On the Well-Posedness of a Mathematical Model of Quorum-Sensing in Patchy Biofilm Communities

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Abstract

We analyze a system of reaction-diffusion equations that models quorum-sensing in a growing biofilm. The model comprises two nonlinear diffusion effects: a porous medium type degeneracy, and super diffusion. We prove the well-posedness of the model. In particular, we present for the first time a uniqueness result for this type of problem. Moreover, we illustrate the behavior of model solutions in numerical simulations.

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1 Introduction

Most bacteria live in biofilm communities rather than in planktonic cultures. Biofilms are bacterial accumulations forming on biotic or abiotic surfaces (called substrata) in aqueous surroundings. Whenever the environmental conditions allow for bacterial growth, cells attach to the substratum and start to grow and divide. They produce a gel-like layer, the so-called EPS (extracellular polymeric substances) [13]. Embedded in the self-produced EPS biofilm bacteria are better protected against harmful environmental impacts than planktonic bacteria. For example, cells in biofilm colonies are more resistant against antibiotic agents, and the EPS protects them against mechanical wash-out [13].

Biofilms are important in applications in various fields. They are beneficially used in environmental engineering technologies, e.g. for groundwater protection and wastewater treatment. However, in other occurrences biofilms can be harmful. If they form
on implants and natural surfaces in the human body, they can provoke bacterial infections. Biofilm contamination can lead to health risks in food processing environments, and biofouling of industrial equipment or ships can cause severe economic defects for the industry.

Quorum-sensing is a cell-cell communication mechanism used by bacteria to coordinate gene expression and behavior in groups based on the local density of the bacterial population [12]. Bacteria constantly produce and release low amounts of signaling molecules (also called autoinducers). When the concentration of autoinducers passes a certain threshold, the cells are rapidly induced, and switch from a so-called down-regulated to an up-regulated state. In an up-regulated state they typically produce the signaling molecule at a highly increased rate.

Quorum sensing is not yet very well-understood. Different biological theories and interpretations exist [12], which are currently actively researched, both in experimental microbiology and in mathematical and theoretical biology, primarily for planktonic bacterial populations but also in the context of biofilms. In this paper we are concerned with analytical aspects of the biofilm growth and quorum sensing model introduced in [10].

Mathematical models of biofilms have been studied for several decades. They range from traditional one-dimensional models that describe biofilms as homogeneous layers, to more recent two- and three-dimensional biofilm models that account for the spatial heterogeneity of biofilm communities that can be observed in the lab. For the latter a variety of mathematical modeling concepts has been suggested, including discrete stochastic particle based models, discrete stochastic cellular automata, and deterministic continuum models based on the description of the mechanical properties of biofilms [23]. The model that we study is based on an interpretation of a biofilm as a continuous, spatially structured microbial population. It is a system of four highly nonlinear reaction-diffusion equations for the dependent variables volume fractions of up-regulated and down-regulated cells, concentration of a growth limiting nutrient and concentration of the signaling molecule. The model was originally proposed in [10], where in numerical simulations the contribution of environmental hydrodynamics to the transport of signaling molecules and its effect on inter-colony communication and up-regulation was studied. Analytical aspects of the model were not addressed; for example the question of well-posedness was left open. This will be studied in our article.

The quorum-sensing model extends the single-species biofilm growth model that was originally proposed in [6]. It is combined with a model for quorum-sensing in planktonic cultures that was suggested in [16]. The prototype biofilm model [6] consists of two reaction-diffusion equations for the biomass density and the growth limiting substrate. The diffusion coefficient for biomass vanishes for vanishing biomass density and it blows up if the biomass density approaches an upper bound. Thus, the model contains two nonlinear diffusion effects. It degenerates like the porous medium equation and it shows super diffusion. This prototype model was mathematically analyzed and numerically studied in a series of papers, for both mathematical and biological interest (cf. [3, 5, 7, 9]). In particular, an existence and uniqueness result could be established.

The prototype single-species single-substrate biofilm model has been previously
extended to model biofilms which consist of several types of biomass and account for multiple dissolved substrates. The model introduced in [2] describes the diffusive resistance of biofilms against the penetration by antibiotics. In [19] an amensalistic biofilm control system was modeled (a beneficial biofilm controls the growth of a pathogenic biofilm). In both articles, existence proofs for the solutions were given, and numerical studies were presented. The structure of the governing equations of the mentioned multi-species models is similar, however, differs essentially from the mono-species model. Therefore, the analytical results for the prototype model could not all be carried over to the more involved dual-species case. For example, the question of uniqueness of solutions remained unanswered in [2] and [19].

Compared to the models in [2, 19], the particularity of the quorum sensing model is, that adding the governing equations for the two biomass fractions, i.e. for the up- and down-regulated cells, we recover exactly the mono-species biofilm model. Taking advantage of the results obtained in [9] for the single-species model we are able to prove the existence and uniqueness of solutions of the quorum-sensing model and the continuous dependence of solutions on initial data. We want to emphasize that it is the first time a uniqueness result is obtained for multi-species diffusion-reaction models of biofilms that extend the prototype model [6]. Our proof of the existence of solutions is based on the non-degenerate approximations developed in [9]. However, our approach in the present paper is different and leads to a uniqueness result for the solutions. We hope that this will help us to answer the question of uniqueness of solutions for the antibiotic and probiotic model, which was left open in the articles [2] and [19].

2 Mathematical Model

A mathematical description of quorum-sensing in biofilms requires to distinguish two types of bacteria, the up-regulated cells and the down-regulated cells, and to include a mechanism by which cells switch between these two states.

We are concerned with the model of quorum sensing in biofilm communities proposed in [10], which extends the mono-species biofilm growth model [6] and combines it with a mathematical model of quorum-sensing for suspended populations [18]. The dependent model variables are the volume fraction occupied by the down-regulated and up-regulated cells, the concentration of the signaling molecule, and the concentration of the growth-limiting nutrient. The EPS is implicitly taken into account, in the sense that biomass volume fractions describe the sum of biomass and EPS assuming that their volume ratio is constant. Since the number of cells that can be accommodated per unit volume is limited by a given constant, the volume fraction occupied by biomass can also be understood as a measure for biomass density.

The model is formulated in terms of a system of nonlinear reaction-diffusion equations in a bounded spatial domain \( \Omega \subset \mathbb{R}^n \), \( n \in \{1, 2, 3\} \). The spatial independent variable is denoted by \( x \in \Omega \) and \( t \geq 0 \) denotes the time variable. The dependent variables \( X \) and \( Y \) denote the volume fractions occupied by down- and up-regulated biomass, respectively. The dependent variables \( A \) and \( S \) denote the concentrations of the autoinducer and of the growth controlling substrate. Both are assumed to be dis-
solved and do not occupy space. In dimensionless form, these four dependent variables satisfy the parabolic system

\[
\begin{align*}
\partial_t X &= d \nabla \cdot (D_M(M) \nabla X) + k_3 \frac{XS}{k_3 + S} - k_4 X - k_5 A^m X + k_5 Y \\
\partial_t Y &= d \nabla \cdot (D_M(M) \nabla Y) + k_3 \frac{YS}{k_3 + S} - k_4 Y + k_5 A^m X - k_5 Y \\
\partial_t S &= \nabla \cdot (D_S(M) \nabla S) - k_1 \frac{SM}{k_2 + S} \\
\partial_t A &= \nabla \cdot (D_A(M) \nabla A) - \gamma A + \alpha X + (\alpha + \beta)Y.
\end{align*}
\] (1)

The constants \(d, k_2\) and \(\gamma\) are positive, \(m \geq 1\) and the coefficients \(k_1, k_3, k_4, k_5, \alpha\) and \(\beta\) are non-negative. The total biomass fraction \(M = X + Y\) denotes the volume fraction occupied by up-regulated or down-regulated cells. The biomass components are normalized with respect to the physically maximal possible cell density, hence we necessarily require \(M = X + Y \leq 1\). The autoinducer concentration \(A\) is normalized with respect to the threshold concentration for induction. Thus, induction occurs locally in the biofilm if \(A\) reaches approximately 1 from below. If \(A\) locally decreases from a value larger than 1 to a value below 1, down-regulation at constant rate \(k_5\) will dominate. Finally, the substrate concentration \(S\) is normalized with respect to a characteristic value for the system, such as the nutrient concentration at the boundary of the domain, if Dirichlet conditions are applied.

The solid region occupied by the biofilm as well as the liquid area are assumed to be continua. The actual biofilm is then described by the region \(\Omega_2(t) := \{x \in \Omega \mid M(x, t) > 0\}\) and the liquid surroundings by \(\Omega_1(t) := \{x \in \Omega \mid M(x, t) = 0\}\). The substratum, on which the biofilm grows, is part of the boundary \(\partial \Omega\).

In our model, induction switches the cells between down- and up-regulated states, without changing their growth behavior. This includes, for example, microbial systems in which induction affects only virulence factors, or the composition of EPS but not their production rates. Under this hypothesis we can assume that the spatial spreading of both biomass fractions is described by the same diffusion operator

\[D_M(M) := \frac{M^a}{(1 - M)^b}\]

with \(a, b \geq 1\). The biomass motility constant \(d > 0\) in the equations for the biomass components is small compared to the diffusion coefficients \(D_S\) and \(D_A\) of the dissolved substrates. This reflects that the cells are to some extent immobilized in the EPS matrix. Spatial expansion of the biofilm is driven by biomass accumulation. The biomass diffusion coefficient \(D_M(M)\) vanishes when the total biomass approaches zero and blows up when the biomass density tends to its maximum value. The polynomial degeneracy \(M^a\) is well-known from the porous medium equation, it guarantees that spatial spreading is negligible for low values of \(M\) and yields the separation of biofilm and liquid phase, i.e. a finite speed of interface propagation. Spreading of biomass only takes place when the total biomass fraction takes values close to its maximal possible value. For \(M = 1\) instantaneous spreading occurs, known as the effect of super diffusion. The singularity at \(M = 1\) ensures the maximal bound for the biomass density, which is a physical limitation as the number of cells that fits into a unit volume is bounded. Since biomass is produced as long as sufficient nutrients are available, this
upper bound cannot be guaranteed by the growth terms alone. The degeneracy $M^a$
alone does not yield this maximum bound for the cell density, while the singularity $(1-M)^{-b}$
do not guarantee the separation of biofilm and liquid region by a sharp interface.
Consequently, both nonlinear diffusion effects together are required to describe spatial
expansion of the biofilm.

The diffusion coefficients of the dissolved substrates depend on the cell density
as well, however in a non-critical way. The diffusion coefficients $D_S$ and $D_A$ are lower
inside the biofilm than in the surrounding liquid region. In [10] the linearization ansatz
\[ D_{S,A}(M) = D_{S,A}(0) - M(D_{S,A}(0) - D_{S,A}(1)), \]
is made, where $D_{S,A}(0)$ denotes the diffusion coefficient in water and and $D_{S,A}(1)$
the diffusion coefficient in a fully compressed biofilm. Hence, the functions $D_S(M)$
and $D_A(M)$ are bounded from below and above by a positive constant and essentially
behave like Fickian diffusion. In fact, in many cases, in particular for substrates of
small molecule size, such as oxygen, carbon, etc., $D_{S,A}(0) \approx D_{S,A}(1)$. Without loss of
generality in the sequel we assume
\[
D_S(M) = d_1 \\
D_A(M) = d_2,
\]
where the constants $d_1$ and $d_2$ are positive.

Apart from the spatial spreading of biomass and the diffusive transport of signaling
molecules and nutrients the following processes are included in the model:

- Up-regulated and down-regulated biomass is produced due to the consumption
  of nutrients. This mechanism is described by Monod reaction terms, where the
  constant $k_3$ reflects the maximum specific growth rate, and $k_2$ the Monod half
  saturation constant. The constant $k_1$ is the maximum specific consumption rate,
  which can be computed from the maximum growth rate and a yield coefficient
  that indicates how much substrate is required to produce a unit of biomass.
  Generally, $k_1 \gg k_3$ holds. For our non-dimensional formulation we choose the
  time-scale for growth, i.e. $1/k_3$, for normalization. Thus, $k_3 = 1$.

- Natural cell death is included and described by the lysis rate $k_4$. This effect can
  be dominant compared to cell growth, if the substrate concentration becomes
  sufficiently small.

- The signaling molecules decay abiotically at rate $\gamma$.

- Due to an increase of the autoinducer concentration $A$ down-regulated cells are
  converted into up-regulated cells at rate $\kappa_5 A^m$. Modeling this by mass action
  kinetics we obtain for the degree of polymerization $m$ in the synthesis of the
  signaling molecule, $m = 2$. We lump additional secondary processes into this
  constant and obtain a value $2 < m < 3$ [10]. Up-regulated cells are converted
  back to down-regulated cells at constant rate $\kappa_5$. If $A < 1$ the latter effect
  dominates, if $A > 1$ up-regulation is super-linear.
• Finally, down-regulated cells produce the signaling molecule at rate $\alpha$, while up-regulated cells produce it at the increased rate $\alpha + \beta$, where $\beta$ is one order of magnitude larger than $\alpha$. For technical reasons, we will require in our analysis $\alpha + \beta > \gamma$, i.e. the signaling molecule production rate of the up-regulated cells is higher than the abiotic decay rate. For all practical purposes, this is not a severe model restriction; see also Table 4.1, where a set of parameters is compiled from the literature. If the opposite was true, the autoinducer molecules would decay faster than they are produced in an up-regulated system and no noteworthy accumulation could take place.

It remains to specify initial and boundary values for the biomass fractions and substrate concentrations to complete the model (2), which will be made more precise in the following section.

3 Analysis

3.1 Preliminaries

We study, for technical reasons, the model in the auxiliary form

$$
\begin{align*}
\partial_t X &= d \nabla \cdot (D_M(M) \nabla X) + k_3 \frac{XS}{k_2+S} - k_4 X - k_5 |A|^m X + k_5 |Y| \\
\partial_t Y &= d \nabla \cdot (D_M(M) \nabla Y) + k_3 \frac{YS}{k_2+S} - k_4 Y + k_5 |A|^m X - k_5 |Y| \\
\partial_t S &= d_1 \Delta S - k_1 \frac{SM}{k_2+S} \\
\partial_t A &= d_2 \Delta A - \gamma A + \alpha X + (\alpha + \beta)Y.
\end{align*}
$$

but point out that non-negative solutions of (1) solve (2) and vice versa, i.e. after non-negativity is shown $|.|$ can be removed from the first and second equation of (2) to obtain (1).

For simplicity we assume homogeneous Dirichlet boundary conditions for the biomass components $X$ and $Y$ and the concentration of the signaling molecule $A$, and constant Dirichlet conditions for the nutrient concentration $S$

$$
\begin{align*}
X|_{\partial \Omega} &= Y|_{\partial \Omega} = A|_{\partial \Omega} = 0 \\
S|_{\partial \Omega} &= 1.
\end{align*}
$$

If the biofilm is contained in the inner region of $\Omega$, away from its boundary, this situation describes a growing biofilm in the absence of a substratum. Such biofilms are often called microbial flocs, which play a major role in biological wastewater treatment. The boundary conditions imposed on the concentration of nutrients reflect a constant unlimited nutrient supply at the boundary of the considered domain. Similarly, keeping $A = 0$ at the boundary, enforces a removal of autoinducers from the domain. These are very specific boundary conditions, primarily chosen for convenience. However, the solution theory we develop in the following sections easily carries over to more general boundary values, which are relevant and often more appropriate for applications.
The initial data for the model variables are given by
\[ X|_{t=0} = X_0, \quad Y|_{t=0} = Y_0, \quad S|_{t=0} = S_0, \quad A|_{t=0} = A_0 \]
with \( S_0, X_0, Y_0, A_0 \in L^2(\Omega) \) satisfying the compatibility conditions and
\[
\begin{cases}
0 \leq S_0(x) \leq 1, & 0 \leq A_0(x) \leq 1 \\
X_0(x) \geq 0, & Y_0(x) \geq 0, \quad X_0(x) + Y_0(x) \leq 1
\end{cases}
\]
for almost every \( x \in \Omega \). In fact, usually, the initial autoinducer concentration \( A_0 \equiv 0 \).

For \( T > 0 \) we denote the parabolic cylinder by \( Q_T := \Omega \times [0,T] \).

**Definition 3.1.** We call the vector valued function \((X, Y, A, S)\) a solution of system (2) with boundary and initial data (3) and (4), if its components belong to the class
\[
X, Y, A, S \in C([0, T]\); L^2(\Omega)) \cap L^\infty(Q_T)
\]
\[
A, S \in L^2((0, T); H^1(\Omega))
\]
\[
D_M(M) \nabla X , D_M(M) \nabla Y \in L^2((0, T); L^2(\Omega))
\]
for any \( T > 0 \) and satisfy system (2) in distributional sense.

To be more precise, if \((X, Y, A, S)\) is a solution according to Definition 3.1, then the equality
\[
\int_{\Omega} X(x,T) \varphi(x) dx - \int_{\Omega} X_0(x) \varphi(x) dx = -d \int_{Q_T} D_M(M(x,t)) \nabla X(x,t) \cdot \nabla \varphi(x) dt dx
\]
\[
+ \int_{Q_T} \left( k_3 \frac{X(x,t)S(x,t)}{k_2 + S(x,t)} - k_4 X(x,t) - k_5 |A(x,t)|^m X(x,t) + k_5 |Y(x,t)| \right) \varphi(x) dt dx
\]
holds for all test-functions \( \varphi \in C_0^\infty(\Omega) \) and almost every \( T > 0 \). The determining equations for the other components of the solution are defined in an analogous way.

Compared to other biofilm models with several particulate substances, such as [2, 19], the particularity of the quorum-sensing model (2) is that we recover the single-species biofilm growth model for the total biomass fraction \( M \) and the nutrient concentration \( S \). Indeed, adding the equations for the biomass fractions \( X \) and \( Y \) in system (2) we obtain
\[
\begin{cases}
\partial_t M = d \nabla \cdot (D_M(M) \nabla M) + k_3 \frac{MS}{k_2 + S} - k_4 M \\
\partial_t S = d_1 \Delta S - k_5 \frac{SM}{k_2 + S}
\end{cases}
\]
with initial and boundary values
\[
\begin{cases}
M|_{\partial \Omega} = 0, & S|_{\partial \Omega} = 1 \\
M|_{t=0} = M_0 = X_0 + Y_0, & S|_{t=0} = S_0,
\end{cases}
\]
which is exactly the single species biofilm-model proposed in [6]. A solution theory for this system was developed in [9]. Our proof of the well-posedness of the quorum-sensing model will be essentially based on the results obtained for the mono-species model. For the convenience of the reader we recall and summarize all relevant properties of the solutions of system (6), which will be used in the sequel. The following theorem yields existence and regularity results for the solutions.
Theorem 3.2. If the initial data satisfy
\[
\begin{cases}
S_0 \in L^\infty(\Omega) \cap H^1(\Omega) \\
0 \leq S_0(x) \leq 1, \quad S_0|_{\partial\Omega} = 1 \\
M_0 \in L^\infty(\Omega), \quad F(M_0) \in H^1_0(\Omega) \\
M_0 \geq 0, \quad ||M_0||_{L^\infty(\Omega)} < 1,
\end{cases}
\]
where \(F(M) := \int_0^M \frac{e^{z^s}}{(1-z^s)^{\kappa}} \, dz, \quad 0 \leq M < 1,\) then there exists a unique solution \((M, S)\) satisfying (6) in the sense of distributions and the solution belongs to the class
\[
\begin{cases}
M, S \in L^\infty(\Omega \times \mathbb{R}_+) \cap C(\mathbb{R}_+; L^2(\Omega)) \\
F(M), S \in L^\infty(\mathbb{R}_+; H^1(\Omega)) \cap C(\mathbb{R}_+; L^2(\Omega)) \\
0 \leq S(x,t), M(x,t) \leq 1, \quad ||M||_{L^\infty(\Omega \times \mathbb{R}_+)} < 1.
\end{cases}
\]
Furthermore, the following estimates hold
\[
\begin{align*}
||S(t)||_{H^1(\Omega)} &+ ||F(M(t))||_{H^1(\Omega)}^2 \leq C( ||S_0||_{H^1(\Omega)}^2 + ||F(M_0)||_{H^1(\Omega)}^2 + 1) \\
||S(t)||_{H^1(\Omega)} &+ ||\partial_t S(t)||_{H^{-1}(\Omega)} + ||F(M(t))||_{H^1(\Omega)}^2 \\
&+ ||M(t)||_{H^1(\Omega)} + ||\partial_t M(t)||_{H^{-1}(\Omega)} \leq C(1 + \frac{1}{t^{\kappa}}),
\end{align*}
\]
for some constant \(C \geq 0,\) where \(0 < s < \frac{1}{1+\kappa}\) and \(\kappa \geq 1.\) The constants are independent of the initial data \((S_0, M_0).\)

For further details and the proof see Theorem 3.1 in [9]. Moreover, the semigroup generated by the solutions of system (6) is Lipschitz-continuous in \(L^1(\Omega)\)-norm. The following result recalls Theorem 3.2 of [9].

Proposition 3.3. Let \((S, M)\) and \((\tilde{S}, \tilde{M})\) be two solutions of system (6) corresponding to initial data \((S_0, M_0),\) respectively \((\tilde{S}_0, \tilde{M}_0),\) and the initial data satisfy the assumptions of the previous theorem. Then, the following estimate holds
\[
||S(t) - \tilde{S}(t)||_{L^1(\Omega)} + ||M(t) - \tilde{M}(t)||_{L^1(\Omega)} \leq e^{(k_1+k_2+k_3)t} \left( ||S_0 - \tilde{S}_0||_{L^1(\Omega)} + ||M_0 - \tilde{M}_0||_{L^1(\Omega)} \right).
\]
In particular, the solution is unique within class (8).

Another important result for our analysis is that the biomass density does not attain the singularity as long as the initial concentration does not take this value (cf. Proposition 3.3 in [3]).

Proposition 3.4. If the initial data \((S_0, M_0)\) satisfy the assumptions of Theorem 3.2 and there exists some \(\delta \in (0, 1)\) such that
\[
||M_0||_{L^\infty(\Omega)} = 1 - \delta,
\]
then the corresponding solution \((S, M)\) satisfies
\[
||M(t)||_{L^\infty(\Omega)} \leq 1 - \eta
\]
for \(t > 0\) and some \(\eta \in (0, 1),\) where the constant \(\eta\) depends on \(\delta\) and \(\Omega\) only.
Consequently, the substrate concentration $S$ and the total biomass density $M$ can be regarded as known functions and the original system (2) reduces to a system of equations for the biomass fraction $X$ and the concentration of the quorum-sensing signaling molecule $A$

$$\begin{align*}
\partial_t X &= d \nabla \cdot (D \nabla X) + \frac{k_3 S}{k_2 + S} X - k_4 X - k_5 |A|^m X + k_5 (M - X), \\
\partial_t A &= d_2 \Delta A - \gamma A + \alpha X + (\alpha + \beta)(M - X),
\end{align*}$$

where the diffusion coefficient of the biomass fraction is defined by

$$D(x, t) := \frac{M(x, t)}{a(1 - M(x, t))^b}.$$ 

Here, we used the positivity of the biomass component $Y$, which will be proved in Section 3.3. We rewrite this non-autonomous semi-linear system with bounded coefficients as

$$\begin{cases}
\partial_t X = d \nabla \cdot (D \nabla X) + g X - k_5 |A|^m X + h \\
\partial_t A = d_2 \Delta A - \gamma A - \beta X + l,
\end{cases} \tag{9}$$

where the interaction terms are given by the known functions

$$\begin{align*}
g(x, t) &= k_3 \frac{S(x, t)}{k_2 + S(x, t)} - k_4 - k_5, \\
h(x, t) &= k_5 M(x, t) \geq 0, \\
l(x, t) &= (\alpha + \beta) M(x, t) \geq 0.
\end{align*}$$

Note that all coefficient functions are bounded, $g, h, l \in L^\infty(\Omega \times \mathbb{R}^n)$ by Theorem 3.2, and the diffusion coefficient $D$ is non-negative and bounded by Theorem 3.3. Indeed, if the initial density satisfies $0 \leq M_0 < 1 - \delta$ for some $\delta \in (0, 1)$, then there exists a positive constant $\eta \in (0, 1)$ such that $0 \leq M(x, t) \leq 1 - \eta$ for almost all $t > 0$ and $x \in \Omega$. Consequently,

$$0 \leq D(x, t) = \frac{(M(x, t))^a}{(1 - M(x, t))^b} \leq \frac{1}{(1 - M(x, t))^b} \leq \frac{1}{\eta^b},$$

that is, $D$ is non-negative and satisfies $D \in L^\infty(\Omega \times \mathbb{R}^+_+)$.

The solution theory can be extended to less regular initial data and other boundary conditions. Moreover, it was shown in [9] that the semi-group generated by the solutions of system (6) is continuous in $L^1(\Omega)$-norm and possesses a compact global attractor.

### 3.2 Uniqueness

In this paragraph we prove the uniqueness and $L^2(\Omega)$-Lipschitz-continuity of solutions with respect to initial data of the semi-linear parabolic system (9) with bounded coefficients, which degenerates when the total biomass density $M$ approaches zero. We consider initial data $X_0, Y_0, A_0 \in H^1_0(\Omega)$, $S_0 \in H^1(\Omega)$ such that $S_0|\partial\Omega = 1$ and

$$0 \leq S_0, X_0, Y_0, A_0 \leq 1, \quad \|X_0 + Y_0\|_{L^\infty(\Omega)} < 1.$$
Theorem 3.5. We assume that the initial data \((X_0, Y_0, S_0, A_0)\) satisfy the assumptions stated above. Then, there exists at most one non-negative solution \((X, A)\) of system (9) within the class of solutions considered in Definition 3.1.

Proof. We assume \((X, A)\) and \((\bar{X}, \bar{A})\) are two such solutions corresponding to initial data \((X_0, A_0)\) and define their differences \(u := X - \bar{X}\) and \(v := A - \bar{A}\). Then, \(v\) belongs to the space \(L^2((0, T); H^1_0(\Omega))\), \(u\) satisfies \(D_M(M(t))\nabla u(t) \in L^2(\Omega)\) for almost every \(t \in (0, T]\) and \(\partial_t u, \partial_v v \in L^2((0, T); H^{-1}(\Omega))\) for some \(T > 0\). Moreover, the functions \(u\) and \(v\) satisfy the system

\[
\begin{aligned}
\partial_t u &= d\nabla \cdot (D\nabla u) + gu - k_5(A^m X - \bar{A}^m \bar{X}) \\
\partial_t v &= d_2 \Delta v - \gamma v - \beta u
\end{aligned}
\]

with zero initial and boundary conditions

\[
\begin{aligned}
v|_{t=0} &= u|_{t=0} = 0 \\
u|_{\partial \Omega} &= v|_{\partial \Omega} = 0.
\end{aligned}
\]

If we formally multiply the second equation by \(v\) and integrate over \(\Omega\), we obtain the estimate

\[
\frac{1}{2} \frac{d}{dt} \|v(\cdot, t)\|_{L^2(\Omega)}^2 = -d_2 \|\nabla v(\cdot, t)\|_{L^2(\Omega)}^2 - \gamma \|v(\cdot, t)\|_{L^2(\Omega)}^2 - \beta \langle u(\cdot, t)v(\cdot, t) \rangle_{L^2(\Omega)}
\]

\[
\leq -\gamma \|v(\cdot, t)\|_{L^2(\Omega)}^2 - \beta \langle u(\cdot, t)v(\cdot, t) \rangle_{L^2(\Omega)}
\]

where we used the positivity of \(d_2\). Multiplying the first equation by \(u\) and integrating over \(\Omega\) yields

\[
\frac{1}{2} \frac{d}{dt} \|u(\cdot, t)\|_{L^2(\Omega)}^2 = -d \int_\Omega \partial_t \nabla u(x, t)^2 dx + \int_\Omega g(x, t)|u(x, t)|^2 dx \\
- k_5 \int_\Omega [A^m(x, t)X(x, t) - \bar{A}^m(x, t)\bar{X}(x, t)] u(x, t) dx.
\]

In order to estimate the last integral we observe

\[
A^m X - \bar{A}^m \bar{X} = A^m u + \bar{X}(A^m - \bar{A}^m) = A^m u + v \bar{X} m \int_0^1 (sA + (1-s)\bar{A})^m - 1 ds.
\]

Since \(\partial_t \nabla u(x, t)\) and \(\partial_t \nabla v(x, t)\) are non-negative we obtain

\[
\frac{1}{2} \frac{d}{dt} \|u(\cdot, t)\|_{L^2(\Omega)}^2 \leq \int_\Omega g(x, t)|u(x, t)|^2 dx + k_5 \int_\Omega A^m(x, t)u^2(x, t) dx \\
+ k_5 \int_\Omega \bar{X}(x, t)v(x, t) u(x, t) m \int_0^1 (sA(x, t) + (1-s)\bar{A}(x, t))^{m-1} ds dx \\
\leq C_1 \|u(\cdot, t)\|_{L^2(\Omega)}^2 + C_2 \langle u(\cdot, t)v(\cdot, t) \rangle_{L^2(\Omega)}.
\]
for some constants \(C_1, C_2 \geq 0\). Here, we used that the functions \(A, \tilde{A}, \tilde{X}\) and \(g\) belong to the class \(L^{\infty}(Q_T)\). Adding both inequalities and using the Cauchy-Schwarz inequality yields

\[
\frac{d}{dt} (\|u(., t)\|_{L^2(\Omega)}^2 + \|v(., t)\|_{L^2(\Omega)}^2) \leq C_3 (\|u(., t)\|_{L^2(\Omega)}^2 + \|v(., t)\|_{L^2(\Omega)}^2),
\]

(10)

for some \(C_3 \geq 0\). Invoking Gronwall’s Lemma and the initial conditions \(u|_{t=0} = v|_{t=0} = 0\), it follows \(u = v = 0\) almost everywhere.

For the definiteness of the integrals appearing in the estimates of our proof we refer to the next paragraph.

Note that the proof of Theorem 3.5 implies the Lipschitz-continuity in \(L^2(\Omega)\)-norm of the semigroup generated by the solutions of the initial-/boundary-value problem (9).

**Corollary 3.6.** Let \((X, A)\) and \((\tilde{X}, \tilde{A})\) be two solutions of system (9) within the class of the previous theorem corresponding to initial data \((X_0, A_0)\), respectively \((\tilde{X}_0, \tilde{A}_0)\). Then, the following estimate holds

\[
\|X(., t) - \tilde{X}(., t)\|_{L^2(\Omega)}^2 + \|A(., t) - \tilde{A}(., t)\|_{L^2(\Omega)}^2 \\
\leq e^{Ct} \left( \|X_0 - \tilde{X}_0\|_{L^2(\Omega)}^2 + \|A_0 - \tilde{A}_0\|_{L^2(\Omega)}^2 \right),
\]

for some constant \(C \geq 0\).

**Proof.** The estimate follows immediately from inequality (10) in the proof of Theorem 3.5 and Gronwall’s Lemma.

Hence, assuming existence and uniqueness of solutions, the semi-group generated by the solutions of system (9) is Lipschitz-continuous in the topology of \(L^2(\Omega) \times L^2(\Omega)\)

\[
\|(X(t) - \tilde{X}(t), A(t) - \tilde{A}(t))\|_{L^2(\Omega) \times L^2(\Omega)} \leq e^{Ct} \|(X(0) - \tilde{X}(0), A(0) - \tilde{A}(0))\|_{L^2(\Omega) \times L^2(\Omega)}.
\]

As we pointed out in the preliminary paragraph of this section the question of uniqueness of solutions of the original system (2) reduces to prove the uniqueness of solutions of the semi-linear system (9). We formally obtained the uniqueness of solutions of the quorum-sensing model, the existence of solutions within the stated class will be shown in the following paragraph.

### 3.3 Existence

In order to prove the existence of solutions of the original system we consider non-degenerate auxiliary systems and show that the solutions of the auxiliary systems converge to the solution of the degenerate problem when the regularization parameter tends to zero. The ideas are based on the method developed in [9] for the mono-species model and the strategy applied in [2] and [19] to prove the existence of solutions of
functions are given by

\[
\begin{align*}
\frac{∂}{∂t} M &= d∇ \cdot (D_{\epsilon,M}(M)∇ M) + k_3\frac{YS}{K_2+S} - k_4 M - k_5 |A|^m M + k_5 |Y| \\
\frac{∂}{∂t} Y &= d∇ \cdot (D_{\epsilon,M}(M)∇ Y) + k_4\frac{YS}{K_2+S} - k_4 Y + k_5 |A|^m M - k_5 |Y| \\
\frac{∂}{∂t} S &= d_1 Δ S - k_1\frac{SM}{K_2+S} \\
\frac{∂}{∂t} A &= d_2 Δ A - γ A + α X + (α + β) Y,
\end{align*}
\]

(11)

where the regularized diffusion coefficient is defined as

\[
D_{\epsilon,M}(z) := \begin{cases} 
\frac{(z+\epsilon)^{α}}{(1-z)^{β}} & z \leq 1 - \epsilon \\
\frac{1}{z^{α}} & z \geq 1 - \epsilon.
\end{cases}
\]

Furthermore, we assume the initial data is regular and smooth, namely, that it belongs to the class

\[
\begin{align*}
S_0 &\in L^∞(Ω) \cap H^1(Ω), \quad 0 \leq S_0(x) \leq 1, \quad S_0|_{∂Ω} = 1 \\
A_0 &\in L^∞(Ω) \cap H^1_0(Ω), \quad 0 \leq A_0(x) \leq 1 \\
M_0 &= X_0 + Y_0 \in L^∞(Ω), \quad X_0, Y_0, F(M_0) \in H^1_0(Ω) \\
X_0, Y_0 &\geq 0, \quad \|M_0\|_{L^∞(Ω)} < 1,
\end{align*}
\]

(12)

where \(F(M) := \int_{0}^{M} \frac{x^n}{(1-z)\pi} dz\), for \(0 \leq M < 1\).

Adding the equations for the biomass components \(X\) and \(Y\) of system (11) we recover the non-degenerate auxiliary system for the single-species model

\[
\begin{align*}
\frac{∂}{∂t} M &= d∇ \cdot (D_{\epsilon,M}(M)∇ M) + k_3\frac{MS}{K_2+S} - k_4 M \\
\frac{∂}{∂t} S &= d_1 Δ S - k_1\frac{SM}{K_2+S},
\end{align*}
\]

(13)

which is a regularized version of (6). In [9] it was shown that for every (sufficiently small) \(\epsilon > 0\) there exists a unique solution \((S_ε, M_ε)\) of system (13) and the solutions are uniformly bounded with respect to the regularization parameter \(\epsilon\). Moreover, if the initial data belongs to class (12), the solution \(M_ε\) is separated from the singularity. To be more precise, there exists a constant \(η \in (0, 1)\), which is independent of \(\epsilon\), such that \(M_ε(x,t) < 1 - \eta\) holds for all \(x \in Ω, t > 0\) (cf. Proposition 6 in [9]).

Hence, we may regard \(M_ε = X_ε + Y_ε\) and \(S_ε\) as known functions and the problem reduces to prove the existence of solutions of the semi-linear system

\[
\begin{align*}
\frac{∂}{∂t} X &= d∇ \cdot (D_{ε,M}(X)∇ X) + g_ε X - k_5 |A|^m X + h_ε \\
\frac{∂}{∂t} A &= d_2 Δ A - γ A - β X + l_ε \\
X|_{∂Ω} &= 0, \quad A|_{∂Ω} = 0 \\
X|_{t=0} &= X_0, \quad A|_{t=0} = A_0.
\end{align*}
\]

(14)

The diffusion coefficient is defined as \(D_ε(x,t) := D_{ε,M}(M_ε(x,t))\) and the interaction functions are given by

\[
\begin{align*}
g_ε(x,t) &:= k_3\frac{S_ε(x,t)}{K_2+S_ε(x,t)} - k_4 - k_5 \\
h_ε(x,t) &:= k_5 M_ε(x,t) \geq 0 \\
l_ε(x,t) &:= (α + β) M_ε(x,t) \geq 0,
\end{align*}
\]

(12)
where \((M_\varepsilon, S_\varepsilon)\) denotes the solution of the non-degenerate approximation (13). Here, we already used the positivity of the biomass component \(Y_\varepsilon\), which will be proved in the following lemma. In order to abbreviate the notation we introduce the new reaction terms \(f_1^\varepsilon\) and \(f_2^\varepsilon\),

\[
\begin{align*}
  f_1^\varepsilon(x, t, X(x, t), A(x, t)) &:= g_\varepsilon(x, t)X(x, t) - k_5|A(x, t)|^\alpha X(x, t) + h_\varepsilon(x, t) \\
  f_2^\varepsilon(x, t, X(x, t), A(x, t)) &:= -\gamma A(x, t) - \beta X(x, t) + l_\varepsilon(x, t).
\end{align*}
\]

We first show that all components of the solution of the non-degenerate approximation are non-negative and bounded.

**Lemma 3.7.** The components of the solution \((X_\varepsilon, Y_\varepsilon, S_\varepsilon, A_\varepsilon)\) of the auxiliary system (11) are non-negative and belong to the class \(L^\infty(\Omega \times \mathbb{R}_+).\)

**Proof.** The substrate concentration \(S_\varepsilon\) and the total biomass density \(M_\varepsilon = X_\varepsilon + Y_\varepsilon\) are non-negative and bounded by 1 according to Proposition 6 in [9]. We will show that the components \(X_\varepsilon, Y_\varepsilon\) and \(A_\varepsilon\) are non-negative. As \(X_\varepsilon + Y_\varepsilon = M_\varepsilon \leq 1\) this immediately implies the boundedness of the biomass fractions \(X_\varepsilon\) and \(Y_\varepsilon\). The boundedness of the molecule concentration \(A_\varepsilon\) then follows by a comparison theorem for scalar parabolic equations (cf. [22]). Indeed, the constant \(A_{\text{max}} := \frac{\alpha + \beta}{\gamma} > 1\) is a supersolution for \(A_\varepsilon\). It satisfies \(A_{\text{max}}|_{\partial \Omega} \geq 0 = A_\varepsilon|_{\partial \Omega}, A_{\text{max}}|_{t=0} \geq A_0 = A_\varepsilon|_{t=0}\) and

\[
\partial_t A_{\text{max}} - d_2 \Delta A_{\text{max}} + \gamma A_{\text{max}} - \alpha X_\varepsilon - (\alpha + \beta)Y_\varepsilon = \gamma A_{\text{max}} - \alpha X_\varepsilon - (\alpha + \beta)Y_\varepsilon \geq \gamma A_{\text{max}} - \alpha - \beta = 0,
\]

where we used that \(\alpha + \beta > \gamma\) (cf. Section 2). It remains to prove the positivity of the components \(X_\varepsilon, Y_\varepsilon\) and \(A_\varepsilon\). To this end we again apply a comparison theorem for parabolic equations to the biomass fraction of down-regulated cells: The constant \(\tilde{X} = 0\) is a subsolution for \(X_\varepsilon\). Indeed, it satisfies \(X_\varepsilon|_{\partial \Omega} \geq 0 = \tilde{X}|_{\partial \Omega}, X_0 = X_\varepsilon|_{t=0} \geq 0 = \tilde{X}|_{t=0}\) and

\[
\partial_t \tilde{X} - d_\nabla \cdot (D_\varepsilon(M_\varepsilon)\nabla \tilde{X}) - k_3 \frac{\tilde{X} S_\varepsilon}{k_2 + S_\varepsilon} + k_4 \tilde{X} + k_5|A_\varepsilon|^\alpha \tilde{X} - k_5|Y_\varepsilon| = -k_5|Y_\varepsilon| \leq 0.
\]

By the same arguments and owing to the positivity of \(X_\varepsilon\), the constant solution \(\tilde{Y} = 0\) is also a subsolution for \(Y_\varepsilon\), so we conclude \(Y_\varepsilon \geq 0\). Finally follows \(A_\varepsilon \geq 0\), by comparing with the subsolution \(\tilde{A} = 0\) for the biomass fraction \(A_\varepsilon\) and using the fact that the components \(X_\varepsilon\) and \(Y_\varepsilon\) are non-negative. \(\square\)

Having established positivity and uniform boundedness of solutions we are in a position to prove the existence of solutions of the reduced system (14). To this end we treat the region where the total biomass density becomes small and its complement in \(Q_T := \Omega \times [0, T]\) separately. In [9] it was shown that the solution \((S, M)\) of the single-species model is obtained via the \(L^2(\Omega)\)-limit of the solutions \((S_\varepsilon, M_\varepsilon)\) of the non-degenerate approximations

\[
S(t) = \lim_{\varepsilon \to 0} S_\varepsilon(t), \quad M(t) = \lim_{\varepsilon \to 0} M_\varepsilon(t)
\]
in \( C([0, T]; L^2(\Omega)) \), where \( T > 0 \) is arbitrary. We now define the domains

\[
Q_{\delta, T} := \{(x, t) \in Q_T \mid M(t, x) < \delta\}
\]

and \( Q^0_{\delta, T} := Q_T \setminus Q_{\delta, T} \) for some \( \delta \in (0, 1) \). Note that both subsets are open due to the Hölder-continuity of the solution \( M \) (cf. \[2\]).

**Lemma 3.8.** We assume the initial data belongs to class (12). Then, for all sufficiently small \( \epsilon > 0 \) there exists a unique solution \((A_\epsilon, X_\epsilon)\) of the auxiliary system (14) satisfying

\[
X_\epsilon, A_\epsilon \in L^2((0, T); H^1_0(\Omega)) \cap C([0, T]; L^2(\Omega)) \cap L^\infty(Q_T)
\]

\[\partial_t X_\epsilon, \partial_t A_\epsilon \in L^2((0, T); H^{-1}(\Omega)).\]

Moreover, the solutions are uniformly bounded with respect to \( \epsilon \) and satisfy the estimates

\[
\max_{t \in [0, T]} \|X_\epsilon(\cdot, t)\|_{L^2(\Omega)} + \|X_\epsilon\|_{L^2((0, T); H^1_0(\Omega))} + \|\partial_t X_\epsilon\|_{L^2((0, T); H^{-1}(\Omega))} \leq C_4^\epsilon \left(1 + \|X_0\|_{L^2(\Omega)}\right)
\]

\[
\max_{t \in [0, T]} \|A_\epsilon(\cdot, t)\|_{L^2(\Omega)} + \|A_\epsilon\|_{L^2((0, T); H^1_0(\Omega))} + \|\partial_t A_\epsilon\|_{L^2((0, T); H^{-1}(\Omega))} \leq C_5(1 + \|A_0\|_{L^2(\Omega)}),
\]

for some constants \( C_4^\epsilon, C_5 \geq 0 \), where \( C_5 \) is independent of \( \epsilon \). The solutions are even Hölder-continuous

\[X_\epsilon \in C^{\alpha, \frac{\alpha}{2}}(Q_T), \quad A_\epsilon \in C^{\alpha, \frac{\alpha}{2}}(Q_T)\]

for some \( \alpha, \alpha > 0 \). The Hölder constant \( \alpha_\epsilon \) depends on the parameter \( \epsilon \), the data and uniform bound of the approximate solutions only, the constant \( \alpha \) is independent of \( \epsilon \).

Finally, restricted to the domain \( Q^0_{\delta, T} \) the solutions \( X_\epsilon \) satisfy all estimates uniformly. To be more precise, the constant \( C_4^\epsilon \) in the inequality above and the Hölder constant \( \alpha_\epsilon \) are independent of \( \epsilon > 0 \) for the family of approximate solutions \( \{\tilde{X}_\epsilon\} \), where \( \tilde{X}_\epsilon := X_\epsilon|_{Q^0_{\delta, T}} \).

**Proof.** If the initial data \( M_0 \) and \( S_0 \) belong to class (12) the total biomass density \( M_\epsilon \) satisfies \( M_\epsilon(t, x) < 1 - \eta \) in \( Q_T \) for some \( \eta \in (0, 1) \), and the constant \( \eta \) is independent of \( \epsilon \). This implies that the diffusion coefficient \( D_\epsilon \) is positive and uniformly bounded from above by a constant independent of \( \epsilon \). Indeed, for all \( \epsilon < \eta \)

\[
e^a \leq D_\epsilon(M_\epsilon(x, t)) = \frac{(M_\epsilon(x, t) + \epsilon)^a}{(1 - M_\epsilon(x, t))^b} \leq \frac{(1 - \eta + \epsilon)^a}{(1 - (1 - \eta))^b} \leq \frac{1}{\eta^b}
\]

holds, that is \( D_\epsilon \in L^\infty(Q_T) \) and strictly positive. Hence, for all sufficiently small \( \epsilon > 0 \) the semi-linear auxiliary system (14) is regular and uniformly parabolic. The functions \( g_\epsilon, h_\epsilon, l_\epsilon, A_\epsilon \) and \( X_\epsilon \) are uniformly bounded with respect to the regularization parameter \( \epsilon \) by Lemma 3.7, which implies that the interaction functions \( f^1_\epsilon \) and \( f^2_\epsilon \) are uniformly bounded in \( Q_T \). By standard arguments (Galerkin approximations) follow the existence and uniqueness of the approximate solution \((X_\epsilon, A_\epsilon)\) belonging to the class stated in the lemma and satisfying the given estimates (cf. \[21\]). Moreover, the Hölder-continuity of solutions follows from Theorem 10.1, Chapter III in \[20\].

Note that due to the uniform boundedness of the approximate solutions the component \( A_\epsilon \) satisfies the semi-linear equation

\[
\partial_t A_\epsilon - d_2 \Delta A_\epsilon = H_\epsilon,
\]
Lemma 3.9. If $\epsilon > 0$ is sufficiently small, the product $\sqrt{\mathcal{D}_s} \nabla X_\epsilon$ is uniformly bounded in $L^2(Q_T)$ and the approximate solutions satisfy $X_\epsilon(t) \in H^s(\Omega)$ for some $s > 0$ and almost every $t > 0$. Moreover, there exists $\epsilon_0 > 0$ such that for all $\epsilon < \epsilon_0$

$$\|X_\epsilon\|_{L^2((0,T);H^s(\Omega))} \leq C$$

holds, where the constant $C \geq 0$ is independent of $\epsilon$.

Proof. Multiplying the first equation of system (14) by $X_\epsilon$ and integrating over $\Omega$ we obtain

$$\frac{1}{2} \frac{d}{dt} \|X_\epsilon(\cdot,t)\|_{L^2(\Omega)}^2 + d \int_\Omega \mathcal{D}_s(x,t) |\nabla X_\epsilon(x,t)|^2 \, dx = \int_\Omega X_\epsilon(x,t) f_1(x,t, X_\epsilon(x,t), A_\epsilon(x,t)) \, dx \leq C_6,$$

for some constant $C_6 \geq 0$. Due to Lemma 3.7 the constant $C_6$ is independent of $\epsilon$. By integrating this inequality from 0 to $T > 0$ follows the first statement of the lemma.

Furthermore, for sufficiently small $\epsilon > 0$ we obtain $X_\epsilon \leq M_\epsilon \leq 1 - \eta$ and consequently

$$X_\epsilon^a \leq D_{\epsilon,M}(X_\epsilon) = \frac{(X_\epsilon + \epsilon)^a}{(1 - X_\epsilon)^b} \leq \frac{(X_\epsilon + Y_\epsilon + \epsilon)^a}{(1 - (X_\epsilon + Y_\epsilon))^b} = D_{\epsilon,M}(M_\epsilon)$$

holds. So we derive the estimate

$$\int_\Omega X_\epsilon^a(x,t) |\nabla X_\epsilon(x,t)|^2 \, dx \leq \int_\Omega D_{\epsilon,M}(M_\epsilon(x,t)) |\nabla X_\epsilon(x,t)|^2 \, dx \leq C_7,$$

for some constant $C_7 \geq 0$ independent of the regularization parameter $\epsilon > 0$. This shows that $X_\epsilon^{\frac{a}{2}}(t) |\nabla X_\epsilon(t)| \in L^2(\Omega)$ or equivalently, $X_\epsilon^{\frac{a}{2}+1}(t) \in H^1(\Omega)$ for almost every $t \in [0,T]$. Finally, if a function satisfies $\varphi^\beta \in H^1(\Omega)$ for some $\beta > 1$, then $\varphi \in W^{x,2\beta}(\Omega)$
holds for all $s \leq \frac{1}{\beta}$. This implies $X_\epsilon(t) \in W^{s,2(\frac{s}{2}+1)}(\Omega)$ for $s \leq \frac{1}{\beta} + 1$. Since the domain $\Omega$ is bounded and $a \geq 1$ the embedding $W^{s,2a}(\Omega) \hookrightarrow H^s(\Omega)$ is continuous and we deduce $X_\epsilon(t) \in H^s(\Omega)$ for some positive $s > 0$. In particular, this proves that the family of approximate solutions $\{X_\epsilon\}$ is uniformly bounded in the Hilbert space $L^2((0,T);H^s(\Omega))$.

\section*{Lemma 3.10.} There exist functions

$$X^* \in L^\infty(Q_T) \cap L^2((0,T); H^s(\Omega))$$

$$A^* \in L^\infty(Q_T) \cap L^2((0,T); H_0^1(\Omega))$$

and a sequence $(\epsilon_k)_{k \in \mathbb{N}}$ tending to zero for $k \to \infty$ such that the family of solutions of the auxiliary systems (14) converge weakly

$$X_{\epsilon_k} \rightharpoonup X^*,$$

$$A_{\epsilon_k} \rightharpoonup A^*$$

in $L^2((0,T); H^s(\Omega))$, respectively $L^2((0,T); H_0^1(\Omega))$, and strongly

$$X_{\epsilon_k} \rightarrow X^*,$$

$$A_{\epsilon_k} \rightarrow A^*$$

in $C([0,T];L^2(\Omega))$ when $k$ tends to infinity.

\section*{Proof.} We will prove the convergence and existence of the limit for the biomass fraction $X^*$, the arguments are similar for the molecule concentration $A^*$. By Lemma 3.9 for sufficiently small $\epsilon > 0$ the family of approximate solutions $\{X_\epsilon\}_{\epsilon > 0}$ is uniformly bounded in the Hilbert space $L^2((0,T);H^s(\Omega))$ for some $s > 0$. Hence, there exists an element $X^* \in L^2((0,T);H^s(\Omega))$ and a sequence $(\epsilon_k)_{k \in \mathbb{N}}$ tending to zero for $k \to \infty$ such that the sequence $(X_{\epsilon_k})_{k \in \mathbb{N}}$ converges weakly to $X^*$ in $L^2((0,T); H^s(\Omega))$.

Furthermore, due to Lemma 3.9 the product $\sqrt{D_\epsilon} \nabla X_\epsilon$ is uniformly bounded in $L^2(Q_T)$ and the diffusion coefficient satisfies $D_\epsilon \in L^\infty(Q_T)$. Consequently, we obtain

$$\|D_\epsilon |\nabla X_\epsilon|\|_{L^2(Q_T)}^2 \leq \|D_\epsilon\|_{L^\infty(Q_T)} \|\sqrt{D_\epsilon} |\nabla X_\epsilon|\|_{L^2(Q_T)} \leq c,$$

for some constant $c \geq 0$ independent of $\epsilon$, which implies the uniform boundedness of $\partial_t X_\epsilon$ in $L^2((0,T);H^{-1}(\Omega))$.

By Theorem 1.5, Chapter II in [1] now follows the strong convergence of the sequence of approximate solutions in $C([0,T];L^2(\Omega))$. 

It remains to show that the limits of the approximate solutions yield the solution of the degenerate problem.

\section*{Theorem 3.11.} The limits $X^*$ and $A^*$ of the solutions of the non-degenerate approximations are the unique weak solutions of the reduced system (9). In particular, there exists a unique solution of the quorum-sensing model (2).

\section*{Proof.} We show that we can pass to the limit $\epsilon \to 0$ in the distributional formulation of the non-degenerate auxiliary system (14). We will only prove the convergence for the biomass fraction $X^*$ as the arguments are the same or even simplify for the molecule.
concentration $A^*$. The functions $X_\epsilon$ are weak solutions of the auxiliary systems (14), that is

$$\int_\Omega X_\epsilon(x, T)\varphi(x)dx - \int_\Omega X_0(x)\varphi(x)dx = -d\int_{Q_T} D_\epsilon(x, t)\nabla X_\epsilon(x, t) \cdot \nabla \varphi(x)dtdx + \int_{Q_T} f_1^\epsilon(x, t, A_\epsilon(x, t), X_\epsilon(x, t))\varphi(x)dtdx$$

holds for all test-functions $\varphi \in C_0^\infty(\Omega)$ and almost every $T > 0$. As the family of approximate solutions is uniformly bounded in $L^\infty(Q_T)$ by Lemma 3.7, passing to the limit in the integrals is immediate, except for the diffusion term. Hence, it remains to show the convergence of the term

$$\int_{Q_T} D_\epsilon(x, t)\nabla X_\epsilon(x, t) \cdot \nabla \varphi(x)dtdx$$

when the regularization parameter $\epsilon$ tends to zero. Note that the integrals are well-defined due to Lemma 3.9. We split the difference and treat the domains $Q_{\delta,T}$ and $Q_{\delta,T}^\epsilon$ separately. To this end we define

$$R_\epsilon := I_\epsilon + J_\epsilon := \int_{Q_{\delta,T}} (D_\epsilon(x, t)\nabla X_\epsilon(x, t) - D_M(M(x, t))\nabla X(x, t)) \cdot \nabla \varphi(x)dtdx$$

$$+ \int_{Q_{\delta,T}^\epsilon} (D_\epsilon(x, t)\nabla X_\epsilon(x, t) - D_M(M(x, t))\nabla X(x, t)) \cdot \nabla \varphi(x)dtdx,$$

which does not depend on the parameter $\delta > 0$, and show that the term $R_\epsilon$ vanishes when $\epsilon$ tends to zero. To estimate the integral $J_\epsilon$ we express the difference in the following way

$$D_\epsilon \nabla X_\epsilon - D_M(M) \nabla X = (D_\epsilon(M_\epsilon) - D_M(M)) \nabla X_\epsilon + D_M(M) (\nabla X_\epsilon - \nabla X).$$

For the first term of the integral we obtain

$$\left\langle (D_\epsilon(M_\epsilon) - D_M(M)) \nabla X_\epsilon, \nabla \varphi \right\rangle_{L^2(Q_{\delta,T})} \leq \|D_\epsilon(M_\epsilon) - D_M(M)\|_{L^\infty(Q_{\delta,T})} \|\nabla X_\epsilon, \nabla \varphi\|_{L^2(Q_{\delta,T})}$$

$$\leq \|D_\epsilon(M_\epsilon) - D_M(M)\|_{L^\infty(Q_{\delta,T})} \|\nabla \varphi\|_{L^2(Q_{\delta,T})} \|\nabla X_\epsilon\|_{L^2(Q_{\delta,T})}$$

$$\leq C_8 \|D_\epsilon(M_\epsilon) - D_M(M)\|_{L^\infty(Q_{\delta,T})}$$

for some constant $C_8 \geq 0$. Here, we used the Cauchy-Schwarz inequality and the uniform boundedness of the family of approximate solutions $\{X_\epsilon\}$, when restricted to the domain $Q_{\delta,T}^\epsilon$ in the norm induced by $L^2((0, T); H^1_0(\Omega))$ (cf. Lemma 3.8). The family of solutions $M_\epsilon$ of the non-degenerate approximations of the single-species model is uniformly bounded in the Hölder space $C^\alpha, \frac{\alpha}{2}(Q_T)$ for some $\alpha > 0$ (cf. [2]), which implies
strong convergence in $C(Q_T)$. Furthermore, the solutions of the auxiliary systems satisfy the uniform estimate $M_{\epsilon} \leq 1 - \eta$ and consequently, also $M \leq 1 - \eta$ holds. On the interval $[0, 1 - \eta]$ the truncated function $D_{\epsilon,M} : [0, 1 - \eta] \to \mathbb{R}$ converges uniformly to $D_M$ when $\epsilon$ tends to zero. Splitting further the remaining term

$$\|D_{\epsilon,M}(M_{\epsilon}) - D_M(M)\|_{L^\infty(Q_{\delta,T}^\epsilon)} \leq \|D_{\epsilon,M}(M_{\epsilon}) - D_{\epsilon,M}(M)\|_{L^\infty(Q_{\delta,T}^\epsilon)} + \|D_{\epsilon,M}(M) - D_M(M)\|_{L^\infty(Q_{\delta,T}^\epsilon)}$$

we, therefore, note that it vanishes when $\epsilon$ tends to zero.

Finally, the convergence of the second integral of $J_{\epsilon}$

$$\langle D_M(M) (\nabla X_\epsilon - \nabla X^\star), \nabla \varphi \rangle_{L^2(Q_{\delta,T}^\epsilon)}$$

is an immediate consequence of Lemma 3.8. Indeed, restricted to the domain $Q_{\delta,T}^\epsilon$ the family of approximate solutions is uniformly bounded in the norm induced by $L^2((0, T); H_0^1(\Omega))$, which implies weak convergence in this space. Since the diffusion coefficient $D_M(M)$ belongs to $L^\infty(Q_T)$ by Proposition 3.4, the product $D_M(M)\nabla \varphi$ defines an element in the dual space and it follows the convergence of the integral. Summarizing the above estimates we conclude that there exists an $\epsilon_0 > 0$, which is independent of $\delta$, such that the term $J_{\epsilon}$ becomes arbitrarily small for all $\epsilon < \epsilon_0$.

It remains to estimate the integral $I_{\epsilon}$. Recall that the domain $Q_{\delta,T}^\epsilon$ was defined as the subset of $Q_T$ where $M < \delta$. As $M_{\epsilon}$ converges strongly to $M$ in $C(Q_T)$ there exists $\epsilon_1 > 0$ such that $M_{\epsilon}(x, t) < 2\delta$ holds on $Q_{\delta,T}^\epsilon$ for all $\epsilon < \epsilon_1$. If $\epsilon > 0$ is sufficiently small it therefore follows

$$D_{\epsilon}(x, t) = D_{\epsilon,M}(M_{\epsilon}(x, t)) = \frac{(M_{\epsilon}(x, t) + \epsilon)^a}{(1 - M_{\epsilon}(x, t))^b} \leq \frac{(3\delta)^a}{(1 - 2\delta)^b}$$

for all $(x, t) \in Q_{\delta,T}^\epsilon$.

Furthermore, the product $\sqrt{D_{\epsilon}}|\nabla X_\epsilon|$ is uniformly bounded in $L^2(Q_T)$ by Lemma 3.9, which allows us to use Hölder’s inequality to estimate the integral

$$\int_{Q_{\delta,T}^\epsilon} D_{\epsilon}(x, t) \nabla X_\epsilon(x, t) \cdot \nabla \varphi(x) dtdx \leq \|\sqrt{D_{\epsilon}}|\nabla X_\epsilon|\|_{L^2(Q_T)} \|\sqrt{D_{\epsilon}}|\nabla \varphi|\|_{L^2(Q_{\delta,T}^\epsilon)}$$

$$\leq C_9 \left( \int_{Q_{\delta,T}^\epsilon} D_{\epsilon}(x, t)|\nabla \varphi(x)|^2 dtdx \right)^{\frac{1}{2}} \leq C_9 (\frac{3\delta)^{\frac{b}{2}}}{(1 - 2\delta)^{\frac{b}{2}}} \|\varphi\|_{L^2((0, T); H^1(\Omega))}^2$$

where the constant $C_9 \geq 0$. Estimating the second integral of $I_{\epsilon}$ in the same way we obtain

$$I_{\epsilon} \leq \int_{Q_{\delta,T}^\epsilon} |D_{\epsilon}(x, t) \nabla X_\epsilon(x, t) \cdot \nabla \varphi(x)| dtdx$$

$$+ \int_{Q_{\delta,T}^\epsilon} |D_M(M(x, t)) \nabla X(x, t) \cdot \nabla \varphi(x)| dtdx \leq C_{10} \frac{(3\delta)^{\frac{b}{2}}}{(1 - 2\delta)^{\frac{b}{2}}}$$

for some constant $C_{10} \geq 0$. 

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To conclude the proof of the theorem let \( \mu > 0 \) be arbitrary. We first choose \( \delta > 0 \) and a corresponding \( \epsilon_1 > 0 \) such that
\[
I_\epsilon < \frac{\mu}{2}
\]
for all \( \epsilon < \epsilon_1 \). According to the first part of the proof there exists \( \epsilon_0 > 0 \), which does not dependent on \( \delta > 0 \) such that
\[
J_\epsilon < \frac{\mu}{2}
\]
for all \( \epsilon < \epsilon_0 \). Consequently, we obtain
\[
R_\epsilon = I_\epsilon + J_\epsilon < \mu
\]
for all \( \epsilon < \min\{\epsilon_0, \epsilon_1\} \).

This proves the existence of a solution \((X, A)\) of the reduced system (9), the uniqueness of the solution follows by Theorem 3.5. The existence and uniqueness of solutions of the original system (2) now follows from the existence and uniqueness of the solution \((S, M)\) of the single species model.

Similar as in the article [9], our proof of the well-posedness of the quorum sensing model can be extended to less regular initial data and more general boundary conditions for the solutions. The boundary conditions for the dissolved substrates \(S\) and \(A\), which describe mechanisms of substrate replenishment and autoinducer removal are thereby rather uncritical. For the biomass volume fractions \(X\) and \(Y\) the results carry over as long as the values remain below the threshold singularity. This is the case if \(X + Y < 1\) is specified somewhere on the boundary. Note, that due to the finite speed of interface propagation the biomass boundary conditions in fact are not always and everywhere active.

### 4 Two-dimensional Numerical Simulations

Although we could establish the well-posedness of the biofilm quorum sensing model, we are currently not able to describe the solutions of the model qualitatively based on rigorous analytical arguments. Therefore, we will study them in computer simulations.

#### 4.1 Computational preliminaries

For the numerical integration of the model we use a Mickens-type non-local (in time) discretization of the nonlinear diffusion operator and a standard Finite Difference based Finite Volume method for the spatial discretization on a regular grid. This semi-implicit method was first described in [5] for the class of density-dependent diffusion-reaction systems arising in mono-species biofilm models and then extended to multi-species systems in [14, 15]. In every time step it requires the solution of four sparse linear systems, one for each dependent variable, for which the stabilized biconjugated gradient method is used. The algorithm is implemented in Fortran 95, and the computing intensive tasks to determine the nonlinear reaction terms and to solve the linear systems
Table 1: Dimensionless model parameters used in this study, adapted from [10], after changing the induction threshold and the bulk substrate concentration.

<table>
<thead>
<tr>
<th>parameter</th>
<th>symbol</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>substrate consumption rate</td>
<td>$k_1$</td>
<td>794</td>
</tr>
<tr>
<td>Monod half saturation concentration</td>
<td>$k_2$</td>
<td>0.2</td>
</tr>
<tr>
<td>maximum biomass growth rate</td>
<td>$k_3$</td>
<td>1</td>
</tr>
<tr>
<td>cell lysis rate</td>
<td>$k_4$</td>
<td>0.0667</td>
</tr>
<tr>
<td>up-regulation rate</td>
<td>$k_5$</td>
<td>52.7</td>
</tr>
<tr>
<td>polymerisation exponent</td>
<td>$m$</td>
<td>2.5</td>
</tr>
<tr>
<td>AHL production rate of down-regulated cells</td>
<td>$\alpha$</td>
<td>92</td>
</tr>
<tr>
<td>increased AHL production activity by up-regulated cells</td>
<td>$\beta$</td>
<td>920</td>
</tr>
<tr>
<td>abiotic AHL decay rate</td>
<td>$\gamma$</td>
<td>0.02218</td>
</tr>
<tr>
<td>diffusion coefficient of substrate</td>
<td>$d_1$</td>
<td>16.7</td>
</tr>
<tr>
<td>diffusion coefficient of autoinducer</td>
<td>$d_2$</td>
<td>12.9</td>
</tr>
<tr>
<td>biomass motility coefficient</td>
<td>$a$</td>
<td>4</td>
</tr>
<tr>
<td>biofilm interface exponent</td>
<td>$b$</td>
<td>4</td>
</tr>
<tr>
<td>biofilm threshold exponent</td>
<td>$\lambda$</td>
<td>1.5</td>
</tr>
<tr>
<td>mass transfer boundary layer thickness</td>
<td>$L$</td>
<td>1</td>
</tr>
</tbody>
</table>

The biological and physical parameter values used in our simulations are summarized in Table 4.1. These are the same values that have been used previously in [10], with the exception of the induction threshold parameter $\tau$, which was reduced from 70 nM to 10 nM as discussed in [11], and the bulk substrate concentration, which has been reduced by a factor 5. Both parameters are used in the non-dimensionalization. Therefore, these two modifications result in a change of the quantitative values of several dimensionless parameters used in our simulations, compared to [10]. The system modeled by these parameter values corresponds to a Pseudomonas putida biofilm, the growth of which is controlled by carbon as the limiting substrate $S$. The signaling molecules are Acyl Homoserine Lactones (AHL).

In addition to the visualization of the spatial structure of the biofilms we will also plot the total amount of biomass fractions and autoinducers relative to the size of the domain

$$X_{total}(t) = \frac{1}{|\Omega|} \int_{\Omega} X(t, x) dx, \quad Y_{total}(t) = \frac{1}{|\Omega|} \int_{\Omega} Y(t, x) dx,$$

and

$$A_{total}(t) = \frac{1}{|\Omega|} \int_{\Omega} A(t, x) dx.$$
4.2 Microbial flocs

In the first simulation we consider a quadratic domain of size $L \times L$, discretized by $200 \times 200$ grid cells.

The initial conditions are chosen such that at $t = 0$ down-regulated biomass is only located in a heterogeneous region $\Omega_2(0)$ in the center of the domain. Initially, no up-regulated biomass and no AHL is assumed to be in the system. At $t = 0$ the substrate concentration in the interior is everywhere at the same level as the boundary concentration, i.e.

$$A_0 = Y_0 = 0, \quad S_0 = 1 \quad \text{in} \quad \Omega, \quad X_0 > 0 \quad \text{in} \quad \Omega_2(0), \quad X_0 = 0 \quad \text{in} \quad \Omega_1(0).$$

The boundary conditions used in this simulation are the Dirichlet boundary conditions (3). This situation describes a heterogeneous microbial floc in the middle of the domain, which will grow as a consequence of substrate supply.

The development and up-regulation of the floc under Dirichlet conditions is shown in Figure 1. The biofilm is represented by the ratio of down-regulated to overall biomass, $Z = X / (X + Y)$ in the biofilm region $\Omega_2(t)$, while $Z = 0$ in the aqueous phase $\Omega_1(t)$. Moreover, we plot iso-concentration lines for the autoinducer $A$, coded in greyscale.

Initially the floc is formed by three overlapping circles, which start growing and eventually expand spatially, when the biomass density reaches 1. At $t = 1$, this originally heterogeneous shape of the floc is still visible, the entire floc is down-regulated. Substrate $S$ is not strongly growth limiting and the floc expands. Here, and in all subsequent time-steps, the highest AHL concentrations are found in the center of the floc, from where they diffuse toward the boundary of the domain where the AHL concentration is kept at $A = 0$. At $t = 2.5$ the floc is still entirely down-regulated, but its shape becomes homogeneous and almost spherical. This is the analogy of the microbial floc to biofilms which have been found to grow in compact homogeneous layers when substrates are not severely limited. At $t = 4.0$ in the inner core of the floc, a small amount of up-regulated cells is observed (max $Z \leq 0.98$, i.e. up to 2% of the biomass locally are upregulated), while at $t = 4.3$ we note the onset of major up-regulation. At first the biomass in the inner regions undergoes switching, where the AHL concentration is highest. At $t = 4.8$ and $t = 6.5$ the floc is everywhere dominated by up-regulated biomass, although the up-regulation gradient from the center of the floc to the interface is clearly observable. The highest fractions of down-regulated cells can be found in the outer-most layers.

The lumped quantities $X_{\text{total}}$, $Y_{\text{total}}$ and $A_{\text{total}}$ are plotted in the left panel of Figure 2. The switch from a down- to an up-regulated system happens instantaneously, at $t \approx 4.2$. After this switching time the biofilm develops at an unchanged rate, although now dominated by up-regulated cells.

We compare the situation of homogeneous Dirichlet conditions for AHL with a simulation where we pose homogeneous Neumann conditions for the autoinducer instead, cf. the right panel of Figure 2. This models the case where autoinducers cannot leave the domain and, therefore, accumulate faster. Consequently, the onset of quorum sensing occurs much sooner under Neumann conditions than under Dirichlet conditions.
Figure 1: Development and up-regulation of a microbial floc under homogeneous Dirichlet conditions for AHL. Shown are for different $t$ the fraction of down-regulated biomass, $Z := X/(X + Y)$ (colored), and isolines of the AHL concentration.
Figure 2: Comparison of a quorum sensing simulation of a microbial floc under different boundary conditions for AHL: Plotted are $X_{total}$, $Y_{total}$ and $A_{total}$ for homogeneous Dirichlet conditions (left) and for homogeneous Neumann conditions (right) for the autoinducer $A$.

$t \approx 0.5$ vs. $t \approx 4$. This reflects the physical interpretation of the boundary conditions given above: removal of AHL from the system leads to a delay in up-regulation, i.e. not only the number of cells in the system affects up-regulation but also external mass transfer, in this case removal of autoinducers from the system. In the case of Neumann conditions, as a consequence of unhindered accumulation of AHL in the system, very high autoinducer concentrations are reached. Soon after induction occurs, all biomass in the system is up-regulated. At $t = 1.2$ less than 0.1 % of the entire biomass is still down-regulated (this condition was implemented as one stopping criterion for the simulation).

On the other hand, in the case of homogeneous Dirichlet conditions for AHL, much more biomass is produced before the onset of up-regulation, while autoinducers accumulate slower. Up-regulation occurs almost instantaneously, the down-regulated biomass drops to a small fraction and remains low. At $t \approx 7$, we observe a slow increase, which is a boundary effect: The domain $\Omega_2(t)$ expands and the amount of biomass in the system increases. The biofilm/water interface comes close to the boundary of the domain. The expanding and growing of biomass in the system leads to lower substrate concentrations and higher AHL concentrations in the system. In conjunction with the Dirichlet conditions for $A$ and $S$ this has two consequences: The flux of $A$ out of the system across the boundary of the domain increases, and so does the flux of substrate into the system. This slows down up-regulation in the outer layers of the flocs and promotes growth of down-regulated biomass. As seen in Figure 1, the largest concentrations of down-regulated cells can be found in the outer layers of the floc. As the floc expands, the outer layer of the almost spherical floc grows bigger.

### 4.3 Biofilms

As a second example we simulate quorum sensing in a growing biofilm community that consists of several bacterial colonies. The domain $\Omega$ is rectangular of size $\Omega = L \times H$, 

discretized by $400 \times 200$ grid cells. The substratum is randomly inoculated by four small pockets of down-regulated biomass, where the biomass density in these pockets is chosen randomly between two given values, $0.2 \leq X \leq 0.4$.

The bottom boundary is the substratum which is impermeable to biomass, substrate and AHL. This is described by homogeneous Neumann boundary conditions. Also at the lateral boundaries homogeneous Neumann conditions are posed for all dependent variables. These can be understood as symmetry boundary conditions and permit to interpret our domain as one half of a continuously repeating segment of an infinite domain.

The top boundary requires a different treatment. This is the boundary through which growth limiting substrate $S$ is added to the system and autoinducer AHL removed. Assuming that the bulk liquid at a height $\lambda$ above the computational domain is completely mixed at bulk concentration $S = 1$ and with molecule concentration $A = 0$, this is described by the Robin boundary conditions

$$S + \lambda \partial_n S = 1, \quad A + \lambda \partial_n A = 0,$$

on the top boundary, where $\partial_n$ denotes, as usual, the outer normal derivative. The new parameter $\lambda$ resembles the concentration boundary layer thickness of traditional one-dimensional biofilm models, see also [4]. Under this analogy, large values $\lambda$ correspond to small removal rates of AHL and supply rates of substrate, and *vice versa*. In one-dimensional biofilm models, this parameter is frequently used to qualitatively mimick the effect of bulk flow hydrodynamics on mass transfer into and out of the biofilm. Small values of $\lambda$ correspond to fast bulk flow, large values to slow bulk flow. However, only recently a quantitative relationship between bulk flow velocity and the parameter $\lambda$ was found for one application [17]. The Robin boundary conditions can be understood as a combination or interpolation of the two boundary conditions used in the previous section. Compared to the homogeneous Dirichlet conditions, they correspond to a slower replenishment of nutrients and removal of autoinducers [4].

For both biomass fractions we pose homogeneous Dirichlet conditions at the top boundary. However, since the simulations will always terminate before the biofilm reaches the top boundary, these are, due to the finite speed of interface propagation, in fact, without relevance.

An alternative interpretation of these boundary conditions is a biofilm growing in a small rectangular crack of depth $H + \lambda$ in the wall of a much larger completely mixed vessel. In this case, the lateral boundaries can be considered substratum as well.

The initial conditions are chosen as follows: Down-regulated biomass is placed only in small pockets at the bottom boundary, i.e. on the substratum, at an initial biomass density of $X_0 < 1$, while in the biggest part $\Omega_1(0)$ of the domain $X_0 = 0$. Depending on the simulation conducted, these pockets can be located randomly or their location can be a priori prescribed. The substrate concentration $S_0 \equiv 1$ takes the bulk concentration value everywhere. Initially, no up-regulated cells and no AHL are in the system, i.e.

$$A_0 = Y_0 = 0, \quad S_0 = 1 \quad \text{in} \quad \Omega,$$

$$X_0 > 0 \quad \text{in} \quad \Omega_2(0), \quad X_0 = 0 \quad \text{in} \quad \Omega_1(0).$$
After the simulation starts, the biomass starts growing. First, this leads to a consolidation inside the original biomass pockets, where biomass $M$ increases without notable spatial expansion. Expansion starts locally when and where the biomass density $M$ approaches 1. Eventually, neighboring colonies merge with neighboring colonies. As long as substrate $S$ is not severely limited the total biomass density $M \approx 1$ in the biofilm. This growth behavior of biofilms according to the underlying diffusion-reaction model has been described in much detail previously, e.g. in [6, 7] and is not repeated here. Instead we focus on the onset of quorum-sensing activity.

In Figure 3 we show for six time instances the biofilm structure, the AHL concentration $A$, and the spatial composition of the biofilm from down- and up-regulated biomass $X$ and $Y$. The latter is again represented in terms of the ratio of down-regulated biomass to total biomass, $Z := X/(X + Y)$ in $\Omega_2(t)$ (while $Z = 0$ in $\Omega_1(t)$). In the first shown time step (a), at $t = 7.00$, all colonies are essentially down-regulated, due to the low AHL concentration $A < 0.08$. The AHL concentrations are largest in the inner layers of the biofilm colonies, close to the substratum. From the biofilm colonies the signaling molecules diffuse into to the aqueous phase. Similarly, at (b) $t = 8.5$ with $A < 0.247$ the biofilm remains down-regulated. Note that between the first two plotted time-steps all biofilm colonies continued growing and that the two colonies in the middle of the substratum started merging. Induction starts at (c) $t = 9.24$, where the AHL concentration reaches $A \approx 1$ in the clustered region where the colonies are dense, i.e. where more bacteria, and hence AHL producers, are concentrated. Some AHL diffuses from the biofilm colonies into the aqueous phase. This diffusion loss is more pronounced in the smaller isolated colony on the right than in the larger biofilm cluster region. In the clustered colonies, first the bacteria in the inner layers, close to the substratum, upregulate and we observe a gradient of down-regulated cells from the inner layers to the biofilm/water interface in these colonies, i.e. a clearly heterogeneous distribution of biomass within the biofilm. The fraction of down-regulated cells $Z$ in the clustered region of the biofilm is smaller than in the smaller isolated colony on the right. Consequently, more AHL are produced there. This leads to a flux of AHL toward the single colony, and thus contributes to an increase of up-regulation there. As a consequence, the up-regulation pattern in this nearly hemi-spherical colony is not symmetric, but skewed toward the larger neighboring colony.

The next snapshot is taken shortly thereafter, at (d) $t = 9.28$, when the average AHL concentration in the domain reaches the threshold value $A \approx 1$. The picture is qualitatively the same but more cells are now up-regulated in all colonies and the AHL concentration has risen to a maximum value of 1.36. The difference between the three clustered colonies and the isolated colony is still clearly observable. Moreover, all colonies are still in a growing phase.

At (e) $t = 9.78$ AHL concentration $A$ is everywhere in the domain clearly above the switching threshold 1. The colonies to the left merged. Only a small fraction of cells in the biofilm colonies is still down-regulated, this fraction is slightly higher in the isolated colony to the right.

The fraction of down-regulated cells decreases even more until (f) $t = 11.28$, where it only accounts locally for approximately 1% of the cells. The AHL concentration has now risen to a maximum value of 5.23 in the biofilm and a minimum value of 3.70
Figure 3: Biofilm structure and fraction $Z = X/(X + Y)$ of down-regulated cells along with the iso-lines of AHL concentration for selected times.

Thus, the up-regulation process happens very fast, at around $t \approx 9 \sim 10$. This reflects that the up-regulation rate $\kappa_5$ is much larger than the growth rate of the bacterial population, i.e. has a much smaller characteristic time-scale.

Note that the biofilm keeps growing during the entire observation period. The two middle colonies merge between $t = 7.0$ and $t = 8.5$ and then with the left most colony at around $t = 9.3$. The semi-spherical shape of the left colony indicates that the biofilm does not suffer severe substrate limitations yet, which would induce a growth preference toward the food source.

The overall time evolution of the biofilm is summarized in Figure 4, where the lumped quantities $X_{total}$, $Y_{total}$ and $A_{total}$ are plotted. Initially, the biofilm is almost entirely down-regulated and shows the exponential growth that is typical for non sub-
strate limited systems. Autoinducers are produced at a low rate. Only at around $t \approx 9$ enough AHL is accumulated to induce up-regulation. The switch from a mainly down-regulated to a biofilm dominated by up-regulated cells is almost immediate. This switch also induces a drastic jump in AHL accumulation due to the higher production rate of up-regulated cells. After the switch has passed the population continues growing as an almost entirely up-regulated biofilm.

The simulations in Figure 3 show the effect of spatial arrangement of cell colonies on the biofilm. In other words, the switching behavior in one colony can be affected by the size and location of other colonies. This supports the recent hypothesis of efficiency sensing [12], which aims at combining quorum sensing in the strict sense with the related concept of diffusion sensing. The former is commonly thought of as a mechanism to measure the size of the population, while the latter is thought of as a mechanism to explore the spatial characteristics of the environment. Of course, both effects are super-imposed, the AHL concentration measured by a cell depends on both and both effects cannot be separated in this measurement. This together with the simulations in the previous section shows the role that environmental conditions play for quorum sensing, due to their effect on mass transfer.

In the previous study [10] the effect of convective transport of autoinducer molecules in the bulk liquid on inter colony communication and up-regulation was studied. Our simulations in the present article demonstrated that also the purely diffusive transport of autoinducers can affect the onset of switching greatly. In other words, spatial effects are crucial in quorum sensing and can overwrite the meaning of quorum sensing in the strict sense, namely the notion of quorum sensing as a mechanism by which bacteria sense the size of their population. In fact, under the influence of mass transport, AHL concentrations are not a good indicator for population density, as they are alternated by effects such as the spatial distribution of cells and the size and shape of the domain in which they live.

Figure 4: Evolution of the biofilm over time: shown is the amount of down- and up-regulated cells, as well as the amount of AHL in the system.
5 Conclusion

We studied a degenerate density-dependent diffusion-reaction system that models quorum sensing in bacterial biofilms. Our main analytical result is the well-posedness of the initial-boundary value problem. While similar existence proofs for models of this type have been given previously, our work constitutes the first uniqueness result for such systems. This was possible because of a specific property of the quorum-sensing model, which previously studied models of other biofilm processes did not possess. More specifically, this property allowed us to make use of known uniqueness and regularity results for the scalar case. Nevertheless, in forthcoming work we shall aim at extending the ideas underlying our uniqueness proof so that it becomes applicable to other systems as well.

In addition to the well-posedness proof, we showed computer simulations of the numerical model, which indicated that quorum sensing in spatially structured biofilms can be dominated by mass transfer effects. In other words, quorum sensing is not only based on cell numbers but also on their locations relative to each other, and on the boundary conditions. This ties in with the recently suggested concept of efficiency sensing, which combines quorum sensing in the strict sense with diffusion sensing as a mechanism by which bacteria explore their spatial environment.

References


