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Three-Dimensional Model of the Release and Diffusion of Paclitaxel in the Stent-Polymer-Wall-Lumen System of a Blood Vessel

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SOMMAIRE

Les stents sont utilisés en cardiologie interventionnelle pour garder ouvert un vaisseau malade. Les nouveaux stents sont recouverts d'un agent médicinal pour prévenir l'obstruction prématurée suite à la prolifération de cellules musculaires lisses (CML) dans la lumière du vaisseau. Afin de réaliser le taux nécessaire de largage de médicament pendant la période thérapeutique désirée, la tendance est aux largages biphasiques ou possiblement polyphasiques à partir d'un mélange de polymères dégradables. Blanchet-Delfour-Garon [7] ont introduit une équation différentielle ordinaire quadratique à 2 paramètres et Garon-Delfour [42] une équation différentielle partielle 3D quadratique à 2 paramètres pour caractériser la dynamique du largage du médicament pour chaque polymère. Les deux paramètres de ces modèles peuvent être obtenus expérimentalement à partir du protocole de mesures de Lao et al. pour des polymères purs et pour des mélanges de polymères en créant des conditions de réservoir infini. Ces équations constituent un outil pratique pour simuler numériquement et théoriquement le largage 3D d'un médicament imprégné dans une mince couche de polymère vers la paroi et la lumière du vaisseau sanguin aux fins d'évaluation et de design d'un stent.

L'objectif principal de la recherche était de passer d'une surface plate de polymère à la surface courbe qui recouvre un véritable stent de géométrie complexe. En premier lieu, le modèle à diffusion linéaire (et les résultats) de Delfour Garon-Longo [31] pour un vaisseau modélisé par un cylindre droit ont été généralisés au cas d'un vaisseau avec surface cylindrique courbe en introduisant les conditions de transparence appropriées à l'entrée et à la sortie. Ce modèle a ensuite été utilisé pour obtenir les équations de la dose et de la concentration normalisée. En second lieu, les conditions de transparence et le largage quadratique ont été intégrés à l'équation aux dérivées partielles 3D de Garon-Delfour [42]. Ce deuxiéme modèle non linéaire a ensuite été utilisé pour étudier la concentration normalisée en fonction de l'épaisseur du polymère et de la constante de diffusion du milieu ambiant.

Mots clés : largage de médicament, polymères biodégradables, paclitaxel, équation de Riccati, équation différentielle partielle en espace-temps, simulation numérique.

SUMMARY

Stents are used in interventional cardiology in order to keep a diseased vessel open. New stents are coated with a medicinal agent that prevents the early reclosing caused by the proliferation of smooth muscle cells (SMC). In order to obtain the desired release kinetics for the SMC-controlling drug during the required therapeutic period, the current strategy focuses on biphasic or possibly polyphasic release from blends of degradable polymers. Blanchet-Delfour-Garon [7] introduced an ordinary differential equation with two parameters and Garon-Delfour [42] a partial differential equation with two parameters to model the release kinetics. The parameters are all obtained from experimental release curves of Lao et al. [60] for pure polymers and polymer blends under infinite sink conditions. They are practical tools to numerically and theoretically simulate the 3D drug release from a thin coating of polymer to the aggregated wall and lumen of the blood vessel in order to facilitate the design and evaluation of the coating.

The primary objective of this research was to pass from the thin, flat midsurface coating to the thin coating of a realistic 3D stent with curved and complex surface. To begin, the linearly diffusive model (and the results) of Delfour-Garon-Longo [31] that were obtained for a vessel with flat surface were extended to the case of a vessel with curved surface by finding the appropriate boundary conditions. The resulting model was then analysed from the point of view of the dose and the normalised concentration. Secondly, the resulting boundary condition from the 3D partial differential equation of Garon-Delfour was introduced into the model. This second nonlinear model was then used to study the normalised concentration as a function of the thickness of the polymer and the diffusion constant of the surrounding medium.

Keywords : Drug release kinetics, biodegradable polymers, paclitaxel, Riccati equation, time- space partial differential equation, numerical simulation.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning	Page
SMC	Smooth muscle cells	xxi
DES	Drug-eluting stents	xxi
PCL	Polycaprolactone	xxi
PLGA	(Poly) dl-lactide-co-glycolide	xxi
PLGAPEG	(Poly) dl-lactide-co-glycolide with polyethylene glycol	xxi
ODE	Ordinary Differential Equations	xxi
PDE	Partial Differential Equations	xxii
a.e.	Almost everywhere	3

LIST OF NOTATION

This list of notation only includes notation used for new calculations. As such, notation from chapter 3 is omitted, as that section pertains to previous articles and uses their notation. Common notation, such as $L^2(\Omega)$ and $H^1(\Omega)$ have also been omitted.

Notation	Meaning	Page
R	radius of the wall of the vessel	1
C	curve that is the center line of the vessel	1
r	radius of the lumen of the vessel	1
$T_{\varphi(z)}C$	the tangent space to C at the point $\varphi(z) \in C$	2
H^1	the Haussdorf measure of dimension 1	2
$d_A(x)$	the distance function from a set A	3
$U_h(A)$	the open dilation of the set A	3
A_h	the closed dilation of the set A	3
$\Pi_A(y)$	the set of projections of y onto A	3
$p_A(y)$	the (unique) projection of y onto A	3
U	the blood vessel	4
U_l	the lumen of the blood vessel	4
U_w	the wall of the blood vessel	4
D_w	the diffusion constant in the wall	4
D_l	the diffusion constant in the lumen	4
V	the velocity of the blood	4
R	the loss coefficient in U_w	4
U	the blood vessel	4
U_l	the lumen of the blood vessel	4
U_w	the wall of the blood vessel	4

D_w	the diffusion constant in the wall	4
D_l	the diffusion constant in the lumen	4
V	the velocity of the blood	4
R	the loss coefficient in U_w	4
n_A	the normal to the set A	5
∂A	the boundary of the set A	5
$c(x,t)$	the concentration of product	5
$c_0(x)$	the initial concentration of product	5
Ω_l (Ω_l^i, Ω_l^o)	the lumen in the central section (resp. the incoming and outgoing section)	5-6
Ω_w (Ω_w^i, Ω_w^o)	the wall in the central section (resp. the incoming and outgoing section)	5-6
Γ_0	the interface between Ω^i and Ω	6
Γ_L	the interface between Ω and Ω^o	6
Γ	the boundary of Ω	7
Γ_{lw}	the interface between U_l and U_w within Ω	7
Γ_{ext}	the lateral boundary of Ω	7
$\Gamma_{-\infty}$	orthogonal cross section of Ω^i "far away" from Γ_0	9
Γ_∞	orthogonal cross section of Ω^o "far away" from Γ_L	10
$q(x)$	the dose of product	14
D_p	the diffusion constant in the polymer	15
Σ	the target region for the stent in Γ_{lw}	15
Σ_s	the area associated with a stent	16
Σ_χ	the area associated with a characteristic function χ	16
h	the thickness of the polymer on the stent	16
Ω_p^h	the polymer in the central section	16
Ω_w^h	the wall in the central section (after stent insertion)	16
Γ_{pw}^h	the interface between Ω_p^h and Ω_w^h	16
Γ_{lw}^h	the interface between Ω_p^h and Ω_l	16
Ω_χ	the domain occupied by the central section with the stent removed	19
M_0	the initial mass of product	20
$c_0^h(x)$	the initial concentration of product	20
c_0^h	the (uniformly distributed) concentration of product	20
$\hat{c}^h(x)$ (or $\hat{c}(x)$)	the normalised concentration of product	20
$M_p(t)$	the mass of product in the polymer	21
$m_p(t)$	the normalised mass of product in the polymer	21
$q_h(x)$	the dose of product in Ω_χ	22
$b_{\Omega_l}(x)$	the oriented distance function to Ω_l	23
$U_{2h}(\Sigma)$	the tubular neighbourhood of Σ	23
$U_h^+(\Sigma)$	the "upper" tubular neighbourhood of Σ	24
$H(X)$	the mean curvature of $\partial\Omega_l$	25
$K(X)$	the Gauss curvature of $\partial\Omega_l$	25
$\bar{c}(x,t)$	the concentration of product in Ω_χ (after compressing the polymer)	31
$\beta(h)$ (or β)	the geometric conservation factor	31
$\hat{c}(x,t)$	the normalised concentration of product in Ω_χ(after compressing the polymer)	33
$\bar{q}(x)$	the dose of the normalised concentration in Ω_χ(after compressing the polymer)	35
$\bar{c}_p$	the concentration averaged along the normal	60

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INTRODUCTION

The topic of this mémoire is best introduced by quoting the following sections from [42] whose content is somewhat standard from papers on the subject.

> Stents are used in interventional cardiology to keep a diseased vessel open after angioplasty. This procedure is known to damage the endothelium at the insertion site and thus to favour the occurrence of in-stent restenosis through the proliferation of smooth muscle cells (SMC) within the lumen of the vessel. To control the abnormal behaviour of SMC, stents are coated with polymers that slowly release drug through diffusion into the wall of the vessel (drug-eluting stents or DES). These drugs are designed to control the rate of mitosis of SMC until the regeneration of the endothelium. In order to achieve prescribed drug release kinetics over the required therapeutic period, the current design strategies focus on bi-phasic and possibly multi-phasic[1] releases from blends of biodegradable polymers (cf. Batycky et al [3] in 1997).
>
> In that spirit, Lao and Venkatraman [60] published the experimental release profile of paclitaxel from three neat polymer matrices: PCL (Polycaprolactone), PLGA (dl-lactide-co-glycolide) and PLGAPEG (PLGA with polyethylene glycol). Lao et al [62] also considered polymer blends and proposed empirical models to predict the release profiles. The three neat polymers are representative of a broad spectrum of biodegradable polymers (cf. [63]).
>
> The experimental paclitaxel release profiles suggest two types of release: S-curve type and exponential type. S-curve behaviours are similar to the ones encountered in the study of the logistic equation of populations. Blanchet et al [7] introduced a two-parameter quadratic Ordinary Differential Equation (ODE) model that reproduces with high accuracy the experimental normalized drug release curves from neat PCL, PLGAPEG, and PLGA polymer matrices. The one dimensional model of Lao et al [62] uses from 5 to 8 parameters. The

[1] A bi-phasic strategy consists in delivering the treatment in two phases. For instance, in the first phase of drug release, the immediate release dose fraction reaches a therapeutic drug level, while the second extended release phase provides the dose fraction required to maintain an effective therapeutic level for a prolonged period.

simplicity of the ODE model indicates that somehow the quadratic structure captures the complex microphysics and chemistry of the release process for a broad range of polymers and polymer blends. This suggests the introduction of a quadratic time-space three dimensional (3D) partial differential equation (PDE) model of the paclitaxel release that mimics the ODE model.[2] The complexity of the dynamics inside the polymer is captured through a quadratic condition at the interface between the polymer and the surrounding medium specified by the two parameters of the ODE model. In so doing, we avoid resorting to a time-dependent or a nonlinear diffusion in the polymer.[3]

One important advantage of this model is to realistically and economically permit the 3D simulation of the release of paclitaxel from DES coated with a thin film of biodegradable polymers including the ones for which an incomplete release[4] is experimentally observed (recall that the paclitaxel is hydrophobic). Indeed, modelling the 3D diffusion from the polymer coating on a DES into the artery wall and the blood flow in the lumen involves complex phenomena at different spatial scales.[5] This requires the use of highly detailed 3D models resulting in cost prohibitive parameter identification and computations. So it is imperative to develop a *simple macroscopic model* of the diffusion of the drug in the polymer film that simultaneously captures the *surface erosion* and the *collapsing of the polymer matrix* for simulation and design purposes. In such a process the relative scales of the key parameters are of paramount importance, so that the macroscopic simulation of the drug release from a DES can be limited to the region occupied by the arterial wall and its lumen.

The objective of this mémoire is to revisit some recent three-dimensional models of drug release from the polymeric coating of a stent to the wall/lumen of a blood vessel and extend them to a curved blood vessel. Our work is to be placed within the broad context of integrated wall-lumen modelling of blood vessels and design and control of medical devices such as in M. C. Delfour, A. Garon, and V. Longo [**31**], É. Bourgeois and M. C. Delfour [**8**],

[2]An earlier purely theoretical 3D partial differential equation (PDE) model involving a quadratic semi-permeable membrane condition at the interface and a diffusion constant inside the polymer was introduced by Delfour [**28**].

[3]Thereby reducing the physical and computational complexity of mass transfer to ultimately predict the concentration of paclitaxel in the arterial wall.

[4]Cf. Lao et al [**60**, page 13].

[5]The modeling complexity is increasing significantly due to the large differences in the spatial scales of the media (assuming a $1\,mm$ arterial wall thickness and a $10\,\mu m$ polymer coating thickness) in which the processes of mass transfer occur.

M. C. Delfour and A. Garon [30], M. C. Delfour [28], , J. Siepmann and N. A. Peppas [77], and P. Zunino and al. [92].

Chapter 1 introduces a section of a curved blood vessel made up of the lumen and the wall. In order to isolate the section from the complex circulatory systems, transparency conditions are introduced at the inlet and at the outlet of the vessel in the form of Robin boundary conditions.

In Chapter 2 the stent is introduced as a zero thickness device and the polymer as a thin domain within the wall. The polymer is modelled as a linearly diffusive medium as was done in Delfour, Garon and Longo [31] for a blood vessel represented as a straight cylinder. This chapter generalizes the equations for the concentration and the dose from a right cylinder to a curved cylinder by introducing the proper geometrical concepts and integrating them into the new equations.

Chapter 3 deals with the modelling of the drug release from a polymeric film starting from laboratory measurements in a controlled environment. Experimentally, the release does not look as the release from a linearly diffusive medium. To better appreciate and understand the drug release from polymers, we describe the experimental and mathematical modelling work of Lao et al [60, 62, 63] on the release of paclitaxel from biodegradable neat polymers and polymer blends. Their work emphasized fitting to experimental data over purely mechanistic models that yield exponential type release curves and completely miss S-curve type release observed for highly degradable polymers. In that context, we describe the highly accurate two-parameter quadratic ODE model of Blancher, Delfour, and Garon [7]. From this Garon and Delfour [42] introduced a new quadratic PDE model of the 3D normalized concentrations in the polymer and the medium for the release of paclitaxel from a thin polymer film in a laboratory vial. In that context the local mass flux at the interface is completely specified by the two parameters of the ODE model. Extensive numerical simulations of the drug release of paclitaxel from the three neat polymers of Lao et al [60] have been performed to validate the model. The results are summarized in the form of normalised drug release curves as a function of the thickness of the film and the diffusion constant in the medium. The effects of the thickness of the polymer and of the diffusion constant in the surrounding medium are studied. The model readily extends to polymer blends. In this chapter, their model is generalised to a one-sided release in preparation for the release from the polymeric coating of a stent.

Chapter 4 incorporates the three-dimensional release model of Garon and Delfour [42] for a flat polymeric film in a vial to a stent inserted in a curved segment of blood vessel. The

resulting concentration model is then analysed with respect to the normalised concentration in order to identify the parameters.

The primary objective of this research was to model the release of drugs used to effectively control the growth of SMC to prevent restenosis. Such drugs do not help the reconstruction of the endothelium. Fortunately, there are medicinal agents that stimulate the growth of endothelial cells and the reconstruction of the endothelium. This opens the research to more ambitious projects combining the control of SMC and the regeneration of the endothelium. For further readings along those lines, the reader is referred to the following papers:

- Y. Xia, F. Boey, and S.. S. Venkatraman [**91**], *Surface modification of poly(L-lactic acid) with biomolecules to promote endothelialization*;
- R. A. Byrne, M. Joner, and A. Kastrati [**12**], *Stent thrombosis and restenosis: what have we learned and where are we going?* (this paper describes the present state of the art);
- W. K. E. Ip, N. Hoshi, D. S. Shouval, S. Snapper, and R. Medzhitov [**50**], *Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages*;
- S. Gonca [**44**], *Extracellular Matrix Proteomics Reveals Interplay of Aggrecan and Aggrecanases in Vascular Remodeling of Stented Coronary Arteries* (this paper deals with the rheology of the matrix).

Another complementary aspect to the modelling of the drug release is the identification of pertinent *susceptibility models* that accurately describe the effect of the distribution of the drug concentration on the SMC. In that direction, several papers are available on *log-kill laws* such as in [**13**] for larvicides in rivers and for the control of *solid* or *liquid* cancer depending on the degree of penetration of the drug in the tissues:

- G. W. Swan [**86**], *Cancer chemotherapy:optimal control using the Verhulst-Pearl equation* and P.-F. Verhulst [**89**], *Recherches mathématiques sur la loi d'accroissement de la population*;
- H. Byrne and D. Drasdo [**11**], *Individual-based and continuum models of growing cell populations: a comparison*;
- K. R. Fister and J. C. Panetta [**39**], *Optimal control applied to competing chemotherapeutic cell-kill strategies.*

Finally, the models and equation presented below are developed for arbitrary stent designs. In practice however, the stent must be structurally capable of holding the blood vessel open, and mechanically able to resist excessive degradation. These aspects are assumed to be verified during the stent design, and so are not discussed here. Further reading on this topic may be found in:

- F. Witte and A. Eliezer [**33**], *Degradation of Implant Materials*, Chapter 5:*Degradable Metals*.

Chapter 1

MODELING OF A SECTION OF BLOOD VESSEL

1.1. Preliminaries

We consider a diseased section of a blood vessel and study the evolution of the *concentration* of a medical agent released from the polymer coating of a stent to the wall and the lumen of the vessel. In this section, we begin by determining appropriate boundary conditions that reflect the natural flow of a medicinal agent within the body. At this stage the conditions do not depend on the stent, and so, for simplicity, the introduction of the stent will only be discussed in future chapters.

We assume that the vessel is a curved tube of radius $R > 0$ around a smooth curve C that can be regarded as the center line of the tube. It is assumed that the *curvatures* of C are not too large, in order for the lateral surface of the tube to remain smooth (no kinks). A second, curved inner tube of radius r, $0 < r < R$, is introduced around the same center line C. This tube of radius r will be the *lumen* of the vessel and the region between the two tubes will be the *wall* of the vessel.

Since we are only considering a section of the vessel, assumptions need to be made about the flow of blood entering and exiting the section. So, at the *inlet* we assume that the incoming vessel is an infinitely long straight cylinder of radius R containing a cylinder of radius r. Similarly, at the *outlet* we assume that the outgoing vessel is an infinitely long straight cylinder of radius R containing a cylinder of radius r. In each tube on both sides of the targeted section, we assume that the normal component of the flow of the blood is the same in each orthogonal section, that is, that the flow of blood is independent of which orthogonal section is chosen. The next step will be to introduce *transparency conditions* for the concentration at the inner and outer orthogonal sections which will be of the *Robin* type.

1.2. Parametrization and Characterization of a Smooth Curve

1.2.1. Parametrization of a Curve in $\mathbb{R}^3$

A curve C in $\mathbb{R}^3$ can be defined classically as the image of the real axis by a smooth function

$$z \mapsto \phi(z) : \mathbb{R} \to \mathbb{R}^3, \quad C \stackrel{\text{def}}{=} \phi(\mathbb{R}). \tag{1.2.1}$$

Assume that ϕ is C^2 and that there exists $0 < \alpha \leq \beta$ such that

$$\forall z_1, z_2 \in \mathbb{R}, \quad \alpha \left| z_2 - z_1 \right| \leq \left\| \phi(z_2) - \phi(z_1) \right\|_{\mathbb{R}^3} \leq \beta \left| z_2 - z_1 \right|. \tag{1.2.2}$$

This ensures that ϕ is injective , that the curve C is not self-intersecting and that the derivative $\phi'(z) \in \mathbb{R}^3$ exists and is continuous

$$\alpha \leq \left\| \phi'(z) \right\|_{\mathbb{R}^3} \leq \beta.$$

Since $\left\| \phi'(z) \right\|_{\mathbb{R}^3} \geq \alpha > 0$, we can assume that ϕ is *unit speed* by parametrising the curve with respect to the arc length. Thus $\left\| \phi'(z) \right\|_{\mathbb{R}^3} = 1 \quad \forall z \in \mathbb{R}$.
The vector $\phi'(z)$ in $\mathbb{R}^3$ is the tangent to the curve C at the point $x = \phi(z)$ and the tangent space $T_{\phi(z)}C$ to C in $\phi(z)$ is a line through $\phi(z)$ with orientation $\phi'(z)$

$$T_{\phi(z)}C = \mathbb{R}\, \phi'(z). \tag{1.2.3}$$

Denote by H^1 the Hausdorff measure[1] of dimension 1 in $\mathbb{R}^3$. The integral of an H^1-measurable function $f : C \to \mathbb{R}$ is defined as

$$\int_C f \, dH^1 = \int_{\mathbb{R}} f(\phi(z)) \sqrt{\phi'(z)^\top \phi'(z)} \, dz, \tag{1.2.4}$$

where $\phi'(z)^\top$ is the transpose of the vector $\phi'(z)$ and $\phi'(z)^\top \phi'(z)$ is a positive scalar. Since ϕ is unit speed, we have that

$$\sqrt{\phi'(z)^\top \phi'(z)} = 1, \quad \text{a.e. in } \mathbb{R}$$

so that the length of an interval $[a,b]$ on the line $\mathbb{R}$ is equal to the length along the curve between the points $\phi(a)$ and $\phi(b)$. Given $L > 0$ and $f = 1$

$$\int_{\phi((0,L))} f \, dH^1 = \int_0^L f \circ \phi \, dz, \quad \int_{\phi((0,L))} dH^1 = \int_0^L dz = L.$$

[1] See [34, page 65] for the definition and for more details. In our case, the Haussdorf and the Lebesgue measure are equivalent [34, page 70], and so the integral is simply the standard integral in $\mathbb{R}^3$.

1.2.2. Characterisation of the Smoothness via Distance Functions

We first recall the definition and several properties of the distance function.[2] Given a non-empty subset A, $\varnothing \neq A \subset \mathbb{R}^N$, and $h > 0$, define the *distance function* and the *open* and *closed h-dilations* of A as follows

$$d_A(x) \stackrel{\text{def}}{=} \inf_{a\in A} \|a - x\|_{\mathbb{R}^N}, \quad U_h(A) \stackrel{\text{def}}{=} \{y \in \mathbb{R}^N : d_A(y) < h\}, \tag{1.2.5}$$

$$A_h \stackrel{\text{def}}{=} \{y \in \mathbb{R}^N : d_A(y) \leq h\}. \tag{1.2.6}$$

By definition, $d_A(x) = d_{\overline{A}}(x)$, $U_h(\overline{A}) = U_h(A)$, and $\overline{A}_h = A_h$. Denote by $\Pi_A(y)$ the *set of projections* $p \in A$ of y onto $\overline{A}$

$$\Pi_A(y) \stackrel{\text{def}}{=} \{p \in A : \|p - y\| = d_A(y)\}. \tag{1.2.7}$$

The projections are solutions of the following minimization problem

$$d_A(y)^2 = \|p - y\|^2 = \inf_{a\in\overline{A}} \|a - y\|^2.$$

The set $\Pi_A(y)$ is always compact and non-empty.

The function d_A is Lipschizian of constant 1 on $\mathbb{R}^N$

$$\forall y,z \in \mathbb{R}^N, \quad \|d_A(z) - d_A(y)\| \leq \|z - y\|$$

and, by Rademacher's Theorem[3], ∇d_A exists and $\|\nabla d_A(y)\| = 1$ a.e. in $\mathbb{R}^N$. The function $d_A^2(y)$ is Hadamard semi-differentiable and

$$d_H d_A^2(y; v) = \inf_{p\in\Pi_A(y)} 2\,(p - y)\cdot v.$$

In particular, if $y \in A$, $p_A(y) = y$, $\Pi_A(y) = \{y\}$, and $\nabla d_A^2(y) = 0$.
When $\Pi_A(y) = \{p_A(y)\}$ is a singleton, d_A^2 is Fréchet differentiable at y and

$$\nabla d_A^2(y) = 2\,(p_A(y) - y) \quad \Rightarrow\ p_A(y) = y - \frac{1}{2}\nabla d_A^2(y)$$

and it can be verified that p_A is a projection in the *mathematical sense*:

$$p_A(p_A(y)) = p_A(y) - \frac{1}{2}\nabla d_A(p_A(y))^2 = p_A(y) - 0 = p_A(y)$$

and $p_A \circ p_A = p_A$. In general, the function

$$f_A(y) \stackrel{\text{def}}{=} \frac{1}{2}\left(\|y\|^2 - d_A^2(y)\right) \tag{1.2.8}$$

[2] See [29] or [32] for proofs and more details.
[3] [34, page 81] or [38, page 216].

which is convex and continuous on $\mathbb{R}^N$ [32, Thm. 3.2 (ii), page 282] plays a special role. It is locally Lipschitzian, Hadamard semi-differentiable in $\mathbb{R}^N$,

$$d_H f_A(y;v) = y \cdot v - \frac{1}{2} d_H d_A^2(y;v),$$

and (by Rademacher's Theorem) Fréchet differentiable almost everywhere in $\mathbb{R}^N$. When, $\Pi_A(y) = \{p_A(y)\}$ is a singleton, d_A^2 is Fréchet diferentiable and

$$\nabla f_A(y) = y - \frac{1}{2}\nabla d_A^2(y) = p_A(y).$$

We have the following theorem.

Theorem 1.2.1 (Poly and Raby [74]). *Let $x \in A \subset \mathbb{R}^N$ and $k \geq 2$ be an integer.*

(i) *Assume that there exists an open subset $U(x)$ of $\mathbb{R}^N$ containing x such that $d_A^2 \in C^k(\overline{U(x)})$, $k \geq 2$. Then, $\overline{A}$ is a C^k submanifold of $\mathbb{R}^N$ of dimension $d = \mathrm{rank}\, D^2 f_A(x)$ at x, where*

$$f_A(x) \stackrel{\text{def}}{=} \frac{1}{2}\left(\|x\|^2 - d_A^2(x)\right). \tag{1.2.9}$$

(ii) *Assume that A is a C^k submanifold of $\mathbb{R}^N$ of dimension d at x. Then, d_A^2 is C^k in a neighbourhood of x and $\mathrm{rank}\, D^2 f_A(x) = d$.*

1.3. Geometry of Vessel and Concentration of Product

1.3.1. Equations for the Concentration in the Vessel

Going back to our curve C, the center line of our vessel, we assume that $d_C^2 \in C^2(U_R(C))$ for some $R > 0$. Then, for $y \in U_R(C)$, $\nabla f_C(y)$ is the projection $p_C(y)$ of y onto C and $\mathrm{im}\, D^2 f_C(y)$ is the tangent to C at the point $p_C(y)$. The vessel U, the lumen U_l, and the wall U_w are the open domains defined as follows

$$\begin{gathered} U = U_R \stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < R\}, \\ U_l \stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < r\}, \quad U_w \stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : r < d_C(x) < R\}. \end{gathered} \tag{1.3.1}$$

Let D_w and D_l be the respective diffusion constants in U_l and U_w and let V be the velocity of the blood in U. There is no loss in the lumen, but let $R \geq 0$ be the loss coefficient in U_w to account for the metabolism of the drug. The motion of the blood in the lumen is at best periodic. Yet, the period is small compared to the time constant associated with the diffusion. In such a situation, it is convenient to work with a velocity averaged over the period. We further assume that this *averaged velocity* $V \in H^1(U_l)^3$ is the solution of the

Stokes equation in the whole lumen U_l. In particular,

$$\operatorname{div} V = 0 \text{ in } U_l \text{ and } V \cdot n_{U_l} = 0 \text{ on } \partial U_l, \tag{1.3.2}$$

where ∂U_l is the lateral boundary of U_l and n_{U_l} is the *normal* to U_l

$$\partial U_l \stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) = r\}. \tag{1.3.3}$$

At this juncture it is convenient to introduce the following global notation in U: the *loss coefficient* $R(x)$, the *diffusion coefficient* $D(x)$, and the *blood velocity* $V(x) \in \mathbb{R}^3$ in U are defined from the corresponding quantities in the lumen and in the wall

$$D(x) = \begin{cases} D_l, & x \in U_l \\ D_w, & x \in U_w \end{cases} \quad V(x) = \begin{cases} V_l(x), & x \in U_l \\ 0, & x \in U_w \end{cases} \quad R(x) = \begin{cases} 0, & x \in U_l \\ R, & x \in U_w. \end{cases} \tag{1.3.4}$$

We assume that the concentration of product, $c(x,t)$, satisfies a diffusion-advection equation in the lumen and a diffusion-reaction equation in the wall. This corresponds to the following equations:

$$\begin{aligned} &\frac{\partial c(x,t)}{\partial t} - \operatorname{div}\,(D(x)\nabla c(x,t)) + V(x)\cdot\nabla c(x,t) + R(x)c(x,t) = 0 \text{ in } U, \\ &\frac{\partial c(t)}{\partial n_U} = 0 \text{ on } \partial U, \quad D_w \frac{\partial c(t)}{\partial n_{U_w}} + D_l \frac{\partial c(t)}{\partial n_{U_l}} = 0 \text{ on } \partial U_w \cap \partial U_l, \\ &c(x,0) = c_0(x) \text{ in } U, \end{aligned} \tag{1.3.5}$$

where $c(t)$ denotes the function $x \mapsto c(x,t)$ and ∂U is the lateral boundary of the infinite tube U.

1.3.2. Central, Incoming, and Outgoing Sections

For analysis and control purpose, we restrict our attention to a central or therapeutic region of the vessel where the stent will be introduced. It is chosen sufficiently long so that the flow of blood at both end is sufficiently regular. This defines three regions (see Figure 1.1); the *central section* between $\phi(0)$ and $\phi(L)$

$$\begin{aligned} \Omega &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < R \text{ and } p_C(x) \in \phi(0,L)\}, \\ \Omega_l &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < r \text{ and } p_C(x) \in \phi(0,L)\}, \\ \Omega_w &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : r < d_C(x) < R \text{ and } p_C(x) \in \phi(0,L)\}; \end{aligned} \tag{1.3.6}$$

the *incoming section* between $\phi(-\infty)$ and $\phi(0)$

$$\begin{aligned}\Omega^i &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < R \text{ and } p_C(x) \in \phi(-\infty,0)\},\\ \Omega^i_l &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < r \text{ and } p_C(x) \in \phi(-\infty,0)\},\\ \Omega^i_w &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : r < d_C(x) < R \text{ and } p_C(x) \in \phi(-\infty,0)\};\end{aligned} \tag{1.3.7}$$

the *outgoing section* between $\phi(L)$ and $\phi(+\infty)$

$$\begin{aligned}\Omega^o &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < R \text{ and } p_C(x) \in \phi(L,+\infty)\},\\ \Omega^o_l &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : d_C(x) < r \text{ and } p_C(x) \in \phi(L,+\infty)\},\\ \Omega^o_w &\stackrel{\text{def}}{=} \{x \in \mathbb{R}^3 : r < d_C(x) < R \text{ and } p_C(x) \in \phi(L,+\infty)\}.\end{aligned} \tag{1.3.8}$$

The interface between Ω^i and Ω, as well as the one between Ω and Ω^o, are *orthogonal cross sections*

$$\Gamma_0 \stackrel{\text{def}}{=} \{x \in \ker D^2 f_C(\phi(0)) : d_C(x) < R\}, \tag{1.3.9}$$

$$\Gamma_L \stackrel{\text{def}}{=} \{x \in \ker D^2 f_C(\phi(L)) : d_C(x) < R\} \tag{1.3.10}$$

through the points $\phi(0)$ and $\phi(L)$.

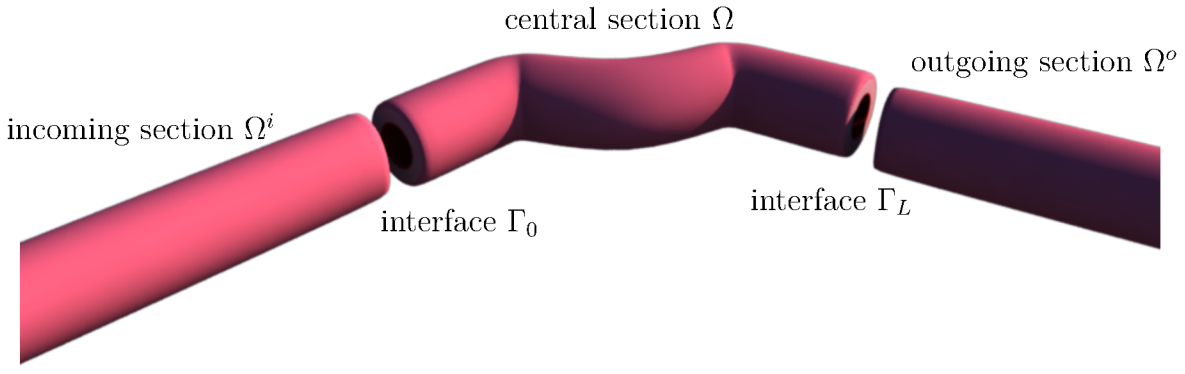

FIGURE 1.1. Vessel separated into the three sections.

1.3.3. Transparency Conditions in Γ_0 and Γ_L

The objective is to find boundary conditions on Γ_0 and Γ_L to isolate the central section Ω from Ω^i and Ω^o and obtain an equation for the concentration only on Ω. There are several ways to do that; For instance, we could impose a pressure gradient between Γ_0 and Γ_L, however we choose to do it by introducing *transparency conditions* in the form of boundary conditions of the *Robin type*

$$D\frac{\partial c(t)}{\partial n_\Omega} + \beta_0\, c(t) = 0 \text{ on } \Gamma_0 \quad \text{and} \quad D\frac{\partial c(t)}{\partial n_\Omega} + \beta_L\, c(t) = 0 \text{ on } \Gamma_L, \tag{1.3.11}$$

where $\beta_0 : \Gamma_0 \to \mathbb{R}$ and $\beta_L : \Gamma_L \to \mathbb{R}$ are non-negative functions to be determined.

The boundary Γ of Ω is made up of Γ_0, Γ_L, $\Gamma_{lw} = \partial U_l \cap \partial U_w \cap \Omega$, and its *lateral boundary* Γ_{ext} where the normal derivative of the concentration is zero. In the end we obtain the following equation for the concentration c in Ω:

$$\begin{aligned}
&\frac{\partial c(x,t)}{\partial t} - \text{div } (D(x)\nabla c(x,t)) + V(x)\cdot\nabla c(x,t) + R(x)c(x,t) = 0 \text{ in } \Omega,\\
&D\frac{\partial c(t)}{\partial n_\Omega} + \beta_0\, c(t) = 0 \text{ on } \Gamma_0,\ D\frac{\partial c(t)}{\partial n_\Omega} + \beta_L\, c(t) = 0 \text{ on } \Gamma_L,\ D\frac{\partial c(t)}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext},\\
&D_w\frac{\partial c}{\partial n_{U_w}} + D_l\frac{\partial c}{\partial n_{U_l}} \text{ on } \Gamma_{lw},\ c(x,0) = c_0(x) \text{ in } \Omega.
\end{aligned} \tag{1.3.12}$$

The source term will come from the initial concentration.

1.3.4. Associated Bilinear Form and Existence of Solutions

Given $u, v \in H^1(\Omega)$, consider the bilinear form associated with (1.3.12)

$$a(u,v) \stackrel{\text{def}}{=} \int_\Omega -\text{div } (D\nabla u)\, v + V\cdot\nabla u\, v + R\, u\, v\, dx. \tag{1.3.13}$$

Upon integration by parts

$$\begin{aligned}
a(u,v) &= \int_\Omega D\nabla u\cdot\nabla v + V\cdot\nabla u\, v + R\, u\, v\, dx - \int_{\Gamma_0} D\frac{\partial u}{\partial n_\Omega}\, v\, d\Gamma - \int_{\Gamma_L} D\frac{\partial u}{\partial n_\Omega}\, v\, d\Gamma\\
&= \int_\Omega D\nabla u\cdot\nabla v + V\cdot\nabla u\, v + R\, u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma.
\end{aligned} \tag{1.3.14}$$

This is a continuous bilinear form on $H^1(\Omega)$ with a non-symmetric term $V\cdot\nabla u\, v$. It can be decomposed as the sum of two bilinear forms

$$\begin{aligned}
a_0(u,v) &= \int_\Omega D\nabla u\cdot\nabla v + R\, u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma\\
b(u,v) &= \int_\Omega V\cdot\nabla u\, v\, dx.
\end{aligned} \tag{1.3.15}$$

Looking at each term in the expression of $a_0(u,u)$,

$$\int_\Omega D\,|\nabla u|^2\,dx \geq \underbrace{\min\{D_l,D_w\}}_{>0}\,\|\nabla u\|_{L^2(\Omega)}, \quad \int_\Omega \underbrace{R}_{\geq 0} u^2\,dx \geq 0,$$

and assuming that

$$\boxed{\beta_0 \geq 0 \text{ on } \Gamma_0 \quad \text{and} \quad \beta_L \geq 0 \text{ on } \Gamma_L,} \tag{1.3.16}$$

a_0 generates a V-H *coercive* operator A_0 with $V = H^1(\Omega)$ and $H = L^2(\Omega)$. The bilinear form b generates a continuous linear operator $B : V \to H$. So the operator A generated by a is the sum $A_0 + B$.

By [4, Thms. 1.1 and 1.2, pages 178-179] the sum $A = A_0 + B$ is V-H coercive and the weak parabolic equation on the time interval $[0,T]$

$$\begin{aligned} &\frac{d}{dt}\,(c(t),v)_{L^2(\Omega)} + a(c(t),v) = 0, \quad \forall v \in H^1(\Omega) \\ &c(0) = c_0 \in L^2(\Omega) \end{aligned} \tag{1.3.17}$$

has a unique solution in $W(0,T) = \{u \in L^2\,(0,T;H^1(\Omega)) : u' \in L^2\,(0,T;H^1(\Omega)')\}$, where $L^2(\Omega)$ and its dual $L^2(\Omega)'$ have been identified.

In order to have $a(u,u) \geq 0$, we must look more closely at the term

$$\int_\Omega V \cdot \nabla u\, u\,dx = \int_\Omega V \cdot \frac{1}{2}\nabla u^2\,dx = \int_\Omega \frac{1}{2}\mathrm{div}\,(V\,u^2)\,dx = \int_{\Gamma_0} \frac{1}{2} V \cdot n\,u^2\,d\Gamma + \int_{\Gamma_L} \frac{1}{2} V \cdot n\,u^2\,d\Gamma.$$

By using this identity, $a(u,u)$ can be rewritten as

$$a(u,u) = \int_\Omega D\,|\nabla u|^2 + R\,u^2\,dx + \int_{\Gamma_0} \left(\beta_0 + \frac{1}{2}V \cdot n\right) u^2\,d\Gamma + \int_{\Gamma_L} \left(\beta_L + \frac{1}{2}V \cdot n\right) u^2\,d\Gamma$$

and we further need to assume that the two boundary terms verify the conditions

$$\beta_0 + \frac{1}{2}V \cdot n \geq 0 \text{ on } \Gamma_0 \quad \text{and} \quad \beta_L + \frac{1}{2}V \cdot n \geq 0 \text{ on } \Gamma_L. \tag{1.3.18}$$

In order for a to be *coercive*, we need, in addition, an $\alpha > 0$ and a subset $\gamma_0 \subset \Gamma_0$ of non zero measure such that

$$\left(\beta_0 + \frac{1}{2}V \cdot n\right) \geq \alpha > 0 \text{ on } \gamma_0. \tag{1.3.19}$$

This gives

$$a(u,u) \geq \min\{D_l,D_w\}\,\|\nabla u\|^2_{L^2(\Omega)} + R\,\|u\|^2_{L^2(\Omega)} + \alpha\,\|u\|^2_{L^2_{\gamma_0}}.$$

Since the *geodesic distance*[4] between two points in Ω is bounded by a constant times the distance between those two points, the norm in $H^1(\Omega)$ is equivalent to the norm

$$\left[\|\nabla u\|^2_{L^2(\Omega)} + \|u\|^2_{L^2_{\gamma_0}}\right]^{1/2}.$$

1.4. Transparency Conditions: Determination of β_0 and β_L

To obtain the functions β_0 and β_L at the interface Γ_0 between Ω^i and Ω and at the interface Γ_L between Ω and Ω^o, it is sufficient to work with the "static part" of the evolution equation (1.3.5)

$$\begin{aligned} &-\text{div}\,(D\nabla u) + V\cdot\nabla u + Ru = 0 \text{ in } U,\\ &\frac{\partial u}{\partial n_U} = 0 \text{ on } \partial U,\ D_w\frac{\partial u}{\partial n_{U_w}} + D_l\frac{\partial u}{\partial n_{U_l}} = 0 \text{ on } \partial U_w\cap\partial U_l, \end{aligned} \tag{1.4.1}$$

where we have not included the source term that will come from the initial condition. Note that ∂U is the exterior lateral boundary of U. This equation will be integrated by parts on each domain Ω^i, Ω, and Ω^o to obtain transmission conditions at the interfaces Γ_0 and Γ_L at the inlet ($z = 0$) and at the outlet ($z = L$) of the therapeutic section Ω. Physically, it amounts to following the transfers of mass of product across the interfaces and assume conditions at an orthogonal section uphill ($z = -\infty$) and at an orthogonal section downhill ($z = +\infty$). These integral conditions will then be strengthened by making them pointwise to obtain the Robin conditions. By adding reasonable conditions on the normal component of the velocity at both ends, V-H coercivity or coercivity for the variational formulation is verified. That will ensure existence and uniqueness of the solution of the evolution equation in the therapeutic section.

1.4.1. Bilinear Form in Ω

Recall that we have assumed that there is no loss in the lumen U_l (that is, $R = 0$ in U_l), and that there is no transport term in the wall (that is, $V = 0$ in U_w).

The boundary of the domain Ω^i is made up of three parts: Γ_0, $\Gamma_{-\infty}$, and Γ^i_{ext}, the lateral boundary of Ω^i. Consider (1.4.1) in Ω^i

$$\begin{aligned} &-\text{div}\left(D\nabla u^i\right) + V\cdot\nabla u^i = 0 \text{ in } \Omega^i,\\ &\frac{\partial u^i}{\partial n_U} = 0 \text{ on } \Gamma^i_{ext},\quad D_w\frac{\partial u^i}{\partial n_{U_w}} + D_l\frac{\partial u^i}{\partial n_{U_l}} = 0 \text{ on } \partial\Omega^i_w\cap\partial\Omega^i_l. \end{aligned} \tag{1.4.2}$$

[4]The geodesic distance between two points in Ω is the length of the shortest path in Ω connecting the two. For a precise definition, see [5, page 364].

Since $\operatorname{div} V = 0$,

$$V \cdot \nabla u^i = \begin{cases} 0, & \text{in } \Omega_w^i \\ \operatorname{div}(V\, u^i) & \text{in } \Omega_l^i \end{cases} \tag{1.4.3}$$

applying Green's formula [5] we have

$$\begin{aligned} 0 &= \int_{\Omega^i} \operatorname{div}\left(V\, u^i - D_l \nabla u^i\right) d\Gamma = \int_{\partial\Omega^i} \left(V \cdot n_{\partial\Omega^i}\, u^i - D \frac{\partial u^i}{\partial n_{\partial\Omega^i}}\right) d\Gamma \\ &= \int_{\Gamma_0} \left(V \cdot n_{\partial\Omega^i}\, u^i - D \frac{\partial u^i}{\partial n_{\partial\Omega^i}}\right) d\Gamma + \int_{\Gamma_{-\infty}} \left(V \cdot n_{\partial\Omega^i}\, u^i - D \frac{\partial u^i}{\partial n_{\partial\Omega^i}}\right) d\Gamma, \end{aligned}$$

where $\Gamma_{-\infty}$ can be seen as the orthogonal cross section of the tube far away from Γ_0. Assume that

$$V \cdot n_{\partial\Omega^i} \geq 0 \text{ on } \Gamma_0, \quad V \cdot n_{\partial\Omega^i}|_{\Gamma_0} = -V \cdot n_{\partial\Omega^i}|_{\Gamma_{-\infty}}, \quad u^i|_{\Gamma_{-\infty}} = 0, \text{ and } \left.\frac{\partial u^i}{\partial n_{\partial\Omega^i}}\right|_{\Gamma_{-\infty}} = 0.$$

Then

$$\begin{aligned} 0 &= \int_{\Gamma_0} \left(V \cdot n_{\partial\Omega^i}\, u^i - D \frac{\partial u^i}{\partial n_{\partial\Omega^i}}\right) d\Gamma \\ &= \int_{\Gamma_{0w}} -D_w \frac{\partial u^i}{\partial n_{\partial\Omega^i}}\, d\Gamma + \int_{\Gamma_{0l}} \left(V \cdot n_{\partial\Omega^i}\, u^i - D_l \frac{\partial u^i}{\partial n_{\partial\Omega^i}}\right) d\Gamma, \end{aligned} \tag{1.4.4}$$

where $\Gamma_0 = \Gamma_{0w} \cup \Gamma_{0l}$ and Γ_{0w} and Γ_{0l} are the two parts of Γ_0. Finally, we strengthen this integral condition by turning it into a pointwise condition

$$\boxed{D_w \frac{\partial u^i}{\partial n_{\partial\Omega^i}} = 0 \text{ on } \Gamma_{0w}} \quad \text{and} \quad \boxed{V \cdot n_{\partial\Omega^i}\, u^i - D_l \frac{\partial u^i}{\partial n_{\partial\Omega^i}} = 0 \text{ on } \Gamma_{0l}.} \tag{1.4.5}$$

We have something similar on Ω^o; The boundary of the domain Ω^o is made up of three parts: Γ_L, Γ_∞, and Γ_{ext}^o, the lateral boundary of Ω^o. We get

$$0 = \int_{\Gamma_L} \left(V \cdot n_{\partial\Omega^o}\, u^o - D \frac{\partial u^o}{\partial n_{\partial\Omega^o}}\right) d\Gamma + \int_{\Gamma_\infty} \left(V \cdot n_{\partial\Omega^o}\, u^o - D \frac{\partial u^o}{\partial n_{\partial\Omega^o}}\right) d\Gamma, \tag{1.4.6}$$

where Γ_∞ can be seen as the orthogonal cross section of the tube far away from Γ_L. We assume that

$$\begin{gathered} V \cdot n_{\partial\Omega^o} \geq 0 \text{ on } \Gamma_L, \quad V \cdot n_{\partial\Omega^o}|_{\Gamma_L} = -V \cdot n_{\partial\Omega^o}|_{\Gamma_\infty}, \\ u^o|_{\Gamma_\infty} = u^o|_{\Gamma_L}, \text{ and } \left.\frac{\partial u^o}{\partial n_{\partial\Omega^o}}\right|_{\Gamma_\infty} = 0. \end{gathered}$$

[5] [10, page 316].

Then

$$0 = \int_{\Gamma_L} \left(V \cdot n_{\partial\Omega^L}\, u^0 - D \frac{\partial u^o}{\partial n_{\partial\Omega^o}} \right) d\Gamma = - \int_{\Gamma_{Lw}} D_w \frac{\partial u^o}{\partial n_{\partial\Omega^o}}\, d\Gamma - \int_{\Gamma_{Ll}} D_l \frac{\partial u^o}{\partial n_{\partial\Omega^o}}\, d\Gamma. \tag{1.4.7}$$

We also strengthen this integral condition by changing it into a pointwise condition

$$\boxed{D_w \frac{\partial u^o}{\partial n_{\partial\Omega^o}} = 0 \text{ on } \Gamma_{Lw}} \quad \text{and} \quad \boxed{0 = D_l \frac{\partial u^0}{\partial n_{\partial\Omega^0}} \text{ on } \Gamma_{Ll}.} \tag{1.4.8}$$

On the central section the boundary of the domain Ω is made up of three parts: Γ_L, Γ_0, and Γ_{ext}, the lateral boundary of Ω. Consider (1.4.1) on Ω

$$\begin{aligned} &0 = -\text{div } (D\nabla u) + V \cdot \nabla u + Ru \text{ in } \Omega, \\ &\frac{\partial c}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext}, \quad D_w \frac{\partial c}{\partial n_{\Omega_w}} + D_l \frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \partial\Omega_w \cap \partial\Omega_l. \end{aligned} \tag{1.4.9}$$

From the transmission conditions across Γ_0 and Γ_L, we get two sets of identities

$$\begin{aligned} 0 = D_w \frac{\partial u^i}{\partial n_{\partial\Omega^i}} &= -D_w \frac{\partial u}{\partial n_{\partial\Omega}} \text{ on } \Gamma_{0w} \\ 0 = V \cdot n_{\partial\Omega^i}\, u^i - D_l \frac{\partial u^i}{\partial n_{\partial\Omega^i}} &= -V \cdot n_{\partial\Omega}\, u + D_l \frac{\partial u}{\partial n_{\partial\Omega}} \text{ on } \Gamma_{0l}. \end{aligned}$$

and

$$\begin{aligned} 0 = D_w \frac{\partial u^o}{\partial n_{\partial\Omega^o}} &= -D_w \frac{\partial u}{\partial n_{\partial\Omega}} \text{ on } \Gamma_{Lw} \\ 0 = -D_l \frac{\partial u^o}{\partial n_{\partial\Omega^o}} &= D_l \frac{\partial u}{\partial n_{\partial\Omega}} \text{ on } \Gamma_{Ll}. \end{aligned}$$

This completes the set of boundary and interface conditions on Ω and the functions β_0 and β_L are given by the following expressions

$$\beta_0(x) = \begin{Bmatrix} -V \cdot n_{\partial\Omega}, & x \in \Gamma_{0l} \\ 0, & x \in \Gamma_{0w} \end{Bmatrix} \quad \text{and} \quad \beta_L = 0 \text{ on } \Gamma_L. \tag{1.4.10}$$

As a result $\beta_L(x) \geq 0$ on Γ_L and $\beta_0(x) \geq 0$ on Γ_0 if and only if

$$V \cdot n_{\partial\Omega} \leq 0 \text{ on } \Gamma_{0l} \tag{1.4.11}$$

which means that the flow of blood is coming into the segment Ω at its entry through Γ_0. Moreover, the conditions (1.3.18) are also verified

$$\begin{aligned} &\beta_0 + \frac{1}{2} V \cdot n = -V \cdot n_{\partial\Omega} + \frac{1}{2} V \cdot n_{\partial\Omega} = -\frac{1}{2} V \cdot n_{\partial\Omega} \geq 0 \text{ on } \Gamma_{0l} \\ &\beta_L + \frac{1}{2} V \cdot n = 0 \geq 0 \text{ on } \Gamma_L. \end{aligned} \tag{1.4.12}$$

If we further assume that

$$\exists \gamma_0 \subset \Gamma_0 \text{ of non-zero measure and } \exists \alpha > 0 \text{ such that } -V \cdot n \geq \alpha \text{ on } \gamma_0, \tag{1.4.13}$$

then a is coercive.

1.4.2. Related Transparency Conditions in Dimension One

The approach followed in the previous section is related to the one used in Chalifour and Delfour [**13**] to model the evolution of the concentration of larvicide in a targeted (finite) segment of river (typically 12km for the Amoutchou river in Togo, West Africa). In order to perform analysis and control over the segment, it was necessary to introduce *transparency conditions* at the two ends of the segment to isolate it from the whole river bassin. In view of the length of the segment, the river was considered to be one-dimensional and boundary conditions of the Robin type were introduced at both ends. In their analysis $\Omega = (0,L)$, and $R(x) \geq 0$, $D(x) \geq \alpha > 0$, and $V(x) \geq 0$ are functions defined on $[0,L]$. The constants β_0 and β_L are given by expressions that incorporate the loss term R

$$\beta_0 = \frac{1}{2}\left[\sqrt{V(0)^2 + 4R(0)\,D(0)} + V(0)\right], \tag{1.4.14}$$

$$\beta_L = \frac{1}{2}\left[\sqrt{V(L)^2 + 4R(L)\,D(L)} - V(L)\right]. \tag{1.4.15}$$

Our problem is similar but three-dimensional, and the one-dimensional analysis cannot be carried out without some additional hypotheses. Note that when $R = 0$, we get our transparency conditions.

1.5. Summary of the Assumptions, Existence Theorems, and Dose

Given the continuous bilinear form on $H^1(\Omega)$

$$a(u,v) = \int_\Omega D\nabla u \cdot \nabla v + V \cdot \nabla u\, v + R\, u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma, \tag{1.5.1}$$

where

$$\beta_0(x) = \begin{Bmatrix} -V \cdot n_{\partial\Omega}, & x \in \Gamma_{0l} \\ 0, & x \in \Gamma_{0w} \end{Bmatrix} \quad \text{and} \quad \beta_L = 0 \text{ on } \Gamma_L, \tag{1.5.2}$$

it is V-H coercive ($V = H^1(\Omega)$ and $H = L^2(\Omega)$) if

$$\begin{gathered} \min\{D_w, D_l\} > 0, \quad R_w \geq 0 \\ V \cdot n_{\partial\Omega} \leq 0 \text{ on } \Gamma_{0l}, \quad V \cdot n_{\partial\Omega} \geq 0 \text{ on } \Gamma_{Ll}, \end{gathered} \tag{1.5.3}$$

that is, the normal velocity of the flow is entering the lumen Ω_l through Γ_0 and exiting through Γ_L.

By [4, Thms. 1.1 and 1.2, pages 178-179] with the V-H coercivity of a, the weak parabolic equation on the time interval $[0,T]$

$$\begin{aligned} &\frac{d}{dt}\,(c(t), v)_{L^2(\Omega)} + a(c(t), v) = 0, \quad \forall v \in H^1(\Omega) \\ &c(0) = c_0 \in L^2(\Omega) \end{aligned} \tag{1.5.4}$$

has a unique solution in $W(0,T) = \{u \in L^2(0,T; H^1(\Omega) : u' \in L^2(0,T; H^1(\Omega)'\}$, where $L^2(\Omega)$ and its dual $L^2(\Omega)'$ have been identified.

To be more concrete this abstract equation corresponds to the partial differential equation system (1.3.12)

$$\begin{aligned} &\frac{\partial c(x,t)}{\partial t} - \text{div } (D(x)\nabla c(x,t)) + V(x) \cdot \nabla c(x,t) + R(x)c(x,t) = 0 \text{ in } \Omega, \\ &D\frac{\partial c(t)}{\partial n_\Omega} + \beta_0\, c(t) = 0 \text{ on } \Gamma_0,\ D\frac{\partial c(t)}{\partial n_\Omega} + \beta_L\, c(t) = 0 \text{ on } \Gamma_L,\ D\frac{\partial c(t)}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext}, \\ &D_w\frac{\partial c}{\partial n_{U_w}} + D_l\frac{\partial c}{\partial n_{U_l}} = 0 \text{ on } \Gamma_{lw},\ c(x,0) = c_0(x) \text{ in } \Omega, \end{aligned} \tag{1.5.5}$$

where R, V, and D are defined as in (1.3.4)

$$D(x) = \begin{cases} D_l, & x \in U_l \\ D_w, & x \in U_w \end{cases} \quad V(x) = \begin{cases} V_l(x), & x \in U_l \\ 0, & x \in U_w \end{cases} \quad R(x) = \begin{cases} 0, & x \in U_l \\ R, & x \in U_w. \end{cases} \tag{1.5.6}$$

Under the V-H coercivity assumption on a, the asymptotic concentration as T goes to infinity depends on the initial concentration and is not necessarily zero. Under the stronger coercivity assumption on a, the asymptotic concentration goes to zero as T goes to infinity regardless of the initial concentration. The bilinear form a is coercive if, for instance, in addition to assumptions (1.5.3),

$$\exists \gamma_0 \subset \Gamma_0 \text{ of non-zero measure and } \exists \alpha > 0 \text{ such that } -V \cdot n \geq \alpha \text{ on } \gamma_0. \tag{1.5.7}$$

Since the parabolic equation is linear, we can define the notion of *dose* in Ω

$$q(x) \stackrel{\text{def}}{=} \int_0^{+\infty} c(x,t)\, dt, \quad x \in \Omega, \tag{1.5.8}$$

as initially introduced in Chalifour-Delfour [**13**] for the *river blindness problem* and extended in Delfour-Garon-Longo [**31**] to the stenting problem. For the larvicide problem it was experimentally established that the dose is proportional to the rate of mortality of the black fly larvae. Imposing a minimum dose level at every point of the river guarantees that a targeted percentage of the larvae will be destroyed. It is not clear that such a rule would apply to the smooth muscle cells in the presence of a specific drug. Nonetheless, applying the dose to the time derivative of (1.5.5) gives

$$\int_0^{+\infty} \frac{\partial c}{\partial t}(x,t)\, dt = -c_0(x). \tag{1.5.9}$$

Since the hypothesis that a is coercive implies that $\lim_{t\to+\infty} c(t) = 0$. And if we assume that all the functions D, R and V are constant in the respective domains of the lumen and the wall, the equation of the dose is

$$\begin{aligned}
&-\text{div}\ (D\nabla q(x)) + V\cdot\nabla q(x) + R\, q(x) = c_0(x) \text{ in } \Omega,\\
&D\frac{\partial q}{\partial n_\Omega} + \beta_0\, q = 0 \text{ on } \Gamma_0,\ D\frac{\partial q}{\partial n_\Omega} + \beta_L\, q = 0 \text{ on } \Gamma_L,\ D\frac{\partial q}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext},\\
&D_w\frac{\partial q}{\partial n_{U_w}} + D_l\frac{\partial q}{\partial n_{U_l}} = 0 \text{ on } \Gamma_{lw}
\end{aligned} \tag{1.5.10}$$

or, in variational form,

$$\exists u \in H^1(\Omega),\ \forall v \in H^1(\Omega), \quad a(u,v) = \int_\Omega c_0\, v\, dx. \tag{1.5.11}$$

As can be readily seen, the coercivity of a is needed to get a unique solution.

Chapter 2

MODELING THE STENT AND ITS POLYMERIC COATING

2.1. Preliminaries

In Chapter 1, the segment of vessel Ω was divided between the domains occupied by the lumen Ω_l and the wall Ω_w. To prevent early restenosis due to the proliferation of smooth muscle cells a *drug eluding stent* (DES) will be inserted in the lumen. To do that a delivering catheter is inflated to expand and deploy the stent which maintains the opening. The balloon is then deflated and the catheter removed. Within a month, the stent becomes incorporated into the artery wall. So the stent is forced and maintained against the wall of the vessel. Since the stent is very thin, it will be assumed to have zero thickness and, as a consequence, will be a subset of the interface

$$\Gamma_{lw} \stackrel{\text{def}}{=} \Gamma_w \cap \Gamma_l = \overline{\Omega_w} \cap \overline{\Omega_l}. \tag{2.1.1}$$

Since the stent is forced and maintained against the wall, the polymeric coating will be assumed to be a thin layer on top of the stent within the original wall.

This type of model has been introduced by Delfour, Garon, and Longo [**31**] for a straight, cylindrical vessel where the polymer was assumed to be a material with linear diffusion characterised by a constant D_p. In this chapter we generalise this model to a curved vessel with the transparency conditions developed in Chapter 1. We also obtain equations for the *dose* and the *normalised concentration* , and discuss their limit as the thickness of the polymer goes to zero. A second model will also be introduced for a very thin polymer.

2.2. Modeling of the Stent and its Polymeric Coating

2.2.1. Specification of the Stent and the Polymeric Domain

We designate a subset, Σ, of the interface Γ_{lw} as the *target region* where the stent will be deployed against the wall. It is assumed to be far enough away from the boundaries Γ_0

and Γ_L so as not to interfere with the boundary conditions ($\Sigma \cap (\Gamma_0 \cup \Gamma_L) = \varnothing$). Within the target region Σ, we associate with a stent, $\Sigma_s \subset \Sigma$, the *characteristic function*:

$$\chi_{\Sigma_s}(x) = \begin{cases} 1, & \text{if } x \in \Sigma_s, \\ 0, & \text{else.} \end{cases} \tag{2.2.1}$$

While the characteristic function can be defined via the stent, conversely starting from a (measurable) characteristic function $\chi \in L^\infty(\Sigma)$ we can define the stent via

$$\Sigma_\chi \stackrel{\text{def}}{=} \{x \in \Sigma |\, \chi(x) = 1\}. \tag{2.2.2}$$

This method was developed in [31, sec. 5.3] for arbitrary stents[1] and later used by Bourgeois and Delfour [8] to study the limit behaviour of the concentration and the dose as the scale of the pattern of the stent gets asymptotically smaller. This is the so-called *asymptotic stent* which depends on the ratio between the surface occupied by the stent and the surface of the target region. Its advantage is to be able to specify any pattern with a single function. Due to this, we will use the notation Σ_χ for the stent.

Both sides of the stent can be coated with drug-infused polymer. However, for our purposes we assume that the coating is only on the *upper* side.[2] We denote by h the (uniform) thickness of the polymer on the upper side. We then partition the domain Ω_w into the domain occupied by the polymer and the reduced domain occupied by the wall (see Figures 2.1 and 2.2)

$$\Omega_p^h \stackrel{\text{def}}{=} \{x \in \Omega_w \,:\, p_\Sigma(x) \in \Sigma_s \text{ and } r < d_C(x) < r + h\}, \tag{2.2.3}$$

$$\Omega_w^h \stackrel{\text{def}}{=} \Omega_w \backslash \Omega_p^h, \tag{2.2.4}$$

where it is assumed that the projection $p_\Sigma(x)$ of the point x onto Σ is a singleton. The notation emphasises the dependence on h. This creates the new interface

$$\Gamma_{pw}^h \stackrel{\text{def}}{=} \overline{\Omega_p^h} \cap \overline{\Omega_w^h} \text{ between the wall and the polymer} \tag{2.2.5}$$

while the former interface Γ_{lw} between the lumen and the wall is now made of two pieces:

$$\begin{aligned} &\Gamma_{lp} \stackrel{\text{def}}{=} \Sigma_\chi \text{ specified by the stent} \\ &\Gamma_{lw}^h \stackrel{\text{def}}{=} \overline{\Omega}_l \cap \overline{\Omega_w^h} \text{ between the lumen and the wall.} \end{aligned} \tag{2.2.6}$$

[1] Even if the heading of the section was "Extension to general periodic stents", it didn't require the periodicity.
[2] That is, the side adjacent to the wall Ω_w.

It is important to distinguish between the two since at the interface Γ_{lw}^h we will have a transmission condition of the form

$$D_w \frac{\partial c}{\partial n_{\Omega_w}} + D_l \frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw}^h, \tag{2.2.7}$$

and the continuity of the concentration c across that interface, while at the interface $\Gamma_{lp} = \Sigma_\chi$ the stent will be a barrier between Ω_p and Ω_l. Given a diffusion constant $D_p > 0$ in Ω_p^h, the boundary conditions on each side of Γ_{lp} will be

$$D_p \frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ and } D_l \frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lp} = \Sigma_\chi \tag{2.2.8}$$

and the concentration will be discontinuous across the interface created by the stent.

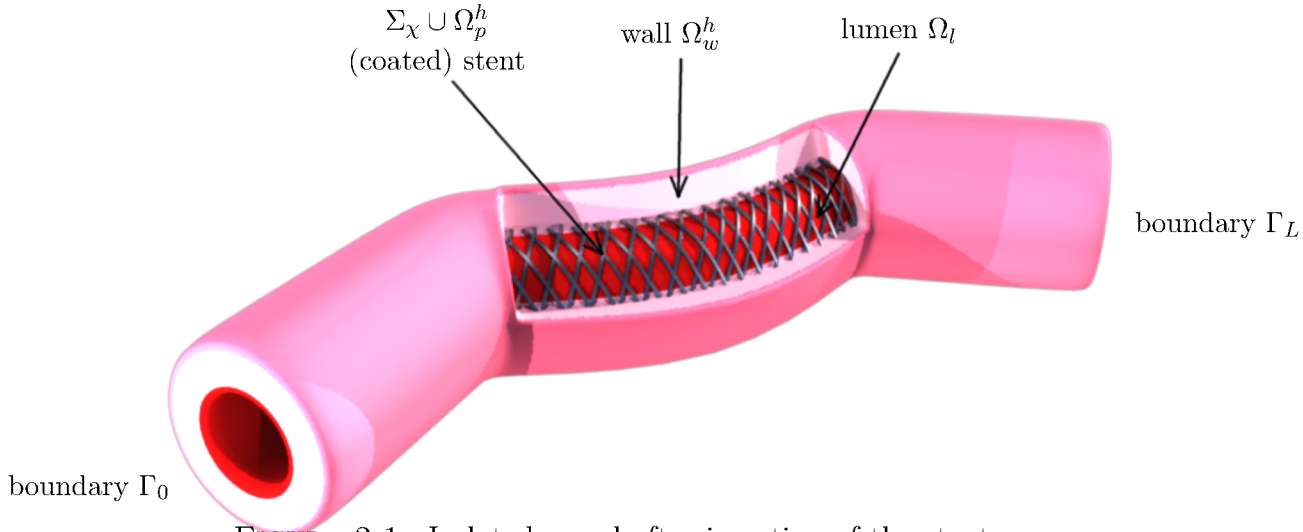

FIGURE 2.1. Isolated vessel after insertion of the stent.

2.2.2. New Equations for the Concentration for a Polymer of Thickness h

We will now add the stent, the associated polymeric domain, and the associated boundary conditions to the partial differential equation model (1.5.5) in the segment of vessel Ω.

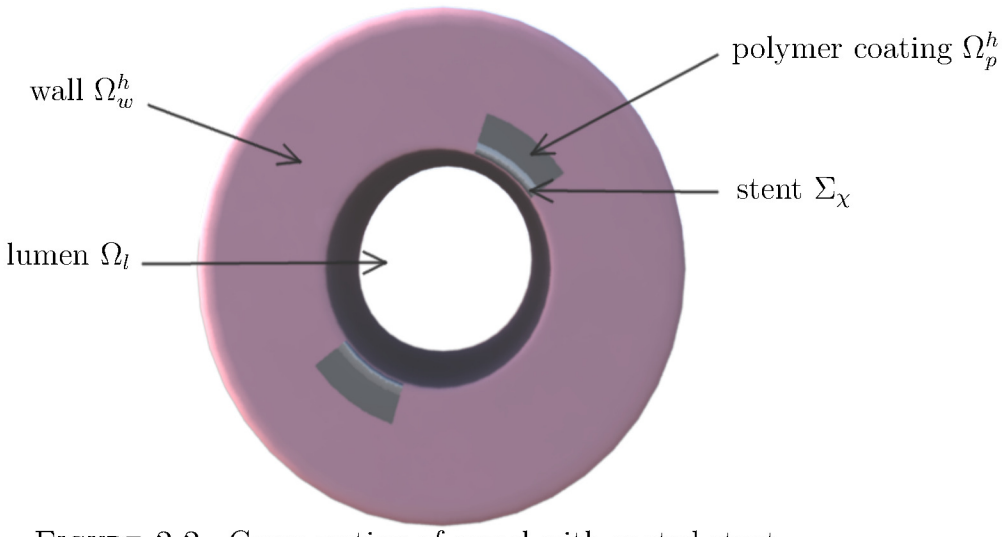

FIGURE 2.2. Cross section of vessel with coated stent.

We redefine the functions R, V, and D to include Ω_p^h

$$D(x) = \begin{cases} D_l, & x \in \Omega_l \\ D_w, & x \in \Omega_w^h \\ D_p, & x \in \Omega_p^h \end{cases} \quad V(x) = \begin{cases} V_l(x), & x \in \Omega_l \\ 0, & x \in \Omega_w^h \\ 0, & x \in \Omega_p^h \end{cases} \quad R(x) = \begin{cases} 0, & x \in \Omega_l \\ R_w, & x \in \Omega_w^h \\ R_p, & x \in \Omega_p^h, \end{cases} \tag{2.2.9}$$

where we can distinguish between the rate of loss $R_w \geq 0$ in the wall and the rate $R_p \geq 0$ in the polymer.

The new boundary/interface conditions are

$$\begin{aligned} &D\frac{\partial c}{\partial n_\Omega} + \beta_0\, c = 0 \text{ on } \Gamma_0,\ D\frac{\partial c}{\partial n_\Omega} + \beta_L\, c = 0 \text{ on } \Gamma_L,\ D\frac{\partial c}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext}, \\ &D_w\frac{\partial c}{\partial n_{\Omega_w^h}} + D_l\frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw}^h \text{ (at the interface lumen/wall)} \\ &D_w\frac{\partial c}{\partial n_{\Omega_w^h}} + D_p\frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{pw} \text{ (at the interface polymer/wall)} \\ &D_p\frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{lp} \quad D_l\frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lp} \text{ (at the interface lumen/polymer).} \end{aligned} \tag{2.2.10}$$

The equations for the concentration are then readily extended from the previous section in each subdomain

$$\begin{aligned} &\frac{\partial c}{\partial t} - \text{div } (D_w \nabla c) + R_w\, c = 0 \text{ in } \Omega_w^h, \\ &\frac{\partial c}{\partial t} - \text{div } (D_l \nabla c) + V_l \cdot \nabla c = 0 \text{ in } \Omega_l, \\ &\frac{\partial c}{\partial t} - \text{div } (D_p \nabla c) + R_p\, c = 0 \text{ in } \Omega_p^h. \end{aligned} \tag{2.2.11}$$

As in Chapter 1 we now construct the bilinear form a, but there is an important change. The presence of the stent creates a barrier or a *crack(s)* within the domain Ω. This means that the new domain is

$$\Omega_\chi \stackrel{\text{def}}{=} \Omega \backslash \Sigma_\chi = \{x \in \Omega : x \notin \Sigma_\chi\}. \tag{2.2.12}$$

We can also use the notation $\Omega(\chi)$. It is not Lipschitzian anymore, but the geodesic distance between two points in Ω_χ is still bounded by a constant times the distance between those two points and the norm in $H^1(\Omega_\chi)$ is equivalent to the norm

$$\left[\|\nabla u\|^2_{L^2(\Omega_\chi)} + \|u\|^2_{L^2_{\gamma_0}}\right]^{1/2} \qquad \text{for } \varnothing \neq \gamma_0 \subset \Gamma_0$$

where γ_0 has strictly positive two-dimensional Hausdorff measure.

Define the following bilinear form on $H^1(\Omega_\chi)$

$$\begin{aligned} a(u,v) \stackrel{\text{def}}{=} & \int_{\Omega_l} -\text{div}\ (D_l \nabla u)\ v + V_l \cdot \nabla u\, v\, dx \\ & + \int_{\Omega^h_w} -\text{div}\ (D_w \nabla u)\ v + R_w\, u\, v\, dx + \int_{\Omega^h_p} -\text{div}\ (D_p \nabla u)\ v + R_p\, u\, v\, dx. \end{aligned} \tag{2.2.13}$$

Since the interface conditions are symmetric with respect to the normals, upon integration by parts we get the same expression as in Chapter 1 but with Ω_χ in place of Ω

$$\begin{aligned} a(u,v) &= \int_{\Omega_\chi} D\nabla u \cdot \nabla v + V \cdot \nabla u\, v + R\, u\, v\, dx - \int_{\Gamma_0} D \frac{\partial u}{\partial n_{\Omega_\chi}}\, v\, d\Gamma - \int_{\Gamma_L} D \frac{\partial u}{\partial n_{\Omega_\chi}}\, v\, d\Gamma \\ &= \int_{\Omega_\chi} D\nabla u \cdot \nabla v + V \cdot \nabla u\, v + R\, u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma, \end{aligned} \tag{2.2.14}$$

where R, V, and D are defined as in (2.2.9). Again, this is a continuous bilinear form on $H^1(\Omega_\chi)$ with a non-symmetric term $V \cdot \nabla u\, v$. It can be decomposed as the sum of two bilinear forms

$$\begin{aligned} a_0(u,v) &= \int_{\Omega_\chi} D\nabla u \cdot \nabla v + R\, u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma \\ b(u,v) &= \int_{\Omega_\chi} V \cdot \nabla u\, v\, dx. \end{aligned} \tag{2.2.15}$$

As in Chapter 1 the concentration is solution of the equation

$$\begin{aligned}
&\frac{\partial c(x,t)}{\partial t} - \text{div } (D(x)\nabla c(x,t)) + V(x)\cdot\nabla c(x,t) + R(x)c(x,t) = 0 \text{ in } \Omega_\chi,\\
&D\frac{\partial c(t)}{\partial n_{\Omega_\chi}} + \beta_0\, c(t) = 0 \text{ on } \Gamma_0,\ D\frac{\partial c(t)}{\partial n_{\Omega_\chi}} + \beta_L\, c(t) = 0 \text{ on } \Gamma_L,\ D\frac{\partial c(t)}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext},\\
&c(x,0) = c_0(x) \text{ in } \Omega_\chi,
\end{aligned} \tag{2.2.16}$$

with the boundary interface/conditions (2.2.10). Assuming that

$$\boxed{\beta_0 \geq 0 \text{ on } \Gamma_0 \quad \text{and} \quad \beta_L \geq 0 \text{ on } \Gamma_L,} \tag{2.2.17}$$

a_0 generates a V-H coercive operator A_0 with $V = H^1(\Omega_\chi)$ and $H = L^2(\Omega_\chi)$. The bilinear form b generates a continuous linear operator $B : V \to H$. So the operator A generated by a is the sum $A_0 + B$. By [4, Thms. 1.1 and 1.2, pages 178-179] the sum $A = A_0 + B$ is V-H coercive and the weak parabolic equation on the time interval $[0,T]$

$$\begin{aligned}
&\frac{d}{dt}\,(c(t),v)_{L^2(\Omega_\chi)} + a(c(t),v) = 0, \quad \forall v \in H^1(\Omega_\chi)\\
&c(0) = c_0 \in L^2(\Omega_\chi)
\end{aligned} \tag{2.2.18}$$

has a unique solution in $W(0,T) = \{u \in L^2\,(0,T; H^1(\Omega_\chi)) : u' \in L^2\,(0,T; H^1(\Omega_\chi)')\}$, where $L^2(\Omega_\chi)$ and its dual $L^2(\Omega_\chi)'$ have been identified.

2.2.3. Equations for the Normalised Concentration

We assume that the initial mass of product, M_0, is uniformly distributed within our polymer. Thus

$$c_0^h(x) = \begin{cases} \dfrac{M_0}{\left|\Omega_p^h\right|} \stackrel{\text{def}}{=} c_0^h, & x \in \Omega_p^h \\ 0, & \text{else.} \end{cases} \tag{2.2.19}$$

We then define the *normalised concentration*

$$\hat{c}^h(x,t) \stackrel{\text{def}}{=} \frac{c^h(x,t)}{c_0^h}, \tag{2.2.20}$$

where the concentrations $c(x,t) = c^h(x,t)$, c_0^h, and $\hat{c}^h(x,t)$ all depend on h. But now $\hat{c}^h(x,t)$ is a number between 0 and 1 ,which makes it possible to study its behaviour as h goes to zero. For simplicity of the notation, the superscript h will be dropped.

Since the equations in (2.2.16) are all linear, we obtain a system of equations for the normalised concentration by substituting $\hat{c}$ for c and altering the initial condition

$$\begin{aligned}
&\frac{\partial \hat{c}(x,t)}{\partial t} - \text{div } (D(x)\nabla \hat{c}(x,t)) + V(x)\cdot\nabla\hat{c}(x,t) + R(x)\hat{c}(x,t) = 0 \text{ in } \Omega_\chi,\\
&\hat{c}(x,0) = \begin{cases} 1, & x \in \Omega_p^h,\\ 0, & \text{else,}\end{cases}
\end{aligned} \tag{2.2.21}$$

with boundary and interface conditions

$$\begin{aligned}
&D\frac{\partial \hat{c}}{\partial n_\Omega} + \beta_0\,\hat{c} = 0 \text{ on } \Gamma_0,\ D\frac{\partial \hat{c}}{\partial n_\Omega} + \beta_L\,\hat{c} = 0 \text{ on } \Gamma_L,\ D\frac{\partial \hat{c}}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext},\\
&D_w\frac{\partial \hat{c}}{\partial n_{\Omega_w^h}} + D_l\frac{\partial \hat{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw}^h \text{ (at the interface lumen/wall)}\\
&D_w\frac{\partial \hat{c}}{\partial n_{\Omega_w^h}} + D_p\frac{\partial \hat{c}}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{pw} \text{ (at the interface polymer/wall)}\\
&D_p\frac{\partial \hat{c}}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{lp} \quad D_l\frac{\partial \hat{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lp} \text{ (at the interface lumen/polymer).}
\end{aligned} \tag{2.2.22}$$

The next step is to see if the normalised concentration can be related to the normalised mass of product in the polymer. The *mass of product* $M_p(t)$ and the *normalised mass of product* $m_p(t)$ in the polymer at time t are defined as follows

$$M_p(t) \overset{\text{def}}{=} \int_{\Omega_p^h} c(x,t)\,dx, \quad m_p(t) \overset{\text{def}}{=} \frac{M_p(t)}{M_0}. \tag{2.2.23}$$

$m_p(t)$ is then related to $\hat{c}(x,t)$ by

$$m_p(t) = \frac{1}{M_0}\int_{\Omega_p^h} c(x,t)\,dx = \frac{1}{\left|\Omega_p^h\right|}\int_{\Omega_p^h} \hat{c}(x,t)\,dx \tag{2.2.24}$$

$$\implies \frac{dm_p(t)}{dt} = \frac{1}{\left|\Omega_p^h\right|}\int_{\Omega_p^h} \frac{\partial \hat{c}(x,t)}{\partial t}\,dx. \tag{2.2.25}$$

We then combine this equation with (2.2.21) reduced to the subdomain Ω_p^h to obtain a system of equations for $m_p(t)$

$$\frac{dm_p}{dt} - \frac{1}{\left|\Omega_p^h\right|}\int_{\Omega_p^h} \text{div}\,(D_p\nabla\hat{c})\,dx + \frac{1}{\left|\Omega_p^h\right|}\int_{\Omega_p^h} R_p\,\hat{c}\,dx = 0. \tag{2.2.26}$$

Applying the divergence theorem somewhat simplifies the equations

$$\begin{aligned} &\frac{dm_p}{dt} - \frac{D_p}{\left|\Omega_p^h\right|}\int_{\partial\Omega_p^h}\frac{\partial\hat{c}}{\partial n_p}\,d\Gamma + \frac{R_p}{\left|\Omega_p^h\right|}\int_{\Omega_p^h}\hat{c}\,dx = 0, \\ \implies &\frac{dm_p}{dt} - \frac{D_p}{\left|\Omega_p^h\right|}\int_{\Gamma_{pw}}\frac{\partial\hat{c}}{\partial n_p}\,d\Gamma + R_p\,m_p = 0. \end{aligned} \tag{2.2.27}$$

For this first model, this is as far as we are able to push the equations. Contrary to future models, we are not able to obtain an ODE for the normalised mass in the polymer $m_p(t)$ as h goes to zero.

2.2.4. Equations for the Dose

When $c(t)$ goes to zero as t goes to infinity, it is possible to introduce the notion of dose

$$q(x) \overset{\text{def}}{=} \int_0^\infty c(x,t)\,dt, \quad x \in \Omega_\chi, \tag{2.2.28}$$

as in [13] and [31]. Since all of the equations are linear in terms of the concentration, we obtain the following equations for the dose

$$\begin{aligned} &-\text{div}\,(D(x)\nabla q(x)) + V(x)\cdot\nabla q(x) + R(x)\,q(x) = c_0(x) \text{ in } \Omega_\chi, \\ &D\frac{\partial q}{\partial n_{\Omega_\chi}} + \beta_0\,q = 0 \text{ on } \Gamma_0,\ D\frac{\partial q}{\partial n_{\Omega_\chi}} + \beta_L\,q = 0 \text{ on } \Gamma_L,\ D\frac{\partial q}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}, \end{aligned} \tag{2.2.29}$$

or in terms of the bilinear form

$$\exists q \in H^1(\Omega_\chi),\ \forall v \in H^1(\Omega_\chi), \quad a(q,v) = \ell(v), \quad \ell(v) \overset{\text{def}}{=} \int_{\Omega_p^h} c_0\,v\,dx, \tag{2.2.30}$$

As before, we assume that the initial mass of product, M_0, is evenly distributed within the polymer. Therefore, our linear function ℓ depends on h and we emphasize this dependence by adding the subscript h to ℓ

$$c_0(x) = c_0^h(x) = \begin{cases} \dfrac{M_0}{|\Omega_p^h|} \text{ in } \Omega_p^h \\ 0 \text{ in } \Omega_\chi \setminus \Omega_p^h \end{cases} \quad \Rightarrow\ \ell_h(v) \overset{\text{def}}{=} \int_{\Omega_p^h}\frac{M_0}{|\Omega_p^h|}\,v\,dx, \tag{2.2.31}$$

where $|\Omega_p^h|$ is the volume of Ω_p^h. Recalling that everything depends on h, one should really write

$$\exists q_h \in H^1(\Omega_\chi),\ \forall v \in H^1(\Omega_\chi), \quad a_h(q_h,v) = \ell_h(v), \quad \ell_h(v) \overset{\text{def}}{=} \int_{\Omega_p^h}\frac{M_0}{|\Omega_p^h|}\,v\,dx, \tag{2.2.32}$$

$$a_h(u,v) = \int_{\Omega_w^h} D_w \nabla u \cdot \nabla v + R_w\, u\, v\, dx + \int_{\Omega_p^h} D_p \nabla u \cdot \nabla v + R_p\, u\, v\, dx \\ + \int_{\Omega_l} D_l \nabla u \cdot \nabla v + V_l \cdot \nabla u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma. \tag{2.2.33}$$

It is possible to study the behaviour of q_h as h goes to zero. But the target area is a piece of curved cylinder and so we need some general results to get the asymptotic equations that were obtained for a straight piece of cylinder in [31].

2.2.5. Local Coordinate System on Σ and Oriented Distance Function to Ω_l

Remark 2.2.1. *Unless otherwise stated, the definitions and results from this section can be found in* [29]. *More details can also be found in* [32].

The volume of the domain Ω_p^h can be computed exactly by assuming that Ω_l is of *class* $C^{1,1}$ in a neighbourhood of Σ [3] via the *oriented distance function* b_{Ω_l} to Ω_l,

$$b_{\Omega_l}(x) \stackrel{\text{def}}{=} d_{\Omega_l}(x) - d_{\mathbb{R}^3 \setminus \Omega_l}(x), \tag{2.2.34}$$

where $d_A(x)$ is the distance from x to a set A

$$d_A(x) \stackrel{\text{def}}{=} \inf_{a \in A} |x - a|. \tag{2.2.35}$$

The set Ω_l is $C^{1,1}$ at a point $x \in \partial\Omega_l$ if and only if there exists $k > 0$ such that $b_{\Omega_l} \in C^{1,1}(\overline{B_k(x)})$. To be on the safe side assume that $b_{\Omega_l} \in C^{1,1}(\overline{B_{2h}(x)})$ at each $x \in \Sigma$. The *tubular neighbourhood* of Σ is

$$U_{2h}(\Sigma) \stackrel{\text{def}}{=} \left\{ x \in \mathbb{R}^3 : p_{\partial\Omega_l}(x) \in \Sigma \text{ and } |b_{\Omega_l}(x)| < 2h \right\}, \tag{2.2.36}$$

Recall that the target region $\Sigma \subset \partial\Omega_l$ is far from Γ_0 and Γ_L. If we further assume that

$$\Sigma \subset \left\{ x \in \partial\Omega_l : d_{\Gamma_0}(x) > 2h \text{ and } d_{\Gamma_L}(x) > 2h \right\}, \tag{2.2.37}$$

there is a natural change of variables that will be defined via the bijection $T_z(x)$ below. This condition makes $U_{2h}(\Sigma)$ a "hollow tube" rather than a "sausage" with hemispheric ends. At $X \in \Sigma$, the vector $\nabla b_{\Omega_l}(X)$ is the *outward unit normal* to Ω_l and the matrix $D^2 b_{\Omega_l}(X)$ is the *curvature matrix* of $\partial\Omega_l$. Since $D^2 b_{\Omega_l}(X) \nabla b_{\Omega_l}(X) = 0$, 0 is an eigenvalue and $\det D^2 b_{\Omega_l}(X) = 0$. The other eigenvalues are the *principal curvatures*[4] of $\partial\Omega_l$ at X.

[3] Intuitively, a domain is said to be of class $C^{1,1}$ if its boundary can be mapped into a subset of $\mathbb{R}^m$ for some $m \in \mathbb{N}$ by a C^1, Lipschitzian function. See [32, chapter 2] for more details on $C^{1,1}$ domains as well as rigorous definitions.

[4] See [5, section 10.6] for more details on curvatures.

Since $b_{\Omega_l} \in C^{1,1}(\overline{B_{2h}(x)})$, the projection of each point of $B_{2h}(x)$ onto $\partial\Omega_l$ is unique. Consider the following region

$$U_h^+(\Sigma) \stackrel{\text{def}}{=} \Big\{ x \in \mathbb{R}^3 : p_{\partial\Omega_l}(x) \in \Sigma \text{ and } 0 < b_{\Omega_l}(x) < h \Big\} \tag{2.2.38}$$

that contains the polymer and part of the wall near Σ. The following bi-Lipschitzian bijection is well-defined

$$x \mapsto T(x) \stackrel{\text{def}}{=} (p_{\partial\Omega_l}(x), b_{\Omega_l}(x)) : U_h^+(\Sigma) \to \Sigma \times (0,h) \tag{2.2.39}$$

$$(X,z) \mapsto T^{-1}(X,z) = X + z\,\nabla b_{\Omega_l}(X) : \Sigma \times (0,h) \to U_h^+(\Sigma). \tag{2.2.40}$$

This bijection makes it possible to express a function in Euclidean coordinates $x \in U_h^+(\Sigma) \subset \mathbb{R}^3$ or in local coordinates $(X,z) \in \Sigma \times (0,h)$. We introduce the convenient notation $X \to T_z(X) \stackrel{\text{def}}{=} T^{-1}(X,z) = X + z\,\nabla b_{\Omega_l}(X)$. The change of variable formula for a function $f : U_h^+(\Sigma) \to \mathbb{R}$ is given by Federer's formula[5]

$$\begin{aligned} \int_{U_h^+(\Sigma)} f(x)\,dx &= \int_0^h \int_\Sigma f(T_z(X)) \det D_X T_z(X)\,dX\,dz \\ &= \int_\Sigma \left[\int_0^h f(T_z(X)) \det D_X T_z(X)\,dz \right] dX, \end{aligned} \tag{2.2.41}$$

where the Jacobian matrix is

$$D_X T_z(X) = I + z\,D^2 b_{\Omega_l}(X), \quad X \in \Sigma. \tag{2.2.42}$$

Here $D_X T_z$ denotes the Jacobian matrix of the mapping $X \mapsto T_z(X) = X + z\,\nabla b_{\Omega_l}(X)$. For small z its determinant is strictly positive since $|\nabla b_{\Omega_l}(X)| = 1$. For instance, for the volume with $f = 1$

$$\int_{U_h^+(\Sigma)} dx = \int_\Sigma \int_0^h \det D_X T_z(X)\,dz\,dX. \tag{2.2.43}$$

In dimension 3, denote by $\kappa_1(X)$ and $\kappa_2(X)$ the two principal curvatures of $\partial\Omega_l$ at $X \in \Sigma$. Then, for each $(X,z) \in \Sigma \times (0,h)$,

$$\det D_X T_z(X) = \det\left[I + z\,D^2 b_{\Omega_l}(X)\right] = 1 + z\,H(X) + z^2\,K(X), \tag{2.2.44}$$

[5]The original can be found in [38, page 243]. An alternate version, which is closer to the one used here, can be found in [29, page 90].

where $H = \kappa_1 + \kappa_2 = \Delta b_{\Omega_l}$ is the *mean curvature* (of mathematicians)[6] and $K = \kappa_1\,\kappa_2$ is the *Gauss curvature*. Coming back to the volume integral

$$\int_{U_h^+(\Sigma)} dx = \int_\Sigma \int_0^h 1 + z\,H + z^2\,K\,dz\,dX = \int_\Sigma h + \frac{h^2}{2}\,H + \frac{h^3}{3}\,K\,dX. \tag{2.2.45}$$

As for the domain occupied by the polymer

$$\int_{\Omega_p^h} dx = \int_{U_h^+(\Sigma)} \chi \circ p_{\partial\Omega_l}\,dx = \int_\Sigma \int_0^h (\chi \circ p_{\partial\Omega_l}) \circ T_z\,(1 + z\,H + z^2\,K)\,dz\,dX. \tag{2.2.46}$$

But $\chi \circ p_{\partial\Omega_l} \circ T_z = \chi$ and the expression simplifies

$$\begin{aligned}\int_{\Omega_p^h} dx = \int_{U_h^+(\Sigma)} \chi \circ p_{\partial\Omega_l}\,dx &= \int_\Sigma \chi \int_0^h 1 + z\,H + z^2\,K\,dz\,dX \\ &= \int_{\Sigma_\chi} h + \frac{h^2}{2}\,H + \frac{h^3}{3}\,K\,dX.\end{aligned} \tag{2.2.47}$$

In particular, the initial concentration in Ω_p^h is given by the expression

$$c_0^h(x) = \begin{cases} \dfrac{M_0}{\int_{\Sigma_\chi} h + \frac{h^2}{2}\,H + \frac{h^3}{3}\,K\,d\Sigma}, & \text{in } \Omega_p^h, \\ 0, & \text{elsewhere.}\end{cases} \tag{2.2.48}$$

So, as the thickness h goes to zero, the initial concentration will explode making the asymptotic analysis difficult.

2.2.6. Back to the Asymptotic Dose

Going back to the system (2.2.32)-(2.2.33) for the dose with a polymer of thickness h

$$\exists q_h \in H^1(\Omega_\chi),\ \forall v \in H^1(\Omega_\chi), \quad a_h(q_h,v) = \ell_h(v), \quad \ell_h(v) \stackrel{\text{def}}{=} \int_{\Omega_p^h} \frac{M_0}{|\Omega_p^h|}\,v\,dx, \tag{2.2.49}$$

$$\begin{aligned}a_h(u,v) = &\int_{\Omega_w^h} D_w \nabla u \cdot \nabla v + R_w\,u\,v\,dx + \int_{\Omega_p^h} D_p \nabla u \cdot \nabla v + R_p\,u\,v\,dx \\ &+ \int_{\Omega_l} D_l \nabla u \cdot \nabla v + V_l \cdot \nabla u\,v\,dx + \int_{\Gamma_0} \beta_0\,u\,v\,d\Gamma + \int_{\Gamma_L} \beta_L\,u\,v\,d\Gamma.\end{aligned} \tag{2.2.50}$$

[6] In Physics and Engineering mean curvature means $(\kappa_1 + \kappa_2)/2$; See [5, section 10.6] for more details on the subject of curvatures.

Since as $h \to 0$ we have that $\Omega_p^h \to \Sigma_\chi$, a set of zero measure in $\mathbb{R}^3$, it is readily seen that for all $u,v \in H^1(\Omega_\chi)$

$$a_h(u,v) \to a(u,v) = \int_{\Omega_w} D_w \nabla u \cdot \nabla v + R_w\, u\, v\, dx \\ + \int_{\Omega_l} D_l \nabla u \cdot \nabla v + V_l \cdot \nabla u\, v\, dx + \int_{\Gamma_0} \beta_0\, u\, v\, d\Gamma + \int_{\Gamma_L} \beta_L\, u\, v\, d\Gamma.$$

The bilinear form a_h is coercive with a coercivity constant independent of h

$$a_h(u,u) \geq \min\{D_w, D_p, D_l\}\, \|\nabla u\|^2_{L^2(0,1)} + \|u\|^2_{L^2_{\gamma_0}}$$

under assumptions (1.5.3) plus

$$\exists \gamma_0 \subset \Gamma_0 \text{ of non-zero measure and } \exists \alpha > 0 \text{ such that } -V \cdot n \geq \alpha \text{ on } \gamma_0. \tag{2.2.51}$$

So there is an $\alpha > 0$ such that

$$\boxed{a_h(u,u) \geq \alpha\, \|u\|^2_{H^1(\Omega_\chi)}.} \tag{2.2.52}$$

As for the linear form

$$\ell_h(v) = \int_{\Omega_p^h} \frac{M_0}{|\Omega_p^h|}\, v\, dx = \frac{M_0}{\int_{\Sigma_\chi} 1 + \frac{h}{2} H + \frac{h^2}{3} K\, dX} \frac{1}{h} \int_{\Omega_p^h} v\, dx.$$

The first term is bounded by a constant independent of h as h goes to zero since

$$\left| \frac{M_0}{\int_{\Sigma_\chi} 1 + \frac{h}{2} H + \frac{h^2}{3} K\, dX} \right| \leq \frac{M_0}{|\Sigma_\chi| - \frac{h}{2} \int_{\Sigma_\chi} |H|\, dX - \frac{h^2}{3} \int_{\Sigma_\chi} |K|\, dX}.$$

So, there exists $\bar{h}$ and C such that for all $0 < h \leq \bar{h}$

$$\left| \frac{M_0}{\int_{\Sigma_\chi} 1 + \frac{h}{2} H + \frac{h^2}{3} K\, dX} \right| \leq C.$$

As for the second term we use the change of variable formula (2.2.41)

$$\frac{1}{h} \int_{\Omega_p^h} v\, dx = \int_\Sigma \chi \left[\frac{1}{h} \int_0^h v \circ T_z\,(X)(1 + z\, H + z^2\, K)\, dz \right] dX \to \int_\Sigma \chi\, v\, dX = \int_{\Sigma_\chi} v\, dX,$$

$$\exists c,\, \forall v \in H^1(\Omega_\chi), \quad \left| \int_{\Sigma_\chi} v\, dX \right| \leq \int_\Sigma |v|\, dX \leq c\, \|v\|_{H^1(\Omega_\chi)}. \tag{2.2.53}$$

The convergence of the integral is not entirely trivial; for each fixed $X \in \Sigma$ consider the functions $f(h)$ and $g(h)$ defined by

$$f(h) \stackrel{\text{def}}{=} h, \quad g(h) \stackrel{\text{def}}{=} \int_0^h v \circ T_z\,(X)(1 + z\, H + z^2\, K)\, dz.$$

We are thus interested in the limit

$$\lim_{h\to 0}\frac{g(h)}{f(h)}=\lim_{h\to 0}\underbrace{\frac{1}{h}}_{\frac{1}{f(h)}}\underbrace{\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz}_{g(h)}\,. \tag{2.2.54}$$

Applying L'Hôpital's rule[7], we have

$$\lim_{h\to 0}\frac{g(h)}{f(h)}=\lim_{h\to 0}\frac{g'(h)}{f'(h)}=\lim_{h\to 0}\frac{\partial}{\partial h}\left(\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz\right).$$

Leibniz's integral rule[8] implies that

$$\frac{\partial}{\partial h}\left(\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz\right)=v\circ T_h\,(X)\left(1+h\,H+h^2\,K\right).$$

And so returning to (2.2.54) we have that

$$\begin{aligned}\lim_{h\to 0}\frac{1}{h}\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz&=\lim_{h\to 0}v\circ T_h\,(X)\left(1+h\,H+h^2\,K\right)\\&=v\circ T_0\,(X).\end{aligned}$$

But $T_z(X)=X+z\,\nabla b_{\Omega_l}(X)$, which implies that $T_0(X)=X$ and $T_0=i$, the identity function on Σ. Thus $\lim_{h\to 0}\frac{1}{h}\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz=v(X)$. Moreover, since the domain Σ_χ and the characteristic function χ are independent of h, we have

$$\begin{aligned}&\lim_{h\to 0}\int_\Sigma\chi\left[\frac{1}{h}\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz\right]dX\\&=\int_\Sigma\chi\left[\lim_{h\to 0}\frac{1}{h}\int_0^h v\circ T_z\,(X)(1+z\,H+z^2\,K)\,dz\right]dX=\int_\Sigma\chi\,v\,dX=\int_{\Sigma_\chi}v\,dX.\end{aligned}$$

So, there exists $\bar h$ and C' such that for all $0<h\le\bar h$

$$\left|\frac{1}{h}\int_{\Omega_p^h}v\,dx\right|\le C'\,\|v\|_{H^1(\Omega_\chi)}\quad\Rightarrow\ \boxed{\forall v\in H^1(\Omega_\chi),\quad|\ell_h(v)|\le c\,C'\,\|v\|_{H^1(\Omega_\chi)}} \tag{2.2.55}$$

$$\boxed{\ell_h(v)\to\ell_0(v)\stackrel{\text{def}}{=}\frac{M_0}{|\Sigma_\chi|}\int_{\Sigma_\chi}v\,dx.} \tag{2.2.56}$$

We are now ready to study the limit of q_h as h goes to zero: from (2.2.32)

$$\exists q_h\in H^1(\Omega_\chi),\ \forall v\in H^1(\Omega_\chi),\quad a_h(q_h,v)=\ell_h(v)\quad\Rightarrow\ a_h(q_h,q_h)=\ell_h(q_h),$$

[7] See, for instance, [**90**, page 35].
[8] See, for instance, [**40**, page 615].

by substituting $v = q_h \in H^1(\Omega_\chi)$. By using the bounds in (2.2.52) and (2.2.55)

$$\alpha \, \|q_h\|^2_{H^1(\Omega_\chi)} \leq a_h(q_h,q_h) = \ell_h(q_h) \leq c\, C' \, \|q_h\|_{H^1(\Omega_\chi)} \quad \|q_h\|_{H^1(\Omega_\chi)} \leq c\, C' \, /\alpha.$$

The sequence q_h is bounded, and so there exists $q \in H^1(\Omega_\chi)$ and a sequence $\{q_{h_n}\}$ such that $q_{h_n} \rightharpoonup q$ in $H^1(\Omega_\chi)$-weak and

$$\forall v \in H^1(\Omega_\chi), \quad a(q,v) \leftarrow a_{h_n}(q_{h_n},v) = \ell_{h_n}(v) \to \ell_0(v).$$

But the solution of the variational equation $a(q,v) = \ell_0(v)$ is unique and, hence, $q = \lim_{h\to 0} q_h$. Finally, $q \in H^1(\Omega_\chi)$ is the unique solution of

$$\boxed{\begin{array}{l} \displaystyle\int_{\Omega_w} D_w \nabla q \cdot \nabla v + R_w \, q \, v \, dx \\ \displaystyle + \int_{\Omega_l} D_l \nabla q \cdot \nabla v + V_l \cdot \nabla q \, v \, dx + \int_{\Gamma_0} \beta_0 \, q \, v \, d\Gamma + \int_{\Gamma_L} \beta_L \, q \, v \, d\Gamma = \frac{M_0}{|\Sigma_\chi|} \int_{\Sigma_\chi} v \, dx. \end{array}} \tag{2.2.57}$$

2.3. Second Model: Shrinking the Domain Occupied by the Polymer

In the previous section the domain Ω_p^h occupied by the polymer is characterised by the characteristic function χ and its thickness h. Yet, the size of Ω_p^h is very small and Ω_w^h is almost equal to Ω_w. So it is natural to attempt to neglect Ω_p^h and to replace it by an appropriate condition at Σ_χ characterised by some parameters that will depend on h (as shown in Figures 2.3 and 2.4). As before, since the initial mass M_0 of product is constant, the initial concentration c_0^h in Ω_p^h is assumed to be uniform

$$c_0^h(x) \stackrel{\text{def}}{=} \begin{cases} M_0 / \displaystyle\int_{\Omega_p^h} dx, & \text{in } \Omega_p^h \\ 0, & \text{elsewhere.} \end{cases} \tag{2.3.1}$$

The first objective is to shrink Ω_p^h to Σ_χ and incorporate h in an appropriate condition on Σ_χ. The second objective is to study the behaviour of the concentration c_h as h goes to

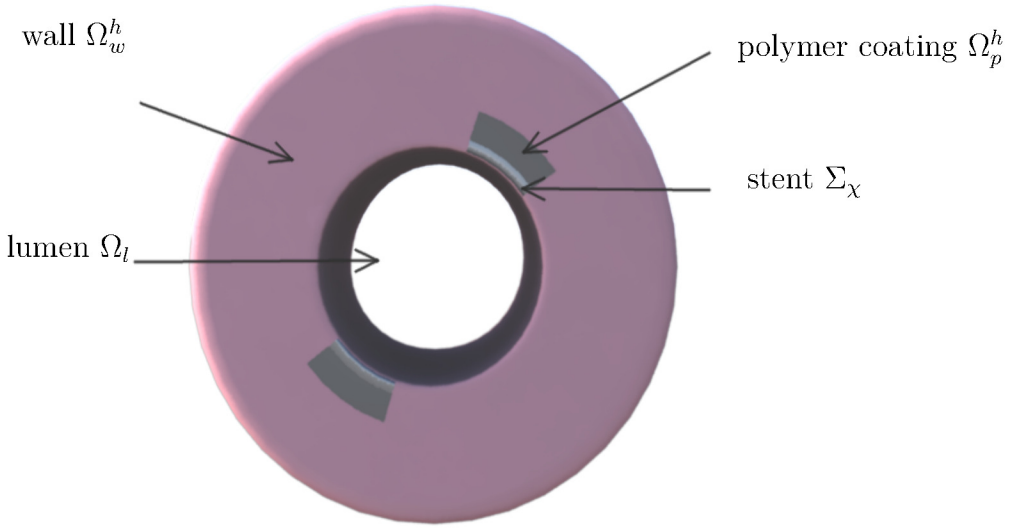

FIGURE 2.3. Cross section of stented vessel before coating compression.

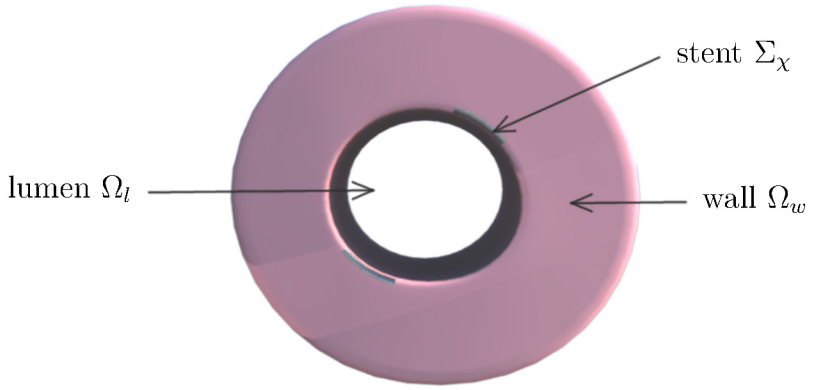

FIGURE 2.4. Cross section of stented vessel after coating compression.

zero. This cannot be done directly since the initial concentration will explode as h goes to zero. As a first step we go from the model of Delfour, Garon, and Longo [31] to the one of Garon and Delfour [42] initially introduced for a nonlinear quadratic release.

2.3.1. Shrinking Ω_p^h to Σ_χ for a fixed h

Recall the equations (2.2.11) for the concentration in each subdomain

$$\begin{aligned}
&\frac{\partial c}{\partial t} - \text{div } (D_w \nabla c) + R_w\, c = 0 \text{ in } \Omega_w^h,\\
&\frac{\partial c}{\partial t} - \text{div } (D_l \nabla c) + V_l \cdot \nabla c = 0 \text{ in } \Omega_l,\\
&\frac{\partial c}{\partial t} - \text{div } (D_p \nabla c) + R_p\, c = 0 \text{ in } \Omega_p^h,
\end{aligned} \tag{2.3.2}$$

and the condition at the interface polymer/wall

$$D_w \frac{\partial c}{\partial n_{\Omega_w^h}} + D_p \frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{pw}^h \stackrel{\text{def}}{=} \overline{\Omega_p^h} \cap \overline{\Omega_w^h}, \tag{2.3.3}$$

and on each side of the interface polymer/lumen Γ_{lp}

$$D_p \frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ and } D_l \frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lp} = \overline{\Omega_l} \cap \overline{\Omega_p^h} = \Sigma_\chi. \tag{2.3.4}$$

At $t \geq 0$, the mass of product in the polymer is

$$M_p(t) \stackrel{\text{def}}{=} \int_{\Omega_p^h} c_p(x,t)\, dx,$$

where $c_p(x,t)$ is the restriction of $c(x,t)$ to Ω_p^h. Using the change of variables

$$M_p(t) \stackrel{\text{def}}{=} \int_\Sigma \chi(x) \left[\int_0^h c_p(T_z(X),t)\, (z + \frac{z^2}{2} H(X) + \frac{z^3}{3} K(X))\, dz \right] d\Sigma.$$

Define the concentration averaged along the normal in each point of Σ_χ

$$\bar{c}_p(X,t) \stackrel{\text{def}}{=} \frac{1}{h} \left[\int_0^h c_p(T_z(X),t) \left(z + \frac{z^2}{2} H(X) + \frac{z^3}{3} K(X) \right) dz \right]$$

$$\boxed{\bar{c}_p(t) \stackrel{\text{def}}{=} \frac{1}{h} \left[\int_0^h (c_p(t) \circ T_z) \left(z + \frac{z^2}{2} H + \frac{z^3}{3} K \right) dz \right] \text{ on } \Sigma_\chi,}$$

where $\bar{c}_p(t) : [0,\infty) \to L^2(\Sigma_\chi)$. By definition

$$M_p(t) = \int_{\Omega_p^h} c_p(x,t)\, dx = h \int_{\Sigma_\chi} \bar{c}_p(X,t)\, d\Sigma \tag{2.3.5}$$

$$\int_{\Omega_p^h} \frac{\partial c_p}{\partial t}(x,t)\, dx = h \int_{\Sigma_\chi} \frac{\partial \bar{c}_p}{\partial t}(X,t)\, d\Sigma \tag{2.3.6}$$

Upon substitution into the third equation of (2.2.11) on Ω_p^h

$$\begin{aligned} h\int_{\Sigma_\chi}\frac{\partial \bar{c}_p}{\partial t}(X,t)\,d\Sigma &= \int_{\Omega_p^h} \text{div }(D_p\nabla c_p) - R_p\,c_p\,dx \\ &= \int_{\partial\Omega_p^h} D_p\frac{\partial c_p}{\partial n_{\Omega_p^h}}\,dx - R_p\int_{\Omega_p^h} c_p\,dx \\ &= \int_{\Gamma_{wp}^h} D_p\frac{\partial c_p}{\partial n_{\Omega_p^h}}\,dx - R_p h\int_{\Sigma_\chi}\bar{c}_p(X,t)\,d\Sigma, \end{aligned} \tag{2.3.7}$$

since $D_p\frac{\partial c}{\partial n_{\Omega_p^h}} = 0$ on $\Gamma_{0w}\cup\Gamma_{Lw}\cup\Gamma_{lp}$. Using the transmission condition across Γ_{wp}^h

$$-\int_{\Gamma_{wp}^h} D_w\frac{\partial c_w}{\partial n_{\Omega_w^h}}\,d\Gamma = h\int_{\Sigma_\chi}\left(\frac{\partial \bar{c}_p}{\partial t}(X,t) + R_p\bar{c}_p(X,t)\right)d\Sigma = \int_{\Gamma_{wp}^h} D_p\frac{\partial c_p}{\partial n_{\Omega_p^h}}\,d\Gamma. \tag{2.3.8}$$

The interface $\Gamma_{wp}^h = \partial\Omega_p^h\backslash\Sigma_\chi$ is made of the upper part of $\partial\Omega_p^h$ parallel to Σ_χ and the lateral part of height h. We want to neglect the integral over the lateral part and identify the integral on the upper part of Γ_{wp}^h with the integral on Σ_χ.

We proceed in two steps. In step (a), we take care of the first two integrals in (2.3.8) and in step (b) of the last two integrals.

(a) First replace the first equation (2.2.11) for c on Ω_w^h by the same equation on the larger original domain Ω_w. Denote by $\bar{c}$ the new solution of

$$\begin{aligned} &\frac{\partial \bar{c}}{\partial t} - \text{div }(D_w\nabla\bar{c}) + R_w\,\bar{c} = 0 \text{ in } \Omega_w, \\ &\frac{\partial \bar{c}}{\partial t} - \text{div }(D_l\nabla\bar{c}) + V_l\cdot\nabla\bar{c} = 0 \text{ in } \Omega_l. \end{aligned} \tag{2.3.9}$$

In enlarging the domain Ω_w^h to Ω_w and confining Ω_p^h to Σ_χ the total mass

$$M_{wp}(t) = \int_{\Omega_w^h} c_w(t,x)\,dx + \int_{\Omega_p^h} c_p(t,x)\,dx = \int_{\Omega_w^h} c_w(t,x)\,dx + h\int_{\Sigma_\chi}\bar{c}_p(X,t)\,dX$$

of drug must be preserved as we replace c_w by $\bar{c}$:

$$M_{wp}(t) = \beta(h)\int_{\Omega_w}\bar{c}(t,x)\,dx + h\int_{\Sigma_\chi}\bar{c}_p(X,t)\,dX, \quad \beta(h)\overset{\text{def}}{=}\frac{|\Omega_w^h|}{|\Omega_w|}, \tag{2.3.10}$$

where $\beta(h)$ is a *geometric factor* that is almost 1 since $|\Omega_w| = |\Omega_w^h| + |\Omega_p^h| \approx |\Omega_w^h|$. In what follows we just write β. This will give

$$\int_{\Gamma_{wp}^h} D_w\frac{\partial c_w}{\partial n_{\Omega_w^h}}\,d\Gamma \approx \beta\int_{\Sigma_\chi} D_w\frac{\partial \bar{c}}{\partial n_{\Omega_w}}\,d\Sigma$$

$$\int_{\Sigma_\chi}\beta\,D_w\frac{\partial \bar{c}}{\partial n_{\Omega_w}} + h\left(\frac{\partial \bar{c}_p}{\partial t}(X,t) + R_p\bar{c}_p(X,t)\right)d\Sigma = 0.$$

Assume that this integral identity is valid pointwise

$$\boxed{\beta\, D_w \frac{\partial \bar{c}}{\partial n_{\Omega_w}} + h\, \left(\frac{\partial \bar{c}_p}{\partial t}(X,t) + R_p \bar{c}_p(X,t) \right) = 0 \quad \text{on } \Sigma_\chi.} \tag{2.3.11}$$

(b) To complete our system of equation we need an equation for $\bar{c}_p$ on Σ_χ. So we go back to the second part of the transmission condition (2.3.8)

$$\int_{\Gamma^h_{wp}} D_p \frac{\partial c_p}{\partial n_{\Omega^h_p}}\, d\Gamma = h \int_{\Sigma_\chi} \left(\frac{\partial \bar{c}_p}{\partial t}(X,t) + R_p \bar{c}_p(X,t) \right) d\Sigma. \tag{2.3.12}$$

The simplest thing to do is to approximate the normal derivative. Drop the variable t for the moment and consider the function $z \mapsto c(z,X) \stackrel{\text{def}}{=} c_p(T_x(X))$ and

$$\frac{\partial c_p}{\partial z}(z,X) = \nabla c_p(T_x(X)) \cdot \frac{\partial T_z(X)}{\partial z} = (\nabla c_p \cdot \nabla b_{\Omega_l})(T_z(X)) = \frac{\partial c_p}{\partial n_{\Omega^h_p}}(T_z(X)).$$

At points X away from the edges we can approximate the function $z \mapsto c(z,X)$ by linear interpolation via the points $c(0,X)$ and $c(h,X)$

$$\begin{aligned} c(x,X) &= c(0,X) + (c(h,X) - c(0,X))\frac{z}{h}, \\ \Rightarrow \frac{\partial c_p}{\partial z}(z,X) &= \frac{c(h,X) - c(0,X)}{h}, \quad \bar{c}_p(X) = \frac{c(h,X) + c(0,X)}{2}. \end{aligned}$$

By continuity of c, $c_p(h,X) = c_w(h,X) \approx \bar{c}(X)$ and

$$\begin{aligned} \frac{\partial c_p}{\partial z}(h,X) &\approx \frac{c_p(h,X) - c_p(0,X)}{h} = 2\, \frac{\bar{c}(X) - \bar{c}_p(X)}{h} \\ \Rightarrow \int_{\Gamma^h_{wp}} D_p \frac{\partial c_p}{\partial n_{\Omega^h_p}}\, d\Gamma &\approx \int_{\Sigma_\chi} \frac{\partial c_p}{\partial z}(h,X)\, d\Gamma \approx \frac{2}{h} \int_{\Sigma_\chi} D_p\, (\bar{c} - \bar{c}_p)\, d\Gamma. \end{aligned}$$

Finally,

$$\frac{2}{h} \int_{\Sigma_\chi} D_p\, (\bar{c} - \bar{c}_p)\, d\Gamma \approx h \int_{\Sigma_\chi} \left(\frac{\partial \bar{c}_p}{\partial t}(X,t) + R_p \bar{c}_p(X,t) \right) d\Sigma. \tag{2.3.13}$$

Assuming that this integral identity is verified pointwise

$$\begin{aligned} &\frac{\partial \bar{c}_p}{\partial t}(X,t) - \frac{2\, D_p}{h^2}\, (\bar{c}_p(X,t) - \bar{c}(X,t)) + R_p\, \bar{c}_p(X,t) = 0 \text{ on } \Sigma_\chi \\ &\bar{c}_p(X,0) = \frac{M_0}{\int_{\Sigma_\chi} \left(h + \frac{h^2}{2}\, H + \frac{h^3}{3}\, K \right) d\Sigma} \text{ on } \Sigma_\chi, \end{aligned} \tag{2.3.14}$$

2.3.2. Summary of the Equations for the Concentrations $(\bar{c}, \bar{c}_p)$

The pair $\bar{c}(t) : \Omega_\chi \to \mathbb{R}$ and $\bar{c}_p(t) : \Gamma_\chi \to \mathbb{R}$, is solution of the coupled system

$$\begin{cases} \dfrac{\partial \bar{c}}{\partial t} - \text{div } (D_w \nabla \bar{c}) + R_w \, \bar{c} = 0 \text{ in } \Omega_w, \\ \dfrac{\partial \bar{c}}{\partial t} - \text{div } (D_l \nabla \bar{c}) + V_l \cdot \nabla \bar{c} = 0 \text{ in } \Omega_l, \\ \bar{c}(0) = 0 \text{ in } \Omega_\chi, \\ D_w \dfrac{\partial \bar{c}}{\partial n_{\Omega_w}} + D_l \dfrac{\partial \bar{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw} \backslash \Sigma_\chi, \\ \beta \, D_w \dfrac{\partial \bar{c}}{\partial n_{\Omega_w}} + \dfrac{2}{h} D_p \, (\bar{c}_p - \bar{c}) = 0 \text{ on } \Sigma_\chi, \quad D_l \dfrac{\partial \bar{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi. \\ D \dfrac{\partial \bar{c}}{\partial n_{\Omega_\chi}} + \beta_0 \, \bar{c} = 0 \text{ on } \Gamma_0, \; D \dfrac{\partial \bar{c}}{\partial n_{\Omega_\chi}} + \beta_L \, \bar{c} = 0 \text{ on } \Gamma_L, \; D \dfrac{\partial \bar{c}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}, \end{cases} \tag{2.3.15}$$

$$\begin{cases} \dfrac{\partial \bar{c}_p}{\partial t} + \dfrac{2 \, D_p}{h^2} \, (\bar{c}_p - \bar{c}) + R_p \, \bar{c}_p = 0 \text{ on } \Sigma_\chi, \\ \bar{c}_p(0) = \dfrac{M_0}{\int_{\Sigma_\chi} \left(h + \frac{h^2}{2} H + \frac{h^3}{3} K \right) d\Sigma} \text{ on } \Sigma_\chi, \end{cases} \tag{2.3.16}$$

where R, V, and D are defined as

$$D(x) = \begin{cases} D_l, & x \in \Omega_l, \\ D_w, & x \in \Omega_w, \end{cases} \quad V(x) = \begin{cases} V_l(x), & x \in \Omega_l, \\ 0, & x \in \Omega_w, \end{cases} \quad R(x) = \begin{cases} 0, & x \in \Omega_l, \\ R_w, & x \in \Omega_w. \end{cases} \tag{2.3.17}$$

2.3.3. Equations for the Normalised Concentration

In this section we follow the construction of [42], where we recreate the drug-release ODE obtained in [7] for the normalised mass released into the wall from our system of equations. We do this by examining the effect on the equations (2.3.15)-(2.3.16) as we let the thickness h go to zero. However, this results in the initial concentration $\bar{c}_p(0)$ going to infinity. To prevent this, we define $c_0^h \overset{\text{def}}{=} M_0 / \left| \Omega_p^h \right|$ as before, and the *normalised concentrations* with respect to c_0^h

$$\hat{c}(x,t) \overset{\text{def}}{=} \frac{c(x,t)}{c_0^h}, x \in \Omega_\chi, \quad \hat{c}_p(X,t) \overset{\text{def}}{=} \frac{\bar{c}_p(X,t)}{c_0^h}, X \in \Sigma_\chi. \tag{2.3.18}$$

Since all of the equations in (2.3.15)-(2.3.16) are linear, they remain valid when substituting the normalised concentration. The only modification is to the initial condition $\bar{c}_p(0)$

$$\begin{cases} \dfrac{\partial \hat{c}}{\partial t} - \text{div}\,(D_w \nabla \hat{c}) + R_w\,\hat{c} = 0 \text{ in } \Omega_w, \\ \dfrac{\partial \hat{c}}{\partial t} - \text{div}\,(D_l \nabla \hat{c}) + V_l \cdot \nabla \hat{c} = 0 \text{ in } \Omega_l, \\ \hat{c}(0) = 0 \text{ in } \Omega_\chi, \\ D_w \dfrac{\partial \hat{c}}{\partial n_{\Omega_w}} + D_l \dfrac{\partial \hat{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw} \backslash \Sigma_\chi, \\ \beta\, D_w \dfrac{\partial \hat{c}}{\partial n_{\Omega_w}} + \dfrac{2}{h} D_p\,(\hat{c}_p - \hat{c}) = 0 \text{ on } \Sigma_\chi, \quad D_l \dfrac{\partial \hat{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi. \\ D \dfrac{\partial \hat{c}}{\partial n_{\Omega_\chi}} + \beta_0\,\hat{c} = 0 \text{ on } \Gamma_0,\ D \dfrac{\partial \hat{c}}{\partial n_{\Omega_\chi}} + \beta_L\,\hat{c} = 0 \text{ on } \Gamma_L,\ D \dfrac{\partial \hat{c}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}, \end{cases} \tag{2.3.19}$$

$$\begin{cases} \dfrac{\partial \hat{c}_p}{\partial t} + \dfrac{2}{h^2} D_p \beta\,(\hat{c}_p - \hat{c}) + R_p\,\hat{c}_p = 0 \text{ on } \Sigma_\chi, \\ \hat{c}_p(0) = 1. \end{cases} \tag{2.3.20}$$

The *normalised mass* in the polymer is defined as

$$m_p(t) \overset{\text{def}}{=} \frac{M_p(t)}{M_0}. \tag{2.3.21}$$

where

$$M_p(t) = h \int_{\Sigma_\chi} \bar{c}_p(X,t)\, d\Sigma \quad \text{ and } \quad c_0^h = \frac{M_0}{\int_{\Sigma_\chi} h + \frac{h^2}{2} H + \frac{h^3}{3} K\, d\Sigma}$$

We have that

$$\begin{aligned} m_p(t) = \frac{h}{M_0} \int_{\Sigma_\chi} \bar{c}_p(X,t)\, d\Sigma = \frac{1}{\int_{\Sigma_\chi} 1 + \frac{h}{2} H + \frac{h^2}{3} K\, d\Sigma} \int_{\Sigma_\chi} \hat{c}_p(X,t)\, d\Sigma \\ \implies \frac{dm_p(t)}{dt} = \frac{1}{\int_{\Sigma_\chi} 1 + \frac{h}{2} H + \frac{h^2}{3} K\, d\Sigma} \int_{\Sigma_\chi} \frac{\partial \hat{c}_p(X,t)}{\partial t}\, d\Sigma. \end{aligned} \tag{2.3.22}$$

If we set $\left|\Sigma_\chi^h\right| \overset{\text{def}}{=} \int_{\Sigma_\chi} 1 + \frac{h}{2} H + \frac{h^2}{3} K\, d\Sigma$ and then combine (2.3.22) with (2.3.20), we obtain a PDE for m_p

$$\begin{aligned} &\frac{dm_p}{dt} + \frac{2\beta\, D_p}{h^2 \left|\Sigma_\chi^h\right|} \int_{\Sigma_\chi} \hat{c}_p - \hat{c}\, d\Sigma + \frac{R_p}{\left|\Sigma_\chi^h\right|} \int_{\Sigma_\chi} \hat{c}_p\, d\Sigma = 0, \\ &m_p(0) = \frac{1}{\left|\Sigma_\chi^h\right|} \int_{\Sigma_\chi} \hat{c}_p(0)\, d\Sigma = 1. \end{aligned} \tag{2.3.23}$$

As we take the limit $h \to 0$, we have that $\hat{c} \to 0$ and $\left|\Sigma_\chi^h\right| \to |\Sigma_\chi|$. From there, the first equation of (2.3.23) would simplify and we would obtain a system of equations for the normalized mass of product in the polymer

$$\begin{aligned} \frac{dm_p}{dt} + \frac{2\beta}{h^2\,|\Sigma_\chi|} D_p \int_{\Sigma_\chi} \hat{c}_p \, d\Sigma + \frac{1}{|\Sigma_\chi|} \int_{\Sigma_\chi} R_p \, \hat{c}_p \, d\Sigma = 0 \\ \implies \frac{\partial m_p}{\partial t} + \frac{2\beta}{h^2} D_p m_p + R_p m_p = 0, \end{aligned} \tag{2.3.24}$$

with initial condition $m_p(0) = 1$. This would lead to the equation for the normalised mass released to the wall

$$\begin{aligned} \frac{\partial m_w}{\partial t} &= \frac{2\beta}{h^2} D_p \, (1 - m_w) + R_p \, (1 - m_w) \\ m_w(0) &= 0 \end{aligned} \tag{2.3.25}$$

Unfortunately, there is an h^2 at the denominator of the coefficient in front of the diffusion term and the whole argument collapses. As in section 2.2.3, we cannot get a nice ODE for the normalised mass m_p.

2.3.4. Equations for the Dose and the Asymptotic Dose

As in Chapter 1 it is possible to introduce the *dose* when both $\bar{c}(t)$ and $\bar{c}_p(t)$ go to zero as t goes to infinity

$$\bar{q}(x) \stackrel{\text{def}}{=} \int_0^\infty \bar{c}(x,t) \, dt, \quad \bar{q}_p(x) \stackrel{\text{def}}{=} \int_0^\infty \bar{c}_p(x,t) \, dt. \tag{2.3.26}$$

The resulting equations are

$$\begin{cases} -\operatorname{div}\,(D_w \nabla \bar{q}) + R_w \, \bar{q} = 0 \text{ in } \Omega_w, \\ -\operatorname{div}\,(D_l \nabla \bar{q}) + V_l \cdot \nabla \bar{q} = 0 \text{ in } \Omega_l, \\ D_w \dfrac{\partial \bar{q}}{\partial n_{\Omega_w}} + D_l \dfrac{\partial \bar{q}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw} \backslash \Sigma_\chi, \\ \beta \, D_w \dfrac{\partial \bar{q}}{\partial n_{\Omega_w}} + \dfrac{2}{h} \, D_p \, (\bar{q}_p - \bar{q}) = 0 \text{ on } \Sigma_\chi, \quad D_l \dfrac{\partial \bar{q}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi. \\ D \dfrac{\partial \bar{q}}{\partial n_{\Omega_\chi}} + \beta_0 \, \bar{q} = 0 \text{ on } \Gamma_0, \; D \dfrac{\partial \bar{q}}{\partial n_{\Omega_\chi}} + \beta_L \, \bar{q} = 0 \text{ on } \Gamma_L, \; D \dfrac{\partial \bar{q}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}, \end{cases} \tag{2.3.27}$$

$$\frac{2\,D_p}{h^2} \, (\bar{q}_p - \bar{q}) + R_p \, \bar{q}_p = \bar{c}_p(0) = \frac{M_0}{\int_{\Sigma_\chi} \left(h + \frac{h^2}{2} \, H + \frac{h^3}{3} \, K\right) \, d\Sigma} \text{ on } \Sigma_\chi. \tag{2.3.28}$$

From the last equation, we can solve explicitly for $\bar{q}_p$ as a function of $\bar{q}$

$$\begin{aligned}
&\left(2\,D_p\,+h^2\,R_p\right)\,\bar{q}_p = 2\,D_p\,\bar{q} + h^2\,\bar{c}_p(0)\\
\Rightarrow\ \bar{q}_p &= \frac{2\,D_p}{2\,D_p+h^2\,R_p}\,\bar{q} + h^2\,\frac{1}{2\,D_p+h^2\,R_p}\,\bar{c}_p(0)\\
&= \frac{2\,D_p}{2\,D_p+h^2\,R_p}\,\bar{q} + h\,\frac{1}{2\,D_p+h^2\,R_p}\,\frac{M_0}{\int_{\Sigma_\chi}\left(1+\frac{h}{2}\,H+\frac{h^2}{3}\,K\right)\,d\Sigma}.
\end{aligned} \tag{2.3.29}$$

Since the variable $\bar{q}_p$ appears only once in the interface equation on Σ_χ, it can be eliminated

$$\bar{q}_p - \bar{q} = -h^2\,\frac{R_p}{2\,D_p+h^2\,R_p}\,\bar{q} + h^2\,\frac{1}{2\,D_p\,+h^2\,R_p}\,\bar{c}_p(0)$$

to get a system of equation for $\bar{q}$

$$\begin{cases}
-\text{ div }\left(D_w\nabla\bar{q}\right) + R_w\,\bar{q} = 0 \text{ in } \Omega_w,\\
-\text{ div }\left(D_l\nabla\bar{q}\right) + V_l\cdot\nabla\bar{q} = 0 \text{ in } \Omega_l,\\
D_w\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_w}} + D_l\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw}\backslash\Sigma_\chi,\\
\beta\,D_w\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_w}} - h\,\dfrac{2\,D_p\,R_p}{2\,D_p+h^2\,R_p}\,\bar{q} + \dfrac{2\,D_p}{2\,D_p+h^2\,R_p}\,\dfrac{M_0}{\int_{\Sigma_\chi}\left(1+\frac{h}{2}\,H+\frac{h^2}{3}\,K\right)\,d\Sigma} = 0 \text{ on } \Sigma_\chi,\\
D_l\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi.\\
D\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_\chi}} + \beta_0\,\bar{q} = 0 \text{ on } \Gamma_0,\ D\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_\chi}} + \beta_L\,\bar{q} = 0 \text{ on } \Gamma_L,\ D\,\dfrac{\partial\bar{q}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext},
\end{cases} \tag{2.3.30}$$

Note that the term

$$\frac{M_0}{\int_{\Sigma_\chi}\left(1+\frac{h}{2}\,H+\frac{h^2}{3}\,K\right)\,d\Sigma} \tag{2.3.31}$$

is a density per unit area.

When h goes to zero, $\bar{q}_p = \bar{q}$ on Σ_χ and $\bar{q}$ is solution of the system

$$\begin{cases} -\text{ div } (D_w \nabla \bar{q}) + R_w\, \bar{q} = 0 \text{ in } \Omega_w, \\ -\text{ div } (D_l \nabla \bar{q}) + V_l \cdot \nabla \bar{q} = 0 \text{ in } \Omega_l, \\ D_w \dfrac{\partial \bar{q}}{\partial n_{\Omega_w}} + D_l \dfrac{\partial \bar{q}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw} \backslash \Sigma_\chi, \\ D_w \dfrac{\partial \bar{q}}{\partial n_{\Omega_w}} + \dfrac{M_0}{|\Sigma_\xi|} = 0 \text{ on } \Sigma_\chi, \quad D_l \dfrac{\partial \bar{q}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi. \\ D \dfrac{\partial \bar{q}}{\partial n_{\Omega_\chi}} + \beta_0\, \bar{q} = 0 \text{ on } \Gamma_0,\ D \dfrac{\partial \bar{q}}{\partial n_{\Omega_\chi}} + \beta_L\, \bar{q} = 0 \text{ on } \Gamma_L,\ D \dfrac{\partial \bar{q}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}. \end{cases} \tag{2.3.32}$$

It is the same equation as (2.2.57) obtained in the previous section.

Chapter 3

QUADRATIC DRUG RELEASE FROM A THIN, FLAT POLYMERIC FILM

3.1. Introduction

The underlying assumption for the models introduced in Chapter 2 was that the polymer behaves as a homogeneous, linearly diffusive material with diffusion constant D_p and a standard *transmission condition* at the interface between the wall and the polymer. A polymer, and even more so highly *degradable polymers*, are quite different environments. They are made up of an internal matrix subject to deterioration, dislocation, and surface erosion.[1] The molecules of drug must find their way out through deficiencies of the polymer depending on the relative size of the interior holes or paths compared to the size of the molecule of drug.

Physically, we are closer to models of *semi-permeable membranes* obeying some form of Fick's law. Mathematically, such models have been studied within the framework of the *Neumann sieve model* by Damlamian [**27**] in 1986 where two linearly diffusive domains are separated by an interface punctured with small holes. Depending on the nature of the holes and the rate at which their size goes to zero, several cases are to be considered. In our context, it would mean a condition of the form

$$\beta\, D_w \frac{\partial c_w}{\partial n_{\Omega_w}} + A_1\ (c_p - c_w) = 0 \text{ on } \partial\Omega_w^h \cap \partial\Omega_p^h, \tag{3.1.1}$$

where A_1 is a *term coming from nowhere*[2] which is related to the *mathematical capacity* of the holes. This condition is of the same form as condition

$$\beta\, D_w \frac{\partial \bar{c}}{\partial n_{\Omega_w}} + \frac{2}{h}\, D_p\ (\bar{c}_p - \bar{c}) = 0 \text{ on } \Sigma_\chi,$$

[1] More information on the subject can be found in [**33**, chapter 5], which discusses various stent compositions and their effects on deterioration and erosion.

[2] See Cioranescu and Murat [**24, 25**] in 1982, [**26**] in 1997, and the very elegant theory of *periodic unfolding* by Cioranescu, Damlamian, and Griso [**18, 19, 20, 21**].

in equation (2.3.15) of Chapter 2 (but missing a factor of h at the denominator), and the underlying physics are quite different.

This chapter briefly surveys recent work of A. Garon and M. C. Delfour [42] on a three-dimensional, quadratic partial differential equation model of the drug release from a thin film of biodegradable polymer to a surrounding medium. Its very innovative feature is to go directly from the experimental normalised release curves of L. L. Lao and S. S. Venkatraman [60] to a flux condition at the interface between the polymer and the medium. In order to do so, it only requires the identification of the two parameters of the highly accurate ordinary differential equation model of G. Blanchet, M. C. Delfour, and A. Garon [7] In the context of drug eluting stents, it is a practical and economical tool to theoretically and numerically simulate the 3D release of drug from the thin polymer film to the integrated wall and lumen of the blood vessel for evaluation and design. This approach avoids resorting to time-dependent or nonlinear diffusion in the polymer.

3.2. Measurements and the Two-parameter ODE Model

3.2.1. Neat Polymers

The objective of the experiment of L. L. Lao and S. S. Venkatraman [60] was to get the release profile of paclitaxel from three neat polymer matrices of PCL (Polycaprolactone), PLGA (dl-lactide-co-glycolide) and PLGAPEG (PLGA with polyethylene glycol), and construct a semi-empirical model for prediction and design. They are representative of a broad spectrum of biodegradable polymers ranging from hydrophobic to hydrophilic (cf., for instance, [63]). In hydrophilic polymers the internal bounds between the chains are weakened and this adds to the surface erosion phenomenon. The drug release mechanism within a polymer matrix depends on many factors such as the affinity of the drug with the surrounding medium (water). Specifically, paclitaxel is hydrophobic and this might explain the fact that some of the drug blended into the polymer matrix is not released and cannot participate to the treatment of the diseased wall. The main criticism expressed in [62] of available models for drug release from eroding surfaces is that they fail to faithfully reproduce experimental data for highly degradable polymers (the S-curve behaviour in Figure 3.2). The reader is referred to the introduction of the paper of Lao et al [62] for a comprehensive review of the literature.

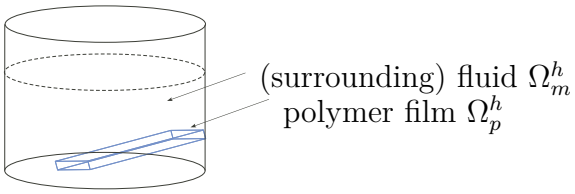

FIGURE 3.1. The polymer film Ω_p^h and the (surrounding) medium Ω_m^h in the vial (not to scale). Reproduced from [42, Fig. 1]. Copyright ©2014 Society for Industrial and Applied Mathematics. Reprinted with permission. All rights reserved.

Each polymer sample consisted of a thin square film ($12\,mm \times 12\,mm$) of thickness $80\,\mu m$ uniformly loaded with $4\,\mu g$ of paclitaxel. The film was placed in a vial and the vial was filled with a fluid solution that we shall call the *surrounding medium* (see Figure 3.1). The vial is closed without circulation of the fluid. The time t is measured in *days*. The surrounding fluid was removed and analysed every two days and replaced by a fresh solution. The measurements were presented in the form of a normalised release curve, that is, the *total mass* $M_m(t)$ *of paclitaxel released* to the medium at time t divided by its initial mass M_0 in the polymer.

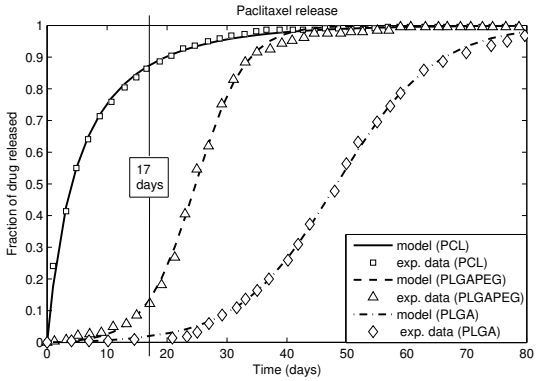

FIGURE 3.2. Quadratic ODE model [7] and experimental [60, Figure 1] normalised paclitaxel release curves as a function of the time t for the neat PCL, PLGAPEG, and PLGA. Copyright ©2011 Society for Industrial and Applied Mathematics. Reprinted with permission. All rights reserved.

A quick look at the paclitaxel release profiles of Lao et al [60, Figure 1] reproduced in Figure 3.2 suggests two types of release: S-curve type and exponential type. Many drug release experimental curves in literature show an S-type behaviour, but are theoretically

approximated by an exponential (see, for instance, the MCC core curve in Siepmann and Siepmann [81, Fig. 3, page 354] reproduced in Figure 3.3).

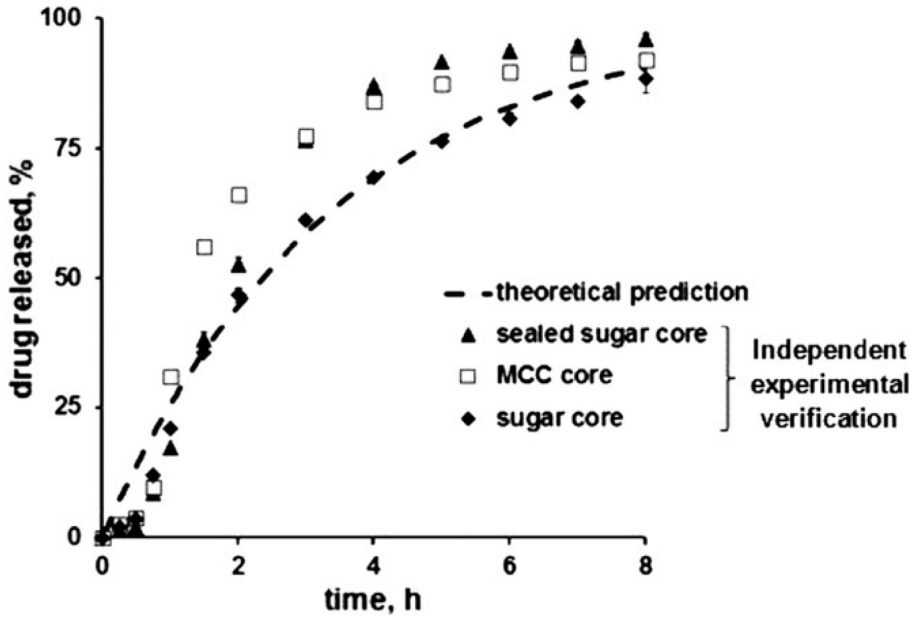

FIGURE 3.3. Theoretically predicted (dotted curve) and experimentally verified (symbols) diltiazem HCl release kinetics from coated pellets in 0.1 N HCl... Reprinted from Journal of Controlled Release [81, Fig. 3], Copyright ©2012, with permission from Elsevier.

It is fair to say that the paper of Lao et al [62, p. 797] has changed the focus by emphasising the fitting to experimental data over mechanistic theories such as the erosion models of T. Higuchi [46] (*Rate of Release of Medicaments from Ointment*) in 1961 and [47] (*Theoretical Analysis of Rate of Release of Solid Drugs Dispersed in Solid Matrices*) in 1963 that cannot generate release curves of the S-type.

S-curve behaviours are similar to the ones encountered in the study of the logistic equation of populations. This led Blanchet et al [7] to fitting the normalised experimental data of Lao et al [60] with the solution of the following quadratic ODE

$$\frac{dm}{dt}(t) = a_1\ (1 - m(t)) + a_2\ (1 - m(t))^2\,, \quad m(0) = 0, \tag{3.2.1}$$

where $m(t)$ is the ratio of the *released mass of drug* $M_m(t)$ to the medium at *time* t divided by the *initial mass of drug* M_0 at time 0. The time t is expressed in *days*. The two *parameters* a_1 and a_2 expressed in $days^{-1}$ completely specify the release. Total release is achieved when $m(t)$ goes to 1 as the time t goes to infinity, but partial release is also possible by changing the asymptotic value $m_\infty = \lim_{t\to\infty} m(t)$ to a number between 0 and 1. It was shown in [7] that four cases can occur under the conditions $m(0) = 0$ and $m'(0) = a_1 + a_2 > 0$. In all cases $a_1 \geq 0$ but a_2 can be positive (exponential type), zero (true exponential) or negative (S-type).

In our context, $0 \leq m(t) \leq 1$ and it is further necessary that $m'(0) > 0$ to initiate the release. This yields a first condition on the two parameters : $m'(0) = a_1 + a_2 > 0$. When $a_2 = 0$, the ODE is linear, and it is necessary that $a_1 > 0$ to get 1 as the asymptotic limit: $m(t) = (1 - e^{-a_1 t})$. When $a_2 \neq 0$, $m(t)$ is given in closed form by

$$m(t) = \begin{cases} (a_2 + a_1)\ \dfrac{1 - e^{-a_1\, t}}{a_2 + a_1 - a_2\, e^{-a_1\, t}}, & \text{if } a_1 \neq 0, \\ \dfrac{a_2\, t}{1 + a_2\, t}, & \text{if } a_1 = 0. \end{cases} \tag{3.2.2}$$

As t goes to infinity,

$$m(t) \to \begin{cases} 1, & \text{if } a_1 \geq 0 \\ 1 + a_1/a_2, & \text{if } a_1 < 0. \end{cases} \tag{3.2.3}$$

Under the conditions $m(0) = 0$ and $m'(0) > 0$, the following four cases can occur:

Case 1) (True S type) $a_1 > 0$, $a_2 < 0$, and $-2 < a_1/a_2 < -1$. The *point of inflexion* of the S-curve occurs at the positive time

$$t_c = -(1/a_1)\ \log\left(\frac{a_1 + a_2}{-a_2}\right) > 0,$$

since $0 < (a_1 + a_2)/(-a_2) < 1$;

Case 2) (S type) $a_1 > 0$, $a_2 < 0$, and $a_1/a_2 \leq -2$. The *point of inflexion* occurs at the negative time

$$t_c = -(1/a_1)\ \log\left(\frac{a_1 + a_2}{-a_2}\right) \leq 0$$

since $1 < (a_1 + a_2)/(-a_2)$;

Case 3) (Exponential type) $a_1 \geq 0$ and $a_2 > 0$. The *blow up time*[3] occurs at time

$$t_c = \begin{cases} -(1/a_1)\,\log\left(1 + \dfrac{a_1}{a_2}\right) < 0, & \text{if } a_1 > 0, \\ -\,1/a_2 < 0, & \text{if } a_1 = 0; \end{cases} \tag{3.2.4}$$

Case 4) (True exponential) $a_1 > 0$ and $a_2 = 0$. The *blow up time* occurs at $-\infty$

$$m(t) = \left(1 - e^{-a_1\,t}\right), \quad t_c = -\infty.$$

The four cases are illustrated below in Figure 3.4 with parameters in Table 3. I

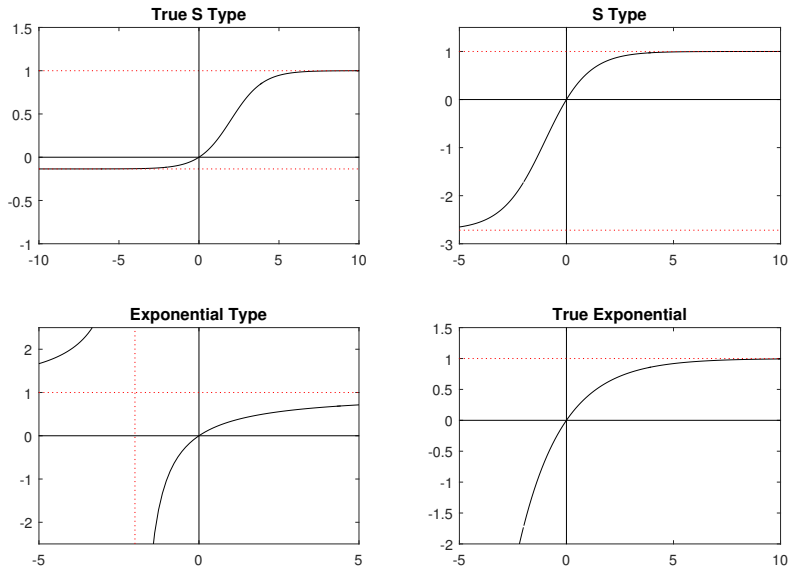

FIGURE 3.4. Example release curves showing the four possible types. See Table 3. I for parameters and values.

[3]In cases 3), 4), and 5), the point of inflexion at time t_c becomes a negative blow up time where the solution first goes to $+\infty$ and then comes back from $-\infty$. There are no singularities or point of inflexion for positive times. This gives an exponential type curve behaviour that is sharper than a pure exponential.

TABLE 3. I. Parameters and values for example release curves in Figure 3.4.

Type	a_1	a_2	Point of Inflexion	Blow Up Time
True S type	1	$\frac{-1}{1+e^{-2}}$	2	-
S type	1	$\frac{-1}{1+e}$	-2	-
Exponential type	0	0.5	-	-2
True exponential	0.5	0	-	$-\infty$

Since in all cases $a_1 \geq 0$, $m_\infty = 1$. For $a_2 < 0$, $m_\infty = 1 + a_1/a_2 < 1$, and for $a_2 > 0$ $m_\infty = 1 + a_1/a_2 > 1$. For $a_1 = 0$ and $a_2 > 0$, $m(t) \to 1$ as $t \to \pm\infty$ and $m(t) \to -\infty$ as $t \to -1/a_2$.

TABLE 3. II. Identified parameters of paclitaxel release from neat PCL, neat PLGA, neat PLGAPEG films from the measurement of $M(t)/M_\infty$ ([7, Table 2.1]).

Parameters	Neat PCL	Neat PLGAPEG	Neat PLGA
$a_1\,\text{day}^{-1}$	0.07050	0.24013	0.12273
$a_2\,\text{day}^{-1}$	0.13950	-0.23950	-0.12240
case	3)	1)	1)
t_c (days)	-5.8	24.7	48.2

The simplicity of the model for a broad range of polymers indicates that somehow the quadratic structure captures the complex microphysics and chemistry of the release process. This type of model also reproduces with much higher accuracy the normalised release curves from polymer blends than the one of Lao et al [62].

The quadratic equations offer some similarity with the Kedem-Katchalsky [57, 58] equations (see also [56, 53, 83]) for the modelling of the mass flux across a membrane under osmotic and hydrostatic pressures jump. For the special case of zero hydrostatic pressure across the membrane, the Kedem-Katchalsky equations reduce to

$$J_s = k_1 (c_p - c_m) + k_2 (c_p - c_m)(c_p + c_m) \tag{3.2.5}$$

and the quadratic term becomes $c_p^2 - c_m^2$ instead of $(c_p - c_m)^2$ in the quadratic model. In the absence of fluid flow, k_2 is zero, and J_s reduces to a linear equation. The context is different since the quadratic terms in our analysis are present without fluid flow through porous media. However, the reader can appreciate that the underlying mathematical structures used in some of the works on thin porous media and quadratic semipermeable membranes presents some interesting similarities. See the book of A. Katchalsky and P. F. Urran [**56**] on *Nonequilibrium thermodynamic in biophysics* and articles on biological membranes of O. Kedem and A. Katchalsky [**57**] on *Thermodynamic analysis of the permeability of biological membranes to non-electrolytes* and [**58**] on *A physical interpretation of the phenomenological coefficients of membrane permeability* and A. Katchalsky and O, Kkedem [**55**] on *Thermodynamics of flow processes in biological systems*in 1962.

As a final remark, quadratic ODEs are classical in population models such as the Verhulst logistic equation [**89**], but there is a whole spectrum of related non-quadratic models that can be used for less standard problems (see, for instance Tsoularis [**85**]). The quadratic law (3.2.1) (and later (3.3.10)) works well for polymers such as PCL and PLGA , but other types of functions can be envisioned if they provide a better fit to the drug release curves.

3.2.2. Polymer Blends

In order to achieve prescribed drug release kinetics some authors have been investigating biphasic and possibly multiphasic releases. Blending two or more polymers with different drug release profiles and time constants is used to create two or more time synchronised phases to closely achieve a desired drug release profile over a longer therapeutic period (see, for instance, the release curves in Figure 3.5). Lao, Venkatraman, and Peppas [**62**] proposed and tested novel models for drug (notably paclitaxel) release from films made of neat PCL, neat PLGA, and their blends:

> For applications involving drug-eluting stents, controlled paclitaxel release of up to 3 months is desirable to combat restenosis (renarrowing of arteries) which is usually most active during this period. However, as seen from the release data for the neat polymers, release from neat PCL has an unacceptably short duration of release with high burst, whereas release of paclitaxel from neat PLGA has an unacceptably long induction period of zero to little release. Therefore, a blend of PCL and PLGA would give an intermediate (and acceptable) release profile that reflects the complementary effect of the two components. PCL contributes to paclitaxel release in the first half (up to 30 days) while PLGA contributes in the latter half (up to 85 days) of the release.

Looking at the release data from [62, Fig. 8–10] for polymer blends (see also Figure 3.5), it is quite clear that to model real polymer blends such as the nondegradable PCL with the biodegradable PLGA, it will not be sufficient to adjust the parameters a_1 and a_2 in the ODE model.

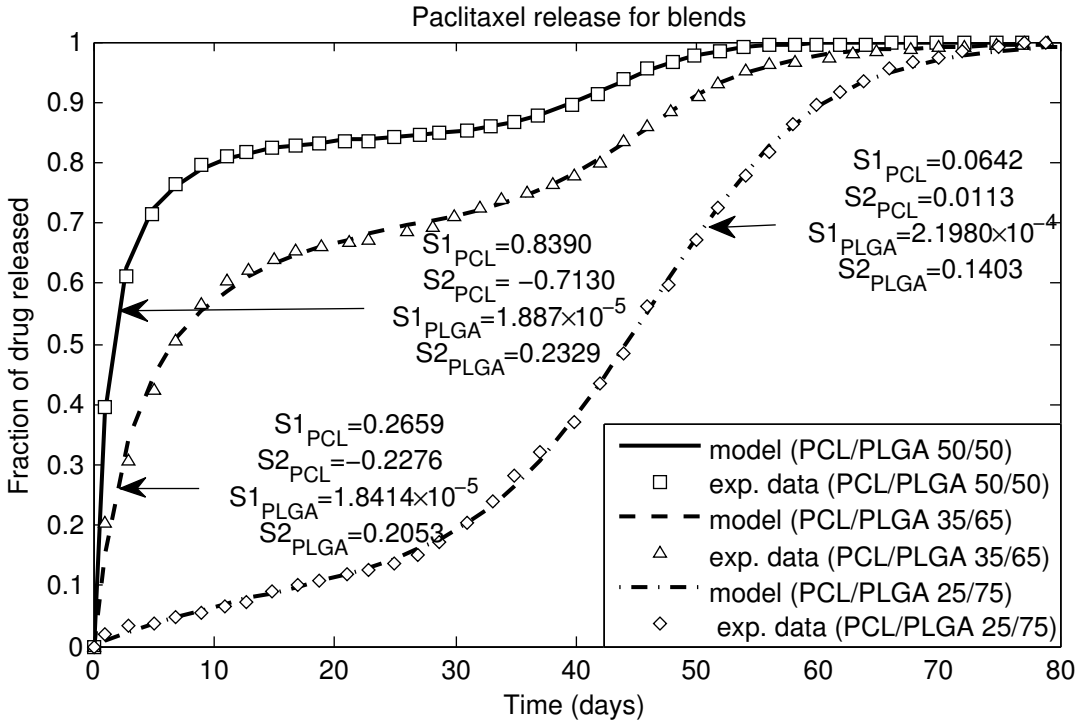

FIGURE 3.5. Model and experimental data of paclitaxel release with time for blends. See table 3. III for parameters. Reproduced from [7, Fig. 3.1] that used data from [62, Fig. 8–10]. Copyright ©2011 Society for Industrial and Applied Mathematics. Reprinted with permission. All rights reserved.

Lao, Venkatraman, and Peppas [62, eqs. (5) and (7) on p. 798, eq. (8) on p. 799, eq. (10) on p. 801] introduce a *partitioning of the release* (f_{PCL},f_{PLGA}) where f_{PCL} and f_{PLGA} are the respective fractions of the initial masses of PCL and PLGA (see [62, Equation (10)]) with $5+8+1$ parameters. However, [62, Figures 8, 9b, and 10] show that the straight substitution

TABLE 3. III. Model parameters of paclitaxel release from blend PLGA/PCL 50/50, PCL/PLGA 35/65, and PCL/PLGA 25/75 films. Reproduced from [7, Table 3.1]. Copyright ©2011 Society for Industrial and Applied Mathematics. Reprinted with permission. All rights reserved.

Parameters	PCL/PLGA 50/50	PCL/PLGA 35/65	PCL/PLGA 25/75
$a_{1_{PCL}}$	0.12600	0.03830	0.07550
$a_{2_{PCL}}$	0.71300	0.22760	-0.01130
$a_{1_{PLGA}}$	0.23292	0.20532	0.14052
$a_{2_{PLGA}}$	-0.23290	-0.20530	-0.14030
f_{PCL}	84.56%	74.92%	12.32%
f_{PLGA}	15.44%	25.08%	87.68%

of the parameters of the ODE models for PCL and PCLA of Table 3. II with the partition parameter is not sufficient to get really good fits with experimental data. The matching with the data deteriorates in going from 50/50 blends to 35/65 and seriously deteriorates for 25/75.

To correct this, Blanchet, Delfour and Garon [7] adopted a slightly more elaborate approach based on the following assumptions:

(a) the blend of two neat polymers in the presence of paclitaxel yields two new polymers since the matrices are modified at the microscopic level;

(b) the total mass of paclitaxel redistributes itself among the two new polymers in a way that is not necessary proportional to the relative fractions of polymers.

In practical terms this means that we shall now identify five parameters: two for each new polymer plus the fraction parameter:

$$m(t) = f_{PCL}\, m_{PCL}(t) + f_{PCLA}\, m_{PLGA}(t), \quad 0 < f_{PCL} < 1,\ f_{PLGA} = 1 - f_{PCL}, \tag{3.2.6}$$

where f_{PCL} rougthly corresponds to the level of the first plateau in the experimental release curves of Figure 3.5.[4] The results of the identification process are shown in Table 3. III. This successful approach readily extends to blends of n polymers

$$m(t) = \sum_{i=1}^{n} f_i\, m_i(t), \quad f_i \geq 0, \sum_{i=1}^{n} f_i = 1, \tag{3.2.7}$$

$$\frac{dm_i}{dt}(t) = a_{i1}\ (1 - m_i(t)) + a_{i2}\ (1 - m_i(t))^2, \quad m_i(0) = 0, \tag{3.2.8}$$

with n pairs (a_{i1},a_{i2}) of parameters and n factors $0 \leq f_i \leq 1$, such that $f_1 + \cdots + f_n = 1$ that roughly correspond to each plateau in the release curve. Release curves of the type shown in

[4]Computations using LSQCURVEFIT in MATLAB, which solves nonlinear least squares problems.

Figure 3.5 are common in the literature (see, for instance, Faisant, Akiki, Siepmann, Benoit, and Siepmann [**35**, Figures 5 and 6, page 194]), but have not been approximated by a system of quadratic ODE of the type (3.2.7).

3.3. Three Dimensional Model for the Experimental Setup

3.3.1. From the ODE to the PDE Model

To our best knowledge, the quadratic ODE model that Blanchet, Delfour and Garon [**7**] introduced in 2011 was the first semi-empirical drug release model in the literature that provides an excellent fit for a broad range of biodegradable neat polymers. The robustness of the model and the fact that only two parameters had to be identified indicated that the model was not purely empirical and that somehow it was implicitly capturing some important mechanistic features.

The new PDE model was developed to provide a three-dimensional simulation model for drug release from DES where the parameters of the model could be obtained directly from the experimental release curves. A choice had to be made. One can start from first principles and find a way to go from the micro scale to the macro scale in order to obtain at least a qualitative model with a minimal number of parameters to be identified. This is a delicate exercise since it is difficult to evaluate *a priori* the contribution of each parameter and decide which ones are to be retained. A mathematical approach was chosen starting from a PDE model with a quadratic structure at the macroscopic level, postponing the microphysical interpretations and justifications to a later time. Yet, it is not a purely abstract model since it incorporates basic principles such as the conservation of the mass and the standard diffusion equation in the surrounding medium. Since the polymer is very thin compared to other dimensions, it was reasonable to reduce it to a zero thickness surface and to lump all the chemistry and the physics inside the polymer as a quadratic flux through the surface, resulting in a jump in the normal derivative across the surface.

Like the quadratic ODE model, the three-dimensional PDE model is semi-empirical and it could effectively be used to *drive the experiment* in order to better understand the complex underlying microphysics and, in turn, the *experiment* can put the *theory* back on track and prevent systematic model deviations.

3.3.2. Experimental Set-up

We start by describing the experimental setup as well as summarising the equations and relevent explanations used for the model developed by Garon and Delfour [**42**], the detailed

description of which can be found in Lao et al [60]. In this section, we only retain the elements required in the modelling.

The release takes place from all sides of the film as if it was "floating" in the medium. The *thickness* $2h > 0$ of the polymer film is very small compared to all the other geometric parameters. Denote by Ω_p^h the open parallelepipedic domain associated with the polymer and by Ω_m^h the open domain associated with the medium (cf. Figure 3.1). Their boundaries will be denoted Γ_p^h and Γ_m^h, respectively. Denote by Σ_0 the *midsurface* of the polymer film

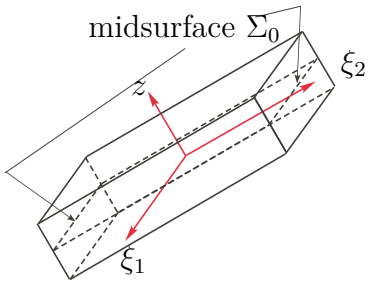

FIGURE 3.6. Domain Ω_p^h occupied by the polymer of thickness $2h$, *midsurface* Σ_0, and coordinate system $x = (\xi_1, \xi_2, z)$ at the center of the polymer film. Reproduced from [42, Fig. 3]. Copyright ©2014 Society for Industrial and Applied Mathematics. Reprinted with permission. All rights reserved.

Ω_p^h.

Consider the coordinate system $x = (\xi_1.\xi_2,z)$ of Figure 3.6 with the origin at the center of the polymer film, the z-axis orthogonal to the film, and the ξ_1 and ξ_2 axes in the plane of the midsurface.[5] So, in the polymer domain Ω_p^h, $-h < z < h$. Denote by $\Gamma_{int}^h = \Gamma_p^h \cap \Gamma_m^h$ the *interface* between the polymer and the medium. Since the vial is closed without circulation of the fluid (the medium), a zero Neumann boundary conditions was assumed on $\Gamma_{ext}^h = (\Gamma_p^h \cup \Gamma_m^h) \backslash \Gamma_{int}^h$. The volumes of the polymer and the medium will be denoted $|\Omega_p^h|$ and $|\Omega_m^h|$. The surface area of their boundaries and their interface will be denoted $|\Gamma_p^h|$, $|\Gamma_m^h|$, and $|\Gamma_{int}^h|$. Since the vial was closed, given an initial mass M_0 of drug in the polymer, the *conservation of the total mass* at time t was assumed. In addition, the equations of linear diffusion in the medium were assumed to be verified by the concentration in the medium. A local flux function was introduced by using a z-average of c_p and by reducing the polymer domain to

[5]This approach can be readily extended to curved polymer films by introducing local curvilinear coordinates and bases in the curved midsurface Σ_0.

the zero-thickness midsurface which results in a jump condition on the normal derivative across the midsurface Σ_0.

3.3.3. From equations on Ω_m^h to equations on Ω_m

Denote by $c_m(x,t)$ and $c_p(x,t)$ the respective concentrations of drug in the medium Ω_m^h and in the polymer Ω_p^h at time $t \geq 0$ and at point $x = (\xi_1,\xi_2,z)$. Assume that the linear diffusion equations are verified in the medium

$$\begin{cases} \dfrac{\partial c_m}{\partial t} = \operatorname{div}(D_m \nabla c_m) \text{ in } \Omega_m^h, \quad c_m(x,0) = 0 \text{ in } \Omega_m^h, \\ D_m \dfrac{\partial c_m}{\partial n_m} = F(c_m,c_p) \text{ on } \Gamma_{int}^h, \quad D_m \dfrac{\partial c_m}{\partial n_m} = 0 \text{ on } \Gamma_{ext}^h, \end{cases} \tag{3.3.1}$$

where $D_m > 0$ is the *diffusion constant* in the medium, and the form of the *flux* $F(c_m,c_p)$ at the interface Γ_{int}^h is to be specified. As mentioned previously, the total mass of drug M_0 is assumed to be preserved at all time $t \geq 0$

$$\int_{\Omega_p^h} c_p(x,t)\,dx + \int_{\Omega_m^h} c_m(x,t)\,dx = M_0. \tag{3.3.2}$$

Taking the time derivative then applying (3.3.1) and Green's formula implies that

$$\begin{aligned} \Rightarrow\ 0 &= \int_{\Omega_p^h} \frac{\partial c_p}{\partial t}(x,t)\,dx + \int_{\Omega_m^h} \frac{\partial c_m}{\partial t}(x,t)\,dx \\ &= \int_{\Omega_p^h} \frac{\partial c_p}{\partial t}(x,t)\,dx - \int_{\Gamma_{int}^h} D_m \frac{\partial c_m}{\partial n_m}(x,t)\,d\Gamma, \end{aligned} \tag{3.3.3}$$

where n_m is the outward normal to Ω_m^h.

Define the *z-averaged concentration* in the polymer

$$\bar{c}_p(\xi,t) \overset{\text{def}}{=} \frac{1}{2h} \int_{-h}^{h} c_p(\xi,z,t)\,dz, \quad \xi = (\xi_1,\xi_2) \in \Sigma_0 \tag{3.3.4}$$

which is defined on Σ_0 rather than on the interface Γ_{int}^h. The volume of the polymer film is

$$|\Omega_p^h| = 2h\,|\Sigma_0|, \tag{3.3.5}$$

where $|\Sigma_0|$ is the area of the midsurface. At $t = 0$ the concentration of drug in the polymer film is assumed to be uniform, that is

$$c_p(x,0) = c_0^h \overset{\text{def}}{=} \frac{M_0}{|\Omega_p^h|} = \frac{1}{2h}\frac{M_0}{|\Sigma_0|} = \bar{c}_p(\xi,0), \tag{3.3.6}$$

where $M_0/|\Sigma_0|$ is a *surfacic concentration* in kg/m^2.

The variable $\bar{c}_p$ is defined on the midsurface Σ_0 whereas the boundary condition on $D_m \partial c_m / \partial n_m$ is defined on the interface Γ_{int}^h which creates a small mismatch to fix. Since

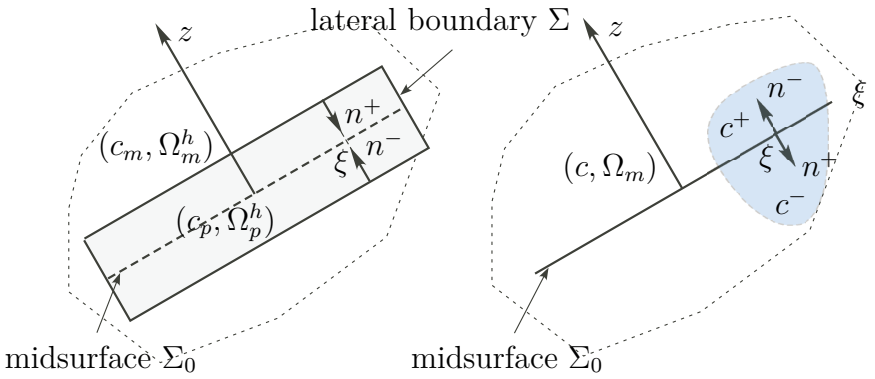

FIGURE 3.7. Cross-section of the shrinking of the domain Ω_p^h to Σ_0 as $h \to 0$. Reproduced from [42, Fig.4]. Copyright ©2014 Society for Industrial and Applied Mathematics. Reprinted with permission. All rights reserved.

the thickness $2h$ is very small, replace the domain Ω_m^h by the slightly larger open domain $\Omega_m \overset{\text{def}}{=} \text{int}\left(\overline{\Omega_m^h \cup \Omega_p^h}\right)$ occupied by the fluid and the polymer. The polymer thus reduces to the zero-thickness midsurface Σ_0 (see Figure 3.7). Another point of view is to consider the midsurface Σ_0 as a *crack* in Ω_m and introduce the new domain (medium) $\Omega \overset{\text{def}}{=} \Omega_m \backslash \Sigma_0$ for which $|\Omega| = |\Omega_m|$. In practice $\Sigma_0 \cap \Gamma_m = \varnothing$ and $\Gamma_m = \partial\Omega_m$, that is, the polymer does not touch the exterior boundary. Hence $\partial\Omega = \Sigma_0 \cup \Gamma_m$ and $\Gamma_{ext} = \Gamma_m$.

Since Ω is slightly larger than Ω_m^h, the equation for the conservation of the mass must be adjusted

$$2h \int_{\Sigma_0} \bar{c}_p(\xi,t)\, d\xi + \beta(h) \int_{\Omega} c(x,t)\, dx = M_0 \tag{3.3.7}$$

by introducing the *geometric conservation factor* $\beta(h) = |\Omega_m^h|/|\Omega| = |\Omega_m^h|/|\Omega_m| = 1 - 2h\,|\Sigma_0|/|\Omega_m|$ to take into account the slight increase in the volume of the medium going from $|\Omega_m^h|$ to $|\Omega_m|$.

The orientation of the midsurface is naturally defined by the choice of our (local) coordinate system. Denote by n^- the unit normal to the midsurface Σ_0 pointing "up" [6] and by

[6] that is, in the direction defined as the positive direction along the z-axis by the coordinate system

n^+ the unit normal pointing "down" [7]. Denote by c^+ and c^- the respective concentrations above and below Σ_0 in a neighbourhood of a point $\xi \in \Sigma_0$ as shown in Figure 3.7. Define the respective *jumps* in the concentration and in the normal derivative across Σ_0

$$[c] \stackrel{\text{def}}{=} c^+ - c^-, \quad \left[\frac{\partial c}{\partial n}\right] \stackrel{\text{def}}{=} \frac{\partial c^+}{\partial n^+} + \frac{\partial c^-}{\partial n^-} = \left(\nabla c^+ - \nabla c^-\right) \cdot n^+. \tag{3.3.8}$$

From (3.3.7)

$$\begin{aligned} 0 &= 2h \int_{\Sigma_0} \frac{\partial \bar{c}_p}{\partial t}(\xi,t)\, d\xi + \beta(h) \int_\Omega \frac{\partial c}{\partial t}(x,t)\, dx \\ &= 2h \int_{\Sigma_0} \frac{\partial \bar{c}_p}{\partial t}(\xi,t)\, d\xi - \beta(h) \int_{\Sigma_0} D_m \left[\frac{\partial c}{\partial n_{n_{\Omega_m}}}(\xi,t)\right] d\xi \end{aligned}$$

since $\partial\Omega = \Sigma_0 \cup \Gamma_{ext}$ and

$$D_m \frac{\partial c}{\partial n} = 0 \text{ on } \Gamma_{ext}.$$

The first assumption in [42] is that this identity is valid pointwise

$$\boxed{2h\, \frac{\partial \bar{c}_p}{\partial t} = \beta(h)\, D_m \left[\frac{\partial c}{\partial n_{n_\Omega}}\right] \text{ on } \Sigma_0} \tag{3.3.9}$$

and the second assumption is the flux condition

$$\boxed{\frac{\partial \bar{c}_p}{\partial t}(\xi,t) + A_1\, (\bar{c}_p(\xi,t) - c(\xi,t)) + \frac{A_2}{c_0^h}\, (\bar{c}_p(\xi,t) - c(\xi,t))^2 = 0 \text{ on } \Sigma_0} \tag{3.3.10}$$

which characterises each polymer. Under these two assumptions, Garon and Delfour [42] obtained the following 3D system of equations on the larger domain Ω_m for c coupled with an equation on the zero thickness midsurface for $\bar{c}_p$:

$$\left.\begin{cases} \dfrac{\partial \bar{c}_p}{\partial t}(\xi,t) + A_1\, (\bar{c}_p(\xi,t) - c(\xi,t)) + A_2\, \dfrac{1}{c_0^h}\, (\bar{c}_p(\xi,t) - c(\xi,t))^2 = 0, \\ \bar{c}_p(\xi,0) = c_0^h, \end{cases}\right\}, \quad \forall \xi \in \Sigma_0, \tag{3.3.11}$$

$$\begin{cases} \dfrac{\partial c}{\partial t} = \operatorname{div}(D_m \nabla c) \text{ in } \Omega_m, \quad c(x,0) = 0 \text{ in } \Omega_m, \\ D_m \left[\dfrac{\partial c}{\partial n}\right] = -\dfrac{2h}{\beta h}\, \dfrac{\partial \bar{c}_p}{\partial t} \text{ and } [c] = 0 \text{ on } \Sigma_0, \quad D_m \dfrac{\partial c}{\partial n} = 0 \text{ on } \Gamma_m = \Gamma_{ext}. \end{cases} \tag{3.3.12}$$

The diffusion constant D_m is known but the parameters A_1 and A_2 must be obtained from the experimental release curves.

[7] that is, in the direction defined as the negative direction along the z-axis by the coordinate system

It is important to notice that the conditions (3.3.9) and (3.3.10) are *local conditions* at each point of the interface between the polymer and the diffusive medium. They characterise the microphysics of the polymer, and do not depend on the geometry nor the exterior boundary conditions for the concentration in the medium. Moreover, we shall see in the next section that the two parameters A_1 and A_2 are the two numbers a_1 and a_2 that arise from the experimental measurements under a *quasi-infinite sink condition*.

3.3.4. Asymptotic Convergence to the ODE Model as h Goes to 0

In order to relate the parameters A_1 and A_2 to the experimental release curves that have been fitted by the ODE model of G. Blanchet, M. C. Delfour, and A. Garon [7], an asymptotic analysis is performed on the system (3.3.11)-(3.3.12).

As the thickness h goes to zero the initial concentration $\bar{c}_p(\xi,0)$ goes to infinity. By introducing the *normalised concentrations* with respect to c_0^h

$$\hat{c}_p(\xi,t) \stackrel{\text{def}}{=} \frac{\bar{c}_p(\xi,t)}{c_0^h},\ \xi \in \Sigma_0, \quad \hat{c}(x,t) \stackrel{\text{def}}{=} \frac{c(x,t)}{c_0^h},\ x \in \Omega_m, \tag{3.3.13}$$

both normalised concentrations will remain bounded. We get the new system

$$\begin{cases} \dfrac{\partial \hat{c}_p}{\partial t}(\xi,t) + A_1\ (\hat{c}_p(\xi,t) - \hat{c}(\xi,t)) + A_2\ (\hat{c}_p(\xi,t) - \hat{c}(\xi,t))^2 = 0, \\ \hat{c}_p(\xi,0) = 1, \quad \xi \in \Sigma_0, \end{cases} \tag{3.3.14}$$

$$\begin{cases} \dfrac{\partial \hat{c}}{\partial t} = \operatorname{div}(D_m \nabla \hat{c}) \text{ in } \Omega_m, \quad \hat{c}(x,0) = 0 \text{ in } \Omega_m, \\ D_m \left[\dfrac{\partial \hat{c}}{\partial n}\right] = -\dfrac{2h}{\beta h} \dfrac{\partial \hat{c}_p}{\partial t} \text{ and } [\hat{c}] = 0 \text{ on } \Sigma_0, \quad D_m \dfrac{\partial \hat{c}}{\partial n} = 0 \text{ on } \Gamma_m. \end{cases} \tag{3.3.15}$$

Since the normalised mass m_p in the polymer is related to $\hat{c}_p$ as follows

$$m_p(t) = \frac{1}{|\Sigma_0|} \int_{\Sigma_0} \hat{c}_p(\xi,t)\, d\xi, \tag{3.3.16}$$

we get the following equation for $m_p(t)$ from equation (3.3.14): given $\hat{c}_p(\xi,t)$

$$\begin{cases} \dfrac{dm_p}{dt}(t) + A_1 \dfrac{1}{|\Sigma_0|} \displaystyle\int_{\Sigma_0} \hat{c}_p(\xi,t) - \hat{c}(\xi,t)\, d\xi + A_2 \dfrac{1}{|\Sigma_0|} \int_{\Sigma_0} (\hat{c}_p(\xi,t) - \hat{c}(\xi,t))^2\ d\xi \\ m_p(0) = 1. \end{cases} \tag{3.3.17}$$

In the limit as $h \to 0$, $\hat{c}(\xi,t)$ goes to zero. Since the first equation in (3.3.14) becomes independent of ξ and the initial conditions are identical for all ξ, the solution $\hat{c}_p(\xi,t)$ is also

independent of ξ:

$$\begin{cases} \dfrac{\partial \hat{c}_p}{\partial t}(\xi,t) + A_1\,\hat{c}_p(\xi,t) + A_2\,\hat{c}_p(\xi,t)^2 = 0, \\ \hat{c}_p(\xi,0) = 1, \quad \xi \in \Sigma_0. \end{cases}$$

After simplifying equation (3.3.17) with the identity (3.3.16), we see that $m_p(t)$ and $\hat{c}_p(t)$ are solutions to the same ODE and thus $m_p(t) = \hat{c}_p(t)$. We then recover an ODE for the normalised mass in the polymer

$$\frac{dm_p}{dt}(t) + A_1\,m_p(t) + A_2\,m_p(t)^2 = 0, \quad m_p(0) = 1, \tag{3.3.18}$$

and the equation for the normalised mass $m_m(t) = 1 - m_p(t)$ released to the medium

$$\frac{dm_m}{dt}(t) = A_1\,(1 - m_m(t)) + A_2\,(1 - m_m(t))^2\,, \quad m_m(0) = 0. \tag{3.3.19}$$

This is precisely equation (3.2.1) of the highly accurate ODE model developed by G. Blanchet, M. C. Delfour, and A. Garon [7] to identify the parameters a_1 and a_2 from the release curves. By choosing $A_1 = a_1$ and $A_2 = a_2$, we get the three-dimensional PDE model whose solution asymptotically yields the experimental release curves of Lao et al [60] as $h \to 0$.

3.4. One-Sided Drug Release

In Lao's experiment, it was assumed that the polymer film is *floating* in the medium, and thus the drug release occurs on both sides of the film. However, for coated stents, the stent itself acts as a physical barrier and so the release only occurs on one side. The analysis is the same but, for later reference, we explicit the case where a polymer of thickness h is attached to the bottom of the vial. In this situation the vertical coordinate z is perpendicular to the bottom of the vial and runs from 0 to h, and the midsurface Σ_0 is the contact surface between the bottom of the film and the vial. The set Σ_0 is now a part of the boundary Γ_m of Ω_m. The boundary Γ_{ext} must be replaced by $\Gamma_m \backslash \Sigma_0$ and the open set $\Omega = \Omega_m \backslash \Sigma_0$ coincides with Ω_m.

The *z-averaged concentration* in the polymer is modified as follows

$$\bar{c}_p(\xi,t) \stackrel{\text{def}}{=} \frac{1}{h}\int_0^h c_p(\xi,z,t)\,dz, \quad \xi = (\xi_1,\xi_2) \in \Sigma_0. \tag{3.4.1}$$

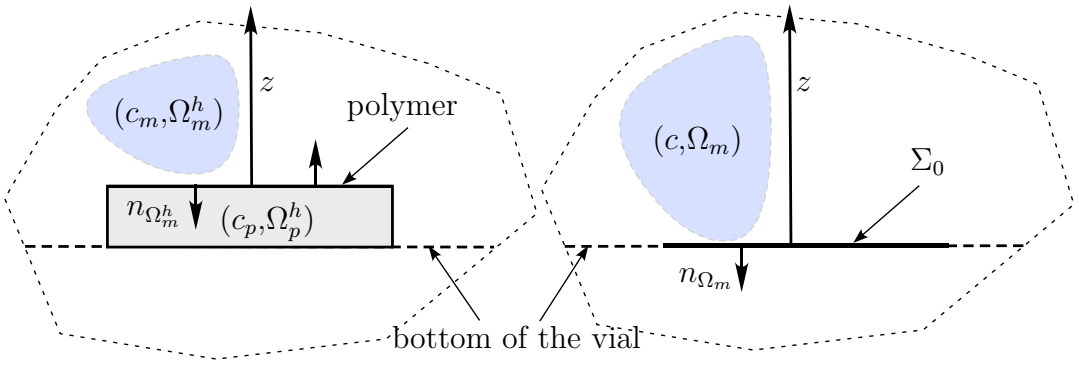

FIGURE 3.8. Cross-section of the shrinking of the domain Ω_p^h to Σ_0 as $h \to 0$.

The volume of the polymer film is

$$|\Omega_p^h| = h\,|\Sigma_0|. \tag{3.4.2}$$

At $t = 0$ the concentration of drug in the polymer film is assumed to be uniform, that is

$$c_p(x,0) = c_0^h \overset{\text{def}}{=} \frac{M_0}{|\Omega_p^h|} = \frac{1}{h}\frac{M_0}{|\Sigma_0|} = \bar{c}_p(\xi,0), \tag{3.4.3}$$

where $M_0/|\Sigma_0|$ is a *surfacic concentration* in kg/m^2.

Since Ω_m is slightly larger than Ω_m^h, the equation for the conservation of the mass must be adjusted

$$h \int_{\Sigma_0} \bar{c}_p(\xi,t)\,d\xi + \beta(h) \int_{\Omega_m} c(x,t)\,dx = M_0 \tag{3.4.4}$$

by introducing the *geometric conservation factor* $\beta(h) = |\Omega_m^h|/|\Omega_m| = 1 - h\,|\Sigma_0|/|\Omega_m|$ to take into account the increase in the volume of the medium from $|\Omega_m^h|$ to $|\Omega_m|$. Since the release only occurs on one side of the polymer, there is no longer a *jump* $[c] = c^+ - c^-$ in the concentration and the normal derivative $\left[\frac{\partial c}{\partial n}\right] = \frac{\partial c^+}{\partial n^+} - \frac{\partial c^-}{\partial n^-}$at the boundary Σ_0. Instead, from (3.4.4), the boundary conditions are

$$D_m \frac{\partial c}{\partial n} = 0 \text{ on } \Gamma_m \backslash \Sigma_0.$$

and

$$\begin{aligned} 0 &= h \int_{\Sigma_0} \frac{\partial \bar{c}_p}{\partial t}(\xi,t)\,d\xi + \beta(h) \int_{\Omega_m} \frac{\partial c}{\partial t}(x,t)\,dx \\ &= h \int_{\Sigma_0} \frac{\partial \bar{c}_p}{\partial t}(\xi,t)\,d\xi - \beta(h) \int_{\Sigma_0} D_m \frac{\partial c}{\partial n_{n_{\Omega_m}}}(\xi,t)\,d\xi \end{aligned}$$

The first assumption (3.3.9) becomes

$$\boxed{h\,\frac{\partial \bar{c}_p}{\partial t} = \beta(h)\,D_m \frac{\partial c}{\partial n_{n_\Omega}} \text{ on } \Sigma_0} \tag{3.4.5}$$

and the second assumption (3.3.10) becomes

$$\boxed{\frac{\partial \bar{c}_p}{\partial t}(\xi,t) + A_1\ (\bar{c}_p(\xi,t) - c(\xi,t)) + \frac{A_2}{c_0^h}\ (\bar{c}_p(\xi,t) - c(\xi,t))^2 = 0 \text{ on } \Sigma_0} \tag{3.4.6}$$

which characterises each polymer. Under these assumptions, we obtain the following 3D system of equations on the larger domain Ω_m for the pair $(c, \bar{c}_p)$:

$$\left.\begin{cases} \dfrac{\partial \bar{c}_p}{\partial t}(\xi,t) + A_1\ (\bar{c}_p(\xi,t) - c(\xi,t)) + A_2\,\dfrac{1}{c_0^h}\ (\bar{c}_p(\xi,t) - c(\xi,t))^2 = 0 \\ \bar{c}_p(\xi,0) = c_0^h, \end{cases}\right\}, \forall \xi \in \Sigma_0, \tag{3.4.7}$$

$$\begin{cases} \dfrac{\partial c}{\partial t} = \operatorname{div}(D_m \nabla c) \text{ in } \Omega_m, \quad c(x,0) = 0 \text{ in } \Omega_m, \\ D_m \dfrac{\partial c}{\partial n} = -\dfrac{h}{\beta(h)}\,\dfrac{\partial \bar{c}_p}{\partial t} \text{ on } \Sigma_0, \quad D_m \dfrac{\partial c}{\partial n} = 0 \text{ on } \Gamma_m \backslash \Sigma_0. \end{cases} \tag{3.4.8}$$

The diffusion constant D_m is known but the parameters $A_1 = a_1$ and $A_2 = a_2$ are obtained from experimental release curves.

The assumptions (3.4.5) and (3.4.6) are *local conditions* at each point of the interface between the thin polymer and the linearly diffusive medium. They have been derived within the context of Lao's experiment with an infinite sink to reveal the release mechanism in the polymer when put in contact with a medium. When the medium is changed parameters may change, but the equations will remain valid. Looking at things differently, one can say that they are *constitutive laws* governing the release of drugs from a thin polymeric film. Since the conditions are local they remain valid for curved films. We shall use them in Chapter 4 for the curved wall of a blood vessel which is modelled as a linearly diffusive medium with loss term coupled with blood flow in the lumen.

3.5. Sink Condition and One-dimensional Model of Lao

Experimentally, the *sink condition* is achieved when the following two conditions are satisfied: (1) the polymer film is immersed into a vial containing a large volume of fluid, and (2) the diffusion coefficient is sufficiently large to prevent the formation of a concentration boundary layer at the interface between the polymer and the surrounding medium. In practice, this results in low – almost zero – paclitaxel concentration in the neighbourhood of

the interface. The diffusion coefficient can be increased by adding a solubility agent in the surrounding medium (see Lao et al [**63**, p. 1056]):

> However, for paclitaxel release, the release medium comprised of PBS pH 7.4 and 10% (v/v) solubility enhancer, that is, DMSO [the solubility agent was added to prevent paclitaxel saturation and mimic the infinite "sink condition." No plasticization effect . . .].

As can be readily seen from the equations (3.3.14)-(3.3.15), the same asymptotic model can be obtained by making the diffusion constant D_m very large while keeping h constant. The two effects can be combined. As the ratio D_m/h goes to infinity, we get a set of equations for the asymptotic solution of the equations which only depends on the experimental parameters a_1 and a_2. In order to have the ratio D_m/h go to infinity in a laboratory setting, the thickness is fixed and the D_m is increased by adding an *accelerator* to drive the system into its asymptotic state; Experimentally, it is easier to increase D_m than decrease h, but the end result is the same.

Remark 3.5.1. *Physically, and according to the 3D quadratic model, there is a boundary layer next to the exterior boundary of the polymer, and a finite flux across the interface between the polymer and the medium. In their mathematical model Lao et al* [**63**, Eqs (1) to (7), p. 1059–1060] *induce the release of paclitaxel by imposing an* idealistic zero concentration *at the boundaries of the polymer. Then the resulting simple, one-dimensional diffusion model is solved by using standard infinite series of exponentials. It turns out that this model is physically unrealistic since the flux between the polymer and the medium would be infinite as shown in Appendix B.*

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Chapter 4

QUADRATIC RELEASE FROM A COATED STENT IN A CURVED VESSEL

4.1. The PDE Quadratic Model

We start with the model of Chapter 2, but we don't assume linear diffusion in the polymeric domain Ω_p^h. The concentration $c_p \stackrel{\text{def}}{=} c|_{\Omega_p^h}$ in Ω_p^h will be handled as in Chapter 3 by introducing the averaged concentration $\bar{c}_p$ and enlarging the domain occupied by the wall from Ω_w^h to $\Omega_w = \text{int}\,(\overline{\Omega_p^h} \cup \overline{\Omega_w^h})$ together with two assumptions similar to the two assumptions (3.4.5) and (3.4.6) of Chapter 3 that are characteristic of the interaction of a thin polymer with a linear-diffusive medium.

With the notation of Chapter 2

$$\begin{aligned}
&\frac{\partial c_w}{\partial t} - \text{div}\,(D_w \nabla c_w) + R_w\, c_w = 0 \text{ in } \Omega_w^h, \quad c_w(x,0) = 0\\
&\frac{\partial c_l}{\partial t} - \text{div}\,(D_l \nabla c_l) + V_l \cdot \nabla c_l = 0 \text{ in } \Omega_l, \quad c_l(x,0) = 0,\\
&c_p(x,0) = \frac{M_0}{|\Omega_p^h|}, \quad |\Omega_p^h| = \int_{\Sigma_\chi} \left(h + \frac{h^2}{2}\, H + \frac{h^3}{3}\, K \right) d\Sigma.
\end{aligned} \tag{4.1.1}$$

The initial condition can be written in the more compact form

$$c_0^h(x) = \begin{cases} \dfrac{M_0}{\int_{\Sigma_\chi} \left(h + \frac{h^2}{2}\, H + \frac{h^3}{3}\, K \right) d\Sigma}, & \text{in } \Omega_p^h, \\ 0, & \text{in } \Omega_w^h \cup \Omega_l. \end{cases} \tag{4.1.2}$$

The boundary/interface conditions are

$$\begin{aligned}
&D\frac{\partial c}{\partial n_\Omega} + \beta_0\, c = 0 \text{ on } \Gamma_0,\ D\frac{\partial c}{\partial n_\Omega} + \beta_L\, c = 0 \text{ on } \Gamma_L,\ D\frac{\partial c}{\partial n_\Omega} = 0 \text{ on } \Gamma_{ext},\\
&D_w\frac{\partial c}{\partial n_{\Omega_w^h}} + D_l\frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw}^h \text{ (at the interface lumen/wall)}\\
&D_w\frac{\partial c}{\partial n_{\Omega_w^h}} + D_p\frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{pw} \text{ (at the interface polymer/wall)}\\
&D_p\frac{\partial c}{\partial n_{\Omega_p^h}} = 0 \text{ on } \Gamma_{lp} \quad D_l\frac{\partial c}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lp} \text{ (at the interface lumen/polymer).}
\end{aligned} \tag{4.1.3}$$

with

$$D(x) = \begin{cases} D_l, & x \in \Omega_l \\ D_w, & x \in \Omega_w^h \end{cases} \quad V(x) = \begin{cases} V_l(x), & x \in \Omega_l \\ 0, & x \in \Omega_w^h \end{cases} \quad R(x) = \begin{cases} 0, & x \in \Omega_l \\ R_w, & x \in \Omega_w^h. \end{cases} \tag{4.1.4}$$

At $t \geq 0$, the mass of product in the polymer is

$$M_p(t) \stackrel{\text{def}}{=} \int_{\Omega_p^h} c_p(x,t)\, dx.$$

Using the change of variables

$$M_p(t) \stackrel{\text{def}}{=} \int_\Sigma \chi(x) \left[\int_0^h c_p(T_z(X),t)\, (z + \frac{z^2}{2}H(X) + \frac{z^3}{3}K(X))\, dz\right] d\Sigma.$$

Define the concentration averaged along the normal in each point of Σ_χ

$$\bar{c}_p(X,t) \stackrel{\text{def}}{=} \frac{1}{h}\left[\int_0^h c_p(T_z(X),t)\, \left(z + \frac{z^2}{2}H(X) + \frac{z^3}{3}K(X)\right)\, dz\right]$$

$$\boxed{\bar{c}_p(t) \stackrel{\text{def}}{=} \frac{1}{h}\left[\int_0^h (c_p(t) \circ T_z)\, \left(z + \frac{z^2}{2}H + \frac{z^3}{3}K\right)\, dz\right] \text{ on } \Sigma_\chi,}$$

where $\bar{c}_p(t) : [0,\infty) \to L^2(\Sigma_\chi)$. By definition

$$M_p(t) = \int_{\Omega_p^h} c_p(x,t)\, dx = h\int_{\Sigma_\chi} \bar{c}_p(X,t)\, d\Sigma \tag{4.1.5}$$

$$\int_{\Omega_p^h} \frac{\partial c_p}{\partial t}(x,t)\, dx = h\int_{\Sigma_\chi} \frac{\partial \bar{c}_p}{\partial t}(X,t)\, d\Sigma \tag{4.1.6}$$

As in chapter 2, replace the first equation (4.1.1) for c_w on Ω_w^h by the following equation on the larger domain Ω_m for the concentration $\bar{c}_w$

$$\frac{\partial \bar{c}_w}{\partial t} - \text{div } (D_w \nabla \bar{c}_w) + R_w\, \bar{c}_w = 0 \text{ in } \Omega_w, \quad \bar{c}_w(x,0) = 0. \tag{4.1.7}$$

To complete the system of equation, we now add the two assumptions (3.4.5) and (3.4.6) of Chapter 3 by replacing the linearly diffusive domain Ω_m by Ω_p, $2h$ by h, and the jump in the normal derivative by the normal derivative. The two assumptions are:

$$\boxed{h\,\frac{\partial \bar{c}_p}{\partial t} = \beta(h)\,D_m \frac{\partial \bar{c}_w}{\partial n_{n_{\Omega_p}}} \text{ on } \Sigma_\chi} \tag{4.1.8}$$

$$\boxed{\frac{\partial \bar{c}_p}{\partial t}(\xi,t) + A_1\,(\bar{c}_p(\xi,t) - \bar{c}_w(\xi,t)) + \frac{A_2}{c_0^h}\,(\bar{c}_p(\xi,t) - \bar{c}_w(\xi,t))^2 = 0 \text{ on } \Sigma_\chi}. \tag{4.1.9}$$

Recall that those assumptions are *local conditions* at each point of the interface between the thin polymer and the linearly diffusive medium. They remain valid for curved films and a linearly diffusive medium with loss term coupled with circulation in the lumen.

4.2. Summary of the Equations for the Concentrations $(\bar{c}, \bar{c}_p)$

The new system of equations is now defined on a domain Ω_χ that does not depend on h. Yet, even if h is not emphasised in the notation of the solution $(\bar{c}_p, \bar{c})$ of the equations, it is dependent on h through the geometrical factor $\beta(h)$ and the initial condition M_0/c_0^h that goes to infinity as h goes to zero.

The pair $\bar{c}(t) : \Omega_\chi \to \mathbb{R}$ and $\bar{c}_p(t) : \Gamma_\chi \to \mathbb{R}$, is solution of the coupled system

$$\begin{cases} \dfrac{\partial \bar{c}}{\partial t} - \text{div}\,(D\nabla \bar{c}) + V \cdot \nabla \bar{c} + R\,\bar{c} = 0 \text{ in } \Omega_\chi, \\ \bar{c}(0) = 0 \text{ in } \Omega_\chi, \\ D_w \dfrac{\partial \bar{c}}{\partial n_{\Omega_w}} + D_l \dfrac{\partial \bar{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw} \backslash \Sigma_\chi, \\ \beta(h)\,D_w \dfrac{\partial \bar{c}}{\partial n_{\Omega_w}} = h\,\dfrac{\partial \bar{c}_p}{\partial t} \text{ on } \Sigma_\chi, \quad D_l \dfrac{\partial \bar{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi. \\ D \dfrac{\partial \bar{c}}{\partial n_{\Omega_\chi}} + \beta_0\,\bar{c} = 0 \text{ on } \Gamma_0,\ D \dfrac{\partial \bar{c}}{\partial n_{\Omega_\chi}} + \beta_L\,\bar{c} = 0 \text{ on } \Gamma_L,\ D \dfrac{\partial \bar{c}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}, \end{cases} \tag{4.2.1}$$

$$\begin{cases} \dfrac{\partial \bar{c}_p}{\partial t} + A_1\,(\bar{c}_p - \bar{c}) + \dfrac{A_2}{c_0^h}\,(\bar{c}_p - \bar{c})^2 + R_p\,\bar{c}_p = 0 \text{ on } \Sigma_\chi, \\ \bar{c}_p(0) = \dfrac{M_0}{\int_{\Sigma_\chi} \left(h + \frac{h^2}{2}\,H + \frac{h^3}{3}\,K\right)\,d\Sigma} \text{ on } \Sigma_\chi, \end{cases} \tag{4.2.2}$$

where R, V, and D are defined as

$$D(x) = \begin{cases} D_l, & x \in \Omega_l, \\ D_w, & x \in \Omega_w, \end{cases} \quad V(x) = \begin{cases} V_l(x), & x \in \Omega_l, \\ 0, & x \in \Omega_w, \end{cases} \quad R(x) = \begin{cases} 0, & x \in \Omega_l, \\ R_w, & x \in \Omega_w. \end{cases} \tag{4.2.3}$$

Or, in static variational form, $\exists(u,\bar{u}_p) \in H^1(\Omega_\chi) \times \mathbb{R}$ such that

$$a\left((u,\bar{u}_p),(v,\bar{v}_p)\right) = 0, \quad \forall(v,\bar{v}_p) \in H^1(\Omega_\chi) \times \mathbb{R}, \tag{4.2.4}$$

where

$$\begin{aligned} &a\left((u,\bar{u}_p),(v,\bar{v}_p)\right) \\ &= \int_{\Omega_\chi} D\nabla u \cdot \nabla v + V \cdot \nabla uv + Ruv \, dx + \int_{\Gamma_0} \beta_0 uv \, d\Gamma + \int_{\Gamma_L} \beta_L uv \, d\Gamma \\ &+ \int_{\Sigma_\chi} A_1 \left(\bar{c}_p - \bar{c}\right)\left(\bar{v}_p - v\right) + \frac{A_2}{c_0^h}\left(\bar{c}_p - \bar{c}\right)^2\left(\bar{v}_p - v\right) + R_p \, \bar{c}_p(\bar{v}_p - v) \, d\Sigma. \end{aligned} \tag{4.2.5}$$

Questions of existence and uniqueness of the solution to system (4.2.1)-(4.2.2) or (4.2.4)-(4.2.5) enter the domain of non-linear control, which goes beyond the scope of this work. In addition, contrary to [42], the mass of product is not constant in the vessel (since there is a loss term as well as the transparency conditions), which makes it impossible to decouple $\bar{c}_p$ and $\bar{c}$.

4.3. Normalised Concentration

In this section we follow the construction of [42], where we recreate the drug-release ODE obtained in [7] for the normalised mass released into the wall from our system of equations. We do this by examining the effect on the equations as we let the thickness h go to zero. However, this results in the initial concentration $\bar{c}_p(0)$ going to infinity. To prevent this, we define the *normalised concentrations* with respect to c_0^h

$$\hat{c}(x,t) \overset{\text{def}}{=} \frac{c(x,t)}{c_0^h}, x \in \Omega_\chi, \quad \hat{c}_p(X,t) \overset{\text{def}}{=} \frac{\bar{c}_p(X,t)}{c_0^h}, X \in \Sigma_\chi. \tag{4.3.1}$$

Since almost all of the equations in (4.2.1) are linear, they remain valid when substituting the normalised concentration. The only parts that are affected are the quadratic terms on

Σ_χ and the initial condition $\hat{c}_p(0)$:

$$\begin{cases} \dfrac{\partial \hat{c}}{\partial t} - \operatorname{div}\,(D\nabla\hat{c}) + R_w\,\hat{c} + V\cdot\nabla\hat{c} = 0 \text{ in } \Omega_\chi, \\ \hat{c}(0) = 0 \text{ in } \Omega_\chi, \\ D_w\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_w}} + D_l\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Gamma_{lw}\backslash\Sigma_\chi, \\ \beta(h)\,D_w\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_w}} = h\,\dfrac{\partial \hat{c}_p}{\partial t} \text{ on } \Sigma_\chi, \quad D_l\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_l}} = 0 \text{ on } \Sigma_\chi. \\ D\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_\chi}} + \beta_0\,\hat{c} = 0 \text{ on } \Gamma_0,\ D\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_\chi}} + \beta_L\,\hat{c} = 0 \text{ on } \Gamma_L,\ D\,\dfrac{\partial \hat{c}}{\partial n_{\Omega_\chi}} = 0 \text{ on } \Gamma_{ext}, \end{cases} \tag{4.3.2}$$

$$\begin{cases} \dfrac{\partial \hat{c}_p}{\partial t} + A_1\,(\hat{c}_p - \hat{c}) + A_2\,(\hat{c}_p - \hat{c})^2 + R_p\,\hat{c}_p = 0 \text{ on } \Sigma_\chi, \\ \hat{c}_p(0) = 1. \end{cases} \tag{4.3.3}$$

The *normalised mass* in the polymer is defined as

$$m_p(t) \overset{\text{def}}{=} \frac{M_p(t)}{M_0}. \tag{4.3.4}$$

Since

$$M_p(t) = h\int_{\Sigma_\chi} \bar{c}_p(X,t)\,d\Sigma \quad \text{and} \quad c_0^h = \frac{M_0}{\int_{\Sigma_\chi} h + \frac{h^2}{2}H + \frac{h^3}{3}K\,d\Sigma},$$

we have that

$$\begin{aligned} m_p(t) &= \frac{h}{M_0}\int_{\Sigma_\chi} \bar{c}_p(X,t)\,d\Sigma = \frac{hc_0^h}{M_0}\int_{\Sigma_\chi} \hat{c}_p(X,t)\,d\Sigma \\ \implies \frac{dm_p(t)}{dt} &= \frac{1}{\int_{\Sigma_\chi} 1 + \frac{h}{2}H + \frac{h^2}{3}K\,d\Sigma}\int_{\Sigma_\chi} \frac{\partial \hat{c}_p(X,t)}{\partial t}\,d\Sigma. \end{aligned} \tag{4.3.5}$$

If we introduce the *area*

$$\left|\Sigma_\chi^h\right| \overset{\text{def}}{=} |\Omega_p^h|/h = \int_{\Sigma_\chi} 1 + \frac{h}{2}H + \frac{h^2}{3}K\,d\Sigma$$

and then combine (4.3.5) with (4.3.3), we obtain an ODE for m_p

$$\begin{cases} \dfrac{dm_p}{dt} + \dfrac{A_1}{\left|\Sigma_\chi^h\right|}\displaystyle\int_{\Sigma_\chi} \hat{c}_p - \hat{c}\,d\Sigma + \frac{A_2}{\left|\Sigma_\chi^h\right|}\int_{\Sigma_\chi} (\hat{c}_p - \hat{c})^2\,d\Sigma + \frac{1}{\left|\Sigma_\chi^h\right|}\int_{\Sigma_\chi} R_p\,\hat{c}_p\,d\Sigma = 0, \\ m_p(0) = \dfrac{1}{\left|\Sigma_\chi^h\right|}\displaystyle\int_{\Sigma_\chi} \bar{c}_p(0)\,d\Sigma = 1. \end{cases} \tag{4.3.6}$$

We are then interested in the effect on the equations as we take the the limit $h \to 0$. To start, we have that $\hat{c} \to 0$ and $\left|\Sigma_\chi^h\right| \to |\Sigma_\chi|$. From there, (4.3.6) simplifies and for all $X \in \Sigma_\chi$ we have

$$\begin{cases} \dfrac{dm_p}{dt} + \dfrac{A_1}{|\Sigma_\chi|}\displaystyle\int_{\Sigma_\chi} \hat{c}_p \, d\Sigma + \dfrac{A_2}{|\Sigma_\chi|}\displaystyle\int_{\Sigma_\chi} (\hat{c}_p)^2 \, d\Sigma + \dfrac{1}{|\Sigma_\chi|}\displaystyle\int_{\Sigma_\chi} R_p \, \hat{c}_p \, d\Sigma = 0, \quad X \in \Sigma_\chi, \\ m_p(0) = 1. \end{cases} \tag{4.3.7}$$

Since $\hat{c} = 0$ in equation (4.3.3), the solution of that equation is independent of the point $X \in \Sigma_\chi$. It then reduces to the following ODE in time

$$\begin{cases} \dfrac{d\hat{c}_p}{dt} + A_1 \, \hat{c}_p + A_2 \, (\hat{c}_p)^2 + R_p \, \hat{c}_p = 0, \\ \hat{c}_p(0) = 1, \end{cases}$$

whose solution is independent of the point $X \in \Sigma_\chi$: $\hat{c}_p(X,t) = \hat{c}_p(t)$. As a consequence, since

$$m_p(t) = \frac{hc_0^h}{M_0}\int_{\Sigma_\chi} \hat{c}_p(X,t) \, d\Sigma \quad \text{and} \quad \frac{hc_0^h}{M_0} = \frac{1}{\int_{\Sigma_\chi} 1 + \frac{h^2}{1} H + \frac{h^3}{2} K \, d\Sigma},$$

as h goes to zero $m_p(t) \to \hat{c}_p(t)$ and (4.3) implies that

$$\begin{cases} \dfrac{dm_p}{dt} + A_1 \, m_p + A_2 \, m_p^2 + R_p \, m_p = 0, \\ m(0) = 1, \end{cases}$$

This leads to the equation for the normalised released mass to the wall $m_w(t) = 1 - m_p(t)$

$$\begin{cases} \dfrac{dm_w}{dt} = A_1 \, (1 - m_w) + A_2 \, (1 - m_w)^2 + R_p \, (1 - m_w), \\ m_w(0) = 0, \end{cases} \tag{4.3.8}$$

which corresponds to the ODE equation from [7] with $a_1 = A_1$, $a_2 = A_2$, and an added loss factor R_p. As with the model for a straight vessel, the parameters for the curvilinear vessel can easily be obtained from experimental release curves such as those in [60].

CONCLUSION

The model presented here is a significant improvement from the one presented in [31]. It includes the flux function from [42] as boundary condition, which eliminates the factor of h in the denominator of the normalised equations (that led to infinite flux at the boundary). The normalised equation reduces to the ODE model from [7], and so the parameters can be easily calculated from release curves such as the ones presented in [61].

It is worth mentioning possible improvements to the model, which could serve as a subject for further research. The first two relate to the blood flow. Firstly, the pulsatile effects of blood flow have been eliminated by taking the average over the period, however this computational limitations is fairly standard; since blood flow occurs in the scale of seconds whereas drug release occurs on the scale of days, it would be computationally infeasible to use a small enough time scale to account for the pulse. For further reading on the subject, the reader is referred to

- C.C. O'Brien, V.B. Kolachalama, T.J. Barber, A. Simmons, and E.R. Edelman [68], *Impact of Flow Pulsatility on Arterial Drug Distribution in Stent-Based Therapy.*

Their findings provide significant insight into the subject. However, their results show that the effects may be stent and vessel dependent, while our model is intended to be as general as possible. Further refinements for particular stent design could be included during simulations. Secondly, the method used here to obtain the transparency conditions require that there is no blood flow in the wall of the vessel. In reality, while much slower than in the lumen, there is some flow within the wall as well. Depending on the type of drug used, this can result in the concentration obeying a form of diffusion-advection-reaction equation in the wall. For further reading into the subject of blood flow modelling, the reader is referred to the very in-depth article

- N. Bessonov, A. Sequeira, S. Simakov, Yu. Vassilevskii, and V. Volpert [6], *Methods of Blood Flow Modelling.*

An important assumption for the model is that both the lumen and the wall have a uniform thickness. This results in the change of variables to the tubular neighbourhood and the resulting integral formula, a necessary component of our analysis.

As mentioned in the introduction, the goal of this mémoire was to create an efficient and accurate model for the concentration of drug used to control the proliferation of smooth muscle cells. Future research could be done to incorporate a multi-phasic release that includes medicinal agents that help regenerate the endothelium in addition to those used to control the smooth muscle cells. We once again refer the readers interested in the subject to the following papers:

- Y. Xia, F. Boey, and S.. S. Venkatraman [**91**], *Surface modification of poly(L-lactic acid) with biomolecules to promote endothelialization*;
- R. A. Byrne, M. Joner, and A. Kastrati [**12**], *Stent thrombosis and restenosis: what have we learned and where are we going?* (this paper describes the present state of the art);
- W. K. E. Ip, N. Hoshi, D. S. Shouval, S. Snapper, and R. Medzhitov [**50**], *Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages*;
- S. Gonca [**44**], *Extracellular Matrix Proteomics Reveals Interplay of Aggrecan and Aggrecanases in Vascular Remodeling of Stented Coronary Arteries* (this paper deals with the rheology of the matrix).

Further research on the subject can be devoted to removing or weakening these restrictions, as well as continuing the analysis on the non linear problem (2.3.15)-(2.3.16) (or (4.2.4)-(4.2.5)) in order to gain more insight into the solution obtained.

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Appendix A

ELEMENTS OF FUNCTIONAL ANALYSIS, OPTIMISATION, SOBOLEV SPACE AND THEORY OF DISTRIBUTIONS

A.0.1. Functional Analysis

For the convenience of the reader, we present some definitions and preliminary notions necessary for our calculations. We start with a basic, but important, definition that occurs frequently in this work. Two norms on a space V, $\|\cdot\|$ and $|\cdot|$, are said to be *equivalent*[1] if there exists $\alpha, \beta > 0$ such that

$$\forall x \in V, \quad \alpha \|x\| \leq |x| \leq \beta \|x\| . \tag{A.0.1}$$

In particular, equivalent norms induce the same topology, and thus functions that are continuous for one norm will be continuous for the other.

Remark A.0.1. *The previous definition is valid for any space for which there is a norm. Moreover, some of the definitions and theorems that will be presented below can be defined more generally on Banach spaces or even simply normed vector spaces. However, since the spaces involved in our model are Hilbert spaces, we give the definitions in that context rather than specify what degree of regularity is required for each notion and result. In some cases this will also allow for simpler or more intuive characterisations. The general definitions, and accompanying results, can be found in* [64] *and* [9].

Let V be a Hilbert space (complete inner product space) on a field K, with inner product denoted $(\cdot\,,\,\cdot)$. We define the *dual space* of V, denoted V', as the set of linear and continuous functions $V \to K$. For all $\phi \in H'$, and for all $f \in H$, we denote $< \phi, f >$ as the *duality pairing*, which evaluates the functional ϕ at f. Since V is a Hilbert space, we then have the following theorem that characterises all of the elements of the dual space:

Theorem A.0.1. *(Riesz-Fréchet representation theorem, adapted from* [9, Théorème V.5, page 81]*)*

[1] An equivalent definition is given in [64, page 37]; it suffices to take $c = \min(\alpha, \beta^{-1})$.

$\forall \phi \in H', \exists! f \in H$ *such that*

$$< \phi, v >= (f, v), \quad \forall v \in H. \tag{A.0.2}$$

This allows us to identify V and V' by matching an element of V with the linear function it generates via the inner product:

$$v \in V \equiv (v, \cdot) \in V', \quad \forall v \in V. \tag{A.0.3}$$

The *weak topology* on V is defined as the *coarsest* topology on V for which all functions in V' are continuous. If V is finite-dimensional, then the strong topology[2] and the weak topology coincide. However, if V is infinite-dimensional, then the weak topology is strictly coarser than the strong topology.[3]

Having defined a weaker topology, we need to distinguish between convergence in one topology or the other. Let $\{x_n\}$ be a sequence in V. We say that $\{x_n\}$ converges weakly to $x \in V$ (denoted $\{x_n\} \rightharpoonup x$) if $\{x_n\}$ converges to x in the weak topology. In particular, since V is a Hilbert space, then the Riesz-Fréchet representation theorem implies that

$$\{x_n\} \rightharpoonup x \quad \iff \quad < x_n, y > \to < x, y >, \quad \forall y \in V. \tag{A.0.4}$$

The weak topology and weak convergence have many interesting properties, but for brevity we only mention one here (that we use in chapter 2): If $\{x_n\}$ is a bounded sequence in V, then $\exists x \in V$ such that $\{x_n\} \rightharpoonup x$.[4]

A.0.2. Optimisation

We now introduce the notions of optimisation that are used in this mémoire. The general definitions can be found in [4], however for simplicity they have been adapted for non time-dependant generators as occur in our equations.

Let V and H be two Hilbert spaces with the notation

$(\cdot\,, \cdot)$ is the inner product,

$\|\cdot\|$ is the norm (from the inner product),

$< \cdot\,, \cdot >$ is the duality pairing from a space and its dual.

Where needed, the applications will include a subscript to indicated in which space the operation takes place.

[2] that is, the topology induced by the norm.

[3] [64, Theorem 1, page 118].

[4] [64, Theorem 9, page 105]. Note that every Hilbert space is a reflexive Banach space. It then suffices to take the subset C as the closed ball of radius defined by the bound on $\{x_n\}$.

Assume that there is a continuous injection from V to H. Let $A \in \mathcal{L}(V,V')$ be a continuous, measurable linear operator such that

$$\exists c > 0 \text{ such that } | < Av,w >_V | \leq c \|v\| \, \|w\|, \quad \forall v,w \in V. \tag{A.0.5}$$

We introduce the following definitions:

Definition A.0.1. *([4, page 178])*

Let $A \in \mathcal{L}(V,V')$ be a continuous linear operator. We say that A is V-H coercive *if there exist $\alpha > 0$ and $\lambda \in \mathbb{R}$ such that*

$$\forall v \in V, < Av,v >_V + \lambda \|v\|_H^2 \geq \alpha \|v\|_V^2 . \tag{A.0.6}$$

If this holds true when $\lambda = 0$, then A is said to be coercive[5].

A.0.3. Sobolev Spaces and Theory of Distributions

The following definitions and results are taken from [48], with occasional modifications to the notation. Let Ω be an open subset of $\mathbb{R}^n$, and $K \subset \Omega$ be a compact subset. We define $\mathcal{D}^m(K)$ as the vector space of all functions $\phi : \mathbb{R}^n \to \mathbb{R}$ whose partial derivatives of order up to m exist and are continuous, and whose *support*[6] is contained in K. The set $\mathcal{D}^m(K)$ is non-empty[7] and, more importantly, is dense in $L^p(K), p = 1,2,\ldots$ [8]. Since this is the case, we have the reversed inclusion for the dual space:

$$\mathcal{D}^m(K) \subset L^p(K) \implies L^p(K)' \subset \mathcal{D}^m(K)' \quad p = 1,2,\ldots. \tag{A.0.7}$$

Let $\alpha = (\alpha_1, \ldots, \alpha_n) \in \mathbb{N}^n$ be a *multi-index* and denote by $|\alpha| = \alpha_1 + \cdots + \alpha_n$ the *order* of the multi-index. Given a function $\phi : \mathbb{R}^n \to \mathbb{R}$, introduce the notation

$$\partial^\alpha \phi \stackrel{\text{def}}{=} (\partial_1^{\alpha_1} \ldots \partial_n^{\alpha_n})\phi = \frac{\partial^{|\alpha|}\phi}{\partial_{x_1}^{\alpha_1} \ldots \partial_{x_n}^{\alpha_p}}.$$

We define the *semi-norms* $q_\alpha(\phi)$, by

$$q_\alpha(\phi) \stackrel{\text{def}}{=} \max_{x \in K} |\partial^\alpha \phi(x)|. \tag{A.0.8}$$

The set of functions $V_{\alpha,\varepsilon} \stackrel{\text{def}}{=} \{\phi \in \mathcal{D}^m(K) | q_\alpha(\phi) \leq \varepsilon\}$ forms a *fundamental system of neighbourhoods* for K[9]. The topology on $\mathcal{D}(\Omega)$ is defined as the finest topology for which all of the canonical injections i_k

$$\mathcal{D}(K) \stackrel{i_k}{\hookrightarrow} \mathcal{D}(\Omega) \tag{A.0.9}$$

[5] [4, page 175].
[6] The support of a function is the closure of the set of points for which the function is non-zero.
[7] [48, page 166].
[8] [88, page 22].
[9] [48, page 88 and page 90].

are continuous for all compact subsets $K \subset \Omega$[10].

A *distribution* on Ω is defined as a continuous linear form on $\mathcal{D}(\Omega)$. In other words, distributions are the elements of the dual space $\mathcal{D}(\Omega)'$. In particular, from (A.0.7), every element of $L^2(\Omega)'$ is also an element of $\mathcal{D}(\Omega)'$. Since $L^2(\Omega)$ is a Hilbert space, the Riesz representation theorem implies that we can construct elements of $\mathcal{D}(\Omega)'$ via the scalar product in L^2. More precisely, for $f \in L^2(\Omega)$ we define $T_f \in \mathcal{D}(\Omega)'$ as

$$\phi \mapsto T_f(\phi) \stackrel{\text{def}}{=} \int_\Omega f(x)\phi(x)\,dx : \mathcal{D}(\Omega) \to \mathbb{R}. \tag{A.0.10}$$

This definition allows us to define a notion of first order partial derivative[11] $\partial_j : \mathcal{D}(\Omega)' \to \mathcal{D}(\Omega)'$ (for j a *single* index). For $f \in C^1(\Omega)$ we want to ensure that the derivative associated with T_f is the same as the distribution associated with $\partial_j f$, that is to say that $\partial_j T_f = T_{\partial_j f}$. If we start from the right-hand side and apply integration by parts and the compact support of functions in $D(\Omega)$, for all $\phi \in \mathcal{D}(\Omega)$ we have

$$\begin{aligned}\int_\Omega \partial_j f(x)\phi(x)\,dx &= \int_{\partial\Omega} f(x)\phi(x)\,dx - \int_\Omega f(x)\partial_j\phi(x)\,dx \\ &= -\int_\Omega f(x)\partial_j\phi(x)\,dx.\end{aligned} \tag{A.0.11}$$

Or, in terms of the duality pairing

$$< T_{\partial_j f}, \phi >= - < T_f, \partial_j \phi > . \tag{A.0.12}$$

This naturally leads to the desired definition for the derivative: $\partial_j T$ is defined as the distribution such that

$$< \partial_j T, \phi >= - < T, \partial_j \phi >, \forall \phi \in \mathcal{D}(\Omega). \tag{A.0.13}$$

By induction, this definition can be extended to derivation of any order: For $\alpha \in \mathbb{N}^n$ a multi-index, define $\partial^\alpha T$ as the distribution such that

$$< \partial^\alpha T, \phi >= (-1)^{|\alpha|} < T, \partial^\alpha \phi >, \forall \phi \in \mathcal{D}(\Omega). \tag{A.0.14}$$

We say that a function g is the derivative *in the sense of distributions* of a function f if the distribution associated with g is the distributional derivative of the distribution associated with f, that is if $T_g = \partial T_f$. In general this requires a lower degree of regularity than the standard derivative (see [**48**, examples 4.1-4.3]).

This weaker notion of derivative allows us to easily define Sobolev Spaces. We present here the definitions given in [**14**, chapter 2] with additional definitions, as well as results

[10] [**48**, page 165].

[11] The definitions can be found in [**48**, chapter 4], however the notation has been modified to be more consistent with the previous set of definitions.

from [10, chapter 9]. We define[12] $W^{1,p}(\Omega)$ as the set of functions in $L^p(\Omega)$ for which all of its first-order partial derivatives *(in the sense of distributions)* are in $L^p(\Omega)$:

$$W^{1,p}(\Omega) = \{f \in L^p(\Omega) | \partial_m f \in L^p(\Omega),\, m = 1, \ldots, n\}\,. \tag{A.0.15}$$

We set $H^1(\Omega) = W^{1,2}(\Omega)$. We set the norm on $W^{1,p}(\Omega)$ as

$$\|f\|_{W^{1,p}} = \|f\|_L^2 + \sum_{m=1}^{n} \|\partial_m f\|_{L^2} \tag{A.0.16}$$

and the inner product on $H^1(\Omega)$ as

$$(u,v)_{H^1} = (u,v)_{L^2} + \sum_{m=1}^{n} (\partial_m u, \partial_m v)_{L^2}\,. \tag{A.0.17}$$

$W^{1,p}(\Omega)$ is a Banach space $\forall 1 \leq p \leq +\infty$ (which is reflexive for $p \neq 1, +\infty$ and separable for $p \neq +\infty$) and $H^1(\Omega)$ is a separable Hilbert space.[13]

Similarly, we define $W^{m,p}(\Omega), k = 2,3,\ldots$ as the set of functions in $L^p(\Omega)$ for which all of its partial derivatives ∂^α *(in the sense of distributions)* of order m are in $L^p(\Omega)$ or, equivalently

$$W^{m,p}(\Omega) = \{f \in L^p(\Omega) | \partial^\alpha f \in L^p(\Omega),\, |\alpha| \leq m\}\,, \tag{A.0.18}$$

and we set $H^m(\Omega) = W^{m,2}(\Omega)$. The norm on $W^{m,p}(\Omega)$ is defined as

$$\|f\|_{W^{m,p}} = \left(\sum_{|\alpha| \leq m} \int_\Omega |\partial^\alpha f|^2 \, dx \right)^{\frac{1}{2}} \tag{A.0.19}$$

and the inner product on $H^m(\Omega)$ is

$$(u,v)_{H^m} = (u,v)_{L^2} + \sum_{|\alpha|=1}^{m} (\partial^\alpha u, \partial^\alpha v)_{L^2}\,. \tag{A.0.20}$$

As before, $W^{m,p}(\Omega)$ is a Banach space $\forall 1 \leq p \leq +\infty$ and $H^m(\Omega)$ is a Hilbert space.[14]

[12] The definition given here is not found in [14], only a definition for the spaces $H^m(\Omega)$. Equivalent definitions for the spaces $W^{1,p}$ and $W^{k,p}$ can be found in [10, pages 263 and 271], however for consistency and simplicity we give the version presented here.

[13] [10, page 264]. Note that while the definition given for the spaces is different than the one presented here, remark 3 on page 264 clarifies that the two definitions are equivalent.

[14] [10, page 271]

Appendix B

ONE-DIMENSIONAL MODEL AND SINK CONDITION OF LAO

The following section is a transcript of a calculation made by A. Garon [41] that shows that the one-dimensional model in [62] with zero boundary conditions results in an infinite flux across the interface between the polymer and the medium that is physically unrealistic.

B.1. Detailed Computations

Let

$$\frac{\partial u}{\partial t} = c^2 \frac{\partial^2 u}{\partial u^2} \quad x \in]0,L[\,, \tag{B.1.1}$$

with initial conditions

$$u(x,0) = u_0, \quad \text{a constant},$$

and boundary conditions

$$u(L,t) = 0, \quad \text{the "sink" condition},$$
$$\frac{\partial u}{\partial x}(0,t) = 0.$$

We proceed by standard separation of variables method. That is, let F, a function of space, and G, a function of time, such that

$$u(x,t) = F(x)G(t)$$

Taking partial derivatives and applying (B.1.1) leads to

$$\frac{\dot{G}}{c^2 G} = \frac{F''}{F} = \text{cnst} = -p^2,$$

where $p > 0$ to ensure that the function is decreasing. From there we have that

$$F'' + p^2 F = 0,$$

$$\implies F(x) = A\cos(px) + B\sin(px).$$

The boundary conditions then become

$$\begin{cases} u(L,t) = F(L)G(t) = 0, \quad \forall t, \\ \dfrac{\partial u}{\partial x}(0,t) = F'(0)G(t) = 0, \quad \forall t. \end{cases} \tag{B.1.2}$$

Using the boundary condition at $x = L$, we obtain

$$\begin{aligned} u(L,t) = \{A\cos(pL) + B\sin(pL)\}\, G(t) = 0, \\ \implies A\cos(pL) + B\sin(pL) = 0. \end{aligned}$$

And from the boundary condition at $x = 0$, we have that

$$\begin{aligned} \frac{\partial u}{\partial x}(0,t) = \{-A\sin(px)p + B\cos(px)p\}_{x=0}\, G(t) = 0, \\ -Ap\underbrace{\sin(p\cdot 0)}_{\emptyset} + Bp\underbrace{\cos(p\cdot 0)}_{1} = 0, \\ \implies B = 0. \end{aligned}$$

Thus

$$\begin{aligned} A\cos(pL) = 0, \\ \implies \cos(pL) = 0, \\ \implies pL = \frac{\pi}{2}, \frac{3\pi}{2}, \frac{5\pi}{2}, \frac{7\pi}{2}, \dots \end{aligned}$$

We set

$$p = \frac{2n-1}{2}\frac{\pi}{L} \quad n = 1, \dots$$

$$\boxed{p_n = \left(n - \frac{1}{2}\right)\frac{\pi}{L}} \quad n = 1,2,3, \dots$$

We denote

$$\boxed{F_n(x) = \cos(p_n x)}$$

We now examine the time-dependant equation

$$\begin{aligned} \frac{dG}{G} &= -c^2p^2\, dt \\ G &= \mathrm{e}^{-c^2p^2t} \\ \implies &\boxed{G_n(t) = \mathrm{e}^{-c^2p_n^2t}}. \end{aligned}$$

Which leads to the equations

$$u_n(x,t) = F_n(x)G_n(t)$$

For which the general solution is given by

$$u(x,t) = \sum_{n=1}^{\infty} B_n \cos(p_n x)\, \mathrm{e}^{-c^2 p_n^2 t}$$

Applying the initial conditions then leads to

$$u(x,0) = \sum_{n=1}^{\infty} B_n \cos(p_n x) = u_0.$$

Lemma B.1.1. *For $m,n \geq 1$*

$$\frac{2}{L}\int_0^L \cos(p_n x)\cos(p_m x)\,dx = \begin{cases} 1, & m = n, \\ 0, & m \neq n. \end{cases}$$

Proof.

$$\cos(p_n x)\cos(p_m x) = \frac{\cos\left((p_n + p_m)x\right) + \cos\left((p_n - p_m)x\right)}{2},$$

$$\int_0^L \cos\left((p_n + p_m)x\right)\,dx = \frac{1}{p_n + p_m}\sin\left((p_n + p_m)x\right)\Big|_0^L.$$

$$= \frac{1}{p_n + p_m}\sin\left((p_n + p_m)L\right) \tag{B.1.3}$$

$$\int_0^L \cos\left((p_n - p_m)x\right)\,dx = \frac{1}{p_n - p_m}\sin\left((p_n - p_m)x\right). \tag{B.1.4}$$

We have

$$\text{(B.1.3)} \implies p_n + p_m = (m + n - 1)\frac{\pi}{L},$$

$$\implies \sin\left((p_n + p_m)L\right) = \sin\left(\underbrace{(m + n - 1)}_{\in\mathbb{Z}}\pi\right) = 0,$$

$$\text{(B.1.4)} \implies p_n - p_m = (n - m)\frac{\pi}{L},$$

$$\implies \sin\left(\underbrace{(n - m)}_{\in\mathbb{Z}}\pi\right) = 0, \text{ if } n - m \neq 0.$$

And if $n = m$, we have

$$\frac{1}{\frac{\pi}{L}(n-m)}\sin\left((n-m)\pi\right) = \frac{L}{\pi(n-m)}\left(x - \frac{x^3}{3!} + \dots\right)_{x=(n-m)\pi},$$

$$= L\left(1 - \underbrace{\cdots}_{\emptyset \text{ if } n=m}\right),$$
$$= L.$$

Thus

$$\int_0^L \cos(p_n x)\cos(p_m x)\,dx = \begin{cases} 0, & m \neq n, \\ \dfrac{L}{2}, & m = n. \end{cases}$$

And

$$\frac{2}{L}\int_0^L \cos(p_n x)\cos(p_m x)\,dx = \begin{cases} 0, & m \neq n, \\ 1, & m = n. \end{cases}$$

□

We now return to the initial condition and apply the lemma

$$\begin{aligned} u_0 &= \sum_{n=1}^{\infty} B_n \cos(p_n x), \\ \implies u_0\cos(p_m x) &= \sum_{n=1}^{\infty} B_n \cos(p_n x)\cos(p_m x), \\ \implies \frac{2}{L}\int_0^L u_0\cos(p_m x)\,dx &= \sum_{n=1}^{\infty} B_n \frac{2}{L}\int_0^L \cos(pn_x)\cos(p_m x)\,dx, \\ \implies \frac{2}{L}\int_0^L u_0\cos(p_m x)\,dx &= B_m. \end{aligned}$$

Moreover, we have that

$$\begin{aligned} \int_0^L \cos(p_m x)\,dx &= \frac{1}{p_m}\sin(p_m x)|_0^L\,, \\ &= \frac{1}{p_m}\sin(p_m L). \end{aligned}$$

Remark B.1.1. *In general, for $m = 1,2,\ldots,$ we have $p_m L = \frac{m\pi}{2}$ and*

$$\sin(p_m L) = \begin{cases} 1, & \textit{if } m \textit{ is odd}, \\ -1, & \textit{if } m \textit{ is even}. \end{cases} \tag{B.1.5}$$

Thus,

$$\begin{aligned} &\sin(p_m L) = (-1)^{m-1}, \quad m \geq 1, \\ &\implies \int_0^L \cos(p_m x)\,dx = \frac{(-1)^{m-1}}{p_m}. \end{aligned} \tag{B.1.6}$$

This allows us to calculate the explicitly calculate the initial condition

$$B_m = u_0\frac{2}{L}\int_0^L \cos(p_m x)\,dx,$$

$$\implies B_m = u_0 \frac{2}{L} \frac{(-1)^{m-1}}{p_m},$$

$$\text{or } \boxed{B_m = u_0 \frac{4}{(2m-1)\pi} (-1)^{m-1}.}$$

To summarise, we have:

$$p_n = \frac{2n-1}{2} \frac{\pi}{L},$$
$$B_n = u_0 \frac{4}{(2n-1)\pi} (-1)^{m-1},$$
$$u(x,t) = \sum_{n=1}^{\infty} B_n \cos(p_n x)\, \mathrm{e}^{-c^2 p_n^2 t}\,.$$

Remark B.1.2. *If we denote* $\hat{u} \overset{\text{def}}{=} \frac{u(x,t)}{u_0}$ *the* normalised *concentration, then the previous calculations imply that*

$$\hat{u}(x,0) = \sum_{n=1}^{\infty} \hat{B}_n \cos(p_n x)\, \mathrm{e}^{-c^2 p_n^2 t},$$
$$\hat{B}_n = \frac{4}{(2n-1)\pi} (-1)^{m-1},$$
$$\sum_{n=1}^{\infty} \hat{B}_n \cos(p_n x) = 1.$$

We have that

$$M(t) = \int_0^L \hat{u}(x,t)\, dx,$$
$$M(0) = \int_0^L \hat{u}(x,0)\, dx = L.$$

And thus, if we calculate the normalised mass in the polymer, we have

$$\begin{aligned}
m_p(t) = \frac{M(t)}{M(0)} &= \frac{1}{L} \int_0^L \hat{u}(x,t)\, dx, \\
&= \frac{1}{L} \left(\sum_{n=1}^{\infty} \hat{B}_n\, \mathrm{e}^{-c^2 p_n^2 t} \int_0^L \cos(p_n x)\, dx \right), \\
&= \frac{1}{L} \left(\sum_{n=1}^{\infty} \hat{B}_n\, \mathrm{e}^{-c^2 p_n^2 t}\, \frac{(-1)^{n-1}}{p_n} \right), \\
&= \sum_{n=1}^{\infty} \hat{B}_n \frac{(-1)^{n-1} 2}{(2n-1)\pi}\, \mathrm{e}^{-c^2 p_n^2 t}, \\
&= \sum_{n=1}^{\infty} \frac{4}{(2n-1)\pi} (-1)^{n-1} \frac{(-1)^{n-1} 2}{(2n-1)\pi}\, \mathrm{e}^{-c^2 p_n^2 t}, \\
&= \sum_{n=1}^{\infty} \frac{8(-1)^{2n-2}}{(2n-1)^2\, \pi^2}\, \mathrm{e}^{-c^2 p_n^2 t}\,.
\end{aligned}$$

Remark B.1.3. *In particular, if we examine the (normalised) initial mass of product in the polymer, we have* $m_p(0) = \sum_{n=1}^{\infty} \frac{8(-1)^{2n-2}}{(2n-1)^2\pi^2} = 1$.

We now proceed to examine the normalised mass of product in the medium $m(t) = 1 - m_p(t)$. By substitution, we have

$$\boxed{m(t) = 1 - \sum_{n=1}^{\infty} \left[\frac{8}{(2n-1)^2\pi^2}\right] \mathrm{e}^{-c^2 p_n^2 t}}$$

We then differentiate this equation to calculate the flow of the released mass at $t = 0$

$$\begin{aligned}
\frac{dm}{dt} &= a_0(1-m) + a_1(1-m)^2, \\
&= -\sum_{n=1}^{\infty} \left[\frac{8}{(2n-1)^2\pi^2}\right] (-c^2 p_n^2)\, \mathrm{e}^{-c^2 p_n^2 t}, \\
\implies \left.\frac{dm}{dt}\right|_{t=0} &= a_0 + a_1 = \sum_{n=1}^{\infty} \left[\frac{8}{(2n-1)^2\pi^2}\right] c^2 p_n^2.
\end{aligned}$$

If we simplify $a_0 + a_1$, we have

$$\begin{aligned}
a_0 + a_1 &= c^2 \sum_{n=1}^{\infty} \left[\frac{8}{(2n-1)^2\pi^2}\right] \left(\frac{2n-1}{2}\right)^2 \pi^2, \\
&= c^2 \sum_{n=1}^{\infty} 2 = \infty.
\end{aligned}$$

We also calculate the flow of the normalised concentration

$$\begin{aligned}
\hat{u}(x,t) &= \sum_{n=1}^{\infty} \hat{B}_n \cos(p_n x)\, \mathrm{e}^{-c^2 p n^2 t}, \\
\implies \frac{\partial \hat{u}}{\partial x} &= -\sum_{n=1}^{\infty} \hat{B}_n p_n \sin(p_n x)\, \mathrm{e}^{-c^2 p n^2 t}, \\
\implies \left.\frac{\partial \hat{u}}{\partial x}\right|_{x=L} &= -\sum_{n=1}^{\infty} \hat{B}_n p_n \sin(p_n L)\, \mathrm{e}^{-c^2 p n^2 t}, \\
\implies \left.\frac{\partial \hat{u}}{\partial x}\right|_{x=L} &= -\sum_{n=1}^{\infty} \hat{B}_n p_n (-1)^{n-1}\, \mathrm{e}^{-c^2 p n^2 t}\,. \qquad \text{(B.1.7)}
\end{aligned}$$

But

$$\begin{aligned}
\hat{B}_n p_n (-1)^{n-1} &= \frac{4}{(2n-1)\pi}(-1)^{n-1}\frac{(2n-1)\pi}{2L}(-1)^{n-1}, \\
&= \frac{2}{L}.
\end{aligned}$$

We apply this to equation (B.1.7) to obtain

$$\left.\frac{\partial \hat{u}}{\partial x}\right|_{x=L} = -\frac{2}{L}\sum_{n=1}^{\infty} \mathrm{e}^{-c^2 p_n^2 t},$$

$$\underbrace{c^2 \left.\frac{\partial \hat{u}}{\partial x}\right|_{x=L}}_{\text{flow leaving the polymer}} = -\frac{2}{L}\sum_{n=1}^{\infty} \mathrm{e}^{-c^2 p_n^2 t}\,.$$

Evaluating this equation at $t = 0 \implies -c^2 p_n^2 t = 0$, we have that

$$\begin{aligned} c^2 \frac{\partial \hat{u}}{\partial x} &= -\frac{2c^2}{L}\sum_{n=1}^{\infty} 1 \\ &= -\infty. \end{aligned}$$