 1 = \frac{1}{1 - \alpha} \int_0^\beta (1 - 2\gamma \ln(\rho))^{-1/2} d\rho.
\]

Defining \( \phi = [1 - 2\gamma \ln(\omega/\mu)]^{1/2}, \text{ and } \beta = 1/\sqrt{2\gamma}, \) we obtain:

\[
z = 1 + \frac{1}{1 - \alpha} \int_{\phi}^{\infty} \frac{e^{\beta^2(1-\phi^2)}}{\gamma} d\phi = 1 + \frac{2\beta^2}{1 - \alpha} e^{2\beta^2} \left( \int_0^{\infty} e^{-\beta^2\phi^2} d\phi - \int_0^{\phi} e^{-\beta^2\phi^2} d\phi \right) = 1 + \frac{\sqrt{\pi}}{1 - \alpha} e^{\beta^2} \text{erfc}(\beta\phi). \tag{4.38}
\]
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The original concentration, \( \hat{c}_{r_0} \), is now given by:

\[
\hat{c}_{r_0} = \frac{f(\phi, \beta)}{\alpha[1 - \alpha + f(\phi, \beta)]},
\]

where:

\[
f(\phi, \beta) = \sqrt{\pi} \beta e^{\beta^2} \text{erfc}(\beta \phi).
\]

It is easily seen that:

\[
\phi = 1 \text{ on } \xi = 0, \quad \phi \to \infty \text{ as } \xi \to \infty, \quad \text{and, } \frac{d\phi}{d\xi} \geq 0 \text{ for } 0 \leq \xi < \infty,
\]

so that \( \phi \in [1, \infty) \). Setting \( \xi = 0 \) in (4.39) gives:

\[
f(1, \beta) = \alpha,
\]

and it is readily shown that this has a unique solution \( \beta \) for each \( \alpha \), so that there is a one-to-one correspondence between \( \beta \) and \( \alpha \). From (4.36), (4.37) and the definition of \( \phi \), we have that:

\[
\frac{1}{z} \left( \frac{2\xi}{\alpha} + \omega \right) = (1 - \alpha) \mu \phi,
\]

and since \( \omega = \mu e^{\beta^2(1-\phi^2)} \), we may solve (4.41) for \( \xi \) to obtain:

\[
\xi = \frac{\hat{x}}{2\sqrt{t}} = \frac{\beta}{1 - \alpha} \left[ (1 - \alpha + f(\phi, \beta)) - e^{\beta^2(1-\phi^2)} \right].
\]

The solution \( \hat{c}_{r_0}(\hat{x}, t) \) may now be constructed using (4.39), (4.40) and (4.42) as follows. First note that \( \alpha = 1/\eta \) is a parameter appearing in the problem and is known. Hence (4.40) may be used to determine \( \beta \). With \( \alpha, \beta \) in hand, (4.42) may be used to determine \( \phi \) for a given choice \( (\hat{x}, t) \). Once \( \alpha, \beta, \phi \) have been determined, \( \hat{c}_{r_0}(\hat{x}, t) \) follows using (4.39).
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4.3. Drug clearance: uniform initial drug distribution

4.3.1. Boundary and initial conditions

I now consider a simple problem to investigate the removal of drug from a tissue subsequent to its deposition. I should emphasise that the model considered here only incorporates one mechanism for drug elimination, namely, diffusion in the unbound state. However, in some systems, other mechanisms such as metabolism, blood vessel uptake and convection may also be active in drug removal [60, 93, 114, 133, 141, 170].

In non-dimensional variables, the tissue is taken to occupy \(-1 < x < 1\), and to be initially uniformly loaded with drug. Perfect sink boundary conditions for the drug are imposed at the surfaces \(x = -1\) and \(x = 1\), so that:

\[
\frac{\partial c_T}{\partial t} = \frac{\partial}{\partial x} \left( D_{\text{eff}}(c_T) \frac{\partial c_T}{\partial x} \right), \quad -1 < x < 1, \quad t > 0, \\
c_T(\pm 1, t) = 0 \quad \text{for} \quad t \geq 0, \\
c_T(x, 0) = 1 \quad \text{for} \quad -1 < x < 1.
\] (4.43)

4.3.2. Strongly retained drug, \(K_b \gg 1\)

I consider the case \(\eta < 1\) in (4.43) so that the initial concentration of drug exceeds the concentration of binding sites - recall that our proposed strategy for loading the drug is to present it to the tissue at sufficiently high concentration for in-diffusion to be rapid. We speculate that the predictions of the model described here could be tested experimentally by measuring in vitro the amount of drug released from appropriately prepared slices of drug-loaded tissue into a fluid environment [28, 80, 87].

I now describe the asymptotic behaviour of (4.43) in the limit \(K_b \to \infty\); recall from Table 4.1 that \(K_b \gg 1\) for many systems of interest. There are three time scales in all to consider.
4.3. Drug clearance: uniform initial drug distribution

4.3.2.1. Short time scale, \( t = O(L^2/D) \)

This is the time scale over which the unbound drug out-diffuses, and in dimensionless terms it corresponds to \( t = O(1) \). The problem \( (4.43) \) is clearly symmetric about \( x = 0 \), and so we need only consider the domain \( 0 < x < 1 \) by imposing the following symmetry condition on \( x = 0 \):

\[
\frac{\partial c}{\partial x} = 0 \quad \text{on} \quad x = 0.
\]

In \( t = O(1) \), \( x = O(1) \), we pose \( c_t \sim c^{s}_{T0} (x, t) \) as \( K_b \to \infty \), to obtain the linear problem:

\[
\begin{align*}
\frac{\partial c^{s}_{T0}}{\partial t} &= \frac{\partial^2 c^{s}_{T0}}{\partial x^2}, \\
\frac{\partial c^{s}_{T0}}{\partial x} (0, t) &= 0 \quad \text{for} \quad t \geq 0, \\
c^{s}_{T0} (1, t) &= \eta \quad \text{for} \quad t \geq 0, \\
c^{s}_{T0} (x, 0) &= 1 \quad \text{for} \quad 0 < x < 1.
\end{align*}
\]  

This linear problem can be solved analytically using the method of separation of variables \([26]\), to obtain:

\[
c^{s}_{T0} (x, t) = \eta + \frac{4(1 - \eta)}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{2n - 1} \exp \left( \frac{-(2n - 1)^2 \pi^2 t}{4} \right) \cos \left( \frac{(2n - 1) \pi x}{2} \right).
\]

4.3.2.2. Long time scale, \( t = O(1) \)

As \( t \rightarrow \infty \), the problem can be approximated by:

\[
\begin{align*}
\frac{\partial c^{s}_{T0}}{\partial x} &= \frac{\partial^2 c^{s}_{T0}}{\partial x^2}, \\
\frac{\partial c^{s}_{T0}}{\partial x} (0, t) &= 0 \quad \text{for} \quad t > 0, \\
c^{s}_{T0} (1, t) &= \eta \quad \text{for} \quad t > 0, \\
c^{s}_{T0} (x, 0) &= 1 \quad \text{for} \quad 0 < x < 1.
\end{align*}
\]  

This long time scale approximation can be solved using standard techniques, to obtain:

\[
c^{s}_{T0} (x, t) = \eta + \frac{4(1 - \eta)}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{2n - 1} \exp \left( \frac{-(2n - 1)^2 \pi^2 t}{4} \right) \cos \left( \frac{(2n - 1) \pi x}{2} \right).
\]
4. A reaction-diffusion model for drug redistribution in tissue

The perfect sink boundary conditions in (4.43) are not met by this solution since $c_{T0}(\pm 1, t) = \eta$. The solution drops from approximately $\eta$ to small values over asymptotically narrow regions at the surfaces $x = \pm 1$; this is clearly seen in the numerical solution with $t = 0.2$ in Figure 4.7. There are in fact two asymptotic regions near $x = \pm 1$, and I now discuss these.

$x^*, t = O(1), x = 1 + K^{-1/2}_b x^*$

Writing $c_T(x, t) = \eta + K^{-1/2}_b c_T^*(x^*, t)$ and posing $c_T^* \sim c_{T0}^*(x^*, t)$ in $x^*, t = O(1)$ as $K_b \to \infty$, one obtains:

$$
\frac{\partial}{\partial x^*} \left( D_{\text{eff}}(c_{T0}^*) \frac{\partial c_{T0}^*}{\partial x^*} \right) = 0,
$$

where $D_{\text{eff}}(c_{T0}^*)$ is given by (4.21). Integrating this equation twice gives:

$$
c_{T0}^* = \frac{(\gamma(t)x^* + \nu(t))^2 - 4\eta^2}{2(\gamma(t)x^* + \nu(t))},
$$

where $\gamma(t), \nu(t)$ are determined by matching. Imposing $|c_{T0}^*| \to \infty$ as $x^* \to 0^-$ implies that $\nu(t) = 0$, and then:

$$
c_{T0}^* = \frac{\gamma(t)^2 x^* - 4\eta^2}{2\gamma(t)x^*}.
$$

The function $\gamma(t)$ is determined by matching the drug fluxes in $x = O(1)$ and $x^* = O(1)$; we have that:

$$
\lim_{x \to 1^-} \left( - \frac{\partial c_{T0}^*}{\partial x} \right) = \lim_{x^* \to -\infty} \left( -D_{\text{eff}}(c_{T0}^*) \frac{\partial c_{T0}^*}{\partial x^*} \right),
$$

which immediately yields that:

$$
\gamma(t) = 4(\eta - 1) \sum_{n=1}^{\infty} \exp \left( -\frac{(2n - 1)^2 \pi^2 t}{4} \right).
$$

In view of the behavior of (4.46) as $x^* \to 0^-$, it is clear that another scaling is required, and I now discuss this.
4.3. Drug clearance: uniform initial drug distribution

\[ \hat{x}, t = O(1), x = 1 + K_b^{-1} \hat{x} \]

In \( \hat{x}, t = O(1) \), we pose \( c_T \sim \hat{c}_{T0}(\hat{x}, t) \) as \( K_b \to \infty \), to obtain

\[ \frac{\partial}{\partial \hat{x}} \left( \frac{\eta^2}{(\eta - \hat{c}_{T0})^2} \frac{\partial \hat{c}_{T0}}{\partial \hat{x}} \right) = 0. \]

Integrating this expression twice and imposing \( \hat{c}_{T0} \to 0 \) as \( \hat{x} \to 0^+ \) gives:

\[ \hat{c}_{T0} = \frac{\eta \delta(t) \hat{x}}{\delta(t) \hat{x} + \eta}, \]

where the function \( \delta(t) \) is now determined by matching drug fluxes in \( x^* = O(1) \) and \( \hat{x} = O(1) \). It is found that:

\[ \lim_{\hat{x} \to -\infty} \left( \frac{\eta^2}{(\eta - \hat{c}_{T0})^2} \frac{\partial \hat{c}_{T0}}{\partial \hat{x}} \right) = \lim_{x^* \to 0^-} \left( D_{eff}(c^*_{T0}) \frac{\partial c^*_{T0}}{\partial x^*} \right) = \gamma(t), \]

which gives:

\[ \delta(t) = \gamma(t), \]

completing the asymptotic analysis for \( t = O(1) \).

In Figure 4.7, numerical solutions of (4.43) for the total drug concentration are displayed for various times with \( K_b = 100 \) and \( \eta = 1/2 \). The top curve in this figure corresponds to the short time scale, \( t = O(L^2/D) \).

4.3.2.2. Intermediate time scale, \( t = \left( \frac{2}{\pi^2} \ln(K_b) + O(1) \right) L^2/D \)

On this time scale, the total concentration of drug in the tissue bulk is approximately equal to the binding site concentration; see the middle curve of Figure 4.7. The scaling for this intermediate time scale is motivated by noting that:

\[ c^*_{T0}(x, t) \sim \eta + \frac{4(1 - \eta)}{\pi} \exp \left( -\frac{\pi^2 t}{4} \right) \cos \left( \frac{\pi x}{2} \right) \text{ for } t \gg 1, \]

from which it follows that:

\[ c^*_{T0} = \eta + O(K_b^{-1/2}), \text{ for } T_i = O(1), t = \frac{2}{\pi^2} \ln(K_b) + T_i. \]
4. A reaction-diffusion model for drug redistribution in tissue

We write \( c_T = \eta + K_b^{-1/2} c^I_T(x, T_i) \) and in \( x, T_i = O(1) \), pose \( c^I_T \sim c^I_{T0}(x, T_i) \) as \( K_b \to \infty \) to obtain:

\[
\frac{\partial c^I_{T0}}{\partial T_i} = \frac{\partial}{\partial x} \left( D_{\text{eff}}(c^I_{T0}) \frac{\partial c^I_{T0}}{\partial x} \right) \quad \text{for} \quad -1 < x < 1, -\infty < T_i < +\infty,
\]

\[
c^I_{T0}(\pm 1, T_i) = 0 \quad \text{for} \quad -\infty < T_i < +\infty, \tag{4.47}
\]

\[
c^I_{T0}(x, T_i) \sim 4 \left( 1 - \eta \right) \frac{\pi}{\pi x} \exp \left( -\frac{\pi^2 T_i}{4} \right) \cos \left( \frac{\pi x}{2} \right) \quad \text{as} \ T_i \to -\infty.
\]

Since for this scaling \( c_T \sim \eta \), boundary layers are required for the perfect sink conditions at \( x = \pm 1 \) to be satisfied.

\[
x^*, T_i = O(1), x = 1 + K_b^{-1/2} x^*
\]

In \( x^*, T_i = O(1) \), we pose \( c_T \sim \tilde{c}^I_T(x^*, T_i) \) as \( K_b \to \infty \), to obtain:

\[
\frac{\partial \tilde{c}^I_T}{\partial T_i} = \frac{\partial}{\partial x^*} \left( \frac{\eta^2}{(\eta - \tilde{c}^I_T)^2} \frac{\partial \tilde{c}^I_T}{\partial x^*} \right), \quad -\infty < x^* < 0, -\infty < T_i < +\infty,
\]

Figure 4.7. Numerical solutions of (4.43) for the total drug for various times with \( K_b = 100 \) and \( \eta = 1/2 \). The top curve corresponds to the short time scale, the middle curve to the intermediate time scale, and the bottom curve to the long time scale; see Section 4.3.
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\[
\frac{\partial c_c}{\partial T}(0, T_i) = 0 \quad \text{for} \quad -\infty < T_i < +\infty, \quad (4.48)
\]

\[
\frac{\partial c_c}{\partial T}(x^*, T_i) \rightarrow \eta \quad \text{as} \quad x^* \rightarrow -\infty, \quad \text{and for} \quad -\infty < T_i < +\infty,
\]

\[
\lim_{x^* \to -\infty} \left( -\frac{\eta^2}{(\eta - c_c^{T_0})^2} \frac{\partial^2 c_c^{T_0}}{\partial x^*} \right) \quad = \lim_{x \to -1} \left( -D_{\text{eff}}(c_c^{T_0}) \frac{\partial c_c^{T_0}}{\partial x} \right).
\]

This completes the analysis of this case.

4.3.2.3. Long time scale, \( t = O(K_b L^2/D) \)

From the point of view of applications, this is perhaps the most important time scale because it determines the maximum period over which significant amounts of the drug can be present and active in the tissue. In dimensionless terms, it occurs at \( t = O(K_b) \), and writing \( t = K_b T \), we pose \( c_T \sim c_{L T_0}(x, T) \) in \( T = O(1) \), \( |x| < 1 \) as \( K_b \to \infty \) to obtain the leading order problem:

\[
\frac{\partial c_{L T_0}}{\partial T} = \frac{\partial}{\partial x} \left( \frac{\eta^2}{(\eta - c_{L T_0})^2} \frac{\partial c_{L T_0}}{\partial x} \right), \quad -1 < x < 1, T > 0,
\]

\[
c_{L T_0}(\pm 1, T) = 0 \quad \text{for} \quad T \geq 0,
\]

\[
c_{L T_0}(x, T) \to \eta \quad \text{as} \quad T \to 0, \quad \text{and for} \quad -1 < x < 1.
\]

Here \( c_{L T_0} \to 0 \) as \( T \to \infty \), and so the drug is eliminated from the tissue on this time scale; see the bottom curve of Figure 4.7.

4.3.3. Release profiles

A quantity that is frequently measured in experiments is the fraction of the available drug that has been released from a system by a given time. Here the fraction of drug released from the tissue by time \( t \) is given by:

\[
\frac{M(t)}{M(\infty)} = 1 - \frac{1}{2} \int_{-1}^{1} c_T dx,
\]

and some numerical results for this quantity are displayed in Figure 4.8.

In Figure 4.8 (a), I display release profiles for \( K_b = 1000 \) and various values of \( \eta \). For those curves which have the initial concentration of drug exceeding that of the binding sites \( (\eta < 1) \), it is noteworthy that the curves rise steeply.
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Figure 4.8. Numerical solutions of (4.43) for the drug fraction released as a function of time. In (a), $K_b = 1000$ and $\eta$ is varied. In (b), $\eta = 1/2$ and $K_b$ is varied.
4.4. A simple model for drug elution from an implanted stent

for $t = O(1)$, and then flatten out for $t \gg 1$. The steep portion of the curve corresponds to the rapid out-diffusion of the free component, while the flat portion of the curve corresponds to the slow release of the strongly bound component subsequent to the free component exiting the system. It is noted that the release behaviour changes dramatically as $\eta$ is increased through the value 1 (corresponding to $b^* = c^*$), and since $\eta = b^*/c^*$ is a quantity that may be varied in experiments, this strong effect may be observable. In Figure 4.8 (b), we plot solutions for $\eta = 1/2$ and various values of the binding constant $K_b$; the sensitivity of the release behaviour on the value of $K_b$ is evident in these plots. The top curve in Figure 4.8 (b) corresponds to the case of no binding sites, and has been included for comparison.

Hence, for drug/tissue systems in which diffusion and strong reversible binding are the dominant mechanisms, significant insight may be obtained simply from a knowledge of the three parameters $L^2/D$, $K_b \gg 1$ and $b^*$. By overwhelming the available binding sites $b^*$, the drug may be loaded onto the tissue via diffusion on the short time scale $t = O(L^2/D)$; however, subsequent to deposition, the drug may be present and active in the tissue on the long time scale $t = O(K_bL^2/D)$.

4.4. A simple model for drug elution from an implanted stent

4.4.1. Introduction

In Chapter 1, drug-eluting stents (DESs) and their implantation in blood vessels were briefly discussed. In this section, I present and briefly analyse a somewhat simple-minded model to describe the redistribution of drug in a coronary artery wall subsequent to its elution from an implanted DES. In Figure 4.10 I have reproduced a figure from Chapter 1 that depicts the implantation of a DES in a coronary artery.

Accurately modelling the kinetics of drug in vivo subsequent to its release from a stent coating is very challenging because there are numerous factors that
4. A reaction-diffusion model for drug redistribution in tissue

![Diagram of a drug-eluting stent in a diseased coronary artery]

Figure 4.9. The deployment of a drug-eluting stent in a diseased coronary artery. The stent is coated with a drug-loaded polymer, and subsequent to deployment of the stent, drug releases from the stent coating into the artery wall.

...can affect the drug behaviour. For example, drug redistribution will depend on its diffusive and convective character in the artery wall, and the artery wall is known to contain three distinct substructures through its thickness [86]. Furthermore, compressed atherosclerotic plaque is likely to form part of the drug’s tissue environment near to the inner wall of the artery because of the stent implantation procedure. Also, the drug may bind specifically and non-specifically with receptors in the tissue, and specific binding in particular can have a very strong effect on drug kinetics. Other complicating factors include the details of the construction and drug loading of the polymer coating, and drug washout through the inner and outer walls of the artery. Added to this, and for obvious reasons, there is a scarcity of experimental data for drug release from stents implanted in vivo.

Mathematical models of varying complexity and sophistication have been proposed to model drug release from a DES. In a recent study, McGinty et al. [93] have developed a hierarchy of mathematical models to describe elution from stents that incorporate many of the phenomena referred to above; earlier references for stent modelling can also be found in this study. The model considered here is closely related to the models described in Sakharov et al.
A simple model for drug elution from an implanted stent

Although the model I shall consider contains many simplifying assumptions, it is in my view capable of providing some useful order of magnitude estimates for the key quantities of interest. It will be seen that three independent small dimensionless parameters usually arise in the system, which complicates an asymptotic analysis, but does allow for useful qualitative information to be extracted.

4.4.2. Model equations

![Diagram showing drug diffusion from a polymer coating into the artery wall.](image)

Figure 4.10. Drug diffuses from a polymer coating into the artery wall. In the arterial tissue, drug molecules can associate with and dissociate from specific binding sites, and can diffuse in their free form. Drug molecules may also be convected by the outward movement of plasma through the artery wall.

For simplicity, I again consider a one-dimensional problem, and suppose that the polymer coating is located at $-L_p < x < 0$, with $x = 0$ giving the interface between the polymer and the artery wall, and $L_p$ denoting the thickness of the polymer coating. It is supposed that there is a stent strut located at $x = -L_p$ through which the drug cannot penetrate. I denote by $c_p(x,t)$ the concentration of drug in the polymer at penetration $x$ and time $t$, and suppose that this concentration is governed by Fick’s law, so that (in dimensional variables):
4. A reaction-diffusion model for drug redistribution in tissue

\[ \frac{\partial c_p}{\partial t} = D_p \frac{\partial^2 c_p}{\partial x^2} \quad \text{in} \quad -L_p < x < 0, \quad t > 0, \]
\[ \frac{\partial c_p}{\partial x}(-L_p, t) = 0 \quad \text{for} \quad t \geq 0, \]
\[ c_p(x, 0) = c^* \quad \text{for} \quad -L_p < x < 0, \]

where \( D_p \) is the constant diffusivity of the drug in the polymer coating, and \( c^* \) is the uniform initial drug concentration in the polymer. It should be emphasised that all of the assumptions I am making here concerning the drug and the polymer are certainly not true of all stents. For example, the polymer coating may not be uniformly loaded, and the drug concentration need not be below solubility throughout the coating [159,176]. Furthermore, some modern stent coatings are manufactured using biodegradable materials. However, it should also be remembered here that the manufacturer has control over the design of the polymer coating and the drug loading, and there is a case to be made for designing the system so that its behaviour may be adequately described by a simple mathematical model. Certainly, using a polymer/drug system where the release behaviour is difficult to characterise or is poorly understood [159] seems contrary in view of the complexity of the situation in vivo.

In the arterial tissue, it is supposed that the drug can associate with and dissociate from its specific binding sites, and that it can diffuse in its free form and be convected by the outward movement of plasma through the arterial wall. I shall use the same notation as that of the previous sections, and write \( a(x, t), b(x, t), c(x, t) \) for the concentration of bound drug, specific binding sites, and free drug, respectively, at location \( x \) and time \( t \). Following [93,176], I suppose that the convection velocity of the plasma is constant, and I denote it by \( V_a \). The governing equations for \( a, b, c \) are now:

\[ \frac{\partial a}{\partial t} = k_{on} bc - k_{off} a, \quad 0 < x < L_a, \quad t > 0, \]
\[ \frac{\partial b}{\partial t} = -k_{on} bc + k_{off} a, \quad 0 < x < L_a, \quad t > 0, \]
\[ \frac{\partial c}{\partial t} + V_a \frac{\partial c}{\partial x} = D_a \frac{\partial^2 c}{\partial x^2} - k_{on} bc + k_{off} a, \quad 0 < x < L_a, \quad t > 0, \]
\[ c(L_a, t) = 0 \quad \text{for} \quad t > 0, \]
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\[ a(x, 0) = 0, \quad b(x, 0) = b^*, \quad c(x, 0) = 0 \quad \text{for } 0 < x < L_a, \]

where \( k_{on}, k_{off} \) are rate constants as before, \( D_a \) is the diffusivity of the drug in the arterial tissue, and \( b^* \) is the equilibrium concentration of specific binding site for the drug in the arterial tissue. The problem is completed by imposing continuity in the drug concentration and drug flux at the polymer-artery wall interface, so that:

\[
c_p(0^-, t) = c(0^+, t), \quad \left( -D_p \frac{\partial c_p}{\partial x} \right)_{x=0^-} = \left( -D_a \frac{\partial c}{\partial x} \right)_{x=0^+} + (V_a c)_{x=0^+} \quad \text{for } t \geq 0.
\]

(4.52)

Defining the non-dimensional variables:

\[
\bar{t} = \frac{t}{(L_p^2/D_p)}, \quad \bar{x} = \frac{x}{L_p}, \quad \bar{a} = \frac{a}{b^*}, \quad \bar{b} = \frac{b}{b^*}, \quad \bar{c} = \frac{c}{c^*}, \quad \bar{c}_p = \frac{c_p}{c^*},
\]

the following dimensionless equations are obtained (dropping overbars):

**Polymer coating:**

\[
\frac{\partial c_p}{\partial t} = \frac{\partial^2 c_p}{\partial x^2}, \quad -1 < x < 0, t > 0,
\]

\[
\frac{\partial c_p}{\partial x} (-1, t) = 0 \quad \text{for } t \geq 0,
\]

\[
c_p(x, 0) = 1 \quad \text{for } -1 < x < 0;
\]

(4.53)

**Arterial tissue:**

\[
\varepsilon \frac{\partial}{\partial t} (\eta + c) - \frac{\eta}{L} \frac{\partial c}{\partial x} = \frac{\partial^2 c}{\partial x^2} - \frac{P e}{L} \frac{\partial c}{\partial x}, \quad 0 < x < L, t > 0,
\]

\[
a + b = 1, \quad \eta = K_{ibc}, \quad 0 < x < L, t > 0,
\]

\[
c(L, t) = 0 \quad \text{for } t \geq 0,
\]

\[
c(x, 0) = 0 \quad \text{for } 0 < x < L;
\]

(4.54)

**Polymer/artery wall interface:**

\[
c_p(0^-, t) = c(0^+, t), \quad \left( -\varepsilon \frac{\partial c_p}{\partial x} \right)_{x=0^-} = \left( -\frac{\partial c}{\partial x} \right)_{x=0^+} + \left( \frac{P e}{L} c \right)_{x=0^+} \quad \text{for } t \geq 0,
\]

(4.55)

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where:
\[ L = \frac{L_a}{L_p}, \quad \varepsilon = \frac{D_p}{D_a}, \quad Pe = \frac{V_a L_a}{D_a}, \quad \eta = \frac{b^*}{c^*}, \quad K_b = \frac{k_{on} b^*}{k_{off}}. \quad (4.56) \]

The three equations in (4.54)\textsubscript{1} and (4.54)\textsubscript{2} were derived in a manner similar to that described in the previous sections of this chapter.

4.4.3. Designing a stent coating system

In Tables 4.5, 4.6, 4.7 and 4.8, values for the parameters appearing in the model above are displayed. In Table 4.5, I display parameter values for commercially available stents. Some of the data displayed in Tables 4.2 and 4.3 is also relevant here.

The point of view taken in the current analysis is that of a stent manufacturer who wishes to design a drug-loaded polymer coating. The constraints on the manufacturer are that the polymer must be monolithic and nondegradable, and that the drug must be uniformly dispersed throughout the polymer bulk at a concentration below solubility. Of course, none of these constraints are actually necessary, but are chosen to ensure that the mathematical model considered here is appropriate; designing the coating system so that it can be reliably described by a simple model is clearly advantageous. The drug delivery industry has extensive experience in designing monolithic polymeric devices.

The manufacturer wishes to design the system so that a sufficient amount of drug is released into the artery wall for a sufficient period to prevent restenosis. More precisely, the manufacturer wishes to design the system so that a significant proportion of the specific binding sites in the artery wall are occupied by the drug for a period of some months subsequent to the stent being implanted.

The task then is to identify a parameter regime for the governing equations that achieves the stated goal subject to the constraints. From (4.56), it is seen that there are five independent dimensionless parameters that can in principle be independently varied to tune the system. However, two of these parameters, \( K_b \) and \( Pe \), are largely determined by the nature of the drug, and since most modern stent systems use either sirolimus (or one of its close relatives) or paclitaxel, there is not much scope for varying these. The parameter \( L \) may
Table 4.5. Data for some commercially available drug-eluting stents.

<table>
<thead>
<tr>
<th>DES</th>
<th>Strut thickness</th>
<th>Polymer thickness ($L_p$)</th>
<th>Drug</th>
<th>Drug dose</th>
<th>Life time</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher</td>
<td>140 µm</td>
<td>12.6 µm</td>
<td>Sirolimus</td>
<td>140 µg/cm² of stent surface area</td>
<td>80% of drug released within 30 days</td>
<td>[17,89]</td>
</tr>
<tr>
<td>Taxus</td>
<td>132 µm</td>
<td>16 µm</td>
<td>Paclitaxel</td>
<td>100 µg/cm² of stent surface area</td>
<td>Early 48 hours burst, followed by slow release over 10 days</td>
<td>[17,89]</td>
</tr>
<tr>
<td>Endeavor</td>
<td>91 µm</td>
<td>5.3 µm</td>
<td>Zotarolimus</td>
<td>100 µg/cm of stent length</td>
<td>95% of drug released within 15 days</td>
<td>[17,89]</td>
</tr>
<tr>
<td>Xience V</td>
<td>81 µm</td>
<td>7.6 µm</td>
<td>Everolimus</td>
<td>100 µg/cm² of stent surface area</td>
<td>80% of drug released within 30 days</td>
<td>[17,89]</td>
</tr>
<tr>
<td>Cardiomind Sparrow</td>
<td>67 µm</td>
<td>8 µm</td>
<td>Sirolimus</td>
<td>60 µg/cm of stent length</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>Jactax</td>
<td>97 µm</td>
<td>≤ 1 µm</td>
<td>Paclitaxel</td>
<td>5.75 µg/cm of stent length</td>
<td>Full release of drug within 60 days</td>
<td>[17,48]</td>
</tr>
</tbody>
</table>
4. A reaction-diffusion model for drug redistribution in tissue

Table 4.6. Data for drug diffusivities in polymers [6].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diffusivity $D_p$ (mm$^2$/s)</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>$5.7 \times 10^{-7}$</td>
<td>Poly(D,L-lactide-co-glycolide)</td>
</tr>
<tr>
<td></td>
<td>$4.9 \times 10^{-10}$</td>
<td>Poly(D,L-lactide)</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>$4.5 \times 10^{-9}$</td>
<td>Poly(D,L-lactide-co-glycolide)</td>
</tr>
<tr>
<td></td>
<td>$3.1 \times 10^{-10}$</td>
<td>Poly(D,L-lactide)</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>$1.6 \times 10^{-8}$</td>
<td>Poly(D,L-lactide-co-glycolide)</td>
</tr>
<tr>
<td></td>
<td>$4.35 \times 10^{-10}$</td>
<td>Poly(D,L-lactide)</td>
</tr>
</tbody>
</table>

Table 4.7. Data for transmural velocities and pressures in the arterial wall.

<table>
<thead>
<tr>
<th>Artery</th>
<th>Transmural velocity $(\times 10^{-5}$ mm/s)</th>
<th>Transmural pressure (mmHg)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine coronary</td>
<td>5.8</td>
<td>50</td>
<td>55, 176</td>
</tr>
<tr>
<td>Rabbit carotid</td>
<td>1.85 ± 0.33</td>
<td>110</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>8.9 ± 6.8</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Rabbit thoracic aorta</td>
<td>2.8 ± 0.9</td>
<td>70</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>4.4 ± 1.4</td>
<td>180</td>
<td>169</td>
</tr>
<tr>
<td>Rabbit femoral artery</td>
<td>3.3 ± 1.3</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>8.1 ± 2.4</td>
<td>60</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>9.9 ± 2.5</td>
<td>90</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 4.8. Values for some of the non-dimensional parameters appearing in the model for some commercially available drug/stent systems. For the purposes of calculation, the values $L_a = 0.75$ mm and $V_a = 6 \times 10^{-5}$ mm/s [176] have been chosen. The remaining values used can be found in Tables 4.1, 4.3 and 4.5.

<table>
<thead>
<tr>
<th>Stent/ Drug</th>
<th>$L = L_a/L_p$</th>
<th>$Pe = V_aL_a/D_a$</th>
<th>$K_b = k_{on}b^*/k_{off}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher/ Rapamycin</td>
<td>60</td>
<td>0.2</td>
<td>1700</td>
</tr>
<tr>
<td>Taxus/ Paclitaxel</td>
<td>47</td>
<td>17</td>
<td>400</td>
</tr>
<tr>
<td>Endeavor/ Zotarolimus</td>
<td>141</td>
<td>0.2</td>
<td>1700</td>
</tr>
<tr>
<td>Xience V/ Everolimus</td>
<td>99</td>
<td>0.2</td>
<td>1700</td>
</tr>
<tr>
<td>Cardiomind Sparrow/ Rapamycin</td>
<td>94</td>
<td>0.2</td>
<td>1700</td>
</tr>
</tbody>
</table>
be varied by changing the thickness of the polymer. However, the parameters 
\( \varepsilon = D_p/D_a \) and \( \eta = b^* / c^* \) are probably the most convenient to use to optimise 
the system since the diffusivity and the drug-loading for the polymer are readily 
changed.

I first turn my attention to the selection of appropriate values for the pa-
rameter \( \varepsilon \). A drug-eluting stent implanted in a coronary artery is required to 
release drug for a period of at least a few months subsequent to its deployment 
in order to prevent restenosis [17,89]. Hence, since I am assuming here that 
diffusion is the only mechanism for drug transport in the polymer coating, it 
is required that the drug diffusion time scale in the polymer, \( L_p^2 / D_p \), should 
be of the order of some weeks. For the sake of definiteness, I suppose that:

\[
L_p^2 / D_p \sim 2 \text{ weeks.} \quad (4.57)
\]

Inspecting Table 4.5, it is seen that \( L_p \sim 10 \mu \text{m} \), and (4.57) then implies that 
for the drug to release from the polymer over an appropriate time scale, the 
polymer should be fabricated so that:

\[
D_p \sim 10^{-10} \text{ mm}^2/\text{s} \text{ or smaller.} \quad (4.58)
\]

It is noteworthy that over half of the diffusivities \( D_p \) displayed in Table 4.6 
are \( O(10^{-10}) \) mm\(^2\)/s, although it should be said that the polymers listed in 
this table are not the same as those used in the manufacture of commercially 
available stents.

Inspecting the data in Table 4.3, it is seen that if \( D_p \sim 10^{-10} \text{ mm}^2/\text{s} \), then:

\[
\varepsilon = \frac{D_p}{D_a} \sim \begin{cases} 
10^{-6} & \text{for rapamycin,} \\
10^{-4} & \text{for paclitaxel,} \\
10^{-5} & \text{for heparin,} \\
10^{-5} & \text{for dextran.}
\end{cases} \quad (4.59)
\]

If \( \varepsilon \) is of order \( 10^{-4} \) or smaller, then it is clear from Table 4.8 that for com-
mercially available stenting systems, we have:

\[
\varepsilon \ll 1/K_b \ll 1/L \ll 1. \quad (4.60)
\]
4. A reaction-diffusion model for drug redistribution in tissue

It would seem from this that $\varepsilon \to 0$ is a sensible limit to consider to analyse the behaviour of (4.53), (4.54) and (4.55). This is indeed the case, but care must be taken to ensure that combinations of $K_b$ and $L$ do not arise in the system which may interfere with the accuracy of the results. I shall comment further on this danger below.

I now turn my attention to the selection of the parameter $\eta$, which corresponds to choosing a drug loading concentration for the polymer. After briefly investigating various limits for the governing equations, I propose the following:

$$\frac{\eta}{K_b} = O(\varepsilon),$$

with $\varepsilon \ll 1$ as explained above, or, in dimensional terms:

$$\frac{c^*}{K_D} = O \left( \frac{D_a}{D_p} \right), \quad \text{with} \quad D_p \ll D_a,$$

where $K_D = k_{on}/k_{off}$ is the dissociation constant for the drug from its specific binding sites. I now justify this choice by carrying out an asymptotic analysis of the governing equations in the limit $\varepsilon \to 0$, with $\eta/K_b = O(\varepsilon)$.

4.4.4. Preparing the polymer coating:

$$\frac{c^*}{K_p} = O \left( \frac{D_a}{D_p} \right), \quad D_p/D_a \ll 1$$

I write $\eta/K_b = \mu \varepsilon$ with $\mu = O(1)$, so that the second equation in (4.54) becomes:

$$\mu \varepsilon a = bc.$$

Since $K_b \gg 1$ for most of the drugs of interest, I shall also make the choice $K_b = O(\varepsilon^{-1/2})$ here, which implies that $\eta = O(\varepsilon^{1/2})$. However, this choice is not particularly significant since most of the more important results I shall derive below depend only on the requirement that $\eta/K_b = O(\varepsilon), \varepsilon \ll 1$. I write $\eta = \varepsilon^{1/2} \eta^*$ with $\eta^* = O(1)$.

There are two time scales to consider in the limit $\varepsilon \to 0$: a short time scale $t = O(\varepsilon)$, and a longer time scale $t = O(1)$. 

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4.4. A simple model for drug elution from an implanted stent

4.4.4. Short time scale, \( t = O(\varepsilon) \)

In dimensional terms, this time scale is given by \( t = O(L_p^2/D_a) \). Writing \( t = \varepsilon \hat{t} \), it is found that \( c_p \sim 1 \) in \(-1 < x < 0\), \( \hat{t} = O(1) \).

In \( 0 < x < L \), \( \hat{t} = O(1) \), we have \( a = 1 + O(\varepsilon^{1/2}) \), \( b, c = O(\varepsilon^{1/2}) \), and we pose:

\[
a \sim 1 + \varepsilon^{1/2} \hat{a}_0(x, \hat{t}), \quad b \sim \varepsilon^{1/2} \hat{b}_0(x, \hat{t}), \quad c \sim \varepsilon^{1/2} \hat{c}_0(x, \hat{t}) \quad \text{as } \varepsilon \to 0,
\]

to obtain:

\[
\hat{a}_0(x, \hat{t}) = -\frac{\mu}{\hat{c}_0(x, \hat{t})}, \quad \hat{b}_0(x, \hat{t}) = \frac{\mu}{\hat{c}_0(x, \hat{t})},
\]

and:

\[
\frac{\partial \hat{c}_0}{\partial \hat{t}} = \frac{\partial^2 \hat{c}_0}{\partial x^2} - \frac{Pe}{L} \frac{\partial \hat{c}_0}{\partial x}, \quad 0 < x < L, \hat{t} > 0. \tag{4.61}
\]

Recalling that \( L \gg 1 \), it is clear from (4.61) that the drug traverses the artery wall on the time scale \( \hat{t} = O(L^2) \), or \( t = O(\varepsilon L^2) \), which corresponds in dimensional terms to \( t = O(L_p^2/D_a) \), the diffusion time scale for the free drug in the artery wall. We deduce from this that in order for the asymptotic approximations to be valid, it is required that \( \varepsilon \ll 1/L^2 \), or, in dimensional terms:

\[
D_p \ll \frac{L_p^2}{L_a^2} D_a, \quad \text{or} \quad \frac{L_p^2}{D_p} \gg \frac{L_a^2}{D_a}, \tag{4.62}
\]

which implies that the drug diffusion time scale in the polymer must be much longer than the free drug diffusion time scale in the artery wall. For sirolimus, this implies that \( L_p^2/D_p \gg 1 \) hours, and for paclitaxel it requires that \( L_p^2/D_p \gg 2 \) days. However, we are insisting that \( L_p^2/D_p \sim 2 \) weeks here, as previously discussed, so these criteria are met.

The specification of the problem for \( \hat{c}_0(x, \hat{t}) \) requires the derivation of a boundary condition for \( \hat{c}_0 \) on \( x = 0 \). This is obtained by noting that there is a boundary layer near the surface of the polymer where it interfaces with the artery tissue. This layer is located at \( \hat{x} = O(1), \hat{x} < 0 \) where \( x = \varepsilon^{1/2} \hat{x} \), and in \( \hat{x}, \hat{t} = O(1) \), we pose \( c_p \sim \hat{c}_{po}(\hat{x}, \hat{t}) \) to obtain:
\[
\frac{\partial \hat{c}_{p0}}{\partial \hat{t}} = \frac{\partial^2 \hat{c}_{p0}}{\partial \hat{x}^2}, \quad -\infty < \hat{x} < 0, \hat{t} > 0,
\]
\[
\hat{c}_{p0}(\hat{x}, \hat{t}) \to 1 \quad \text{as} \quad \hat{x} \to -\infty, \hat{t} \geq 0,
\]
\[
\hat{c}_{p0}(0^-, \hat{t}) = 0 \quad \text{for} \quad \hat{t} \geq 0,
\]

and this self-similar problem has solution:

\[
\hat{c}_{p0}(\hat{x}, \hat{t}) = -\text{erf} \left( \frac{\hat{x}}{2\sqrt{\hat{t}}} \right),
\]

The perfect sink boundary condition on \( x = 0^- \) in (4.63) is noteworthy because it implies that at leading order the problem for the drug concentration in the polymer decouples from that in the tissue. It also implies that \textit{in vitro} experimental release studies should adequately mimic the release behaviour from the polymer \textit{in vivo} on this time scale (and for longer times too, as we shall see). It follows from (4.64) that, in dimensional unscaled variables, the fraction of drug released from the polymer for short times is approximated by:

\[
\frac{M(t)}{M(\infty)} \sim 2 \sqrt{\frac{D_p t}{\pi}} \quad \text{for} \quad t = O \left( \frac{L_p^2}{D_a} \right).
\]

The boundary condition for \( \hat{c}_o \) on \( x = 0 \) is now obtained by matching the drug fluxes across \( x = 0 \) (see equation (4.55)):

\[
\lim_{\hat{x} \to 0^-} \left( -\frac{\partial \hat{c}_{p0}}{\partial \hat{x}} \right) = \lim_{\hat{x} \to 0^+} \left( -\frac{\partial \hat{c}_o}{\partial x} + \frac{P \hat{e}}{L} \hat{c}_o \right),
\]

to obtain:

\[
- \frac{\partial \hat{c}_o}{\partial x}(0^+, \hat{t}) + \frac{P \hat{e}}{L} \hat{c}_o(0^+, \hat{t}) = \frac{1}{\sqrt{\pi\hat{t}}} \quad \text{for} \quad \hat{t} \geq 0.
\]

Two more boundary conditions are required for \( \hat{c}_o \), and these are motivated by considering numerical solutions for the short time scale. In Figure 4.11, I plot some numerical solutions to (4.53), (4.54) and (4.55) for \( \varepsilon = 10^{-6} \) and \( t = O(\varepsilon L^2) \) and for parameter values appropriate to sirolimus. It is clearly
4.4. A simple model for drug elution from an implanted stent

seen in this figure that the drug traverses the artery wall on this time scale, and that there is a sharp diffusion front tracking to the right. I denote the location of this front by \( x = q(\hat{t}; \varepsilon) \) for \( \varepsilon \ll 1 \). There is a narrow layer near \( x = q \) at \( z = O(1) \) where \( x = q(\hat{t}; \varepsilon) + \varepsilon^{1/2} z, \varepsilon \ll 1 \). In \( z = O(1), \hat{t} = O(1) \), I pose:

\[
a \sim \tilde{a}_o(z, \hat{t}), \quad b \sim \tilde{b}_o(z, \hat{t}), \quad c \sim \varepsilon \tilde{c}_o(z, \hat{t}), \quad q \sim q_o(\hat{t}) \quad \text{as} \quad \varepsilon \to 0,
\]

to obtain:

\[
-\dot{q}_o \eta^* \frac{\partial \tilde{a}_o}{\partial z} = \frac{\partial^2 \tilde{c}_o}{\partial z^2}, \quad \tilde{a}_o + \tilde{b}_o = 1, \quad \mu \tilde{a}_o = \tilde{b}_o \tilde{c}_o,
\]

and integrating these equations gives:

\[
\alpha(t) - \dot{q}_o \eta^* z = \mu \ln(\tilde{c}_o) + \tilde{c}_o, \quad \tilde{a}_o = \frac{\tilde{c}_o}{\mu + \tilde{c}_o}, \quad \tilde{b}_o = \frac{\mu}{\mu + \tilde{c}_o},
\]

where \( \alpha(t) \) is an arbitrary function of integration. Matching fluxes and concentrations gives:

\[
\lim_{x \to q_o} \left( -\frac{\partial \tilde{c}_o}{\partial x} \right) = \lim_{z \to -\infty} \left( -\frac{\partial \tilde{c}_o}{\partial z} \right), \quad \tilde{c}_o \to 0 \quad \text{as} \quad x \to q_o^-,
\]

which leads to:

\[
\frac{\partial \tilde{c}_o}{\partial x} = -\dot{q}_o \eta^*, \quad \tilde{c}_o = 0 \quad \text{on} \quad x = q_o.
\]

Combining our results, the complete initial boundary value problem for \( \tilde{c}_o \) may now be displayed:

\[
\begin{align*}
\frac{\partial \tilde{c}_o}{\partial \hat{t}} & = \frac{\partial^2 \tilde{c}_o}{\partial x^2} - \frac{Pe}{L} \frac{\partial \tilde{c}_o}{\partial x}, \quad 0 < x < q_o(\hat{t}), \hat{t} > 0, \\
- \frac{\partial \tilde{c}_o}{\partial x} + \frac{Pe}{L} \tilde{c}_o & = \frac{1}{\sqrt{\pi \hat{t}}} \quad \text{on} \quad x = 0, \hat{t} \geq 0, \\
\frac{\partial \tilde{c}_o}{\partial x} & = -\dot{q}_o \eta^*, \quad \tilde{c}_o = 0 \quad \text{on} \quad x = q_o(\hat{t}), \hat{t} \geq 0, \\
q_o(\hat{t} = 0) & = 0.
\end{align*}
\]
Figure 4.11. Numerical solutions to the initial boundary value problem (4.53), (4.54) and (4.55) for various dimensional times $t = O(L^2_a/D_a)$, the diffusion time scale for free drug in the artery wall. The drug penetrates the artery wall on this time scale and this is evident in the figures. I have plotted profiles for the bound drug in the artery wall in (a), and the free drug in the polymer and the artery wall in (b). The parameter values used are $L = 60, \varepsilon = 10^{-6}, \eta = 0.002, K_b = 1700,$ and $Pe = 0.2$. 
4.4.4.2. Long time scale, $t = O(1)$

This is the time scale over which the drug empties from the polymer coating, and in dimensional terms, it is given by $t = O(L_p^2 / D_p)$. In $-1 < x < 0$, $t = O(1)$, we pose $c_p \sim c_{po}(x, t)$ as $\varepsilon \rightarrow 0$, to obtain:

$$
\frac{\partial c_{po}}{\partial t} - \frac{\partial^2 c_{po}}{\partial x^2}, \quad -1 < x < 0, \quad t > 0,
$$

$$
\left. \frac{\partial c_{po}}{\partial x} \right|_{x = 0} = 0 \quad \text{for} \quad t \geq 0,
$$

$$
c_{po}(0^-, t) = 0 \quad \text{for} \quad t \geq 0,
$$

$$
c_{po}(x, 0) = 1 \quad \text{for} \quad -1 < x < 0.
$$

Notice that on this time scale, we also have a perfect sink boundary condition for the drug on $x = 0^-$. This is obtained by matching with the free drug concentration at $x = 0^+$; see below. Hence, the leading order problem for the drug concentration in the polymer again decouples from the leading order problem in the tissue. Solving (4.68) yields:

$$
c_{po}(x, t) = -\frac{4}{\pi} \sum_{n=1}^{\infty} \frac{1}{2n-1} \sin \left( \frac{(2n-1)\pi x}{2} \right) \exp \left( -\frac{(2n-1)^2\pi^2 t}{4} \right). \quad (4.69)
$$

The fraction of the total drug released in $t = O(1)$ is easily calculated using this expression; combining the results of this calculation with (4.65) now gives (using dimensional variables):

$$
\frac{M(t)}{M(\infty)} \sim \left\{ \begin{array}{ll}
2 \sqrt{\frac{D_p t}{\pi L_p^2}} & \text{for} \; t = O \left( \frac{L_p^2}{D_a} \right), \\
1 - \frac{8}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \exp \left( -\frac{(2n-1)^2\pi^2 D_p t}{4L_p^2} \right) & \text{for} \; t = O \left( \frac{L_p^2}{D_p} \right). 
\end{array} \right. \quad (4.70)
$$

In $0 < x < L$, $t = O(1)$, we have $a, b = O(1), c = O(\varepsilon)$, and pose:

$$
a \sim a_0(x, t), \quad b \sim b_0(x, t), \quad c \sim \varepsilon c_0(x, t) \quad \text{as} \quad \varepsilon \rightarrow 0,
$$

to obtain:

$$
a_0(x, t) = \frac{c_0(x, t)}{\mu + c_0(x, t)}, \quad b_0(x, t) = \frac{\mu}{\mu + c_0(x, t)}, \quad (4.71)
$$
A reaction-diffusion model for drug redistribution in tissue

\[
\frac{\partial^2 c_0}{\partial x^2} - \frac{P_e}{L} \frac{\partial c_0}{\partial x} = 0, \quad 0 < x < L, \quad t > 0,
\]

\[
- \frac{\partial c_0}{\partial x}(0^+, t) + \frac{P_e}{L} c_0(0^+, t) = \gamma(t) \quad \text{for} \quad t \geq 0,
\]

\[
c_0(L, t) = 0 \quad \text{for} \quad t \geq 0,
\]

where:

\[
\gamma(t) = -\frac{\partial c_{pm}}{\partial x}(0^-, t) = 2 \sum_{n=1}^{\infty} \exp \left( -\frac{(2n-1)^2 \pi^2 t}{4} \right),
\]

is the leading order flux of drug from the polymer into the tissue across \( x = 0 \) for \( t = O(1) \). These equations imply that the behaviour in the arterial tissue is approximately quasistatic, with the time dependence only entering via a time-varying flux of drug from the polymer coating, \( \gamma(t) \). Integrating (4.72) leads to the following approximation:

\[
c(x, t) \sim \frac{\varepsilon \gamma(t) L}{P_e} (1 - e^{-P_e(1-x/L)}),
\]

so that:

\[
a(x, t) \sim \frac{\gamma(t) L}{\mu P_e + \gamma(t) L (1 - e^{-P_e(1-x/L)})},
\]

\[
b(x, t) \sim \frac{\mu P_e}{\mu P_e + \gamma(t) L (1 - e^{-P_e(1-x/L)})};
\]

similar forms have recently been noted by Tzafriri et al. [176]. Hence, at the midpoint of the artery wall, we have:

\[
a(L/2, t) \sim \frac{\gamma(t) L}{\mu P_e + \gamma(t) L (1 - e^{-P_e(1-x/L)}/2)}.
\]

Recalling that \( 1/\varepsilon \gg L \gg 1 \), we have that:

\[
a(L/2, t) \sim 1 \quad \text{for} \quad \gamma(t) = O(1),
\]

so that we have approximately full occupancy of the specific binding sites at the centre of the artery wall on the time scale \( \gamma(t) = O(1) \). This suggests
that the parameter regime we have chosen for the design of the coating system should produce satisfactory results.

In Figure 4.12, I plot some numerical solutions to (4.53), (4.54) and (4.55) for $\varepsilon = 10^{-6}$ and $t = O(1)$. It is confirmed in this figure that to a good approximation the behaviour is indeed quasistatic in the artery tissue, with the shape of the profiles scarcely changing for successive times. I also note that a significant proportion of the specific binding sites away from the outer wall of the artery are occupied for $\gamma(t) = O(1)$.

The average occupancy of the specific binding sites over the thickness of the artery wall is given by:

$$m_a(t) = \frac{1}{L} \int_0^L a(x,t) dx.$$  

In Figure 4.13, I plot this quantity as a function of time for $\varepsilon = 10^{-6}$ and various values of $\eta$, with the other parameter values being appropriate for sirolimus. The rapid climb in the profiles near $t = 0$ corresponds to the initial layer $t = O(\varepsilon L^2)$; this rapid behaviour has been observed in experimental studies [176]. I also note that a significant proportion of the binding sites are occupied for a period of a few months. Using (4.75), we obtain the useful approximation:

$$m_a(t) \sim 1 + \frac{\ln \left( \frac{1}{1 + \frac{2\varepsilon L}{\mu Pe} \left(1 - e^{-Pe} \right)} \right)}{Pe \left(1 + \frac{2\varepsilon L}{\mu Pe} \right)}$$

for $t \gg \varepsilon L^2$. 

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4. A reaction-diffusion model for drug redistribution in tissue

Figure 4.12. Numerical solutions to the initial boundary value problem (4.53), (4.54) and (4.55) for various dimensional times $t = O(L_p^2/D_p)$. On this time scale, the behaviour in the arterial tissue is quasistatic, and is driven temporally by the decreasing flux of drug from the stent coating. I have plotted profiles for the bound drug in the artery wall in (a), and the free drug in the polymer and the artery wall in (b). The parameter values used are $L = 60, \varepsilon = 10^{-6}, \eta = 0.002, K_b = 1700$, and $Pe = 0.2$. 
4.4. A simple model for drug elution from an implanted stent

Figure 4.13. Plots of the average bound drug, $m_a(t)$, in the artery wall as a function of time $t$ for various values of $\eta$, and with $L = 60$, $\varepsilon = 10^{-6}$, $K_b = 1700$, and $Pe = 0.2$. On the vertical scale, 1 corresponds to full occupancy of the specific binding sites. The rapid rise in the profiles near $t = 0$ corresponds to the short time scale over which free drug in the tissue crosses the artery wall. It is seen that there is significant occupancy of the binding sites for a period of a few months subsequent to the stent being implanted.
5. Modelling pulsatile drug release from a thermoresponsive polymer

In this chapter, the first mathematical model that describes the pulsatile release of drug from a thermoresponsive polymer is developed. The work was carried out in collaboration with experimental scientists (Ms. Rongbing Yang and Dr. Yury Rochev) at the National Centre for Biomedical Engineering Science at NUI Galway. These experimentalists carried out pulsatile drug release experiments and produced data that is well described by the model developed in this chapter. The pulsatile release profiles are obtained by changing the temperature of the dissolution medium. There are two stages of release behaviour: fast release when the polymer is in a swollen state and slow (yet significant and non-negligible) release when the polymer is in a collapsed state. By altering the release time in the swollen state, approximately equal doses of drug were delivered in each cycle of the pulsatile release. Diffusion coefficients at different temperatures (including temperatures corresponding to both the fully swollen and collapsed states) are estimated by fitting the experimental data with theoretical release profiles generated by the model. It is found that the drug diffusivity in the collapsed polymer is two orders of magnitude smaller than that in the swollen polymer. The model also predicts that the effective lifetime of the system lies in the approximate range 1 to 42 hours (95% of drug released), depending on how long the system was kept at low temperature (below the LCST). Therefore this system can be used to obtain a controllable pulsatile release profile for small molecule drugs thereby enabling optimum therapeutic effects.
5. Modelling pulsatile drug release from a thermoresponsive polymer

5.1. Thermoresponsive polymers

Thermoresponsive polymers (TRPs) are environmentally sensitive hydrogels that can absorb a large amount of water and alter their properties in response to external changes in the environment \[66,82\]. In particular, TRPs can undergo dramatic changes in conformation in response to a small change in temperature; see Figure 5.1. The lower critical solution temperature (LCST) is the temperature at which the phase transition between an open porous hydrophilic network and a condensed, collapsed hydrophobic state occurs. At temperatures above the LCST, TRPs are hydrophobic and expel water to become dense and dry. Below the LCST, they are hydrophilic and absorb water to become swollen \[66,82\]. By exploiting this special property, thermoresponsive hydrogels have been used to obtain on-off drug release profiles where the on state corresponds to the swollen polymer, and the off state corresponds to the collapsed polymer \[9,25,192\].

![Figure 5.1](image.png)

Figure 5.1. Thermoresponsive polymers can undergo dramatic changes in conformation in response to a small change in temperature. In the above, a polymer in an aqueous solution swells/collapses as its temperature is varied across a lower critical solution temperature (LCST).

Poly(N-isopropylacrylamide) (pNIPAm) is a typical thermoresponsive hydrogel that has been widely investigated \[81,82,196\]. One of the reasons that PNIPAm has attracted so much attention is because its LCST in aqueous solution is approximately 32°C \[50,195\], which is close to body temperature. Also,
5.1. Thermoresponsive polymers

the transition between the hydrophobic and hydrophilic states of PNIPAm occurs over a narrow temperature region [193]. This property can be exploited to design an on-off switch to control drug delivery by varying temperature. If we maintain the temperature below the LCST, the polymer swells, the drug diffusivity increases, and drug release is switched on. If we then suddenly switch the temperature to above the LCST, the polymer collapses, water is expelled, the drug diffusivity decreases, and drug release is switched off [9,25,192].

**Thermoresponsive polymers as drug delivery vehicles**

![Diagram showing drug release](image)

Figure 5.2. (a) Off/slow release when the polymer is in the collapsed state; (b) on/fast release when the polymer is in the swollen state.

Most local drug delivery systems aim to maintain the drug concentration at some appropriate therapeutic level for a specified period of time, and this objective is frequently achieved using sustained release dosage forms [14,62,92]. For some drugs, however, an optimum therapeutic effect comes from a periodically fluctuating drug concentration [70]. Pulsed or pulsatile drug release systems have been developed to realise such behaviour [9,16,25]. The pulsatile release system possesses a cycle with two distinct release stages: on/fast release and off/slow release. The release duration time for the slow release stage is normally much longer than that for the fast stage, and the release rate is much smaller.

The majority of existing pulsatile release systems can be classified into two categories [70]: stimuli-induced systems [81,100,145,146] and time-controlled
5. Modelling pulsatile drug release from a thermoresponsive polymer

systems [58, 64, 84, 88]. Stimuli-induced systems have been developed based on thermal, chemical, and electrical stimuli. Time-controlled release systems can only release drug at pre-programmed time points, whereas stimuli-induced pulsatile release systems are more easily manipulated. However, systems based on thermal stimuli are particularly convenient since they can be designed and operated without significantly affecting the other critical parameters of the system. Therefore, thermoresponsive polymers have been used to design pulsatile release systems based on their particular behavior.

Many pulsatile drug delivery systems have been fabricated based on PNI-PAm, examples being: microspheres [40, 103], hydrogel matrices [19, 25], membranes [81], thin films [67] and porous systems. For these various delivery systems, the release time for a single cycle ranged from approximately 20 minutes [40] to 15 hours [25]. Although some behaviour characteristic of zero-order release has been observed in pulsatile PNIPAm systems [40], the release profiles obtained in this study are diffusion dominated. The parameters that can be used to tune drug release from the systems include the initial drug loading concentration, the geometrical dimensions of the system (such as thickness and surface area), and the durations the device is left switched on/off. The governing mathematical model described here incorporates all of these quantities.

Some models have previously been developed to describe drug release from non-pulsatile swelling systems [16, 26, 39, 70, 152, 156]. However, to our knowledge, no previous studies have attempted to model the pulsatile release of drug from a system based on a thermoresponsive polymer.

In this chapter, a simple mathematical model has been developed to characterize the drug release behaviour from thin thermoresponsive hydrogel films loaded with rhodamine B. The objective of the study was to develop a new controllable drug delivery system based on thin UV-crosslinked thermoresponsive films which can be characterised and tuned with the aid of a mathematical model.
5.2. A mathematical model for pulsatile release

A thin PNIPAm film was loaded with a model drug and immersed in an aqueous solution as shown in Figure 5.3. Drug diffusion in the film is assumed to be one-dimensional with the drug concentration varying through the depth of the film. The release behaviour is considered for the case in which the temperature of the film is quickly and repeatedly switched between a value above the LCST and a value below the LCST. When the film is held at a temperature above the LCST, it is in a condensed state, and I denote by $H_c, D_c$ the constant thickness and diffusivity of the condensed film, respectively. If the film is held at a temperature below the LCST, it is in a swollen state, and I denote by $H_s, D_s$ the constant thickness and diffusivity of the swollen film, respectively. The lateral dimensions of the film are fixed because they are constrained by the wall of the containing well, and swelling/collapsing can only occur in the $x$ direction; see Figure 5.3. It shall be found, as would be expected, that $D_c \ll D_s$, so that alternating the temperature between values above and below the LCST results in a release profile with an on/off pulsatile character.

The time the polymer was left in either the fully swollen or fully collapsed state was typically of the order of minutes. However, in the experimental work here, the time it took for the thin polymer film to either fully swell or fully collapse was considerably shorter than a minute. Hence, in the current model, I assume that the swelling and collapsing processes occur instantaneously. This assumption simplifies the problem considerably since incorporating the detail of the swelling or collapsing behaviour in the model would require the tracking of moving boundaries [156]. This would lead to a much more challenging mathematical problem, from which an analytical expression for the release profile could not be in general obtained. In Chapter 7, I shall consider a more sophisticated model that tracks the motion of moving boundaries during the swelling and collapsing processes.

At time $t = 0$, the film is at the temperature above the LCST and is fully collapsed. At time $t = t_1$, the temperature of the film is taken to instantaneously switch to the value below the LCST and the film is fully swollen; at
5. Modelling pulsatile drug release from a thermoresponsive polymer

time \( t = t_2 \), the film instantaneously reverts to the collapsed state, and so on (collapsed → swollen → collapsed → ...).

Figure 5.3. The experimental setup for the drug release experiment: (a) without stirring, and, (b) with stirring. The thermoresponsive polymer film releases drug into a surrounding aqueous solution.

5.2.1. Model equations

The motion of the drug molecules through the film is assumed to be governed by Fick’s law, and I denote by \( c(x, t) \) the concentration of drug at penetration \( x \) and time \( t \) in the film. A radial coordinate need not be considered here because of the impenetrable vertical walls. If \( H(t) \), \( D(t) \) denote the thickness of the film and the drug diffusivity at time \( t \), respectively, then under the assumptions stated above, the concentration \( c(x, t) \) of drug in the film is governed by:

\[
\frac{\partial c}{\partial t} = D(t) \frac{\partial^2 c}{\partial x^2} \quad \text{for} \quad 0 < x < H(t), \tag{5.1}
\]

with \( D(t) = \begin{cases} 
D_c, & 0 \leq t < t_1, \\
D_s, & t_1 \leq t < t_2, \\
D_c, & t_2 \leq t < t_3, \\
\vdots
\end{cases} \)

and \( H(t) = \begin{cases} 
H_c, & 0 \leq t < t_1, \\
H_s, & t_1 \leq t < t_2, \\
H_c, & t_2 \leq t < t_3, \\
\vdots
\end{cases} \)

This model is solved subject to the following boundary and initial conditions:
5.2. A mathematical model for pulsatile release

(i) The film is initially uniformly loaded drug, so I take \( c = c_0 \) at \( t = 0 \) in \( 0 < x < H_c \), where \( c_0 \) is constant.

(ii) The bottom of the film (see Figure 5.3), \( x = 0 \), is attached to a plastic cover slip substrate, which is taken to be impermeable to the drug, and so I impose \(-D \frac{\partial c}{\partial x} = 0\) on \( x = 0 \) for \( t \geq 0 \).

(iii) Perfect sink conditions are assumed for the drug at the top surface of the film which is in contact with the eluting medium, and so I set \( c = 0 \) on \( x = H(t) \) for \( t \geq 0 \).

Perfect sink boundary conditions are justified by recalling that the release medium is regularly replaced, and the drug concentration in the medium is reset to zero with each replacement. Also, the diffusivity of rhodamine B in water is \( O(10^{-6}) \) cm\(^2\)/s \([127]\), which is much larger than its values in the film, which lie in the range \( O(10^{-9} - 10^{-11}) \) cm\(^2\)/s (this study).

The initial collapsed state: \( 0 \leq t < t_1 \)

The governing equations are now given by:

\[
\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} \quad \text{in} \quad 0 < x < H_c, \ t > 0,
\]

\[
\frac{\partial c}{\partial x}(0,t) = 0, \quad c(H_c, t) = 0 \quad \text{for} \ t \geq 0,
\]

\[
c(x,0) = c_0 \quad \text{for} \ 0 < x < H_c.
\]

This linear problem is readily solved analytically by separating variables \([26]\) to obtain:

\[
c(x,t) = \frac{4c_0}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{2n-1} \exp \left( \frac{-\lambda_n D_c t}{H_c^2} \right) \cos \left( \frac{\sqrt{\lambda_n} x}{H_c} \right),
\]

where \( \lambda_n = \frac{(2n-1)^2 \pi^2}{4}, n = 1, 2, 3, ... \)

The first swollen state: \( t_1 \leq t < t_2 \)
5. Modelling pulsatile drug release from a thermoresponsive polymer

The governing equations are now:

\[
\frac{\partial c}{\partial t} = D_s \frac{\partial^2 c}{\partial x^2} \quad \text{in } 0 < x < H_s, t > t_1,
\]

\[
\frac{\partial c}{\partial x}(0, t) = 0, \quad c(H_s, t) = 0 \quad \text{for } t \geq t_1, \tag{5.4}
\]

\[
c(x, t_1) = \frac{H_c}{H_s} \frac{4c_0}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{2n-1} \exp \left( -\frac{\lambda_n D_c t_1}{H_c^2} \right) \cos \left( \frac{\sqrt{\lambda_n} x}{H_c} \right) \quad \text{for } 0 < x < H_s,
\]

where the ratio \(H_c/H_s\) has been included in the condition at \(t = t_1\) to account for the swelling of the domain. This system is also readily solved, to obtain:

\[
c(x, t) = \frac{H_c}{H_s} \frac{4c_0}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{2n-1} \exp \left( -\lambda_n \left( \frac{D_c t_1}{H_c^2} + \frac{D_s (t - t_1)}{H_s^2} \right) \right) \cos \left( \frac{\sqrt{\lambda_n} x}{H_c} \right). \tag{5.5}
\]

**The second collapsed state: \( t_2 \leq t < t_3 \)**

Proceeding as above, we find that:

\[
c(x, t) = \frac{4c_0}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n+1} \exp \left( -\lambda_n \left( \frac{D_c t_1}{H_c^2} + \frac{D_s (t_2 - t_1)}{H_s^2} + \frac{D_c (t - t_2)}{H_c^2} \right) \right)}{2n-1} \cos \left( \frac{\sqrt{\lambda_n} x}{H_c} \right). \tag{5.6}
\]

The pattern emerging from (5.3), (5.5), and (5.6) is now clear. The amount of drug released per unit area from the film by time \(t\) is given by:

\[
M(t) = H_c c_0 - \int_0^{H(t)} c(x, t) dx.
\]

Using the formulae derived above, the fraction of drug released from the film by time \(t\) is found to be:

\[
\frac{M(t)}{M(\infty)} = \begin{cases} 
1 - \sum_{n=1}^{\infty} \frac{2}{\lambda_n} \exp \left( -\lambda_n \left( \frac{D_c t_1}{H_c^2} \right) \right), & 0 \leq t < t_1, \\
1 - \sum_{n=1}^{\infty} \frac{2}{\lambda_n} \exp \left( -\lambda_n \left( \frac{D_c t_1}{H_c^2} + \frac{D_s (t_2 - t_1)}{H_s^2} \right) \right), & t_1 \leq t < t_2, \\
1 - \sum_{n=1}^{\infty} \frac{2}{\lambda_n} \exp \left( -\lambda_n \left( \frac{D_c t_1}{H_c^2} + \frac{D_s (t_2 - t_1)}{H_s^2} + \frac{D_c (t - t_2)}{H_c^2} \right) \right), & t_2 \leq t < t_3, \\
\vdots
\end{cases} \tag{5.7}
\]
For the case in which the temperature in the film is held fixed for all
time (non-pulsatile), the appropriate result can be obtained by simply setting
\( D_c/H^2_c = D_s/H^2_s = D/H^2 \) (constant) in equation (5.7) to obtain:

\[
\frac{M(t)}{M(\infty)} = 1 - \frac{8}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \exp \left( -\frac{(2n-1)^2 \pi^2 Dt}{4H^2} \right), \text{ for all } t > 0.
\] (5.8)

5.2.2. Discussion

Equation (5.7) gives an analytical expression for \( M(t) \), the total drug re-
leased from the pulsatile system by time \( t \). The development of such an ex-
pression is of significant practical value in both the design and operation of
a pulsatile release device. In the design stage, it can be used to predict the
thickness, surface area, and initial drug load to be used so that the result-
ing device can deliver doses of appropriate strength over an appropriate time
scale. In the operation stage, it can be used to devise a detailed schedule for
when the device should be switched on and off so as to deliver the required
doses at the desired time intervals. We can also estimate the diffusivity \( D \)
at different temperature by fitting the theoretical release profile given by (5.8)
to the experimental data using the least squares method.

To see how (5.7) might be used in practice, a hypothetical example is con-
sidered. Suppose it is required to deliver \( n \) equal doses of a drug, with each
dose delivering an amount of drug \( d \). It is further supposed that there is a
fixed time interval \( T \) between the delivery of each dose. In this example, it
shall be assumed that some mechanism has been devised that quickly switches
the device on and off and that the parameters \( D_c/H^2_c \) and \( D_s/H^2_s \) are known; a
procedure for estimating these parameters from experimental data is described
later in this chapter.

The total drug loaded onto the device, \( M(\infty) \), which of course must exceed
\( nd \) here, can be controlled by varying either the volume of the device or the
initial drug concentration. It is supposed that the device is deployed in the off
state at time \( t = 0 \) and that it is first switched on at \( t = t_1 \). To determine the
time \( t = t_2 \) at which the device should be switched off, we solve the equation:
5. Modelling pulsatile drug release from a thermoresponsive polymer

\[ M(t_2) - M(t_1) = d \quad (5.9) \]

for \( t_2 \) where \( M(t) \) is given by (5.7); notice that this ensures that the required dose \( d \) is delivered over the time interval \((t_1, t_2)\). Although (5.9) gives rise to a rather complicated expression for \( t_2 \) that cannot be solved analytically, \( t_2 \) can be readily estimated numerically with the aid of mathematical packages such as MATLAB or MAPLE. The device is switched on for the second time at \( t = t_2 + T \), and then switched off again at \( t = t_3 \) where \( t_3 \) is determined by numerically solving: \( M(t_3) - M(t_2 + T) = d \). Proceeding in this way, it is clear how a schedule may be devised for switching the device on and off so as to deliver the required doses at the desired intervals.

The appropriate release formula for an isothermal system which does not swell or collapse is given by (5.8). This simpler form is very familiar and has been used on numerous occasions previously to describe diffusion from a planar sheet [26]. I now obtain an estimate for the time it takes for a release device with a single constant diffusivity to empty its drug load; more precisely, the time it takes for there to be only a small fraction \( r \ll 1 \) of the initial drug load left remaining in the device is estimated. This time is such that \( Dt/H^2 \gg 1 \) and from (5.8) the following approximation is obtained:

\[ \frac{M(t)}{M(\infty)} \approx 1 - \frac{8}{\pi^2} \exp \left( -\frac{\pi^2 Dt}{4H^2} \right) \quad \text{for} \quad \frac{Dt}{H^2} \gg 1. \]

This expression is used to solve for \( t_r \), in \( \frac{M(t_r)}{M(\infty)} = 1 - r \) to obtain:

\[ t_r = \frac{4H^2}{\pi^2 D} \ln \left( \frac{8}{\pi^2 r} \right), \quad (5.10) \]

as the estimate for the time at which there is a fraction \( r \ll 1 \) of the initial drug left in the device. Equation (5.10) can be used to estimate the effective life-span of the pulsatile device. Clearly the device will have its minimum effective life-span, \( t_{\text{min}} \), if it is continually left on, so that

\[ t_{\text{min}} = \frac{4H^2_s}{\pi^2 D_s} \ln \left( \frac{8}{\pi^2 r} \right). \]
The device will have its maximum effective life-span, $t_{\text{max}}$, if it is continually left off, and:

$$t_{\text{max}} = 4H^2c^2 \frac{\ln \left( \frac{8}{\pi^2r} \right)}{D_c}.$$ 

The effective life-span of the pulsatile device then lies in the range $[t_{\text{min}}, t_{\text{max}}]$, and these useful quantities are readily calculated; for the system described in this chapter, $t_{\text{min}}$ is approximately 1 hour and $t_{\text{max}}$ is approximately 42 hours for 95% of drug released ($r = 5\%$).

In equation (5.10), it is seen that there is a strong quadratic dependency on the thickness of the film, but that the dependence on the diffusivity is weaker, being inversely proportional to only the first power. The diffusivities $D_c$ and $D_s$ are determined largely by the nature of the material being used, although there is some flexibility in material choice and preparation. The thickness of the film, however, is a quantity that can be readily varied in practice, and given that the release time scales have a strong dependence on film thickness, it is probably the most effective parameter to vary when designing a release device.

5.3. Experimental setup

5.3.1. Preparation of crosslinkable pNIPAm

Poly(NIPAm-co-ABzPh) was copolymerized from N-isopropylacrylamide (NIPAm) and the UV sensitive crosslinker, acrylamidobenzophenone (ABzPh) (molar ratio is 98.8 mol%:1.2 mol%, 5 g of total monomers). The mixture was precipitated in n-hexane after polymerization at 60°C for 24 hours. Precipitation was repeated three times using acetone as a solvent and n-hexane as a non-solvent. The polymer was dried at 45°C in a vacuum oven, and after three precipitations, the yield was 70%.

The lower critical solution temperature (LCST) of p(NIPAm-co-ABzPh) was determined by a cloud point measurement obtained on a Cary 100 UV-VIS spectrophotometer equipped with a temperature controller, and twelve-position sample holder. Polymer aqueous solution (3.5 ml of 1 mg/ml) in a
cuvette was heated at a rate of 0.1°C/min whilst obtaining the absorbance at 500 nm wavelength. The solution temperature was determined by using an internal temperature probe with a resolution of 0.5°C and an accuracy of ±0.1°C.

5.3.2. Preparation of films

Crosslinkable pNIPAm solution was prepared in dry methanol (2% w/w polymer/methanol). Aliquots (50 µl and 125 µl) of the solution were applied evenly to the wells of 24-well polystyrene tissue culture plates with polyethylene plastic cover slips (diameter 25 mm). The resulting 5 µm thick films were dried in a methanol atmosphere at room temperature overnight, and then were dried under vacuum at 40°C for 4 hours. Crosslinking was initiated by exposure of the covered plates to UV light at an intensity of 400 mW/cm² for 20 minutes, followed by inversion of the plates and exposure for a further 20 minutes. The polystyrene plates served as a long pass filter for UV light during irradiation. All loading and release experiments were carried out on copolymer films cast on 24-well tissue culture plates.

5.3.3. Drug loading and distribution in the film

The model drug rhodamine B was used in the release experiments. Crosslinked dry films of thickness 5 µm were placed in a 24-well plate, and rhodamine B (50 µl, 0.4 mM) solution in dehydrated methanol was cast on top of the films. The samples were dried in ethanol atmosphere at room temperature and then dried under vacuum at 40°C for 4 hours. Before the release experiment, 40°C distilled water was used to rinse off the rhodamine B on the surface of the films; and after the release, 4°C distilled water was used for extracting the remaining rhodamine B. In order to obtain the loading efficiency, all wash solutions were collected to determine the rhodamine B concentration using a plate reader. The drug loading efficiency was found by calculating one minus rinsed drug/total drug, expressed as a percentage; see Table 5.1. The total drug was composed of three parts: the rinsed fraction prior to release,
5.3. Experimental setup

Table 5.1. Calculating the drug loading efficiency.

<table>
<thead>
<tr>
<th>The total drug loading amount (mg)</th>
<th>Rinsed off (mg)</th>
<th>Total released (mg)</th>
<th>Loading efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.0007 ± 0.0003</td>
<td>0.009 ± 0.002</td>
<td>92 ± 6</td>
</tr>
</tbody>
</table>

the fraction released during the experiments, and the fraction extracted upon completion of the experiments.

To determine the drug distribution in the film, a 38.5 µl aliquot of copolymer solution was applied to glass bottom culture dishes. The resulting 5 µm thick films were dried and crosslinked as previously described. Rhodamine B-methanol solution was added to the surface of each film and dried at room temperature in methanol atmosphere and then dried under vacuum at 40°C for 4 hours. In order to confirm the film thickness and to determine the rhodamine B distribution in the film, images were recorded at room temperature using a Leica TCS SL confocal system and z-stack technique \[67\]. Figure 5.4 confirms that the loaded drug was initially distributed uniformly. Using z-stack images, the three dimensional distribution of the fluorescent drug in the dry film was established. Confocal microscopy was used to determine the thickness of the film. The measurement was performed at six random locations on the film and the thickness of the dry films was found to lie in the range 5.0 µm ±0.2 µm in

Figure 5.4. 3D-fluorescent images of rhodamine B distributed in a dry film. The red dots represent the fluorescent signal of rhodamine B.
5. Modelling pulsatile drug release from a thermoresponsive polymer

each case.

5.3.4. Drug release kinetics *in vitro*

The drug loaded samples were soaked in 2 ml of distilled water in order to carry out drug release kinetic studies at different temperatures *in vitro*. The samples were first rinsed twice with 40°C distilled water to remove the rhodamine B on the surface of the films. Then 1 ml of the dissolution medium was withdrawn and analysed by plate reader at regular time intervals; and the same volume of fresh distilled water was added to replace the volume of the extracted samples. To extract any residual drug remaining in the samples, 4°C distilled water was injected into the wells and left for 30 minutes. To maintain the film at the desired temperature, a thermal plate was used for the experiments without stirring (see Figure 5.3 (a)), and a hotplate combined with magnetic stirrer were used for the experiments with stirring (see Figure 5.3 (b)). All of the experiments were carried out in triplicate, and release profiles were obtained with and without stirring. To obtain the drug concentration, all of the sampling solutions were placed in a black 96-well plate, and then deposited in a plate reader.

5.3.5. Pulsatile release

In the experiments, the effect of thermal cycling on rhodamine B release from UV-crosslinked thermoresponsive polymer films was investigated. Firstly, to remove the rhodamine B on the surface of the films, the drug loaded samples were rinsed twice with 40°C distilled water. Then the films were soaked into 1 ml of warm distilled water (40°C). To obtain pulsatile release cycles, all the dissolution medium was withdrawn and replaced by 1ml of cold fresh water (4°C) at pre-determined time intervals; and then all of the dissolution medium was replaced by the same amount of warm fresh water (40°C) after a pre-calculated time period. To extract any residual drug remaining in the samples, 4°C distilled water was injected into the wells and left for 30 minutes. To maintain the film at the desired temperature, a thermal plate was used (see Figure 5.3 (a)). The results of these experiments were compared with simula-
5.4. Comparison with experimental data and parameter estimation

5.4.1. Parameter estimation

I shall consider first experiments in which the temperature is held fixed (non-pulsatile) throughout the experiment; see Figure 5.5. In these experiments, the fraction of total drug released from the system, \( M(t)/M(\infty) \), is measured for various temperatures, ranging from 4°C to 40°C. For each release experiment, the temperature is kept fixed so that the appropriate theoretical release profile is given by equation (5.8). This expression is fitted to the experimental data using the method of least squares with \( D/H^2 \) being the unknown parameter to be estimated. Once the estimate for \( D/H^2 \) has been obtained, the drug diffusivity, \( D \), follows immediately if the thickness, \( H \), is known. Using the mathematical package MAPLE, it is easy to solve numerically the nonlinear equation for \( D/H^2 \) arising from the least squares fitting procedure. The estimates obtained for \( D/H^2 \) are displayed in Figures 5.6.

In Figure 5.5, a selection of the experimental release profiles, together with theoretical curves generated by the mathematical model which have been fitted to the experimental data are displayed. The selection includes examples where the film is fully collapsed, fully swollen, and in an intermediate state between these two extremes. It is observed that there is a very good fit between the theoretical curves and experimental data in all cases. The results show that the rate at which drug releases from the system decreases significantly as the temperature is increased through the range 27°C to 34°C. However, for ranges...
5. Modelling pulsatile drug release from a thermoresponsive polymer

Figure 5.5. Constant temperature (non-pulsatile) drug release profiles for rhodamine B (20 nmol/film) from 5 µm thick UV-crosslinked polymer films: (a) Release profiles without stirring. (b) Release profiles with stirring. The continuous line curves correspond to solutions (5.8) of the mathematical model that have been fitted to the experimental data using the method of least squares.
below 27°C or above 34°C, the release rate is less sensitive to temperature changes.

From Figure 5.5 (a) and (b), it can be seen that stirring makes little difference to the release profiles if the temperature is held below the LCST (4°C and 25°C). When the temperature is above the LCST (37°C), the release was slightly slower without stirring. At 32°C, the drug release rate increases dramatically with stirring. However 32°C is close to the polymer’s LCST, and the composition of the polymer is uncertain in this regime. The model described here is not appropriate for this regime, and reproducible experimental results close to the LCST could not be obtained.

### 5.4.2. Temperature dependence of the drug diffusivity across the LCST

![Graph showing temperature dependence of drug diffusivity](image)

**Figure 5.6.** Transmittance curve for the uncrosslinked polymer in aqueous solution together with $D/H^2$ values for the crosslinked film. The $D/H^2$ values were obtained by fitting a theoretical curve to release data and the transmittance (continuous line) was obtained using a UV-Vis spectrophotometer. The polymer concentration was 1 mg/ml in double distilled water and the heating ratio was 0.1°C/min.

In Figure 5.6, the transmittance versus temperature for the heating of the copolymer pNIPAm-co-ABzPh aqueous solution is displayed. The data shows
that the transition temperature lies in the range 28°C to 30°C. The scaled diffusivities $D/H^2$ in the polymer are estimated at different temperatures by fitting the theoretical release profile given by equation (5.8) with the experimental data as described above, and the results are displayed in Figure 5.6. As the temperature is increased through the LCST, the data reveals that the scaled diffusivity $D/H^2$ decreases by approximately one order of magnitude, which conforms to our intuitive expectations since this temperature change corresponds to the transition from the swollen to the shrunken state for the film. In this study, the volume phase transition of the films is in the range of 22°C to 30°C. This transition temperature range is 6°C wider than that for the uncrosslinked polymer in aqueous solution. However, it should be noted that the LCST for the polymer in aqueous solution was found to be 3°C higher than that for the crosslinked film.

5.4.3. Lifetime of the system

In Figure 5.7, the long-term release profiles for rhodamine B are displayed for 4°C and 37°C. The system is held at 4°C and 37°C for 2 and 48 hours, respectively, in order to acquire the lifetime of the system. At 4°C, 98.6 ± 0.4% of the rhodamine B was released in one hour, but at 37°C, 91.1 ± 1.7% of the model drug released in 42 hours.

It is noteworthy that there is some discrepancy between the theoretical profile and the experimental data in Figure 5.7 (b). This can be accounted for by noting that a non-negligible fraction of the drug has been retained by the collapsed polymer even after 40 hours of release. If the data is re-scaled so that the last data point of Figure 5.7 (b) corresponds to 100% release, we obtain a better fit. This suggests that for the collapsed polymer, a small fraction of the drug releases extremely slowly, if at all. However, I have not attempted to incorporate this effect in the current modelling.

5.4.4. Pulsatile release results

In Figure 5.8, a theoretical curve based on equation (5.7) has been fitted to pulsatile experimental drug release data. In the experiment, the temperature
5.4. Comparison with experimental data and parameter estimation

Figure 5.7. Lifetime of the system. (a) Release profile of rhodamine B at 4°C over 2 hours. (b) Release profile of rhodamine B at 37°C over 48 hours.
Figure 5.8. (a) Pulsatile release profile where the temperature alternates between 4°C and 40°C. The cumulative release of rhodamine B (20 nmol/film) from 5 µm thick UV-crosslinked polymer films in distilled water at 4°C and 40°C were sampled at selected time points. The data points have been fitted to the mathematical model using equation (5.7). (b) Release rate profile corresponding to the cumulative release profile in (a).
5.4. Comparison with experimental data and parameter estimation

Figure 5.9. Pulsatile release profiles for the UV-crosslinked polymer films where the temperature is varied between (a) 25°C and 37°C, (b) 28°C and 37°C, and, (c) 30°C and 37°C.
is repeatedly switched between 40°C (above the LCST, slow release) and 4°C (below the LCST, fast release). The parameters $D_c/H_c^2, D_s/H_s^2$ used were obtained from non-pulsatile experiments. As would be expected, the resulting release profile has a clear on/off pulsatile character. In the experiment, the system was held in the off state for a fixed three minutes in each cycle, but the time it was left in the on state was increased with increasing cycle number so as to achieve an approximately uniform dose for each cycle. However, for the first cycle, a larger dose was delivered. In Figure 5.8, it is clear that a total of six pulses were obtained in all. The analytical results reveal that $D_s/H_s^2$ is one order of magnitude greater than $D_c/H_c^2$, which is consistent with the results of the fixed temperature experiments. The fit is again quite good indicating that our model, despite the simplifying assumptions made in its development, is adequate for capturing the essential features of the release behaviour. However, it should be noted that it is very difficult to realise a temperature transition of 36°C (from 4°C to 40°C) in vivo. Therefore, I shall show that the system is capable of successfully exhibiting pulsatile release profiles for temperature transitions as modest as 7°C.

Having established that the model adequately fits the experimental data, it is used to aid in the design of three further pulsatile release experiments; see Figure 5.9. Specifically, the model has been used to estimate when the temperature of the polymer should be changed in the experiments so as to ensure that there would be five release cycles, each of duration 20 minutes approximately, and that between 10% and 20% of the total drug would be released in each cycle. The results show that these objectives were broadly achieved, except for the first temperature drop where less than 10% of the drug was released. It is also noteworthy that there is a much smaller jump in the temperature for these experiments, with 12°C for the pulsatile release of 25°C and 37°C, 9°C for the pulsatile release of 28°C and 37°C, and only 7°C for the pulsatile release of 30°C and 37°C. Clearly, these temperature transitions are much more realistic from the point of view of applications than a 4°C to 40°C transition.
5.5. Conclusion

In this chapter, the capability of poly(NIPAm-co-ABzPh) for incorporating the pulsatile releasing of rhodamine B at designated time points has been investigated. There are two stages of release: slow diffusion when the temperature is above the LCST, and swelling followed by more rapid diffusion when the temperature drops below the LCST. The behaviour of the system is adequately described by a mathematical model which has been developed based on Fick’s law. Using the model, a formula for the fraction of drug released as a function of time has been constructed. Pulsatile release is observed, and successfully modelled by the release formula (5.7) by choosing appropriate diffusivities. By carefully controlling the release time, the release dosage for each cycle can be held at approximately 10% of the total drug available. However, in the first release cycle, the minimum practicable release time is about 30 seconds, and this may be too long to keep the dose delivered below 10%; see Figures 5.8 and 5.9. An estimate for the effective life time of this system is also provided by the model, and this is found to lie in the approximate range 1 to 42 hours. In my view, pulsatile systems such as the one developed and analysed here will form important components of future technologies that realise the goal of controlled drug release in vivo.
6. A theoretical assessment of a drug delivery system based on a thermoresponsive polymer and a cooling device

In Chapter 5, a mathematical model to describe the pulsatile release of a model drug from a thermoresponsive polymer was developed. In the experimental system, the temperature was rapidly switched above and below the LCST with the aid of a hot plate and by changing the elution medium appropriately. However, changing the temperature of a polymer-based biomedical device implanted in vivo is clearly a much more challenging proposition. In this chapter, I shall discuss some proposals for externally dropping the temperature of a thermoresponsive polymer implanted in vivo below its LCST, and use mathematical modelling to evaluate the properties an associated cooling device should have in order for the system to be realised in practice.

6.1. Introduction

Thermoresponsive polymers undergo a volume phase transition in aqueous solution when the temperature of their fluid environment is varied across a critical value. If the polymer goes from being in a swollen, hydrophilic state to a shrunken, hydrophobic state as the temperature is increased through the critical value, the critical temperature is referred to as the lower critical solution temperature (LCST). The LCST of a thermoresponsive polymer can be readily
6. A theoretical assessment of a pulsatile drug delivery system

varied by, for example, changing the pH or composition of its fluid environment, by varying the molecular weight of the polymer, or by the incorporation of hydrophilic or hydrophobic groups \[29, 57, 65, 162, 186\]. LCST values as low as \(-7.5^\circ C\) \[186\] and as high as \(80^\circ C\) \[122\] have been observed experimentally. Poly(N-isopropylacrylamide) (pNIPAm) is one of most well-studied thermoresponsive polymers \[81, 196\]. Its LCST is close to \(32^\circ C\) \[50, 195\] and it has a sharp phase transition in a narrow temperature region \[193\]. Furthermore, the LCST of pNIPAm can be easily increased to near human physiological temperature \((37^\circ C)\) \[63, 108\].

Thermoresponsive polymers have numerous potential applications in areas such as drug delivery \[58, 81, 84, 88, 145\], gene delivery \[171, 194\], tissue engineering \[105, 109\], chemical valve technology \[21\], and catalysis \[20\]. However, a biomedical device based on a thermoresponsive polymer that enables the pulsatile release of drug in vivo has yet to be developed, principally because of the difficulty of locally decreasing the temperature of human tissue in vivo. Nevertheless, there have been some practical proposals that involve externally increasing the temperature of a thermoresponsive polymer to achieve controlled release in vivo \[145\].

I now briefly discuss some potential mechanisms to achieve the cooling of the polymer in vivo. A potential chemically-based cooling mechanism is to add a substance to the polymer’s fluid environment that gives rise to an endothermic chemical process. In an endothermic process, heat is absorbed from the environment as the reactions involved proceed causing a drop in its temperature. The dissolution of ammonium nitrate in water is an example of an endothermic process; when ammonium nitrate is dissolved in water at room temperature at a concentration of 1 M, a drop in fluid temperature of 6 K is observed. However, the choice of substances that could be safely used in vivo is very limited because most endothermic reactions involve toxic chemicals \[179\].

Another candidate mechanism for externally dropping the temperature of the polymer is based on the Peltier effect, which is a thermoelectric phenomenon \[106\]. The Peltier effect arises at the junction of two dissimilar conductors through which a current is flowing, and refers to the transfer of heat from one of the conductors to the other across the junction. The Peltier
effect allows for the transfer of heat at the junction against the temperature gradient, and cooling devices have been manufactured based on this effect. Bi$_2$Te$_3$ and Bi$_2$Se$_3$ are amongst the best performing thermoelectric materials at room temperature. A thermoelectric cooling device based on the Peltier effect has recently been developed by Morizane et al. for the treatment of spinal cord injury in rats, although the cooling component of their device was deployed outside of the body as it was too large to be implanted in vivo. However, extremely thin thermoelectric cooling devices can now be fabricated that are less than 200 µm thick, making feasible the development of devices that may be implanted in vivo.

The magnetocaloric effect (MCE) provides another possible mechanism for externally lowering the temperature of the cooling material. The MCE refers to the heating or cooling of magnetic materials due to the application of time-varying magnetic fields. The effect, which has been substantially understood for a long time, is caused by the change in magnetic entropy of a material due to the application or removal of an external magnetic field. Specifically, the cooling of a magnetic material is caused by an increase in its magnetic entropy when an external magnetic field is removed. The MCE has been a subject of considerable interest since 1997 when Pecharsky and Gschneidner discovered a giant MCE in some Gd$_5$(Si$_x$Ge$_{1-x}$)$_4$ alloys. Many alloys have subsequently been found to possess a colossal MCE, although only some of these were found to undergo their maximum temperature change close to room temperature and ambient pressure. Of these, only a very few were found to possess their MCE peak near physiological temperature (37°C). In 2006, De Campos et al. reported that the MCE peak of Mg$_{1-x}$Fe$_x$As is at 37°C when $x$ is 0.003.

The three cooling technologies just described can in principle be used to locally decrease the temperature of tissue in the body. It should be emphasised, however, that a system will only be of practical value if it can be manufactured at a sufficiently small scale for it to be implanted in vivo.

In this chapter, a mathematical model is formulated to investigate the feasibility of developing a pulsatile drug release system that is based on dropping the temperature of a thermoresponsive drug-loaded polymer coating below its
6. A theoretical assessment of a pulsatile drug delivery system

LCST. The candidate cooling mechanisms discussed above are not incorporated in the modelling presented here. Rather, the model is used to determine the properties a cooling system should have for a drug release device to produce practically useful pulsatile release profiles.

6.2. Mathematical Model

6.2.1. Introduction

Figure 6.1. A schematic representation of (a) a polymer coated cooling device in a water environment, and (b) a slice of the cooling material, polymer, and water at time $t = 0$ in the semi-infinite domain $-H_M < x < \infty$. The complete system lies along the infinite domain $-\infty < x < \infty$, but is symmetric about the centreline of the cooling material at $x = -H_M$. 
The proposed release system is composed of a thermoresponsive drug-loaded polymer bonded to a cooling device which consists of a slab of cooling material. The device and polymer are immersed in water that is initially held at a temperature above the polymer’s LCST, so that the polymer is collapsed and drug release is negligible; see Figure 6.1 (a). Drug delivery is initiated by quickly lowering the temperature of the cooling material sufficiently for the temperature throughout the adjacent polymer to drop to below its LCST, thereby causing the polymer to swell. Drug then releases from the swollen polymer. Drug release spontaneously switches off again when heat conduction from the fluid environment raises the polymer temperature to above its LCST causing it to collapse. In the current theoretical study, mathematical modelling is used to assess the feasibility of a system of this kind.

6.2.2. Modelling assumptions

The principal assumptions made in formulating the mathematical model are now listed.

(i) Heat conduction in the cooling material, polymer and water is governed by Fourier’s law of conduction.

(ii) The thermal conductivity and diffusivity of the cooling material, polymer and water are taken to be constant. The thickness of the cooling material and polymer are also assumed constant and the water is taken to occupy an infinite domain. Although these are reasonable assumptions for the cooling material and the water, they are not valid for a thermoresponsive polymer since its properties and thickness change during the swelling and collapsing processes. However, for the important case of a thin polymer film, these assumptions are frequently acceptable since it will be shown in this study that the polymer temperature can then be dominated by the properties of the cooling material and the water. For polymers whose thickness is comparable to that of the cooling material, the assumptions of constant polymer conductivity, thermal diffusivity and thickness may be viewed as providing a starting point for the analysis of the system. In
6. A theoretical assessment of a pulsatile drug delivery system

the next chapter, I shall develop and analyze a model that takes account of polymer swelling and collapsing.

(iii) The temperature and heat flux are taken to be continuous at the cooling material-polymer and polymer-water interfaces.

(iv) It is assumed that the presence of drug does not affect the thermal properties of the polymer or the water. The model thus does not incorporate drug concentrations, and is used instead to predict the evolution of the temperature profiles in the cooling material, polymer and water. In my view, this is sufficient to establish the feasibility of the system.

(v) The temperature of the cooling material may be instantaneously dropped to the same value throughout its volume. There is no further cooling of the system subsequent to this. These assumptions will not affect the conclusions of the modelling presented here since allowing for a finite cooling period will only serve to delay the reheating of the system by the fluid environment, thereby prolonging the time the polymer remains swollen.

(vi) The phase transition for the polymer is assumed to be perfectly sharp, so that for temperatures immediately above its LCST, the polymer collapses fully.

6.2.3. Geometry and model equations

For simplicity, the cooling device is taken to be composed of an infinite slab of homogeneous material of thickness $2H_M$ that occupies $-2H_M < x < 0, \ -\infty < y, z < \infty$. At $x = -2H_M$ and $x = 0$, the cooling material is taken to be in thermal contact with polymer films of thickness $H_P$. At $x = -2H_M - H_P$ and $x = H_P$, the polymer films are in turn taken to be in thermal contact with water that occupies $-\infty < x < -2H_M - H_P$ and $H_P < x < \infty$. Water is chosen as the fluid medium here since it is the dominant component of biological fluids. The system is clearly symmetric about the centreline of the cooling material.
at \( x = -H_M \), and so a symmetry condition is imposed at \( x = -H_M \), and the semi-infinite domain \(-H_M < x < \infty\) only is considered; see Fig. 6.1(b).

The temperatures in the cooling material, polymer and water at location \( x \) and time \( t \) are denoted by \( T_M(x, t) \), \( T_P(x, t) \) and \( T_W(x, t) \), respectively. The initial temperature of the entire system is taken to be at the constant temperature of the water, \( T^i_w \), say. Since the behaviour of the device in the human body is being modelled, \( T^i_w \) is taken to be 37°C in the numerical calculations here. The LCST of the thermoresponsive polymer is denoted by \( T_L \), and it is supposed that \( T_L < T^i_w \) so that the polymer is initially in its collapsed state.

At time \( t = 0 \), it is assumed that the temperature throughout the cooling material is instantaneously lowered to \( T^i_M < T_L \). The purpose of the analysis of this chapter is to investigate the subsequent temperature evolution for \( t > 0 \) in the adjoining polymer, and in particular, the possibility of the polymer temperature dropping to below its LCST throughout its thickness so that it can swell and release drug. The subsequent reheating of the polymer above its LCST due to heat conduction from the adjacent fluid medium will also be tracked.

In view of the discussion immediately above and the modelling assumptions of the previous section, the temperature in the cooling material \( T_M(x, t) \) satisfies:

\[
\frac{\partial T_M}{\partial t} = k_M \frac{\partial^2 T_M}{\partial x^2} \quad \text{for} \quad -H_M < x < 0, \quad t > 0, \\
\frac{\partial T_M}{\partial x}(-H_M, t) = 0 \quad \text{for} \quad t \geq 0, \\
T_M(x, 0) = T^i_M \quad \text{for} \quad -H_M < x < 0, 
\]

(6.1)

where \( k_M \) is the constant thermal diffusivity of the material. The boundary condition (6.1) is the symmetry condition that allows the spatial domain to be halved.

For simplicity, I do not attempt to model the behaviour of a true swelling or collapsing thermoresponsive polymer in the current study, and confine our attention instead to polymers that can be adequately characterised by a constant thermal diffusivity and thickness; this in my view provides a sensible
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starting point for evaluating the feasibility of the proposed system. Also, from
the point of view of applications, the thin polymer film limit (Section 6.3.2)
is probably of most interest, and the temperature in the polymer is usually
simply a function of time at leading order in this case. The temperature in
the polymer \( T_p(x,t) \) thus satisfies:

\[
\frac{\partial T_p}{\partial t} = k_p \frac{\partial^2 T_p}{\partial x^2} \quad \text{for } 0 < x < H_p, t > 0,
\]

\[
T_p(x,0) = T_w^i \quad \text{for } 0 < x < H_p,
\]

where \( k_p \) is the constant thermal diffusivity of the polymer.

The temperature in the external water medium \( T_w(x,t) \) satisfies:

\[
\frac{\partial T_w}{\partial t} = k_w \frac{\partial^2 T_w}{\partial x^2} \quad \text{for } H_p < x < \infty, t > 0,
\]

\[
T_w(x,0) = T_w^i \quad \text{for } H_p < x < \infty,
\]

\[
T_w(x,t) \rightarrow T_w^i \quad \text{as } x \rightarrow \infty, t \geq 0,
\]

where \( k_w \) is the constant thermal diffusivity of the water. To complete the
model, I impose continuity in the temperature and the heat flux at the cooling
material-polymer interface and the polymer-water interface, so that:

\[
T_M(0,t) = T_p(0,t), \quad -K_M \frac{\partial T_M}{\partial x}(0,t) = -K_p \frac{\partial T_p}{\partial x}(0,t) \quad \text{for } t \geq 0,
\]

\[
T_p(H_p,t) = T_w(H_p,t), \quad -K_p \frac{\partial T_p}{\partial x}(H_p,t) = -K_w \frac{\partial T_w}{\partial x}(H_p,t) \quad \text{for } t \geq 0,
\]

where \( K_M, K_p, K_w \) give the thermal conductivities of the cooling material,
polymer, and water, respectively. The thermal diffusivities are related to the
thermal conductivities via the following equations:

\[
k_M = \frac{K_M}{\rho_M c_M}, \quad k_p = \frac{K_p}{\rho_p c_p}, \quad k_w = \frac{K_w}{\rho_w c_w},
\]

where, using an obvious notation, the \( \rho \)'s give the densities and the \( c \)'s give
the specific heat capacities of the three media.

The mathematical model is now complete and consists of equations (6.1)-(6.4).
6.3. Results and Discussion

6.3.1. Non-dimensionalisation and non-dimensional parameters

The independent non-dimensional parameters that may be varied to tune the system are identified by non-dimensionalising the governing equations (6.1)-(6.4). I introduce the following dimensionless variables:

\[
\bar{x} = \frac{x}{H_M}, \quad \bar{t} = \frac{t}{(H_M^2/k_M)}, \quad \bar{T}_M = \frac{T_M}{T_i^M}, \quad \bar{T}_P = \frac{T_P}{T_i^M}, \quad \bar{T}_W = \frac{T_W}{T_i^M},
\]

and define the non-dimensional parameters:

\[
\varepsilon = \frac{H_P}{H_M}, \quad T_{i/M/W} = \frac{T_i^M}{T_i^W}, \quad K_{P/M} = \frac{K_P}{K_M}, \quad K_{W/P} = \frac{K_W}{K_P}, \quad K_{P/M} = \frac{k_P}{k_M} = \frac{\rho_M c_M}{\rho_P c_P}, \quad K_{W/P} = \frac{k_W}{k_M} = \frac{\rho_W c_W}{\rho_P c_P},
\]

(6.6)

to obtain the dimensionless equations (immediately dropping the overbars):

**Cooling Material:**

\[
\frac{\partial T_M}{\partial t} = \frac{\partial^2 T_M}{\partial x^2} \quad \text{for} \quad -1 < x < 0, t > 0,
\]

\[
\frac{\partial T_M}{\partial x}(-1, t) = 0 \quad \text{for} \quad t \geq 0;
\]

\[
T_M(x, 0) = T_{i/M/W} \quad \text{for} \quad -1 < x < 0;
\]

(6.7)

**Cooling material/polymer interface:**

\[
T_M(0, t) = T_P(0, t), \quad -\frac{\partial T_M}{\partial x}(0, t) = -K_{P/M}\frac{\partial T_P}{\partial x}(0, t) \quad \text{for} \quad t \geq 0;
\]

(6.8)

**Polymer:**

\[
\frac{\partial T_P}{\partial t} = k_{P/M}\frac{\partial^2 T_P}{\partial x^2} \quad \text{for} \quad 0 < x < \varepsilon, t > 0,
\]

\[
T_P(x, 0) = 1 \quad \text{for} \quad 0 < x < \varepsilon;
\]

(6.9)
6. A theoretical assessment of a pulsatile drug delivery system

Polymer/water interface:

\[ T_P(\varepsilon, t) = T_W(\varepsilon, t), \quad -\frac{\partial T_P}{\partial x}(\varepsilon, t) = -K_{W/P} \frac{\partial T_W}{\partial x}(\varepsilon, t) \quad \text{for } t \geq 0; \quad (6.10) \]

Water:

\[ \frac{\partial T_W}{\partial t} = k_{W/M} \frac{\partial^2 T_W}{\partial x^2} \quad \text{for } \varepsilon < x < \infty, t > 0, \]

\[ T_W(x, 0) = 1 \quad \text{for } \varepsilon < x < \infty, \]

\[ T_W(x, t) \rightarrow 1 \quad \text{as } x \rightarrow \infty, t \geq 0. \quad (6.11) \]

It is noteworthy that for a given polymer and cooling material, there are two parameters that may be independently varied to tune the system, namely the temperature ratio, \( T_{iM/W} \), and the geometrical parameter, \( \varepsilon \). The remaining four quantities appearing in equation (6.6) are material parameters, and are fixed for a given choice of polymer and cooling material. If both the cooling material and the polymer are allowed to change, then in principle all six parameters in equation (6.6) may be independently varied.

The problem defined by equation (6.7)-(6.11) is linear and analytical progress is possible using, for example, the method of Laplace transforms [18]. However, the algebra arising is quite heavy and I prefer instead to solve the full problem numerically. Fortunately, a convenient analytical solution may be written down at leading order in the thin polymer film limit (which is probably the most important case from the point of view of applications), and this is considered now.

6.3.2. The thin polymer film limit

I shall consider the case where the thickness of the polymer film is small compared to the thickness of the cooling material, which corresponds to the asymptotic limit \( \varepsilon = H_P/H_M \rightarrow 0 \). I take the remaining parameters to be \( O(1) \), and pose as \( \varepsilon \rightarrow 0 \) for \( t = O(1) \):

\[ T_M \sim T_{Mo}(x, t) \quad \text{in } -1 < x < 0, \quad T_W \sim T_{Wo}(x, t) \quad \text{in } x > 0. \]
It is easily shown that $T_{M0}$ satisfies (6.7), $T_{W0}$ satisfies equation (6.11) with $\varepsilon = 0$, and:

$$T_{M0}(0,t) = T_{W0}(0,t), \quad -\frac{\partial T_{M0}}{\partial x}(0,t) = -K_{W/M} \frac{\partial T_{W0}}{\partial x}(0,t) \quad \text{for } t \geq 0,$$

where $K_{W/M} = K_{P/M}K_{W/P} = K_{W}/K_{M}$. This leading order problem can be readily solved using Laplace transforms; similar problems are considered in [18], for example. The Laplace transform for a function $T(x,t)$ is defined by:

$$\tilde{T}(x;p) = \int_0^\infty e^{-pt}T(x,t)dt,$$

where $p$ is a number whose real part is positive and large enough to make this integral convergent. Taking the Laplace transforms for the problems for $T_{M0}$ and $T_{W0}$ then gives:

$$\frac{d^2\tilde{T}_{M0}}{dx^2} - p\tilde{T}_{M0} + T_{iM/W} = 0, \quad -1 < x < 0,$$

$$\frac{d^2\tilde{T}_{W0}}{dx^2} - \frac{p}{K_{W/M}}\tilde{T}_{W0} + \frac{1}{K_{W/M}} = 0, \quad x > 0,$$

$$\frac{dT_{M0}}{dx} = 0 \quad \text{on } x = -1,$$

$$\tilde{T}_{M0} = \tilde{T}_{W0}, \quad -\frac{dT_{M0}}{dx} = -K_{W/M} \frac{d\tilde{T}_{W0}}{dx} \quad \text{on } x = 0.$$ 

Solving this system gives:

$$T_{M0} = \frac{1}{p} \left\{ T_{iM/W} - (T_{iM/W} - 1) \frac{K_{W/M} \left[ \cosh(\sqrt{p}x) + \tanh(\sqrt{p}) \sinh(\sqrt{p}x) \right]}{K_{W/M} + \tanh(\sqrt{p})\sqrt{K_{W/M}}} \right\},$$

(6.12)

$$\tilde{T}_{W0} = \frac{1}{p} \left\{ 1 + \frac{(T_{iM/W} - 1) \tanh(\sqrt{p}) \exp \left( -\sqrt{p/k_{W/M}x} \right)}{K_{W/M}\sqrt{k_{W/M}} + \tanh(\sqrt{p})} \right\}.$$
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We can rewrite (6.12) in the following equivalent form:

\[
\tilde{T}_{M0} = \frac{1}{p} \left\{ T_{iM/W} - \frac{1}{2} (T_{iM/W} - 1) (1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left[ e^{-\sqrt{\rho}(2n-x)} + e^{-\sqrt{\rho}(2(n+1)+x)} \right] \right\},
\]

\[
\tilde{T}_{W0} = \frac{1}{p} \left\{ 1 + \frac{1}{2} (T_{iM/W} - 1) (1 + \alpha) \sum_{n=0}^{\infty} \alpha^n \left[ e^{-\sqrt{\rho}(2n+x/\sqrt{K_{W/M}})} - e^{-\sqrt{\rho}(2(n+1)+x/\sqrt{K_{W/M}})} \right] \right\};
\]

and taking the inverse Laplace transform of these yields the solutions:

\[
T_{M0} = T_{iM/W} - \frac{1}{2} (T_{iM/W} - 1) (1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left[ \text{erfc} \left( \frac{2n-x}{2\sqrt{t}} \right) + \text{erfc} \left( \frac{2(n+1)+x}{2\sqrt{t}} \right) \right],
\]

\[
T_{W0} = 1 + \frac{1}{2} (T_{iM/W} - 1) (1 + \alpha) \sum_{n=0}^{\infty} \alpha^n \left[ \text{erfc} \left( \frac{2n+x/\sqrt{K_{W/M}}}{2\sqrt{t}} \right) - \text{erfc} \left( \frac{2(n+1)+x/\sqrt{K_{W/M}}}{2\sqrt{t}} \right) \right],
\]

where:

\[
\alpha = \sqrt{K_{W/M}} - K_{W/M} = \sqrt{K_{M} \rho_{M} c_{M}} - \sqrt{K_{W} \rho_{W} c_{W}} = \frac{I_{M} - I_{W}}{I_{M} + I_{W}},
\]

and where:

\[
I_{M} = \sqrt{K_{M} \rho_{M} c_{M}}, \quad I_{W} = \sqrt{K_{W} \rho_{W} c_{W}},
\]
give the thermal inertias of the cooling material and the water, respectively. It is clear from (6.15) that \(|\alpha| < 1\). It is noteworthy that at leading order, the temperature in the polymer does not depend on position, and is also independent of the conductivity, thermal diffusivity and the thickness of the polymer. Hence, for a thin polymer film, the temperature in the polymer will frequently be dominated by the properties of the cooling material and the water medium, as would be expected, and is given at leading order by:

\[
T_{P0}(t) = T_{M0}(0,t) = T_{iM/W} - \frac{1}{2} (T_{iM/W} - 1) (1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left[ \text{erfc} \left( \frac{n}{\sqrt{k_{M} t}} \right) + \text{erfc} \left( \frac{n+1}{\sqrt{k_{M} t}} \right) \right],
\]

or, in dimensional terms:

\[
T_{P0}(t) = T_{M} - \frac{1}{2} (T_{M} - T_{W})(1-\alpha) \sum_{n=0}^{\infty} \alpha^n \left[ \text{erfc} \left( \frac{H_{M} n}{\sqrt{K_{M} t}} \right) + \text{erfc} \left( \frac{H_{M} (n+1)}{\sqrt{K_{M} t}} \right) \right].
\]
6.3. Results and Discussion

An elementary calculation shows that $T_{P0}$ is an increasing function of time for $|\alpha| < 1$ and $T_M^i < T_W^i$, so that the polymer has its minimum temperature at leading order immediately after the temperature in the cooling material has been lowered. From equation (6.16), this minimum temperature is given by:

$$T_{P0}(t) \to \frac{1}{2} \left( (1 + \alpha)T_M^i + (1 - \alpha)T_W^i \right) \quad \text{as } t \to 0^+,$$

which is a weighted average of the initial temperatures of the cooling material and the water, with the weights being determined by the thermal inertias. As time progresses, the leading order temperature of the polymer increases toward the initial water temperature, $T_W^i$. Hence, in the thin film limit, a necessary condition for the polymer to fully swell is that:

$$\frac{I_MT_M^i + I_WT_W^i}{I_M + I_W} < T_L, \quad \text{or,} \quad T_M^i < T_L - \frac{I_W}{I_M}(T_W^i - T_L). \quad (6.17)$$

The second inequality in (6.17) is of considerable practical value since it provides an upper bound for the temperature the cooling material must be dropped to for drug release to be initiated.

If inequality (6.17) is satisfied, it is of interest to estimate the time $t = t_L$ by which the polymer has heated back up to its LCST, as $t_L$ would then provide an estimate for the duration the polymer remains below the LCST. If we pose $t_L \sim t_{L0}$ as $\varepsilon \to 0$, then $T_{P0}(t_{L0}) = T_L$, and using equation (6.16):

$$\sum_{n=0}^{\infty} \alpha^n \left[ \text{erfc} \left( \frac{H_M n}{\sqrt{k_M t_{L0}}} \right) + \text{erfc} \left( \frac{H_M (n + 1)}{\sqrt{k_M t_{L0}}} \right) \right] = \frac{2}{1 - \alpha} \frac{T_L - T_M^i}{T_W^i - T_M^i}. \quad (6.18)$$

Elementary calculations show that equation (6.18) has a unique solution $0 < t_{L0} < \infty$ provided $|\alpha| < 1$, $T_M^i < T_L < T_W^i$, and inequality (6.17) is satisfied. It also follows from equation (6.18) that $t_{L0}$ has the general dimensional structure:

$$t_{L0} = \frac{H_M^2}{k_M} \left( \frac{T_L - T_M^i}{T_W^i - T_M^i}, \sqrt{\frac{k_W^i - k_W^i}{k_W^i + k_W^i}} \right), \quad (6.19)$$

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for some function \( F \), or:

\[ t_{L0} = t_M F(\theta, \alpha), \quad (6.20) \]

where:

\[ t_M = \frac{H_M^2}{k_M}, \quad \theta = \frac{T_L - T_M^i}{T_W - T_M^i}. \quad (6.21) \]

It is noted that \( 0 < \theta < 1 \) for \( T_M^i < T_L < T_W^i \) and that inequality \( (6.17) \) corresponds to \( \theta > (1 - \alpha)/2 \). In Table 6.1, I display values for \( F(\theta, \alpha) \) in the range \((1 - \alpha)/2 < \theta < 1, |\alpha| < 1\), which were found by numerically solving equation \( (6.18) \) using the mathematical package MAPLE.

The formula \((6.19)\) is instructive because it immediately implies that in the thin film limit, the duration the polymer is held below its LCST is proportional to the square of the thickness of the cooling material. Since \( F(\theta, \alpha) > 0 \) for \((1 - \alpha)/2 < \theta < 1, |\alpha| < 1\), it is in principle possible to adjust the thickness of the cooling material so as to maintain the polymer in the swollen state for a desired time interval for any parameter pair \( \theta, \alpha \) with \((1 - \alpha)/2 < \theta < 1, |\alpha| < 1\).

Furthermore, since the dependence on the thickness of the cooling material is quadratic, it is an effective parameter to adjust to tune the system. In Figure 6.2, I display the leading order polymer temperature for various thicknesses \( H_M \), and the strong quadratic dependency on \( H_M \) is evident in these plots. It is also noteworthy in equation \((6.19)\) that the three temperature parameters \( T_M^i, T_L, T_W^i \) appear only in a single divided difference ratio. However, it remains to show that the system is realisable for realistic parameter values, and this issue is now addressed.

6.3.3. Cooling materials

The feasibility of a particular system may be evaluated using the formula \( (6.20) \) since \( t_{L0} \) estimates the time the polymer will remain in the swollen state. In \( (6.20) \), it is seen that \( t_{L0} \) depends on the three parameters \( t_M, \theta \) and \( \alpha \). The parameter \( t_M \) depends on the properties of the cooling material only, \( \theta \) depends on the three temperature scales that arise in the system (one each for the cooling material, polymer and water), and \( \alpha \) depends on the ratio of
Table 6.1. Table of values for $F(\theta, \alpha)$ in the range $(1 - \alpha)/2 < \theta < 1$ and $0 \leq \alpha < 1$.

<table>
<thead>
<tr>
<th>$\theta$</th>
<th>$\alpha = 0$</th>
<th>$\alpha = 0.2$</th>
<th>$\alpha = 0.4$</th>
<th>$\alpha = 0.6$</th>
<th>$\alpha = 0.64$</th>
<th>$\alpha = 0.8$</th>
<th>$\alpha = 0.83$</th>
<th>$\alpha = 0.87$</th>
<th>$\alpha = 0.9$</th>
<th>$\alpha = 0.92$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta = 0.05$</td>
<td>0.01</td>
<td>0.72</td>
<td>1.61</td>
<td>3.05</td>
<td>5.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td>$\theta = 0.10$</td>
<td>1.57</td>
<td>2.37</td>
<td>4.46</td>
<td>7.98</td>
<td>12.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.20$</td>
<td>0.60</td>
<td>3.38</td>
<td>4.94</td>
<td>9.01</td>
<td>15.90</td>
<td>25.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.25$</td>
<td>0.98</td>
<td>1.37</td>
<td>6.06</td>
<td>8.76</td>
<td>15.80</td>
<td>27.70</td>
<td>44.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.30$</td>
<td>1.79</td>
<td>2.39</td>
<td>9.89</td>
<td>14.23</td>
<td>25.53</td>
<td>44.66</td>
<td>71.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.35$</td>
<td>0.82</td>
<td>2.90</td>
<td>3.81</td>
<td>15.27</td>
<td>21.91</td>
<td>39.22</td>
<td>68.52</td>
<td>109.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.40$</td>
<td>1.40</td>
<td>4.41</td>
<td>5.76</td>
<td>22.77</td>
<td>32.62</td>
<td>58.31</td>
<td>101.81</td>
<td>162.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.45$</td>
<td>0.76</td>
<td>2.15</td>
<td>6.51</td>
<td>8.47</td>
<td>33.22</td>
<td>47.55</td>
<td>84.95</td>
<td>148.24</td>
<td>236.56</td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.50$</td>
<td>1.25</td>
<td>3.18</td>
<td>9.44</td>
<td>12.26</td>
<td>47.89</td>
<td>68.53</td>
<td>122.37</td>
<td>213.51</td>
<td>340.68</td>
<td></td>
</tr>
<tr>
<td>$\theta = 0.55$</td>
<td>0.74</td>
<td>1.90</td>
<td>4.64</td>
<td>13.61</td>
<td>17.65</td>
<td>68.82</td>
<td>98.44</td>
<td>175.76</td>
<td>306.62</td>
<td>489.24</td>
</tr>
<tr>
<td>$\theta = 0.60$</td>
<td>1.22</td>
<td>2.80</td>
<td>6.73</td>
<td>19.67</td>
<td>25.50</td>
<td>99.35</td>
<td>142.10</td>
<td>253.68</td>
<td>442.54</td>
<td>706.06</td>
</tr>
<tr>
<td>$\theta = 0.65$</td>
<td>1.86</td>
<td>4.13</td>
<td>9.87</td>
<td>28.80</td>
<td>37.33</td>
<td>145.39</td>
<td>207.95</td>
<td>371.24</td>
<td>647.60</td>
<td>1033.23</td>
</tr>
<tr>
<td>$\theta = 0.70$</td>
<td>2.82</td>
<td>6.20</td>
<td>14.80</td>
<td>43.21</td>
<td>56.01</td>
<td>218.17</td>
<td>312.04</td>
<td>557.08</td>
<td>971.80</td>
<td>1550.48</td>
</tr>
<tr>
<td>$\theta = 0.75$</td>
<td>4.40</td>
<td>9.66</td>
<td>23.11</td>
<td>67.53</td>
<td>87.54</td>
<td>341.11</td>
<td>487.91</td>
<td>871.07</td>
<td>1519.58</td>
<td>2424.49</td>
</tr>
<tr>
<td>$\theta = 0.80$</td>
<td>7.27</td>
<td>16.07</td>
<td>38.55</td>
<td>112.83</td>
<td>146.28</td>
<td>570.27</td>
<td>815.72</td>
<td>1456.40</td>
<td>2540.75</td>
<td>4053.94</td>
</tr>
<tr>
<td>$\theta = 0.85$</td>
<td>13.47</td>
<td>29.96</td>
<td>72.11</td>
<td>211.39</td>
<td>274.11</td>
<td>1069.06</td>
<td>1529.29</td>
<td>2730.53</td>
<td>4763.69</td>
<td>7602.26</td>
</tr>
</tbody>
</table>
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Table 6.2. Parameters values for some potential cooling materials [18,61,73,98].

<table>
<thead>
<tr>
<th>Material</th>
<th>Volumetric Heat Capacity ($c_p$ J m$^{-3}$K$^{-1}$)</th>
<th>Thermal Conductivity ($K$ J m$^{-1}$K$^{-1}$s$^{-1}$)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>$4.2 \times 10^6$</td>
<td>0.6</td>
<td>0.00</td>
</tr>
<tr>
<td>Copper</td>
<td>$3.4 \times 10^6$</td>
<td>386.0</td>
<td>0.92</td>
</tr>
<tr>
<td>Aluminum</td>
<td>$2.4 \times 10^6$</td>
<td>204.0</td>
<td>0.87</td>
</tr>
<tr>
<td>Stainless Steel 316</td>
<td>$3.9 \times 10^6$</td>
<td>13.4</td>
<td>0.64</td>
</tr>
</tbody>
</table>

the thermal inertias of the cooling material and water. It is noteworthy that in the thin film limit, the properties of the polymer only enter at leading order via its LCST in the parameter $\theta$. However, it is clear that the properties of the cooling material are critical to the behaviour of the system.

In Table 6.2, parameter values for four potential cooling materials are displayed. However, only two of these materials, water and copper, are evaluated in detail here. Water is chosen because it may be used as the medium for a cooling system based on endothermic chemical reactions. Copper has a large thermal and electrical conductivity, and has been chosen to represent metallic materials; thermoelectric and magnetocaloric cooling technologies typically involve metals.

In Figure 6.2 (a), the leading order polymer temperature, $T_{p0}(t)$, has been plotted as a function of time, with copper being the cooling material. In the plot, $T_{iM}^a = 32^\circ C$, $T_{iW}^a = 37^\circ C$ (physiological temperature), and various thicknesses for the cooling material are used, ranging from 2 mm to 8 mm. The strong dependency of the behaviour on cooling material thickness is evident in these plots. If, for example, the LCST of the polymer is $35.5^\circ C$, then it is clear from the figure that a drug release time of some minutes may be achieved for a device thickness of some millimetres if a temperature drop of the order of $5^\circ C$ can be induced in the cooling material. A drug release duration of a couple minutes for a single dose can be appropriate for many systems of practical interest; see, for example, [192].

In Figure 6.2 (b), plots for the leading order time it takes the polymer to reheat to its LCST, $t_{r0}$, are given as a function of $T_{iM}^a$, the temperature to which the cooling material is initially dropped. In these plots, parameter values for
6.3. Results and Discussion

Figure 6.2. (a) The leading order temperature of the polymer as a function of time, $T_{P0}(t)$, with copper being the cooling material. Here the initial temperature of cooling device and water are $T_i^M = 32^\circ C$ and $T_i^W = 37^\circ C$, respectively, and various cooling material thicknesses, $2H_M$, have been used. (b) The leading order time it takes the polymer to heat back up to its LCST as a function of $T_i^M$ for various cooling material thicknesses. Here, the LCST is $T_{L} = 35.5^\circ C$, the initial temperature of the water is $T_i^W = 37^\circ C$, and plots for both copper and water being the cooling material are displayed.
both copper and water being the cooling material are used, and $T_L = 35.5^\circ C$, $T_W = 37^\circ C$. It is evident from this figure that the system is realisable for reasonable parameter values for both materials.

### 6.3.4. Thicker polymers

The case where the polymer thickness is not small compared to that of the cooling material is now very briefly considered. For this case, the full set of equations (6.1)-(6.4) are integrated numerically. However, it should be emphasised again here that some of the modelling assumptions may not now be valid; see Section 6.2.

In Figure 6.3, numerical solutions for the temperature of the polymer at its interface with the water medium are plotted as functions of time, that is, $T_p(H_P, t)$ versus $t$. The model predicts that the polymer will remain swollen while $T_p(H_P, t) < T_L$ since $T_p(x, t)$ has its maximum value at $x = H_P$. In the figure, parameter values for poly(methyl methacrylate) [47] have been used for the polymer; poly(methyl methacrylate) is known to have similar properties to pNIPAm in its collapsed state. The cooling material is water in Figure 6.3 (a), and copper in Figure 6.3 (b). The model predicts, as would be expected, that thicker polymers are more difficult to cool thoroughly, although the results also indicate that the system can be feasible for ratios $H_P/H_M$ as large as $O(1/10)$. The temperature profiles in the cooling material, polymer, and water as functions of position and for various times are displayed in Figure 6.4.

### 6.3.5. Incorporating a heat source in the modelling

A limitation of the modelling presented here is that no attempt has been made to incorporate the possible presence of heat sources or sinks. In the human body, tissues generate heat via metabolic processes, and blood flowing in or nearby to tissue can exchange thermal energy with it. The subject of bioheat transfer has been extensively studied in the past, and numerous mathematical models have been proposed to describe it [3,119,125,167,183].

The model presented here can be justified for systems where heat conduction due to the initial temperature difference between the cooling material and the
Figure 6.3. Plots of the temperature at the polymer-water interface as a function of time for various ratios of the polymer thickness $H_P$ to half the cooling device thickness $H_M$, with $H_M = 3$ mm. The cooling material is water in (a), and copper in (b). The thermal diffusivity and conductivity chosen for the polymer are $k_P = 1 \times 10^{-7}$ m$^2$ s$^{-1}$ and $K_P = 0.15$ J m$^{-1}$K$^{-1}$s$^{-1}$, respectively. The initial temperature of the cooling device and the water are $T_M = 32^\circ$C and $T_W = 37^\circ$C, respectively.
Figure 6.4. Plots of temperature profiles in the cooling material, polymer, and water as functions of position and for various times. In (a), the cooling material is water, and in (b), copper; see Table 6.2 for the thermal parameter values used. The other parameter values used are: $H_M = 3$ mm, $H_P = 0.6$ mm, $T_M^i = 32^\circ$C, $T_P^i = 37^\circ$C, $T_W = 37^\circ$C, $k_p = 1 \times 10^{-7} \text{m}^2\text{s}^{-1}$, and $K_P = 0.15 \text{Jm}^{-1}\text{K}^{-1}\text{s}^{-1}$. 

6. A theoretical assessment of a pulsatile drug delivery system
water makes the dominant contribution to heat transfer in the polymer as it reheats to its LCST. Fourier’s law implies that heat transfer via conduction at a given location is proportional to the temperature gradient at that location. In this system, the temperature gradients in and near a thin polymer are large for times $t \ll \frac{H_p^2}{k_m}$ and $t = O(\frac{H_p^2}{k_m})$ compared to these gradients for times $t \gg \frac{H_p^2}{k_m}$ (with the dimensionless parameters other than $H_p/H_m$ being $O(1)$), so that heat conduction in the polymer is strong in this sense for $t = O(\frac{H_p^2}{k_m})$ or smaller. However, it should be emphasised that the model presented here cannot be used to estimate the time taken for a polymer to reheat to 37°C in the human body. This is because the model predicts that $T_p \rightarrow 37°C$ as $t \rightarrow \infty$, and since heat conduction becomes weaker as time progresses, other factors that can contribute to heat transfer, such as the presence of blood vessels or metabolism, can become significant, or even dominant, as time goes on.

A simple illustrative calculation is now presented that models the presence of a constant heat source at 37°C that is at a distance $H_W$ from the polymer. This is achieved by replacing the boundary condition $T_w \rightarrow 37°C$ as $x \rightarrow +\infty$ by:

$$T_w = 37°C \text{ on } x = H_p + H_W.$$  \hspace{1cm} (6.22)

This condition could serve as a crude model for the presence of a major artery at $x = H_p + H_W$, for example; more realistic models for heat transfer in the body can be found in the literature cited above. Numerical solutions corresponding to the boundary condition (6.22) are presented in Figure 6.5, and the results are broadly as expected. It is seen that for $H_W \leq 6$ mm, the profiles for the first few minutes are close to the $H_W \rightarrow \infty$ curve, but that the curves with $H_W = 1, 6, 12$ mm recover to close to 37°C much more quickly than the $H_W \rightarrow \infty$ curve. This suggests that for some geometries and materials, heat conduction due to the initial temperature difference between the cooling material and the water can make the major contribution to heat transfer in the polymer in the first few minutes. In Table 6.3, numerical estimates for the time taken for the polymer to reheat to its LCST and to 36.9°C are displayed for various separations between the polymer and the constant heat source, $H_W$.
6. A theoretical assessment of a pulsatile drug delivery system

![Graph showing temperature on polymer surface as a function of time for different separations.](image)

Figure 6.5. Numerical solutions for the temperature at the polymer-water interface as a function of time, and for various separations $H_W$ between the polymer and a constant heat source held at 37°C. The polymer is of thickness $H_P = 150 \, \mu m$, and the cooling material is water of thickness $H_M = 3 \, mm$. The thermal diffusivity and conductivity chosen for the polymer are $k_P = 1 \times 10^{-7} m^2 s^{-1}$ and $K_P = 0.15 \, J m^{-1}K^{-1}s^{-1}$, respectively. The initial temperature of the cooling device and the water are $T_{iM} = 32^\circ C$ and $T_{iW} = 37^\circ C$, respectively. The time taken for the polymer to heat back to its LCST ($t_L$) and 36.9°C are listed in Table 6.3.

6.4. Conclusions

A mathematical model has been developed to evaluate the feasibility of a proposed local drug delivery that may be implanted in vivo. The delivery system is composed of an appropriate cooling material coated by a drug-loaded thermoresponsive polymer film. Some candidate cooling mechanisms for the device have been proposed based on endothermic chemical reactions, thermoelectric effects, and the magnetocaloric effect. In the thin polymer film limit, the model provides an upper bound for the temperature the cooling material must be dropped to for drug delivery to be initiated. The independent non-dimensional parameters governing the behaviour of the system have also been identified. For thin polymers, a useful formula has been derived to estimate...
Table 6.3. Estimated times taken for the polymer to heat back to its LCST, $T_L = 35.5^\circ C$ ($t_L$), and to 36.9$^\circ C$ ($t_{36.9^\circ C}$), with water being cooling material. The times are estimated for various separations $H_W$ between the polymer and the heat source. The thickness of the cooling material and the polymer here are $2H_M = 6\, \text{mm}$ and $H_P = 150\, \mu\text{m}$, respectively. The initial temperature of the cooling material is $T_M = 32^\circ C$, and of the water is $T_W = 37^\circ C$.

<table>
<thead>
<tr>
<th>$H_W$ (mm)</th>
<th>$t_L$ (min)</th>
<th>$t_{36.9^\circ C}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>2.85</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>6.5</td>
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<td>6</td>
<td>2.4</td>
<td>13.3</td>
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<td>56.0</td>
</tr>
<tr>
<td>30</td>
<td>3.0</td>
<td>115.0</td>
</tr>
<tr>
<td>$\infty$</td>
<td>3.0</td>
<td>840.0</td>
</tr>
</tbody>
</table>

the duration the polymer will remain swollen in a single cycle; in particular, it is found that this duration is proportional to the square of the cooling material thickness. A calculation that incorporates a constant heat source in the modelling has also been presented, and the results indicate that while the presence of heat sources in the body cause the polymer to recover to 37$^\circ C$ on a realistic time scale, heat conduction due to the initial temperature difference between the water and the cooling material can make the dominant contribution to heat transfer in the polymer for sufficiently small times. Finally, it has been established that the system may be realised for realistic materials and parameter values.
7. Discussion

In this chapter, I shall give a critical evaluation of the modelling work presented in the thesis. I identify strengths and weaknesses of the models, and make some suggestions as to how they can be improved. Preliminary work on some more sophisticated models is also presented.

7.1. Affinity-based models

7.1.1. Strengths and weaknesses

In Chapters 2 and 3, models that describe the release of growth factors from affinity-based delivery systems are analysed in considerable detail. For both models, parameter regimes are successfully identified that ensure that at least a fraction of the growth factor releases slowly from the host fibrin matrices. The key observation in these chapters is that the binding constants are usually the most important parameters appearing in affinity-based models of this kind. The binding constants give the ratio of the initially available binding sites to the dissociation constant of the binding molecules from those sites. It has been established that if these constants are large for a particular system, then a proportion, if not all, of the growth factor will release slowly. This observation is supported by analytical and numerical work and by comparison with experimental data, and may be of value in the design of future release systems.

However, it should also be said that these models are deficient in a number of respects. For example, the model for the heparin-based delivery system described in Chapter 2 does not take account of the possible presence of free peptide in the system, and assumes that all of the peptide covalently cross-links
7. Discussion

to the fibrin matrix. This is unlikely to be the case in practice. If a significant proportion of the peptide is free, this will compete with the bound peptide for heparin, and the release behaviour of the system will be significantly affected. A model for a heparin-based delivery system incorporating free peptide is very briefly describe in the next subsection.

Another weakness of the models in Chapters 2 and 3 is that they were constructed to model release from *in vitro* experimental systems. It is very difficult to design *in vivo* release experiments for these systems, and *in vitro* studies often provide convenient and useful alternatives. However, the *in vitro* experiments do not include some important features of the situation *in vivo*, such as the presence of cells that release enzymes that cause the degradation of the fibrin matrix [90,184]. I shall briefly consider below how matrix degradation may be incorporated in the modelling.

7.1.2. Addressing the weaknesses

7.1.2.1. A heparin-based model incorporating free peptide

Figure 7.1. A fibrin matrix containing the nine species of the model (7.2).
A model of this kind was first formulated by Wood & Sakiyama-Elbert [188]. The description for this model is very similar to those for the models already discussed in Chapter 2 and 3, and so I shall be brief here. The model contains nine species, and the following notation is used:

- \( G \) is an unbound growth factor molecule (mobile);
- \( H \) is an unbound heparin molecule (mobile);
- \( GH \) is an unbound growth factor-heparin complex (mobile);
- \( PU \) is an unbound peptide molecule (mobile);
- \( PB \) is a bound peptide molecule (immobile);
- \( HPU \) is an unbound heparin-peptide complex (mobile);
- \( HPB \) is a bound heparin-peptide complex (immobile);
- \( GHPU \) is an unbound growth factor-heparin-peptide complex (mobile);
- \( GHPB \) is a bound growth factor-heparin-peptide complex (immobile).

In Figure 7.1, these nine species have been depicted schematically in the fibrin matrix. The possible interactions between these species are represented by the following seven chemical reactions:

\[
\begin{align*}
G + H & \overset{k_f}{\underset{k_r}{\rightleftharpoons}} GH \\
H + PU & \overset{K_F}{\underset{K_R}{\rightleftharpoons}} HPU \\
H + PB & \overset{k_f}{\underset{k_r}{\rightleftharpoons}} HPB \\
G + HPU & \overset{k_f}{\underset{k_r}{\overset{K_F}{\underset{K_R}{\rightleftharpoons}}}} GHPU \\
G + HPB & \overset{k_f}{\underset{k_r}{\overset{K_F}{\underset{K_R}{\rightleftharpoons}}}} GHPB \\
GH + PU & \overset{K_F}{\underset{K_R}{\overset{k_f}{\underset{k_r}{\rightleftharpoons}}}} GHPU \\
GH + PB & \overset{K_F}{\underset{K_R}{\overset{k_f}{\underset{k_r}{\rightleftharpoons}}}} GHPB
\end{align*}
\]

where \( k_f, k_r, K_F, K_R \) are the reaction rate constants as shown. The one-dimensional form for the equations will be displayed here, and I denote the spatial variable by \( x \) and the time variable by \( t \). Following the notation adopted in Chapters 2 and 3, I denote by \( c_G(x, t) \) the concentration of free growth factor \( G \) at location \( x \) and time \( t \), with the notation for the other eight species then following in an obvious fashion. In view of the above discussion, the governing equations for the concentrations of the nine species are given by:
\[ \frac{\partial c_G}{\partial t} = D_G \frac{\partial^2 c_G}{\partial x^2} - k_f c_G (c_H + c_{HPU} + c_{HPB}) + k_r (c_{GH} + c_{GHPU} + c_{GHPB}), \]
\[ \frac{\partial c_H}{\partial t} = D_H \frac{\partial^2 c_H}{\partial x^2} - k_f c_G c_H - \kappa_{f} c_H (c_{PU} + c_{PB}) + k_r c_G + \kappa_{R} (c_{HPU} + c_{HPB}), \]
\[ \frac{\partial c_{GH}}{\partial t} = D_{GH} \frac{\partial^2 c_{GH}}{\partial x^2} + k_f c_G c_H - \kappa_{f} c_H (c_{PU} + c_{PB}) - k_r c_G + \kappa_{R} (c_{HPU} + c_{HPB}), \]
\[ \frac{\partial c_{CPU}}{\partial t} = D_{CPU} \frac{\partial^2 c_{CPU}}{\partial x^2} - \kappa_{f} c_{CPU} (c_H + c_{GH}) + \kappa_{R} (c_{HPU} + c_{GHPU}), \]
\[ \frac{\partial c_{GHPU}}{\partial t} = D_{GHPU} \frac{\partial^2 c_{GHPU}}{\partial x^2} + k_f c_G c_{GHPU} + \kappa_{f} c_{GHPU} - (k_r + \kappa_{R}) c_{GHPB}, \]
\[ \frac{\partial c_{CPB}}{\partial t} = -k_f c_G c_{CPB} + \kappa_{f} c_{CPB} + k_r c_{GHPB} - \kappa_{R} c_{HPB}, \]
\[ \frac{\partial c_{GHPB}}{\partial t} = k_f c_G c_{GHPB} - \kappa_{R} c_{GHPB}, \]

where \( D_G, D_H, D_{GH}, D_{CPU}, D_{GHPU} \) and \( D_{GHPB} \) are the diffusivities for the free growth factor, free heparin, growth factor-heparin complex, unbound peptide, heparin-unbound peptide complex, and growth factor-heparin-unbound peptide complex, respectively.

In Chapter 2, the typical setup for release experiments from the fibrin matrices is described. The boundary conditions that should be used to model this setup here are:

\[ \begin{align*}
\frac{\partial c_G}{\partial x}(0, t) &= 0, & \frac{\partial c_H}{\partial x}(0, t) &= 0, & \frac{\partial c_{GH}}{\partial x}(0, t) &= 0, \\
\frac{\partial c_{CPU}}{\partial x}(0, t) &= 0, & \frac{\partial c_{GHPU}}{\partial x}(0, t) &= 0, & \frac{\partial c_{GHPB}}{\partial x}(0, t) &= 0, \\
c_G(L, t) &= 0, & c_H(L, t) &= 0, & c_{GH}(L, t) &= 0, \\
c_{CPU}(L, t) &= 0, & c_{GHPU}(L, t) &= 0, & c_{GHPB}(L, t) &= 0,
\end{align*} \]

for \( t \geq 0 \), and where, as before, \( x = 0 \) gives the base of the container, and \( x = L \) denotes the interface between the fibrin matrix and the eluting medium.
The appropriate initial conditions are given by:

\[
\begin{align*}
    c_G(x, 0) &= c^0_G, & c_H(x, 0) &= c^0_H, & c_{GH}(x, 0) &= c^0_{GH}, & c_{PU}(x, 0) &= c^0_{PU}, \\
    c_{PB}(x, 0) &= c^0_{PB}, & c_{HPU}(x, 0) &= c^0_{HPU}, & c_{HPB}(x, 0) &= c^0_{HPB}, \\
    c_{GHPU}(x, 0) &= c^0_{GHPU}, & c_{GHPB}(x, 0) &= c^0_{GHPB} & \text{for } 0 < x < L,
\end{align*}
\]  

(7.4)

where \(c^0_i\) denotes the initial concentrations of species \(i\), for \(i\) being G, H, GH, PU, PB, HPU, HPB, GHPU and GHPB.

Equations (7.2), (7.3) and (7.4) constitute an initial boundary value problem for the concentrations of the nine species. The system is clearly formidable, but the techniques used in Chapter 2 and 3 to analyse smaller, but similar, models can be employed here as well. It should be noted again here that all of the free peptide will exit the experimental system on a diffusion time scale since there is no mechanism available to replenish it. As the concentration of free peptide tends to zero, the system of equations (7.2), (7.3) and (7.4) reduces to the smaller system discussed in Chapter 2. The advantage of the more elaborate formulation given here is that it should provide a description of the entire (all times) experimental profiles, including the initial stages of release when free peptide can play a significant role; recall that the model described in Chapter 2 could only be used to describe a portion of the experimental profiles (see Figure 2.10).

**7.1.2.2. Incorporating matrix degradation in the modelling**

Plasmin is a naturally occurring enzyme in the human body that can dissolve fibrin blood clots. Plasmin is released from the liver into the circulatory system in its inactive form, plasminogen [4,164]. Enzymes released from cells invading the fibrin matrix convert the plasminogen into its active form plasmin, and this plasmin proceeds to degrade the matrix [4,90,164]. For the model described by equations (7.2), the degradation of the matrix can be represented by the following three chemical reactions:

\[
\begin{align*}
    \text{PB} & \xrightarrow{K_{PB}(c_{PB})} \text{PU} & \text{HPB} & \xrightarrow{K_{HPB}(c_{HPB})} \text{HPU} & \text{GHPB} & \xrightarrow{K_{GHPB}(c_{GHPB})} \text{GHPU}
\end{align*}
\]  

(7.5)
7. Discussion

where \( K_r(X) \) describes Michaelis-Menton kinetics \[90,184\], with:

\[
K_r(X) = \frac{\sigma V_{\text{max}} [\text{Plasmin}] X}{\sigma K_M + X},
\]

(7.6)

and where \( X \) can be \( c_{PB}, c_{HPB} \) or \( c_{GHPB} \). In (7.6), \( K_M \) is the Michaelis-Menton constant, \([\text{Plasmin}]\) denotes the concentration of plasmin, \( V_{\text{max}} \) is the maximum rate of plasmin cleavage, and \( \sigma \) is the number of peptide binding sites per molecule of fibrinogen.

The reactions (7.5) are easily incorporated in the governing equations (7.2); for example, the equations for \( c_{PU} \) and \( c_{PB} \) require the incorporation of one extra term each, and are modified to:

\[
\frac{\partial c_{PU}}{\partial t} = D_{PU} \frac{\partial^2 c_{PU}}{\partial x^2} - \kappa_f c_{PU}(c_H + c_{GH}) + \kappa_r (c_{HPU} + c_{GHPU}) + \frac{\sigma V_{\text{max}} [\text{Plasmin}] c_{PB}}{\sigma K_M + c_{PB}};
\]

\[
\frac{\partial c_{PB}}{\partial t} = -\kappa_f c_{PB}(c_H + c_{GH}) + \kappa_r (c_{HPB} + c_{GHPB}) - \frac{\sigma V_{\text{max}} [\text{Plasmin}] c_{PB}}{\sigma K_M + c_{PB}}.
\]

7.2. The model for pulsatile release

7.2.1. Strengths and weaknesses

In Chapter 5, a model to describe the pulsatile release of drug from thin thermoresponsive films was developed \[192\]. The governing equation in this model is a linear diffusion equation with a time dependent diffusivity that can take on just two values; one value for the polymer in its swollen state, and another (much smaller) value for when the polymer is collapsed. The model was used to describe drug release from an experimental system developed by colleagues at the NCBES. In the experiments, the release behaviour of rhodamine B from very thin (of the order of 10 \( \mu \)m thick) cross-linked pNIPAm films was evaluated, and the data generated by the experiments was found to match the theoretical profiles very well. To my knowledge, this is the first time pulsatile drug release from a thermoresponsive polymer has been modelled mathematically.

A key assumption made in the development of the model in Chapter 5 is
that the transition between the swollen and collapsed states for the polymer may be taken to be instantaneous. This is justified for the very thin polymers being modelled in Chapter 5 since, for these, the time taken for the polymer to swell or collapse is short compared to the times the polymer remains in its collapsed or swollen states. However, for thicker polymers, the swelling and collapsing processes may need to be incorporated in the modelling. I shall now present a generic model that describes the swelling and collapsing processes in a polymer. The model is adapted from an earlier swelling model [153–155,165] that was successfully used to describe drug release from the polymer hydroxypropyl methylcellulose (HPMC). It should be emphasised here that the work I shall now present is preliminary, and that no claim is being made here that it is appropriate for a specific thermoresponsive system. In particular, I do not claim that it is appropriate for the pNIPAm-based system described in Chapter 5 of this thesis. However, it does produce results that have the correct qualitative character, and, in my view, it provides a useful template for the first detailed model of pulsatile release.

### 7.2.2. Addressing the weaknesses: a model incorporating the swelling and collapsing processes

#### 7.2.2.1. Modelling polymer swelling

At time $t = 0$, it is supposed that $x = 0$ gives the location of a planar interface separating a dry thermoresponsive polymer that occupies $x > 0$ from an aqueous medium occupying $x < 0$. The temperature of the entire system is supposed to be at a constant value $T$ at time $t = 0$, and that $T < T_L$ where $T_L$ is the LCST of the polymer. Hence, for $t > 0$, water will diffuse into the bulk of the polymer causing it to swell and release drug. The swelling process introduces two moving boundaries that need to be tracked. One of these boundaries, which shall be denoted by $x = s_w(t)$, separates the fluid medium from the swelling polymer, and it moves to the left. This boundary is sometimes referred to as the erosion front, and it has been depicted schematically in Figure 7.2. The other moving boundary, which shall be denoted by
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Figure 7.2. A thermoresponsive polymer below its LCST in an aqueous environment absorbs fluid and swells. Note that at least two moving boundaries need to be located: an erosion front separating the fluid from the swelling polymer, and a swelling front separating the swelling polymer from the dry polymer [156].

\[ x = s_e(t), \] separates the swelling polymer from the dry polymer, and it moves to the right. It is sometimes referred to as the swelling front; see Figure 7.2.

Figure 7.3. Photograph of a cross section of a hydroxypropyl methylcellulose cylindrical matrix (HPMC) after one hour of swelling release. This photograph is taken from Colombo et al. [24].

In Figure 7.3 I display a photograph taken from [24] of a cross section of a cylindrical polymer composed of HPMC; the erosion and swelling fronts are clearly visible in this photograph. However, it should be emphasised here that, while HPMC is a swellable polymer, it is not thermoresponsive as a change in temperature will not induce it to collapse again. In the photograph, a third
front, which has been labelled the diffusion front, is also discernible. This boundary moves, and separates the region on its outside, where drug is fully dissolved, from the region on its inside, where the drug is present in both dissolved and undissolved form. For the purposes of the current discussion, I shall suppose that the drug concentration is below solubility everywhere in the polymer, so that a diffusion front does not arise. Incorporating a diffusion front in the modelling below would be straightforward however; see Section 1.4.2.2 for an example of a problem containing a diffusion front.

The governing equations in $s_w(t) < x < s_c(t)$

I begin by introducing some notation. At a point $x$ in $(s_w(t), s_c(t))$ and time $t$, I denote by:

- $\phi(x, t)$: the volume fraction of water;
- $\phi_p(x, t)$: the volume fraction of polymer;
- $c(x, t)$: the volume fraction of drug.

We can extend the definition of these quantities to the entire domain $-\infty < x < +\infty$ by setting:

- $\phi(x, t) = 1, \phi_p(x, t) = 0, c(x, t) = 0$ (diluteness) for $x < s_w(t)$,
- $\phi(x, t) = 0, \phi_p(x, t) = 1 - c_0, c(x, t) = c_0$ for $x > s_c(t)$,

where $c_0$ measures the uniform initial drug load in the polymer. It is then clear that:

$$\phi(x, t) + \phi_p(x, t) + c(x, t) = 1$$

for all $-\infty < x < +\infty, t \geq 0$. Following [155], I shall assume that the equations governing the evolution of $\phi(x, t)$ and $c(x, t)$ in $s_w(t) < x < s_c(t)$ take the form:

$$\frac{\partial \phi}{\partial t} = \frac{\partial}{\partial x} \left( D(\phi) \frac{\partial \phi}{\partial x} \right), \quad \frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left( D^*(\phi) \frac{\partial c}{\partial x} \right),$$

(7.7)

for $t > 0$, where:

$$D(\phi) = D_0 \exp(\beta \phi), \quad D^*(\phi) = D_0^* \exp(\beta^* \phi),$$

(7.8)
and where $D_0, D_0^*, \beta, \beta^*$ are positive constants. The exponential dependence for the diffusivities in (7.8) implies that the mobility of the water and drug molecules increases with increasing water content. The exponential form (7.8) has been used by a number of authors previously to model swelling processes in polymers and other materials; see, for example, Fujita [39], Korsmeyer et al. [71,72], Siepmann et al. [153,154], McGuinness et al. [94], and Barry & Caunce [12].

**Boundary conditions on** $x = s_w(t)$

Three boundary conditions are imposed on $s_w(t)$; one each for $\phi(x,t)$ and $c(x,t)$, and a third involving the speed of the front $x = s_w(t)$. A perfect sink boundary condition for the drug is chosen, so that:

$$c(s_w(t), t) = 0 \text{ for } t > 0. \quad (7.9)$$

It is assumed that the water fraction at $x = s_w(t)$ is at the maximum value the polymer can sustain, $\phi_w$, say, so that:

$$\phi(s_w(t), t) = \phi_w^* \text{ for } t > 0. \quad (7.10)$$

The quantity $\phi_w^*$ is a material parameter for the polymer, and it can be temperature dependent; I shall return to this issue below. The final boundary condition at $x = s_w(t)$ may be conveniently obtained by considering the flux of fluid across it. In a small time $\Delta t$, the volume of fluid crossing the surface per unit area, $\Delta Q_w$, may be approximated by:

$$\Delta Q_w \approx -\left( D(\phi) \frac{\partial \phi}{\partial x} \right)_{x=s_w(t)} \Delta t. \quad (7.11)$$

The amount of fluid per unit area lost to the domain $x < s_w$ in time $\Delta t$ is approximated by $- (1 - \phi_w^*)(s_w(t + \Delta t) - s_w(t))$, so that:

$$\Delta Q_w \approx - (1 - \phi_w^*)(s_w(t + \Delta t) - s_w(t)). \quad (7.12)$$

Equating (7.11) and (7.12), and taking the limit $\Delta t \to 0$ then gives:
7.2. The model for pulsatile release

\[-D(\phi) \frac{\partial \phi}{\partial x} = -(1 - \phi_w^s) \frac{ds_w}{dt}\] on \(x = s_w^+(t),\) \(7.13\)

which provides the third boundary condition on \(x = s_w(t).\)

**Boundary conditions on** \(x = s_c(t)\)

The boundary condition for \(c\) is simply:

\[c(s_c(t), t) = c_0, \text{ for } t > 0,\] \(7.14\)

where \(c_0\) gives the initial drug load in the polymer. It is assumed that a critical minimum water fraction, \(\phi_c^s,\) say, is required to initiate the phase change in the polymer from its condensed state to its swollen state. Hence, we impose:

\[\phi(s_c(t), t) = \phi_c^s, \text{ for } t > 0.\] \(7.15\)

Here \(\phi_c^s\) is clearly another material parameter for the polymer, and for swelling to be possible, it needs to be less than the maximum water content the polymer can hold, so that \(\phi_c^s < \phi_w^s.\) The final boundary condition is obtained by considering the fluid flux across \(x = s_c(t),\) and it is found that:

\[-D(\phi) \frac{\partial \phi}{\partial x} = \phi_c^s \frac{ds_c}{dt}\] on \(x = s_c^-(t),\) \(7.16\)

The derivation of \((7.16)\) is very similar to that for \((7.13),\) and is omitted here.

**The complete initial boundary value problem for swelling**

In view of \((7.7), (7.8), (7.10), (7.13), (7.15),\) and \((7.16),\) the following initial boundary value problem for \(\phi(x, t)\) is now obtained:

\[\frac{\partial \phi}{\partial t} = D_0 \frac{\partial}{\partial x} \left( e^{\beta \phi} \frac{\partial \phi}{\partial x} \right), \text{ for } s_w(t) < x < s_c(t), t > 0,\]

\[\phi = \phi_w^s, -D_0 e^{\beta \phi} \frac{\partial \phi}{\partial x} = -(1 - \phi_w^s) \frac{ds_w}{dt}\] on \(x = s_w^+(t), t > 0,\) \(7.17\)

\[\phi = \phi_c^s, -D_0 e^{\beta \phi} \frac{\partial \phi}{\partial x} = \phi_c^s \frac{ds_c}{dt}\] on \(x = s_c^-(t), t > 0,\)

\[s_w(t = 0) = 0, s_c(t = 0) = 0.\]
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It is noteworthy that this problem does not involve $c(x,t)$, so that the problem that determines $\phi(x,t)$ is not coupled to that for $c(x,t)$. The problem that determines $c(x,t)$ is given by (see (7.7), (7.8), (7.9), and (7.14)):

$$\frac{\partial c}{\partial t} = D_0^* \frac{\partial}{\partial x} \left( e^{\beta^* \phi} \frac{\partial c}{\partial x} \right), \quad s_w(t) < x < s_c(t), \, t > 0,$$

$$c(s_w^+(t), t) = 0 \quad \text{for} \quad t > 0,$$

$$c(s_c^-(t), t) = c_0 \quad \text{for} \quad t > 0.$$  \hspace{1cm} (7.18)

The problem (7.17) may be solved for $\phi(x,t), s_w(t)$, and $s_c(t)$. These quantities may then be treated as data in the problem (7.18), which may be solved for $c(x,t)$.

**A similarity reduction for the swelling problem**

The problems (7.17) and (7.18) have the following similarity structure:

$$\phi(x,t) = \Phi(\xi), \quad c(x,t) = C(\xi), \quad s_w(t) = -\theta \sqrt{t}, \quad s_c(t) = \psi \sqrt{t}, \quad \xi = x/\sqrt{t},$$

where $\theta, \psi$ are constants. In these variables, (7.17) and (7.18) reduce to the following nonlinear ordinary differential equation problems:

$$-\frac{\xi}{2} \frac{d\Phi}{d\xi} = D_0 \frac{d}{d\xi} \left( e^{\beta \Phi} \frac{d\Phi}{d\xi} \right), \quad -\theta < \xi < \psi,$$

$$\Phi = \phi_w^*, \quad -D_0 e^{\beta \Phi} \frac{d\Phi}{d\xi} = \frac{\theta}{2} (1 - \phi_w^*) \quad \text{on} \quad \xi = -\theta,$$  \hspace{1cm} (7.19)

$$\Phi = \phi_c^*, \quad -D_0 e^{\beta \Phi} \frac{d\Phi}{d\xi} = \frac{\psi}{2} \phi_c^* \quad \text{on} \quad \xi = \psi,$$

and:

$$-\frac{\xi}{2} \frac{dC}{d\xi} = D_0^* \frac{d}{d\xi} \left( e^{\beta^* \Phi} \frac{dC}{d\xi} \right), \quad -\theta < \xi < \psi,$$

$$C(-\theta) = 0, \quad C(\psi) = c_0.$$  \hspace{1cm} (7.20)

For the (admittedly unrealistic) case $\beta = \beta^* = 0$, the equations (7.19) and (7.20) linearise, and the problem may be solved explicitly to obtain:
7.2. The model for pulsatile release

\[ \Phi(\xi) = \phi_w^s + (\phi_c^s - \phi_w^s) \frac{\text{erf} \left( \frac{\xi}{2\sqrt{D_0}} \right) - \text{erf} \left( -\frac{\theta}{2\sqrt{D_0}} \right)}{\text{erf} \left( \frac{\psi}{2\sqrt{D_0}} \right) - \text{erf} \left( -\frac{\theta}{2\sqrt{D_0}} \right)}, \]

\[ C(\xi) = c_0 \frac{\text{erf} \left( \frac{\psi}{2\sqrt{D_0^*}} \right) - \text{erf} \left( -\frac{\theta}{2\sqrt{D_0^*}} \right)}{\text{erf} \left( \frac{\psi}{2\sqrt{D_0^*}} \right) - \text{erf} \left( -\frac{\theta}{2\sqrt{D_0^*}} \right)}, \]  

(7.21)

where \( \theta, \psi \) are determined by solving the coupled algebraic equations:

\[ \theta \exp \left( \frac{\theta^2}{4D_0} \right) \left[ \text{erf} \left( -\frac{\theta}{2\sqrt{D_0}} \right) - \text{erf} \left( \frac{\psi}{2\sqrt{D_0}} \right) \right] = 2\sqrt{\frac{D_0}{\pi}} \frac{\phi_c^s - \phi_w^s}{1 - \phi_w^s}, \]

\[ \psi \exp \left( \frac{\psi^2}{4D_0} \right) \left[ \text{erf} \left( -\frac{\theta}{2\sqrt{D_0}} \right) - \text{erf} \left( \frac{\psi}{2\sqrt{D_0}} \right) \right] = 2\sqrt{\frac{D_0}{\pi}} \frac{\phi_c^s - \phi_w^s}{\phi_c^s}. \]  

(7.22)

Analytical solutions of this kind are of value because they provide a useful check on the accuracy of numerical schemes, as we shall see below.

7.2.2.2. Modelling polymer collapse

I now describe how the collapsing process for the thermoresponsive polymer may be described mathematically. It is supposed that the polymer is heated to a temperature \( T \) above its LCST, so that \( T > T_L \), and the polymer collapses.

The collapsing behaviour may be modelled by changing the values of \( \phi_w^s \) and \( \phi_c^s \) appropriately in the boundary conditions when the temperature of the system is above the LCST.

Recall that for \( T < T_L \), we had that:

\[ \phi(s_w(t), t) = \phi_w^s, \quad \phi(s_c(t), t) = \phi_c^s, \quad \phi_w^s > \phi_c^s. \]  

(7.23)

For \( T > T_L \), these boundary conditions are replaced by:

\[ \phi(s_w(t), t) = 0, \quad \phi(s_c(t), t) = 1. \]  

(7.24)

In (7.24), the first boundary condition implies that when the polymer is above its LCST, it can retain no water. The second boundary condition implies that above the LCST, the phase change from the condensed to the swollen state
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for the polymer cannot be initiated irrespective of how high the water content in a neighbouring portion of the polymer is. The conditions (7.23) and (7.24) may be equivalently written as:

\[ \phi(s_w(t), t) = \phi_w(T), \quad \phi(s_c(t), t) = \phi_c(T), \quad (7.25) \]

where we have the following binary dependencies:

\[ \phi_w(T) = \begin{cases} \phi^*_w & \text{for } T < T_L, \\ 0 & \text{for } T > T_L, \end{cases} \]

with \( 0 < \phi^*_w < 1 \), and,

\[ \phi_c(T) = \begin{cases} \phi^*_c & \text{for } T < T_L, \\ 1 & \text{for } T > T_L, \end{cases} \]

with \( \phi^*_w > \phi^*_c > 0 \). With these conditions, I shall now demonstrate numerically that:

\[ \frac{ds_w}{dt} < 0, \quad \frac{ds_c}{dt} > 0 \quad \text{for } T < T_L \text{ (swelling)}, \]

and

\[ \frac{ds_w}{dt} > 0, \quad \frac{ds_c}{dt} < 0 \quad \text{for } T > T_L \text{ (collapsing)}. \]

7.2.2.3. Numerical solutions in one dimension

The numerical method

Figure 7.4. The spatial finite difference grid for the moving boundary problem (7.17).
I now describe the numerical procedure that was used to solve the initial boundary value problem (7.17) and (7.18). The procedure is based on a finite difference front-tracking scheme described in a book by Crank [27]. At any time $t > 0$, the spatial domain in which the equations must be solved occupies $s_w(t) < x < s_c(t)$, and this is covered by a uniform spatial grid of points:

$$(i_w - 1)\delta x, i_w\delta x, (i_w + 1)\delta x, ..., 0, \delta x, ..., (i_c - 1)\delta x, i_c\delta x, (i_c + 1)\delta x,$$

where $\delta x$ is the uniform spacing, and $(i_w - 1)\delta x < s_w(t) < i_w\delta x, i_c\delta x < s_c(t) < (i_c + 1)\delta x$; see Figure 7.4. The time domain is also discretised uniformly, with $\delta t$ being the time-step. Hence, the continuous domain $s_w(t) < x < s_c(t), t \geq 0$ is replaced by the discrete grid $(x_k, t_j) = (k\delta x, j\delta t)$ for $i_w - 1 \leq k \leq i_c + 1$, $j \geq 0$, and I denote by $\phi_{k,j}$ the numerical approximation to $\phi(x_k, t_j)$.

**Interior points:** $i_w + 1 \leq k \leq i_c - 1, j \geq 0$

The governing equation for the water fraction (7.17) is rewritten as:

$$\frac{\partial \phi}{\partial t} = D'(\phi) \left( \frac{\partial \phi}{\partial x} \right)^2 + D(\phi) \frac{\partial^2 \phi}{\partial x^2}.$$ 

Using forward difference approximations for the time derivative and standard central difference approximations for the first and second order spatial derivatives, the following explicit time-stepping scheme is obtained:

$$\phi_{k+1,j} = \phi_{k,j} + \delta t \left( D'(\phi_{k,j}) \left( \frac{\phi_{k+1,j} - \phi_{k-1,j}}{2\delta x} \right)^2 + D(\phi_{k,j}) \frac{\phi_{k-1,j} - 2\phi_{k,j} + \phi_{k+1,j}}{(\delta x)^2} \right),$$

for $i_w + 1 \leq k \leq i_c - 1, j \geq 0$.

**Points near the front $x = s_c(t)$**

The moving boundary $x = s_c(t)$ may be written as $x = (i_c + r_{c,j})\delta x$ where $0 < r_{c,j} < 1$. I consider three grid points: the moving boundary point $(i_c + r_{c,j})\delta x$, and the two points immediately to its left: $i_c\delta x$ and $(i_c - 1)\delta x$. For convenience, I introduce the notation: $x_0 = (i_c - 1)\delta x, x_1 = i_c\delta x$, and $x_2 = (i_c + r_{c,j})\delta x$; see Figure 7.4 These points are not equally spaced and so care must be taken in calculating finite difference approximations for the derivatives. Lagrangian interpolation is used.
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by writing:

\[ f(x) = \phi(x, t_j) \text{ and } f(x) \approx \sum_{i=0}^{2} l_i(x) f(x_i), \quad (7.26) \]

where:

\[ l_i(x) = \frac{p_2(x)}{(x - x_i)p_2(x_i)}, \quad p_2(x) = (x - x_0)(x - x_1)(x - x_2), \quad i = 0, 1, 2. \]

The first derivative of \( f(x) \) may then be approximated by:

\[ \frac{df}{dx}(x) \approx \sum_{i=0}^{2} \frac{1}{\delta x} \left( \frac{f(x_0)}{(x_0 - x_1)(x_0 - x_2)} \right), \quad (7.27) \]

and the second derivative by:

\[ \frac{d^2f}{dx^2}(x) \approx 2 \left\{ \frac{f(x_0)}{(x_0 - x_1)(x_0 - x_2)} + \frac{f(x_1)}{(x_1 - x_0)(x_1 - x_2)} + \frac{f(x_2)}{(x_2 - x_0)(x_2 - x_1)} \right\}. \quad (7.28) \]

Recalling (7.26), and setting \( x = i_c \delta x, (i_c + r_{c,j}) \delta x \) in (7.27) gives:

\[ \frac{\partial \phi}{\partial x}(i_c \delta x, t_j) \approx \frac{1}{\delta x} \left( \frac{r_{c,j} \phi_{i_c-1,j}}{r_{c,j} + 1} - \frac{(r_{c,j} - 1)\phi_{i_c,j}}{r_{c,j}} - \frac{\phi^s_{c,j}}{r_{c,j}(r_{c,j} + 1)} \right), \quad (7.29) \]

\[ \frac{\partial \phi}{\partial x}((i_c + r_{c,j}) \delta x, t_j) \approx \frac{1}{\delta x} \left( \frac{r_{c,j} \phi_{i_c-1,j}}{r_{c,j} + 1} - \frac{(r_{c,j} + 1)\phi_{i_c,j}}{r_{c,j}} + \frac{2r_{c,j} + 1}{r_{c,j}(r_{c,j} + 1)} \phi^s_{c,j} \right). \quad (7.30) \]

From (7.28), we have that:

\[ \frac{\partial^2 \phi}{\partial x^2}(i_c \delta x, t_j) \approx \frac{2}{(\delta x)^2} \left( \frac{\phi_{i_c-1,j}}{r_{c,j} + 1} - \frac{\phi_{i_c,j}}{r_{c,j}} + \frac{\phi^s_{c,j}}{r_{c,j}(r_{c,j} + 1)} \right). \quad (7.31) \]

The formulae (7.29) and (7.31) provide the required finite difference approximations for implementing the explicit time-stepping scheme at the point \( x = i_c \delta x \). It is found that:

\[ \phi_{i_c,j+1} = \phi_{i_c,j} + \frac{\delta t D}{(\delta x)^2} \left( \frac{r_{c,j} \phi_{i_c-1,j}}{r_{c,j} + 1} - \frac{(r_{c,j} - 1)\phi_{i_c,j}}{r_{c,j}} - \frac{\phi^s_{c,j}}{r_{c,j}(r_{c,j} + 1)} \right)^2 + \frac{2\delta t D}{(\delta x)^2} \left( \frac{\phi_{i_c-1,j}}{r_{c,j} + 1} - \frac{\phi_{i_c,j}}{r_{c,j}} + \frac{\phi^s_{c,j}}{r_{c,j}(r_{c,j} + 1)} \right). \]

I denote by \( s_{c,j} \) the numerical approximation to \( s_c(t_j) \), and using the second formula
7.2. The model for pulsatile release

in (7.17) and (7.30), the following time-stepping scheme for \( s_c(t) \) is obtained:

\[
s_{c,j+1} = s_{c,j} - \frac{\delta t}{\delta x} D(\phi_s^c) \left( \frac{r_{c,j}(\phi_{i-1,c,j}^s)}{r_{c,j}+1} - \frac{(r_{c,j}+1)\phi_{i-1,c,j}^s}{r_{c,j} (r_{c,j}+1)} \right), \quad j = 0, 1, 2, \ldots
\]

and then:

\[
r_{c,j+1} = \left( s_{c,j+1} - i_c \delta x \right) / \delta x, \quad j = 0, 1, 2, \ldots
\]

At the first iteration \( j \) for which \( r_{c,j+1} > 1 \), \( i_c \) is replaced by \( i_c + 1 \), and \( r_{c,j+1} \) is replaced by \( r_{c,j+1} - 1 \). In this way, the motion of the moving boundary is tracked. The other moving boundary, \( x = s_w(t) \), is dealt with similarly. The collapsing problem is also dealt with in a similar manner.

Numerical results

Numerical solutions to (7.17) and (7.18) using the scheme just described are displayed in Figure 7.5-7.7. In Figure 7.5 I plot solutions for the volume fraction of water in the polymer, \( \phi(x,t) \), for both the swelling and collapsing processes. In Figure 7.6 I plot the drug fraction, \( c(x,t) \), in the polymer using the data \( \phi(x,t), s_c(t), s_w(t) \) that were calculated for Figure 7.5. In Figure 7.7 the accuracy of the numerical scheme was tested by plotting the exact similarity solution (7.21) against a corresponding numerical solution on the same graph, and it is seen that the agreement is excellent.

7.2.3. The swelling and collapsing model in two dimensions

Model equations

I now briefly discuss a two-dimensional generalisation of the one-dimensional swelling and collapsing problem discussed in the previous subsection. In this problem, a dry condensed polymer initially occupies a region \( \Omega_1(0) \) in the \( (x,y) \) plane; see Figure 7.8. The remainder of the plane, \( \Omega_1^c(0) \), is occupied by an aqueous medium. At time \( t = 0 \), it is supposed that the temperature of the entire system is below the LCST of the polymer, so that for \( t > 0 \), water diffuses into the polymer causing it to swell. For \( t > 0 \), there are two moving curves that need to be tracked: a swelling front, which I denote by \( \Gamma_1(t) \), and an erosion front, denoted by \( \Gamma_2(t) \); see Figure 7.8. Using the notation introduced in the previous subsection and in Figure 7.8 the initial boundary value problem governing the water fraction, \( \phi(x,y,t) \), in
Figure 7.5. Numerical solutions for the volume fraction of water, $\phi(x,t)$, with $D = 10^{-2} \exp(\phi)$, $\phi_w^* = 0.9$ and $\phi_c^* = 0.2$, and for various times. In (a), I am solving the swelling problem (7.17) for $t < 1$. At time $t = 1$, the boundary conditions for $\phi(x,t)$ are changed to (7.24), so that the polymer collapses for $t \geq 1$. In (b), I plot profiles for $\phi(x,t)$ in the collapsing polymer for various times $t \geq 1$. 
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Figure 7.6. Volume fraction of drug, \( c(x, t) \), with \( D^* = 10^{-3} \exp(\phi) \), \( \phi^*_w = 0.9 \) and \( \phi^*_c = 0.2 \) at various times corresponding to the swelling process in Figure 7.5. The concentration \( c(x, t) \) was calculated by solving (7.18), and using data for \( \phi(x, t), s_c(t), s_w(t) \) generated by solving (7.17) as described in Figure 7.5.

Figure 7.7. Comparison between a numerical solution (solid line) and the analytical solution (7.21) (dash line) for the volume fraction of water, \( \phi(x, t) \), and volume fraction of drug, \( c(x, t) \), corresponding to the swelling process at time \( t = 1 \). In this case, we have \( \beta = \beta^* = 0 \) with \( D_0 = 10^{-2}, D_0^* = 10^{-3}, \phi^*_w = 0.9 \) and \( \phi^*_c = 0.2 \).
7. Discussion

Figure 7.8. A thermoresponsive polymer below its LCST absorbs water and swells. Two moving fronts need to be located: a swelling front $\Gamma_1(t)$, and an erosion front $\Gamma_2(t)$.

$\Omega_2(t) \setminus \Omega_1(t)$ is given by:

$$\frac{\partial \phi}{\partial t} = \nabla \cdot (D(\phi) \nabla \phi) \quad \text{in} \quad \Omega_2(t) \setminus \Omega_1(t), \quad t > 0,$$

$$\phi = \phi_c^s, \quad -D(\phi) \frac{\partial \phi}{\partial n_1} = \phi_c V_1n \quad \text{on} \quad \Gamma_1(t), \quad t > 0,$$

$$\phi = \phi_w^s, \quad -D(\phi) \frac{\partial \phi}{\partial n_2} = -(1 - \phi_w)V_2n \quad \text{on} \quad \Gamma_2(t), \quad t > 0,$$

$$\Gamma_1(t = 0) = \Gamma_2(t = 0) = \partial \Omega_1(0).$$

(7.32)

where $\partial \phi/\partial n_1 = (\nabla \phi) \cdot n_1$, $\partial \phi/\partial n_2 = (\nabla \phi) \cdot n_2$, and where $n_1, n_2$ are the unit normals of $\Gamma_1(t), \Gamma_2(t)$, respectively, pointing out of the region $\Omega_2(t) \setminus \Omega_1(t)$. Also, $V_1n, V_2n$ denote the normal velocities of $\Gamma_1(t), \Gamma_2(t)$, respectively. The problem (7.32) can in principle be solved for $\phi(x, y, t), \Gamma_1(t), \Gamma_2(t)$. Once $\phi(x, y, t), \Gamma_1(t), \Gamma_2(t)$ have been determined, they can be used as data in the following problem for the drug concentration, $c(x, y, t)$:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D^*(\phi) \nabla c) \quad \text{in} \quad \Omega_2(t) \setminus \Omega_1(t), \quad t > 0,$$

$$c(x, y, t) = c_0 \quad \text{on} \quad \Gamma_1(t), \quad t > 0,$$

$$c(x, y, t) = 0 \quad \text{on} \quad \Gamma_2(t), \quad t > 0.$$

(7.33)
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The collapsing process is modelled in an identical manner to that of the one-dimensional problem.

For the case $\beta = 0, D(\phi) = 1$, and equation (7.32) reduces to the linear heat equation. I have constructed numerical solutions to (7.32) for this case by explicitly time-stepping (7.32) for $\phi(x, y, t)$ on a uniform grid in the usual way. The moving curves $\Gamma_1(t), \Gamma_2(t)$ were tracked using a level set method for Stefan problems. This method was first proposed in [22], and a detailed description of it can be found there. In Figure 7.9 I display numerical solutions for both the swelling and collapsing processes for $\Omega_1(0) = \{(x, y) | \sqrt{x^2 + y^2} < 0.14\}$, and in these plots, it is seen that the motion of the curves $\Gamma_1(t), \Gamma_2(t)$ has the expected qualitative character.

7.3. A model for a proposed drug delivery device for in vivo implantation

7.3.1. Strengths and weaknesses

In Chapter 6, a theoretical assessment of a novel drug delivery device for in vivo implantation was presented. The proposed delivery device consists of a cooling material coated by a drug-loaded thermoresponsive polymer film. Drug release is initiated by remotely dropping the temperature of the cooling material sufficiently for the temperature throughout the polymer coating to drop below its LCST, causing the polymer to swell and release drug. Drug release switches off again when heat conduction from the surrounding fluid medium raises the polymer temperature to above the LCST causing the polymer to collapse. The model predicts that the duration a thin polymer will continue to release drug in a single cycle is proportional to the square of the thickness of the cooling material. This simple result is significant since it implies that it is in principle possible to adjust the thickness of the cooling material so as to maintain the polymer in a swollen state for a desired time interval. A calculation incorporating a constant heat source in the modelling was also presented, and the results indicate that heat conduction due to the initial temperature difference between the water and the cooling material can make the dominant contribution to heat transfer in the polymer for sufficiently small times.

However, there is ample scope for improving upon this model. One of the shortcomings of the model is that it does not include the swelling and shrinking behaviour
7. Discussion

Figure 7.9. Some numerical solutions for the swelling front $\Gamma_1(t)$ and the erosion front $\Gamma_2(t)$. These curves were determined by solving the problem (7.32) using a level set method, and the parameters used were $D = 1$, $\phi_{sw} = 0.8$ and $\phi_{sc} = 0.2$. At time $t = 0$, the polymer occupied $\Omega_1(0) = \{(x, y) | \sqrt{x^2 + y^2} < 0.14\}$. In the top figure, $t \leq 0.001$, and the polymer is swelling. At $t = 0.001$, the boundary conditions for $\phi(x, y, t)$ are changed to (7.24), so that the polymer collapses for $t > 0.001$. In the bottom figure, curves corresponding to collapse are displayed.
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of the thermoresponsive polymer. This assumption can be valid when modelling heat transfer if the thickness of the polymer is small compared to that of the cooling material, but will not be true if the cooling material and polymer are of comparable thickness. A detailed model for the swelling and collapsing behaviours of a thermoresponsive polymer has been proposed in the previous section. It should also be noted that no attempt was made in the modelling to incorporate drug concentrations which, after all, are the quantities of primary interest in applications. Nevertheless, it should be further noted here that the principal purpose of the study was to establish the feasibility of the proposed device, and tracking the temperature evolution in the system is sufficient to achieve this.

Another deficiency of the modelling presented in Chapter 6 is that no serious attempt was made to allow for the presence of heat sources or sinks. In the human body, tissues generate heat via metabolic processes, and blood flowing in or nearby to tissue can exchange thermal energy with it. In the next subsection, I briefly sketch how such effects may be included in the modelling.

7.3.2. Addressing the weakness: a model incorporating heat sources and sinks

It is envisaged that the proposed drug delivery device would be implanted in human tissue. Heat transfer in the body, and tissue in particular, has been extensively studied in the past, and numerous mathematical models have been proposed to describe it; see, for example, [3,119,125,167,183]. Many of these models are based on early work by Pennes [119], who developed an equation to describe heat transfer in a tissue. This equation, which is commonly referred to as the bioheat equation, takes the following form:

\[
\rho c \frac{\partial T}{\partial t} = K \nabla^2 T + \dot{q}_m + \dot{q}_p,
\]

(7.34)

where \(T = T(r,t)\) is the temperature of the tissue at location \(r\) and time \(t\), and \(\rho, c, K\) give the density, heat capacity, and conductivity (assumed constant here), respectively, of the tissue. Here \(\dot{q}_m\) and \(\dot{q}_p\) give the metabolic and perfusion heat source terms, respectively. The perfusion term accounts for the exchange of thermal energy between the tissue and the blood, and, depending on the context, it can be either a source or a sink term.

In the Pennes model, the blood is assumed to enter the tissue at the arterial
temperature, $T_a$, say, and to exit the capillaries at the local temperature of the tissue, $T$. The thermal energy transferred to, or extracted from, the tissue is then taken to be proportional to the difference between $T_a$ and $T$. Pennes wrote:

$$\dot{q}_p = \rho_b c_b \omega (T_a - T),$$  \hspace{1cm} (7.35)

where $\rho_b, c_b$ give the density and specific heat capacity, respectively, of the blood, and $\omega$ is a tissue-dependent parameter called the perfusion rate. Substituting (7.35) in (7.34) yields:

$$\rho c \frac{\partial T}{\partial t} = K \nabla^2 T + \rho_b c_b \omega (T_a - T) + \dot{q}_m.$$  \hspace{1cm} (7.36)

In the model described in Chapter 6, the equation for $T_w$ would be replaced by an equation of the form (7.36). Clearly, the particular form for (7.36) to be used, and its associated boundary and initial conditions, will depend on the tissue being considered and the location of the device in it.
A. Appendix

Transition regions that arise in the limit $\varepsilon \to 0$

Figure A.1. A schematic representation of the nine asymptotic regions that arise in the $(c_T^G, c_T^H)$ plane in the limit $\varepsilon \to 0$.

In this appendix, I fill in some missing asymptotic details of the analysis given in Section 2.3.1. We write $K_{bh} = 1/\varepsilon$, $K_{b\nu} = \mu/\varepsilon$ and consider the limit $\varepsilon \to 0$ in (2.16) for fixed $O(1)$ values of $c_T^G$ and $c_T^H$, and with $\mu$ and all the remaining dimensionless parameters in (2.16) being $O(1)$. In this limit, there are nine asymptotic regions in all to be considered, given by:

(I): $c_T^H < c_T^G$, $c_T^H < c_P^0$;

(II): $c_T^H < c_T^G$, $c_T^H > c_P^0$;

(III): $c_T^H > c_T^G$, $c_T^H > c_P^0$;

(IV): $c_T^H > c_T^G$, $c_T^H < c_P^0$;

(I-II): $c_T^H < c_T^G$, $\alpha = O(1)$ where $c_P^0 = c_T^H + \varepsilon^{1/2}\alpha$;
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(III-IV): $c_H^T > c_G^T$, $\alpha = O(1)$ where $c_H^0 = c_H^T + \varepsilon^{1/2}\alpha$;

(II-III): $c_H^T > c_P^0$, $\gamma = O(1)$ where $c_G^T = c_H^T + \varepsilon^{1/2}\gamma$;

(IV-I): $c_H^T < c_P^0$, $\gamma = O(1)$ where $c_G^T = c_H^T + \varepsilon^{1/2}\gamma$;

(M): $\alpha, \gamma = O(1)$ where $c_G^T = c_H^T + \varepsilon^{1/2}\gamma$, $c_P^0 = c_H^T + \varepsilon^{1/2}\alpha$.

In Figure [A.1] the location of these regions is indicated in the $(c_G^T, c_H^T)$ plane. The expressions I shall display here are in dimensional variables. In the limit $\varepsilon \to 0$, it is found that (using the series command in MAPLE):

$$
D_G^T - D_G \sim \begin{cases} 
-D_G \\
-2 \left\{ \frac{D_G(\alpha \varepsilon^{1/2}(\alpha \varepsilon^{1/2} + \alpha^* ))^2}{2\gamma^2} - \frac{D_G T_G^2}{\alpha^*(\alpha \varepsilon^{1/2} + \alpha^*)} \right\} \\
(D_G - D_G) \gamma^2 + \frac{2(D_G - D_G)c_H^0 c_T^0}{\gamma^2} + 2D_G c_H^0 c_T^0 \\
\frac{D_G c_H^0 c_G^0}{\gamma^2} \\
\frac{2D_G c_H^0 c_H^0}{\gamma^2} + 2D_G c_H^0 c_H^0 \\
\varepsilon \left\{ \frac{D_G c_H^0 c_G^0}{\gamma^2} - \frac{D_G c_H^0 c_H^0}{\gamma^2} \right\} \\
- \frac{D_G}{2} \left(1 + \frac{\gamma^2}{\gamma^2} \right)
\end{cases}
$$

and,

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For the fraction of bound growth factor in the matrix, $f_B(x, t)$, we find as $\varepsilon \to 0$ that:

$$f_B(x, t) \sim \begin{cases} 
\frac{c_T^T}{c_G^T} & \text{for } c_H^T < c_G^T, c_H^T < c_p^T, \\
\frac{c_H^T}{c_G^T} - \frac{2\varepsilon^{1/2}c_H^T}{c_G^T (\alpha + \alpha^*\mu^{1/2})} & \text{for } c_H^T < c_G^T, \gamma = O(1), c_p^T = c_H^T + \varepsilon^{1/2}\alpha, \\
\frac{c_p^0}{c_T^0} + \frac{\varepsilon^{1/2}c_H^T}{c_T^0} \left( \gamma + \frac{2\varepsilon^{1/2}c_H^T}{c_T^0} \right) & \text{for } c_H^T > c_p^0, \gamma = O(1), c_G^T = c_H^T + \varepsilon^{1/2}\gamma, \\
\frac{c_h^0}{c_T^0} - \frac{2\varepsilon^{1/2}c_h^T}{c_T^0 (\alpha + \alpha^*\mu^{1/2})} & \text{for } c_H^T > c_G^T, c_H^T > c_p^0, \\
1 & \text{for } c_H^T > c_G^T, c_H^T < c_p^0, \\
1 - \frac{2\varepsilon^{1/2}}{\gamma + \gamma^*} & \text{for } c_H^T < c_p^0, \gamma = O(1), c_G^T = c_H^T + \varepsilon^{1/2}\gamma. 
\end{cases}$$

(A.3)
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