ANALYSIS AND CONTROL OF A BIOFILM

DISINFECTION MODEL

by

Barbara Szomolay

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Dr. Isaac Klapper

Approved for the Department of Mathematics

Dr. Ken Bowers

Approved for the Division of Graduate Education

Dr. Carl A. Fox
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Barbara Szomolay

August, 2006
This thesis is dedicated to my parents
who have always been supportive
and to Martin. Thank you for everything.
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The goal of this dissertation is to study a complex biofilm model with a phenotypic structure presented in [34]. The model in [34] is extended - growth and detachment is added, making the new model more interesting in applications. The crucial feature of our model is that cells are able to enter an adapted resistant state when challenged with antimicrobials (adaptation). We study this model in both a qualitative and quantitative manner. Existence and uniqueness of solutions is shown as well as the existence and non-uniqueness of steady-state solutions. Another question of interest is the effective dosing of biocide, i.e. exploring dosing strategies that could minimize the number of living cells or biofilm thickness. Constant and periodic dosing regimes are modelled numerically and studied analytically. One of our main results is that on and off dosing is significantly better than the other dosing types. The model presented in this dissertation contributes to a better understanding of one of the resistant mechanisms in biofilms.
CHAPTER 1

THE BIOFILM MODEL

Introduction

*Biofilms* are structured communities of bacterial cells that live adherent to a surface or interface and which are surrounded in a self-produced extracellular matrix. It has been estimated that 99% of all bacteria live in biofilm communities. It is now recognized that biofilm formation is an important aspect of many, if not most, bacterial infections, including urinary tract infections (caused by *Escherichia coli*), catheter infections (caused by *Staphylococcus aureus*), child middle-ear infections (caused by *Haemophilus influenza*), dental plaque formation, and gingivitis. Less common but more threatening are biofilm infections that cause serious morbidity and mortality. These include infections of permanent indwelling devices such as joint prostheses and heart valves, also caused by *S. aureus*; and infections in cystic fibrosis patients caused by *Pseudomonas aeruginosa* (see [20]). Thus bacterial biofilm formation is an extremely serious medical problem, the treatment of which costs in excess of $1 billion annually in the USA alone. In addition, established biofilms can tolerate antimicrobial agents at concentrations of 10-1000-times greater than those needed to kill genetically equivalent planktonic (free-swimming) bacteria, making them extremely difficult to
eradicate from living hosts. Understanding the mechanisms that control the formation of biofilms and could lead to their reduction (and if possible, eradication) are important for prevention of biofilm infection and its removal.

Studying the processes that take place inside a biofilm is difficult since their thickness is on the order of 10 to 100 microns. Therefore, experiments are hard to design and perform. By using mathematical models, particular (simplified) processes can be studied in a biofilm setting. Mathematical models for biofilm processes have been formulated since the 70’s and 80’s. These first models were ordinary or partial differential equations assuming a biofilm develops as a flat layer. New technologies, however, revealed that in reality biofilms grow in highly irregular spatial structures. Consequently, multi-dimensional models describing spatial non-uniformities were developed in the 90’s, in addition to one-dimensional models which are still useful tools for the analysis of biological interactions ([10], [19], [1], [8]). There are a couple of papers which study the solutions of biofilm models mathematically. As an example we could mention the van Loosdrecht’s et al., [21] and Efendiev’s et al., [11] studies of a nonlinear density-dependent system of diffusion-reaction equations describing disinfection of biofilm by antibiotics. Dockery & Klapper, [8] study finger formation in biofilms. In what follows, we will classify the related biofilm literature according to the following topics:
Resistance

Resistance is an ability of a microorganism to grow in the presence of an elevated level of an antimicrobial. Briefly, a resistant strain is one for which the MIC is increased (MIC - Minimum Inhibitory Concentration - the lowest concentration of the antimicrobial agent that still inhibits bacterial growth). By this criterion, biofilm cells do not necessarily show increased resistance. With some exceptions, biofilm cells do not grow better than planktonic cells in the presence of a broad range of antimicrobials. However, in most biofilm susceptibility studies, only survival of cells in a biofilm rather than the ability of a biofilm to grow is recorded. Accordingly, the reported ”resistance” describes an increased resistance of cells to killing (see [20]). In biofilms, poor antibiotic penetration, nutrient limitation and slow growth, adaptive stress responses, and formation of persister cells are considered to be responsible for biofilm resistance ([27], [33], [20], [22], [25]).

One of the best-known of these biofilm-specific properties is the development of antibiotic resistance that can be up to 1,000-fold greater than planktonic cells (see [23]). There are numerous in vitro results in which biofilms exhibit reduced susceptibility to antimicrobials compared with planktonic cells ([12], [4], [7]). We study the longtime behavior of solutions of a simpler but nonlinear biofilm model (without growth and detachment) in Chapter 2. In particular, we have shown that thin biofilms behave like planktonic populations. The long-time behavior of solutions
indicates that there are only adapted cells remaining for thick biofilms as opposed to thin biofilms.

**Phenotypic tolerance**

One current area of intense focus in biofilm research has been determining the biofilm phenotype of different organisms. The biofilm phenotype is defined as the patterns of protein and gene expression associated with biofilm cultures in comparison to those associated with planktonic culture (see [24]). It has been shown by Wiuff et al., [36] that phenotypic tolerance can impair the efficacy of treatment more than antibiotic decay or inherited resistance (which are also responsible for bacterial mortality). Using a mathematical model, Wiuff argued that phenotypic tolerance can have a profound effect on the rate of clearance of the bacteria and under some conditions can prevent clearance that would be achieved in the absence of tolerance. Since the biofilm phenotype can be described in terms of the genes expressed by biofilm-associated cells, in the future, treatments may be based on inhibition of genes involved in cell attachment and biofilm formation (see [9]). For *Pseudomonas aeruginosa* biofilms, it has been hypothesized that new genes are expressed when bacteria attach to a surface and begin to form a biofilm and that some of the resulting gene products reduce the susceptibility of cells to antimicrobial agents including oxidative biocides such as monochloramine and hydrogen peroxide (see [4]).
Our biofilm model describes a bacterial population consisting of two phenotypes. Phenotypic tolerance is expressed through the formation of a specific phenotype, adapted cells, as a response to antimicrobial challenges. The Chambless et al., [3] 3-D biofilm computer model predicts that slow penetration combined with an adaptive stress response offers greater protection. In this case, the antimicrobial fails to eradicate the biofilm due to the transformation of live cells into persister cells, which are immune to the antimicrobial agent and are invulnerable to killing. One of the assumptions of Chambless’ computer model is that the persister cells in an antimicrobial-treated biofilm should retain their antimicrobial tolerance for some time even if they are dispersed from the biofilm. Persister cells may revert to the unadapted state if they are grown in the absence of the antimicrobial agent, but the process of persister cells returning to the unadapted state was not incorporated in [3]. It is assumed in [28] that persister cells exposed to substrate revert to the unadapted state faster than persister cells that are deprived of substrate, i.e. substrate does have an effect on reversion. In our model abundance of substrate will be assumed. In case of adaptation, however, reversion is not negligible, otherwise, all the cells would convert to the adapted state in a short time period. Hence, we assume that the adapted-unadapted reversion rate is a constant independent of the presence of biocide.
Dosing

There are several studies on biofilm dosing strategies for biofilm control. Cogan et al., [6] predict in their model of physiological resistance that exposing the biofilm to low concentration doses of antimicrobial agent for longer time is more effective than short time dosing with high antimicrobial agent concentration. They also find that reversing the bulk fluid flow during the antimicrobial agent application increases the effectiveness of the treatment. On the other hand, according to experimental studies by Grobe et al., [16] and Sanderson & Stewart, [29] treating biofilms with concentrated dose of biocide is more effective than using prolonged doses of a lower concentration. Other modelling studies indicate that a relative dosing/withdrawal time is an important factor in determining the effectiveness of such a treatment ([32], [5]). Grant & Brott, [15] show that concentration is a critical factor for control since increased frequency of dosing is only effective if the concentration employed is biofilm growth inhibiting. In Steuernagel & Polani’s, [31] simulations, persistent organisms have to be fought using tailored eradication strategies. It is argued that if treatment has to be limited, than the application of medication should be concentrated towards the beginning and end of the treatment period, i.e., a two-shot approach can yield optimal results. This is because the delayed response of persisters due to their hibernating behavior yields to a tradeoff between eradication of active versus persister cells. Their optimal strategy finds the strongest suppression of persisters at one end and the strongest suppression of active bacteria at the other end of the treatment.
This finding deviates from current clinical practise, and may therefore help to simplify and optimize treatments.

One of our goals in this thesis is to suggest optimal dosing strategies that would suppress the resistance of bacteria or minimize biofilm thickness. We also take into account the cost of biocide. For given cost of biocide we look for an optimal treatment. To our best knowledge, this is the first time the cost of biocide has been considered in this type of problem. We study three types of dosing strategies - constant dosing, periodic dosing (biocide dose is positive during the antibiotic treatment) and periodic dosing with withdrawal time that is called on and off dosing. In some cases periodic dosing is a slightly more effective than constant dosing. Our analysis of on and off dosing confirms that it is more efficient than the other dosing types and that short dosing time combined with a higher dose at the time of dosing is the most optimal, i.e. a delta-function type dosing regiment is the most effective. Our results in all three types of dosing indicate that if the biocide cost is small, it is better to treat the biofilm than to leave it untreated which corresponds to real-life expectations. If the cost of biocide is too high, the best course of action is not to treat biofilm at all.

**Detachment**

The rate of erosion detachment is influenced by shear stress, nutrient supply and biofilm thickness (see [17]). According to von Loosdrecht *et al.*, [21], detachment
plays a significant role in the morphology of biofilms. In systems with a high detachment (or shear) force, detachment will be in the form of erosion, giving smoother biofilms. Systems with a low detachment force tend to give a more porous biofilm and detachment occurs mainly by sloughing. Experimental results by Srinivasan et al., [30] indicate that detachment and disinfection rate coefficients are important factors influencing biofilm susceptibility to antimicrobial challenge. Therefore, our model also includes detachment forces with a commonly used detachment rate of the form $\sigma L^2$ for some $\sigma > 0$ (see [17]). However, our existence results for solutions of the PDE model apply to any positive continuous function $f(L)$ and our existence results for the corresponding steady-state solutions apply to any detachment rate $f(L)$ such that $\frac{f(L)}{L} \to \infty$ as $L \to \infty$.

In this thesis, a one dimensional biofilm model is presented and the solutions of this model are analyzed. Specific objectives of this thesis are:

- investigate phenotypic resistance (the bacterial population, though genetically homogeneous, is physiologically heterogenous with respect to its susceptibility, which during antibiotic exposure leads to an increased fraction of the phenotypically tolerant bacteria and thus to a decrease in the overall bacterial mortality)

- study the efficacy of antimicrobial agents leading to the proposal of new dosing strategies.
We proposed to build on the mathematical models developed previously. Our objective in [34] was to investigate a 1-D biofilm model the main feature of which is that cells are able to enter an adapted resistant state in the presence of biocide. Results indicate, that for a sufficiently thick biofilm, bacteria in the biofilm demonstrates more adaptive resistance in response to antimicrobial stress than do planktonic bacteria. It is important that a mathematical model with background in biology carries model features that are reasonable in real life applications. Therefore, in Chapter 2 we show that the model introduced in [34] has nonnegative and bounded solutions on smooth domains in $\mathbb{R}^2$ and $\mathbb{R}^3$.

The biofilm models introduced in [34] and Chapter 2 neglect growth and detachment. However, these model assumptions are only valid on a short time scale. Our goal was to come up with a more realistic model that can be used in applications in both a qualitative and quantitative manner. The phenotypic structure presented in [34] and Chapter 2 forms the basis of a more complicated biofilm model we study in this Thesis. On long time scales, growth and detachment of a biofilm population cannot be neglected. Hence, our model incorporates growth and detachment and we assume that there is no substrate-limitation, i.e. there is abundance of nutrients. Under these conditions we qualitatively investigate the extended model, in particular,
we show the existence and uniqueness of solutions as well as the existence and non-uniqueness of steady-state solutions. Moreover, the results of numerical simulations for each of the dosing protocols are explained either heuristically or analytically.

The outline of the thesis is the following: in Chapter 1 the dimensional and dimensionless form of the biofilm model is presented as well as the minimizing functionals that will be used to optimize the cost of a biocide treatment later in Chapters 5 and 6. Chapter 2 deals with a simpler biofilm model (without growth and detachment) for which existence of solutions are shown and longtime behavior of solutions are studied. In Chapters 3 and 4 the existence of solutions of the more complicated biofilm model as well as the existence of steady-state solutions is proved. Chapter 5 deals with the simplest dosing strategy - constant dosing and Chapter 6 includes the analysis of the periodic type dosing regiment.

Model Assumptions

Assumptions 1-5 refer to the model without growth and detachment discussed in Chapter 2. Assumptions 6-8 refer to the modifications made in the simple biofilm model in Chapter 2 and hence, more complicated model that is studied in Chapters 3-6.

1. The biofilm is attached to a flat slab called the substratum that is non-reactive towards the biofilm.
Table 1. Model parameters and variables.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Units</th>
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<tr>
<td>$b_a, b_u$</td>
<td>adapted/unadapted cell disinfection rate</td>
<td>cm$^3$(g s)$^{-1}$</td>
</tr>
<tr>
<td>$B$</td>
<td>locally applied biocide concentration</td>
<td>g/cm$^3$</td>
</tr>
<tr>
<td>$B_0$</td>
<td>externally applied biocide concentration</td>
<td>g/cm$^3$</td>
</tr>
<tr>
<td>$C$</td>
<td>locally applied substrate concentration</td>
<td>g/cm$^3$</td>
</tr>
<tr>
<td>$C_0$</td>
<td>externally applied substrate concentration</td>
<td>g/cm$^3$</td>
</tr>
<tr>
<td>$D_B, D_C$</td>
<td>biocide/substrate diffusion rate</td>
<td>cm$^2$/s</td>
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<tr>
<td>$D$</td>
<td>diffusion rate</td>
<td>cm$^2$/s</td>
</tr>
<tr>
<td>$f_a, f_{ad}, f_u, f_{ud}$</td>
<td>detachment rates for each of the cell-types</td>
<td>cm$^2$(g s)$^{-1}$</td>
</tr>
<tr>
<td>$f_0$</td>
<td>detachment rate</td>
<td>cm$^2$(g s)$^{-1}$</td>
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<tr>
<td>$k_a, k_u$</td>
<td>biocide-adapted/unadapted cell reaction rate</td>
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<tr>
<td>$k$</td>
<td>biocide-cell reaction rate</td>
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<td>$K_a, K_u$</td>
<td>adapted/unadapted Monod constant</td>
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<td>$K$</td>
<td>Monod constant</td>
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<td>biofilm thickness</td>
<td>cm</td>
</tr>
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<td>$m_0$</td>
<td>unadapted-unadapted cell transformation rate</td>
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<tr>
<td>$\mu_a, \mu_u$</td>
<td>adapted/unadapted maximum growth rate</td>
<td>1/s</td>
</tr>
<tr>
<td>$\mu$</td>
<td>maximum growth rate</td>
<td>1/s</td>
</tr>
<tr>
<td>$r_0$</td>
<td>adapted-unadapted cell reversion rate</td>
<td>1/s</td>
</tr>
<tr>
<td>$v$</td>
<td>velocity</td>
<td>cm/s</td>
</tr>
<tr>
<td>$X_u$</td>
<td>unadapted cell density</td>
<td>cells/cm$^3$</td>
</tr>
<tr>
<td>$X_{ud}$</td>
<td>dead unadapted cell density</td>
<td>cells/cm$^3$</td>
</tr>
<tr>
<td>$X_a$</td>
<td>adapted cell density</td>
<td>cells/cm$^3$</td>
</tr>
<tr>
<td>$X_{ad}$</td>
<td>dead adapted cell density</td>
<td>cells/cm$^3$</td>
</tr>
<tr>
<td>$X_0$</td>
<td>total cell density</td>
<td>cells/cm$^3$</td>
</tr>
<tr>
<td>$Y_a, Y_u$</td>
<td>adapted/unadapted yield constant</td>
<td>g/g</td>
</tr>
<tr>
<td>$Y$</td>
<td>yield constant</td>
<td>g/g</td>
</tr>
<tr>
<td>$\zeta_a, \zeta_u$</td>
<td>adapted/unadapted decay rate</td>
<td>1/s</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>decay rate</td>
<td>1/s</td>
</tr>
</tbody>
</table>
2. Biocide is applied through the *biofilm-bulk fluid interface* at a given concentration. The total cell-density is constant in space and time (incompressibility).

3. Living cells are transformed to dead cells at rates proportional to the biocide concentration.

4. Biocide is consumed by reactions with biomass at rate proportional to the biocide concentration and biocide is diffusing within the biofilm according to Fick’s law. It is assumed that even dead cells will continue to degrade the antimicrobial agents.

5. Living, unadapted cells transform to living, adapted cells at a constant rate (transformation to adapted resistant state).

6. Living, adapted cells revert to living, unadapted cells at a constant rate (reversion to unadapted state).

7. The biofilm both grows and detaches and the growth of living cells is governed by Monod kinetics. We assume that *saturation* of substrate occurs, i.e. there is no substrate-limitation.

8. Cells within the biofilm are not mobile. Their movement only occurs as the surrounding material expands due to growth. Hence, the flux of biomass constituents is the product of velocity and cell-density.
Derivation of the Model

The model is derived from mass balance principles that describe the biocide concentration, substrate concentration and biomass constituents within the biofilm. This system of equations is coupled with an equation that describes the evolution of biofilm thickness. Derivation of similar equations using mass-balance principles is done in detail in [26]. Therefore, we leave it as a reference.

Bacterial population will be assumed to comprise four phenotypes, \( X_u \) - unadapted cells, \( X_{ud} \) - dead unadapted cells, \( X_a \) - adapted cells and \( X_{ad} \) - dead adapted cells, subject to condition \( X_u + X_{ud} + X_a + X_{ad} = X_0 \), where \( X_0 \) is constant in space and time. We assume that there is one growth-limiting substrate, \( C \) and one antibiotic, \( B \). The population of unadapted cells changes due to growth, death due to antibiotic action, loss due to transition to adapted cells and gain as the adapted cells revert back to unadapted cells. The population of adapted cells changes due to growth, death and loss due to reversion. The dead cell population changes by disinfection of living cells to dead ones. Thus, the equations for the unadapted and adapted phenotypes become

\[
\frac{\partial X_u}{\partial t} + \frac{\partial}{\partial x} (X_u v) = n_u(X_u, C) - d_u(X_u, B) - a(X_u, B) + r(X_a, B), \quad (1.1)
\]
\[
\frac{\partial X_{ud}}{\partial t} + \frac{\partial}{\partial x} (X_{ud} v) = d_u(X_u, B), \quad (1.2)
\]
\[
\frac{\partial X_a}{\partial t} + \frac{\partial}{\partial x} (X_a v) = n_a(X_a, C) - d_a(X_a, B) + a(X_u, B) - r(X_a, B), \quad (1.3)
\]
\[
\frac{\partial X_{ad}}{\partial t} + \frac{\partial}{\partial x} (X_{ad} v) = d_a(X_a, B). \quad (1.4)
\]
The functions $n_u, n_a$ represent the net growth, $d_u, d_a$ represent disinfection transformations, $a$ adaptation, $r$ reversion, and $v$ velocity. Typically, the growth rate $g$ of living cells is described by Monod kinetics, i.e.

$$g(X, C) = \mu \frac{C}{K + C},$$

where $\mu$ is the maximum growth rate and $K$ Monod constant. We take the net growth to be

$$n(X, C) = g(X, C) - \zeta(C)X,$$

where $\zeta$ is the decay rate. In most of the studies $\zeta$ is taken to be a constant. Adding equations (1.1)-(1.4) gives the following formula for the velocity:

$$\frac{\partial v}{\partial x} = \frac{(n_u(X_u, C) + n_a(X_a, C))/X_0}{X_0}.$$

The equation for biofilm thickness $L$ is given by

$$\frac{dL}{dt} = v(L(t)) - h(L, X_u, X_{ud}, X_a, X_{ad}),$$

where $-h(L, X_u, X_{ud}, X_a, X_{ad})$ is the rate expression for erosion detachment (an interfacial transfer process consisting of the exchange of attached solid material to material dissolved in the biofilm-bulk fluid). Characterization of interfacial processes in biofilms are not well understood and no generally accepted rate expressions are available. We follow Gujer’s rate expression of the form $-\sigma L^2$ for some $\sigma > 0$ and we choose

$$h(L, X_u, X_{ud}, X_a, X_{ad}) = f(X_u, X_{ud}, X_a, X_{ad})L^2,$$
where $f$ is taken to be a linear combination of the cell densities, i.e.,

$$f(X_u, X_{ad}, X_a, X_{ad}) = f_u X_u + f_{ud} X_{ud} + f_a X_a + f_{ad} X_{ad}.$$ 

The equation for biocide concentration $B$ is

$$\frac{\partial B}{\partial t} = D_B \Delta B - m(X_u, X_{ud}, X_a, X_{ad}, B),$$

where $m$ represents the biocide-cell reaction term. An obvious expectation is to have the reaction term describing the interaction of biocide with biomass constituents increasing in both $X$ and $B$. Hence, the simplest way is to choose $m$ to be first order in $X$ and $B$. Adapted and unadapted cell-types react with biocide at a different rate, but living and dead cell-types react at the same rate; that is, the reaction with biocide is assumed to be independent of viability. Under these assumptions the biocide-cell reaction rate becomes

$$m(X_u, X_{ud}, X_a, X_{ad}, B) = k_u (X_u + X_{ud}) B + k_a (X_a + X_{ad}) B,$$

where $k_u, k_a$ are the biocide-cell reaction rates. Finally, the equation for substrate concentration $C$ is

$$\frac{\partial C}{\partial t} = D_C \Delta C - \frac{1}{Y} g(X_u, C) - \frac{1}{Y} g(X_a, C),$$

where $g$ is the growth defined above and $Y$ is the yield constant. Our Model Assumption 7 included the saturation of substrate. This condition will make the model
equations somewhat easier and we will not have to deal with a particular equation for $C$.

The disinfection process is considered as a conversion of viable bacteria into dead bacteria. By the same argument as for the biocide-cell reaction term, disinfection terms are first order in $X$ and $B$. Hence,

$$d(X, B) = bXB,$$

where $b$ is the cell disinfection rate. The conversion of unadapted cells to the adapted ones is assumed to occur at a constant rate as long as the applied biocide concentration is nonzero. Thus,

$$a(X_u, B) = m(B)X_u,$$

where $m(B)$ is a non-zero constant $m_0$ if there is antibiotic present and zero otherwise. Adapted cells can revert to unadapted cells at a rate independent of the biocide concentration, i.e.,

$$r(X_a, B) = r_0X_a,$$

where $r_0$ is the adapted-unadapted cell reversion rate.

To simplify the geometry of the problem, we assume that significant variations occur only in the direction perpendicular to the substratum. Hence, we may consider the one-dimensional case, when the solid biofilm region

$$\Omega = \{x : 0 \leq x \leq L(t)\}$$
is separated from the liquid region by the biofilm-bulk fluid interface $\Gamma$. Note that $\Omega$ evolves with time due to evolution of the biofilm thickness.

Since biomass does not interact or pass through the substratum, no-flux boundary conditions will be placed on it. In 1-D this condition is equivalent to

$$v(0, t)X(0, t) = 0.$$  

Biocide does not interact or pass through the substratum. Hence, no-flux boundary conditions are chosen. The biocide is applied at a rate $b$ that depends on time. The appropriate boundary conditions for biocide concentration are

$$B_x(0, t) = 0, \quad B(L(t), t) = b(t).$$

By a similar argument as above, the boundary conditions for substrate concentration will be no-flux and Dirichlet boundary conditions, i.e.

$$C_x(0, t) = 0, \quad C(L(t), t) = c(t),$$

where $c$ is the time-dependent rate at which the substrate is applied through $\Gamma$.

**Dimensional Model**

Without affecting qualitatively the conclusions of this study, we will assume that the diffusion rates are the same ($D_B = D_C = D$) as well as the biocide-cell reaction rates ($k_a = k_u = k$), Monod constants ($K_a = K_u = K$), maximum growth rates ($\mu_a = \mu_u = \mu$), yield constants ($Y_a = Y_u = Y$) and decay rates ($\zeta_a = \zeta_u = \zeta$). We
also assume that the detachment rates are the same \((f_u = f_{ud} = f_a = f_{ad} = f_0)\), in which case the rate expression for detachment simplifies to

\[-L^2(t)f(X_u, X_{ud}, X_a, X_{ad}) = -f_0X_0L^2(t).\]

Finally, the equations of the 1-D dimensional model become

\[
\begin{align*}
\frac{\partial B}{\partial t} &= D \frac{\partial^2 B}{\partial x^2} - kX_0B \quad (1.5) \\
\frac{\partial C}{\partial t} &= D \frac{\partial^2 C}{\partial x^2} - \frac{1}{V} G(C)(X_a + X_u) \quad (1.6) \\
\frac{\partial X_u}{\partial t} + \frac{\partial}{\partial x}(X_au) &= -(b_uB + m(B))X_u + R(C)X_u + r_0X_a \quad (1.7) \\
\frac{\partial X_{ud}}{\partial t} + \frac{\partial}{\partial x}(X_{ud}v) &= b_uBX_u \quad (1.8) \\
\frac{\partial X_a}{\partial t} + \frac{\partial}{\partial x}(X_av) &= -b_aBX_a + m(B)X_u + R(C)X_a - r_0X_a \quad (1.9) \\
\frac{\partial X_{ad}}{\partial t} + \frac{\partial}{\partial x}(X_{ad}v) &= b_aBX_a \quad (1.10)
\end{align*}
\]

\[
v = \frac{1}{X_0} \int_0^x (R(C(s, t))(X_u(s, t) + X_a(s, t)))ds \quad (1.11)
\]

\[
\frac{dL}{dt} = v(L(t), t) - f_0X_0L^2(t), \quad (1.12)
\]

where

\[
m(B) = \begin{cases} 
0 & \text{if } B = 0 \\
m_0 & \text{if } B > 0.
\end{cases}
\]

The production terms \(G\) and \(R\) are defined as

\[
G(C) = \frac{\mu C}{K + C} \quad \text{and} \quad R(C) = G(C)\zeta. \quad (1.13)
\]
The boundary conditions of the system (1.5)-(1.12) are

\[ B_x(0, t) = 0, \quad B(L(t), t) = b(t) \]  
\[ C_x(0, t) = 0, \quad C(L(t), t) = c(t) \]  
\[ v(0, t)X_u(0, t) = 0, \quad v(0, t)X_{ud}(0, t) = 0 \]  
\[ v(0, t)X_a(0, t) = 0, \quad v(0, t)X_{ad}(0, t) = 0. \]

The initial conditions are taken to be

\[ B(x, 0) = 0, \quad C(x, 0) = 0, \quad X_u(x, 0) = X_0, \quad X_{ud}(x, 0) = 0 \]  
\[ X_a(x, 0) = 0, \quad X_{ad}(x, 0) = 0, \quad L(0) = L_0. \]

| \( \alpha \) | unadapted disinfection time/ growth time |
| \( \beta \) | unadapted disinfection time/ decay time |
| \( \gamma \) | unadapted disinfection time/ adapted transformation time |
| \( \delta \) | unadapted disinfection time/ adapted disinfection time |
| \( \epsilon \) | biocide reaction time/ unadapted disinfection time |
| \( \phi^2 \) | ratio squared of biofilm depth to disinfection layer depth |
| \( \lambda \) | unadapted disinfection time/ cell transformation time |
| \( \kappa \) | maximum growth rate/ biocide reaction rate |
| \( \sigma \) | unadapted disinfection time/ detachment time |
Let \( l \) denote the characteristic length of biofilm and \( B_0 \) denote the characteristic biocide concentration (average values of biofilm thickness and biocide concentration). The spatial and time variables are re-scaled as

\[
\hat{x} = \frac{x}{l}, \quad \hat{t} = \frac{t}{(b_u B_0)^{-1}},
\]

where \( (b_u B_0)^{-1} \) is the disinfection time scale of unadapted cells. The model variables are re-scaled as

\[
\hat{B} = \frac{B}{B_0}, \quad \hat{C} = \frac{C}{K}, \quad \hat{X}_u = \frac{X_u}{X_0}, \quad \hat{X}_{ud} = \frac{X_{ud}}{X_0},
\]

\[
\hat{X}_a = \frac{X_a}{X_0}, \quad \hat{X}_{ad} = \frac{X_{ad}}{X_0}, \quad \hat{v} = \frac{v(b_u B_0)^{-1}}{b_u B_0}, \quad \hat{L} = \frac{L}{l}.
\]

We define the dimensionless parameters

\[
\alpha = \mu(b_u B_0)^{-1}, \quad \beta = \xi(b_u B_0)^{-1}, \quad \delta = b_u b_u^{-1}
\]

\[
\epsilon = b_u B_0 l^2 D^{-1}, \quad \phi^2 = k X_0 l^2 D^{-1}, \quad \gamma = r_0(b_u B_0)^{-1},
\]

\[
\kappa = \mu(Y k K)^{-1}, \quad \lambda = m_0(b_u B_0)^{-1}, \quad \sigma = l f_0 X_0(b_u B_0)^{-1}.
\]

The parameter \( \epsilon \) is the characteristic time of diffusion \( l^2 D^{-1} \) over the disinfection time of unadapted cells \( (b_u B_0)^{-1} \). Discussion of other dimensionless parameters is done in Chapter 2. The production terms \( G \) and \( R \) are re-scaled to

\[
\tilde{G}(\hat{C}) = \alpha \frac{\hat{C}}{1 + \hat{C}} \quad \text{and} \quad \tilde{R}(\hat{C}) = \tilde{G}(\hat{C}) - \beta.
\]
Dropping the hats, the dimensionless model becomes

\[
\epsilon \frac{\partial B}{\partial t} = \frac{\partial^2 B}{\partial x^2} - \phi^2 B \tag{1.15}
\]

\[
\epsilon \frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - \kappa \phi^2 \frac{C}{1 + C}(X_a + X_u) \tag{1.16}
\]

\[
\frac{\partial X_u}{\partial t} + \frac{\partial}{\partial x}(X_u v) = -(B + \lambda(B))X_u + \left(\alpha \frac{C}{1 + C} - \beta\right)X_u + \gamma X_a \tag{1.17}
\]

\[
\frac{\partial X_{ud}}{\partial t} + \frac{\partial}{\partial x}(X_{ud} v) = BX_u \tag{1.18}
\]

\[
\frac{\partial X_a}{\partial t} + \frac{\partial}{\partial x}(X_a v) = -\delta BX_a + \lambda(B)X_u + \left(\alpha \frac{C}{1 + C} - \beta\right)X_a - \gamma X_a \tag{1.19}
\]

\[
\frac{\partial X_{ad}}{\partial t} + \frac{\partial}{\partial x}(X_{ad} v) = \delta BX_a \tag{1.20}
\]

\[
v = \int_0^x \left(\alpha \frac{C(s, t)}{1 + C(s, t)} - \beta\right)(X_u(s, t) + X_a(s, t))ds \tag{1.21}
\]

\[
\frac{dL}{dt} = v(L(t), t) - \sigma L^2(t), \tag{1.22}
\]

where

\[
\lambda(B) = \begin{cases} 
0 & \text{if } B = 0 \\
\lambda & \text{if } B > 0.
\end{cases}
\]

The boundary conditions are given by

\[
B_x(0, t) = 0, \quad B(L(t), t) = b(t)/B_0 := u(t) \tag{1.23}
\]

\[
C_x(0, t) = 0, \quad C(L(t), t) = c(t)/K
\]

\[
v(0, t)X_u(0, t) = 0, \quad v(0, t)X_{ud}(0, t) = 0
\]

\[
v(0, t)X_a(0, t) = 0, \quad v(0, t)X_{ad}(0, t) = 0.
\]

The initial conditions have the form

\[
B(x, 0) = 0, \quad C(x, 0) = 0, \quad X_u(x, 0) = 1, \quad X_{ud}(x, 0) = 0
\]

\[
X_a(x, 0) = 0, \quad X_{ad}(x, 0) = 0, \quad L(0) = L_0/l.
\]
Note that
\[ X_u + X_{ud} + X_a + X_{ad} = 1. \]

We make the following assumptions on the system (1.15)-(1.22):

- there is no nutrient-limitation, i.e. \( \frac{C}{1+C} \approx 1 \) (saturation of substrate is considered in Assumption 7)
- characteristic time for diffusion is small compared to the duration of biocide treatment, i.e. \( \epsilon \ll 1 \)

As a consequence of saturation we obtain \( \alpha \frac{C}{1+C} - \beta \approx \alpha - \beta \) and hence, we may set \( \beta = 0 \). Under the previous assumptions (1.15)-(1.22) becomes

\[
\begin{align*}
\frac{\partial X_u}{\partial t} + \frac{\partial}{\partial x}(X_u v) &= -(B + \lambda(B))X_u + \alpha X_u + \gamma X_a \quad (1.24) \\
\frac{\partial X_{ud}}{\partial t} + \frac{\partial}{\partial x}(X_{ud} v) &= BX_u \quad (1.25) \\
\frac{\partial X_a}{\partial t} + \frac{\partial}{\partial x}(X_a v) &= -\delta BX_a + \lambda(B)X_u + \alpha X_a - \gamma X_a \quad (1.26) \\
\frac{\partial X_{ad}}{\partial t} + \frac{\partial}{\partial x}(X_{ad} v) &= \delta BX_a \quad (1.27)
\end{align*}
\]

\[
v = \int_0^x \alpha(X_u(s,t) + X_a(s,t)) ds \quad (1.28)
\]

\[
\frac{dL}{dt} = v(L(t),t) - \sigma L^2(t), \quad (1.29)
\]

where

\[
B(x,t) = u(t) \frac{\cosh(\phi x)}{\cosh(\phi L(t))}
\]
from equation (1.15) ($\epsilon \ll 1$) and boundary condition (1.23). This form will be considered in Chapter 3-6.

The important dimensionless parameters of interest are $\alpha$, $\lambda$ and $\gamma$ from Table 2. To our best knowledge, there is no information in the literature about the proportion of each of these parameters, i.e. $\alpha/\gamma$, $\lambda/\gamma$, $\alpha/\lambda$ in case of adaptation. According to Phil Stewart (personal communication) the reversion $\gamma$ is 0.01 to 1 times the growth rate $\alpha$. However, in the case when adapted cells do not die ($\delta = 0$), our results from Chapter 4 indicate that the only interesting case for our model is $\alpha/\gamma = o(1)$. Otherwise, if $\alpha \gg \gamma$ and $\delta = 0$, the biocide treatment has negligible influence on biofilm thickness. The reason is that for $u_0 = 0$ the steady-state solutions satisfy $X_u + X_a = 1$ and $L = \frac{\alpha}{\sigma}$ (c.f. Chapter 5). We have a similar scenario when the biocide gets arbitrary large. In this case (c.f. Chapter 5), the steady-state solutions are approximately equal to $X_u + X_a \approx 1 - \epsilon$ and $L \approx \frac{\alpha}{\sigma} - \gamma$, i.e. the biofilm does not change significantly. We are not saying that the above mentioned scenario cannot happen, but in this case the biocide is too weak to have any impact on the biofilm. We suspect that in this growth-dominated case ($\alpha \gg \gamma$ and $\delta = 0$) it makes no longer sense to ignore the different growth rates $\alpha_u$ and $\alpha_a$ corresponding to $X_u$ and $X_a$. In practise, $\alpha_u$ is just a slightly larger than $\alpha_a$. In fact, it can be argued that when the growth rates are different, for $u_0 = 0$ the steady-state biofilm thickness $L$ is controlled
by $\alpha_u$ (growth rate for unadapted cells). On the other hand, for very large $u_0$ the thickness $L$ is controlled by $\alpha_a$ (growth rate for adapted cells) only.

Looking at the other ratio $\lambda/\gamma$, we can derive its expected size only indirectly, by considering the effects of these constants on the populations of adapted and unadapted cells. If we briefly neglect the death rate, which also has effect on the population sizes, $X_u$ - the unadapted and $X_a$ - the adapted cells are directly influenced by the ratio $\lambda/\gamma$. If, for example, $\lambda \gg \gamma$, the number of adapted cells would largely overwhelm the number of unadapted ones ($X_a \gg X_u$) after short time period. However, according to Phil Stewart, the reversion $\gamma$ is perhaps 0.1 times the transformation rate $\lambda$. This excludes the possibility of $\lambda \gg \gamma$. Thus, the conversion from unadapted to adapted state can be larger than reversion from adapted to unadapted state by at most an order of magnitude. In Chapter 5 (constant dosing) we look in detail how $\lambda$ and $\gamma$ influence the ratio $X_a/X_u$. The asymptotics we do there show that for small dose of biocide the size of $X_u \approx \frac{\gamma}{\lambda+\gamma}$ and $X_a = \frac{\lambda}{\lambda+\gamma}$, hence $X_a/X_u \approx \lambda/\gamma$. Since the estimates on the ratio $X_a/X_u$ vary a lot (Phil Stewart), we chose to test $X_a/X_u$ between 0.5 – 10 so that $X_a$ is about 30 – 90% of the bacterial population after treatment.

There are more studies on a different phenotype - persister cells which are somewhat related to our adapted cells. In this case the proportion of persister cells may be 1% or less of the original population (see [3]).
For the reasons we just outlined, we will consider in our numerical simulations constants $\alpha$, $\lambda$ and $\gamma$ to be of approximately same size. It is important to note however, that in the analytical parts of this work we do not make any assumption on size of these constants. The results only require that all three are positive.

**Minimizing Functionals**

Bacterial biofilms show enormous level of antibiotic resistance. In order to reduce costs of biocide use for the control of biofilm formation, optimum dosing strategies are required. Hence, we will introduce minimizing functionals that will be optimized with respect to the biocide concentration in Chapters 5 and 6.

Disinfection of biofilm bacteria depends on the type of antibiotic used. Antibiotics can be bactericidal and bacteriostatic. Bactericidal antibiotics kill bacteria (e.g. penicillins) and bacteriostatic antibiotics inhibit the growth of bacterial cells (e.g. sulphonamides, erythromycin). Hence, we consider two types of minimizing functionals - functional $J$ that minimizes the number of living cells $\int_0^T (X_u + X_a)dx$ over long time and functional $J_L$ that minimizes biofilm thickness over long time. Therefore, we set

$$J(u) = \lim_{T \to \infty} \frac{1}{T} \left[ \int_0^T \int_0^{L(t)} (X_a(x,t) + X_u(x,t)) dx dt + c \int_0^T u(t) dt \right]$$

(1.30)

and

$$J_L(u) = \lim_{T \to \infty} \frac{1}{T} \int_0^T \left( L(t) + cu(t) \right) dt,$$

(1.31)
where $c$ is the cost of biocide dose, $u(t)$ is the externally applied biocide concentration through the interface.

Define

$$S = \{ f \in C[0, \infty) : \lim_{T \to \infty} \frac{1}{T} \int_0^T f(t) dt \text{ exits} \}.$$ 

For example, the constant and periodic functions belong to the class $S$. In particular, we now show that if $f \in S$ is periodic, then $\lim_{T \to \infty} \frac{1}{T} \int_0^T f(t) dt$ is the average value of the function $f$ over a period. Let $T = MP + \Delta T$, where $P$ is the period and $M$ is the number of times the period is attained in $T$. Then

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T f(t) dt = \lim_{M \to \infty} \frac{M}{MP + \Delta T} \int_0^P f(t) dt + \int_{MP}^{MP+\Delta T} \frac{f(t)}{MP + \Delta T} dt = \frac{1}{P} \int_0^P f(t) dt + \lim_{M \to \infty} \int_{MP}^{MP+\Delta T} \frac{f(t)}{MP + \Delta T} dt.$$ 

Note that $\int_{MP}^{MP+\Delta T} \frac{f(t)}{MP + \Delta T} dt \leq \frac{P}{MP + \Delta T} \|f\|_{C[0,P]}$. Taking the limit as $M \to \infty$ we obtain what we wanted.

The class of functions $f$ we are interested in are the functions that are periodic in the limit as $T \to \infty$, meaning that for some periodic function $g$

$$\lim_{T \to \infty} |f(T) - g(T)| = 0.$$ 

Using the fact that $g \in S$, we can show that $f \in S$ and

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T f(t) dt = \lim_{T_0 \to \infty} \frac{1}{P} \int_{T_0}^{T_0+P} f(t) dt, \quad (1.32)$$
where $P$ is the period of the function $g$. This will have very practical consequences since numerically we can approximate $\lim_{T \to \infty} \frac{1}{T} \int_0^T f(t)dt$ by $\frac{1}{P} \int_{T_0}^{T_0+P} f(t)dt$ for sufficiently large $T_0$. We will choose $T_0$ such that $f$ looks on the plots undistinguishable from the periodic function on $[T_0, \infty)$. More generally, for $f \in S$ (not necessary periodic in the limit) we can observe that

$$\lim_{T \to \infty} \frac{1}{T} \int_0^T f(t)dt = \lim_{T \to \infty} \left[ \frac{1}{T} \int_0^{T_0} f(t)dt + \frac{T - T_0}{T - T_0} \int_{T_0}^T f(t)dt \right] = \lim_{T \to \infty} \frac{1}{T - T_0} \int_{T_0}^T f(t)dt.$$

It follows that the value of the functionals is independent of $T_0$.

By (1.32) we obtain for periodic $u(t)$ with period $P$

$$J(u) = \lim_{T \to \infty} \frac{1}{P} \left[ \int_T^{T+P} \int_0^{L(t)} (X_a(x, t) + X_u(x, t))dxdt + c \int_T^{T+P} u(t)dt \right]$$

(1.33)

and

$$J_L(u) = \lim_{T \to \infty} \frac{1}{P} \int_T^{T+P} (L(t) + cu(t))dt.$$ 

(1.34)

This form of the functionals will be considered in Chapter 6 for periodic dosing. In particular, in the case of constant dosing (Chapter 5), when $u(t) = u_0 \geq 0$, numerical simulations suggest that the solutions converge to steady-state solutions as time gets large. This observation changes the functionals in (1.30)-(1.31) to

$$J(u_0) = \lim_{T \to \infty} \int_0^{L(T)} (X_a(x, t) + X_u(x, t))dx + cu_0$$

(1.35)

and

$$J_L(u_0) = \lim_{T \to \infty} L(T) + cu_0.$$ 

(1.36)
CHAPTER 2

BIOFILM MODEL WITHOUT GROWTH

Bacterial biofilms demonstrate resistance in response to antimicrobial stress. This adaptive response is more effective than in corresponding planktonic populations. In this chapter global existence and longtime behavior solutions of a nonlinear reaction-diffusion system without growth described in [34] is studied. The results obtained here confirm those model features that have been expected and are already known in a special linear case (see [34]). In particular, it is shown that the local biocide concentration and the cell densities are nonnegative and obey an upper bound. An important model property is that global existence can be shown for periodic slabs as well (for example, the surface of a cylinder with open top and bottom, i.e. $\Omega = S^1 \times (0,1)$, or, equivalently $\Omega = (0,1) \times (0,1)$ with periodic boundary conditions on the left and right sides) which are more interesting in real-life applications. The optimal minimum of functionals for the linear case will be discussed at the end of this chapter. Based on the mathematical analysis of the prototype biofilm model presented here, further refinements in this model can be added (growth and detachment terms) and a more sophisticated model will be studied in the upcoming chapters.
Introduction

There is mounting evidence that cells in biofilms are able to sense antimicrobial challenges and actively respond by deploying protective stress responses. This behavior has been confirmed by many authors, see the references in Chapter 1 for examples. In [34] we studied a simple no-growth biofilm model describing adaptation of biofilm cells. Due to limited penetration of biocide to deeper regions of the biofilm, sheltered cells are able to enter an adapted resistant state. Unlike thick biofilms, this mechanism is not available to planktonic populations. Since cells in lower biofilm regions adapt and convert from the unadapted cell state to the adapted cell state as a response to antimicrobials, these two phenotypes were considered in the mathematical model studied in [34]. In particular, this model predicts that an adaptive response provides a greater protection to cells in a biofilm than to free-swimming bacteria. Results show that effective disinfection requires biocide concentration that increases quadratically or exponentially with biofilm thickness.

In our model the biomass within the biofilm is assumed to contain four constituents with which the biocide interacts. Interactions between biocide and biomass constituents are of two types, reactions and disinfection transformations. Reactions involve consumption of both biocide and biomass constituents. Disinfection transformations convert one biomass constituent to another, but do not consume biocide. Cells in the biofilm may be killed by the antimicrobial agents, but they may also
respond to this stimulus by decreasing their susceptibility to killing. The kinetics of interactions between biomass constituents and biocide are assumed to be first order with respect to biomass constituent concentration and biocide concentration.

The objective of this study is to mathematically investigate the global existence and longtime behavior of solutions of a more general version of the biofilm model described in [34]. Here we extend the 1-D model presented in [34] to the nonlinear case on smooth bounded domains in $\mathbb{R}^2$ and $\mathbb{R}^3$.

The key assumptions of this model are exactly the same as the assumptions 1-5 in Chapter 1. However, the biofilm neither grows nor detaches.

We consider a bacterial population consisting of four constituents subject to

<table>
<thead>
<tr>
<th>$X_u$</th>
<th>unadapted cell density</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_{ud}$</td>
<td>dead unadapted cell density</td>
</tr>
<tr>
<td>$X_a$</td>
<td>adapted cell density</td>
</tr>
<tr>
<td>$X_{ad}$</td>
<td>dead adapted cell density</td>
</tr>
</tbody>
</table>

$X_u + X_{ud} + X_a + X_{ad} = X_0$, where $X_0$ is constant in space and time. Biofilm bacteria grow under different conditions from those living under planktonic conditions since in the biofilm nutrients and oxygen are limited due to the failure of biocide to penetrate the biofilm. Hence, bacteria in deeper regions of the biofilm turn out to be more resistant to biocide. Diffusion of biocide in the biofilm is slower than in water and it is also slower than the penetration of nutrients or oxygen. Because of the disinfective behavior of biofilm communities, biofilm and planktonic phenotypes must be studied
separately. In the planktonic case, the biocide is assumed to be well mixed. For planktonic systems, the constituent densities are functions of time only; for biofilm systems, the constituent densities depend both on space and time. For both biofilm and planktonic systems, it is assumed that the time scale of observation is short enough so that growth can be neglected.

The outline of this Chapter is the following. First we state the model equations both for biofilm and planktonic systems. We introduce the notation and show that the whole system can be reduced to one equation that depends on the biocide concentration only. Global existence of solutions and their regularity properties will be discussed; we prove that the solutions are smooth on \((0, T) \times \bar{\Omega}\). It will be shown that the solutions are nonnegative and bounded. We then state some consequences of the obtained results. Finally, the longtime behavior of 1-D solutions and the optimal minimum for the linear case will be analyzed.

The biofilm model

To illustrate the theory we will consider a simple example of antibiotic disinfection of biofilms where viable bacteria, corresponding to \(X_u\) and \(X_a\), convert to dead bacteria, corresponding to \(X_{ud}\) and \(X_{ad}\), depending on the concentration of biocide. Adapted and unadapted cell-types react with biocide at a different rate, but living and dead cell-types react at the same rate; that is, the reaction with biocide is assumed to be independent of viability. This is a plausible assumption for oxidizing
biocides. The disinfection process is considered as a conversion of viable bacteria into
dead bacteria. Unadapted cells are able to transform to adapted cells at a rate inde-
pendent of the biocide concentration as a response to antimicrobial challenges. The
boundary conditions for the biocide concentration generalize the boundary conditions
in the 1-D case. The resulting biofilm model reads:

$$\frac{\partial B}{\partial t} = D \Delta B - k_u(X_u + X_{ud})B - k_a(X_a + X_{ad})B \quad \text{in } \Omega T$$ (2.1)

$$\frac{\partial B}{\partial n} \Big|_{\partial \Omega_N} = 0, \quad B \Big|_{\partial \Omega_D} = B_0 \quad \text{for } 0 \leq t \leq T, \quad B(x, 0) = g(x) \quad \text{for } x \in \Omega$$ (2.2)

$$\frac{\partial X_u}{\partial t} = (-b_uB - r_0)X_u \quad X_u(x, 0) = X_0 \quad \text{for } x \in \Omega$$ (2.3)

$$\frac{\partial X_{ud}}{\partial t} = b_uBX_u \quad X_{ud}(x, 0) = 0 \quad \text{for } x \in \Omega$$ (2.4)

$$\frac{\partial X_a}{\partial t} = -b_aBX_a + r_0X_u \quad X_a(x, 0) = 0 \quad \text{for } x \in \Omega$$ (2.5)

$$\frac{\partial X_{ad}}{\partial t} = b_aBX_a \quad X_{ad}(x, 0) = 0 \quad \text{for } x \in \Omega$$ (2.6)

When $\Omega = [0, L]$, where $L$ is the biofilm thickness, the biocide concentration $B$ takes
boundary conditions

$$\frac{\partial B}{\partial x}(0, t) = 0, \quad B(L, t) = B_0,$$

indicating that no flux through the substratum $x = 0$ occurs and that the biocide
concentration at the interface $x = L$ is fixed. Mixed boundary conditions will be
considered as well.

Here $\Omega \subset \mathbb{R}^d \ (d = 1, 2, 3)$ is an open bounded subset with smooth boundary
$\partial \Omega_N \cup \partial \Omega_D$ where $\partial \Omega_N, \partial \Omega_D$ are disjoint, i.e. there are no points on the boundary
where the Neumann condition would change to Dirichlet or reversely. This last assumption is only needed for regularity. As usual, $\Omega_T = \Omega \times (0,T]$ is the parabolic interior and $n$ is the outward normal. The initial concentration of biocide is taken to be a nonnegative function $g \in L^\infty(\Omega)$ with $\|g\|_\infty \leq B_0$. The time $T > 0$ is fixed. The corresponding model parameters are listed in the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_0$</td>
<td>externally applied biocide concentration</td>
</tr>
<tr>
<td>$D$</td>
<td>biocide diffusion constant</td>
</tr>
<tr>
<td>$b_u$</td>
<td>unadapted cell disinfection rate constant</td>
</tr>
<tr>
<td>$b_a$</td>
<td>adapted cell disinfection rate constant</td>
</tr>
<tr>
<td>$k_u$</td>
<td>biocide unadapted cell reaction rate</td>
</tr>
<tr>
<td>$k_a$</td>
<td>biocide adapted cell reaction rate</td>
</tr>
<tr>
<td>$r_0$</td>
<td>unadapted-adapted cell transformation rate</td>
</tr>
</tbody>
</table>

There are interesting examples of domains for which the theory presented below applies. One could think of a periodic slab, say, the surface of a cylinder with open top and bottom, i.e. $\Omega = S^1 \times (0,1)$ (or equivalently by $\Omega = (0,1) \times (0,1)$ with periodic boundary conditions on the left and right sides). However, for briefness and clarity we only consider $\Omega \subset \mathbb{R}^d$ as defined above.

The system (2.1)-(2.6) can be rewritten into a dimensionless form, where the independent variable $x$ is scaled by $\hat{x} = x/C$ for a characteristic value $C > 0$. This dimensionless form agrees with the dimensionless form in the 1-D case given except
that in the dimensionless variables and parameters the number $L$ is everywhere replaced by $L/C$. Another scaling of the dimensionless variable $\mathcal{x}$ by $\mathcal{x} = D\mathcal{\tilde{x}}/b_uB_0C^2$ allows us to take $D = 1$ without loss of generality.

In the case of a planktonic system, biocide can be constantly replenished, i.e. (2.1) is replaced by $B(t) = B_0$, or biocide can be applied at $t = 0$ only, in which case (2.1) is replaced by

$$\frac{\partial B}{\partial t} = -k_u(X_u + X_{ud}) - k_a(X_a + X_{ad}) \quad B(0) = B_0. \quad (2.7)$$

The equations for the constituent densities in the planktonic case are the same as those in the biofilm case except that in the planktonic population all densities are independent of space and the derivatives are ordinary. It is easy to show that all the solutions of the planktonic system are non-negative bounded and analytic.

**Notation**

For simplicity, we will omit the spatial variable $x$ in the functions $B, X_u, X_{ud}, X_a, X_{ad}$ unless needed for emphasis. Integration over time for $X_u$ will be denoted by $\int_0^t X_u(s)ds$; integration over time for $B$ will be denoted by $\int_0^t B(s)ds$.

We will denote the negative Laplacian $-\Delta$ and its fractional semi-powers by $A$ and $A^{\frac{k}{2}}$, respectively. The domains of $A^{\frac{k}{2}}$ for various nonnegative integer values of $k$ are

$$D(A^{\frac{k}{2}}) = \{v \in H^{1,p}(\Omega); \quad v\big|_{\partial\Omega_D} = 0\},$$
\[ D(A) = \{ v \in H^{2,p}(\Omega); \quad \frac{\partial v}{\partial n} \bigg|_{\partial\Omega_N} = 0; \quad v \bigg|_{\partial\Omega_D} = 0 \}, \]

\[ D(A^{\pm}) \subset \{ v \in H^{k,p}(\Omega); \quad \frac{\partial v}{\partial n} \bigg|_{\partial\Omega_N} = 0, \quad v \bigg|_{\partial\Omega_D} = 0 \} \]

for \( k > 2 \) and \( 1 < p < \infty \).

The norms for the spaces \( L^p(\Omega) \) and \( H^{k,p}(\Omega) \) will be denoted by \( \| \cdot \|_p \) and \( \| \cdot \|_{k,p} \), respectively. For any \( 1 < p < \infty \) and \( k \geq 0 \) nonnegative integer we have

\[ \| A^{\pm} v \|_p = \| v \|_{k,p} \quad \text{for} \quad v \in D(A^{\pm}) \]

(see [2]).

The operator norm for a linear mapping \( F \) from a Banach space \( X \) to a Banach space \( Y \) is given by

\[ \| F \|_{X \rightarrow Y} = \sup_{\| v \|_X = 1} \| Fv \|_Y. \]

This notation will be used throughout this chapter.

**Reduction of the system**

The equations (2.3)-(2.4) and (2.5)-(2.6) imply

\[ X_u + X_{ud} = X_0 - r_0 \int_0^t X_u(s)ds \quad (2.8) \]

and

\[ X_a + X_{ad} = r_0 \int_0^t X_u(s)ds. \quad (2.9) \]
From (2.3) we also obtain

\[ X_u = X_0 e^{-ru} \exp\{-b_u \int_0^t B(s) ds\}. \] (2.10)

Let \( \Phi(v) = e^{b_u v} \). Then (2.10) can be written as

\[ X_u = X_0 e^{-ru} \Phi\left(-\int_0^t B(s) ds\right). \] (2.11)

Substituting (2.8)-(2.9) into (2.1) yields

\[ \frac{\partial B}{\partial t} = \Delta B - k_u X_0 B + (k_u - k_a) r_0 B \int_0^t X_u(s) ds. \] (2.12)

When \( k_a > k_u \), we choose \( k = k_u X_0 \) and \( l = (k_a - k_u) r_0 X_0 \). Making use of (2.11), (2.12) becomes

\[ \frac{\partial B}{\partial t} = \Delta B - kB - lB \int_0^t e^{-ru} \Phi\left(-\int_0^s B(u) du\right) ds. \] (2.13)

In other words, the solvability of the system (2.1)-(2.6) reduces to the solvability of the initial/boundary-value problem for the nonlinear parabolic equation (2.13) with boundary conditions (2.2).

**Remark:** Note that if \( k_u = k_a \), then (2.12) is linear. Also, if \( k_u > k_a \), then (2.11) can be rewritten as

\[ \frac{\partial B}{\partial t} = \Delta B - kB - [l + m] \int_0^t e^{-ru} \Phi\left(-\int_0^s B(u) du\right) ds B, \] (2.14)

where \( k = k_u X_0 \), \( l = (2k_u - k_a) X_0 \) and \( m = (k_a - k_u) r_0 X_0 \). Note equations (2.13) and (2.14) are equivalent, but in our case (2.13) will be considered.

Global existence of solutions will be shown for the biologically relevant case \( k_a > k_u \) (biocide consumption by adapted cells dominates), but a similar analysis can be
carried out for the other two cases as well. We would like to point out that the existence does not depend on the fact whether the model is dimensional or not.

Existence and bounds on the weak solutions of the linear PDE

We will show that (2.13) with (2.2) can be associated with a linear parabolic equation with homogeneous boundary conditions, the regularity of solution of which is well-known. Moreover, it can be shown that the $L^\infty$-norm of the weak solution is bounded by $B_0$.

Taking $b(x, t) := B_0 - B(x, t)$ makes the boundary conditions in (2.2) homogeneous. In this case (2.13) with (2.2) becomes

$$
\frac{\partial b}{\partial t} = \Delta b + k(B_0 - b) + l(B_0 - b) \int_0^t e^{-(r_0 + buB_0)s} \Phi \left( \int_0^s b(u) du \right) ds \quad (2.15)
$$

$$
b \bigg|_{\partial \Omega_1} = 0, \quad \frac{\partial b}{\partial n} \bigg|_{\partial \Omega_2} = 0 \quad \text{for} \quad 0 \leq t \leq T, \ b(x, 0) = B_0 - g(x) \quad \text{for} \quad x \in \Omega. \quad (2.16)
$$

Note that (2.15) can be rewritten as

$$
\frac{\partial b}{\partial t} = \Delta b - h_b(t)b + B_0 h_b(t), \quad (2.17)
$$

where

$$
h_b(t) := k + l \int_0^t e^{-(r_0 + buB_0)s} \Phi \left( \int_0^s b(u) du \right) ds.
$$

When $b \in L^\infty([0, T], L^\infty(\Omega))$, then $h_b \in L^\infty([0, T], L^\infty(\Omega))$ with the upper bound $M_b$

$$
\|h_b\|_{L^\infty([0, T], L^\infty(\Omega))} \leq k + l T \Phi(T \|b\|_{L^\infty([0, T], L^\infty(\Omega))}) := M_b.
$$
The previous estimate follows from the inequality \( \|e^v\|_\infty \leq e^{\|v\|_\infty} \) for \( v \in L^\infty(\Omega) \).

Assuming \( b \in L^\infty([0, T], L^\infty(\Omega)) \), we may associate (2.17)-(2.16) with the linear parabolic equation

\[
\frac{\partial u}{\partial t} = \Delta u - h_b(t)u + B_0h_b(t) \quad \text{in } \Omega_T \quad (2.18)
\]

\[
\left. u \right|_{\partial \Omega_1} = 0, \quad \left. \frac{\partial u}{\partial n} \right|_{\partial \Omega_2} = 0 \quad \text{for } 0 \leq t \leq T, \quad u(x, 0) = B_0 - g(x) \quad \text{for } x \in \Omega. \quad (2.19)
\]

It has been shown that (2.18)-(2.19) has a unique weak solution satisfying

\[
u \in C([0, T]; L^p(\Omega)) \bigcap C((0, T]; H^{1,p}(\Omega)) \quad (2.20)
\]

\[
\frac{\partial u}{\partial t} \in C((0, T]; H^{-1,p}(\Omega)) \quad (2.21)
\]

for all \( 1 < p < \infty \) (e.g. [13]).

The statement above can be formulated as a theorem:

**Theorem 2.1** The system (2.18)-(2.19) has a unique weak solution in class (2.20)-(2.21), where by weak solution \( u \) we mean

\[
\int_\Omega \frac{\partial u}{\partial t}(t)vdx = \int_\Omega \nabla u(t)\nabla v(t)dx + \int_\Omega h_b(t)(B_0 - u(t))v(t)dx
\]

for all \( t > 0 \). The test function \( v \in H^{1,q}(\Omega) \) with \( v|_{\partial \Omega_D} = 0 \), where \( \frac{1}{p} + \frac{1}{q} = 1 \) and \( u(0) = B_0 - g \).

The following theorem will be essential for the lower bound on \( B \):

**Theorem 2.2** If \( u \) is a weak solution of (2.18)-(2.19), then

\[
\|u(t)\|_\infty \leq B_0 \quad \text{for } 0 \leq t \leq T
\]
as long as \( \|u(0)\|_\infty \leq B_0 \).

**Proof of Theorem 2.2** We multiply both sides of (2.18) by \( u^p \) and integrate over \( \Omega \). Hence, we get

\[
\frac{1}{p} \frac{d}{dt} \int_{\Omega} |u|^p dx = \int_{\Omega} \Delta uu^p dx - h(t) \int_{\Omega} |u|^{p-2} (|u|^2 - B_0 u) dx.
\]

Integration by parts yields

\[
\frac{d}{dt} \int_{\Omega} |u|^p dx = p(-p-1) \int_{\Omega} |\nabla u|^2 |u|^{p-2} dx - h(t) \int_{\Omega} |u|^{p-2} (|u|^2 - B_0 u) dx.
\]

It follows that

\[
\frac{d}{dt} \|u(t)\|_p^p \leq ph(t) \int_{\Omega} |u|^{p-1} (B_0 - |u|) dx.
\]

Note that \( |u|^{p-1} \in L^q(\Omega) \) with \( q = \frac{p}{p-1} \). By Hölder’s inequality,

\[
\int_{\Omega} |u|^{p-1} \leq \|u\|_p^{p-1} \text{meas}(\Omega)^{\frac{1}{p}}
\]

and so

\[
\frac{d}{dt} \|u(t)\|_p^p \leq ph(t) (\|u(t)\|_p^{p-1} B_0 \text{meas}(\Omega)^{\frac{1}{p}} - \|u(t)\|_p^p).
\]

Finally, let \( y(t) = \|u(t)\|_p^p \), then we have that \( y \) solves the differential inequality

\[
y'(t) \leq ph(t)y(t) \frac{p-1}{p} (C_p - y(t)^{\frac{1}{p}}),
\]

where \( C_p = B_0 \text{meas}(\Omega)^{\frac{1}{p}} \). Assume that \( y(0)^{\frac{1}{p}} \leq C_p \) and assume that \( y(t)^{\frac{1}{p}} > C_p \) for some \( t > 0 \). Then \( y'(t) < 0 \) and \( y(t) < C_p^p \) for \( t > 0 \) which is contradiction. From this we deduce that

\[
\|u(0)\|_p \leq C_p \Rightarrow \|u(t)\|_p \leq C_p \text{ for } 0 \leq t \leq T.
\]
Hence, by taking the limit on both sides we get that

\[ \|u(0)\|_p \leq B_0 \Rightarrow \|u(t)\|_\infty \leq B_0 \text{ for } 0 \leq t \leq T. \]

So \( \|u(t)\|_\infty \) is bounded by \( B_0 \) as long as \( \|u(0)\|_\infty \leq B_0 \). \[\blacksquare\]

**Remark:** This estimate will be essential for the lower bound on \( B \). Notice that the uniform bound on the \( L^p \)–norm of \( u \) results in \( L^\infty \)-regularity, i.e.

\[ u \in L^\infty([0,T];L^\infty(\Omega)). \]

**Existence of weak solutions of the nonlinear PDE**

Using the contraction mapping principle, we can prove that (2.47)-(2.48) has a unique weak solution satisfying the same regularity properties as the weak solution of (2.18)-(2.19).

**Theorem 2.3** The system (2.15)-(2.16) has a unique weak solution in class (2.20)-(2.21), where by weak solution \( b \) we mean

\[ \int_\Omega \frac{\partial b}{\partial t}(t)vdx = \int_\Omega \nabla b(t)\nabla v(t)dx + \int_\Omega h_b(t)(B_0 - b(t))v(t)dx \]

for all \( t > 0 \) for all \( v \in H^{1,q}(\Omega) \) with \( v|_{\partial\Omega_D} = 0 \), where \( \frac{1}{p} + \frac{1}{q} = 1 \) and \( b(0) = B_0 - g \).

**Proof of Theorem 2.3** Let \( X \) be the Banach space

\[ X = \{ b \in L^\infty([0,T];L^\infty(\Omega)); \quad \|b(t)\|_\infty \leq B_0 \}. \]
We will apply the contraction mapping principle in $X$ to show the existence of a unique weak solution.

Define $F : X \to X$ by setting $Fb = u$, where

$$Fb(t) = e^{-tA}b(0) + \int_0^t e^{-(t-s)A}h_b(s)(B_0 - b(s))ds.$$  

It is easy to verify that the regularity given in (2.20)-(2.21) is sufficient for a fixed point to be a weak solution as defined above. Choose $u, \tilde{u} \in X$ and let $u = Fb, \tilde{u} = \tilde{F}b$.

Consequently $b$ satisfies (2.18) for $h_b(t)$, and $\tilde{b}$ satisfies a similar identity for $h_{\tilde{b}}(t)$.

We will show that if $t > 0$ is small enough, then $T$ is a strict contraction.

It is well-known (see [18]) that $e^{-tA} : L^\infty(\Omega) \to L^\infty(\Omega)$ is a contraction semigroup, i.e.

$$\|e^{-tA}\|_{L^\infty(\Omega) \to L^\infty(\Omega)} \leq 1.$$  

Note that for any $b \in X$, the upper bound $M_b$ from the previous sections is uniformly bounded by a constant independent of $b$, i.e.

$$M_b \leq k + lT\Phi(TB_0) := M.$$

Consider

$$\|Fb(t) - F\tilde{b}(t)\|_\infty = \| \int_0^t e^{-(t-s)A}[B_0(h_b(s) - h_{\tilde{b}}(s)) - b(s)h_b(s) + \tilde{b}(s)h_{\tilde{b}}(s)]ds\|_\infty \leq$$  

$$\leq \int_0^t B_0\|h_b(s) - h_{\tilde{b}}(s)\|_\infty + \|b(s)h_b(s) - \tilde{b}(s)h_{\tilde{b}}(s)\|_\infty ds \leq$$  

$$\leq \int_0^t B_0\|h_b(s) - h_{\tilde{b}}(s)\|_\infty + M\|b(s) - \tilde{b}(s)\|_\infty + B_0\|h_b(s) - h_{\tilde{b}}(s)\|_\infty ds \leq$$
\[
\leq \int_0^t M \|b(s) - \tilde{b}(s)\|_\infty ds + 2B_0l \int_0^t \int_0^s \|\Phi\left(\int_0^v b(u)du\right) - \Phi\left(\int_0^v \tilde{b}(u)du\right)\|_\infty dvds.
\]

Since \(b, \tilde{b} \in X\), we have that
\[
\|\Phi\left(\int_0^v b(u)du\right)\|_\infty \leq e^{b_0TB_0} := N.
\]

Therefore, since \(\Phi\) is locally Lipschitz with Lipschitz constant \(N\),
\[
\int_0^t \int_0^s \|\Phi\left(\int_0^v b(u)du\right) - \Phi\left(\int_0^v \tilde{b}(u)du\right)\|_\infty dvds \leq \int_0^t \int_0^s \|\Phi\left(\int_0^v b(u)du\right) - \Phi\left(\int_0^v \tilde{b}(u)du\right)\|_\infty dvds \leq tNT^2 \|b - \tilde{b}\|_{L^\infty([0,T];L^\infty(\Omega))}
\]

and thus
\[
\|Fb(t) - F\tilde{b}(t)\|_\infty \leq t(M + 2B_0lNT^2) \|b - \tilde{b}\|_{L^\infty([0,T];L^\infty(\Omega))}.
\]

It follows that \(F\) is a strict contraction as long as \(t < \frac{1}{M + 2B_0lNT^2}\). Given any \(t > 0\), we select a \(t_1 > 0\) so small that \(t_1 < \frac{1}{M + 2B_0lNT^2}\). We can apply the contraction mapping principle to find a weak solution \(b\) existing on the time interval \([0, t_1]\). Since \(b(t) \in L^\infty(\Omega)\) for \(0 \leq t \leq t_1\), we can assume \(u(t_1) \in L^\infty(\Omega)\). We can then repeat the argument above to extend our solution to the time interval \([t_1, 2t_1]\). Continuing, after finitely many steps we construct a weak solution existing on the full interval \([0, T]\). \(\blacksquare\)

Remark: Note that \(b\) satisfies (2.20)-(2.21) and belongs to \(L^\infty([0, T]; L^\infty(\Omega))\) as well.
In order to show that (2.15)-(2.16) has a smooth solution on $(0, T] \times \bar{\Omega}$, we need the following lemmas:

**Lemma 2.1** If $b(t) \in H^{k,p}(\Omega) \cap L^\infty(\Omega)$, then the function

$$h_b(t) = k + l \int_0^t e^{-(r_0 + b_u B_0)s} \Phi \left( \int_0^s b(u) du \right) ds$$

also belongs to $H^{k,p}(\Omega) \cap L^\infty(\Omega)$.

**Sketch of the proof of Lemma 2.1** We restrict ourselves to the cases $k = 0$ and $k = 1$. For $k \geq 2$ a positive integer, the proof is done analogously.

When $k = 0$, the upper bound for $h(t) \in L^\infty(\Omega)$ is given in the previous sections.

When $k = 1$, then $h(t) \in L^p(\Omega)$ by the previous argument and $b(t) \in H^{1,p}(\Omega) \cap L^\infty(\Omega)$.

Furthermore,

$$\nabla h_b(t) = lb_u \int_0^t e^{-(r_0 + b_u B_0)s} \Phi \left( \int_0^s b(u) du \right) \left( \int_0^s \nabla b(u) du \right) ds.$$ 

Since $\Phi \left( \int_0^s b(u) du \right) \in L^\infty(\Omega)$ and $\int_0^s \nabla b(u) du \in L^p(\Omega)$, it follows that $\nabla h_b(t) \in L^p(\Omega)$ and thus $h_b(t) \in H^{1,p}(\Omega)$.

The following Lemma is used in the proof of Theorem 2.4:

**Lemma 2.2** Suppose $A$ is sectorial in the Banach space $X$ and $Re \sigma(A) > \delta > 0$.

For $\alpha \geq 0$ there exists $C_\alpha < \infty$ such that

$$\|A^\alpha e^{-At}\|_X \leq C_\alpha t^{-\alpha} e^{-\delta t} \text{ for } t > 0.$$
For proof see [18].

Now we are ready to prove the following theorem:

**Theorem 2.4** There is a unique classical solution to (2.15)-(2.16) satisfying

\[ b \in C^\infty((0, T] \times \bar{\Omega}). \]

**Proof of Theorem 2.4** The proof is done by induction. First, assume \( b \in C((0, T]; H^{0,p}(\Omega)) \), i.e. \( b \in C([\tau, T]; H^{0,p}(\Omega) \) for any \( \tau \in (0, T) \). We will show that

\[ b \in C((0, T]; H^{1,p}(\Omega)). \]

Let’s apply \( A^{1/2} \) on

\[ b(t) = e^{-A(t-\tau)}b(\tau) + \int_\tau^t e^{-A(t-s)}h_b(s)(B_0 - b(s))ds, \tag{2.22} \]

where \( \tau \leq t \leq T \). Since \( b(t), h(t) \in L^\infty(\Omega) \), we obtain

\[
\|b(t)\|_{1,p} = \|A^{1/2}b(t)\|_p \leq \|A^{1/2}e^{-A(t-\tau)}b(0)\|_p + \int_\tau^t \|A^{1/2}e^{-A(t-s)}(B_0 - b(s))h_b(s)\|_p ds \\
\leq C \frac{1}{2} t^{-\frac{1}{2}} e^{-\delta(t-\tau)}\|b(0)\|_p + C \frac{1}{2} \int_\tau^t (t-s)^{-\frac{1}{2}} e^{-\delta(t-s)}\|(B_0 - b(s))h_b(s)\|_\infty ds \\
\leq C \frac{1}{4} t^{-\frac{1}{2}} e^{-\delta(t-\tau)}\|b(0)\|_p + 2C \frac{1}{4} MB_0 \sqrt{\frac{\pi}{\delta}}.
\]

It follows that \( b \in C((0, T]; H^{1,p}(\Omega)). \)

Now assume \( b \in C([\tau, T]; H^{k,p}(\Omega) \) for \( p > \frac{n}{k} \). We will show that

\[ b \in C([\tau, T]; H^{k+1,p}(\Omega)). \]
Just as before, let’s apply $A^{k+1}_{\frac{k+1}{2}}$ on (2.22). We have

$$\|b(t)\|_{k+1,p} = \|A^{k+1}_{\frac{k+1}{2}} b(t)\|_p \leq$$

$$\leq \|A^{k+1}_{\frac{k+1}{2}} e^{-A(t-\tau)} b(0)\|_p + \int_\tau^t \|A^{\frac{1}{2}} e^{-A(t-s)} A^{\frac{k}{2}}((B_0 - b(s)) h_b(s))\|_p ds \leq$$

$$\leq C_{k+1} t^{-\frac{k+1}{2}} e^{-\delta(t-\tau)}\|b(0)\|_p + C_1 \int_\tau^t (t-s)^{-\frac{1}{2}} e^{-\delta(t-s)}\|(B_0 - b(s)) h_b(s)\|_{k,p} ds.$$  

By Lemma 2.1, $h_b \in C([\tau,T]; H^{k,p}(\Omega))$. Also, since $p > \frac{n}{k}$, we have

$$\|(B_0 - b(s)) h_b(s)\|_{k,p} \leq \|B_0 - b(s)\|_{k,p} \|h_b(s)\|_{k,p}.$$  

Hence,

$$\|b(t)\|_{k+1,p} \leq C_{k+1} t^{-\frac{k+1}{2}} e^{-\delta(t-\tau)}\|b(0)\|_p + C_1 \int_\tau^t (t-s)^{-\frac{1}{2}} e^{-\delta(t-s)}\|(B_0 - b) h_b\|_{C([\tau,T]; H^{k,p}(\Omega))}.$$  

Since $b(t)$ belongs to $H^{k,p}(\Omega)$ for all $k \geq 0$ and $p$ such that $p > \frac{n}{k}$, it has continuous derivatives of all order and it follows that $b(t) \in C^\infty(\bar{\Omega})$ for all $t > 0$. Similarly, (2.15) yields that $b \in C^1((0,T]; C(\bar{\Omega}))$. Differentiating the same equation with respect to $t$ implies $b_t \in C^1((0,T]; C(\bar{\Omega}))$ and an inductive argument shows that $b_t \in C^\infty((0,T] \times \bar{\Omega})$. □

**Remark:** As a consequence, (3.12) with (2.16) has a unique classical solution satisfying

$$B \in C^\infty((0,T] \times \bar{\Omega}).$$
Finally, we may show that the biocide concentration is nonnegative and obeys the upper bound $B_0$:

**Theorem 2.5** If $B$ is a solution of (2.13) with (2.2), then

$$0 \leq B(t) \leq B_0 \text{ for } 0 \leq t \leq T.$$ 

**Proof of Theorem 2.5** Recall that previously we obtained an upper bound on $u$. Hence, by the continuity of $B$ we have

$$\|B_0 - B(t)\|_\infty \leq B_0 \implies B(t) \geq 0 \text{ for } 0 \leq t \leq T.$$ 

We also would like to get an upper estimate for $B$. From (2.13) it follows that

$$B_t - D \Delta B < 0 \text{ on } \Omega_T.$$ 

We introduce $\Omega_\tau = (\tau, T] \times \Omega$ for $\tau > 0$. Weak maximum principle ([35]) on $\Omega_\tau$ yields

$$\|B(t)\|_\infty \leq B_0 \text{ for } t \geq \tau.$$ 

Taking the limit for $\tau \to 0$ together with the non-negativeness of the initial condition $g$ implies

$$0 \leq B(t) \leq B_0 \text{ for } 0 \leq t \leq T.$$

■
Discussion

We have shown that (2.13) with (2.2) has a nonnegative bounded smooth solution on $(0, T] \times \bar{\Omega}$. To prove this, we have used the equivalence of norms $\| A^k u \|_p$ and $\| u \|_p$ and the smoothing property of sectorial operators.

It is easy to show that the corresponding biofilm constituents $X_u, X_{ud}, X_a, X_{ad}$ are also nonnegative bounded and belong to the class $C^\infty((0, T] \times \bar{\Omega})$. These results correspond to biological expectations.

We can extend the smoothness from $(0, T] \times \bar{\Omega}$ to $[0, T] \times \bar{\Omega}$ by assuming that the initial condition $g \in C^\infty(\Omega)$. In particular, when no biocide is present in the biofilm at $t = 0$ ($g(x) \equiv 0$), the solutions will be $C^\infty([0, T] \times \bar{\Omega})$.

In the specific case when $\Omega$ is a cylinder, i.e. $\Omega = D \times I$ where $I$ is an interval, we again get smoothness on $(0, T] \times \bar{\Omega}$. Suppose $\Omega$ is a cylinder with Dirichlet condition on the top and with Neumann condition elsewhere. Then taking the odd extension of the solutions at the top, even extension of solutions at the bottom and using the method of images results in $C^\infty((0, T] \times \bar{\Omega})$-regularity.

An obvious consequence of the regularity properties is the following: if there were points on the boundary, where the Neumann condition changed to Dirichlet or reversely, then we would obtain the same $C^\infty((0, T] \times \bar{\Omega})$-regularity except these boundary points.
In general, the unadapted-adapted cell transformation rate depends on the biocide concentration. It may be worth replacing the constant \( r_0 \) with a nonnegative bounded continuous function \( r(B) \) and investigating the global existence of solutions in this case.

**Longtime behavior of solutions in 1-D**

Due to the fact that the biofilm model is coupled, it is impossible to say explicitly what happens when the time is large for general values of the parameters \( \phi_u, \phi_a, \lambda \). In some specific cases, however, when these parameters are very small or very large, we can say precisely how the variables \( X_u, X_{ud}, X_a, X_{ad} \) will behave. In this section we will be interested in the asymptotic longtime behavior of the cell densities for the biofilm system as well as for the corresponding planktonic system. This question was answered for the linear biofilm model (when \( \phi_u = \phi_a \)) in [34]. We consider (2.1)-(2.6) in 1-D (\( \Omega = [0, L] \)). First we state the dimensionless form of the 1-D biofilm model.

We scale the independent variables \( x \) and \( t \) by \( \tilde{x} = x/L, \tilde{t} = t b_u B_0 \), so that \( 0 \leq \tilde{x} \leq 1 \). The dependent variables are scaled by \( \tilde{B} = B/B_0 \) and \( \tilde{X}_u = X_u/X_0, \tilde{X}_{ud} = X_{ud}/X_0, \tilde{X}_a = X_a/X_0, \tilde{X}_{ad} = X_{ad}/X_0 \). Note that \( \tilde{X}_u, \tilde{X}_{ud}, \tilde{X}_a, \tilde{X}_{ad} \) all range between
0 and 1. Dropping the tildes, (2.1)-(2.6) in the dimensionless form becomes

\[ \epsilon \phi_u^2 \frac{\partial B}{\partial t} = \frac{\partial^2 B}{\partial x^2} - \phi_u^2 (X_u + X_{ud}) B - \phi_a^2 (X_a + X_{ad}) B \]  \hspace{1cm} (2.23)

\[ \frac{\partial B}{\partial x} (0,t) = 0, \quad B(1,t) = 1, \quad B(x,0) = g(x)/B_0 \]  \hspace{1cm} (2.24)

\[ \frac{\partial X_u}{\partial t} = -(B + \lambda) X_u \quad X_u(x,0) = 1 \]  \hspace{1cm} (2.25)

\[ \frac{\partial X_{ud}}{\partial t} = B X_u \quad X_{ud}(x,0) = 0 \]  \hspace{1cm} (2.26)

\[ \frac{\partial X_a}{\partial t} = -\delta B X_a + \lambda X_u \quad X_a(x,0) = 0 \]  \hspace{1cm} (2.27)

\[ \frac{\partial X_{ad}}{\partial t} = \delta B X_a \quad X_{ad}(x,0) = 0 \]  \hspace{1cm} (2.28)

where \( \phi_u^2 = k_u X_0 L^2/D \) and \( \phi_a^2 = k_a X_0 L^2/D \) are the Thiele moduli for the adapted and unadapted cells, \( \epsilon = b_u B_0/k_u X_0 \), \( \lambda = r_0/b_u B_0 \) and \( \delta = b_a/b_u \).

Remark: We would like to point out that \( \phi_u^2 \) on the left hand-side of (2.23) can be replaced by \( \phi_a^2 \) as well, in which case \( \epsilon \) becomes \( b_u B_0/k_a X_0 \).

Note that \( \sqrt{(D/k_a X_0)} \), which has units of length, is the depth to which biocide can diffuse in the biofilm before a significant fraction is depleted by reaction with adapted phenotypes. Hence \( \phi_a = \sqrt{(D/k_a X_0)/L} \) is the depth in scaled variables of the disinfection layer of the adapted cells (the distance in scaled variables a diffusing quantity can spread in significant concentration). \( \phi_u \) can be interpreted analogously.

In the biofilm case we distinguish two regimes, \( \phi_u \ll 1 \) and \( \phi_a \ll 1 \); thin biofilm and \( \phi_u \gg 1 \) or \( \phi_a \gg 1 \); thick biofilm.
The parameter $\epsilon$ is the ratio of the time scale $(k_u X_0)^{-1}$ over which significant biocide depletion occurs to the time scale $(b_u B_0)^{-1}$ over which significant disinfection occurs. We assume that $\epsilon \ll 1$ in the biofilm case but $\epsilon$ can be much larger in the planktonic case.

The parameter $\lambda$ is the time scale over which significant disinfection occurs to the time scale over which unadapted cells transform to adapted cells, i.e., $\lambda \ll 1$ indicates faster acting biocide and $\lambda \gg 1$ means slower acting biocide. We also suppose that $\delta$, the ratio of adapted to unadapted disinfection rates is small for both biofilm and planktonic cases.

With regards to the previous remarks ($\epsilon \ll 1$ and $\delta \ll 1$), the system (2.23)-(2.28) simplifies to

\[
\frac{\partial^2 B}{\partial x^2} = \phi_u^2 (X_u + X_{ud}) B + \phi_a^2 (X_a + X_{ad}) B
\]

(2.29)

\[
\frac{\partial B}{\partial x}(0) = 0, \quad B(1) = 1
\]

(2.30)

\[
\frac{\partial X_u}{\partial t} = -(B + \lambda) X_u \quad X_u(x, 0) = 1
\]

(2.31)

\[
\frac{\partial X_{ud}}{\partial t} = BX_u \quad X_{ud}(x, 0) = 0
\]

(2.32)

\[
\frac{\partial X_a}{\partial t} = \lambda X_u \quad X_a(x, 0) = 0.
\]

(2.33)

Note that $X_{ad}(t) = 0$ and $X_u + X_{ud} + X_a = 1$. The solutions of (2.31)-(2.33) are
\[ X_u(t) = e^{-(\lambda + \int_0^t B(u)du)} \] (2.34)

\[ X_{ud}(t) = \int_0^t B(s) e^{-(\lambda s + \int_0^s B(u)du)} ds \] (2.35)

\[ X_a(t) = \lambda \int_0^t e^{-(\lambda s + \int_0^s B(u)du)} ds. \] (2.36)

It follows from (2.34) that \( X_u(t) \to 0 \) as \( t \to \infty \). The question of interest is the longtime behavior of solutions \( X_{ud} \) and \( X_a \) when the parameters \( \phi_u, \phi_a \) and \( \lambda \) are varied. Here we present the results obtained:

The linear case, when \( \phi_u = \phi_a \):

\[ X_{ud} \to \frac{B}{B + \lambda}, \quad X_a \to \frac{\lambda}{B + \lambda} \text{ as } t \to \infty \]

When \( \phi_u \) and \( \phi_a \) are approximately the same (\( \phi_u \approx \phi_a \)), then the linear model considered above can be used to obtain both upper and lower estimates for all quantities.

In the thin biofilm case, when \( \phi_u, \phi_a \) are both very small (\( \phi_u \ll 1 \) and \( \phi_a \ll 1 \)), we will see that thin biofilms resemble the behavior of the planktonic systems:

\[ X_{ud} \to \frac{1}{\lambda + 1}, \quad X_a \to \frac{\lambda}{\lambda + 1} \text{ as } t \to \infty \]

In the case \( \min\{\phi_a, \phi_u\} \to \infty \), i.e. the disinfection layer of the adapted as well as the unadapted cells is decreasing, adaptation will dominate within the biofilm:

\[ X_{ud} \to 0, \quad X_a \to 1 \text{ for } x \neq 1, \quad X_a \to \frac{\lambda}{\lambda + 1} \text{ at } x = 1 \text{ as } t \to \infty \]
In the planktonic case, when all densities are independent of space, the results for planktonic systems agree with the results for thin biofilms:

\[ X_{ud} \to \frac{1}{1 + \lambda}, \quad X_a \to \frac{\lambda}{1 + \lambda} \quad \text{as} \quad t \to \infty \]

Now suppose that we vary \( \lambda \). The following results are the same for both biofilm and planktonic systems:

In case of a faster acting biocide (\( \lambda \ll 1 \)) disinfection dominates:

\[ X_{ud} \to 1, \quad X_a \to 0 \quad \text{as} \quad t \to \infty \]

When the biocide action is slower (\( \lambda \gg 1 \)), one can expect that adaptation will dominate:

\[ X_{ud} \to 0, \quad X_a \to 1 \quad \text{as} \quad t \to \infty \]

In the remainder of this section we derive the results stated above.

i) The linear case, when \( \phi = \phi_u = \phi_a \): In this case (2.29) is linear and its solution can be found explicitly

\[ B(x) = \frac{\cosh(\phi x)}{\cosh(\phi)}. \]

Therefore, (2.34)-(2.36) take the form

\[ X_u(t) = e^{-(B + \lambda)t}, \]

\[ X_{ud}(t) = \frac{B}{B + \lambda}(1 - e^{-(B + \lambda)t}), \]

\[ X_a(t) = \frac{\lambda}{B + \lambda}(1 - e^{-(B + \lambda)t}), \]
where $B$ is given above. For large time,

$$X_{ud} \to \frac{B}{B + \lambda}, \quad X_a \to \frac{\lambda}{B + \lambda} \quad \text{as} \quad t \to \infty. \quad (2.37)$$

ii) When $\phi_u$ and $\phi_a$ are approximately the same ($\phi_u \approx \phi_a$):

Unfortunately, we cannot find the solution of (2.29) explicitly. We may, however, approximate the solution of (2.29) by an upper solution $\bar{B}$ and a lower solution $\underline{B}$ (upper and lower solutions for elliptic equations are discussed in [2]). When $\phi_a > \phi_u$, we set

$$\frac{\partial^2 B}{\partial x^2} = \phi^2_u B \quad \frac{\partial B}{\partial x}(0) = 0, \quad \bar{B}(1) = 1 \quad (2.38)$$

and

$$\frac{\partial^2 B}{\partial x^2} = \phi^2_a B \quad \frac{\partial B}{\partial x}(0) = 0, \quad \underline{B}(1) = 1. \quad (2.39)$$

The solutions of (2.38)-(2.39) are

$$\bar{B}(x) = \frac{\cosh(\phi_u x)}{\cosh(\phi_u)}, \quad \underline{B}(x) = \frac{\cosh(\phi_a x)}{\cosh(\phi_a)}.$$

Hence, $B$ is bounded by

$$\frac{\cosh(\phi_u x)}{\cosh(\phi_u)} \leq B(x) \leq \frac{\cosh(\phi_u x)}{\cosh(\phi_u)}.$$

Similarly, when $\phi_a < \phi_u$, we get

$$\frac{\cosh(\phi_u x)}{\cosh(\phi_a)} \leq B(x) \leq \frac{\cosh(\phi_u x)}{\cosh(\phi_a)}.$$
For large time, the upper and lower solutions $X_{ud}$, $X_a$, $X_{ad}$, $X_a$ are just like in (2.37), except that $B$ is replaced by $\overline{B}$ and $\underline{B}$, respectively.

Furthermore, we have the following estimate for $|B(x) - \overline{B}(x)|$:

$$|\frac{\cosh(\phi_u x)}{\cosh(\phi_u)} - \frac{\cosh(\phi_a x)}{\cosh(\phi_a)}| \leq |x \sinh(\phi x) \cosh(\phi) - \cosh(\phi x) \sinh(\phi)||\phi_u - \phi_a|$$

for some $\phi$ between $\phi_u$ and $\phi_a$. Adding and subtracting $\sinh(\phi) \cosh(\phi)$, we get

$$|\overline{B}(x) - B(x)| \leq \cosh(\phi) \left[ \sinh(\phi) + \cosh(\phi) - x(\sinh(\phi x) + \cosh(\phi x)) \right] |\phi_u - \phi_a|.$$  

Hence,

$$|\overline{B}(x) - B(x)| \leq e^\phi \cosh(\phi)(1 - xe^{-\phi(1-x)})|\phi_u - \phi_a|.$$  

Note that if $x$ is close to the interface ($x \approx 1$),

$$|\overline{B}(x) - B(x)| \approx e^\phi \cosh(\phi)(1 - x)|\phi_u - \phi_a|,$$

i.e. $\overline{B}$ and $B$ are closer to each other in the upper regions of the biofilm.

iii) When $\phi_a \ll 1$ and $\phi_u \ll 1$ (thin biofilm): It follows from (2.29) that $B \approx 1$. Therefore,

$$X_{ud} \rightarrow \frac{1}{\lambda + 1}, \quad X_a \rightarrow \frac{\lambda}{\lambda + 1} \text{ as } t \rightarrow \infty.$$  

iv) When $\phi_a \rightarrow \infty$: The second term in the right-side of the equation (2.29) grows very fast. For a short time $0 \leq t \leq t_0$, the first term in the right-side of the equation (2.29) will dominate over the second term. Hence, an upper solution of $B$ is

$$\overline{B}(x) = \frac{\cosh(\phi_u x)}{\cosh(\phi_u)}.$$
We pick $t_0$ such that $X_a(t_0) \geq \lambda \epsilon$ for some $0 < \epsilon \ll 1$. Hence,

$$X_a(t_0) \geq \lambda \int_0^{t_0} e^{-(\lambda + \overline{B}) s} ds \geq \lambda \epsilon,$$

where $\overline{B}$ is given above. Solving this inequality for $t_0$ gives

$$(\lambda + \overline{B}) t_0 + O(t_0^2) > \epsilon (\lambda + \overline{B})$$

from which we get $t_0 \approx \epsilon$.

In what follows we will estimate $X_a(t)$ from below for $t > t_0$. We need an upper estimate for $B$, so let’s look for an upper solution for $B$ that satisfies

$$\frac{\partial^2 B}{\partial x^2} = \phi_a^2 \lambda \epsilon B \quad \frac{\partial B}{\partial x}(0) = 0, \quad B(1) = 1. \quad (2.40)$$

We replaced the second term in the right-side of the equation (2.29) by $\phi_a^2 \lambda \epsilon B$. The solution of (2.40) is

$$\overline{B}(x) = \frac{\cosh(\phi_a \sqrt{\lambda \epsilon} x)}{\cosh(\phi_a \sqrt{\lambda \epsilon})}.$$

We pick $\phi_a$ such that

$$\frac{\cosh(\phi_a \sqrt{\lambda \epsilon} x)}{\cosh(\phi_a \sqrt{\lambda \epsilon})} \leq 2 e^{-\phi_a \sqrt{\lambda \epsilon} (1 - x)} \leq \lambda \epsilon$$

for $0 \leq x < 1$. Hence,

$$\phi_a \geq \frac{\ln(2/\epsilon)}{\sqrt{\lambda \epsilon} (1 - x)}.$$
Note that this choice of $\phi_a$ depends on $x$ and $\lambda$. The previous estimate for $\phi_a$ means that the closer we are to $x = 1$, the bigger the $\phi_a$ is. When $x = 1$, then $B(1) = 1$ and at this point $X_a \to \frac{\lambda}{\lambda + 1}$ as $t \to \infty$.

Finally, for $t \to \infty$,

$$X_a \geq \lambda \varepsilon + \lambda \int_{\varepsilon}^{\infty} e^{-(\lambda s + \lambda \varepsilon(s-\varepsilon))} ds = \lambda \varepsilon + \frac{e^{-\lambda \varepsilon}}{1 + \varepsilon} = 1 - \varepsilon + O(\varepsilon^2)$$

so that $X_a \approx 1 - \varepsilon$. Taking the limit for $\varepsilon \to 0$, we obtain

$$X_{ud} \to 0, \quad X_a \to 1 \text{ for } x \neq 1, \quad X_a \to \frac{\lambda}{\lambda + 1} \text{ at } x = 1 \text{ as } t \to \infty.$$ 

Note that in this case adaptation dominates.

v) When $\phi_u \to \infty$: This case is biologically less relevant (the disinfection layer of the unadapted phenotypes is small compared to the disinfection layer of the adapted ones), but mathematically it differs from iv). The first term in the right-side of the equation in (2.29) will dominate for a long time. We pick a time $t_0$ such that $X_u(t_0) \geq \varepsilon$ for some $0 < \varepsilon \ll 1$. Also, for $0 \leq t \leq t_0$, the biocide concentration can be estimated by an upper solution that satisfies the equation

$$\frac{\partial^2 B}{\partial x^2} = \phi_u^2 \varepsilon B, \quad \frac{\partial B}{\partial x}(0) = 0, \quad B(1) = 1. \quad (2.41)$$

We replaced the first term in the right-side of the equation (2.29) by $\phi_u^2 \varepsilon B$. The solution of (2.41) is

$$B(x) = \frac{\cosh(\phi_u \sqrt{\varepsilon} x)}{\cosh(\phi_u \sqrt{\varepsilon})}.$$
We pick φ_u such that
\[
\frac{\cosh(\phi_u \sqrt{\varepsilon} x)}{\cosh(\phi_u \sqrt{\varepsilon})} \leq 2e^{-\phi_u \sqrt{\varepsilon}(1-x)} \leq \lambda \varepsilon.
\]

Hence,
\[
\phi_u \geq \frac{\ln(2/\varepsilon)}{\sqrt{\varepsilon}(1-x)}.
\]

Note that this choice of φ_u depends on x. Just as before, when x = 1, then \( \overline{B}(1) = 1 \) and \( X_a \to \frac{\lambda}{\lambda+1} \) as \( t \to \infty \).

Now we are ready to find \( t_0 \). We have
\[
X_u(t_0) \geq e^{-\lambda(1+\epsilon)t_0} \geq \epsilon
\]
from which we get \( t_0 \approx \frac{\ln(1/\epsilon)}{\lambda(1+\epsilon)} \).

It follows from (2.32)-(2.33) that
\[
\frac{\partial X_{ud}}{\partial t} \left( \frac{\partial X_a}{\partial t} \right)^{-1} = \frac{B}{\lambda} \approx \varepsilon.
\]

Therefore, we obtain \( X_{ud} \approx \varepsilon X_a \). Also, \( X_a + X_{ud} \approx 1 - \varepsilon \). It follows that
\[
X_a \approx 1 - \frac{2\varepsilon}{1+\varepsilon} \approx 1 - 2\varepsilon, \quad X_{ud} \approx 2\varepsilon \quad \text{for} \quad x \neq 1 \quad \text{as} \quad t \to \infty.
\]

Taking the limit for \( \epsilon \to 0 \), we get the same as in iv).

vi) The planktonic case: Consider (2.7) together with the equations of the constituent densities where the derivatives are ordinary. Recall that in the planktonic populations all densities are independent of space. In the dimensionless form these
The dimensionless parameters $\epsilon$, $\lambda$ and $\delta$ are defined as in the biofilm case and $\xi = k_a/k_u$. In the planktonic case $\epsilon \gg 1$. With regards to the previous remarks, we obtain that $B \approx 1$ both in the replenished and in the non-replenished case. One can see that $X_{ad}(t) = 0$ and $X_u(t) \rightarrow 0$ as $t \rightarrow \infty$ again. For large time, the solutions of (2.44)-(2.45) become

$$X_{ad} \rightarrow \frac{1}{1 + \lambda}, \quad X_a \rightarrow \frac{\lambda}{1 + \lambda} \quad \text{as} \quad t \rightarrow \infty.$$ 

Note that the previous results coincide with results in iii); this implies that thin biofilms behave like planktonic systems.

**Minimizer in the linear case**

In the linear case $\phi = \phi_u = \phi_a$ the biocide $B$ is known explicitly. We introduce functionals $J_1$ and $J_2$ and we will show that their optimal minimum is the delta
function which is impractical but it suggests that a short and intense dosing at the beginning of dosing period is the most effective. There are, however, more sophisticated dosing strategies that will be discussed in Chapters 5 and 6.

In the dimensionless form equations (2.3)-(2.6) become

\[
\frac{\epsilon}{\partial_t} \frac{\partial B}{\partial t} = \frac{\partial^2 B}{\partial x^2} - \phi^2 B, \quad \frac{\partial B}{\partial x}(0, t) = 0, \quad B(1, t) = u(t), \quad B(x, 0) = 0 \tag{2.47}
\]

\[
\frac{\partial X_u}{\partial t} = -(B + \lambda)X_u \quad X_u(x, 0) = 1 \tag{2.48}
\]

\[
\frac{\partial X_{ud}}{\partial t} = BX_u \quad X_{ud}(x, 0) = 0 \tag{2.49}
\]

\[
\frac{\partial X_a}{\partial t} = -\delta BX_a + \lambda X_u \quad X_a(x, 0) = 0 \tag{2.50}
\]

\[
\frac{\partial X_{ad}}{\partial t} = \delta BX_a \quad X_{ad}(x, 0) = 0, \tag{2.51}
\]

where

\[
\delta = b_u b_u^{-1}, \quad \epsilon = b_u k l^2 D^{-1}, \quad \phi^2 = kX_0 l^2 D^{-1}, \quad \lambda = m_0(b_u B_0)^{-1}
\]

from Chapter 1. We may take \( \epsilon \ll 1 \) and we also assume that adapted cells are less susceptible to disinfection than unadapted cells, i.e. \( \delta \ll 1 \). In this case (2.47)-(2.51) changes to

\[
\frac{\partial X_u}{\partial t} = -(B + \lambda)X_u \quad X_u(x, 0) = 1 \tag{2.52}
\]

\[
\frac{\partial X_{ud}}{\partial t} = BX_u \quad X_{ud}(x, 0) = 0 \tag{2.53}
\]

\[
\frac{\partial X_a}{\partial t} = \lambda X_u \quad X_a(x, 0) = 0 \tag{2.54}
\]

\[
\frac{\partial X_{ad}}{\partial t} = 0 \quad X_{ad}(x, 0) = 0. \tag{2.55}
\]
where
\[ B(x,t) = u(t)B_0(x) \text{ with } B_0(x) = \frac{\cosh(\phi x)}{\cosh \phi}. \]

We consider two types of minimizing functionals associated with the system (2.52)-(2.54)
\[
J_1(u) = \lim_{T \to \infty} \frac{1}{T} \int_0^T \int_0^1 \left( X_u(x,t) + X_a(x,t) \right) dx dt
\]
with respect to
\[
\int_0^\infty u(t) dt = m
\]
(minimizing \( J_1 \) so that biocide dose of a given amount \( m \) is added during the treatment) and
\[
J_2(u) = \lim_{T \to \infty} \frac{1}{T} \int_0^T \int_0^1 \left( X_u(x,t) + X_a(x,t) \right) dx dt + c \int_0^\infty u(t) dt,
\]
where \( c \) is the cost of a biocide dose (minimizing \( J_2 \) so that the cost of biocide dose is given). It is easy to see that functional \( J_1 \) would not make sense for the model with growth and hence, we do not have an analogy for \( J_1 \) in Chapter 1. Indeed, it follows from the constraint that \( \lim_{t \to \infty} u(t) = 0 \), i.e. if we stop dosing biocide for a long time in growing biofilm, it will regrow again. On the other hand, functional \( J_2 \) coincides with functional \( J \) from Chapter 1 and so \( J_2 \) makes sense both for the model with and without growth.

Recall that for the model without growth \( X_a(t) \to 0 \) as \( t \to \infty \). Also, numerical simulations suggest that \( X_a \) converges to a steady state as \( T \to \infty \). Hence, functional
$J_1$ changes to

$$J_1(u) = \lim_{T \to \infty} \frac{1}{T} \int_0^T \int_0^1 X_a(x, t) dx dt = \int_0^1 X_a(x) dx, \quad \int_0^\infty u(t) dt = m$$

the minimizer of which is the delta-function $u(t) = m\delta(t)$. From equations (2.52) and (2.54) we have

$$X_u(t) = e^{-\int_0^t (\lambda + B(s)) ds}, \quad X_a(t) = \lambda \int_0^t X_u(s) ds.$$

Using the previous formulas and taking $B(x, t) = m\delta(t)B_0(x)$ it can be shown that

$$\min_u J(u) = \int_0^1 e^{-mB_0(x)} dx.$$

We cannot evaluate $\int_0^1 e^{-mB_0} dx$ exactly, but we may conclude the following for the cases of thick/thin biofilms:

i) When $\phi \gg 1$ (thick biofilm) : Function $B_0$ is small for $0 \leq x \leq 1 - \epsilon$ and then close to 1 for $x \approx 1$. Hence,

$$\int_0^1 e^{-mB_0} dx = \int_0^{1-\epsilon} \left(1 - mB_0 + O(B_0^2)\right) dx + \int_{1-\epsilon}^1 e^{-mB_0} dx \approx$$

$$\approx \int_0^{1-\epsilon} (1 - mB_0) dx + \int_{1-\epsilon}^1 e^{-m} dx \approx$$

$$\approx 1 - \epsilon - m \frac{\sinh(\phi(1 - \epsilon))}{\phi \cosh \phi} + \epsilon e^{-m}.$$

As $\epsilon \to 0_+$, we have

$$\int_0^1 e^{-B_0} dx \approx 1 - m \frac{\tanh \phi}{\phi}.$$

ii) When $\phi \ll 1$ (thin biofilm) : Function $B_0$ is close to 1, hence

$$\int_0^1 e^{-mB_0} dx \approx e^{-m}.$$
In fact, \( e^{-m} \leq \int_0^1 e^{-mB_0} dx \leq 1 \). It can be shown that the minimizer of the other functional

\[
J_2(u) = \int_0^\infty \int_0^1 X_a(x, t) dx dt + c \int_0^\infty u(t) dt
\]

is again \( u(t) = m\delta(t) \), where \( m \) satisfies

\[
\int_0^1 e^{-mB_0} dx = c.
\]
CHAPTER 3

EXISTENCE AND UNIQUENESS OF SOLUTIONS

We will prove the global existence of solutions of the system (3.1)-(3.7) with boundary conditions (3.8) and initial data (3.9). In particular, we will show that if the initial data is of class $C^1$, then the solutions are also of class $C^1$. First we prove using characteristics that given $v$, the system (3.11)-(3.17) has a unique solution. Then we use a fixed point argument to show the existence and uniqueness of $v$. We extend our results to the case when the initial data have $C^k$-regularity for $k$ positive integer. Recall the model equations from chapter 1:

\[
\frac{\partial^2 B}{\partial x^2} = \phi^2 B \\
\frac{\partial X_u}{\partial t} + \frac{\partial}{\partial x}(X_u v) = -(B + \lambda)X_u + \alpha X_u + \gamma X_a \\
\frac{\partial X_{ud}}{\partial t} + \frac{\partial}{\partial x}(X_{ud} v) = BX_u \\
\frac{\partial X_a}{\partial t} + \frac{\partial}{\partial x}(X_a v) = \lambda X_a - \delta BX_a + \alpha X_a - \gamma X_a \\
\frac{\partial X_{ad}}{\partial t} + \frac{\partial}{\partial x}(X_{ad} v) = \delta BX_a \\
\frac{\partial v}{\partial x} = \alpha(X_u + X_a) \\
\frac{dL}{dt} = v(L, \cdot) - \sigma L^2
\]

(3.1) (3.2) (3.3) (3.4) (3.5) (3.6) (3.7)
The boundary conditions are given by

\[
\frac{\partial B}{\partial x}(0, t) = 0, \quad B(L(t), t) = u(t) \quad \text{for} \quad 0 \leq t \leq T,
\]

\[
v(0, t) = 0 \quad \text{for} \quad 0 \leq t \leq T,
\]

(3.8)

where the biocide concentration through the interface \( u \) is a nonnegative function belonging to \( C^1[0, T] \). The initial conditions are

\[
L(0) = L_0,
\]

\[
X_u(x, 0) = g_u(x) \quad \text{for} \quad 0 \leq x \leq L_0,
\]

\[
X_{ud}(x, 0) = g_{ud}(x) \quad \text{for} \quad 0 \leq x \leq L_0,
\]

(3.9)

\[
X_a(x, 0) = g_a(x) \quad \text{for} \quad 0 \leq x \leq L_0,
\]

\[
X_{ad}(x, 0) = g_{ad}(x) \quad \text{for} \quad 0 \leq x \leq L_0,
\]

where the initial data for the cell-densities are taken to be nonnegative functions satisfying \( g_u(x) + g_{ud}(x) + g_a(x) + g_{ad}(x) = 1 \) that belong to \( C^1[0, L_0] \). The initial biofilm thickness \( L_0 \) is a positive constant. We look for solutions on the domain

\[
\Omega = \{(x, t) : \quad 0 \leq x \leq L(t), \quad 0 \leq t \leq T\}.
\]

(3.10)
Note that the system (3.1)-(3.7) is equivalent to

\begin{align}
\frac{\partial^2 B}{\partial x^2} &= \phi^2 B \\
\frac{\partial X_u}{\partial t} + v \frac{\partial X_u}{\partial x} &= (-B - \lambda + \alpha(1 - X_u - X_a))X_u + \gamma X_a \\
\frac{\partial X_{ud}}{\partial t} + v \frac{\partial X_{ud}}{\partial x} &= BX_u - \alpha(X_u + X_a)X_{ud} \tag{3.12} \\
\frac{\partial X_a}{\partial t} + v \frac{\partial X_a}{\partial x} &= \lambda X_u + (-\delta B + \alpha(1 - X_u - X_a) - \gamma)X_a \tag{3.13} \\
\frac{\partial X_{ad}}{\partial t} + v \frac{\partial X_{ad}}{\partial x} &= \delta BX_a - \alpha(X_u + X_a)X_{ad} \tag{3.14} \\
\frac{dL}{dt} &= v(L, .) - \sigma L^2 \tag{3.16} \\
\frac{\partial v}{\partial x} &= \alpha(X_u + X_a). \tag{3.17}
\end{align}

We will use (3.11)-(3.16) instead (3.1)-(3.7) in the proof of the following theorem:

**Theorem 3.1:** The system (3.1)-(3.7) with $C^1$ nonnegative initial data (3.9) satisfying $g_u + g_{ud} + g_a + g_{ad} = 1$ and the boundary condition (3.8) for a nonnegative $C^1$ function $u$ has a unique solution on domain (3.10) for any $T < \infty$. Moreover, the functions $X_u, X_{ud}, X_a, X_{ad}$ are all nonnegative, of class $C^1$ and $X_u + X_{ud} + X_a + X_{ad} = 1$. The function $L$ is positive and of class $C^2$ and the function $v$ belongs to $C^2_x C^1_t$.

**Remark.** The statement of above theorem remains true even if more general detachment term in the equation (3.7) is considered, for example of the form $-\sigma L^\beta$ for some $\beta > 0$. 
Proof of Theorem 3.1: We will prove this theorem by proving some lemmas first. We start by solving an easier problem \((3.11)-(3.16)\) in which \((3.17)\) is ignored and instead we assume that the function \(v\) is given on the box \([0, M] \times [0, T]\), where \(M\) will be specified later.

Let \(v\) be a continuous function defined on the box \([0, M] \times [0, T]\). We will assume that \(v\) and \(\frac{\partial v}{\partial x}\) are continuous with respect to both \(x\) and \(t\), \(v(0) = 0\) and \(0 \leq \frac{\partial v}{\partial x} \leq \alpha\). Hence, \(v(x, t) \leq \alpha x\) for all \(t\) and \(v\) is increasing in \(x\). To simplify our exposition we now extend the function \(v\) in a \(C^1_xC_t\)-fashion onto \([0, \infty) \times [0, T]\). For example, we can take

\[
\bar{v}(x, t) = v(M, t) + \left(x - M\right)\frac{\partial v}{\partial x}(M, t) \quad \text{for } x > M. \tag{3.18}
\]

This guarantees that \(\bar{v}\) and \(\frac{\partial \bar{v}}{\partial x}\) are continuous functions and \(\bar{v}(x, t) \leq \alpha x\).

Since \(\bar{v}\) is given, we use equation \((3.7)\) to compute \(L(t)\) on the interval \([0, T]\). Once \(L\) is known, we may compute \(B\), i.e.

\[
B(t) = u(t) \frac{\cosh(\phi x)}{\cosh(\phi L(t))}.
\]

Note that \((3.12)\) can be rewritten as

\[
\frac{\partial X_u}{\partial t} + \frac{\partial X_u}{\partial x} \bar{v} = -(B + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a.
\]

Let us reduce this PDE to an ODE along some curve \(s(t)\), i.e., find \(s(t)\) such that

\[
\frac{d}{dt} X_u(s(t), t) = -(B + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a.
\]
We may do the same with equations (3.13)-(3.15). By the chain rule, we obtain an equation for the characteristics

\[
\frac{ds}{dt} = \bar{v}(s(t), t), \quad s(0) = x_0, \quad (3.19)
\]

for \( x_0 \in [0, \infty) \). By the assumptions laid on \( v \), there exists a unique local \( C^1 \)-solution on a subinterval of \([0, T]\). Since \( \bar{v}(s,.) \leq \alpha s \), we have that \( s(t) \leq x_0 e^{\alpha t} \) for all \( t \). Hence, there is a unique \( C^1 \)-solution on the full interval \([0, T]\).

Figure 1. Characteristic curves on the box \([0, M] \times [0, T]\).
We restrict the system to the characteristics. In this case equations (3.12)-(3.15) become

\[
\dot{x}_u = -(b + \lambda)x_u + \alpha(1 - x_u - x_a)x_u + \gamma x_a, \quad (3.20)
\]

\[
\dot{x}_{ud} = bx_u - \alpha(x_u + x_a)x_{ud}, \quad (3.21)
\]

\[
\dot{x}_a = \lambda x_u - \delta bx_a + \alpha(1 - x_u - x_a)x_a - \gamma x_a, \quad (3.22)
\]

\[
\dot{x}_{ad} = \delta bx_a - \alpha(x_u + x_a)x_{ad}, \quad (3.23)
\]

where

\[
\dot{x}_u(t) := \frac{\partial X_u}{\partial t}(s(t), t) + \frac{\partial X_u}{\partial x}(s(t), t)\bar{v}(s(t), t), \quad x_u(t) := X_u(s(t), t),
\]

\[
\dot{x}_{ud}(t) := \frac{\partial X_{ud}}{\partial t}(s(t), t) + \frac{\partial X_{ud}}{\partial x}(s(t), t)\bar{v}(s(t), t), \quad x_{ud}(t) := X_{ud}(s(t), t),
\]

\[
\dot{x}_a(t) := \frac{\partial X_a}{\partial t}(s(t), t) + \frac{\partial X_a}{\partial x}(s(t), t)\bar{v}(s(t), t), \quad x_a(t) := X_a(s(t), t),
\]

\[
\dot{x}_{ad}(t) := \frac{\partial X_{ad}}{\partial t}(s(t), t) + \frac{\partial X_{ad}}{\partial x}(s(t), t)\bar{v}(s(t), t), \quad x_{ad}(t) := X_{ad}(s(t), t).
\]

The biocide concentration restricted to the characteristics is given by

\[b(t) := B(s(t), t).\]

The initial data associated with the system (3.20)-(3.23) are given by

\[x_u(0) = g_u(x_0), \quad x_{ud}(0) = g_{ud}(x_0),\]

\[x_a(0) = g_a(x_0), \quad x_{ad}(0) = g_{ad}(x_0).\]

Note that the system (3.20)-(3.23) has a unique local solution since the right-hand sides of the equations are Lipschitz continuous. It also follows that two characteristics never intersect. Indeed, let \(s_1\) be a characteristic with initial condition \(s_1(0) = x_1\).
and $s_2$ a characteristics such that $s_2(0) = x_2$, where $x_1 < x_2$. Then

$$s'_2(0) - s'_1(0) = v(x_2, 0) - v(x_1, 0) \geq 0,$$

since $\frac{\partial v}{\partial x} \geq 0$. The same argument works for any time $t$, and hence we get that $s_2 - s_1$ is a nondecreasing function in $t$. Thus $s_1 \neq s_2$ for all $t \geq 0$.

First we will show that the sum of the solutions to (3.20)-(3.23) is 1. Let $w$ denote the sum $x_u + x_{ud} + x_a + x_{ad}$. Adding equations (3.20)-(3.23) of the previous system we obtain

$$\dot{w} = \alpha (x_u + x_a)(1 - w), \quad w(0) = 1.$$

Let $z = 1 - w$. Then the previous ODE becomes

$$\dot{z} = -\alpha (x_u + x_a)z, \quad z(0) = 0,$$

the solution of which is $z(t) = 0$ for all $t$. Hence, $w(t) = 1$ for all $t$.

Now we are ready to prove that the solutions to (3.20)-(3.23) are nonnegative (and therefore bounded by 1, since $x_u + x_{ud} + x_a + x_{ad} = 1$). Note that the solution to (3.21) and (3.23) is given by

$$x_{ud}(t) = e^{-\alpha \int_0^t (x_u(s) + x_a(s)) ds} g_{ud}(x_0) + \int_0^t x_u(u)b(u) e^{-\alpha \int_u^t (x_u(s) + x_a(s)) ds} du \quad (3.24)$$

and

$$x_{ad}(t) = e^{-\alpha \int_0^t (x_u(s) + x_a(s)) ds} g_{ad}(x_0) + \delta \int_0^t x_a(u)b(u) e^{-\alpha \int_u^t (x_u(s) + x_a(s)) ds} du. \quad (3.25)$$
First we will show that $x_u$ and $x_a$ are nonnegative. Then it will follow from (3.24) and (3.25) that $x_{ud}$ and $x_{ad}$ are nonnegative as well.

To see that $x_u$ and $x_a$ are nonnegative, we argue by contradiction. We will show that

$$\{t \in [0,T] : x_u(t) < 0 \text{ or } x_a(t) < 0\} = \emptyset.$$ 

Assume this claim is false. Then there exists $t_0$ such that

$$t_0 = \inf\{t \in [0,T] : x_u(t) < 0 \text{ or } x_a(t) < 0\}.$$ 

Clearly, at $t_0$ we have that $x_u(t_0) = 0$ or $x_a(t_0) = 0$ or both. We have the following cases:

**Case 1:** If $x_u(t_0) > 0$ and $x_a(t_0) = 0$, then from equation (3.22) it follows that $\dot{x}_a(t_0) > 0$ on $(t_0, t_0 + \delta)$. This contradicts the fact that by the definition of $t_0$ the function $x_a < 0$ on $(t_0, t_0 + \delta)$. Hence this case does not happen.

**Case 2:** If $x_a(t_0) > 0$ and $x_u(t_0) = 0$, then from the equation (3.20) it follows that $\dot{x}_u(t_0) > 0$ on $(t_0, t_0 + \delta)$. This contradicts the fact that from the definition of $t_0$ the function $x_u < 0$ on $(t_0, t_0 + \delta)$. Hence this case also does not happen.

**Case 3:** Finally, if $x_u(t_0) = x_a(t_0) = 0$, then the uniqueness argument for the ODEs (3.20) and (3.22) implies that $x_u(t) = x_a(t) = 0$ for all $t$ on $[0, M]$. Therefore, this case must be again excluded.

It follows from the previous that such a $t_0$ does not exists, hence $x_u(t) \geq 0$ and $x_a(t) \geq 0$ on $[0, T]$. Altogether, all the solutions to (3.20)-(3.23) are nonnegative and
bounded by 1. The boundedness of solutions guarantees that the system (3.20)-(3.23) has a unique $C^1$-solution on the full interval $[0, T]$, i.e. $x_u, x_{ud}, x_a, x_{ad} \in C^1[0, T]$.

In what follows we will consider the dependence of characteristics $s$ satisfying the ODE (3.19) on the initial data $x_0$. Recall that $s$ is of class $C^1$ in the $t$ variable, i.e. $s(x_0, \cdot) \in C^1[0, T]$. We will show that $s$ is $C^1$-dependent on $x_0$, i.e. $s(\cdot, t) \in C^1[0, \infty)$. Consider the initial-value problem

$$\frac{dp}{dt} = f(x_0, t)p, \quad p(0) = 1,$$  \hspace{1cm} (3.26)

where $f(x_0, t) = \frac{\partial u(s, t)}{\partial s}$ and $p = \frac{\partial u}{\partial x_0}$. The ODE (3.26) is obtained by differentiating (3.19) with respect to $x_0$. The solution to (3.26) is given by

$$p(x_0, t) = e^{\int_0^t f(x_0, u)du} > 0.$$  \hspace{1cm} (3.27)

Note that $f(x_0, t)$ is uniformly bounded and continuous in both variables. Hence, $p(\cdot, t) \in C[0, \infty)$, i.e. $s \in C^1([0, \infty) \times [0, T])$.

Just as before, we will consider the dependence of the functions $x_u, x_{ud}, x_a, x_{ad}$ on $x_0$. Recall that $x_u(x_0, \cdot), x_{ud}(x_0, \cdot), x_a(x_0, \cdot), x_{ad}(x_0, \cdot) \in C^1[0, T]$. We will show that the solutions to (3.20)-(3.23) are $C^1$-dependent on $x_0$, i.e. $x_u(\cdot, t), x_{ud}(\cdot, t), x_a(\cdot, t), x_{ad}(\cdot, t) \in C^1[0, \infty)$. Indeed, differentiating equations (3.20)-(3.23) with respect to $x_0$ enables us to obtain an ODE of the form

$$\frac{dy}{dt} = P(x_0, t)y + Q(x_0, t), \quad y(0) = y_0,$$  \hspace{1cm} (3.28)

where the components of $y$ are taken to be

$$y(t) = \begin{bmatrix} \frac{\partial x_u(t)}{\partial x_0}, \frac{\partial x_{ud}(t)}{\partial x_0}, \frac{\partial x_a(t)}{\partial x_0}, \frac{\partial x_{ad}(t)}{\partial x_0} \end{bmatrix}^T.$$
with the initial data

\[ y_0 = \begin{bmatrix} g_u'(x_0), g_{ud}'(x_0), g_a'(x_0), g_{ad}'(x_0) \end{bmatrix}^T. \]

The solution of (3.28) is given by

\[
y(x_0, t) = e^{\int_0^t P(x_0, u)du}y_0 + \int_0^t e^{\int_0^s P(x_0, u)du}Q(x_0, s)ds. \tag{3.29}
\]

The vector-valued functions \( P(x_0, t), Q(x_0, t) \) are continuous on \([0, \infty) \times [0, T]\). Also, the components of \( P \) and \( Q \) are uniformly bounded in \( t \in [0, T] \) and \( x_0 \in [0, \infty) \). It is easy to see that \( y \) is bounded. Let \( \| \cdot \| \) denote the usual matrix norm. From above it follows that there exits a constant \( C > 0 \) independent of \( t \) and \( x_0 \) such that \( \|P\| \leq C \) and \( \|Q\| \leq C \). Therefore, by (3.29) it follows that for \( t \in [0, T] \)

\[
\|y(t)\| \leq e^{CT}(\|y_0\| + CT).
\]

Altogether, there is a unique vector-valued solution on the full interval \([0, T]\) each component of which belongs to \( C[0, \infty) \times C^1[0, T] \) and this is what we wanted.

Recall that \( x_u, x_{ad}, x_a, x_{ad} \in C^1([0, T] \times [0, \infty)) \). We will show that this implies the functions \( X_u, X_{ad}, X_a, X_{ad} \) are \( C^1 \) in both variables. The relationship between \( x_u, x_{ad}, x_a, x_{ad} \) and \( X_u, X_{ad}, X_a, X_{ad} \) is the following:

\[
x_u(x_0, t) = X_u(s(t, x_0), t), \quad x_{ad}(x_0, t) = X_{ad}(s(t, x_0), t),
\]

\[
x_a(x_0, t) = X_a(s(t, x_0), t), \quad x_{ad}(x_0, t) = X_{ad}(s(t, x_0), t).
\]

Define \( x = s(x_0, t) = s_t(x_0) \). Note that \( s_t \) is invertible since \( p = \frac{\partial s}{\partial x_0} > 0 \) in (3.27). Also, since \( s_t \) is \( C^1 \) in both variables, by the Inverse Function Theorem \( s_t^{-1}(x) \) is also
$C^1$ in $x$ and $t$. We may write

$$X_u(x, t) = x_u(s_t^{-1}(x), t) = x_u \circ Y,$$

where $Y : \mathbb{R}^2 \to \mathbb{R}^2$ with $Y(x, t) = (s_t^{-1}(x), t)$. Note that $Y$ is $C^1$ in both variables since $s_t^{-1}(x)$ is of class $C^1$ by the argument above. It follows that $X_u$ is $C^1$ in both variables on $[0, \infty) \times [0, T]$ as the composition of $C^1$-mappings $Y$ with $x_u$. The same argument shows that $X_a$, $X_{ad}$ and $X_{ud}$ are also $C^1$ in $x$ and $t$ on $[0, \infty) \times [0, T]$. Hence, we have established the following lemma:

**Lemma 3.1:** Let $v$ and $\frac{\partial v}{\partial x}$ be continuous with respect to both $x$ and $t$, $v(0) = 0$ and $0 \leq \frac{\partial v}{\partial x} \leq \alpha x$. Then the system (3.11)-(3.15) has a unique solution with functions $X_u, X_{ud}, X_a, X_{ad}$ belonging to $C^1([0, \infty) \times [0, T])$, nonnegative and summing up to 1.

We may easily find an upper bound $M$ on the function $L$ given in the following lemma:

**Lemma 3.2:** The function $L$ satisfying (3.7) is nonnegative, belongs to $C^2$ and has an upper bound $M$, where

$$M = \max \left\{ \frac{\alpha}{\sigma}, L_0 \right\}.$$  \hfill (3.30)

**Proof of Lemma 3.2:**

To show that $L$ with initial data $L(0) = L_0 > 0$ stays positive, we argue with contradiction. Suppose there is a time $t_0$ at which $L(t_0) = 0$. On the other hand, if the initial data is $L(0) = 0$, then $L(t) = 0$ solves (3.7). Two solutions with different initial data cannot intersect each other, it would contradict the uniqueness of solutions.
To see that \( L(t) \leq M \), assume contrarily that there is a \( t_0 \) such that \( L(t_0) = M \) and \( L(t) > M \) on \((t_0, t_0 + \delta)\) for some \( \delta > 0 \). Note that

\[
\frac{dL}{dt} \leq \alpha L - \sigma L^2 < L(\alpha - \sigma M) \leq 0
\]
on \((t_0, t_0 + \delta)\). It follows that \( \frac{dL}{dt} < 0 \) and so \( L(t) < L(t_0) = M \) on \((t_0, t_0 + \delta)\) which is contradiction. ■

Note that we have shown in Lemma 3.1 that the functions \( X_u, X_\alpha \) are \( C^1 \) in both variables. Hence, \( v \) will be \( C^2 \) in \( x \) and \( C^1 \) in \( t \). Since the right hand-side of equation (3.7) is \( C^2 \) in \( L \) and \( C^1 \) in \( t \), there is a unique local \( C^2 \)-solution. Boundedness by \( M \) guarantees a unique \( C^2 \)-solution on the full interval \([0, T]\). This finishes the proof of existence for the system (3.11)-(3.16) under the assumption that \( v \) is known.

In what follows, we will use a fixed point argument to show the existence and uniqueness of \( v \) satisfying the assumptions in Lemma 3.1. We will introduce the function spaces

\[
\mathcal{X} = \{ f : [0, M] \times [0, T_0] \to \mathbb{R} : f, f_x \in C([0, M] \times [0, T_0]) \}
\]
with norm \( \| f \|_{\mathcal{X}} = \| f \|_{C([0, M] \times [0, T_0])} + \| f_x \|_{C([0, M] \times [0, T_0])} \)

and

\[
Z = C([0, M] \times [0, T_0])
\]
with norm \( \| f \|_{Z} = \| f \|_{C([0, M] \times [0, T_0])} \), where \( T_0 \) will be chosen later.

We define the domain of operator \( F \) by

\[
D(F) = \{ v \in \mathcal{X} : v(0) = 0, \quad 0 < \frac{\partial v}{\partial x} \leq \alpha x \text{ for } x > 0 \}
\]
Given \( v \) on \([0, M] \times [0, T]\), we may define its extension \( \tilde{v} \) on \([0, \infty) \times [0, T]\) by formula (3.18). Thus, we may compute \( X_u, \ x_a \) on \([0, \infty) \times [0, T]\) by the method described above. We define the operator \( F : \mathcal{X} \to \mathcal{X} \) as follows

\[
Fv(x, t) = \alpha \int_0^x (X_u(u, t) + X_a(u, t))du, \quad 0 \leq x \leq M, \quad 0 \leq t \leq T,
\]

(3.31)

where \( v \in D(F) \). One can see that \( D(F) \) is a closed subset in \( \mathcal{X} \). We will show that \( F \) has a fixed point by the contraction mapping principle, i.e.

\[
\|Fv - F\tilde{v}\|_{\mathcal{X}} \leq q\|v - \tilde{v}\|_{\mathcal{X}}
\]

for some \( 0 < q < 1 \).

Note that for a mapping \( f \in \mathcal{X} \subset \mathcal{Z} \) the following is true:

\[
\left\| \int_0^x f du \right\|_{\mathcal{X}} \leq K \left\| f \right\|_{\mathcal{Z}}
\]

Indeed, we have

\[
\left\| \int_0^x f du \right\|_{\mathcal{X}} = \left\| \int_0^x f du \right\|_{\mathcal{Z}} + \left\| f \right\|_{\mathcal{Z}} \leq K \left\| f \right\|_{\mathcal{Z}}
\]

with \( K = 1 + M \). This inequality will be needed below.

Consider

\[
\|Fv - F\tilde{v}\|_{\mathcal{X}} = \left\| \alpha \int_0^x (X_u + X_a - \tilde{X}_u - \tilde{X}_a)du \right\|_{\mathcal{X}} \leq
\]

\[
\leq K\alpha \|X_u + X_a - \tilde{X}_u - \tilde{X}_a\|_Z \leq K\alpha (\|X_u - \tilde{X}_u\|_Z + \|X_a - \tilde{X}_a\|_Z),
\]

(3.32)

where \( K \) is defined above. Recall that \( x_u \) and \( x_a \) are \( C^1 \) in both variables. Therefore, they are Lipschitz continuous with respect to \( x_0 \) and \( t \). Estimate

\[
\|X_u - \tilde{X}_u\|_Z = \|x_u \circ Y - x_u \circ \tilde{Y} + x_u \circ \tilde{Y} - \tilde{x}_u \circ \tilde{Y}\|_Z \leq
\]
\[ \|x_u\|_{\text{Lip}} \|Y - \tilde{Y}\|_Z + \|x_u - \tilde{x}_u\|_Z \leq C_u \|Y - \tilde{Y}\|_Z + \|x_u - \tilde{x}_u\|_Z, \tag{3.33} \]

and
\[
\|X_a - \tilde{X}_a\|_Z = \|x_a \circ Y - x_a \circ \tilde{Y} + x_a \circ \tilde{Y} - \tilde{x}_a \circ \tilde{Y}\|_Z \leq \|x_a\|_{\text{Lip}} \|Y - \tilde{Y}\|_Z + \|x_a - \tilde{x}_a\|_Z, \tag{3.34} \]

where \(\|\cdot\|_{\text{Lip}}\) is the Lipschitz-norm with respect to \(t\) and \(x_0\). These for variables \(x_u\) and \(x_a\) are just some constants \(C_u\) and \(C_a\) that only depend on initial conditions of our problem, the total time interval we want to solve the problem, but not on \(v\).

In what follows, we will find an appropriate estimate for the first term \(\|Y - \tilde{Y}\|_Z\) in (3.33) and (3.34). Using the fact that \(s^{-1}_t - \tilde{s}^{-1}_t = s^{-1}_t(\tilde{s}_t - s_t)\tilde{s}^{-1}_t\), we obtain
\[
\|Y - \tilde{Y}\|_Z = \sup_{t \in [0,T_0]} \|s^{-1}_t - \tilde{s}^{-1}_t\|_{C[0,M]} \leq \sup_{t \in [0,T_0]} \|s^{-1}_t\|_{\text{Lip}_x} \sup_{t \in [0,T_0]} \|\tilde{s}^{-1}_t\|_{\text{Lip}_x} \|s - \tilde{s}\|_Z, \tag{3.35} \]

where \(\|\cdot\|_{\text{Lip}_x}\) is the Lipschitz norm with respect to \(x\). Note that (3.19) is equivalent to
\[
s_t(x_0) = x_0 + \int_0^t v(u, s_u(x_0)) \, du. \]

It follows from (3.27) that \(\frac{\partial s_u}{\partial x_0} > 0\). Hence,
\[
\frac{\partial s_t}{\partial x_0} = 1 + \int_0^t \frac{\partial v}{\partial x_0}(u, s_u(x_0)) \frac{\partial s_u}{\partial x_0} \, du \geq 1. \]

Therefore,
\[
\|s^{-1}_t\|_{\text{Lip}_x} \leq \sup_{x_0 \in [0,M]} \frac{1}{\left| \frac{\partial s_t}{\partial x_0} \right|} \leq 1. \]
and so (3.35) can be rewritten as

$$\|Y - \tilde{Y}\|_Z \leq \|s - \tilde{s}\|_Z.$$  \hfill (3.36)

Estimating (3.36) we have

$$\|s - \tilde{s}\|_Z = \left\| \int_0^t v(u, s(u)) - v(u, \tilde{s}(u)) + v(u, \tilde{s}(u)) - \tilde{v}(u, \tilde{s}(u))du \right\|_Z \leq$$

$$\leq T_0\|v\|_{\text{Lip}_x}\|s - \tilde{s}\|_Z + T_0\|v - \tilde{v}\|_Z \leq T_0\|s - \tilde{s}\|_Z + T_0\|v - \tilde{v}\|_Z.$$  \hfill (3.37)

Making use of (3.36) and taking $T_0\alpha \leq \frac{1}{2}$ in (3.37) yields

$$\|Y - \tilde{Y}\|_Z \leq 2T_0\|v - \tilde{v}\|_Z \leq 2T_0\|v - \tilde{v}\|_X.$$  \hfill (3.38)

Now we are ready to estimate the second term $\|x_u - \tilde{x}_u\|_Z$ in (3.33). To do this, we need some estimates first. Note that

$$\|x_u - \tilde{x}_u\|_Z = \left\| \int_0^t -b(u)x_u(u) + b(u)\tilde{x}_u(u) + \lambda(\tilde{x}_u(u) - x_u(u)) +$$

$$+ \alpha(1 - x_u(u) - x_a(u))x_u(u) - \alpha(1 - \tilde{x}_u(u) - \tilde{x}_a(u))\tilde{x}_u(u) + \gamma(x_a(u) - \tilde{x}_a(u))du \right\|_Z \leq$$

$$\leq T_0\|b\|_{C[0,T_0]}\|x_u - \tilde{x}_u\|_Z + \|\tilde{x}_u\|_Z\|b - \tilde{b}\|_{C[0,T_0]} + \lambda\|x_u - \tilde{x}_u\|_Z +$$

$$+ \alpha\|x_u - \tilde{x}_u\|_Z + \alpha\|(x_u + x_a)x_u - (\tilde{x}_u + \tilde{x}_a)\tilde{x}_u\|_Z + \gamma\|x_a - \tilde{x}_a\|_Z,$$  \hfill (3.39)

where the middle term in (3.39) can be estimated as

$$\|(x_u + x_a)x_u - (\tilde{x}_u + \tilde{x}_a)\tilde{x}_u\|_Z \leq \|x_u^2 - \tilde{x}_u^2\|_Z + \|x_a x_u - \tilde{x}_a \tilde{x}_u\|_Z \leq$$

$$\leq 2\|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z + \|x_a - \tilde{x}_a\|_Z$$
by the fact that $x_u, x_u, x_a, x_a, \tilde{x}_u, \tilde{x}_u, \tilde{x}_a, \tilde{x}_a$ are nonnegative and bounded by 1.

Also, there is an upper bound on $b$ independent of $t$:

$$\|b\|_{C[0,T_0]} = \sup_{t \in [0,T_0]} u(t) \frac{\cosh(\phi s(t))}{\cosh(\phi L(t))} \leq \|u\|_{C[0,T]} \cosh(\phi M)$$

It follows from the previous that

$$\|x_u - \tilde{x}_u\|_Z \leq T_0 [C_1 \|x_u - \tilde{x}_u\|_Z + C_2 \|x_a - \tilde{x}_a\|_Z + \|b - \tilde{b}\|_{C[0,T_0]}],$$

(3.40)

where

$$C_1 = \|u\|_{C[0,T]} \cosh(\phi M) + \lambda + 4\alpha, \quad C_2 = \gamma + \alpha.$$

In a similar manner as above we may estimate the second term $\|x_a - \tilde{x}_a\|_Z$ in (3.34). We have

$$\|x_a - \tilde{x}_a\|_Z = \left\| \int_0^t \lambda(x_u(u) - \tilde{x}_u(u)) - \delta x_a(u) \tilde{b}(u) + \\
+ \alpha (1 - x_u(u) - x_a(u)) x_a(u) - \alpha (1 - \tilde{x}_u(u) - \tilde{x}_a(u)) \tilde{x}_a(u) - \gamma (x_a(u) - \tilde{x}_a(u)) du \right\|_Z \leq \\
\leq T_0 \left[ \lambda \|x_u - \tilde{x}_u\|_Z + \delta \|b\|_{C[0,T_0]} \|x_a - \tilde{x}_a\|_Z + \delta \|\tilde{x}_a\|_Z \|b - \tilde{b}\|_{C[0,T_0]} + \\
+ \alpha \|x_a - \tilde{x}_a\|_Z + \alpha \|(x_u + x_a)x_a - (\tilde{x}_u + \tilde{x}_a)\tilde{x}_a\|_Z + \gamma \|x_a - \tilde{x}_a\|_Z \right].$$

(3.41)

Just as before, we may estimate the middle term in (3.41)

$$\|(x_u + x_a)x_a - (\tilde{x}_u + \tilde{x}_a)\tilde{x}_a\|_Z \leq \|x_u^2 - \tilde{x}_u^2\|_Z + \|x_ux_u - \tilde{x}_u\tilde{x}_u\|_Z \leq \\
\leq 2\|x_a - \tilde{x}_a\|_Z + \|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z.$$

We obtain

$$\|x_a - \tilde{x}_a\|_Z \leq T_0 [C_3 \|x_a - \tilde{x}_a\|_Z + C_4 \|x_u - \tilde{x}_u\|_Z + \delta \|b - \tilde{b}\|_{C[0,T_0]}],$$

(3.42)
where
\[ C_3 = \delta \|u\|_{C[0,T]} \cosh(\phi M) + 4\alpha + \gamma, \quad C_4 = \lambda + \alpha. \]

Adding (3.40)-(3.42) one obtains
\[
\|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z \leq T_0 C_{\text{max}} (\|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z) +
+ T_0 (1 + \delta) \|b - \tilde{b}\|_{C[0,T_0]},
\]
where
\[ C_{\text{max}} = \max\{C_1 + C_4, C_2 + C_3\}. \]

Taking \(T_0 C_{\text{max}} \leq \frac{1}{2}\) in (3.43) yields
\[
\|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z \leq 2T_0 (1 + \delta) \|b - \tilde{b}\|_{C[0,T_0]} \leq
\leq 2T_0 (1 + \delta) \|b\|_{\text{Lip}_t} \|L - \tilde{L}\|_{C[0,T_0]},
\]
where \(\|.\|_{\text{Lip}_t}\) is the Lipschitz-norm with respect to \(t\). We may show that an upper bound on \(\frac{db}{dt}\) independent of \(t\) is the following:
\[
\left| \frac{db}{dt} \right| = \phi \left| \frac{\sinh(\phi s)}{\cosh(\phi L)} \frac{ds}{dt} - \tanh(\phi L) \frac{\cosh(\phi s)}{\cosh(\phi L)} \frac{dL}{dt} \right| \leq
\leq \|u'\|_{C[0,T]} \cosh(\phi M) + \|u\|_{C[0,T]} \phi M [\alpha e^{\phi M} + \sigma M \cosh(\phi M)]
\]

Therefore, there exists a positive constant \(C_b\) independent of \(t\) such that \(\|b\|_{\text{Lip}_t} \leq C_b\).

Now we will estimate the term \(\|L - \tilde{L}\|_{C[0,T_0]}\) in (3.44):
\[
\|L - \tilde{L}\|_{C[0,T_0]} \leq \sup_{t \in [0,T_0]} \left\{ \int_0^t |v(u, L(u)) - v(u, \tilde{L}(u)) + v(u, \tilde{L}(u)) - \tilde{v}(u, \tilde{L}(u))| du +
\right. \]
\[ + \sigma \int_0^t |L^2(u) - \tilde{L}^2(u)| du \leq T_0 [\|v\|_X \|L - \tilde{L}\|_{C[0,T_0]} + \|v - \tilde{v}\|_Z + 2\sigma M \|L - \tilde{L}\|_{C[0,T_0]}]. \]

Since \(\|v\|_X \leq \alpha(M + 1)\), we get

\[ \|L - \tilde{L}\|_{C[0,T_0]} \leq T_0 [\alpha(M + 1) \|L - \tilde{L}\|_{C[0,T_0]} + \|v - \tilde{v}\|_Z + 2\sigma M \|L - \tilde{L}\|_{C[0,T_0]}]. \]  

Taking \(T_0 \alpha(M + 1) < \frac{1}{4}\) and \(T_0 2\sigma M < \frac{1}{4}\) in (3.45), we obtain

\[ \|L - \tilde{L}\|_{C[0,T_0]} \leq 2T_0 \|v - \tilde{v}\|_Z \leq 2T_0 \|v - \tilde{v}\|_X. \]  

(3.46)

By (3.46), the inequality in (3.44) becomes

\[ \|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z \leq 4T_0^2 (1 + \delta) C_b \|v - \tilde{v}\|_X. \]  

(3.47)

Now we are back to (3.32). By (3.47), (3.33), (3.34) and (3.38), the inequality in (3.32) changes to

\[ \|Fv - F\tilde{v}\|_X \leq K\alpha(\|Y - \tilde{Y}\|_Z (C_u + C_a) + \|x_u - \tilde{x}_u\|_Z + \|x_a - \tilde{x}_a\|_Z) \leq \]  

\[ \leq K\alpha(2T_0(C_u + C_a) + 4T_0^2 (1 + \delta) C_b) \|v - \tilde{v}\|_X. \]  

(3.48)

Taking \(T_0 \leq 1\) in (3.48) we obtain

\[ \|Fv - F\tilde{v}\|_X \leq 2T_0 K\alpha(C_u + C_a + 2(1 + \delta) C_b) \|v - \tilde{v}\|_X. \]

We choose \(T_0\) sufficiently small so that the mapping \(F\) is contractive. For example, we pick \(T_0\) so small that \(T_0 2K\alpha(C_u + C_a + 2(1 + \delta) C_b) \leq 1/2\). Summarizing the previous choices of \(T_0\), we take

\[ T_0 = \min \left\{ \frac{1}{2\alpha}, \frac{1}{2C_{\max}}, \frac{1}{4\alpha(M + 1)}, \frac{1}{8\sigma M}, \frac{1}{4K\alpha(C_u + C_a + 2(1 + \delta) C_b)} \right\}. \]
The important thing to note is that if we look back at all choices of constants \((C_a, C_u, C_{\text{max}})\) we made, we can observe that they only depend on coefficients \((\alpha, \sigma, \gamma)\), the boundary data \(u(t)\) and \(C^1\) norms of the initial conditions (functions \(g_a, g_u, \ldots\)).

The situation is particularly delicate for constants \(C_a\) and \(C_u\). It is important to notice that when we selected them, we did it already for the full interval \([0, T]\), even though we now look only for a solution on the interval \([0, T_0]\). Hence we will not have to change these two constants in the next step.

By the contraction mapping principle, it follows that the mapping \(F\) has a unique fixed point \(v\) in its domain \(D(F)\). This fixed point is the solution on \([0, M] \times [0, T_0]\). Since \(v(., T_0), X_a(., T_0), \tilde{X}_{ud}(., T_0), \tilde{X}_a(., T_0), \tilde{X}_{ad}(., T_0) \in C^1[0, M]\), we can then repeat the argument above to extend our solution to the time interval \([T_0, 2T_0]\). The important point emphasized earlier is the fact that the size of the constants does not change, hence this is again an interval of same length \(T_0\). Continuing, after finitely many steps we construct a unique solution existing on the full interval \([0, T]\).

At this point we have a 'solution' on \([0, M] \times [0, T]\). We note however, that the true solution is only defined on a subdomain \(\Omega\) of \([0, M] \times [0, T]\) as given in (3.10). The initial data \(g_u, g_{ud}, g_a, g_{ad}\) on the interval \([0, L_0]\) \((L(0) = L_0)\) are of class \(C^1\), nonnegative and they sum up to 1. First we determine the number \(M\) by formula (3.30). We need our data to be defined on \([0, M]\), so we extend the data in a \(C^1\)-fashion onto \([0, M]\) and we denote them by \(\tilde{g}_u, \tilde{g}_{ud}, \tilde{g}_a, \tilde{g}_{ad}\). The existence theorem
above gives us a unique solution of the equations (3.1)-(3.7) on the domain \([0, M] \times [0, T]\). We call the functions corresponding to this solution by \(\tilde{v}, L, \tilde{X}_u, \tilde{X}_{ud}, \tilde{X}_a, \tilde{X}_{ad}\).

Finally, we obtain our true solution defined on the domain \(\Omega\) by taking a restriction of \(\tilde{v}, \tilde{X}_u, \tilde{X}_{ud}, \tilde{X}_a, \tilde{X}_{ad}\) onto the domain \(\Omega\). Hence,

\[
\begin{align*}
  v &= \tilde{v} \bigg|_{\Omega}, \\
  X_u &= \tilde{X}_u \bigg|_{\Omega}, \\
  X_{ud} &= \tilde{X}_{ud} \bigg|_{\Omega}, \\
  X_a &= \tilde{X}_a \bigg|_{\Omega}, \\
  X_{ad} &= \tilde{X}_{ad} \bigg|_{\Omega}
\end{align*}
\]

and the proof of Theorem 3.1 is complete. ■

The following proposition deals with the issue of better regularity of the solutions from Theorem 3.1. Essentially, the more regularity we have on the initial data, the smoother are the solutions.

**Proposition 3.3:** Let all assumptions of Theorem 3.1 on the initial data \(g_u, g_{ud}, g_a, g_{ad}\) be satisfied. In addition, assume that these functions are of class \(C^k\), where \(k \geq 1\) is an integer. Then the solution of the problem (3.1)-(3.7) satisfying the boundary conditions (3.8) has the following regularity:

- functions \(X_u, X_{ud}, X_a, X_{ad}\) are of class \(C^k\) in both variables

- function \(v\) is of class \(C^k_t C^{k+1}_x\)

- function \(L\) is of class \(C^{k+1}\).

These results can be established by showing that function \(s\), and hence mapping \(Y\), and also functions \(x_u, x_{ud}, x_a, x_{ad}\) are of class \(C^k\) in both variables. This fact is easier to prove in variable \(t\), as it follows from standard ODE theory. The \(C^k\) regularity in variable \(x_0\) is a bit harder and can be done in a fashion analogous to
(3.28) where for each partial derivative in the $x_0$ variable we obtain an equation similar to (3.28).

**Numerical Methods**

In the last part of this Chapter we will discuss the numerical methods we use to solve equations (3.1)-(3.8). We note that our numerical methods are directly motivated by the techniques we used to prove existence and uniqueness for this system.

It follows from (3.1) and (3.8) that the biocide concentration is given by

$$B(x, t) = u(t) \frac{\cosh(\phi x)}{\cosh(\phi L(t))}.$$  

Also, (3.6) and (3.7) implies

$$v(x, t) = \alpha \int_0^x (X_u(\zeta, t) + X_a(\zeta, t))d\zeta. \quad (3.49)$$

In order to achieve higher accuracy of our computation we used second-order methods such as the Runge-Kutta trapezoidal method. The integral for $v$ was computed with the trapezoid rule. Our approach is based on the method of characteristics that we will present below. Note that (3.2) can be rewritten as

$$\frac{\partial X_u}{\partial t} + \frac{\partial X_u}{\partial x}v = -X_u \frac{\partial v}{\partial x} - (B + \lambda)X_u + \alpha X_u + \gamma X_a. \quad (3.50)$$

The left hand-side in (3.50) is the directional derivative of $X_u$ in the $x, t$ plane in the direction $(v, 1)$. The flow of the vector field $(v, 1)$ defines characteristics, i.e. the equation for characteristics is

$$\frac{dx}{dt} = v(x(t), t), \quad x(0) = x_0.$$
The time-axis $x = 0$ is also a characteristic, since $v(0, t) = 0$. Hence, the left-boundary conditions for the solutions can be obtained from the method directly.

The Runge-Kutta trapezoidal method requires first computation of preliminary values at the points in the next time-step using Euler’s method and then computation of the ‘real values’ by approximating the average slope at the new points in the next time-step. To illustrate this, consider the general problem

$$\frac{dy}{dt} = f(y(t), t), \quad y(0) = y_0.$$  

The approximate solution in the $i + 1$-st time-step is

$$y_{i+1} = y_i + \frac{h}{2}[f(t_i, y_i) + f(t_{i+1}, \hat{y}_{i+1})],$$

where

$$\hat{y}_{i+1} = y_i + hf(t_i, y_i)$$

is the preliminary value of $y_{i+1}$. This two-stage method was used in the code.

We observe that with passing time the distance between characteristics will increase. If we let this happen for sufficiently long time, we will lose precision, i.e., distance between points on the moving grid will increase. To avoid this, we introduce a new characteristic at the moment when the distance between the original characteristics is greater than $2d$. We compute the initial values on the new characteristic using second order interpolation.

Initially we have uniformly spaced grid points. Let $h$ be the time step-size (taken to be uniform) and $d$ be the initial step-size of space and let $x(i, j)$ be a grid-point
lying on the \( j \)-th characteristic at time \( i h \). For example, \( x(1, j) = jd, j = 1, 2, \ldots \) is the discretization of the x-axis at time \( 1 \).

Let \( x(i - 1, j) \) be the 'real grid-point' lying on the \( j \)-th characteristics in the time-step \( i - 1 \). Variables denoted by a 'hat' will be the first-order approximations to the real values. Along the characteristics we get to the preliminary grid-point

\[
\hat{x}(i, j) = v(i - 1, j) h + x(i - 1, j).
\]

At \( \hat{x}(i, j) \), the value of \( \hat{X}_u(i, j) \) is computed from equation (3.50) as follows

\[
\hat{X}_u(i, j) = h(\hat{u}(i, j) - (\hat{B}(i, j) + \lambda)X_u(i - 1, j) + \\
+ \alpha X_u(i - 1, j) + \gamma X_a(i - 1, j)) + X_u(i - 1, j),
\]

where

\[
\hat{u}(i, j) = X_u(i - 1, j) \alpha (X_u(i - 1, j) + X_a(i - 1, j))
\]
is a help variable related to the term \( X_u \frac{\partial v}{\partial x} \) in (3.50). Using the second stage of the Runge-Kutta method we obtain a preliminary value for the velocity at the preliminary grid-point \( \hat{x}(i, j) \)

\[
\hat{v}(i, j) = \hat{v}(i, j - 1) + \alpha (\hat{X}_u(i, j - 1) + \hat{X}_a(i, j - 1) + \\
+ \hat{X}_u(i, j) + \hat{X}_a(i, j))(\hat{x}(i, j) - \hat{x}(i, j - 1))/2.
\]

Since we have a moving boundary, the velocity at the interface \( \hat{V}(i) \) is computed as the weighted average value of the velocities \( \hat{v}(i, a - 1) \) and \( \hat{v}(i, a) \) for some appropriate index \( a \) such that \( \hat{x}(i, a - 1) \) is the closest point on the characteristic at time \( i \) to
the left of \( \hat{L}(i) \) and \( \hat{x}(i, a) \) is on a characteristic to the right of the interface \( \hat{L}(i) \). Note that the equation for \( L \) is \( \dot{L} = v(L, \cdot) - \sigma L^2 \). Hence in the case \( \sigma = 0 \) (no detachment) \( L \) would just be a characteristic. As there is a detachment, \( \hat{L}(i) \) is always to the left of the last grid point \( \hat{x}(i, a) \), so \( \hat{L}(i) \) is computed via interpolation (hence no extrapolation is required).

Using the previous preliminary values, we obtain the real value of \( L \), i.e.

\[
L(i) = (V(i - 1) - \sigma L(i - 1)^2 + \hat{V}(i) - \sigma \hat{L}(i)^2)h/2 + L(i - 1).
\]

The real grid-point \( x(i, j) \) is given by

\[
x(i, j) = (v(i - 1, j) + \hat{v}(i, j))h/2 + x(i - 1, j).
\]

At \( x(i, j) \) we have to recompute \( \hat{X}_a(i, j) \) to get

\[
\hat{X}_a(i, j) = h(-\hat{u}(i, j) - (B(i, j) + \lambda)X_a(i - 1, j) + \alpha X_a(i - 1, j) + \gamma X_a(i - 1, j)) + X_a(i - 1, j). \tag{3.52}
\]

We choose to do this, since the ‘old’ value of \( X_a \) was computed at the preliminary characteristic point which differs slightly from the ‘real’ one. Note that (3.52) differs from (3.51) just in \( B(i, j) \) which we now obtain from the variables \( x(i, j) \) and \( L(i) \) derived above. In particular this guarantees that in our computation \( B \) is exactly equal to \( u(t) \) at the interface \( L(i) \), it would not be true if we use the old value.
Finally, we get the real value of $X_u(i, j)$ by taking the real value $X_u(i, j - 1)$ and the preliminary value $\hat{X}_u(i, j)$

$$X_u(i, j) = [-u(i, j) - (B(i, j) + \lambda)X_u(i - 1, j) + (\alpha X_u(i - 1, j) +$$

$$+ \gamma X_a(i - 1, j) - \hat{u}(i, j) - (B(i, j) + \lambda)\hat{X}_u(i, j) + \alpha \hat{X}_u(i, j) +$$

$$+ \gamma \hat{X}_a(i, j)]h/2 + X_u(i - 1, j),$$

where

$$u(i, j) = \hat{X}_u(i, j)\alpha (\hat{X}_u(i, j) + \hat{X}_a(i, j)).$$

The other real values $X_{ud}(i, j), X_a(i, j)$ are obtained the same way. Once we have them, we find $v(i, j)$ as defined in (3.49). Again, the velocity on the interface $V(i)$ is computed as the weighted average value of the velocities in the neighboring non-uniform grid-points.

We have to make the moving grid uniform in order to plot the solutions. The value of solutions at the uniform grid-points is computed as the average value of solutions in the neighboring non-uniform grid-points. If the distance between the non-uniform grid-points is bigger than $2d$, an additional grid-point is added to avoid the characteristics being far from each other.

The presented method is second order both in space and time. To verify the order of convergence, we plotted the solutions for various values of the space- and time-grids. Since we do not know the exact solution, we compared solutions for various values of $d/h$ and for fixed $h/d$ with one ‘super’ precise solution that was
obtained by letting the code run for very small values of \( h \) and \( d \). Figures 2 and 3 show the rate of convergence for \( X_a \) when changing \( d \) and \( h \), respectively. The x-axis represents the rate of change in \( d \) and \( h \) and the y-axis corresponds to the absolute error of the solutions on a logarithmic scale. The plots for \( X_a, X_{ud} \) and \( L \) are similar.

Figure 2. Order of asymptotic error for \( X_a \) when changing space-grids is 1.9848.

Figure 3. Order of asymptotic error for \( X_a \) when changing time-grids is 2.2034.
CHAPTER 4

STEADY STATE SOLUTIONS

Numerical testings confirm that if the biocide concentration at the interface is constant, the solutions of the PDE model seem to converge to the steady-state solutions. Assuming that the steady-state solutions exist, we derive certain necessary conditions they have to satisfy. Then we will associate with the steady state solutions an autonomous dynamical system which we will study from the stability point of view. This in turn will allow us to determine exact conditions for existence or nonexistence of such steady state solutions. As it turns out, if a non-zero steady state solution exists, it is not unique, in fact we may construct a whole family of such solutions.

The steady-state equations corresponding to equations (3.1)-(3.6) from the previous Chapter are

\[
\frac{d^2 B}{dx^2} = \phi^2 B \tag{4.1}
\]
\[
\frac{d}{dx}(X_u v) = -(B + \lambda)X_u + \alpha X_a + \gamma X_a \tag{4.2}
\]
\[
\frac{d}{dx}(X_u d v) = BX_u \tag{4.3}
\]
\[
\frac{d}{dx}(X_a v) = \lambda X_u - \delta X_a B + \alpha X_a - \gamma X_a, \tag{4.4}
\]
\[
\frac{d}{dx}(X_a d v) = \delta X_a B, \tag{4.5}
\]
\[
\frac{dv}{dx} = \alpha(X_u + X_a), \quad (4.6)
\]

where \(0 \leq x \leq L\) and \(L\) is the steady-state biofilm thickness.

The boundary conditions of \(B\) and \(v\) are

\[
\frac{\partial B}{\partial x}(0) = 0, \quad B(L) = u_0, \quad v(0) = 0, \quad (4.7)
\]

where \(u_0\) is the constant biocide concentration applied through the steady interface \(L\). For the function \(v\) at \(x = L\) we also have

\[
v(L) = \sigma L^2 \quad (4.8)
\]

as \(\frac{dL}{dt} = 0\). Note that by (4.1) and (4.7) the biocide concentration is

\[
B(x) = u_0 \frac{\cosh(\phi x)}{\cosh(\phi L)}.
\]

It follows from (4.2)-(4.6) that instead of studying the whole system we may restrict ourselves to a system of two equations with unknowns \(X_u, X_a\) which satisfy the ODEs

\[
\frac{dX_u}{dx} v = -(B + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a \quad (4.9)
\]

\[
\frac{dX_a}{dx} v = \lambda X_u - \delta X_a B + \alpha(1 - X_u - X_a)X_a - \gamma X_a, \quad (4.10)
\]

where \(v\) satisfies (4.6). Since the re-parametrization using characteristics has proven successful in Chapter 3, we are going to use it again.

The equation of characteristics corresponding to (4.9)-(4.10) reads

\[
\frac{ds}{dt} = v(s(t)), \quad s(0) = L, \quad (4.11)
\]
where the parameter $t$ is chosen so that the range of the function $s(t)$ is $(0, L]$ or a subset if it. The choice of the initial condition $s(0) = L$ is only for convenience, we may as well choose $s(\zeta) = L$ for any $\zeta$, but this only leads to a solution shifted by $\zeta$ as (4.11) is an autonomous equation.

Define $x_0 \in [0, L]$ such that $v \equiv 0$ on $[0, x_0]$ and $v > 0$ on $(x_0, L]$. It follows that $X_u + X_a = 0$ on $[0, x_0]$, i.e. there are only dead cells remaining in lower regions of the biofilm. (We would like to thank to Neils Overgaard for pointing out to us these solutions with $x_0 > 0$.) Hence, $\frac{dx}{dt} > 0$ on $(x_0, L]$ and $\frac{dx}{dt} \to v(x_0) = 0$ as $s(t) \to x_0 +$. It follows that if $s(t) \to x_0 +$, then $t \to -\infty$. We may see this better by rewriting the ODE (4.11) as

$$
\frac{ds}{d\tau} = -v(s(\tau)), \quad s(0) = L,
$$

(4.12)

where the parameter $\tau = -t$. By assumption we have a steady state solution and the function $v$ is Lipschitz continuous. Hence, this ODE is well posed and $s$ is bounded between 0 and $L$. Now we are guaranteed that (4.12) (and so (4.11)) has a $C^1$-solution on $(-\infty, 0]$.

We have that $s : (-\infty, 0] \to (x_0, L]$ is a $C^1$ bijection. In what follows, we will use this re-parametrization for the steady-state solutions $X_u, X_a$ and $B$. We define

$$
x_u(t) =: X_u(s(t)), \quad x_a(t) =: X_a(s(t)), \quad b(t) =: B(s(t)).
$$
Since \( \frac{dx_u}{dt} = \frac{dX_u}{dx} v \) (and similarly for \( x_a \)), by equations (4.9)-(4.10) the functions \( x_u, x_a \) satisfy

\[
\frac{dx_u}{dt} = -(b + \lambda)x_u + \alpha(1 - x_u - x_a)x_u + \gamma x_a \quad (4.13)
\]

\[
\frac{dx_a}{dt} = \lambda x_u - \delta x_a b + \alpha(1 - x_u - x_a)x_a - \gamma x_a. \quad (4.14)
\]

Note that this previous system does not depend on \( v \). Also, by continuity of \( s \) and \( b \) one obtains \( b(t) \to B(x_0) \) as \( t \to -\infty \). The system (4.13)-(4.14) is still too difficult to study as the function \( b \) depends on \( t \). But by continuity, for all negative \( t \) such that \( |t| \) is sufficiently large, the function \( b \) in this system is almost constant, i.e. the non-autonomous system (4.13)-(4.14) will approximate the corresponding autonomous system as \( t \to -\infty \). Since the systems (4.1)-(4.6) and (4.13)-(4.14) are equivalent (\( X_{ud}, X_{ad} \) are uniquely determined by \( X_u, X_a \)), all the statements related to (4.13)-(4.14) relate to (4.1)-(4.6) as well.

**Stability of Solutions of the Autonomous System**

First we will study the autonomous system

\[
\frac{dx_u}{dt} = -(B_0 + \lambda)x_u + \alpha(1 - x_u - x_a)x_u + \gamma x_a \quad (4.15)
\]

\[
\frac{dx_a}{dt} = \lambda x_u - \delta x_a B_0 + \alpha(1 - x_u - x_a)x_a - \gamma x_a, \quad (4.16)
\]

where

\[
B_0 = u_0 \frac{\cosh(\phi x_0)}{\cosh(\phi L)}.
\]
Once we finish the study of the stability of the easier system (4.15)-(4.16), we will then rigorously relate these results to the properties of the more complicated system (4.13)-(4.14).

The range of solutions for the system (4.15)-(4.16) is a triangle in the first quadrant given by

\[ \Delta = \{(x_u, x_a) \in \mathbb{R}^2 : \ x_u, x_a \geq 0, \ x_u + x_a \leq 1\}. \]

We will show that for any initial data belonging to \( \Delta \) the solution of (4.15)-(4.16) will stay in \( \Delta \) for all \( t \to \infty \), i.e. \( \Delta \) is a positively invariant region. Indeed, it is sufficient to show that the vector \( (\frac{dx_u}{dt}, \frac{dx_a}{dt}) \) of the solution at any point on the boundary of \( \Delta \) points inward. Let \( \partial \Delta_1 = (0, 1] \times \{0\} \). Then for any point on \( \partial \Delta_1 \) the second coordinate \( \frac{dx_a}{dt} = \lambda x_u > 0 \). Similarly, let \( \partial \Delta_2 = \{0\} \times (0, 1] \). Then for any point on \( \partial \Delta_2 \) the first coordinate \( \frac{dx_u}{dt} = -B_0 x_u \). Also, let \( \partial \Delta_3 = \{(x_u, x_a) \in \mathbb{R}^2 : \ x_u, x_a > 0, \ x_u + x_a = 1\} \). Then for any point on \( \partial \Delta_3 \) the sum \( \frac{dx_u}{dt} + \frac{dx_a}{dt} = -B_0 (x_u + \delta x_a) < 0 \), i.e. the vector of the ODE flow points inward in all the three cases. At the origin, \( (\frac{dx_u}{dt}, \frac{dx_a}{dt}) = (0, 0) \).

Obviously, the autonomous system always has a trivial equilibrium \( (x_u, x_a) = (0, 0) \) and possibly a non-trivial one if we can solve the equations

\[
-(B_0 + \lambda)x_u + \alpha (1 - x_u - x_a)x_u + \gamma x_a = 0
\]

\[
\lambda x_u - \delta x_a B_0 + \alpha (1 - x_u - x_a)x_a - \gamma x_a = 0.
\]
Denote

\[ \Gamma = \alpha (1 - x_u - x_a). \]

Then the previous system can be rewritten as a linear system of the form

\[
-(B_0 + \lambda - \Gamma)x_u + \gamma x_a = 0 \quad (4.18)
\]

\[
\lambda x_u + (\Gamma - \delta B_0 - \gamma)x_a = 0, \quad (4.19)
\]

which has a nontrivial solution provided that the determinant of the matrix given by the linear system is zero, i.e.,

\[
(-B_0 - \lambda + \Gamma)(\Gamma - \delta B_0 - \gamma) = \gamma \lambda. \quad (4.20)
\]

Solving for \( \Gamma \) in (4.20) we obtain

\[
\Gamma_{+, -} = \frac{\delta B_0 + \gamma + B_0 + \lambda \pm \sqrt{(\delta B_0 + \gamma + B_0 + \lambda)^2 - 4B_0(\delta B_0 + \delta \lambda + \gamma)}}{2}. \quad (4.21)
\]

Since \( x_u, x_a \in \Delta \), it follows from (4.17) that

\[
\Gamma \leq B_0 + \lambda \quad \text{and} \quad \Gamma \leq \delta B_0 + \gamma. \quad (4.22)
\]

Note that only \( \Gamma_- = \frac{\delta B_0 + \gamma + B_0 + \lambda - \sqrt{(\delta B_0 + \gamma + B_0 + \lambda)^2 - 4B_0(\delta B_0 + \delta \lambda + \gamma)}}{2} \) can satisfy (4.22) (in case of \( \Gamma_+ \), the inequalities in (4.22) change to \( \Gamma_+ \geq B_0 + \lambda \) and \( \Gamma_+ \geq \delta B_0 + \gamma \)). In addition, we need that \( x_a + x_u \leq 1 \) or equivalently, \( \Gamma_- \leq \alpha \). Note that if \( \Gamma_- = \alpha \), then \( x_u = x_a = 0 \), i.e. there is only a trivial equilibrium. Hence, two cases might arise:
\( \Gamma_\geq \alpha \) (the system (4.15)-(4.16) has only a trivial equilibrium \((0, 0)\) in \(\Delta\))

\( \Gamma_\leq \alpha \) (a trivial equilibrium \((0, 0)\) and a nontrivial equilibrium exist in \(\Delta\))

**Remark:** It can be shown (by differentiation) that \(\Gamma_\) is a monotone increasing function of \(B_0\). Also, for \(B_0 \to \infty\) we have that \(\Gamma_-(B_0) \to \gamma\) (if \(\delta = 0\)) or \(\Gamma_-(B_0) \to \infty\) (if \(\delta > 0\)), respectively.

Let’s linearize the system (4.15)-(4.16) about the trivial equilibrium \((0, 0)\). In this case we obtain

\[
\frac{dx_u}{dt} = -(B_0 + \lambda)x_u + \alpha x_u + \gamma x_a \tag{4.23}
\]

\[
\frac{dx_a}{dt} = \lambda x_u - \delta x_a B_0 + \alpha x_a - \gamma x_a. \tag{4.24}
\]

We will find the eigenvalues \(\mu_1, \mu_2\) of the matrix determined by this system of linear ODEs. Instead of finding the roots of the characteristic equation, we will use a little trick. Suppose \(A\) is the matrix corresponding to the system of linear ODEs in (4.23)-(4.24). Then the characteristic matrix \(A - \mu I\) becomes

\[
A - \mu I = \begin{pmatrix} \Gamma - B_0 - \lambda & \gamma \\ \lambda & \Gamma - \delta B_0 - \gamma \end{pmatrix}, \tag{4.25}
\]

where \(\Gamma = \alpha - \mu\). We will see the relationship of this 'new \(\Gamma\)' with the 'old \(\Gamma\)' defined in (4.21). It can be shown that the eigenvalues of \(A\) satisfy

\[
\mu_{+,-} = \alpha - \frac{\delta B_0 + \gamma + B_0 + \lambda \pm \sqrt{(\delta B_0 + \gamma + B_0 + \lambda)^2 - 4B_0(\delta B_0 + \delta \lambda + \gamma)}}{2}.
\]
Note that the square-root expression above is the same as in (4.21). Hence, we may write \( \mu_{+,-} = \alpha - \Gamma_{+,-} \) (or \( \Gamma_{+,-} = \alpha - \mu_{+,-} \)), where \( \Gamma_{+,-} \) is defined in (4.21). Note that \( \mu_- > \mu_+ \).

We consider the following cases:

a) \( \Gamma_- < \alpha < \Gamma_+ \) (\( \mu_+ < 0, \mu_- > 0 \), \( (0,0) \) is a saddle)

b) \( \alpha < \Gamma_- \) (\( \mu_+ < 0, \mu_- < 0 \), \( (0,0) \) is a sink)

c) \( \Gamma_+ < \alpha \) (\( \mu_- > 0, \mu_+ > 0 \), \( (0,0) \) is a source)

It follows that whenever \( (0,0) \) is a source or a saddle (both are unstable), there is a nontrivial equilibrium. These three situations are depicted in Figures 4-5. In these plots the stable equilibrium is denoted by a small square. The point \( (0,0) \) is stable only on Figure 4 b) and it is unstable otherwise.

Let’s take a look at the related eigenvectors. It follows from the characteristic matrix in (4.25) that the coordinates of the eigenvectors can be taken to be

\[
\left(1, \frac{\lambda}{\gamma + \delta B_0 - \Gamma}\right).
\]

Consider the most interesting case, when \( (0,0) \) is a saddle, i.e., \( \mu_+ < 0, \mu_- > 0 \). Using (4.22) and the remark afterwards, it is easy to see that in this case \( \gamma + \delta B_0 - \Gamma_+ < 0 \) and \( \gamma + \delta B_0 - \Gamma_- > 0 \). Hence, the sign of the coordinates of the eigenvectors is \((+, -)\) for \( \mu_+ \) and \((+, +)\) for \( \mu_- \).
Figure 4. Phase portrait of the solutions to the autonomous system (4.15)-(4.14) in the $(x_u, x_a)$-plane. a) Trivial equilibrium is a saddle. b) Trivial equilibrium is a sink. The directions of appropriate vector fields are indicated by small arrows.
We will show that the stable manifold is a line spanned by \((1, \frac{\lambda}{\gamma + \delta B_0 - \Gamma_{+}})\) going through the second and fourth quadrant (in a counterclockwise direction) and the unstable manifold is a line spanned by \((1, \frac{\lambda}{\gamma + \delta B_0 - \Gamma_{-}})\) going through the first and third quadrant. Define the line

\[ l_{13} = \{(x_u, x_a) : x_a = \frac{\lambda}{\gamma + \delta B_0 - \Gamma_{-}} x_u \}. \]

The following lemma shows that the line \(l_{13}\) corresponding to \(\mu_{+} > 0\) is an unstable manifold:

**Lemma 4.1:** The line \(l_{13}\) is an invariant manifold, i.e. if \((x_u(0), x_a(0)) \in l_{13}\), then \((x_u(t), x_a(t)) \in l_{13}\) for all \(t\).
Figure 6. Stability near saddle. The line going from left to right is the stable manifold and the line from top to bottom the unstable manifold of the equilibrium.

**Proof of Lemma 4.1:** Let \((x_u, x_a) \in l_{13}\). Then \(\lambda x_u = (\delta B_0 + \gamma - \Gamma_-) x_a\). Note that if \((x_u, x_a) \in l_{13}\), then \((x_u, x_a)\) also satisfies equation (4.18). Hence, replacing \((B_0 + \lambda)x_u\) by \(\Gamma_- x_u + \gamma x_a\) in (4.15) and \(\lambda x_u\) by \((\delta B_0 + \gamma - \Gamma_-) x_a\) yields

\[
\frac{dx_a}{dx_u} = \frac{dx_a}{dt} \frac{dx_u}{dt}^{-1} = \frac{(-\Gamma_- + \alpha(1 - x_u - x_a)) x_a}{(-\Gamma_- + \alpha(1 - x_u - x_a)) x_u} = \frac{\lambda}{\gamma + \delta B_0 - \Gamma_-}
\]

for any \((x_u, x_a) \neq (0, 0) \in l_{13}\) and that is what we wanted. ■

As a consequence of Lemma 4.1 we obtain that the line corresponding to \(\mu_- < 0\)

\[
l_{24} = \{(x_u, x_a) : \quad x_a = \frac{\lambda}{\gamma + \delta B_0 - \Gamma_+} x_u\}
\]

is a stable invariant manifold. Moreover, the line segment

\[
l_+ = \{(x_u, x_a) : \quad x_a = \frac{\lambda}{\gamma + \delta B_0 - \Gamma_-} x_u, \quad x_u, x_a \in \Delta\}
\]
lying in $\Delta$ is a positively invariant manifold.

Our goal is now to analyze the stability of the system (4.15)-(4.16) in the neighborhood of the nontrivial equilibrium $(\tilde{x}_u, \tilde{x}_a)$. Using the definition of $\Gamma$ and (4.19), we get that the coordinates of the nontrivial equilibrium satisfy the equations

$$\begin{align*}
\tilde{x}_u + \tilde{x}_a &= 1 - \frac{\Gamma_-}{\alpha} \\
\frac{\tilde{x}_u}{\tilde{x}_a} &= \frac{\gamma + \delta B_0 - \Gamma_-}{\lambda}.
\end{align*}$$

(4.26)

We observe that the nontrivial equilibrium lies on the segment $l_+$. Hence, we may establish this fact as a lemma:

**Lemma 4.2:** If $\Gamma_- < \alpha$, then the nontrivial equilibrium $(\tilde{x}_u, \tilde{x}_a)$ of the autonomous system (4.15)-(4.16) belongs to $l_+$ and satisfies

$$\tilde{x}_a = \frac{\lambda}{\gamma + \delta B_0 - \Gamma_-} \tilde{x}_u.$$  

Consider any point $(x_u, x_a)$ in the neighborhood of the nontrivial equilibrium $(\tilde{x}_u, \tilde{x}_a)$, i.e. the coordinates of which may be taken to be $x_u(t) = \tilde{x}_u + \epsilon_u(t), x_a(t) = \tilde{x}_a + \epsilon_a(t)$. Linearizing (4.15)-(4.16) about $(\tilde{x}_u, \tilde{x}_a)$ and neglecting the higher order terms yield that the perturbations $\epsilon_u, \epsilon_a$ satisfy the linear ODEs

$$\begin{align*}
\frac{d\epsilon_u}{dt} &= -(B_0 + \lambda)\epsilon_u + \alpha[\epsilon_a(1 - \tilde{x}_u - \tilde{x}_a) - \tilde{x}_u(\epsilon_u + \epsilon_a)] + \gamma \epsilon_a \\
\frac{d\epsilon_a}{dt} &= -\lambda \epsilon_a + \alpha[\epsilon_a(1 - \tilde{x}_u - \tilde{x}_a) - \tilde{x}_a(\epsilon_u + \epsilon_a)] - (\gamma + \delta B_0)\epsilon_a.
\end{align*}$$
Recall that $\Gamma_\pm = \alpha (1 - \tilde{x}_u - \tilde{x}_a)$. Hence, we may rewrite the previous system as

\[
\frac{d\epsilon_u}{dt} = -(B_0 + \lambda)\epsilon_u + \epsilon_u \Gamma_\pm - \alpha \tilde{x}_u(\epsilon_u + \epsilon_a) + \gamma \epsilon_a,
\]

\[
\frac{d\epsilon_a}{dt} = -\lambda \epsilon_u + \epsilon_a \Gamma_\pm - \alpha \tilde{x}_a(\epsilon_u + \epsilon_a) - (\gamma + \delta B_0)\epsilon_a.
\]

The eigenvalues $\mu_+, \mu_-$ of the matrix given by this linear system solve the characteristic equation

\[
\mu^2 + \mu((\delta + 1)B_0 + \lambda + \gamma + \alpha - 3\Gamma_\pm) + ((\delta + 1)B_0 + \lambda + \gamma - 2\Gamma_\pm)(\alpha - \Gamma_\pm) = 0. \tag{4.27}
\]

Using (4.22) and the fact that the nontrivial equilibrium exists if $\Gamma_- < \alpha$, it can be shown that all the coefficients in (4.27) are positive. Therefore, both eigenvalues are negative ($\mu_+, \mu_- < 0$), i.e. the nontrivial equilibrium $(\tilde{x}_u, \tilde{x}_a)$ is a sink.

In what follows, we will state some assertions about the stability of the autonomous system. We will prove in Theorems 4.1 and 4.2 that if $(0, 0)$ is the only equilibrium, then it is globally asymptotically stable and if there are two equilibria, then the nontrivial equilibrium is globally asymptotically stable.

**Theorem 4.1:** If $\Gamma_- \geq \alpha$, then the trivial equilibrium is globally asymptotically stable.

**Proof of Theorem 4.1:** Let’s consider the $\omega$-limit set of the system (4.15)-(4.16) for any point $X = (x_u, x_a) \in \Delta$. We will show that $\omega(X) = (0, 0)$. It is known from the theory of limit sets that $\omega(X)$ is connected and nonempty. Since the triangular domain $\Delta$ is compact and positively invariant, it contains either a limit cycle or an.
equilibrium point. If $\omega(X)$ had no equilibrium point, i.e. if the $\omega$-limit set was a limit cycle, then by the Poincare-Bendixon theorem $\omega(X)$ would be a closed orbit. Inside the loop of a closed orbit, there must be an equilibrium point, i.e. inside this loop we would have the trivial equilibrium $(0, 0)$. It is, however, not possible, since part of this loop would be outside the triangular domain $\Delta$. Hence, $\omega(X) = (0, 0)$ and so each solution starting in $\Delta$ will converge to $(0, 0)$ as $t \to \infty$ and this is what we wanted.

**Theorem 4.2:** If $\Gamma_- < \alpha$, then the nontrivial equilibrium $(\tilde{x}_u, \tilde{x}_a)$ is globally asymptotically stable.

**Proof of Theorem 4.2:** Just as before, consider the $\omega$-limit of the system (4.15)-(4.16) for any point set through $X = (x_u, x_a) \in \Delta \setminus \{(0, 0)\}$. First we will exclude the trivial equilibrium $(0, 0)$ from the $\omega$-limit set, i.e. we claim that $\omega(X) \neq (0, 0)$. Since the trivial equilibrium is asymptotically unstable, the following cases may arise:

$\mu_1 > 0, \mu_2 > 0$ - By definition of $\omega(X)$ the point $(0, 0)$ cannot belong to the $\omega$-limit set.

$\mu_1 < 0, \mu_2 > 0$ - Recall that in this case there exists exits a stable manifold going through the second and fourth quadrant which is outside the triangular region $\Delta$. Hence any initial condition inside triangle will not go to $(0, 0)$.

It follows that $(0, 0) \notin \omega(X)$ in both of these cases.
Finally, we have to show that $\omega(X) = (\tilde{x}_u, \tilde{x}_a)$. Since $\omega(X)$ is nonempty, by the same argument as in Theorem 4.1, the $\omega$-limit set will be either the nontrivial equilibrium or a limit cycle. Suppose $\omega(X)$ is a limit cycle. Again, by the Poincare-Bendixon theorem $\omega(X)$ would be a closed orbit and inside its loop would lay $(\tilde{x}_u, \tilde{x}_a)$. Recall that the nontrivial equilibrium also lies on a positively invariant segment $l_+$. Hence, the loop around $(\tilde{x}_u, \tilde{x}_a)$ must intersect $l_+$ in at least two points. This is a contradiction with the uniqueness of solutions as two different solutions cannot intersect themselves. Hence, the proof of Theorem 4.2 is complete.

Non-existence/Existence of the Steady-state Solutions

The hardest part of existence is to prove solvability of the non-autonomous system (4.13)-(4.14). Therefore, we start with easier assertions which assume that the steady-state biofilm thickness $L$ is given (Theorems 4.3 and 4.4). To be more specific, we find solutions of (4.1)-(4.6) satisfying (4.7), but we ignore the boundary condition (4.8). In particular, Theorem 4.3 deals with the non-existence of steady-state solutions provided there is only a trivial equilibrium of the autonomous system (4.15)-(4.16). Theorem 4.4 shows the uniqueness of steady-state solutions provided that the autonomous system (4.15)-(4.16) has a nontrivial equilibrium. Finally, in Theorem 4.5 we state the existence of steady-state solutions without assuming that $L$ is given.
**Theorem 4.3:** Suppose $L > 0$ is given and $\Gamma_\gamma \geq \alpha$, where

$$\Gamma_\gamma = \frac{\delta B_0 + \gamma + B_0 + \lambda - \sqrt{(\delta B_0 + \gamma + B_0 + \lambda)^2 - 4B_0(\delta B_0 + \delta \lambda + \gamma)}}{2}$$  \hspace{1cm} (4.28)

and $B_0 = u_0 \frac{\cosh(\phi x_0)}{\cosh(\phi L)}$. Then there is no steady-state solution solving (4.1)-(4.6) of length $L$.

**Proof of Theorem 4.3:** Consider the non-autonomous system (4.13)-(4.14). Recall that there is a one-to-one relation between $X_a$ and $x_u$ (similarly for $X_a$, $x_a$ and $B, b$). This relation is established by the re-parametrization $s : (-\infty, 0] \to (0, L]$, i.e. as $t \to -\infty$, the stability behavior of the non-autonomous system (4.13)-(4.14) more and more resembles the behavior of the autonomous system (4.15)-(4.16). Assume that we know the values $x_a(0)$ and $x_u(0)$. We would like to solve the system (4.13)-(4.14) on the interval $(-\infty, 0]$.

Since the right-hand side of the ODEs in (4.13)-(4.14) is Lipschitz continuous, the solution with initial condition $x_a(0)$ and $x_u(0)$ either exists locally on some interval $(t_0, 0]$ with $t_0 < 0$ or it exists globally on $(-\infty, 0]$. In the first case the solution would leave the region $\Delta$ at finite time which is not what we need since we are looking for solutions on the whole interval $(-\infty, 0]$. In the second case we are in business. The question is the behavior of $(x_u(t), x_a(t))$ as $t \to -\infty$.

Define the $\alpha$-limit set of this solution as the set of all accumulation points as $t \to -\infty$. The $\alpha$-limit set must be nonempty, as our solution belongs to a compact set. What could this $\alpha$-limit set be? Since $b(t) \to B(x_0) = B_0$ for $t \to -\infty$, we get
that the $\alpha$-limit set contains either an equilibrium or a limit cycle of the autonomous system (4.15)-(4.16). But it has been established above that (4.15)-(4.16) has no limit cycle and when $\Gamma_- \geq \alpha$, the only equilibrium is $(0,0)$. So the $\alpha$-limit set is a single point $(0,0)$. We claim that this implies $x_u(t) = x_a(t) = 0$ for all $t$.

If this wasn’t the case we would have $x_u(t) + x_a(t) > 0$ for negative $t$ and $(x_u(t), x_a(t)) \to (0,0)$ as $t \to -\infty$. However, this is impossible. For all $t$ negative, $b(t) > B(x_0) = B_0$ which implies that if we define

$$
\Gamma_-(t) = \frac{\delta b(t) + \gamma + b(t) + \lambda - \sqrt{(\delta b(t) + \gamma + b(t) + \lambda)^2 - 4b(t)(\delta b(t) + \delta \lambda + \gamma)}}{2},
$$

then $\Gamma_-(t) \to \Gamma_- > \alpha$ by monotonicity of $\Gamma$. Hence, for each such $t$ locally when moving back in time the point $(0,0)$ is totally unstable (both its eigenvalues of the linearization are negative). Hence, if $(x_u(t), x_a(t))$ is near zero it cannot approach zero, as we claimed, but only move away from it. Therefore, the only possibility is that $x_u(t) = x_a(t) = 0$ for all $t$, i.e $X_u = X_a = 0$ on $[0, L]$. This, however, implies that $v(x) = 0$ on $[0, L]$ from which $0 = v(L) = \sigma L^2$. This is a contradiction as we assumed $L > 0$.

**Theorem 4.4:** Suppose $L > 0$ is given, $x_0 \in [0, L)$, and $\Gamma_-$ computed from (4.28) for this $x_0$ and $L > 0$ satisfies $\Gamma_- < \alpha$. Then there exists a unique steady-state solution of (4.1)-(4.6) of length $L$ such that

$$
X_a = X_u = 0 \text{ on } [0, x_0], \quad X_a > 0, X_u > 0 \text{ on } (x_0, L].
$$

(4.29)
Moreover, if \( x_0 > 0 \), then the solution has a jump discontinuity at \( x_0 \). The steady-state solutions \( X_u, X_a \) satisfy

\[
\lim_{x \to x_0^+} X_u(x) = \tilde{x}_u, \quad \lim_{x \to x_0^+} X_a(x) = \tilde{x}_a,
\]

where \((\tilde{x}_u, \tilde{x}_a)\) is the nontrivial equilibrium of the autonomous system (4.15)-(4.16).

In the specific case \( x_0 = 0 \) we have the following corollary:

**Corollary 4.1:** Given \( L > 0 \), there exists at most one solution of (4.1)-(4.6) with continuous non-zero functions \( X_u, X_{ud}, X_a, X_{ad}, v \) on the interval \([0, L]\).

**Proof of Theorem 4.4:** As in the proof of Theorem 3, we start by considering the non-autonomous system (4.13)-(4.14) and the re-parametrization \( s : (-\infty, 0] \to (x_0, L] \). Assume that we know the values \( x_u(0) \) and \( x_a(0) \). Recall that \( x_u(0) = X_u(L), x_a(0) = X_a(L) \). Hence, by assumption both \( x_u(0), x_a(0) \) are positive. We would like to solve the system (4.13)-(4.14) on the interval \((-\infty, 0]\).

As above, the question is the behavior of \((x_u(t), x_a(t))\) as \( t \to -\infty \). Again, we only care about solutions that exist on the whole interval. Consider the \( \alpha \)-limit set of such solution. The same considerations as above imply that such a set contains either an equilibrium or a limit cycle of the autonomous systems. We have already established that there is no limit cycle, but in this case there are two equilibria: \((0, 0)\) and \((\tilde{x}_u, \tilde{x}_a)\) (c.f. Lemma 4.2). So either

\[
\lim_{t \to -\infty} x_u(t) = \lim_{t \to -\infty} x_a(t) = 0, \quad \text{or} \quad \lim_{t \to -\infty} x_u(t) = \tilde{x}_u, \lim_{t \to -\infty} x_a(t) = \tilde{x}_a.
\]
We will show that the $\alpha$-limit set contains $(\tilde{x}_u, \tilde{x}_a)$, i.e. the case $\lim_{t \to -\infty} x_a(t) = \lim_{t \to -\infty} x_u(t) = 0$ cannot happen.

**Lemma 4.3:** The $\alpha$-limit set of the non-autonomous system (4.13)-(4.14) is $(\tilde{x}_u, \tilde{x}_a)$.

**Proof of Lemma 4.3:** Assume on the contrary that we have a solution for which $\lim_{t \to -\infty} x_u(t) = \lim_{t \to -\infty} x_a(t) = 0$. Recall first that $\frac{ds}{dt} = v(s(t))$. Hence,

$$L - x_0 = s(0) - s(-\infty) = \int_{-\infty}^{0} v(s(t)) \, dt.$$ 

As $v$ is monotone increasing, it follows that $w(t) = v(s(t)) \to 0$ as $t \to -\infty$. Using the equation for $v$ ($\frac{dv}{dx} = \alpha(X_u + X_a)$) and realizing that in this case $s$ plays the role of $x$, i.e., $x = s(t)$, it follows that

$$\frac{dw}{dt} = \frac{dv}{ds} \frac{ds}{dt} = \alpha(X_u(s(t)) + X_a(s(t)))v(s(t)) = \alpha(x_u(t) + x_a(t))w(t),$$

i.e.,

$$\frac{d}{dt}(\ln w) = \frac{1}{w} \frac{dw}{dt} = \alpha(x_u + x_a).$$

Note that $w(0) = v(L)$. Hence, for any $T > 0$ we have

$$w(-T) = v(L) \exp \left[ -\alpha \int_{T}^{0} (x_a + x_u)(t) \, dt \right].$$

As the limit of the left hand-side is zero, it follows that

$$\int_{-\infty}^{0} (x_a(t) + x_u(t)) \, dt = \infty. \quad (4.30)$$

Recall the autonomous equations (4.15)-(4.16). We have shown in Lemma 4.1 that for this system the line $l_{13}$ is an unstable manifold of the trivial equilibrium$(0, 0)$. It
can be shown easily that any initial condition for \((x_u, x_a)\) that does not lie on \(l_{13}\) must
give rise to a solution that does not exist on the whole interval \((-\infty, 0]\). It follows
that for the autonomous system (4.15)-(4.16) the solution curve \((x_u, x_a) \in l_{13}\). Now
the true \((x_u, x_a)\) solves the non-autonomous system (4.13)-(4.14) which approaches
the autonomous system as \(t \to -\infty\). From this we deduce that the true \((x_u(t), x_a(t))\)
approaches \(l_{13}\) tangentially for \(t \to -\infty\). It follows that near the point \(-\infty\) the
equations for \(x_u, x_a\) can be written in the form (c.f. Proof of Lemma 4.1)

\[
\frac{dx_u}{dt} = (\alpha - \Gamma) x_u + o(x_u) \quad (4.31)
\]

\[
\frac{dx_a}{dt} = (\alpha - \Gamma) x_a + o(x_a). \quad (4.32)
\]

We can also write (4.31) in the form \(\frac{d}{dt}(\ln x_u) = (\alpha - \Gamma) + o(1)\). Hence, the solution
is

\[ x_u(-T) = x_u(0) \exp\left[-(\alpha - \Gamma)T + o(1)T\right] \quad (4.33) \]

We get a similar equation for \(x_a\). Since \(\Gamma_- < \alpha\), the function \(\exp[-(\alpha - \Gamma_-)T]\)
is
integrable on the interval \((-\infty, 0]\). Hence, it follows that

\[ \int_{-\infty}^{0} (x_u(t) + x_a(t))dt < \infty, \]

which contradicts (4.30). Thus, there is no nonzero solution of the non-autonomous
system with the property

\[ \lim_{t \to -\infty} x_a(t) = \lim_{t \to -\infty} x_u(t) = 0. \]
Hence, the only possibility is that $x_u$ approaches $\tilde{x}_u$ and $x_a$ approaches $\tilde{x}_a$ as $t \to -\infty$.

This means that for the original functions $X_u, X_a$ we obtain

$$\lim_{x \to x_0^+} X_a(x) = \tilde{x}_a, \quad \lim_{x \to x_0^+} X_u(x) = \tilde{x}_u. \quad (4.34)$$

and this is what we wanted ■

Existence: We are going to prove by a limiting argument that there is a steady-state solution with the property that $X_a, X_u$ vanishes on $[0, x_0]$ and (4.34) holds. In particular for $x_0 > 0$, the functions $X_u, X_a$ are necessarily discontinuous at this point.

Let us define a sequence of approximate solutions to the true $X_u, X_a$. We can ignore the interval $[0, x_0)$ as the solutions there are defined trivially, i.e., is $X_a = X_u = v = 0$ on $[0, x_0)$. Our main problem is that the system (4.9)-(4.10) together with (4.6) form a system

$$\frac{dX_u}{dx} = \frac{1}{v} [-(B + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a]$$

$$\frac{dX_a}{dx} = \frac{1}{v} [\lambda X_u + \alpha(1 - X_u - X_a)X_a - (\gamma + \delta B)X_a] \quad (4.35)$$

$$\frac{dv}{dx} = \alpha(X_u + X_a)$$

that is singular at $x = x_0$ since $v(x_0) = 0$. Here $B(x) = u_0 \frac{\cosh \phi x}{\cosh \phi L}$. The following lemma establishes that the solutions of the system (4.35) are nonnegative and bounded:
Lemma 4.4: If $X_u, X_a, v$ are solutions to (4.35) that are positive-valued at some $y \in (x_0, L]$, then $X_u, X_a$ stay positive and bounded by 1 on $(y, L]$. As a consequence we get $0 < \frac{dv}{dx} \leq \alpha$ on $(y, L]$.

To avoid the singularity, consider the following. For each $\varepsilon > 0$ we consider functions $X_a^\varepsilon, X_u^\varepsilon, v^\varepsilon$ on the interval $[x_0, L]$ defined as follows:

$$X_a(x) = \tilde{x}_a, \quad X_u(x) = \tilde{x}_u, \quad v(x) = \alpha(\tilde{x}_a + \tilde{x}_u)(x - x_0) \quad \text{for} \ x \in [x_0, x_0 + \varepsilon).$$

On the interval $[x_0 + \varepsilon, L]$ we define $X_a^\varepsilon, X_u^\varepsilon, v^\varepsilon$ by solving (4.35) with initial conditions

$$X_a^\varepsilon(x_0 + \varepsilon) = \tilde{x}_a, \quad X_u^\varepsilon(x_0 + \varepsilon) = \tilde{x}_u, \quad v^\varepsilon(x_0 + \varepsilon) = \alpha(\tilde{x}_a + \tilde{x}_u)\varepsilon.$$

The equations for $X_u^\varepsilon, X_a^\varepsilon, v^\varepsilon$ are well-posed as for any $\varepsilon > 0$ the initial condition for $v^\varepsilon$ is positive. Thus, the right-hand side of the equations satisfies the Lipschitz condition from which local solvability follows. Moreover, by Lemma 4.4 the functions $X_u, X_a$ stay bounded on the interval $[x_0, L]$ and hence, we obtain that the solutions exist in the whole interval up to $x = L$.

We need to prove that the sequence we defined is convergent (or at least its subsequence) as $\varepsilon \to 0+$ and that its limit is a solution to (4.35) on $[x_0, L]$ with initial condition

$$X_u(x_0) = \tilde{x}_u, \quad X_a(x_0) = \tilde{x}_a, \quad v(x_0) = 0. \quad (4.36)$$

However, this is fairly easy. From the fact that $(X_u, X_a) \in [0, 1]^2$ and $0 \leq v(x) \leq \alpha x$ it follows that there is a subsequence $\varepsilon_n \to 0+$ for which $(X_u^\varepsilon, X_a^\varepsilon, v)$ converges at the
point \( x = x_0 + (L - x_0)/2 \). Using the fact that on the interval \([x_0 + (L - x_0)/2, L]\) the ODE system (4.35) for \( X_u, X_a, v \) is regular, we obtain that it continuously depends on the initial condition at \( x_0 + (L - x_0)/2 \). Hence, \((X^\varepsilon_u, X^\varepsilon_a, v^\varepsilon)\) converges uniformly on the whole interval \([x_0 + (L - x_0)/2, L]\). This argument can be repeated at any point \( x = x_0 + (L - x_0)/2^k \) for \( k = 1, 2, 3, \ldots \). Using diagonalization argument, we obtain a subsequence of \( \varepsilon_n \to 0^+ \) such that \((X^\varepsilon_u, X^\varepsilon_a, v^\varepsilon)\) is convergent on the whole interval \((x_0, L]\) and the convergence is locally uniform. Let us denote the limit by \((X_u, X_a, v)\). It follows that this must be a solution to our problem on the interval \((x_0, L]\). However, as we have shown above, if such a solution exists, it necessary satisfies (4.34). Therefore, \((X_u, X_a, v)\) can be extended to the point \( x_0 \) and the resulting functions will be continuous on the interval \([x_0, L]\). This shows the existence.

**Uniqueness:** To prove uniqueness, we have to use the fact that the corresponding autonomous system has an asymptotically stable equilibrium \((\bar{x}_u, \bar{x}_a)\) with two real negative eigenvalues. From the theory of 2d dynamical systems it follows that near \((\bar{x}_u, \bar{x}_a)\) there exists a metric \( d \) that is contractive. What this means is that given two initial conditions for the autonomous system \((X_u^{(1)}, X_a^{(1)})\) and \((X_u^{(2)}, X_a^{(2)})\) that start near \((x_u, x_a)\), say in a ball

\[
B(r) = \{(X_u, X_a); d[(X_u, X_a), (x_u, x_a)] \leq r\},
\]

the distance between the solutions of the autonomous system shrinks, i.e.

\[
d[(X_u^{(1)}(y), X_a^{(1)}(y)), (X_u^{(2)}(y), X_a^{(2)}(y))] \leq d[(X_u^{(1)}(x), X_a^{(1)}(x)), (X_u^{(2)}(x), X_a^{(2)}(x))]\]
for all \( y \geq x \). Equivalently, if we denote

\[
\rho(x) = d[(X_u^{(1)}(x), X_a^{(1)}(x)), (X_u^{(2)}(x), X_a^{(2)}(x))],
\]

then this property can be expressed by \( \frac{d\rho}{dx} \leq 0 \).

We rewrite (4.35) as

\[
\begin{align*}
\frac{dX_a}{dx} &= \frac{1}{v} \left[ -(B_0 + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a + X_u \frac{B_0 - B}{v} \right], \\
\frac{dX_u}{dx} &= \frac{1}{v} \left[ \lambda X_u + \alpha(1 - X_u - X_a)X_a - (\gamma + \delta B_0)X_a + \delta X_a \frac{B_0 - B}{v} \right], \\
\frac{dv}{dx} &= \alpha(X_a + X_u),
\end{align*}
\]

where \( B_0 = u_0 \frac{\cosh(\phi x_0)}{\cosh(\phi L)} \). We will treat the last term in the right-hand side of the first two equations as an “error”. We see that this system is just the autonomous system plus the error terms. Hence, knowing that for the autonomous system we have \( \frac{d\rho}{dx} \leq 0 \), for the distance between two different solutions, the contribution of the “error” terms to \( \frac{d\rho}{dx} \) is at most

\[
C|B_0 - B|(1 + \delta) \left[ \left| \frac{X_u^{(1)}}{v^{(1)}} - \frac{X_u^{(2)}}{v^{(2)}} \right| + \left| \frac{X_a^{(1)}}{v^{(1)}} - \frac{X_a^{(2)}}{v^{(2)}} \right| \right],
\]

where \((X_u^{(1)}, X_u^{(1)}, v^{(1)})\) and \((X_u^{(2)}, X_u^{(2)}, v^{(2)})\) are two solutions to our system on the interval \([x_0, L]\). Note that if \( \rho \) is the Euclidian metric, then \( C = 1 \). From the previous estimate

\[
\frac{d\rho}{dx} \leq C|B_0 - B|(1 + \delta) \left[ \left| \frac{X_u^{(1)}}{v^{(1)}} - \frac{X_u^{(2)}}{v^{(2)}} \right| + \left| \frac{X_a^{(1)}}{v^{(1)}} - \frac{X_a^{(2)}}{v^{(2)}} \right| \right].
\]

We need a good estimate on the right-hand side of (4.38). We may assume that \((X_u^{(i)}, X_a^{(i)}), i = 1, 2\), stays near \((\tilde{x}_u, \tilde{x}_a)\) (which must be true close to \( x = x_0 \)). Hence,
\[ X_u^{(i)} \geq \frac{1}{2} \tilde{x}_u \text{ and } X_a^{(i)} \geq \frac{1}{2} \tilde{x}_a, \text{ and then } v^{(i)}(x) \geq \frac{1}{2} \alpha(\tilde{x}_u + \tilde{x}_a)(x - x_0). \] Using that \( B \) is Lipschitz continuous with some Lipschitz constant \( L \) and \( B_0 = B(x_0) \), we obtain that \( |B_0 - B| \leq L|x - x_0| \). We will estimate the right-hand side of (4.38) as follows:

\[
C(1 + \delta) L |x - x_0| \left( \frac{|v^{(1)} - v^{(2)}| + v^{(1)}|X_u^{(1)} - X_u^{(2)}| + |v^{(1)} - v^{(2)}| + v^{(1)}|X_a^{(1)} - X_a^{(2)}|}{v^{(1)}v^{(2)}} \right) \leq \]

\[
\leq C(1 + \delta) \frac{L(x - x_0)}{\frac{1}{2} \alpha(\tilde{x}_a + \tilde{x}_u)(x - x_0)} \left( |X_u^{(1)} - X_u^{(2)}| + |X_a^{(1)} - X_a^{(2)}| + 2\frac{|v^{(1)} - v^{(2)}|}{v^{(2)}} \right). \]

Finally, since \( |X_u^{(1)} - X_u^{(2)}| + |X_a^{(1)} - X_a^{(2)}| \approx \rho \) (meaning equivalence of norms) and \( |v^{(1)}(x) - v^{(2)}(x)| \leq \alpha \int_{x_0}^{x} \rho(t) dt \) for \( x > x_0 \), one obtains

\[
\frac{d\rho}{dx} \leq C_1 \rho(x) + \frac{C_2}{x - x_0} \int_{x_0}^{x} \rho(t) dt. \]

Here the constants \( C_1, C_2 \) only depend on the parameters of our equation. Define \( \Theta(x) = \sup_{x_0 \leq t \leq x} \rho(t) \). Hence, we get a simpler inequality

\[
\frac{d\Theta}{dx} \leq (C_1 + C_2) \Theta(x), \]

from which

\[
0 \leq \rho(x) \leq \Theta(x) \leq \rho(x_0)e^{(C_1 + C_2)(x - x_0)}. \quad (4.39) \]

From (4.39) uniqueness follows, as \( \rho(x_0) = 0 \). Thus, \( \rho(x) = 0 \) for all \( x > x_0 \). □

**Remark:** As a consequence of Theorem 4.4 we obtain that at \( x = x_0 \) the functions \( X_{ud}, X_{ad} \) satisfy (using equations (4.2), (4.5))

\[
\lim_{x \to x_0^+} X_{ud}(x) = \frac{B_0 \tilde{x}_u}{\alpha(\tilde{x}_u + \tilde{x}_a)}, \quad \lim_{x \to x_0^+} X_{ad}(x) = \delta \frac{B_0 \tilde{x}_a}{\alpha(\tilde{x}_u + \tilde{x}_a)}. \]
In Theorem 4.4 we did not use $v(L) = \sigma L^2$ from (4.7). However, this equation is needed for the existence of steady biofilm thickness $L$. We will combine Theorems 4.3-4.4 into Theorem 4.5 where we do not assume $L$ is given:

**Theorem 4.5:** Given parameters $\alpha, \gamma, \delta, \sigma, \lambda$ there exists $u_{max} > 0$ (allowed to be $\infty$) such that for any $u_0 \in [0, u_{max})$ there is at least one continuous solution to (4.1)-(4.6) satisfying boundary conditions (4.7).

- If $\delta = 0$ and $\gamma \leq \alpha$, then $u_{max} = \infty$.
- Otherwise, $u_{max}$ is a positive constant such that $u_{max} \geq \bar{u}$, where $\bar{u}$ solves the equation $1 - \Gamma_-(\bar{u})/\alpha = 0$, i.e. $\bar{u}$ satisfies

$$\frac{\delta \bar{u} + \gamma + \bar{u} + \lambda - \sqrt{\delta \bar{u} + \gamma + \bar{u} + \lambda)^2 - 4\bar{u}(\delta \bar{u} + \delta \lambda + \gamma)}}{2} = \alpha.$$ 

**Proof of Theorem 4.5:** We define

$$\mathcal{A} = \{z > 0 : \text{for all } 0 \leq u < z \text{ the system (4.1)-(4.6) has a solution}\}.$$ (4.40)

If we show that the set $\mathcal{A}$ is nonempty and that $\bar{u} \in \mathcal{A}$, then we are done, as it would follow that $u_{max}$ defined by $u_{max} = \sup_\mathcal{A} \mathcal{A}$ has all properties we claimed in the statement.

Consider any $u_0$ satisfying $0 \leq u_0 < \bar{u}$ (or any $u_0 > 0$ if $\delta = 0$ and $\gamma \leq \alpha$) and define the function $f(L) = v(L) - \sigma L^2$ on $[0, \infty)$, where $v$ is the velocity function from Theorem 4.4 for a biofilm of width $L$ (take $x_0 = 0$). It is easy to see that $f$ is well defined, as for such $u_0$ the assumptions of Theorem 4.4 are satisfied. Therefore,
the existence of solutions $X_u, X_{ad}, X_a, X_{ad}, v$ of the system (4.1)-(4.6) is guaranteed by Theorem 4.4.

Also $v$ is a continuous function of $L$. Really, recall that the coordinates of the nontrivial equilibrium satisfy the equations (4.26), where $\Gamma$ continuously depends on $L$. But this is exactly the initial data for $x_u$ and $x_a$ satisfying equations (4.15)-(4.16). Since the right-hand sides of the system (4.15)-(4.16) are Lipschitz continuous, the solutions $x_u, x_a$ continuously depend on the initial data $x_u(0), x_a(0)$ as well as on $L$ due to the continuous dependence of initial data on $L$. Now we may switch from $x_u, x_a$ to $X_u, X_a$. Since $v$ is given by $X_u, X_a$, it continuously depends on $L$ and so does the function $f$.

Note that for small $L > 0$ the function $v(L)$ is almost linear, i.e. $v(L) = cL + O(L^2)$ for some positive constant $c$. Hence, $v(L) > 0$ for $L$ small and so is the function $f(L) = v(L) - \sigma L^2 > 0$ for $L$ small. Note that $f(L) < 0$ for $L$ sufficiently large as $v(L) \leq \alpha L$, hence the term $\sigma L^2$ dominates. Hence, using continuity, there will be at least one $L > 0$ such that $f(L) = 0$, i.e. there exists at least one nontrivial steady-state $L$. Thus the proof of Theorem 4.5 is complete.

Remark: It is easy to see that the solutions of (4.1)-(4.6) have $C^\infty$-regularity. Also note that all the conclusions of our stability analysis apply to the detachment rate of the form $-\sigma L^\alpha$ for $\alpha > 1$. In fact more general detachment terms can be handled. The only condition that is required is that the detachment rate is faster than linear.
In this section we only consider continuous solutions, i.e., $x_0 = 0$. The conclusions of Theorem 4.5 does not exclude the possibility that for given $u_0 \in [0, u_{\text{max}})$ there is more than one solution. In fact in some cases this happens. The cause of this is the function $v(L)$ - we only know it is increasing slower than a linear function, but not a lot more. Non-uniqueness/Uniqueness also depends on the choice of the detachment rate. (As it was pointed out in Chapter 1 there are no generally accepted detachment rate expressions.) We will present an example where there are two asymptotically stable steady state solutions. Depending on dose of biocide at the beginning we can decide whether the time dependent solution will converge to the more favorable steady-state solution (the one which has smaller thickness) or the other one. Hence, an appropriate initial dose can influence dosing efficacy. We also have uniqueness of steady-state solutions for small biocide doses.

*Figure 7 a).* We plotted the function $f(L) = v(L) - \sigma L^2$ from Theorem 4.5 versus $L$ for various $u_0$’s. The values of the parameters are $\phi = 1, \alpha = 2, \gamma = 1, \lambda = 1$, $\delta = 0.1, \sigma = 0.4$. As it can be seen the function $f$ intersects the $x$-axis at three different values of $L$ for $u_0 = 10.25$ and $u_0 = 10.5$. For $u_0 = 10$ there is only one intersection point of the function $f$ with the $x$-axis. (For better clarity we zoomed into the neighborhood of $L = 0$ in Figure 7 b).)*
Figure 7. a) Function $f(L) = v(L) - \sigma L^2$ versus $L$ for various $u_0$'s. The values of the parameters are $\phi = 1, \alpha = 2, \gamma = 1, \lambda = 1, \delta = 0.1, \sigma = 0.4$. For $u_0 = 10.25$ and $u_0 = 10.5$ the function $f$ intersects the $x$–axis at three different positive values of $L$. b) We zoomed into the neighborhood of $L = 0$ for better clarity of the previous plot in a).
Figure 8. We plotted the solutions $L$ of the equation $f(L) = 0$ versus $u_0$ for the same value of parameters as in Figure 7. In this example, $\bar{u} \approx 11$ is labelled as a triangle and $u_{\text{max}} \approx 13.6$ is labelled as a square (the same quantities as in Theorem 4.5). Taking a vertical line sufficiently close to $\bar{u}$ intersects the curve at three different points, hence, there are three different solutions of $L$ for $u_0 < \bar{u}$ close enough to $\bar{u}$. Similarly, for $\bar{u} \leq u_0 < u_{\text{max}}$, there are two different intersection points of the line with the curve and so two different solutions of $L$.

Figure 8. Bifurcation diagram - biofilm thickness $L$ versus $u_0$ with $\bar{u} \approx 11$ and $u_{\text{max}} \approx 13.6$. For $u_0 < \bar{u}$ sufficiently close to $\bar{u}$ there are three different solutions and for $\bar{u} \leq u_0 < u_{\text{max}}$ two different solutions. The parameter values are the same as in Figure 7.
Figure 9. For $u_0 = 10.5$ the three intersections points of the function $f$ with the $x$-axis attain the values $L = 3.9121$, $L = 0.79573$ and $L = 0.1759$. The corresponding steady-state solutions $X_u, X_a$ were plotted.

Figure 10 a). Biofilm thickness $L$ as a function of time is plotted for the same value of parameters as in Figure 7. Biocide dose of $u_0 = 17$ is added on the time interval $[0, 15)$, otherwise $u_0 = 10.3$. As can be seen in Figure 8, for $u_0 = 10.3$ there are three different solutions of $L$ (two of them are stable with $L = 0.30526$ and $L = 3.9462$). For initial data $L(0) = 5$ the biofilm thickness $L$ would converge to the larger value $L = 3.9462$. This is also the case in Figure 10 a) where a larger dose of biocide is added in the beginning.

Figure 10 b). Biocide dose of $u_0 = 18$ is added on the time interval $[0, 15)$, otherwise $u_0 = 10.3$. We observe that a sufficiently large initial dose can influence the whole treatment - $L$ converges to the smaller steady-state $L = 0.30526$, i.e., a biocide threshold $17 < u_0 < 18$ affects the success of dosing.

Figure 11 a). For some other parameter values, however, the steady-state is unique. Function $f(L) = v(L) - \sigma L^2$ versus $L$ is plotted for the parameters $u_0 = 1, \phi = 1, \alpha = 1, \gamma = 2, \lambda = 1, \delta = 0.1, \sigma = 0.4$. There is only a single intersection point with the $x$-axis at value $L = 1.893$. The corresponding steady-state solutions are shown in Figure 11 b).
Figure 9. a)-c) Non-uniqueness of the steady state solutions $X_u, X_a$ with different values of steady biofilm thickness $L = 3.9121$ in a), $L = 0.79573$ in b) and $L = 0.1759$ in c). The parameters values are $u_0 = 10.5, \phi = 1, \alpha = 2, \gamma = 1, \lambda = 1, \delta = 0.1, \sigma = 0.4$. 
Figure 10. a) Biofilm thickness $L$ as a function of time for $u_0 = 17$ on $[0, 15)$ and $u_0 = 10.3$ otherwise. The parameter values are $\phi = 1$, $\alpha = 2$, $\gamma = 1$, $\lambda = 1$, $\delta = 0.1$, $\sigma = 0.4$. b) Biofilm thickness $L$ as a function of time for $u_0 = 18$ on $[0, 15)$ and $u_0 = 10.3$ otherwise. The same parameters as in a).
Figure 11. a) Function $f(L) = v(L) - \sigma L^2$ intersects the $x-$axis at a single positive value of $L$. The parameter values are $u_0 = 1, \phi = 1, \alpha = 1, \gamma = 2, \lambda = 1, \delta = 0.1, \sigma = 0.4$. b) Steady state solutions $X_u, X_a$ with steady biofilm thickness $L = 1.893$. 
We can show that at least for small doses of biocide the steady-state solutions are unique. In Chapter 5 we will show that if there is no biocide added \((u_0 = 0)\) than the steady-state solutions satisfy \(L = \frac{a}{\sigma}\) and \(X_u + X_a = 1\). Using these results, we argue that \(\frac{df}{dL}\bigg|_{u_0=0} \neq 0\), where \(f(u_0, L(u_0)) = v(L(u_0)) - \sigma L(u_0)^2\). Indeed,

\[
\frac{df}{dL} = \frac{dv}{dL} - 2\sigma L = \alpha \left[ (X_u + X_a)(L) + \int_0^L \frac{dX_u}{dL} + \frac{dX_a}{dL} \, dx \right] - 2\sigma L.
\]

At \(u_0 = 0\), however, we obtain

\[
\left. \frac{df}{dL} \right|_{u_0=0} = \alpha - 2\sigma \frac{\alpha}{\sigma} = -\alpha < 0
\]

for \(\alpha > 0\). From the implicit function theorem the claim follows.

Remark: The uniqueness of steady-state solutions for small \(u_0\) can be generalized for the case when \(f(L) = v(L) - h(L)\), where \(h\) satisfies

\[
\frac{h(L)}{L} \to 0 \text{ as } L \to 0+, \quad \frac{h(L)}{L} \to \infty \text{ as } L \to \infty, \quad \frac{d^2 h}{dL^2} > 0.
\]

Indeed, the first two assumptions guarantee that the function \(f\) is positive for small \(L\) and negative for large \(L\). Since the function \(h\) is concave up, we have that \(f'\) is decreasing. It there was more than one steady-state solution \(L\) it would imply that somewhere \(f'\) is increasing. Hence we have our statement.

In case of thin biofilms \((\phi L \ll 1)\) the function \(B\) is almost constant, i.e., \(B \approx u_0\). Hence, the steady-state functions \(X_u, X_a\) will satisfy the same equations as \((4.26)\). Moreover, the biofilm thickness is approximately equal to \((\alpha - \Gamma_-)/\sigma\) (using \((4.8))\).
CHAPTER 5

CONSTANT DOSING OF BIOCIDE

We will discuss the simplest dosing strategy - constant (in time) dosing of biocide applied through the interface \( x = L \). Numerical simulations of solutions indicate that regardless of the initial conditions in the long run the solutions to our model converge to steady-state solutions as investigated in the previous chapter.

The cost of biocide plays an important role. Our goal is to minimize functionals \( J, J_L \) that were introduced earlier. Since they depend on the cost of biocide, the minimizing treatment will vary with the cost of the biocide. In particular, we will show that for ‘cheap’ biocide it is always better to treat the biofilm with biocide than to leave it untreated. However, if the biocide is ‘too expensive’, i.e., its cost is over certain threshold, the best course of action is to do nothing (leave the biofilm untreated). To better understand the behavior of functionals \( J, J_L \) we do asymptotic expansions at points \( u_0 = 0 \) and also in one case at \( u_0 = \infty \) (here \( u_0 \) is the dose of biocide at the interface).

Recall what we established in Chapter 4 for the steady state solutions:

- If \( \delta = 0 \) and \( \gamma \leq \alpha \) (adapted cells do not die and growth dominates reversion), then the nonzero steady-state solutions exist for any \( u_0 \in [0, \infty) \) and there is no biocide...
threshold exceeding of which would guarantee that the steady biofilm thickness is $L = 0$.

- In all other cases, nonzero steady-state solution(s) exist only for $u_0 \in [0, u_{\text{max}})$, where $u_{\text{max}}$ is defined as a supremum of the set (4.40). We also have that for sufficiently large $u_0 > u_{\text{max}}'$ the solution under constant dosing converges to $L = 0$ as $t \to \infty$ for any initial condition.

Indeed, it follows from Chapter 4 that a steady-state solution satisfies $L \leq \frac{\sigma}{\delta}$. Recall from this chapter that $B_0 = \frac{u_0 \cosh(\phi_0)}{\cosh(\phi L)}$ and that $\Gamma_-(B_0) \to \infty$ for $\delta > 0$ or $\Gamma_-(B_0) \to \gamma$ for $\delta = 0$ as $B_0 \to \infty$. When $\delta = 0$ and $\gamma > \alpha$, the inequality $\Gamma_- > \alpha$ holds in which case $L = 0$. In the other case $\delta > 0$, since $\Gamma_-$ is increasing, we obtain that there exists a $\hat{B}_0$ such that $\Gamma_-(\hat{B}_0) = \alpha$. It follows that

$$B_0 \geq \frac{u_0}{\cosh(\phi L)} \geq \frac{u_0}{\cosh(\phi \alpha \frac{\sigma}{\delta})} > \hat{B}_0.$$ 

For $u_0 = \cosh(\phi \alpha \frac{\sigma}{\delta}) \hat{B}_0$ we have therefore $\Gamma_- > \alpha$, from which $L = 0$ follows. So,

$$u_{\text{max}}' \leq \cosh(\phi \alpha \frac{\sigma}{\delta}) \hat{B}_0.$$ 

There is a numerical evidence that $u_{\text{max}} = u_{\text{max}}'$, we however do not have any proof of this claim. We do however have an estimate from below for the threshold $u_{\text{max}}$: $u_{\text{max}} \geq \bar{u}$, where $\bar{u}$ is a solution of

$$\frac{\delta \bar{u} + \gamma + \bar{u} + \lambda - \sqrt{(\delta \bar{u} + \gamma + \bar{u} + \lambda)^2 - 4\bar{u}(\delta \bar{u} + \delta \lambda + \gamma)}}{2} = \alpha.$$
There are cases when \( u_{\text{max}} = \bar{u} \); this happens if for given parameters and all \( u_0 \) there is only one nonzero continuous steady state solution (i.e. uniqueness holds). If there is non-uniqueness, then \( u_{\text{max}} > \bar{u} \) (c.f. Figure 8).

The numerical observation that for constant (steady) dosing the solutions of the PDE model tend to steady-state solutions implies important simplification for the functionals we will study. As time \( T \to \infty \), we get that

\[
J(u_0) = \lim_{T \to \infty} \int_0^L (X_a(x, t) + X_u(x, t)) \, dx + cu_0
\]

and

\[
J_L(u_0) = \lim_{T \to \infty} L(T) + cu_0,
\]

where \( u_0 \) is the externally applied biocide concentration and \( c \) is the cost of biocide.

We ran numerical simulations for several sets of parameters.

**Figure 12 a)** The optimal biocide dose \( u_0 \) versus cost \( c \) for parameters \( \phi = 1, \lambda = 0.1, \alpha = 1, \gamma = 0.01, \sigma = 0.4, \delta = 0.1 \) is plotted. Here the biocide threshold is \( u_{\text{max}} \approx 9.9 \), which is exactly the optimal value of \( u_0 \) in the limit \( c \to 0^+ \). If the biocide treatment is too expensive, it is better not to treat the biofilm at all. There is a critical cost threshold \( c_0 \) beyond which it better not to apply any biocide. In this case \( c_0 \) can be found for the two functionals from equations

\[
c_0 = -\frac{dJ_0}{du_0}(0) \quad \text{or} \quad c_0 = -\frac{dL}{du_0}(0),
\]
Figure 12. a) Optimal biocide dose $u_0$ versus cost $c$ with a jump for parameters $\phi = 1, \lambda = 0.1, \alpha = 1, \gamma = 0.01, \sigma = 0.4, \delta = 0.1$. b) Functionals $J, J_L$ versus $u_0$ for some values of $c$. The curves are concave down at $u_0 = 0$. 
where $J_0 = \int_0^L (X_a(x) + X_u(x)) dx$. An interesting phenomenon is the jump of the optimal biocide dose $u_0$ at the threshold $c_0$.

*Figure 12 b*) The minimizing functionals $J, J_L$ versus biocide dose $u_0$ is plotted for some values of the cost $c$ and the same parameter values as in Figure 12. The horizontal line represents the untreated biofilm case, i.e. $u_0 = 0$. For values of the cost $c \geq c_0$ there is a trivial minimum at $u_0 = 0$ and the curves are above the horizontal line. On the other hand, for $c < c_0$ there is a nontrivial minimum that falls below the horizontal line. Note that the functionals $J, J_L$ are concave down at $u_0 = 0$. Indeed, the following proposition can be established by a simple geometric argument.

**Proposition 5.1:** If $\frac{d^2 J}{du_0^2}(0) < 0$ or $\frac{d^2 J_L}{du_0^2}(0) < 0$, then the optimal biocide dose as a function of biocide cost is discontinuous and there is a cost threshold $c_0$ such that for $c \geq c_0$ the optimal minimum is zero.

**Remark:** The counterpositive of this statement is that if there is no jump, then $\frac{d^2 J}{du_0^2}(0) \geq 0$ and $\frac{d^2 J_L}{du_0^2}(0) \geq 0$. The case $\frac{d^2 J}{du_0^2}(0) = 0$ or $\frac{d^2 J_L}{du_0^2}(0) = 0$ is possible, but it is not generic. There are examples which show a smooth way of reaching the critical cost threshold (without jump). Figure 13 is presented to illustrate.

*Figure 13 a*) The optimal biocide dose $u_0$ versus cost $c$ is plotted for parameters $\phi = 1, \lambda = 0.5, \alpha = 0.2, \gamma = 0.1, \sigma = 1, \delta = 0.1$ with biocide threshold $u_{\text{max}} \approx 1.3$
Figure 13. a) Optimal biocide dose $u_0$ versus cost $c$ without a jump for parameters $\phi = 1, \lambda = 0.5, \alpha = 0.2, \gamma = 0.1, \sigma = 1, \delta = 0.1$. b) Functionals $J, J_L$ versus $u_0$ for some values of $c$. The curves are concave up for all $u_0$. 
which is exactly the value of $u_0$ at $c = 0$. In this case there is no jump of the optimal biocide dose $u_0$ at the threshold $c_0$.

*Figure 13 b)* The minimizing functionals $J, J_L$ versus biocide dose $u_0$ are plotted for some values of the cost $c$ and the same parameter values as in Figure 13. Just as before, the horizontal line represents the untreated biofilm case. Note that the functionals $J, J_L$ are concave up for all $u_0$. By simple geometrical arguments we have the following proposition:

**Proposition 5.2:** If $\frac{d^2 J}{du_0^2}(u_0) > 0$ or $\frac{d^2 J_L}{du_0^2}(u_0) > 0$ for all $0 \leq u_0 < u_{\max}$, where $u_{\max}$ is allowed to be $\infty$, then the optimal biocide dose as a function of biocide cost is continuous and there is a cost threshold $c_0$ such that for $c \geq c_0$ the optimal minimum is zero.

Recall from Chapter 4 that in a model with $\delta = 0$ and $\alpha > \gamma$ there is a nontrivial steady biofilm thickness $L$ for all $u_0$, i.e. there is no biocide threshold that would guarantee $L = 0$. Figure 14 is presented as an example. This case is different from the previous ones since the biofilm could never be eliminated.

*Figure 14 a)* The optimal biocide dose $u_0$ versus cost $c$ is plotted for parameters $\phi = 1, \lambda = 1, \alpha = 1, \gamma = 0.1, \sigma = 0.4, \delta = 0$. We observe that the cheaper the treatment is, the more biocide can be used. Indeed, there is a vertical asymptote at
\( c = 0 \) even though the top of the curves is chopped off. There is no jump, i.e., the cost threshold \( c_0 \) is reached continuously.

**Figure 14 b)** The minimizing functionals \( J, J_L \) versus biocide dose \( u_0 \) is plotted for some values of the cost \( c \) and the same parameter values as in Figure 14. The functionals \( J, J_L \) are concave up for all \( u_0 = 0 \). For \( c = 0 \) the curves approach a positive horizontal asymptote as \( u_0 \to \infty \).

**Analysis of the first derivative of \( J, J_L \)**

We are interested in investigating the quantity \( \frac{dJ_L}{du_0}(0) \) at \( c = 0 \) (a similar analysis can be done for \( \frac{dJ}{du_0}(0) \) at \( c = 0 \)). We will show that this quantity is negative which means that for low costs of the biocide constant dosing is more effective than the untreated biofilm. We will present the proof below.

From Chapter 4 the functions \( X_u, X_a \) and the steady biofilm thickness \( L \) satisfy the equations

\[
\frac{dX_u}{dx} = -(B + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a \quad (5.3)
\]

\[
\frac{dX_a}{dx} = \lambda X_u - \delta X_a B + \alpha(1 - X_u - X_a)X_a - \gamma X_a \quad (5.4)
\]

\[
v(L) = \sigma L^2. \tag{5.5}
\]

Consider the first-order expansions of the functions \( X_u, X_a \) and \( L \) about \( u_0 = 0 \), i.e. we have \( X_u = X_u^{(0)}(x) + X_u^{(1)}(x)u_0 + O(u_0^2) \), \( X_a = X_a^{(0)}(x) + X_a^{(1)}(x)u_0 + O(u_0^2) \).
Figure 14. a) Optimal biocide dose $u_0$ versus cost $c$ with a jump for parameters $\phi = 1, \lambda = 1, \alpha = 1, \gamma = 0.1, \sigma = 0.4, \delta = 0$. b) Functionals $J, J_L$ versus $u_0$ for some values of $c$. The curves are concave up for all $u_0$. 
and \( L = L^{(0)} + L^{(1)}u_0 + O(u_0^2) \). The first-order expansion of the biocide \( B(x) \) is

\[ a_1(x)u_0, \text{ where } a_1(x) = \frac{\cosh \phi x}{\cosh(\phi L_0)}. \]

Recall from the previous chapter that

\[ \Gamma - (B_0) = \frac{\delta B_0 + \gamma + B_0 + \lambda - \sqrt{(\delta B_0 + \gamma + B_0 + \lambda)^2 - 4B_0(\delta B_0 + \delta \lambda + \gamma)}}{2}, \quad (5.6) \]

where \( B_0 = \frac{u_0}{\cosh(\phi L)} \). Now the square-root expression in (5.6) can be written as

\[
\sqrt{(\delta B_0 + \gamma + B_0 + \lambda)^2 - 4B_0(\delta B_0 + \delta \lambda + \gamma)} = \\
\sqrt{(\gamma + \lambda)^2 + 2B_0(1 - \delta)(\lambda - \gamma) + B_0^2(1 - \delta)^2} = \\
(\gamma + \lambda) \sqrt{1 + \frac{2B_0(1 - \delta)(\lambda - \gamma) + B_0^2(1 - \delta)^2}{(\gamma + \lambda)^2}} = \\
\gamma + \lambda + \frac{B_0(1 - \delta)(\lambda - \gamma)}{\gamma + \lambda} + O(u_0^2)
\]

from which \( \Gamma - = \frac{B_0(\gamma + \delta \lambda)}{\gamma + \lambda} + O(u_0^2) \). Since \( B_0 = \frac{u_0}{\cosh(\phi L)} + O(u_0^2) \), we obtain that \( \Gamma - = Au_0 + O(u_0^2) \), where \( A = \frac{\gamma + \delta \lambda}{\cosh(\phi L_0)(\gamma + \lambda)} \).

At \( x = 0 \), the steady-state solutions \( X_u, X_a \) satisfy the equations from Chapter 4

\[ X_u + X_a = 1 - \frac{\Gamma -}{\alpha} \quad (5.7) \]

\[ \lambda X_a + (\Gamma - - \delta B_0 - \gamma)X_a = 0. \]

Recall from Chapter 1 that

\[ \lambda(B) = \begin{cases} 
\lambda & \text{if } B = 0 \\
0 & \text{if } B > 0 
\end{cases}, \]

hence the functions \( X_u, X_a \) are discontinuous at \( u_0 = 0 \). For \( u_0 \to 0^+ \) we get that \( \Gamma - (0) \to 0 \), hence \( X_u^0(0) \to \frac{\lambda}{\lambda + \gamma} \) and \( X_a^0(0) \to \frac{\lambda}{\lambda + \gamma} \). But when \( u_0 = 0 \), we get
$X_u(0) = 1$ and $X_a(0) = 0$. Notice however one positive fact. Even though $X_u$ and $X_a$ are discontinuous at $B = 0$, the functionals $J$ and $J_L$ are still continuous at this point. Since $X_u^{(0)} + X_a^{(0)} = 1$, we obtain $v(x) = \alpha x$ from which $v(L) = \alpha L = \sigma L^2$ and $L = \frac{\sigma}{\alpha}$. It follows that $J(0) = J_L(0) = \frac{\sigma}{\alpha}$. This implies these $J$ and $J_L$ are continuous at zero, as they do not depend on $\lambda$ at this point.

For this reason we can do the following trick. We will assume for the rest of this chapter, that $\lambda$ is not a step function but a constant. This modifies values of $X_u$ and $X_a$ at zero - makes them continuous (in fact smooth), but does not influence results on $J$ and $J_L$ as these do not depend on $\lambda$ at zero. This assumption will make the rest of this chapter more readable, as we will not have to pay special attention to the point $u_0 = 0$.

After making this modification, using the equations (5.3)-(5.4) we can verify that the zero-th order coefficients are constant in $x$ at $u_0 = 0$, i.e. $X_u^0(x) = \frac{\gamma}{\lambda + \gamma}$ and $X_a^0(x) = \frac{\lambda}{\lambda + \gamma}$.

We will compare the coefficients of the first-order terms in the expansion of equations (5.3)-(5.4). We obtain

\[
\alpha x \frac{dX_u^{(1)}}{dx} = -X_u^{(0)}a_1(x) - \lambda X_u^{(1)} + \alpha (X_u^{(1)} + X_a^{(1)})X_u^{(0)} + \gamma X_a^{(1)} \quad (5.8)
\]

\[
\alpha x \frac{dX_a^{(1)}}{dx} = \lambda X_a^{(1)} - \delta X_a^{(0)}a_1(x) + \alpha (X_u^{(1)} + X_a^{(1)})X_a^{(0)} - \gamma X_a^{(1)} . \quad (5.9)
\]

Adding equations (5.8)-(5.9) we get

\[
x \frac{dZ}{dx} + Z = -\frac{X_u^{(0)} + \delta X_a^{(0)}}{\alpha} a_1(x), \quad (5.10)
\]
where \( Z(x) = X_u^{(1)}(x) + X_a^{(1)}(x) \). The solution of equation (5.10) is
\[
Z(x) = -\frac{X_u^{(0)} + \delta X_a^{(0)}}{\alpha x} \int_0^x a_1(s) ds = \frac{X_u^{(0)} + \delta X_a^{(0)}}{\alpha \phi \cosh(\phi L_0)} \sinh(\phi x),
\]
where \( Z(0) = \lim_{x \to 0} Z(x) = -\frac{X_u^{(0)} + \delta X_a^{(0)}}{\alpha \cosh(\phi L_0)} \). Hence, the solution of equation (5.10) can be smoothly extended to zero. Note that \( Z(x) < 0 \).

Now we would like to find the coefficients of the expansion of \( L \). Using equation (5.5) and comparing the first-order terms in its expansion, we get \( L_0 = \frac{\alpha}{\sigma} \) and \( L_1 = \int_0^{L_0} Z(x) dx \). The sign of \( L_1 \) shows that the derivative of the functional \( J_L \) with respect to \( u_0 \) is negative at \( c = 0 \), i.e. \( \frac{dJ_L}{du_0}(0) < 0 \) for \( c \) small. In a similar manner \( \frac{dJ}{du_0}(0) < 0 \) for \( c \) small from which the assertion in the beginning of this section follows.

**Analysis of the second derivative of \( J, J_L \)**

Recall if the second derivative of the functionals \( J, J_L \) at \( u_0 = 0 \) is negative, then there is a jump in the plots. On the other hand, if there is no jump, then the second derivative of the functionals \( J, J_L \) at \( u_0 = 0 \) is positive. Hence, we will analyze the quantity \( \frac{d^2J_L}{du_0^2}(0) \) (a similar analysis can be done for \( \frac{d^2J}{du_0^2}(0) \)). An interesting result is that for thin biofilms \( \frac{d^2J_L}{du_0^2}(0), \frac{d^2J}{du_0^2}(0) \) are positive.

Consider the second-order expansion of \( X_u, X_a, B \) and \( L \) about \( u_0 = 0 \), i.e. \( X_u = X_u^{(0)}(x) + X_u^{(1)}(x)u_0 + X_u^{(2)}(x)u_0^2 + O(u_0^3), X_a = X_a^{(0)}(x) + X_a^{(1)}(x)u_0 + X_a^{(2)}(x)u_0^2 + O(u_0^3), B = a_1(x)u_0 + a_2(x)u_0^2 + O(u_0^3) \) and \( L = L_0 + L_1 u_0 + L_2 u_0^2 + O(u_0^3) \), where \( a_1(x) = \)
\[
\frac{\cosh(\phi x)}{\cosh(\phi L_0)}, a_2(x) = -\phi \tanh(\phi L_0) \frac{\cosh(\phi x)}{\cosh(\phi L_0)}. \]

Adding equations (5.3)-(5.4) we obtain
\[
\frac{d}{dx}(X_u + X_a)v = -BX_u - \delta BX_a + \alpha(1 - X_u - X_a)(X_u + X_a). \tag{5.11}
\]

Comparing the coefficients of the second-order terms in the expansion of equation (5.11) we get
\[
\alpha x \frac{dX_u^1}{dx} + (\lambda + \gamma)X_u^1 = -a_1(x)X_u^0 - \alpha ZX_u^0 + \gamma Z. \tag{5.13}
\]

It follows from (5.13) that
\[
X_u^1(x) = \frac{1}{\alpha x} \frac{\lambda + \gamma - 1}{\alpha} \int_0^x s^{\lambda + \gamma - 1} \left(- a_1(s)X_u^0(s) - \alpha Z(s)X_u^0(s) + \gamma Z(s)\right) ds. \tag{5.14}
\]

Similarly, from (5.9) we get
\[
\alpha x \frac{dX_a^1}{dx} + (\lambda + \gamma)X_a^1 = -\delta a_1(x)X_a^0 - \alpha ZX_a^0 + \lambda Z. \tag{5.15}
\]

It follows from (5.15) that
\[
X_a^1(x) = \frac{1}{\alpha x} \frac{\lambda + \gamma - 1}{\alpha} \int_0^x s^{\lambda + \gamma - 1} \left(- \delta a_1(s)X_a^0(s) - \alpha Z(s)X_a^0(s) + \lambda Z(s)\right) ds. \tag{5.16}
\]

Finally, the solution of equation (5.12) is
\[
U(x) = \frac{1}{x} \left[ \int_0^x -a_2(s) \frac{X_u^{(0)}}{\alpha} + \delta X_u^{(0)} - a_1(s) \frac{X_u^{(1)}}{\alpha} + \delta X_u^{(1)} ds - Z \int_0^x Z(s) ds \right]. \tag{5.17}
\]
where $X_a^{(1)}$, $X_a^{(1)}$ are given by (5.14) and (5.16).

To find $L_2$, we use equation (5.5). Comparing the coefficients of its second-order expansion we obtain

$$
\alpha \left( L_2 u_0^2 + u_0 \int_{L_0}^{L_0 + L_1 u_0} Z(x) dx + u_0^2 \int_0^{L_0} U(x) dx \right) = \sigma (L_1^2 + 2L_0 L_2) u_0^2. \tag{5.18}
$$

Since $u_0$ is small, the second term in the left-hand side of (5.18) simplifies to

$$
u_0 \int_{L_0}^{L_0 + L_1 u_0} Z(x) dx = Z(L_0) L_1 u_0^2 + O(u_0^3).$$

Solving for $L_2$ we obtain

$$
L_2 = Z(L_0) L_1 + \int_{L_0}^{L_0} U(x) dx - L_1^2 / L_0. \tag{5.19}
$$

We see that $L_2 = \frac{d^2 J}{du_0^2} (0)$ is a sum of three terms, the first one always positive, the last one negative and the second could either be positive or negative. Hence, in general it would be very hard to analyze the sign of $L_2$. In fact numerical simulations confirm it can be either positive or negative. There is however one special case we are able to handle - when the quantity $\phi L_0$ is small. In this case $L_2 > 0$. By continuity $\frac{d^2 J}{du_0^2} > 0$ near zero. It follows that if we assume the biofilm is thin (so that we only need to know $\frac{d^2 J}{du_0^2}$ near zero) there is no jump, i.e., the functionals $J, J_L$ are concave up.

**Proposition 5.3:** If $\phi L_0 \ll 1$, then $\frac{d^2 J}{du_0^2} (0) > 0$ and $\frac{d^2 J}{du_0^2} (0)$.

**Sketch of the proof:** When $\phi L_0 \ll 1$, then $\cosh(\phi x) \approx 1$. It follows that $B \approx u_0$, i.e. $a_0(x) = 1$ and $a_1(x) = 0$. From equation (5.14) we may solve for $X_a^{1}$ to
obtain

\[ X_u^{(1)} = -\frac{\gamma}{\alpha(\lambda + \gamma)^3}[\gamma^2 + \lambda \gamma + \alpha \lambda + \delta \lambda(\lambda + \gamma - \alpha)] \]

and from (5.16) we have

\[ X_a^{(1)} = -\frac{\lambda}{\alpha(\lambda + \gamma)^3}[\gamma^2 + \lambda \gamma - \alpha \gamma + \delta(\lambda^2 + \lambda \gamma + \alpha \gamma)]. \]

We may similarly solve for \( U \) from (5.17) to get

\[ U = \frac{\gamma \lambda}{\alpha(\lambda + \gamma)^3}(1 - \delta)^2. \]

Finally, by equation (5.19) one can see that \( L_2 = \frac{\gamma \lambda}{\sigma(\lambda + \gamma)^3}(1 - \delta)^2 \) so that \( L_2 > 0 \) if \( \phi L_0 \ll 1 \).

Analysis of the special case \( \alpha \geq \gamma \) and \( \delta = 0 \).

Recall from the beginning of this chapter, that whenever \( \delta > 0 \) or \( \delta = 0 \) and \( \alpha < \gamma \), then there exists a threshold \( u_{\text{max}} < \infty \) such that for \( u_0 > u_{\text{max}} \) the only steady state solution is zero. Hence, if we constantly dose over this amount of biocide the biofilm thickness \( L > 0 \) decreases to zero as \( t \to \infty \). Thus, it makes no sense to study the asymptotics of \( L \) for large (infinite) time as \( u_0 \to \infty \), since \( L \) vanishes past a certain finite threshold \( u_{\text{max}} \).

The only case this does not happen is when \( \alpha \geq \gamma \) and \( \delta = 0 \) (adapted cells do not die). Here, there is no finite biocide threshold that would guarantee \( L \to 0 \). We
will investigate in detail the functional $J_L$ as $u_0 \to \infty$. Similar analysis can be also done for $J$. At the end, we again obtain more specific results for thin biofilms.

Consider the first-order expansion of the functions $X_a, L, B$ about $u_0 = \infty$ and the second-order expansion of $X_u$ about $u_0 = \infty$. The second-order expansion of $X_u$ is necessary in equation (5.20) to obtain all the first-order terms in the right-hand side. We have $X_a = X_a^{(0)}(x) + \frac{X_a^{(1)}(x)}{u_0} + O\left(\frac{1}{u_0^2}\right)$, $L = L_0 + \frac{L_1}{u_0} + O\left(\frac{1}{u_0^2}\right)$, $B = a_0(x)u_0 + a_1(x) + \frac{a_2(x)}{u_0} + O\left(\frac{1}{u_0^2}\right)$ and $X_u = X_u^{(0)}(x) + \frac{X_u^{(1)}(x)}{u_0} + \frac{X_u^{(2)}(x)}{u_0^2} + O\left(\frac{1}{u_0^3}\right)$. The coefficients in the expansion of the biocide are $a_0(x) = \frac{\cosh(\phi x)}{\cosh(\phi L_0)}$, $a_1(x) = -\phi \tanh(\phi L_0) \frac{\cosh(\phi x)}{\cosh(\phi L_0)}$, $a_2(x) = \frac{d^3(1/\cosh(\phi x))}{dx^3}|_{x=L_0}$. The first-order expansion of equation (5.3) about $u_0 = \infty$ is

$$\alpha \int_0^x (X_u^{(0)}(s) + X_a^{(0)}(s))ds \left(\frac{dX_u^{(0)}}{dx} + \frac{1}{u_0} \frac{dX_u^{(1)}}{dx}\right) =$$

$$= -\left(u_0a_0(x) + \frac{a_1(x)}{u_0} + \frac{a_2(x)}{u_0^2} + \lambda\right)\left(X_u^{(0)} + \frac{X_u^{(1)}}{u_0} + \frac{X_u^{(2)}}{u_0^2}\right) +$$

$$+\alpha \left(1 - X_u^{(0)} - X_a^{(0)} - \frac{X_u^{(1)}}{u_0} - \frac{X_a^{(1)}}{u_0}\right)\left(X_u^{(0)} + \frac{X_u^{(1)}}{u_0} + \frac{X_u^{(2)}}{u_0^2}\right) + \gamma\left(X_a^{(0)} + \frac{X_a^{(1)}}{u_0}\right).$$

Note that the terms $-u_0a_0(x)X_u^{(0)}$ and $-a_0(x)X_u^{(1)}(x) + \gamma X_u^{(0)}(x)$ in the right-hand side of (5.20) have to be zeros. Hence, $X_u^{(0)}(x) = 0$ and $X_u^{(1)}(x) = \frac{\gamma X_a^{(0)}(x)}{a_0(x)}$. To find $X_a^{(0)}(x)$ we assume it is constant (does not depend on $x$). Recall from Chapter 4 that $\Gamma_+ \to \gamma$ as $u_0 \to \infty$ if death rate is zero. If $X_a^{(0)}(x)$ is a constant, then $X_a^{(0)}(x) = 1 - \gamma/\alpha$ by equation (5.7). This $X_a^{(0)}(x)$ is a solution to equation (5.4). It follows that $X_u^{(1)}(x) = \frac{\alpha - \gamma}{a_0(x)}$. 


Comparing the coefficients of the first-order terms in the expansion of equation (5.4) we obtain

$$(\alpha - \gamma)x \frac{dX_a^{(1)}}{dx} = \lambda X_u^{(1)} - (\alpha - \gamma)(X_u^{(1)} + X_a^{(1)}).$$

Assuming $\alpha > \gamma$, we may rewrite this ODE as

$$x \frac{dX_a^{(1)}}{dx} + X_a^{(1)} = \left(\frac{\lambda}{\alpha - \gamma} - 1\right) X_u^{(1)}. \tag{5.21}$$

The solution of equation (5.21) is

$$X_a^{(1)}(x) = \frac{1}{x} \int_0^x \left(\frac{\lambda}{\alpha - \gamma} - 1\right) X_u^{(1)}(s)ds,$$

where $X_u^{(1)}(x) = \frac{\alpha - \gamma}{a_0(x)}$. Thus,

$$X_a^{(1)}(x) = \frac{\gamma}{\alpha} (\lambda - \alpha + \gamma) \frac{\cosh(\phi L_0)}{\phi} \frac{\text{arctan}(e^{\phi x}) - \pi/4}{x}.$$

Again, we would like to find the coefficients of $L$. Using equation (5.5) and comparing the first-order terms in its expansion we get

$$L_0 = \frac{\alpha - \gamma}{\sigma}, \quad L_1 = \frac{\alpha}{\alpha - \gamma} \int_0^{L_0} (X_u^{1}(x) + X_a^{1}(x))dx.$$

Hence, substituting into $X_a^{(1)}$, $X_u^{(1)}$ we obtain

$$L_1 = \frac{\gamma}{\phi} \cosh(\phi L_0) \left[ \text{arctan}(e^{\phi L_0}) - \pi/4 + \frac{\lambda - \alpha + \gamma}{\alpha - \gamma} \int_0^{L_0} \frac{\text{arctan}(e^{\phi x}) - \pi/4}{x} dx \right].$$

Note that the coefficient $L_1 > 0$ if $\lambda + \gamma \geq \alpha$ but in general, $L_1$ can change sign. The cases $L_1 > 0$ and $L_1 < 0$ are significantly different.

If $L_1 > 0$, then the optimal minimum of the functional $J_L(u_0) = L_0 + \frac{L_1}{u_0} + cu_0 + O(\frac{1}{u_0})$ is $u_0 \approx \frac{L_1}{c}$. Hence, $J_L$ decreases as $u_0$ gets large. If we consider the dependance
of the optimal minimum \( u_0 \) on the cost \( c \), there will be a vertical asymptote at \( c = 0 \). What this means is that if the biocide is very ‘cheap’, the optimal dosing strategy would be to put large quantity of the biocide to suppress the biofilm.

On the other hand, if \( L_1 < 0 \), situation is a bit counterintuitive. It follows that \( J_L \) is an increasing function for large \( u_0 \), hence in the graph \( c \) versus optimal value of \( u_0 \) (the dose) there will be no vertical asymptote at \( c = 0 \). In this case there is a certain value \( u' \) at which the function \( L(u_0) \) attains its minimum. Any dosing \( u_0 > u' \) does not make any sense - it will not be more effective than the dose \( u' \).

**Remark:** When \( \alpha = \gamma \), then \( L_0 = 0 \) and \( L_1 > 0 \) since \( L \to 0 \) as \( u_0 \to \infty \).

To make the notation simpler, let

\[ F(\phi, L_0) = \arctan(e^{\phi L_0}) - \pi/4 \]

and

\[ G(\phi, L_0) = \int_0^{L_0} \frac{\arctan(e^{\phi x}) - \pi/4}{x} dx. \]

Then \( L_1 \) can be written as

\[ L_1 = \gamma \frac{\cosh(\phi L_0)}{\phi} \left[ F(\phi, L_0) + \frac{\lambda - \alpha + \gamma}{\alpha - \gamma} G(\phi, L_0) \right]. \]

Now let \( J = J_0 + \frac{J_1}{u_0} + O(\frac{1}{u_0^2}) \) be the first-order expansion of the functional \( J \) about \( u_0 = \infty \). It can be shown that

\[ J_1 = \frac{2\gamma}{\alpha} \frac{\cosh(\phi L_0)}{\phi} \left[ (\alpha - \gamma) F(\phi, L_0) + (\lambda - \alpha + \gamma) G(\phi, L_0) \right]. \]
Finally, in the case the biofilm is thin ($\phi L_0 \ll 1$) the situation is can be analyzed completely. It is easy to show that both $L_1$ and $J_1$ are positive.

**Proposition 4.4:** If $\phi L_0 \ll 1$, then $L_1 > 0$ and $J_1 > 0$.

**Sketch of the proof:** We may approximate the integral in the formula for $L_1$ by the first-order expansion of the function $\arctan(e^{\phi x})$ about $x = 0$. Since $\arctan(e^{\phi x}) = \pi/4 + \frac{\phi x}{2} + O(x^2)$, we have

$$L_1 = \gamma \frac{\cosh(\phi L_0)}{\phi} \left[ \frac{\phi L_0}{2} + \frac{\lambda - \alpha + \gamma}{\alpha - \gamma} \left( \frac{\phi L_0}{2} \right) \right] + O(\phi^2 L_0^2) = \frac{\lambda \gamma}{2\sigma} \cosh(\phi L_0) + O(\phi^2 L_0^2)$$

which is positive since $\phi L_0 \ll 1$. Also, for thin biofilms we may write $J_1$ as

$$J_1 = \frac{2\gamma}{\alpha} \frac{\cosh(\phi L_0)}{\phi} \left[ (\alpha - \gamma) \frac{\phi L_0}{2} + (\lambda - \alpha + \gamma) \frac{\phi L_0}{2} \right] + O(\phi^2 L_0^2) = \gamma \frac{\lambda}{\sigma} (1 - \gamma/\alpha) \cosh(\phi L_0) + O(\phi^2 L_0^2)$$

which is again positive for $\alpha > \gamma$.

**Remark:** In case of thick biofilms ($\phi L_0 \gg 1$) the term $G(\phi, L_0)$ is a lot bigger than $F(\phi, L_0)$. Hence, the coefficients next to $G(\phi, L_0)$, i.e. $\frac{\lambda - \alpha + \gamma}{\alpha - \gamma}$ for $L_1$ and $\lambda - \alpha + \gamma$ for $J_1$ will determine the sign of $L_1, J_1$. 
CHAPTER 6

PERIODIC DOSING OF BIOCIDES

In Chapter 5 we discussed the simplest dosing strategy - constant dosing, but in practice more sophisticated dosing strategies are required. Here, we aim to model and analyze other dosing techniques - periodic dosing (biocide is positive for all time) and on and off dosing (biocide is zero during withdrawal time). Our numerical simulations show that periodic dosing can be more effective than constant dosing, but the difference between these two dosing strategies is relatively small.

Significantly, the on and off dosing strategy seems to be more effective than the constant dosing method. The main reason for this is that during the withdrawal time no new adapted cells are created. Hence, the unadapted-adapted reversion rate $\lambda$ is zero. The analytical explanation why the on and off dosing is ‘better’ is based on Theorem 6.3 which is proved and also numerically verified in this Chapter. This Theorem shows that in the high frequency limit (i.e., when the total period goes to zero) the on and off dosing converges to a steady state limit (c.f. Chapter 4) with modified constant $\lambda$. For example, when the dosing and withdrawal time during the period are equal, the limit corresponds to value of $\lambda/2$, i.e., half of the original value. Note that this is exactly the average value of the function $\lambda$ over the dosing period.
This is important, as smaller $\lambda$ means smaller adaptation of cells to biocide. Hence the biocide kills more biofilm bacteria more effectively.

Each section of this Chapter has two parts - a theoretical part where the problem is studied analytically, and a numerical part where analytical conclusions are verified. Given fixed values of the parameters, frequency and amplitude were varied for both periodic and on and off dosing strategies. For a given cost of biocide, we optimize the minimizing functionals with respect to the biocide dose in the case of on and off dosing. We did not do a cost optimal study in the case of periodic dosing, as the differences between periodic and constant dosing are minimal. Hence, the plots we would obtain would be essentially the same as in the previous Chapter on constant dosing.

Recall the model equations from Chapter 1:

\[
\frac{\partial^2 B}{\partial x^2} = \phi^2 B 
\]

\[
\frac{\partial X_u}{\partial t} + v \frac{\partial X_u}{\partial x} = -(B + \lambda)X_u + \alpha(1 - X_u - X_a)X_u + \gamma X_a
\]

\[
\frac{\partial X_{ud}}{\partial t} + v \frac{\partial X_{ud}}{\partial x} = BX_u - \alpha(X_u + X_a)X_{ud}
\]

\[
\frac{\partial X_a}{\partial t} + v \frac{\partial X_a}{\partial x} = \lambda X_u - \delta BX_a + \alpha(1 - X_u - X_a)X_a - \gamma X_a
\]

\[
\frac{\partial X_{ad}}{\partial t} + v \frac{\partial X_{ad}}{\partial x} = \delta BX_a - \alpha(X_u + X_a)X_{ad}
\]

\[
\frac{\partial v}{\partial x} = \alpha(X_u + X_a)
\]

\[
\frac{dL}{dt} = v(L, \cdot) - \sigma L^2
\]
The boundary conditions are given by

\[ \frac{\partial B}{\partial x}(0, t) = 0, \quad B(L(t), t) = u(t) \quad \text{for} \quad 0 \leq t \leq P \]

\[ v(0, t) = 0 \quad \text{for} \quad 0 \leq t \leq P, \quad (6.8) \]

where the biocide concentration at the interface \( u \) is a nonnegative piecewise continuous periodic function of period \( P \). Minimizing functionals (1.33)-(1.34) from Chapter 1 will be used in our analysis. We start with periodic dosing.

**Periodic Dosing**

It is possible to establish the existence of periodic solutions for the system (6.1)-(6.7) of period \( P \) which satisfies the boundary conditions (6.8). The technique would be similar to the one we presented for existence of steady state solutions. We, however, will not do it - the precise construction would be very complicated and lengthy. Instead, we will satisfy ourselves with numerical evidence that these solutions indeed exist. In fact, numerical simulations suggest that given any initial data \( g_u, g_{ud}, g_a, g_{ad} \) and a periodic function \( u \), the solution of the system (6.1)-(6.7) becomes periodic as \( t \to \infty \) with length of period identical to the period of \( u \). In some cases, depending on parameters and the function \( u \), as in the steady state situation the limiting solution
is nonzero. In other cases the thickness of biofilm goes to zero, i.e., the only periodic solution for such a set of parameters is the trivial solution.

Our goal is to study how the length of the period influences the resulting periodic solution. We introduce the following notation. Let \( u \) be a positive, periodic, continuous (or more generally piecewise continuous) function with period 1. For any positive number \( \omega > 0 \) we introduce the function

\[
u^\omega(t) = u(\omega t), \quad \text{for } t \in R.
\] (6.9)

Note that \( u^\omega \) is a periodic function of period \( 1/\omega \) and hence, \( \omega \) is the frequency.

Denote by \( B^\omega, X_u^\omega, X_{ud}^\omega, X_a^\omega, v^\omega, L^\omega \) the corresponding periodic solution of the system (6.1)-(6.7). We would like to study what happens as \( \omega \to 0^+ \) and \( \omega \to \infty \).

We claim the following:

**Theorem 6.1** Let \( u > 0 \) and let \( u_0 = \int_0^1 u(t)dt \) be the average value of \( u \) over \([0, 1]\).

Then any increasing sequence \( \omega_1, \omega_2, \omega_3, \ldots \) such that \( \omega_n \to \infty \) has a subsequence \((\omega_n)_i \in N\) satisfying

\[
L^\infty = \lim_{i \to \infty} L^{\omega_n}(t) \quad \text{uniformly for all } t > 0,
\]

and all functions \( B^{\omega_n}(x, t), X_u^{\omega_n}(x, t), X_{ud}^{\omega_n}(x, t), X_a^{\omega_n}(x, t), v^{\omega_n}(x, t) \)
converge for \( x \in [0, L^\infty) \) and \( t > 0 \) to functions \( B^\infty(x), X_u^\infty(x), X_{ud}^\infty(x), X_a^\infty(x), X_{ad}^\infty(x), v^\infty(x) \) that are independent of \( t > 0 \). In the case of the function \( B^\infty \) the
convergence is only in the weak sense, while all other functions converge locally uniformly in $x$. Moreover, these functions satisfy on the interval $[0, L^\infty]$ the equations of a steady-state solution (c.f. Chapter 5) with the boundary condition $B^\infty(L^\infty) = u_0$.

**Remark:** It is possible that two different subsequences of the original sequence $\omega_1, \omega_2, \omega_3, \ldots$ converge to two different limits. This can only happen however, if for the constant dosing with dose $u_0$ and parameters $\alpha, \gamma, \lambda, \delta, \phi$ there is non-uniqueness of steady-state solutions, i.e., there is more than one stable steady-state solution (see Figure 8 for example). If there is uniqueness of steady-state solutions, the limit of the sequence is necessarily unique.

**Proof of Theorem 6.1** All functions $L^{\omega_n}$ are uniformly bounded from above by $\max \{ L(0), \frac{\alpha}{\sigma} \}$ (c.f. Lemma 3.2). Recall also that we have shown there that for $L(t) > \frac{\alpha}{\sigma}$ we have $\frac{dL}{dt} < 0$ from which it would follow that $L(P) < L(0)$ if we had that $L(0) > \frac{\alpha}{\sigma}$. But $L(P) = L(0)$ since our solution has period $P$, hence $L(t) \leq \frac{\alpha}{\sigma}$ for all $t \geq 0$.

We claim that (6.7) implies

$$-\frac{\alpha^2}{\sigma} \leq -\sigma(L^{\omega_n}(t))^2 \leq \frac{dL^{\omega_n}}{dt} = v(L^{\omega_n}) - \sigma(L^{\omega_n})^2 \leq v(L^{\omega_n}) \leq \alpha L^{\omega_n}(t) \leq \frac{\alpha^2}{\sigma}.$$ 

Hence the functions $L^{\omega_n}$ are uniformly Lipschitz in $t$, hence equicontinuous. By Ascoli theorem there exist subsequence $(n_i)$ such that the sequence of functions $L^{\omega_{n_i}}$ is convergent. Since the length of the period goes to zero the limit must be a constant
function which we call $L^\infty$. If this limit is zero, the proof is complete - in this case $L^\infty = 0$ which corresponds to the trivial steady state solution.

The second case is more interesting. It follows from above, that $L^\infty$ is constant in $t$. Hence, since functions $B^{\omega_n}$ are explicitly determined by $L^{\omega_n}$, we have that

$$\frac{\cosh(\phi x)}{\cosh(\phi L^{\omega_n}(t))} \to \frac{\cosh(\phi x)}{\cosh(\phi L^\infty)}$$

uniformly in $x$

and

$$u^{\omega_n}(t) \to u_0 \text{ weakly, i.e., for any } \psi \in C^\infty_0(R): \int u^{\omega_n}(t)\psi(t)dt \to u_0 \int \psi(t)dt,$$

as $\omega_n \to \infty$. This follows immediately from the fact that $u_0$ is the average value of each function $u^\omega$. From this the product function $B^{\omega_n}(x, t) = u(t)\frac{\cosh(\phi x)}{\cosh(\phi L^{\omega_n}(t))}$ will converge weakly to $B^\infty(x) = u_0\frac{\cosh(\phi x)}{\cosh(\phi L^\infty)}$, where the weak convergence is understood in $t$, as defined above.

Now for each $\omega_n$, let us introduce new variables which we denote by $\tilde{B}^i$, $\tilde{v}^i$, $\tilde{X}_u^i$, $\tilde{X}_a^i$, $\tilde{X}_{ud}^i$, $\tilde{X}_{ad}^i$ that will only be functions of variable $x$ and not of $t$. We will define them on the interval $[0, \tilde{L}^i]$, where

$$\tilde{L}^i = \inf_t L^{\omega_n}(t).$$
It follows immediately that $\tilde{L}^i \to L^\infty$ as $i \to \infty$. The mentioned functions are defined via averaging over the period, which for index $i$ is $\omega_{n_i}^{-1}$, i.e.,

$$
\tilde{X}_a^i(x) = \omega_{n_i} \int_0^{1/\omega_{n_i}} X_{a^n_i}(x, t) dt,
\tilde{X}_{ad}^i(x) = \omega_{n_i} \int_0^{1/\omega_{n_i}} X_{ad^n_i}(x, t) dt,
\tilde{B}^i(x) = \omega_{n_i} \int_0^{1/\omega_{n_i}} B^{n_i}(x, t) dt,
\tilde{v}^i(x) = \omega_{n_i} \int_0^{1/\omega_{n_i}} v^{n_i}(x, t) dt.
$$

(6.10)

To obtain equations that will be satisfied by these new functions, we will integrate equations (6.1)-(6.6) over the interval $[0, \omega_{n_i}^{-1}]$ and average (i.e., multiply by $\omega_{n_i}$). We have

$$
\tilde{B}^i(x) = \omega_{n_i} \int_0^{1/\omega_{n_i}} u(t) \frac{\cosh(\phi x)}{\cosh[\phi L^{n_i}(t)]} dt = u_0 \frac{\cosh(\phi x)}{\cosh[\phi L^i]} + e_1,
$$

(6.11)

$$
\tilde{v}^i \frac{\partial \tilde{X}_a^i}{\partial x} = -(\tilde{B}^i + \lambda) \tilde{X}_a^i + \alpha (1 - \tilde{X}_a^i - \tilde{X}_a^i) \tilde{X}_a^i + \gamma \tilde{X}_a^i + e_2
$$

(6.12)

$$
\tilde{v}^i \frac{\partial \tilde{X}_{ad}^i}{\partial x} = \tilde{B}^i \tilde{X}_a^i - \alpha (\tilde{X}_a^i + \tilde{X}_a^i) \tilde{X}_{ad}^i + e_3
$$

(6.13)

$$
\tilde{v}^i \frac{\partial \tilde{X}_a^i}{\partial x} = \lambda \tilde{X}_a^i - \delta \tilde{B}^i \tilde{X}_a^i + \alpha (1 - \tilde{X}_a^i - \tilde{X}_a^i) \tilde{X}_a^i - \gamma \tilde{X}_a^i + e_4
$$

(6.14)

$$
\tilde{v}^i \frac{\partial \tilde{X}_{ad}^i}{\partial x} = \delta \tilde{B}^i \tilde{X}_a^i - \alpha (\tilde{X}_a^i + \tilde{X}_a^i) \tilde{X}_{ad}^i + e_5
$$

(6.15)

$$
\frac{\partial \tilde{v}^i}{\partial x} = \alpha (\tilde{X}_a^i + \tilde{X}_a^i)
$$

(6.16)

$$
0 = v(\tilde{L}^i, \ldots) - \sigma [\tilde{L}^i]^2 + e_6.
$$

(6.17)
Here $e_1, e_2, \ldots, e_6$ are the error terms that arise from nonlinear terms. We do not write all of them explicitly, but as an example we look in detail at

$$
\omega_{ni} \int_0^{1/\omega_{ni}} v^{\omega_{ni}} \frac{\partial X_u^{\omega_{ni}}}{\partial x} dt = \omega_{ni} \int_0^{1/\omega_{ni}} \tilde{v} \frac{\partial X_u^{\omega_{ni}}}{\partial x} dt + \omega_{ni} \int_0^{1/\omega_{ni}} (v^{\omega_{ni}} - \tilde{v}) \frac{\partial X_u^{\omega_{ni}}}{\partial x} dt
$$

where $|e| \leq \| \tilde{v} - v^{\omega_{ni}} \|_\infty \left\| \frac{\partial X_u^{\omega_{ni}}}{\partial x} \right\|_\infty$. Similar estimates are worked out for all other nonlinear terms. In total we obtain

$$
|e_1| + \cdots + |e_6| \leq C \| \tilde{L} - L^{\omega_{ni}} \|_\infty + C \| \tilde{v} - v^{\omega_{ni}} \|_\infty \left\| \frac{\partial \tilde{X}^i}{\partial x} \right\|_\infty + C(1 + \| B \|_\infty) \left\| \tilde{X}^i - X^{\omega_{ni}} \right\|_\infty.
$$

(6.18)

Here $\tilde{X}^i$ represents all variables $\tilde{X}_a^i, \tilde{X}_u^i$ etc. All of what follows is based on the following Lemma:

**Lemma 6.1** There exists a constant $K > 0$ depending only on constants $\alpha, \phi, \lambda, \gamma, \sigma$ and $\| u \|_\infty$ such that the periodic solutions of (6.1)-(6.7) are Lipschitz continuous in variable $x$ with Lipschitz constant at most $K$, that is

$$
\max \left\{ \left\| \frac{\partial X_a}{\partial x} \right\|_\infty, \left\| \frac{\partial X_{ad}}{\partial x} \right\|_\infty, \left\| \frac{\partial X_u}{\partial x} \right\|_\infty, \left\| \frac{\partial X_{ud}}{\partial x} \right\|_\infty \right\} \leq K.
$$

(6.19)

The crucial part of the claim in this Lemma is that the bound on the Lipschitz norm is uniform and only depends on the constants and $L^\infty$ norm of $u$. We will not prove it, since this Lemma is closely connected with the question of existence of periodic solutions which we also did not do. However, the proof would go the same as a similar
proof that establishes that the steady state solution is also Lipschitz in $x$. We did not do it explicitly, as it was not necessary, but in the last part of the proof of the existence of steady state solution we derived an estimate on the distance $\rho$ of two steady state solutions in the form $\frac{d\rho}{dx} \leq F(\rho)$. A slight modification of this estimate gives a uniform bound on the $\frac{d}{dx}$ derivative of the solution, which implies the function is Lipschitz. Naturally, the estimates in the periodic case are even more complicated. Indirectly, we also have confirmation of this lemma on the numerical level.

To get back to our proof, once we have these estimates, we use (6.2)-(6.5) to conclude that for some $M$ independent of $i$ we also have that

$$\max \left\{ \left\| \frac{\partial X_{\omega ni}^a}{\partial t} \right\|_\infty, \left\| \frac{\partial X_{\omega ni}^a}{\partial t} \right\|_\infty, \left\| \frac{\partial X_{\omega ni}^u}{\partial t} \right\|_\infty, \left\| \frac{\partial X_{\omega ni}^{ud}}{\partial t} \right\|_\infty \right\} \leq M. \quad (6.20)$$

Using the fact that functions $X_{\omega ni}^a$, $X_{\omega ni}^u$, $X_{\omega ni}^{ad}$ and $X_{\omega ni}^{ud}$ are periodic in $t$ with period $\omega^{-1}_{ni}$, we then conclude that the oscillation (difference between sup and inf values) of these four functions is at most $M\omega^{-1}_{ni} \to 0$ as $i \to \infty$. It follows from (6.18) that

$$|e_1| + \cdots + |e_5| \leq C\omega^{-1}_{ni}, \quad (6.21)$$

where $C$ is a constant depending only on the parameters of the equation and $\|u\|_\infty$.

Now we choose a subsequence a second time. The equations (6.12), (6.14) and (6.16) look exactly as equations for a steady state solution we studied extensively before, plus some error terms. As we have shown, the solutions of these equation are all uniformly bounded and equicontinuous (Lemma 6.1), hence by the Ascoli Theorem
there is a convergent subsequence as \( i \to \infty \). On the other hand, as \( i \to \infty \) the error terms vanish and hence, the limit of this subsequence satisfies exactly the equations for steady-state solution. Let us call this limit \( X_u^\infty, X_a^\infty, v^\infty \). The domain of these functions is the interval \([0, L^\infty)\).

So far we have uniform convergence of \( \tilde{X}_{ij}^i \) to \( X_u^\infty \), of \( \tilde{X}_{ij}^a \) to \( X_a^\infty \) and of \( \tilde{v}^i \) to \( v^\infty \), where \((i_j)_{j \in \mathbb{N}} \) is the selected subsequence. Recalling (6.20), we can drop the tilde and get that also \( X_{ij}^{\omega_{ij}}(x, t) \) converges to \( X_u^\infty(x) \) uniformly for arbitrary \( t \) (and similarly for other functions). This is the sought subsequence. ■

**Remark:** One of our model restrictions included the assumption that the characteristic time for diffusion is small compared to the disinfection time of unadapted cells \( (\epsilon \ll 1) \). In case of high frequency dosing, however, the opposite is true, i.e., the parameter \( \epsilon \) is large. Hence, equation (6.1) changes to

\[
\epsilon \frac{\partial B}{\partial t} = \frac{\partial^2 B}{\partial x^2} - \phi^2 B.
\]

Taking the average of the previous equation over the period \([0, 1/\omega]\) yields

\[
\frac{\partial^2 \tilde{B}}{\partial x^2} = \phi^2 \tilde{B},
\]

where \( \tilde{B} \) is the average function

\[
\tilde{B} = \omega \int_0^{1/\omega} B(x, t)dt.
\]

An argument similar to Lemma 6.1 for function \( B \) implies

\[
\|B - \tilde{B}\|_\infty \leq C \omega^{-1},
\]
where $C$ is some Lipschitz constant depending only on parameters $\alpha, \phi, \lambda, \gamma, \sigma$ and $\|u\|_{\infty}$. It follows that the high frequency limit for $\tilde{B}$ is the same as for $B$. Hence, the conclusion of Theorem 6.1 remains unchanged.

Now we have a look at the other limit $\omega \to 0^+$. In this case the length of period goes to infinity. We will formulate the upcoming Theorem 6.2 in the simplest case - when for each $u_0$ there is a single nonzero steady-state solution. Theorem 6.2 can be modified for the more general case, we, however, choose not to do it to keep the proof reasonably short.

**Theorem 6.2** Let $u$ be a continuous periodic function of period 1 and consider as in (6.9) the functions $u^\omega$ of period $1/\omega$ and their corresponding periodic solutions $B^\omega, X_u^\omega, X_{ad}^\omega, X_a^\omega, \nu^\omega, L^\omega$ of the system (6.1)-(6.7). Assume that for all $t$: $u(t) \in [A_1, A_2]$ and that for each $u_0 \in [A_1, A_2]$ there is a unique nonzero continuous steady-state solution with boundary condition $B(L) = u_0$. Let $J(u_0)$ and $J_L(u_0)$ be the values of the two functionals (1.35)-(1.36) for this steady-state solution. Then

$$\lim_{\omega \to 0^+} J^\omega = \lim_{\omega \to 0^+} \omega \int_0^{1/\omega} \int_0^{L^\omega(t)} (X_u^\omega(x, t) + X_{ad}^\omega(x, t)) dx dt = \int_0^1 J(u(t)) dt,$$

$$\lim_{\omega \to 0^+} J_L^\omega = \lim_{\omega \to 0^+} \omega \int_0^{1/\omega} L^\omega(t) dt = \int_0^1 J_L(u(t)) dt. \quad (6.22)$$

**Proof of Theorem 6.2:** Since $\omega \to 0^+$ means that the length of period goes to infinity and $u$ is a periodic function, it follows that the stretched function $u^\omega$ is extremely slowly varying, i.e. given $\varepsilon > 0$ and an arbitrary large $M > 0$ one can find
sufficiently small $\omega > 0$ such that

$$|u^\omega(t + \tilde{t}) - u^\omega(t)| < \varepsilon, \quad \text{for all } t \in R \text{ and } |\tilde{t}| < M.$$  

Hence, for any fixed $t$ the function $u^\omega$ on the large interval $[t - M, t + M]$ is almost constant and approximately equal to $u^\omega(t)$. What this means is that regardless of what the values of $X_u^\omega$, $X_a^\omega$, $L^\omega$ are at the time $t - M$, as the time progresses to $t$, these functions will be closer and closer to the values of functions for the steady-state solution with boundary value $u^\omega(t)$. Recall that we assume there is a unique stable nonzero steady state solution with this boundary condition. Therefore, the same will be true about the values of functionals $J$ and $J_L$, i.e., for some small $\delta > 0$ at time $t$:

$$\left| \int_0^{L^\omega(t)} (X_u^\omega(x, t) + X_a^\omega(x, t))dx - J(u^\omega(t)) \right| < \delta,$$

$$|L^\omega(t) - J_L(u^\omega(t))| < \delta.$$  \hspace{1cm} (6.23)

Here $\delta$ is a function of $\omega$ and $\delta \rightarrow 0+$ as $\omega \rightarrow 0+$. Once we have this estimate, we integrate over the time interval $[0, 1/\omega]$ and average (divide by $1/\omega$). This leads to

$$\left| \omega \int_0^{1/\omega} \left( X_u^\omega(x, t) + X_a^\omega(x, t) \right)dx dt - \omega \int_0^{1/\omega} J(u^\omega(t))dt \right| < \delta,$$

$$\left| \omega \int_0^{1/\omega} L^\omega(t)dt - \omega \int_0^{1/\omega} J_L(u^\omega(t))dt \right| < \delta.$$
Now, we realize that \( \omega \int_{0}^{1/\omega} J(\omega u(t)) dt = \int_{0}^{1} J(u(t)) dt \) and \( \omega \int_{0}^{1/\omega} J_L(\omega u(t)) dt = \int_{0}^{1} J_L(u(t)) dt \) and hence, the conclusion (6.22) holds. \( \blacksquare \)

**Remark:** An important question is which dosing strategy is more favorable - periodic dosing or constant dosing? It follows from Theorems 6.1 and 6.2 that if

\[
\lim_{\omega \to 0^+} J_\omega = \int_{0}^{1} J(u) dt < J(u_0),
\]

then periodic dosing is more effective than constant dosing for small frequencies \( \omega \). We can actually be even more specific, since (6.24) is essentially a geometrical condition. Intuitively, say, we have a simple function \( u(t) \) that only attains two values; \( u_0 - h \) on the intervals \([n, n + 1/2)\) and \( u_0 + h \) on \([n + 1/2, n + 1)\) for integer \( n \). Such function has average \( u_0 \) and the condition (6.24) is equivalent to

\[
\frac{1}{2}(J(u_0 - h) + J(u_0 + h)) < J(u_0).
\]

But this is just a condition on concavity of the function \( J \). This leads to the following statement:

**Proposition 6.1** Assume that \( J \) is a concave down function on the whole interval \([A_1, A_2]\) and \( u(t) \in [A_1, A_2] \). Then (6.24) holds, i.e., for sufficiently small frequencies \( \omega \) the periodic dosing is more effective that the constant dosing with dose \( u_0 \). Conversely, if \( J \) is concave up on the whole interval \([A_1, A_2]\) and \( u(t) \in [A_1, A_2] \), then for
sufficiently small frequencies $\omega$ the periodic dosing is guaranteed to be worse than the constant dosing with dose $u_0$.

Remark: In most (but not all) cases, we know that for large $u_0$ the functional $J$ must be concave up. The only exception is the case $\gamma < \alpha$ and $\delta = 0$, where for some sets of parameters it is possible to have $J'' < 0$ for large values of $u_0$ (c.f. the last section of Chapter 5, where asymptotics of $J$ and $J_L$ at $u_0 = \infty$ is worked out).

Sketch of the proof: We expand $J$ around $u_0$ using Taylor formula, i.e.,

$$J(u) = J(u_0) + J'(u_0)(u - u_0) + \frac{J''(\xi_u)}{2}(u - u_0)^2,$$

where $\xi_u$ is some number from the interval between $u$ and $u_0$. Next, we replace $u$ by $u(t)$ and integrate $J$ over interval $[0, 1]$.

$$\lim_{\omega \to 0^+} J_\omega = \int_0^1 J(u(t))dt = J(u_0) + \int_0^1 \frac{J''(\xi_u(t))}{2}(u(t) - u_0)^2dt. \quad (6.25)$$

From this the claim follows: clearly, if $J'' < 0$ the right-hand side is smaller than $J(u_0)$ for small amplitudes. On the other hand, if $J'' > 0$ the opposite is true. ■

Remark: To illustrate biological meaning of the assumption of Proposition 6.1 ($J'' < 0$), let us consider the following situation:

At the point $u_0$ the linear approximation of the functional $J$ is given by a tangent line at the point $u_0$ with equation $\ell = J(u_0) + J'(u_0)(u - u_0)$. The assumption $J''(u_0) < 0$ mathematically means that near $u_0$ the graph of $J$ is below the tangent line $\ell$. What it means biologically, is that near $u_0$ the reaction of biofilm to the
increase in the biocide dose faster than linear. That is, if we increase dose near \( u_0 \), the reduction in biocide thickness is higher than expected linear response (given by \( \ell \)).

On the other hand, \( J''(u_0) > 0 \) means exactly the opposite, i.e., the biofilm is reacting to the increase in the biocide dose slower than linear.

To illustrate Theorems 6.1 and 6.2, we choose for our numerical simulations

\[
  u(t) = u_0 + A \sin(2\pi t),
\]

hence

\[
  u(\omega)(t) = u_0 + A \sin(2\pi \omega t),
\]

where \( \omega \) is the frequency and \( A \) is the amplitude. We also introduce the notation that \( J^\omega, J_L^\omega \) are the functionals corresponding to periodic boundary data \( u^\omega(t) \). Our goal is to numerically verify the results of Theorems 6.1 and 6.2, i.e., numerically compute the limits

\[
  \lim_{\omega \to 0^+} J^\omega = \omega \int_0^{1/\omega} J(u_0 + A \sin(2\pi \omega t))dt
\]

and

\[
  \lim_{\omega \to \infty} J^\omega = J(u_0)
\]

(analogously for \( J_L \)) and compare them with the results of our numerical computations of the periodic solutions.

*Figure 15 a).* Minimizing functionals \( J, J_L \) versus frequency \( \omega \) for value of the parameters \( u_0 = 5, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1 \). The upper horizontal line
represents the value of $J, J_L$ for constant dosing $u_0$ (by Theorem 6.1) and the lower horizontal line represents the value of the integral from Theorem 6.2. We can observe that for small frequencies periodic dosing is more effective than constant dosing. This and other plots numerically confirm that for high frequencies constant dosing is preferable to periodic dosing, i.e. for large $\omega$ the functional curves are ‘above’ the upper horizontal line. We, however, do not have an analytical explanation for this phenomenon. An asymptotic expansion in frequency $\omega$ might be capable of checking this observation.

Notice also the tiny ranges on all four plots (Figures 15 a) and b)). To explain this we look at Figure 8 which plots the function $J_L = L$ for the same set of parameters when constant dosing is used. Notice that near $u_0 = 5$ both these functions are very flat - their second derivative is negative, but very close to zero. From this it follows that the term containing $J''$ in (6.25) is small. Hence, the improvement periodic dosing brings is negligible.

Figure 15 b). Minimizing functionals $J, J_L$ versus amplitude $A$ for the same value of the parameters $u_0, \phi, \lambda, \alpha, \gamma, \sigma, \delta$ as Figure 15 a) and $\omega = 1/2\pi$. Just as before, the horizontal line represents the value of $J, J_L$ for constant dosing when $A = 0$. Note that for $\omega = 1/2\pi$ the value of $J$ in Figure 15 a) is slightly above the upper horizontal line, while the value of $J_L$ in Figure 15 a) is below the upper horizontal line. Hence, for functional $J$ changing the amplitude is more effective than constant dosing
Figure 15. a) Minimizing functionals $J, J_L$ versus frequency $\omega$ for value of the parameters $A = 1, u_0 = 5, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1$. For small frequencies periodic dosing is slightly more effective than the constant dosing. Horizontal lines represent limit values computed from Theorems 6.1 and 6.2. b) Minimizing functionals $J, J_L$ versus amplitudes for the same value of the parameters as in Figure 15 a) and $P = 2\pi$. Unlike the other functional $J_L$, functional $J$ for periodic dosing is less effective than constant dosing.
(the functional curve is above the horizontal line), since for this particular \( \omega \): \( J^\omega < J(u_0) \). However, for the other functional \( J^L_L > J_L \) and an increase in the amplitude only makes the situation more unfavorable. This is caused by the phenomena we already mentioned above - for large frequencies \( \omega \) both \( J^\omega \) and \( J^L_L \) are larger than \( J(u_0), J_L(u_0) \), respectively. On the other hand, for small frequencies, the opposite is true, as \( J \) and \( J_L \) are concave down near \( u_0 = 5 \). The middle range of \( \omega \) \( (\omega = o(1)) \) is exactly when the change happens - when periodic dosing becomes better than the constant dosing. The chosen \( \omega = 1/2\pi \) is therefore special in some sense - for one functional \( J \), it is already in the region where periodic dosing is better, but for the other functional \( J_L \), the periodic dosing is still worse. Notice also that both curves on Figure 15 b) look quadratic in the amplitude \( A \). This is not an accident, if we look back at (6.25) we see that

\[
\lim_{\omega \to 0^+} J^\omega - J(u_0) \approx \frac{J''(u_0)}{2} A^2 + o(A^2),
\]

i.e., for small frequencies \( \omega \) this difference is indeed quadratic in \( A \). However, our \( \omega \) is not really small \( (o(1)) \), so this argument is only an indication why the difference is quadratic in \( A \). Unfortunately, our understanding of these frequencies is really the weakest. We know much more what happens for \( \omega \gg 1 \) and \( \omega \ll 1 \).

When \( \lim_{\omega \to 0^+} J^\omega > J(u_0) \), i.e., \( J \) is concave up at \( u_0 \), periodic dosing is less effective than constant dosing. This happens for example for values of the parameters \( A = 1, u_0 = 1.5, \phi = 1, \lambda = 1, \alpha = 1, \gamma = 2, \sigma = 0.4, \delta = 0.1 \). Figure 16 shows that
both functional curves are above the horizontal line corresponding to the value of functionals for constant dosing. Figure 16 is also an example when Theorem 6.2 cannot be used, i.e. we cannot compute $\lim_{\omega \to 0^+} J_\omega$ directly by using this Theorem.

The reason is that in the interval $u \in (u_0 - A, u_0 + A)$ there are values of $u$ for which the only steady-state is zero, i.e., the key assumption of existence of a nonzero steady state solution is violated.

Figure 16. Minimizing functionals $J, J_L$ versus frequency $\omega$ for value of the parameters $A = 1, u_0 = 1.5, \phi = 1, \lambda = 1, \alpha = 1, \gamma = 2, \sigma = 0.4, \delta = 0.1$. In this case periodic dosing is less effective than constant dosing for both functionals.
functionals for periodic dosing (with amplitude 1) and optimal frequency, i.e., for each $u_0$ we found the best frequency minimizing the functional.

Notice however, that despite decimalization in the frequency the functional curves for both periodic and constant dosing are almost identical, in fact they cannot be distinguished, unless magnified. Hence, we only plotted the differences. We can see here that these functionals differ significantly only for larger values of $u_0$. For small values of $u_0$ periodic dosing is only marginally better. The reason for this is the the graph of $J$ (c.f. (8)) is relatively flat, i.e., its second derivative is small. Only for larger values of $u_0$ does the second derivative becomes larger.

Figure 17. Relative error between $J$ and $J_{steady}$ as well as $J_L$ and $J_{steady}$ versus biocide dose $u_0$ for value of the parameters $A = 1, \phi = 1, \lambda = 1, \alpha = 1, \gamma = 2, \sigma = 0.4, \delta = 0.1$ in the case of periodic dosing and constant dosing. The errors are plotted on a log-scale. The pictures show that periodic dosing is slightly more advantageous, but the functionals significantly differ only for larger values of $u_0$.  
Now we study same the situation as in Theorems 6.1 and 6.2, but with the assumption that the periodic function \( u \) is vanishing on a set of positive measure. Say, on the interval \([0, 1]\) the function \( u \) is piecewise continuous and nonnegative. In addition, let the lebesgue measure of the set \( \{ t \in [0, 1]; u(t) > 0 \} \) be \( \mu \), where \( \mu \in (0, 1) \). The function we study in our numerical simulations is the periodic extension of a function \( u \) defined by \( u(t) = u_0/\mu \) on \([0, \mu]\) and \( u(t) = 0 \) on \((\mu, 1]\).

The reason this type of dosing is significantly different than the constant and periodic dosing types studied above is that for \( u_0 = 0 \) the important parameter \( \lambda \) (unadapted-adapted reversion rate) is zero. Recall, that \( \lambda(u_0) \) defined in Chapter 1 is in fact a step function, constant and positive everywhere except the point \( u_0 = 0 \) where it vanishes. As we will see in Theorem 6.3, the ‘effective’ \( \lambda \) for on and off dosing will be just the product of \( \mu \) and the \( \lambda \) for constant dosing, where \( \mu \) is defined above. The ‘effective’ \( \lambda \) is smaller than the original \( \lambda \).

Denote as before \( B^\omega, X^\omega_u, X^\omega_{ad}, x^\omega, L^\omega \) to be the periodic solutions for the re-scaled functions \( u^\omega(t) = u(\omega t) \). We claim the following:

**Theorem 6.3** Let \( u_0 = \int_0^1 u(t)dt \). Then any increasing sequence \( \omega_1, \omega_2, \omega_3, \ldots \) such that \( \omega_n \to \infty \) has a subsequence \((\omega_{n_i})_{i \in \mathbb{N}} \) satisfying

\[
L^\infty = \lim_{i \to \infty} L^{\omega_{n_i}}(t) \quad \text{uniformly for all } t > 0,
\]
and all functions $B^{\omega n_1}(x, t)$, $X_a^{\omega n_1}(x, t)$, $X_u^{\omega n_1}(x, t)$, $X_{ad}^{\omega n_1}(x, t)$, $v^{\omega n_1}(x, t)$ converge for $x \in [0, L^\infty]$ and $t > 0$ to functions $B^\infty(x)$, $X_a^\infty(x)$, $X_u^\infty(x)$, $X_{ad}^\infty(x)$, $X_{ud}^\infty(x)$, $v^\infty(x)$ that are independent of $t > 0$. In the case of function $B^\infty$ the convergence is only in the weak sense, all other functions converge uniformly in $x$. Moreover, these functions satisfy on the interval $[0, L^\infty]$ the equations of a steady-state solution (c.f. Chapter 5) with the boundary condition $B^\infty(L^\infty) = u_0$ and with coefficient $\lambda$ replaced by $\mu \lambda$.

**Remark:** Just like in the case of Theorem 6.1, it is possible that two different subsequences of the our original sequence $\omega_1, \omega_2, \omega_3, \ldots$ converge to two different limits. This only happens if for the constant dosing with dose $u_0$ and parameters $\alpha, \gamma, \lambda, \delta, \phi$ there is non-uniqueness of steady-state solutions, i.e., there is more than one stable steady-state solution. If there is uniqueness of steady-state solutions.

**Proof of Theorem 6.3:** The proof is essentially identical to the proof of Theorem 6.1. The only modification comes from the fact that in equation (6.4) the coefficient $\lambda$ changes to zero on the set where $u^k$ is vanishing. Realizing what this means for the averaging function $\tilde{X}_u^\omega$ we see that

$$\omega \int_{[0,1/\omega] \cap \{\omega > 0\}} \lambda X_a^\omega(x, t) dt \to \mu \lambda \tilde{X}_u^\omega(x), \quad \text{as } \omega \to \infty.$$ 

From this the claim follows. ■

This Theorem is a strong indication that on and off dosing is a better strategy than constant dosing, since smaller $\lambda$ (effectively $\lambda$ is replaced by $\mu \lambda$ in the equations)
means slower adaptation of cells to antimicrobials. The other important parameter \( \gamma \) (reversion rate from adapted to unadapted cells) remains the same. Hence, what happens is that the ratio \( X_a/X_u \), which for small \( u_0 \) is approximately \( \lambda/\gamma \) (see Chapter 5), becomes smaller (about \( \mu \) times smaller). Hence, the biocide kills the biofilm bacteria more effectively as there are more unadapted cells. Another view we might take is that since the reversion rate \( \gamma \) remains constant during the withdrawal time, the adapted cells which were created during the dosing time, revert back to unadapted cells during the withdrawal time. This is particularly noticeable when \( \delta = 0 \) (adapted cells do not die). Such an example with \( \delta = 0 \) is Figure 18.

![Figure 18](image_url)

Figure 18. Minimizing functionals \( J, J_L \) versus \( u_0 \) for value of the parameters \( \phi = 1, \lambda = 1, \alpha = 1, \gamma = 2, \sigma = 0.4, \delta = 0, \mu = 0.1, P = 1 \). Functional curves for on and off dosing are compared with functional curves for constant dosing \( J^{steady}, J_L^{steady} \) when \( \lambda = 1 \) and \( J^\lambda, J_L^\lambda \) when \( \lambda = 0.1 \).
The situation is even more pronounced for larger values of $u_0$. In fact, there are values of $u_0$ for which the constant dosing at the level $u_0$ would not eliminate the biofilm (in the $t \to \infty$ limit), but the on and off dosing does. Figure 18 shows this case. For $u_0$ between values 1.2 and 2 the topmost curves for constant dosing $J^{steady}$ and $J_L^{steady}$ are positive ($\lambda = 1$), but the (dashed) curves corresponding to on and off dosing with $\mu = 0.2$ are vanishing. For comparison, the third pair of curves correspond to constant dosing with value of unadapted to adapted reversion equal to $\lambda \mu = 0.2$. Note the close match of these two curves with the curves for on and off dosing. This shows how much better the on and off dosing strategy is compared to the constant dosing. It also shows how valuable Theorem 6.3 is - although it discusses the limit in frequency $\omega \to \infty$, a very close match is actually achieved even for frequency $\omega = 1$.

In Figure 19 we keep the amount to dose $D$ but we change the frequency $\omega$ of the dosing. Plotted are the functionals $J, J_L$ versus frequency in a log-scale for value of the parameters $u_0 = 5, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1, \mu = 0.2, P = 1$. By Theorem 6.3, $\mu = 0.2$ and so $\mu \lambda = 0.2$ is the ‘new’ $\lambda$ for which steady-state solutions are computed. The horizontal asymptotes correspond to the value of the steady-state functionals with $\lambda = 0.2$. The upper horizontal lines are the values of the steady-state functionals for $\lambda = 1$. 
The following Theorem is an analogue of Theorem 6.2. In fact Theorem 6.2 still holds even for on and off dosing, even though we consider a periodic function $u$ that is not continuous everywhere, only piecewise continuous. For simplicity, we formulate the next Theorem only for the simplest possible dosing.

**Theorem 6.4** Let $u_0 > 0$ be given and let $\mu \in (0, 1)$. Consider a periodic extension of the function $u$ defined by $u(t) = u_0/\mu$ on $[0, \mu]$ and $u(t) = 0$ on $(\mu, 1]$. Assume that for the value $u_0/\mu$ there is a unique nonzero continuous steady-state solution with boundary condition $B(L) = u_0/\mu$. Let $J(u_0/\mu)$ and $J_L(u_0/\mu)$ be the values of
the two functionals (1.35)-(1.36) for this steady-state solution. Let $J_\omega$ and $J_L^\omega$ be the values of the same two functionals for the periodic dosing with boundary condition $w_\omega(t) = u(\omega t)$. Then

$$
\lim_{\omega \to 0^+} J_\omega = \mu J(u_0/\mu) + (1 - \mu) \frac{\alpha}{\sigma},
$$

$$
\lim_{\omega \to 0^+} J_L^\omega = \mu J_L(u_0/\mu) + (1 - \mu) \frac{\alpha}{\sigma}.
$$

(6.26)

Remark:  Note that

$$
\lim_{\mu \to 1^-} \mu J(u_0/\mu) + (1 - \mu) \frac{\alpha}{\sigma} = J(u_0).
$$

The limit $\mu \to 0+$ only makes sense if $\delta \to 0+$ and $\alpha > \gamma$ since in this case there is a nontrivial steady-state for all $u_0$ (this restriction is due to the assumption of Theorem 6.4). Hence, under these assumptions

$$
\lim_{\mu \to 0^+} \mu J(u_0/\mu) + (1 - \mu) \frac{\alpha}{\sigma} = \frac{\alpha}{\sigma}.
$$

Proof of Theorem 6.4:  We know explicitly the value of two functionals $J$ and $J_L$ when there is no dosing. This value is exactly $\frac{\alpha}{\sigma}$. The rest is just an application of Theorem 6.2. Our functions $w_\omega$ are discontinuous on a countable set. However, as $\omega \to 0+$, the distance between discontinuities goes to infinity. From this it is fairly easy to argue that they will not influence the limit $\omega \to 0+$. Indeed, consider for illustration just a single discontinuity, i.e., let $v(t)$ be a function such that $v(t) = 0$ on $(-\infty, 0)$ and $v(t) = u_0/\mu$ on $[0, \infty)$. Let $X_a$, $X_u$, \ldots, $v$, $L$ be the solution corresponding to such boundary data $v$ for $B$. Then for $t \in (-\infty, 0)$ the value of
both $J$ and $J_L$ for an fixed time $t$ is exactly $\frac{2}{\sigma}$. Once time becomes positive, for any given $\varepsilon > 0$ there exists some $M > 0$ with the property that for $t > M$ the values of $J$ and $J_L$ for an fixed time $t$ is $\varepsilon$-close to $J(u_0/\mu)$, $J_L(u_0/\mu)$, respectively. It follows that

$$\lim_{T \to \infty} \left[ \frac{1}{2T} \int_{-T}^{T} \int_0^{L(t)} (X_a(x,t) + X_u(x,t))dxdt - \frac{1}{2} \left( \frac{\alpha}{\sigma} + J(u_0/\mu) \right) \right] \leq \varepsilon,$$

with a similar claim for the other functional $J_L$. As $\varepsilon > 0$ was arbitrary the limit here is actually zero. This shows, that since the ‘transition’ time $M$ is bounded, but $T \to \infty$ (hence $M/T \to 0$), in the limit the discontinuity at zero does not play any role. The argument for a periodic function $u^\omega$ goes along this lines. Again there will be some fixed ‘transition’ time $M$ when the solution switches from one regime to the other. The period $P \to \infty$ (since $\omega \to 0^+$), so $M/P \to 0$. ■

The plots that follow illustrate the behavior of solutions for on and off dosing.

Figure 20. Cell-densities $X_u, X_{ud}, X_a, X_{ad}$ for value of the parameters $u_0 = 8.1, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1, \mu = 0.2, P = 1$. The corresponding plot of biofilm thickness $L$ is Figure 21 a).

Figure 21 a). Biofilm thickness $L$ as a function of time for values of the parameters $u_0 = 8.1, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1$. Recall the bifurcation diagram, Figure 8, where non-uniqueness of solutions was demonstrated for the same parameter values as in this plot. There were two stable steady-state solutions and one unstable. These stable steady-state solutions apparently create a trapping region which, once
Figure 20. Cell-densities $X_u, X_{ud}, X_a, X_{ad}$ for value of the parameters $u_0 = 8.1, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1, \mu = 0.2, P = 1$.

the solution enters, does not want to leave it. For $u_0 = 8.1$ the solution is trapped in this region and it stabilizes there. This solution exhibits fairly larger oscillations.

In Figure 21 b) the biocide dose $u_0 = 10.4$ is slightly larger, all the other parameters remain the same. The solution stays trapped in a similar trapping region as the previous solution for relatively long time interval (25, 150).

However, thanks to larger value of $u_0$ the value $L$ decreases sufficiently for the solution to leave the trapping region and then decay rapidly to zero. Note that in the trapping region the solution decays only very slowly and its oscillations become much larger. Once the solution leaves this region oscillations becomes much smaller.
Figure 21. a) Biofilm thickness $L$ for value of the parameters $u_0 = 8.1, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1, \mu = 0.2, P = 1$. b) $L$ for the same value of parameters as in the previous plot, except that $u_0 = 10.4$. 

(a) $u_0=8.1; \phi=1; \lambda=1; \alpha=2; \gamma=1; \sigma=0.4; \delta=0.1; \text{dosing time}/P=0.2; P=1$

(b) $u_0=10.4; \phi=1; \lambda=1; \alpha=2; \gamma=1; \sigma=0.4; \delta=0.1; \text{dosing time}/P=0.2; P=1$
Figure 22. Minimizing functionals $J, J_L$ versus frequency in a log-scale for value of the parameters $u_0 = 5, \phi = 1, \lambda = 1, \alpha = 2, \gamma = 1, \sigma = 0.4, \delta = 0.1, \mu = 0.2, P = 1$. The horizontal lines represent the value of the functionals for constant dosing with $\lambda = 0.2$ and $\lambda = 1$.

Figure 22. Minimizing functionals $J, J_L$ versus changing value of $\mu$ for parameters $\phi = 1, \lambda = 1, \alpha = 1, \gamma = 2, \sigma = 0.4, \delta = 0, \omega = 1$. What happens here can be easier explained by looking also at the Figure 18, where three different functional curves are presented. The one that is ‘above’ the other two curves corresponds to the steady-state functionals $J_{steady}, J_{L_{steady}}$ for the same parameter values as in Figure 22. Note that these steady-state functionals have biocide threshold around 2. For $u_0$ larger than this threshold the only steady-state is zero. Returning to Figure 22, we see that if $\mu$ is larger than 0.5, the actual biocide dose during dosing time is less than 2 (less than the dose needed for biofilm eradication). Hence, the functional curves look
almost horizontal on this interval. Once \( \mu \) is less than 0.5, the actual biocide dose is larger than 2 and is large enough to eradicate the biofilm as \( \mu \to 0^+ \). This is why the slope to the functional curves gets bigger for \( \mu < 0.5 \).

**Remark:** A remark is in order at this point. The limit \( \mu \to 0^+ \) is for practical purposes not feasible, as the dose \( u(t) \) essentially converges to a \( \delta \)-function. In real life, there is a limit on amount that can be delivered over a given time interval. To fix this problem, we would have to introduce disinfection saturation. That is, we would replace \( B \) in equations for \( X_a \) and \( X_u \) by expression of the form

\[
B_{\text{max}} \frac{B}{1 + B},
\]

where \( B_{\text{max}} \) is a number - the maximum possible dose of biocide that can be applied to the biofilm. Notice, that a term of this form would have no effect on small dosing amounts as for such amounts this term remains almost linear. However, dosing strategies of \( \delta \)-function type would be suppressed as the actual delivered dose is capped by \( B_{\text{max}} \).

**Figure 23 a).** Here we consider functionals \( J \) and \( J_L \) with the cost term \( cu_0 \), where \( c > 0 \) represents the cost of biocide. For each value of \( c \) (horizontal axis), four different values of \( u \) are computed - \( u_0 \) is the best value (i.e., value that minimizes the functional \( J \)) for a given \( c \) for the on and off dosing with values of parameters \( \phi = 1, \lambda = 1, \alpha = 1, \gamma = 2, \sigma = 0.4, \delta = 0, \mu = 0.1, \omega = 1 \). Similarly, \( u_{0L} \) is the minimum for the functional \( J_L \). For comparison, \( u_0^c \) and \( u_{0L}^c \) are the optimal values.
Figure 23. a) Optimal biocide dose versus the cost for the on and off dosing and the constant dosing. Value of the parameters: $\phi = 1$, $\lambda = 1$, $\alpha = 1$, $\gamma = 2$, $\sigma = 0.4$, $\delta = 0$, $\mu = 0.1$, $1/\omega = P = 1$. b) Minimizing functionals $J, J_L$ versus $u_0$ for the same value of the parameters as the previous plot and two different values of the cost $c$. Functional curves $J, J_L$ for the on and off dosing is plotted together with the functional curves $J_{\text{steady}}, J_{L\text{steady}}$ for the constant dosing (these are the almost straight curves that look like tangent lines at $u_0 = 0$).
when the constant dosing strategy is employed. Note that when on and off dosing is used, significantly smaller overall dose is required, hence even when the cost of biocide is higher, the on and off doing strategy is better than no treatment. This threshold is much smaller for the constant dosing, i.e., the ‘no treatment’ option becomes the best for much smaller biocide costs.

*Figure 23 b*). Functionals $J, J_L$ versus $u_0$ are plotted for two different values of the cost $c$ and same value of parameters as on Figure 23 a) for the on and off and the constant dosing. Again the constant dosing is represented by the top curves, i.e., it is worse than the on and off dosing.

*Figure 24* illustrates the effects of $\gamma$ - reversion back from adapted to unadapted cells. In this Figure we fix the dosing time to be 0.2 with the dose $u_0 = 5$, but the length of the withdrawal time $T$ is varied. $T = 0$ correspond to no withdrawal time, i.e., constant dosing.

We call this type of dosing *on and off dosing with bounded biocide dose*. What it represents is a dosing strategy when there is certain upper limit $U$ on the biocide, i.e., for all $t$: $0 \leq u(t) \leq U$. One possible scenario of such dosing that might be interesting is the case when biocide is administered to treat biofilm living inside another living organism. As this living organism may have negative reaction to large quantity of biocide, the maximal dose $U$ that can be given has to be limited.
It is *very important* to emphasize that this scenario neglects the cost of biocide treatment. Recall that the functionals (1.33)-(1.34) include the term

\[ D = \lim_{T \to \infty} \frac{1}{T} \int_{0}^{T} u(t) dt \]

which represents the average dose administered. When multiplied by \( c \), the number \( cD \) is the cost of biocide. In this example \( D \) changes as the withdrawal time \( T \) is varied. Thus, for different \( T \) the cost of treatment is different. For this reason *on and off dosing with bounded biocide dose* should not be *compared* with constant dosing. If we want to compare these two dosing strategies we *should* do it for functions \( u(t) \) that have the same \( D \).

In Figure 24 the average dose \( D \) decreases with increasing withdrawal time \( T \) and it equals to \( D = \mu u_0 = u_0/(0.2 + T) \), i.e., it decreases with \( T \). For the *set of parameters* chosen here functionals \( J \) and \( J_L \) have nontrivial minimum. It means that for this set of parameters when *on and off dosing with bounded biocide dose* is used, it is better to employ on and off dosing with particular withdrawal time \( T \) over constant dosing. There is a small paradox here - the on and off dosing is ‘cheaper’ (has smaller \( D \)) and yet, it produces better results. We *cannot expect* this to happen every time, in fact it does not.

To analytically explain Figure 24 we again use Theorem 6.3. By this Theorem, the on and off dosing is comparable with constant dosing when the dose \( u(t) \) and value of \( \lambda \) is averaged over the period (note the closeness of the full and dashed curves).
Figure 24. Given fixed dosing time of length 0.2 and fixed biocide dose \(u_0 = 5\), the withdrawal time was varied for value of the parameters \(\phi = 1\), \(\alpha = 1\), \(\lambda = 1\), \(\gamma = 0.1\), \(\sigma = 0.4\), \(\delta = 0\), \(\mu = 0.2\). The solid curves \(J, J_L\) represent the value of functionals for on and off dosing, while the dashed curves represent the value of functionals \(J^\mu, J_L^\mu\) for constant dosing with dose being \(\mu u_0\) (the average dose for withdrawal time \(T\)) and with \(\lambda\) being the effective value for such withdrawal time \(\mu \lambda\). Note the close match between these two curves.

Hence, what we have here are two effects that fight each other - one increases and the other one decreases the functionals. As the withdrawal time \(T\) increases, the average dose delivered over time decreases and it is equal to \(\mu u_0 = 5\mu/(T + 0.2)\). This of course pushes the values of functionals \(J, J_L\) up. On the other hand, the “effective” \(\lambda\), i.e., the average value of function \(\lambda\) over the period also decreases (equals to \(\mu \lambda = 0.2/(T + 0.2)\)), which in turn has opposite effect and pushes the values of functionals \(J, J_L\) down.
The result is Figure 24 - for small $T$ the effect of lowering $\lambda$ is stronger and $J$ decreases, for larger $T$ the effect of lowering the average value of dose becomes stronger and $J$ is increasing. Is is fairly easy to see that as $T \to \infty$, the functionals $J, J_L$ must be increasing since for large $T$ the average dose is close to zero and therefore both $J$ and $J_L$ are near their maximal value $\alpha/\sigma$.

When $\phi L \ll 1$ (thin biofilms) the situation is different (c.f. Figure 25). Here both $J$ and $J_L$ only have a trivial minimum at $T = 0$, both increase for $T > 0$ (hence constant dosing cannot be bettered).

Figure 25. Given fixed dosing time of length 0.2 and fixed biocide dose $u_0 = 5$, the withdrawal time was varied. The parameters are the same as in Figure 24 except that $\alpha$ is taken to be 0.1. The result is a thinner biofilm and hence, a 'flatter' function $B$. This makes both functionals $J, J_L$ monotone increasing.
To see this recall that \( B(x, t) = u(t) \frac{\cosh(\phi x)}{\cosh(\phi L)} \). Let us define the ‘flatness’ of \( B \) to be the ratio between the smallest and largest value of \( B \). Clearly, for it is just \( \frac{1}{\cosh(\phi L)} \).

The claim is that for ‘flat’ \( B \), i.e., when \( \frac{1}{\cosh(\phi L)} \) is near 1 (i.e., \( \phi L \ll 1 \)), both \( J \) and \( J_L \) are increasing in \( T \) on the whole interval.

**Proof:** We will prove our claim that when \( B \) is almost flat, i.e., \( B(x, t) \approx u(t) \), then \( J \) and \( J_L \) are monotone (increasing) in \( T \) (withdrawal time). Indeed, let’s consider the simplest case when \( B(x, t) = u(t) \). If the claim is true, the same will hold for any \( B \) almost flat, as the solutions of our equations depends on \( B \) continuously. When \( B \) is a constant, it is possible to compute explicitly the functionals \( J \) and \( J_L \) for ‘effective’ dose \( \mu u_0 \) and ‘effective’ unadapted-adapted reversion rate \( \mu \lambda \) (where \( \mu = \frac{0.2}{0.2 + T} \)). To keep things simple, consider only \( J_L \). We obtain

\[
J_L = \frac{1}{\sigma}(\alpha - \Gamma), \quad \text{where: } \Gamma = \frac{1}{2} \left( \gamma + \mu u_0 + \mu \lambda - \sqrt{(\gamma + \mu u_0 + \mu \lambda)^2 - 4\mu u_0 \gamma} \right).
\]

It is fairly easy to check that \( \Gamma \) is monotone increasing in variable \( \mu \), hence \( J_L \) is monotone decreasing in \( \mu \). But as said above the relation between \( T \) and \( \mu \) is \( 0.2/(T + 0.2) \), hence \( J_L \) must be monotone increasing in \( T \).

An interesting question is to find the optimal withdrawal time \( T \) that minimizes functionals \( J \) and \( J_L \). As we have seen before, for thin biofilms the optimal withdrawal time is zero. When nontrivial minimum exists, it can be found by solving \( \frac{dJ}{d\mu} = 0 \) (similarly for \( J_L \)). This equation is however too hard to solve explicitly, as there is
no known formula for $J, J_L$. Instead, we tried to find the minimum of approximate $J, J_L$ which should give us an approximate value of the minimum.

We used second order expansions in $x$ of the steady-state solutions $X_u, X_a$ with the 'effective' $\mu \lambda$ and biocide dose $\mu u_0$, i.e., we looked for $X_u, X_a$ in the form $X_u = X_u^{(0)}(\mu) + X_u^{(1)}(\mu)x + X_u^{(2)}(\mu)x^2 + O(x^3)$ and $X_a = X_a^{(0)}(\mu) + X_a^{(1)}(\mu)x + X_a^{(2)}(\mu)x^2 + O(x^3)$. Calculations show that $X_u^{(1)}(\mu) = X_a^{(1)}(\mu) = 0$. However, to have a nontrivial minimum we need second order coefficients (for $x^2$). Using Matlab we obtained explicit but extremely complicated formulas for $X_u^{(2)}(\mu)$ and $X_a^{(2)}(\mu)$ from which we computed the second degree approximation of $J_L$ and the minimum. Numerical verifications indicate that the nontrivial minimum obtained by this method is of the same order as the 'true' optimal minimum, however because of the extreme length of the final formula, we decided not to include it here.

In what follows, we look at the dependence of the optimal withdrawal time on the parameters $\lambda, \gamma$ and $\alpha$ obtained numerically. Recall from Chapter 1 that the unadapted-adapted cell transformation rate $m_0$ (associated with $\lambda$) has units of $1$/time. Similarly, the adapted-unadapted cell reversion rate $r_0$ (associated with $\gamma$) and the maximum growth rate $\mu$ (associated with $\alpha$) have the same units. Hence, we introduce three time scales - 'adaptation time' $1/\lambda$, 'reversion time' $1/\gamma$ and 'growth time' $1/\alpha$. Figure 26 a) illustrates the dependence of the optimal withdrawal time on the reversion time for the same value of parameters $u_0, \phi, \alpha, \lambda, \sigma, \delta, \mu$ as Figure 25.
Figure 26. a) Optimal withdrawal time versus ‘reversion time’ $1/\gamma$ for value of the parameters $u_0 = 5, \phi = 1, \alpha = 1, \lambda = 1, \sigma = 0.4, \delta = 0, \mu = 0.2$. b) Optimal withdrawal time versus ‘adaptation time’ $1/\lambda$ for value of the parameters $u_0 = 5, \phi = 1, \alpha = 1, \gamma = 0.1, \sigma = 0.4, \delta = 0, \mu = 0.2$. 
We observe that with increasing reversion time the optimal withdrawal time increases. It corresponds to the biological expectation - smaller reversion means generally more adapted cells. Hence, if we want our treatment to be effective we have to 'increase' $1/\gamma$ by prolonging the withdrawal time.

On the other hand, *Figure 26 b*) illustrates the dependence of the optimal withdrawal time on the adaptation time. Note that on this plot increase in $\lambda$ yields increase in withdrawal time. This at the first sight might look like a paradox. To explain this we look at what an increase in $1/\lambda$ means to the biofilm thickness. Clearly, as $\lambda \to \infty$ the biofilm thickness goes to $\alpha - \gamma \sigma$. It is never above this threshold. Hence intuitively, the optimal treatment would be to apply biocide dose - this rapidly increases $X_a$ as $\lambda$ is big, then to wait a long period without dosing until $X_a$ decreases and $X_u$ regrows so that it is again effective to use the dose.

In *Figure 27* the optimal withdrawal time versus growth time $1/\alpha$ is plotted. With increasing but relatively small growth times the withdrawal time increases rapidly - this is the case for thick biofilms which regrow faster. On the other hand, with increasing but large growth times the withdrawal time decreases - this happens for thin biofilms which regrow longer. A similar scenario can be observed in Figure 25 where the optimal minimum is zero ($1/\alpha = 10$).
Chapter Summary

We will summarize the main results of Chapters 5 and 6 below.

Constant dosing:

For the cost functionals with biocide cost $c$, for each $c > 0$ there exists a minimizer (an optimal biocide dose). If the cost is small enough, there is a nontrivial minimizer, otherwise the minimizer is zero, i.e., it is better to leave the biofilm untreated.

Non-constant dosing (we considered three scenarios):

i) Periodic and on and off dosing. For fixed average dose of biocide $D = \lim_{T \to \infty} \frac{1}{T} \int_0^T u(t)dt$ the frequency, amplitude, withdrawal time and the proportion of dosing

Figure 27. Optimal withdrawal time versus ‘growth time’ $1/\alpha$ for value of the parameters $u_0 = 5, \phi = 1, \lambda = 1, \gamma = 0.1, \sigma = 0.4, \delta = 0, \mu = 0.2$.
time to period is varied. This way we compare multiple dosing strategies that all have the same biocide cost $D$.

**ii) Optimalization of non-constant dosing strategies for given biocide cost $c$.** We consider the functionals in the form $J = J_0 + cD$ and $J_L = J_{0L} + cD$, where $J_0 = \lim_{T \to \infty} \frac{1}{T} \int_0^T \int_0^{L(t)} (X_a(x,t) + X_u(x,t)) dx dt$ and $J_{0L} = \lim_{T \to \infty} \frac{1}{T} \int_0^T L(t) dt$. Given biocide cost $c$, we minimize the sums $J, J_L$, respectively. Note that in this case the average dose of biocide $D$ is not fixed. We only considered the on and off dosing, as the periodic dosing does not differ significantly from constant dosing. Hence, there is almost no difference in the minimum of both functionals for these dosing strategies.

**iii) On and off dosing with bounded biocide dose.** We explore a specific dosing technique - there is an upper limit $U$ on the maximal biocide dose that can be applied, i.e., $0 \leq u(t) \leq U$. We only consider the dosings where either the maximal amount $U$ of biocide dose is applied or no dose is used (withdrawal time), as intuitively, some combination of these should give us the optimal dosing strategy. Just as in ii), the average dose of biocide $D$ is not fixed. For simplicity, the on and off dosing we consider has the same dosing time and the length of withdrawal time is varied. The reason is that when on and off dosing is used the most important factor is the proportion of dosing time to withdrawal time which we vary.

**Results for i):**
Periodic dosing (biocide dose is positive during dosing period):

Periodic dosing with very high frequency (small period) yields results near constant dosing since the limit of functionals in frequency is exactly the same as for constant dosing. Therefore, it is better to simply use the constant dosing as it is much easier to administer than high frequency periodic dosing.

Periodic dosing with very small frequency (long period) may have the functionals both larger or smaller than in the case of constant dosing, depending on convexity or concavity of the functionals $J, J_L$. However, numerical simulations indicate that the potential gain over constant dosing is relatively small - about 1% (see Figure 17).

Our conclusion for periodic dosing is that it potentially yields slightly better results than constant dosing. However, the difference is small and in practical applications insignificant.

On and off dosing (biocide dose is zero during withdrawal period):

In high frequency limit the functionals converge to the steady state solutions for modified constant $\lambda$, i.e. if the proportion of dosing time to period is $\mu \in (0, 1)$, then as the frequency gets very large, the on and off dosing looks like the steady state solution with $\mu \lambda$. This is important as smaller $\lambda$ yields substantially thinner biofilms with smaller proportion of adapted cells (see Figure 19).
The functionals react significantly to change in $\mu$, the smaller $\mu$ is, the smaller values they attain. Hence, by only looking at the model (not considering practical constrains) the optimal dosing strategy would be to take $\mu$ as close to zero as possible. This shows the practical limitations of our model which can be fixed by including disinfection saturation (see the Remark in Chapter 6 concerning this modification).

On and off dosing with very small frequency is similar to periodic dosing with very small frequency since both Theorems 6.2 and 6.4 consider averages in a frequency limit. On the other hand, Theorem 6.4 does not determine which dosing strategy is best - the possibility that on and off dosing for small frequency is worse than steady-state dosing is not excluded.

Our conclusion is that on and off dosing for high frequencies is always better than constant dosing, while on and off dosing for small frequencies can be more preferable to constant dosing or reversely. Numerical simulations indicate that functionals $J, J_L$ always attain their minimum at the endpoints. Hence, we conjecture that the optimal choice is to pick the minimum of the values $\lim_{\omega \to 0^+} J, \lim_{\omega \to \infty} J$. (Same for the other functional $J_L$).

*Results for ii)*:

- When the biocide cost $c$ is small, the nonzero minimizer for on and off dosing has smaller average $D$ than the one for constant dosing, i.e., less biocide is used.
Yet significantly, despite the smaller dose the value of the functionals $J$ and $J_L$ is smaller for on and off dosing, i.e., the biofilm is thinner.

For large $c$, the minimizer of functionals for both constant and on and off dosing is zero, i.e., no dosing is the optimal strategy. However, for constant dosing the trivial minimizer is attained for smaller $c$ (see Figure 23a). Hence, for certain interval of $c$, when the on and off dosing is used the optimal strategy is nonzero, for constant dosing the optimal strategy is no dosing.

Results for iii):

- On and off dosing with bounded biocide dose (constant dosing applied during dosing period and zero biocide dose during withdrawal period):

  Note that here we use only the functionals $J_0$, $J_{L0}$. We ignore the part $cD$ (the average cost of biocide). This quantity decreases with increasing withdrawal time.

  For thin biofilms the optimal withdrawal time is zero (see Figure 25). For certain sets of parameters, however, there is a nontrivial minimizer (see Figure 24). There is a close match between the minimizers of functionals for this dosing strategy and steady-state functionals with $\lambda$ replaced by $\mu\lambda$ and biocide dose $u_0$ replaced by $\mu u_0$. Analytically, we obtained estimates that the approximate nontrivial minimizer satisfies. However, they are too complicated to be used in practise.
In this case the growth time, reversion time and adaptation time have impact on the length of the optimal dosing period as well. Increasing reversion time/adaptation time increases the value of the minimizer. Very small growth time (thick biofilms) and very large growth time (thin biofilms) yield zero withdrawal time, i.e. if there is a limited amount of biocide dose that cannot be exceeded in each time than the optimal choice is constant dosing.

All these results indicate that the on and off dosing deserves a lot of future attention as it can deliver considerably better control of biofilms at significantly lower costs.
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