

ANALYSIS OF A BIOFILM MODEL

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Abstract

Bacterial biofilms demonstrate resistance in response to antimicrobial stress. This adaptive response is more effective than in the corresponding planktonic populations. The topic of this paper is concerned with an investigation of the longtime behavior of solutions to a biofilm model without growth on domains in \mathbb{R}^d ($d = 1, 2, 3$). This analysis is extended to both planktonic and biofilm systems. Results indicate a boundary layer type behavior of solutions in the case of sufficiently thick biofilms. Existence and properties of solutions to the biofilm model are established at the end of the paper.

1 Introduction

Biofilms are matrix-enclosed bacterial populations adherent to surfaces or interfaces. They have enormous impacts in medical, industrial and environmental processes, causing infections, contamination of medical devices, corrosion and thus, leading to higher costs for production and expenses. It has been estimated that biofilms are associated with 65% of nosocomial infections, the treatment of which costs approximately 1 billion US dollars annually in the United States [13]. In addition, bacterial biofilms may be up to 1,000-times more resistant to antimicrobial agents than those in a planktonic state (see [11]). Antibiotic penetration into biofilms can be hampered by multiple resistant mechanism (slow penetration, adaptive stress responses, nutrient limitation, persisters). Understanding the protective mechanisms of biofilms are important for their prevention and removal.

Our study is concerned with the possibility that some of the cells in biofilms actively respond to antimicrobial challenges by deploying adaptive stress responses. This protective mechanism, termed bacterial adaptation, has only recently emerged in the biofilm literature. There is mounting experimental evidence reporting adaptive responses in biofilms. Giwercman et al. [7] reported that the antibiotic imipenem induces high levels of β -lactamase enzyme production in *Pseudomonas aeruginosa* biofilms. Another study by Sanderson & Stewart [16] confirmed that *P. aeruginosa* biofilms treated with repeated doses of monochloramine showed increased resistance at the time of the second application. Elkins et al. [5] reported significant *KatB* catalase induction in *P. aeruginosa* during treatment with hydrogen peroxide suggesting that biofilms were capable of a rapid adaptive response to the oxidant. On the other hand, when the same hydrogen peroxide concentration was applied to planktonic cells, they were unable to make any detectable response. *P. aeruginosa* biofilms showed multiple adaptive responses to different types of antibiotics (Whitley et al. [20], Bagge et al. [2], Elkins et al. [5]). Sailer et al. [15] observed that β -lactam antibiotics increased the synthesis of polysaccharids in *Escherichia coli*. Another type of antibiotics, aminoglycoside, induced biofilm formation in *P. aeruginosa* and *E. coli* (Hoffman et al. [9]).

Mathematical models come in useful especially when experimental studies do not report sufficient information to be able to estimate the magnitude of the parameters. A number of mathematical studies deal with the qualitative properties of solutions to continuum biofilm models. Worth noting is the reaction-diffusion system by Eberl et al. [4] and the fluid model of Dockery & Klapper [3]. In [4], existence and the longtime behavior of solutions of the reaction-diffusion system were discussed. In [3], 1-D moving front solutions were analyzed, showing that under certain conditions fingering instabilities occur. Overgaard, [12] shows that the fluid model of Dockery & Klapper admits solutions in a certain weak sense. Stability of steady-state solutions of a single species 1-D biofilm model (without detachment) was studied in [14].

Our problem has its origin in biofilm modeling, where it stems from the 1-D biofilm model proposed in [18]. The results here indicate that cells in thick biofilms are able to enter an adapted resistant state as opposed to planktonic cells and that effective disinfection requires biocide concentration that increases exponentially or quadratically with biofilm thickness. The analysis of the model was done in the linear case. In this paper the 1-D biofilm model proposed in [18] is extended to smooth bounded domains in \mathbb{R}^2 and \mathbb{R}^3 in the essentially nonlinear case.

Our main result is probably the longtime behavior of solutions. In the biofilm literature different regimes are distinguished - thin biofilms (f.e., thickness $10\text{-}20\mu\text{m}$ in bioreactors), thick biofilms (f.e., thickness $> 100\mu\text{m}$ in bioreactors) and planktonic systems (f.e., only 1% of an ecosystem is represented by planktonic cells). Our longtime behavior analysis is extended to all three cases. We show that in biofilms where the penetration of the antimicrobial is limited, protective adaptation dominates in lower regions of the biofilm. Hence, in the biofilm two layers can be distinguished - a disinfection layer and a protected layer.

In order to mathematically justify that the biofilm model is well-posed, we prove the existence, uniqueness and *a priori* bounds for the solutions. In particular, we show that the solutions are nonnegative and bounded, hence, those model features are confirmed which are necessary in real life applications.

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. To make the model more general, we will assume that the disinfection and reaction rates are functions of biocide concentration. 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. In what follows, we state the key assumptions of the model.

1. The biofilm is attached to a flat slab called the substratum that is non-reactive towards the biofilm.
2. Biocide is applied through the biofilm-bulk fluid interface at a given concentration.
3. Living cells are transformed to dead cells via disinfection transformations that are at most linear with respect to the biocide concentration.

4. Biocide is consumed by reactions with biomass that are at most linear with respect to the biocide concentration and biocide is diffusing within the biofilm according to Fick's law. It will be assumed that even dead cells will continue to degrade the antimicrobial agents. Such is the case for some of the enzyme-based reactions of hydrogen peroxide or β -lactam antibiotics.
5. Living, unadapted cells transform to living, adapted cells at a bounded rate depending on the biocide concentration.
6. Adapted cells are less susceptible to disinfection than are unadapted cells.
7. The biofilm neither grows nor detaches over the time scales of interest.

We consider a bacterial population consisting of four cell states

X_u = unadapted cell density
 X_{ud} = dead unadapted cell density
 X_a = adapted cell density
 X_{ad} = dead adapted cell density

subject to $X_u + X_{ud} + X_a + X_{ad} = X_0$, 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. 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 paper as follows. First we describe the model equations both for biofilm and planktonic systems and we state Theorem 1 for the existence and properties of solutions. In Section 3 the longtime behavior of solutions on domains in \mathbb{R}^d ($d = 1, 2, 3$) is studied, provided that the rates are constants, i.e., they are independent of the biocide concentration. This analysis is done for both biofilm and planktonic systems. In the Appendix the notation is introduced and Theorem 1 is proved.

2 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 as a response to antimicrobial challenges at a bounded rate depending on the biocide concentration. The resulting biofilm model reads:

$$\frac{\partial B}{\partial t} = D\Delta B - k_u(B)(X_u + X_{ud})B - k_a(B)(X_a + X_{ad})B \quad (1)$$

$$\frac{\partial X_u}{\partial t} = -(b_u(B)B + r(B))X_u \quad (2)$$

$$\frac{\partial X_{ud}}{\partial t} = b_u(B)BX_u \quad (3)$$

$$\frac{\partial X_a}{\partial t} = -b_a(B)BX_a + r(B)X_u \quad (4)$$

$$\frac{\partial X_{ad}}{\partial t} = b_a(B)BX_a \quad (5)$$

The boundary conditions for B are given by

$$\frac{\partial B}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad B \Big|_{\partial\Omega_D} = B_0 \quad \text{for } 0 \leq t \leq T \quad (6)$$

indicating that no flux through the solid boundary $\partial\Omega_N$ occurs and that the biocide concentration in the bulk liquid is fixed. At $t = 0$, the variables satisfy

$$B(\cdot, 0) = g, \quad X_u(\cdot, 0) = X_0, \quad X_{ud}(\cdot, 0) = 0, \quad X_a(\cdot, 0) = 0, \quad X_{ad}(\cdot, 0) = 0. \quad (7)$$

Here $\Omega \subset \mathbb{R}^d$ ($d = 1, 2, 3$) is an open bounded domain 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 at which both the Neumann and Dirichlet condition is defined. This last assumption is only needed for regularity.

B_0	externally applied biocide concentration
D	biocide diffusion constant
b_u	unadapted cell disinfection rate
b_a	adapted cell disinfection rate
k_u	biocide unadapted cell reaction rate
k_a	biocide adapted cell reaction rate
r_0	unadapted-adapted cell transformation rate

Table 1: Dimensional parameters.

The coefficients k_u, k_a, r, b_u, b_a depend on biocide B , are nonnegative and Lipschitz continuous on $[0, B_0]$. As usual, n is the outward unit normal vector on $\partial\Omega_N$. 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 Table 1.

In the planktonic case, the biocide can be constantly replenished, i.e., equation (1) is replaced by $B(t) = B_0$, or biocide can be applied at $t = 0$ only, in which case equation (1) is replaced by

$$\frac{\partial B}{\partial t} = -k_u(B)(X_u + X_{ud})B - k_a(B)(X_a + X_{ad})B \quad B(0) = B_0. \quad (8)$$

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 nonnegative bounded and analytic.

Finally, the existence and properties of solutions for the system (1)-(5) is established in Theorem 1. For the proof see the Appendix.

Theorem 1. *Let $k \geq 1$ and $p > 1$ such that $p > \frac{n}{k}$. Assume that the coefficients $k_u, k_a, b_u, b_a, r \in C^{k-1,1}[0, B_0]$ and g is a nonnegative function satisfying $\|g\|_\infty \leq B_0$. Then the system (1)-(5) can be reduced to a single time dependent parabolic equation of B . The function B is nonnegative, bounded by B_0 and belongs to the class*

$$B \in C((0, T]; H^{k,p}(\Omega)), \quad \frac{\partial B}{\partial t} \in C((0, T]; H^{k-2,p}(\Omega)). \quad (9)$$

3 Longtime behavior of solutions

Consider the system (1)-(5) on domain $\Omega \in \mathbb{R}^d$ ($d = 1, 2, 3$) with coefficients independent of B , i.e., $k_u(B) = k_u$, $k_a(B) = k_a$, $b_u(B) = b_u$, $b_a(B) = b_a$, and $r(B) = r_0$. For this particular case, we will state the dimensionless form of the biofilm model. Due to the fact that the equations are coupled, it is impossible to say explicitly what happens when the time is large for general values of the dimensionless parameters. 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. We will state these results for both biofilm and planktonic systems.

3.1 Dimensionless equations

We scale the independent variables x and t by $\tilde{x} = x/L, \tilde{t} = tb_u B_0$, where L is the characteristic biofilm thickness. 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. Note that $0 \leq \tilde{x} \leq 1$ in 1-D. Dropping the tildes, (1)-(5) in the dimensionless form becomes

$$\epsilon \phi_u^2 \frac{\partial B}{\partial t} = \Delta B - \phi_u^2 (X_u + X_{ud})B - \phi_a^2 (X_a + X_{ad})B \quad (10)$$

$$\frac{\partial B}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad B \Big|_{\partial\Omega_D} = 1, \quad B(x, 0) = g(x)/B_0 \quad (11)$$

$$\frac{\partial X_u}{\partial t} = -(B + \lambda)X_u, \quad X_u(x, 0) = 1 \quad (12)$$

$$\frac{\partial X_{ud}}{\partial t} = BX_u, \quad X_{ud}(x, 0) = 0 \quad (13)$$

$$\frac{\partial X_a}{\partial t} = -\delta BX_a + \lambda X_u, \quad X_a(x, 0) = 0 \quad (14)$$

$$\frac{\partial X_{ad}}{\partial t} = \delta BX_a, \quad X_{ad}(x, 0) = 0. \quad (15)$$

The dimensionless parameters are listed below:

$$\epsilon = b_u B_0 / k_u X_0, \quad \phi_u^2 = k_u X_0 L^2 / D, \quad \phi_a^2 = k_a X_0 L^2 / D, \quad \lambda = r_0 / b_u B_0, \quad \delta = b_a / b_u.$$

Remark: We should point out that ϕ_u^2 on the left hand-side of (10) can be replaced by ϕ_a^2 as well, in which case ϵ becomes $b_u B_0/k_a X_0$.

Here ϕ_u^2 and ϕ_a^2 are the Thiele moduli for the adapted and unadapted cells which is a measure of the relative rates of reaction and diffusion of the antimicrobial agent. 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, $1/\phi_a = \sqrt{(D/k_a X_0)}/L$ is the depth in scaled variables of the disinfection layer for the adapted phase (the distance in scaled variables a diffusing quantity can spread in significant concentration). The dimensionless number ϕ_u can be interpreted analogously. In the biofilm case we distinguish two regimes - thin biofilm, when $\max\{\phi_u, \phi_a\} \ll 1$ (biofilm depth is small compared to the depth of the minimal disinfection layer) and thick biofilm, when $\max\{\phi_u, \phi_a\} \gg 1$ (biofilm depth is large compared to the depth of the minimal disinfection layer).

The parameter ϵ 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 ϵ can be much larger in the planktonic case.

The parameter λ 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 δ , 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 (10)-(15) simplifies to

$$\Delta B = \phi_u^2(X_u + X_{ud})B + \phi_a^2 X_a B \quad (16)$$

$$\frac{\partial B}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad B \Big|_{\partial\Omega_D} = 1 \quad (17)$$

$$\frac{\partial X_u}{\partial t} = -(B + \lambda)X_u, \quad X_u(x, 0) = 1 \quad (18)$$

$$\frac{\partial X_{ud}}{\partial t} = B X_u, \quad X_{ud}(x, 0) = 0 \quad (19)$$

$$\frac{\partial X_a}{\partial t} = \lambda X_u, \quad X_a(x, 0) = 0. \quad (20)$$

Note that $X_{ad}(t) = 0$ and $X_u + X_{ud} + X_a = 1$. The solutions of (18)-(20) are

$$X_u(t) = e^{-(\lambda t + \int_0^t B(u) du)} \quad (21)$$

$$X_{ud}(t) = \int_0^t B(s) e^{-(\lambda s + \int_0^s B(u) du)} ds \quad (22)$$

$$X_a(t) = \lambda \int_0^t e^{-(\lambda s + \int_0^s B(u) du)} ds. \quad (23)$$

It follows from (21) that $X_u(t) \rightarrow 0$ as $t \rightarrow \infty$. Biologically, only nonnegative solutions of the system (16)-(20) make sense. In fact, an analysis of the system (10)-(15) as $\epsilon \rightarrow 0+$ can be done to show that the solutions to the problem (16)-(20) are nonnegative. Another approach would be the existence of solutions of the system (16)-(20) using a fixed point argument. In this section, however, the asymptotic properties of solutions are studied. Thus, it is assumed that the solutions to

the problem (16)-(20) are nonnegative.

Remark: In the linear case, when $\phi_u = \phi_a$, it is easy to see that

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

From now on we will focus on the nonlinear case.

3.2 Thin biofilms and planktonic systems

Our goal is to analyze the longtime behavior of cells densities X_a and X_{ud} when the dimensionless numbers ϕ_u, ϕ_a, λ are very small or very large. The simplest asymptotic results (see Theorem 2), among others, can be obtained for thin biofilms and planktonic systems.

Theorem 2. *Consider the system (16)-(20).*

i) *In the thin biofilm case, when $\max\{\phi_u, \phi_a\} \ll 1$ we have the following:*

For any $\epsilon > 0$ and any $x \in \bar{\Omega}$ there exist positive constants t_0, ϕ_{u0} and ϕ_{a0} such that for any $t > t_0$ and any $\phi_u < \phi_{u0}, \phi_a < \phi_{a0}$ it holds

$$0 \leq \frac{1}{\lambda + 1} - X_{ud}(x, t) < \epsilon, \quad 0 \leq \frac{\lambda}{\lambda + 1} - X_a(x, t) < \epsilon.$$

ii) *In the planktonic case the results for planktonic systems agree with the results for thin biofilms:*

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

iii) *The following results are the same for both biofilm and planktonic systems:*

When $\lambda \rightarrow 0+$, disinfection dominates:

$$X_{ud} \rightarrow 1, \quad X_a \rightarrow 0 \quad \text{as } t \rightarrow \infty$$

When $\lambda \rightarrow \infty$, one can expect that adaptation will dominate:

$$X_{ud} \rightarrow 0, \quad X_a \rightarrow 1 \quad \text{as } t \rightarrow \infty$$

Proof of Theorem 2. The proof of parts i) and ii) is trivial, hence, we will only deal with the planktonic case, part iii).

Consider (8) 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 equations become

$$\epsilon \frac{dB}{dt} = -(X_u + X_{ud})B - \kappa(X_a + X_{ad})B, \quad B(0) = 1 \quad (24)$$

$$\frac{dX_u}{dt} = -(B + \lambda)X_u, \quad X_u(0) = 1 \quad (25)$$

$$\frac{dX_{ud}}{dt} = BX_u, \quad X_{ud}(0) = 0 \quad (26)$$

$$\frac{dX_a}{dt} = -\delta BX_a + \lambda X_u, \quad X_a(0) = 0 \quad (27)$$

$$\frac{dX_{ad}}{dt} = \delta BX_a, \quad X_{ad}(0) = 0. \quad (28)$$

The dimensionless parameters $\epsilon, \lambda, \delta$ are defined as in the biofilm case and $\kappa = k_a/k_u$. In the planktonic case $\epsilon \gg 1$ and hence, $B \approx 1$ 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 (26)-(27) become

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

Note that the previous results coincide with the results in i), i.e., thin biofilms behave like planktonic systems. ■

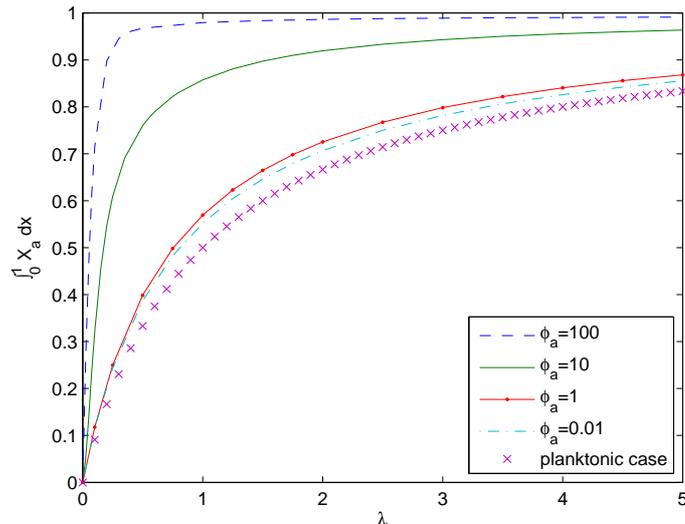


Figure 1: Longtime adapted fraction in 1-D, $\int_0^1 X_a dx$, as a function of λ for various smaller and larger values of ϕ_a . In each case $\phi_u = 1$. The planktonic case corresponds to the 'x'-curve.

The dimensionless number λ measures the effectiveness of biocide action. As formulated in Theorem 2 part iii), when $\lambda \rightarrow 0+$, no adapted cells X_a remain as opposed to $\lambda \rightarrow \infty$. Figure 1 illustrates the longtime adapted fraction in 1-D, $\int_0^1 X_a dx$, as a function of λ for various smaller and larger values of ϕ_a . In the planktonic case $X_a \rightarrow \frac{\lambda}{\lambda+1}$ as $t \rightarrow \infty$ which corresponds to the 'x'-curve. Note that even for small λ , i.e., very strong biocide concentration, efficacy of the treatment is poor especially in the thick biofilms ($\phi_a \gg 1$).

3.3 Thick biofilms

We proceed with a simple example in 1-D. Figure 2 illustrates the ratio X_a/X_{ud} as a function of depth x for various smaller and larger values of ϕ_a . Note the dominance of the adapted phase in the protected layer of the biofilm (roughly $0 < x < 1 - \phi_a^{-1}$) for larger values of ϕ_a . In the disinfection layer, roughly $1 - \phi_a^{-1} < x < 1$, adaptation can be suppressed. It indicates a boundary layer type behavior which is especially noticeable when $\max\{\phi_u, \phi_a\} \rightarrow \infty$. This is established in Theorem 3.

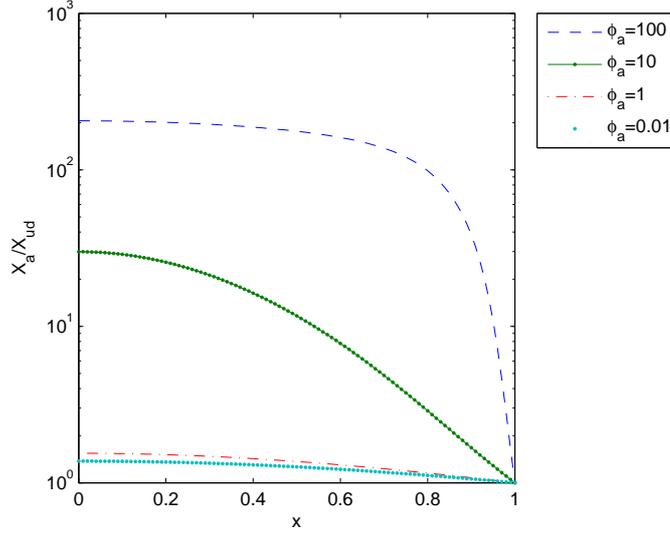


Figure 2: Ratio X_a/X_{ud} in 1-D as a function of depth x for various smaller and larger values of ϕ_a . In each case $\phi_u = 1$ and $\lambda = 1$ and hence, the ratio for a planktonic population would be $X_a/X_{ud} = \lambda = 1$.

Theorem 3. Consider the system (16)-(20).

i) When $\phi_a \rightarrow \infty$, i.e., the disinfection layer for the adapted phase (approximately $1/\phi_a$) is decreasing, we obtain

$$X_{ud} \rightarrow 0, \quad X_a \rightarrow 1 \quad \text{for } x \in \mathcal{U} \quad \text{as } t \rightarrow \infty,$$

where $\mathcal{U} = \bar{\Omega} \setminus \partial\bar{\Omega}_D$. More precisely, for any $\epsilon > 0$ and any $x \in \mathcal{U}$ there exists a time t_0 and a positive constant ϕ_{a0} such that for any $t \geq t_0$ and any $\phi_a \geq \phi_{a0}$ it holds that

$$0 \leq 1 - X_a(x, t) < \epsilon, \quad 0 \leq X_{ud}(x, t) < \epsilon.$$

ii) When $\phi_u \rightarrow \infty$, i.e., the disinfection layer for the unadapted phase (approximately $1/\phi_u$) is decreasing, we obtain

$$X_{ud} \rightarrow 0, \quad X_a \rightarrow 1 \quad \text{for } x \in \mathcal{U} \quad \text{as } t \rightarrow \infty.$$

(This double limit can be written using ϵ -notation just like in i.)

Remark: Note that when $x \in \partial\bar{\Omega}_D$, then $B(x) = 1$ and at these points

$$(X_{ud}, X_a) \rightarrow \left(\frac{1}{\lambda + 1}, \frac{\lambda}{\lambda + 1} \right) \quad \text{to } t \rightarrow \infty.$$

This limit is independent of ϕ_u, ϕ_a . The convergence in Theorems 2 and 3 is point-wise.

In order to prove Theorem 3, we need some preliminary results first.

Lemma 1. Let $Lu_i = -\Delta u_i + \phi^2 u_i$ ($i = 1, 2$) and $u_i \in C^2(\Omega) \cap C^1(\bar{\Omega})$ with mixed boundary conditions $\frac{\partial u_i}{\partial n} \Big|_{\partial\Omega_N} = 0, u_i \Big|_{\partial\Omega_D} = c_i$. If $c_1 \geq c_2$ and $Lu_1 \geq Lu_2$, then $u_1 \geq u_2$ in $\bar{\Omega}$.

Lemma 2. Let u_i ($i = 1, 2$) satisfy the equation $-\Delta u_i + \phi_i^2 u_i = 0$ with mixed boundary conditions $\frac{\partial u_i}{\partial n} \Big|_{\partial\Omega_N} = 0, u_i \Big|_{\partial\Omega_D} = 1$ and let $\phi_1^2 + \phi_2^2 \leq \zeta^2$ for some $\zeta > 0$. Then the following estimate holds

$$\|u_1 - u_2\|_\infty \leq C|\phi_1 - \phi_2|,$$

where the constant C only depends on ζ .

Lemma 3. Consider the boundary-value problem

$$\Delta u = \phi^2 u, \quad u \Big|_{\partial\mathcal{B}} = 1, \quad (29)$$

where $\mathcal{B} = \mathcal{B}(0, R)$ ($d = 2, 3$) is a disk or ball with radius R . Then with increasing ϕ the solution u decays exponentially, i.e., for ϕ large the following holds:

$$\text{Case } d = 2: \quad u(0) \leq C\sqrt{R\phi}e^{-R\phi}$$

$$\text{Case } d = 3: \quad u(0) \leq CR\phi e^{-R\phi}$$

for some positive constant C independent of $\phi \gg 1$.

Proof of Lemma 3. It has been shown in [17] that the solution of equation (29) in a disk ($d = 2$) is $u(r) = J_0(i\phi r)/J_0(i\phi R)$, where $0 \leq r < R$ and J_0 is the zeroth order hyperbolic Bessel function of first kind. Similarly, in a ball ($d = 3$) the solution takes the form $u(r) = (R/r) \sinh(\phi r)/\sinh(\phi R)$ for $0 < r < R$. (Note that solution is radially symmetric.)

When $d = 2$, we use that $J_0(iz) \rightarrow e^z/\sqrt{2\pi z}$ for large z . Thus, we obtain, $u(0) \approx \sqrt{2\pi R\phi}e^{-R\phi}$ for $\phi \gg 1$.

When $d = 3$, we have $u(r) \rightarrow \phi R/\sinh(\phi R)$ as $r \rightarrow 0+$. Hence, we can define $u(0) = 2R\phi/(e^{R\phi} - e^{-R\phi}) \approx 2R\phi e^{-R\phi}$ for $\phi \gg 1$. ■

Lemma 4. Consider the boundary value problem

$$\Delta u = \phi^2 u, \quad \frac{\partial u}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad u \Big|_{\partial\Omega_D} = 1. \quad (30)$$

Then for any $x \in \mathcal{U} = \bar{\Omega} \setminus \partial\bar{\Omega}_D$ there exists a constant $d_x > 0$ depending on x such that the function $u(x)$ decays exponentially as ϕ increases, i.e., for ϕ large the following holds:

$$\text{Case } d = 1: \quad u(x) \leq Ce^{-\phi(1-x)} \text{ for } x \in [0, 1]$$

$$\text{Case } d = 2: \quad u(x) \leq C\sqrt{d_x\phi}e^{-d_x\phi} \text{ for } x \in \mathcal{U}$$

$$\text{Case } d = 3: \quad u(x) \leq Cd_x\phi e^{-d_x\phi} \text{ for } x \in \mathcal{U}$$

for some C positive independent of x .

Proof of Lemma 4. In 1-D the domain $\Omega = [0, 1]$ since $L = 1$. The proof will only deal with the case $d = 2, 3$ since the 1-D case is trivial.

Let $x_0 \in \Omega$ and let $y_0 \in \partial\Omega$ such that $d_x = \|x_0 - y_0\| = \inf_{y \in \partial\Omega} \|x_0 - y\|$. For such x and y_0 consider the n -dimensional ball \mathcal{B} ($d = 2, 3$) centered at x_0 with radius d_x . Consider the boundary value problems (30) and

$$\Delta v = \phi^2 v, \quad v \Big|_{\partial\mathcal{B}} = 1, \quad (31)$$

where $\mathcal{B} = \mathcal{B}(x_0, d_x)$. Note that $u \Big|_{\partial\mathcal{B}} \leq 1$ and $v \Big|_{\partial\mathcal{B}} = 1$. Hence, the comparison principles apply for the solutions u of (30) and v of (45), i.e., $u \leq v$ in \mathcal{B} . For any $x \in \mathcal{B}$ we obtain by Lemma 3 the following:

$$\text{Case } d = 2: \quad u(x) \leq C\sqrt{d_x}\phi e^{-d_x\phi} \text{ for } \phi \gg 1$$

$$\text{Case } d = 3: \quad u(x) \leq Cd_x\phi e^{-d_x\phi} \text{ for } \phi \gg 1$$

On the other hand, if $x_0 \in \partial\Omega_N \setminus \bar{\Omega}_D$, we will follow a standard procedure done in [10]. There exists a mapping which maps a small neighborhood of x_0 onto a neighborhood of z_0 in the upper half-space \mathbb{R}_+^d and straightens the Neumann boundary. Hence, the solution can be extended to a subset of \mathbb{R}^d by reflection with respect to the hyperplane $z_n = 0$, where z are the 'new' x -coordinates. Mapping back the neighborhood of z_0 and exchanging the coordinates to x we can follow the same procedure as before. For all x_0 on the Neumann boundary we may take a ball with radius d_x and we obtain the same exponential decay as for the interior points. ■

Lemma 5. *Consider the system (16)-(20). When ϕ_u and ϕ_a are approximately the same ($\phi_u \approx \phi_a$), we take $\phi_{min} = \min\{\phi_u, \phi_a\}$ and $\phi_{max} = \max\{\phi_u, \phi_a\}$. Then there exists an upper and a lower solution \bar{B} and \underline{B} satisfying*

$$\Delta \bar{B} = \phi_{min}^2 \bar{B}, \quad \frac{\partial \bar{B}}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad \bar{B} \Big|_{\partial\Omega_D} = 1 \quad (32)$$

and

$$\Delta \underline{B} = \phi_{max}^2 \underline{B}, \quad \frac{\partial \underline{B}}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad \underline{B} \Big|_{\partial\Omega_D} = 1 \quad (33)$$

such that $\underline{B} \leq B \leq \bar{B}$. Similar estimates can be obtained for the other cell-densities as well.

Finally, using the previous Lemmas 1-5 we are ready to prove Theorem 3.

Proof of Theorem 3.

i) Case $\phi_a \rightarrow \infty$: The second term in the right-side of equation (16) grows very fast. For a short time $0 \leq t \leq t_0$, the first term in the right-side of equation (16) will dominate over the second term. Since $B \leq \bar{B}$ where \bar{B} solves (32), we can estimate X_a . Note that

$$X_a(t) \geq \lambda \int_0^t e^{-(\lambda + \bar{B})s} ds = \frac{\lambda}{\lambda + \bar{B}} [1 - e^{-(\lambda + \bar{B})t}].$$

Given $0 < \varepsilon \ll 1$, we pick t_0 such that

$$\frac{1 - e^{-(\lambda + \bar{B})t_0}}{\lambda + \bar{B}} = \varepsilon.$$

Solving for t_0 we obtain

$$t_0 = -\frac{1}{\lambda + \bar{B}} \ln(1 - \epsilon(\lambda + \bar{B})) = \epsilon + O(\epsilon^2).$$

Hence, $X_a(t) \geq \lambda\epsilon$ for $t > t_0$.

Now we will estimate the term $\int_{t_0}^{\infty} e^{-(\lambda+B)s} ds$ from below. To do so, we need an upper estimate for B , so let's look for an upper solution \tilde{B} that satisfies

$$\Delta \tilde{B} = \phi_a^2 \lambda \epsilon \tilde{B}, \quad \frac{\partial \tilde{B}}{\partial n} \Big|_{\partial \Omega_N} = 0, \quad \tilde{B} \Big|_{\partial \Omega_D} = 1. \quad (34)$$

We replaced the second term in the right-side of equation (16) by $\phi_a^2 \lambda \epsilon \tilde{B}$. In general, we cannot find the true solution of (34) in \mathbb{R}^d ($d = 2, 3$), but by Lemma 4 we have an upper estimate on it. For example, when $d = 3$, we can pick ϕ_{a0} such that

$$\phi_{a0}^2 \geq \frac{2 \ln(C/\lambda\epsilon)}{d_x \lambda \epsilon}$$

for some $C > 0$. Note that the choice of ϕ_{a0} depends on x and λ . Hence, for any $\phi_a \geq \phi_{a0}$ we have

$$\tilde{B}(x) \leq C d_x \phi_a^2 \lambda \epsilon e^{-d_x \phi_a^2 \lambda \epsilon} \leq C e^{-d_x \phi_a^2 \lambda \epsilon / 2} \leq \lambda \epsilon$$

whenever $x \in \mathcal{U}$. It follows from the previous that

$$\begin{aligned} \lim_{t \rightarrow \infty} X_a(t) &\geq \lambda \epsilon + \lambda \int_{\epsilon}^{\infty} e^{-(\lambda + \tilde{B})s} ds \\ &\geq \lambda \epsilon + \lambda \int_{\epsilon}^{\infty} e^{-(\lambda s + \lambda \epsilon (s - \epsilon))} ds = \lambda \epsilon + \frac{e^{-\lambda \epsilon}}{1 + \epsilon} = 1 - \epsilon + O(\epsilon^2). \end{aligned}$$

Hence, for $\phi_a \rightarrow \infty$,

$$X_{ud} \rightarrow 0, \quad X_a \rightarrow 1 \quad \text{for } x \in \mathcal{U} \text{ as } t \rightarrow \infty.$$

Note that in this case adaptation dominates.

ii) Case $\phi_u \rightarrow \infty$: Mathematically this case differs from *i*). The first term in the right-side of equation in (16) will dominate for a long time. We pick a time t_0 such that $X_u(t_0) = \epsilon$ for some $0 < \epsilon \ll 1$. Hence, $X_u(t) \geq \epsilon$ for $0 \leq t \leq t_0$.

Also, for $0 \leq t \leq t_0$, the biocide concentration can be estimated by an upper solution \bar{B} that satisfies the equation

$$\Delta \bar{B} = \phi_u^2 \epsilon \bar{B}, \quad \frac{\partial \bar{B}}{\partial n} \Big|_{\partial \Omega_N} = 0, \quad \bar{B} \Big|_{\partial \Omega_D} = 1. \quad (35)$$

We replaced the first term in the right-side of the equation (16) by $\phi_u^2 \epsilon \bar{B}$. Again, we cannot find the true solution of (35) in \mathbb{R}^d ($d = 2, 3$), but we can use Lemma 3. For example, when $d = 3$, we can pick ϕ_{u0} such that

$$\phi_{u0}^2 \geq \frac{2 \ln(C/\lambda\epsilon)}{d_x \epsilon}$$

for some $C > 0$. Hence, for any $\phi_u \geq \phi_{u0}$ we have

$$\bar{B}(x) \leq C d_x \phi_u^2 \epsilon e^{-d_x \phi_u^2 \epsilon} \leq C e^{-d_x \phi_u^2 \epsilon / 2} \leq \lambda \epsilon$$

whenever $x \in \mathcal{U}$.

Now we are ready to find t_0 . We have

$$X_u(t_0) = \epsilon \geq e^{-(\lambda+\bar{B})t_0} \geq e^{-\lambda(1+\epsilon)t_0}$$

and hence, we may take $t_0 \geq \frac{\ln(1/\epsilon)}{\lambda(1+\epsilon)}$. It follows from (19)-(20) that

$$\frac{\partial X_{ud}}{\partial t} \left(\frac{\partial X_a}{\partial t} \right)^{-1} = \frac{B}{\lambda} \leq \epsilon \quad \text{for } 0 \leq t \leq t_0.$$

Therefore, we obtain $X_{ud}(t) \leq \epsilon X_a$ for $0 \leq t \leq t_0$. Also, for $t \geq t_0$, we have $X_a(t) + X_{ud}(t) \geq 1 - \epsilon$. It follows that $X_a(t_0) \geq 1 - \epsilon - X_{ud}(t_0) \geq 1 - \epsilon - \epsilon X_a(t_0)$, from which $X_a(t_0) \geq \frac{1-\epsilon}{1+\epsilon}$. Since X_a is monotone increasing, we have $X_a(t) \geq \frac{1-\epsilon}{1+\epsilon}$ for all t . From this the claim follows. ■

Remark: Note that in the case of thick biofilms ($\phi_a \gg 1$ or $\phi_u \gg 1$), the solutions X_{ud}, X_a follow a boundary layer type behavior. In particular, the dead unadapted cell density X_{ud} is $O(1)$ in the $O(\frac{1}{\phi_a})$ -neighborhood or $O(\frac{1}{\phi_u})$ -neighborhood of $\partial\bar{\Omega}_D$.

4 Appendix

In the Appendix Theorem 1 will be proved in several steps. First, the system will be reduced to a nonlinear parabolic equation of B , which in turn will be associated with a linear parabolic equation of B . *A priori* bounds for the solution of the linear parabolic equation will be derived in the first half of the Appendix. This will allow us to show the existence of weak solutions (using a fixed point approach) and to obtain improved regularity as well as bounds for the function B .

4.1 Notation

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

$$D(\mathcal{A}^{\frac{1}{2}}) = \{v \in H^{1,p}(\Omega) : v|_{\partial\Omega_D} = 0\},$$

$$D(\mathcal{A}) = \{v \in H^{2,p}(\Omega) : \frac{\partial v}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad v|_{\partial\Omega_D} = 0\},$$

$$D(\mathcal{A}^{\frac{k}{2}}) \subset \{v \in H^{k,p}(\Omega) : \frac{\partial v}{\partial n} \Big|_{\partial\Omega_N} = 0, \quad v|_{\partial\Omega_D} = 0\}$$

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 (see [1])

$$\|\mathcal{A}^{\frac{k}{2}}v\|_p = \|v\|_{k,p} \quad \text{for } v \in D(\mathcal{A}^{\frac{k}{2}}).$$

4.2 Reduction of the system

Without loss of generality, we can assume that the diffusion constant $D = 1$. After a simple manipulation, the system (1)-(5) can be reduced to a single time dependent parabolic equation

$$\frac{\partial B}{\partial t} = \Delta B - h_B(t)B \quad (36)$$

with boundary conditions (6), where h_B is given by

$$h_B(t) = k_u(B)X_0 + (k_a(B) - k_u(B))X_0 \int_0^t r(B(s))e^{-\int_0^s (b_u(B(v))B(v) + r(B(v)))dv} ds. \quad (37)$$

Taking $A(x, t) = B_0 - B(x, t)$ makes the boundary conditions in (6) homogeneous. In this case equation (36) becomes

$$\frac{\partial A}{\partial t} = \Delta A - h_A(t)A + B_0 h_A(t), \quad (38)$$

where A satisfies

$$A|_{\partial\Omega_D} = 0, \quad \frac{\partial A}{\partial n}|_{\partial\Omega_N} = 0, \quad A(., 0) = B_0 - g. \quad (39)$$

The function h_A is just like h_B except B is replaced by A and k_u, k_a, r, b_u are replaced by $\tilde{k}_u, \tilde{k}_a, \tilde{r}, \tilde{b}_u$, where the ‘‘tilde-notation’’ refers to the shift in the coefficients, i.e., $\tilde{k}_u(A) = k_u(B_0 - A)$ for example.

4.3 A priori bounds

We start with a simpler linear parabolic equation

$$\frac{\partial u}{\partial t} = \Delta u - h(t)u + B_0 h(t), \quad (40)$$

$$u|_{\partial\Omega_D} = 0, \quad \frac{\partial u}{\partial n}|_{\partial\Omega_N} = 0 \text{ for } 0 \leq t \leq T, \quad u(x, 0) = f(x) \text{ for } x \in \Omega, \quad (41)$$

where $B_0 > 0$, h is a nonnegative function of x and t belonging to $L^\infty([0, T] \times \Omega)$ and $f \in L^\infty(\Omega)$ is a nonnegative function such that $\|f\|_\infty \leq B_0$. It is well-known that the system (40)-(41) has a unique weak solution in class

$$u \in C([0, T]; L^p(\Omega)) \cap C((0, T]; H^{1,p}(\Omega)), \quad \frac{\partial u}{\partial t} \in C((0, T]; H^{-1,p}(\Omega)) \quad (42)$$

for all $1 < p < \infty$ (see [19]). Hence, we will only show that the solution u has an upper bound B_0 .

Theorem 4. *The solution to the problem (40)-(41) is bounded by B_0 , i.e.,*

$$\|u(t)\|_\infty \leq B_0 \text{ for } 0 \leq t \leq T.$$

Proof of Theorem 4. We multiply both sides of (40) by $u|u|^{p-2}$ and integrate over Ω . Hence, we get

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

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,

$$\int_{\Omega} |u|^{p-1} \leq \|u\|_p^{p-1} \mathbf{meas}(\Omega)^{\frac{1}{p}}$$

and so

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

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 $C_p = B_0 \mathbf{meas}(\Omega)^{\frac{1}{p}}$. 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 $\|u(0)\|_{\infty} \leq B_0$. ■

Remark: Note that the uniform bound on the L^p -norm of u results in L^{∞} -regularity, i.e.,

$$u \in L^{\infty}([0, T] \times \Omega).$$

The following lemma establishes stronger regularity properties of the solution u . It can be shown that if $h \in C((0, T], H^{k,p}(\Omega))$, then $u \in C((0, T], H^{k+1,p}(\Omega))$.

Theorem 5. *Assume that for given $k \geq 1$ and $p > 1$ such that $p > \frac{n}{k}$ the function $h \in C((0, T], H^{k,p}(\Omega))$. Then the solution to the problem (40)-(41) belongs to the class $C((0, T], H^{k+1,p}(\Omega))$. On the other hand, if $k = 0$, then we assume $h \in L^{\infty}([0, T] \times \Omega)$. In this case the solution to the problem (40)-(41) belongs to $C([0, T], L^p(\Omega)) \cap C((0, T], H^{1,p}(\Omega))$ for $p > 1$.*

Sketch of the Proof of Theorem 5. The case $k = 0$ follows directly from Theorem 1. The case $k \geq 1$ is done by induction and uses a well-known proposition on sectorial operators from [8]:

Proposition 1. *Suppose \mathcal{A} is sectorial in the Banach space X and $\operatorname{Re} \sigma(\mathcal{A}) > \delta > 0$. For $\alpha \geq 0$ there exists $C_{\alpha} < \infty$ such that*

$$\|\mathcal{A}^{\alpha} e^{-At}\|_{X \rightarrow X} \leq C_{\alpha} t^{-\alpha} e^{-\delta t} \text{ for } t > 0.$$

For further details of the sectorialness of $\mathcal{A} = -\Delta$ in $L^p(\Omega)$ see [8]. ■

4.4 Existence and uniqueness of solutions

First we will establish the existence of a unique weak solution to the system (1)-(5). Then Theorem 5 will be used to obtain stronger regularity of the solutions.

Theorem 6. *Assume that the coefficients k_u, k_a, b_u, b_a, r are Lipschitz continuous on $[0, B_0]$ and g is a nonnegative function satisfying $\|g\|_\infty \leq B_0$. Then the system (1)-(5) has a unique weak solution, where the function B is nonnegative and belongs to the class (42). The functions X_u, X_{ud}, X_a, X_{ad} are nonnegative and their regularity properties can be derived from equations (2)-(5).*

Proof of Theorem 6. Recall that the system (1)-(5) can be reduced to equation (36) with boundary conditions (6), where h_B is given by (37). Henceforth, we will deal with the associated homogeneous problem (38)-(39). We will apply the contraction mapping principle to show the existence of a unique weak solution to the problem (38)-(39).

By assumption the coefficients k_u, k_a, r, b_u are Lipschitz continuous on $[0, B_0]$. It follows that the ‘‘shifted’’ coefficients denoted by $\tilde{k}_u, \tilde{k}_a, \tilde{r}, \tilde{b}_u$ have the same L^∞ -norm and Lipschitz constant as the original coefficients, i.e., $\|\tilde{k}_u\|_\infty = \|k_u\|_\infty$ and $L_{\tilde{k}_u} = L_{k_u}$ for example. Hence, in the estimates $\|\tilde{k}_u\|_\infty$ and $L_{\tilde{k}_u}$ will be simply replaced by $\|k_u\|_\infty$ and L_{k_u} .

Let X be the Banach space

$$X = \{A \in L^\infty([0, T] \times \Omega); \quad \|A(t)\|_\infty \leq B_0 \text{ for } 0 \leq t \leq T\}.$$

Thanks to the upper bound on the function $A(t) = B_0 - B(t)$, we have $\|B(t)\|_\infty \geq 0$ for $0 \leq t \leq T$. It follows that $\|h_A(t)\|_\infty \geq 0$ for $0 \leq t \leq T$. Define $\mathcal{F} : X \rightarrow X$ by setting $\mathcal{F}A = u$, where u solves (40). Hence, $\mathcal{F}(A)$ satisfies the implicit integral equation obtained by integrating the linear equation (40) with h replaced by h_A , i.e.,

$$\mathcal{F}A(t) = e^{-tA}(B_0 - g) + \int_0^t e^{-(t-s)A} h_A(s)(B_0 - \mathcal{F}A(s)) ds.$$

Choose $u, \bar{u} \in X$ and let $u = \mathcal{F}A, \bar{u} = \mathcal{F}\bar{A}$. Consequently, A satisfies (40) for $h_A(t)$, and \bar{A} satisfies a similar identity for $h_{\bar{A}}(t)$. We will show that if $t > 0$ is small enough, then \mathcal{F} is a strict contraction.

It is well-known (see [8]) that $e^{-tA} : L^\infty(\Omega) \rightarrow L^\infty(\Omega)$ is a contraction semigroup, i.e.,

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

For $A \in X$, it is easy to see that the function $h_A \in L^\infty([0, T] \times \Omega)$ with an upper bound independent of A

$$M = X_0[\|\tilde{k}_u\|_\infty + \|\tilde{k}_a - \tilde{k}_u\|_\infty T \|\tilde{r}\|_\infty e^{T\|\tilde{b}_u\|_\infty B_0}]. \quad (43)$$

Also, for any $A \in X$, we have that

$$\left\| \int_0^t e^{\int_0^v \tilde{b}_u(A(u))A(u) du} \right\|_\infty \leq e^{T\|\tilde{b}_u\|_\infty B_0} = N. \quad (44)$$

Estimate

$$\begin{aligned} & \|\mathcal{F}A(t) - \mathcal{F}\bar{A}(t)\|_\infty \\ &= \left\| \int_0^t e^{-(t-s)A} [B_0(h_A(s) - h_{\bar{A}}(s)) - \mathcal{F}A(s)h_A(s) + \mathcal{F}\bar{A}(s)h_{\bar{A}}(s)] ds \right\|_\infty \\ &\leq \int_0^t B_0 \|h_A(s) - h_{\bar{A}}(s)\|_\infty + M \|\mathcal{F}A(s) - \mathcal{F}\bar{A}(s)\|_\infty + B_0 \|h_A(s) - h_{\bar{A}}(s)\|_\infty ds. \end{aligned} \quad (45)$$

After a number of manipulations it can be shown that

$$\|h_A(s) - h_{\bar{A}}(s)\|_\infty \leq K_2 X_0 \|A - \bar{A}\|_{L^\infty([0,T] \times \Omega)}. \quad (46)$$

The constant K_2 is given by

$$K_2 = L_{k_u} + \|r\|_\infty N T L_{k_a} + \|k_a\|_\infty K_1 + \|k_u\|_\infty K_1,$$

where

$$K_1 = \|r\|_\infty N T^2 (L_r + B_0 L_{b_u}) + \|r\|_\infty N T^2 (B_0 L_{b_u} + \|b_u\|_\infty) + T N L_r.$$

The constants $L_{k_u}, L_{k_a}, L_r, L_{b_u}$ are the Lipschitz constants for the functions k_u, k_a, r, b_u and the constants M, N are given by (43), (44).

Finally, using (46) we obtain the following estimate for (45)

$$\|\mathcal{F}A(t) - \mathcal{F}\bar{A}(t)\|_\infty \leq 2tB_0X_0K_2\|A - \bar{A}\|_{L^\infty([0,T] \times \Omega)} + tM\|\mathcal{F}A(t) - \mathcal{F}\bar{A}(t)\|_\infty.$$

We choose t so small that $tM < 1/2$. Hence,

$$\|\mathcal{F}A(t) - \mathcal{F}\bar{A}(t)\|_\infty \leq 4tB_0X_0K_2\|A - \bar{A}\|_{L^\infty([0,T] \times \Omega)}.$$

It follows that \mathcal{F} is a strict contraction as long as $t < \min\{\frac{1}{2M}, \frac{1}{4B_0X_0K_2}\}$. Given any $t > 0$, we select a $t_1 > 0$ so small that $t_1 < \min\{\frac{1}{2M}, \frac{1}{4B_0X_0K_2}\}$. We can apply the contraction mapping principle to find a weak solution A existing on the time interval $[0, t_1]$. Since $A(t) \in L^\infty(\Omega)$ for $0 \leq t \leq t_1$, we can assume $A(t_1) \in L^\infty(\Omega)$. Since the value of the constants $\frac{1}{2M}$ and $\frac{1}{4B_0X_0K_2}$ remains unchanged, we can 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 on the full interval $[0, T]$. Using a contraction mapping principle, we have established the existence of a unique nonnegative solution B to the problem (36)-(6) belonging to the class (42). Consequently, the functions X_u, X_{ud}, X_a, X_{ad} are also nonnegative for all x and t . ■

Better regularity of the solution can be obtained provided that the coefficients $k_u, k_a, r, b_u \in C^{k-1,1}[0, B_0]$. In addition, weak maximum principle will guarantee that the solution B is bounded by B_0 .

Theorem 7. *Let B be the solution from Theorem 6. Let $k \geq 1$ and $p > 1$ such that $p > \frac{n}{k}$ and assume that the coefficients $k_u, k_a, b_u, b_a, r \in C^{k-1,1}[0, B_0]$. Then the solution B belongs to the class (9). Moreover, B is nonnegative and bounded by B_0 .*

Proof of Theorem 7: The following lemma is required to establish stronger regularity properties of the solution B .

Lemma 6. *Let $k \geq 1$ and $p > 1$ such that $p > \frac{n}{k}$ and let $B(t)$ belong to $H^{k,p}(\Omega)$. Assume that the coefficients $k_u, k_a, r, b_u \in C^{k-1,1}[0, B_0]$. (The case $k = 1$ corresponds to the class of Lipschitz continuous functions.) Then $h_B(t)$ also belongs to $H^{k,p}(\Omega)$.*

The better regularity is an easy consequence of Lemma 6 and Theorem 5 via the bootstrap method. Now recall from Theorem 6 that h_B is nonnegative. Hence, from (36) it follows that

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

We introduce $\Omega_\tau = (\tau, T] \times \Omega$ for $\tau > 0$. Weak maximum principle [6] on Ω_τ yields

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

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

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

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