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2D reaction-diffusion model of quorum sensing characteristics during all phases of bacterial growth

The paper is devoted to the development of a 2D reaction-diffusion model of the bacterial communication process due to the quorum sensing observed during all bacterial growth phases. The mathematical model is presented by an initial-boundary value problem for a system of semilinear partial differential equations modified in view of the multiphase character of population dynamics. The model is implemented by the finite element method using the COMSOL Multiphysics platform. The results of simulations of chemical compounds characterizing quorum sensing are presented on an example of the bacterial species of *Pseudomonas putida* under variation of parameters of mortality intensity.

Key words: *reaction-diffusion model of quorum sensing, bacterial growth, finite-element modelling, simulation of chemical compounds.*

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Introduction

Reaction-diffusion models are an extremely important class of deterministic models that give rise to qualitatively formalize and quantitatively describe the spatio-temporal dynamic behavior of complex biological systems. In the concept of this approach, a model of bacterial communication can be under consideration [1,2], which is of particular relevance from the point of view of the formation of stable structures of pathogenic bacteria resistant to the action of antibacterial medicines. Basically, a bacterium is considered as a microorganism capable of perceiving the presence of other bacteria through quorum-sensing and reaching on the population size through the production of special signal molecules. Diverse gram-negative bacterial cells communicate with each other by using diffusible N-acyl homoserine lactone (AHL) signal molecules to coordinate gene expression with

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cell population density [3]. Moreover, for numerous bacterial species, signal molecules can be inhibited due to quorum quenching, which is realized by means of producing specific enzymes (for instance, Lactonase enzymes observed in bacteria of *Pseudomonas* genus).

Known models are based on a wide range of methods and approaches, using the apparatus of differential equations, agent-based modeling, the Monte Carlo method, cellular automata, and hybrid algorithms [4,5]. Within the framework of our study, the attention is focused on the development of reaction-diffusion models of the bacterial communication process [6–10]. The basic model of bacterial communication is governed by an initial-boundary value problem for a system of partial differential equations (PDEs) [6,8]. The model provides the estimation of chemical compounds characterizing the quorum sensing in the phase of bacterial population growth followed by relaxation of its numbers to a certain level. In this case, the bacterial growth includes the lag phase, the logarithmic growth phase, and the stationary phase. In particular, in biological experiments, this situation corresponds to the case of continuous cultivation of bacteria in bioreactors.

Nevertheless, the bacterial dynamics curve may also include the death phase due to the influence of various factors, e.g. bacterial growth in batch culture, depletion of the nutrient medium, separation of daughter bacterial colonies, introduction of degrading chemical compounds, and changes in the temperature [11–13]. In this way, it would be a special interest to modify the bacterial communication model, taking into account the whole growth phases of the bacterial community. The ultimate goal of the present study is to develop the 2D reaction-diffusion model of the bacterial communication process, taking into account the law of multiphase dynamics and perform implementation by means of the finite element method using the tools of the COMSOL Multiphysics software.

1 The mathematical problem statement

The mathematical model of the bacterial communication process allows one to estimate space-time distributions of concentrations of the signal substance AHL and the Lactonase enzyme, taking into account the processes of their diffusion, generation, natural degradation, and degradation of AHL by Lactonase [6,8]:

$$\frac{\partial u}{\partial t} = D_{AHL}\Delta u - \gamma_{AHL}u - \gamma_{L\to AHL}Lu + F_1, \quad 0 < x < l,\ 0 < y < l,\ 0 < t \le T, \quad (1)$$

$$\frac{\partial L}{\partial t} = D_L\Delta L - \gamma_L L + F_2, \quad 0 < x < l, \quad 0 < y < l, \quad 0 < t \le T, \quad (2)$$

$$u|_{t=0} = 0, \quad L|_{t=0} = 0, \quad 0 < x < l, \quad 0 < y < l, \quad (3)$$

$$u|_\Gamma = 0, \quad L|_\Gamma = 0, \quad 0 < t \le T, \quad (4)$$

where $u(x,y,t)$ is the AHL concentration and $L(x,y,t)$ is the Lactonase concentration in mol/l; Γ is the boundary of the solution domain, the square $[0,l]\times[0,l]$; $D_{AHL}, D_L, \gamma_{AHL}$, $\gamma_L, \gamma_{L\to AHL}$ are the model parameters; T is the observation time in h; $F_1 = F_1(x,y,t,u)$, $F_2 = F_2(x,y,t,u)$ are the generating terms in mol/(l·h), which are specified as follows:

$$F_m(x,y,t,u) = N(t)\sum_{v=1}^{V} f_m \exp\left(-\frac{(x-x_c^v)^2 + (y-y_c^v)^2}{\sigma^2}\right), \quad m = 1,2, \quad (5)$$

$$f_1(u) = \alpha_u + \beta_u \frac{u^n}{(u_{th})^n + u^n}, \quad f_2(u) = \beta_L \frac{u^n}{(u_{th} + \varepsilon)^n + u^n}, \tag{6}$$

where (x_c^v, y_c^v) is the position of the bacterial colony with the number v; $N(t)$ is the normalized function defined the dynamics of a bacterial population density; σ, ε, α_u, β_u, β_L, u_{th}, n are parameters.

Some remarks concerning the existence and uniqueness of solutions can be found in [6] (see also references therein). The normalized value of the bacterial density, $N(t)$, is described by the following time-dependent function:

$$N(t) = \begin{cases} (1 + \exp(-\mu(t - b_1)))^{-1}, & t \le t_d, \\ a + b\,(1 + \exp(\mu(t - b_2)))^{-1}, & t > t_d, \end{cases} \tag{7}$$

where a, b_1, b_2, μ are approximation parameters; t_d is the start time of inhibition in h.

Hence, the approximation factor takes into account the lag phase (bacteria are getting used to the medium and physical conditions), the logarithmic growth phase (which corresponds to the faster growth – up to the maximum growth rate for the species), the stationary phase (when the number of new cells equals the number of dead cells), and the death phase (when the rate of cell death is faster than regeneration).

2 Simulation results

To perform computer simulations, we apply the COMSOL Multiphysics environment (license agreement No 20/15/230). COMSOL is a universal computer aid engineering software to solve differential problems by means of the finite element method. Compared to numerous analogues, COMSOL allows one to explicitly control the equations and edge conditions describing the process. The numerical experiments are based on the parameters of the bacterial quorum sensing model estimated for the *P. putida* bacterial species in [6,8] as listed in Table 1. The values of the parameters for the population growth model (7) are defined numerically using microbiological data from [14]. The parameters specifying the character and changes of corresponding phases of population dynamics are set to be the follows: $\mu = 1.4\,h^{-1}$, $b_1 = 4\,h$, $b_1 = 18\,h$, $t_d = 12\,h$. In addition, the parameters a and b which are responsible for the "level" of degradation of the bacterial population can be varied. To conduct numerical experiments, we assume also that $V = 5$ bacterial colonies are located at defined positions in the computational domain.

Figure 1a shows the three different strategies for degradation of a bacterial population. In this example, the degradation process starts at $t_d = 12\,h$ and we have $70\%, 50\%$, and approximately 0% surviving bacteria respectively (compared to the maximum value of bacterial population). Figure 1b illustrates the space distributions of the AHL concentration calculated at $a = b = 0.5$ (only 50% of population remains alive after the relaxation period), for the time moment $t = 18\,h$.

The time-dependent profiles of AHL concentrations calculated at central position $(l/2, l/2)$ of the computation domain (where the first bacterial colony is located) are shown in Figure 2. These findings suggest that the 70% and 50% strategies of degradation of population lead to approximately 10% and 22% decreases in AHL concentrations

Table 1: Model parameters for the problem (1)–(7)

Name	Parameter	Numerical value	Dimension
D_{AHL}	Diffusion rate of AHL	100	$\mu m^2/h$
D_L	Diffsion rate of Lactonase	$0.01 \cdot D_{AHL}$	$\mu m^2/h$
γ_{AHL}	Abiotic degradation rate of AHL	0.005545	1/h
γ_L	Abiotic degradation rate of Lactonase	0.5	1/h
$\gamma_{L \to AHL}$	Degradation rate of AHL by Lactonase	$0.65 \cdot 10^9$	1/(mol·h)
α_{AHL}	Low production rate of AHL	$1.058 \cdot 10^{-7}$	mol/(l·h)
β_{AHL}	Increased production rate of AHL	$1.058 \cdot 10^{-6}$	mol/(l·h)
β_L	Production rate of Lactonase	$1.38 \cdot 10^{-6}$	mol/(l·h)
u_{th}	Threshold of AHL concentration	$70 \cdot 10^{-9}$	mol/l
ε	Threshold delay for Lactonase	$5 \cdot 10^{-9}$	mol/l
n	Power parameter	2.5	
l	Linear size of the computational domain	100	μm
T	Time of process observation	50	h

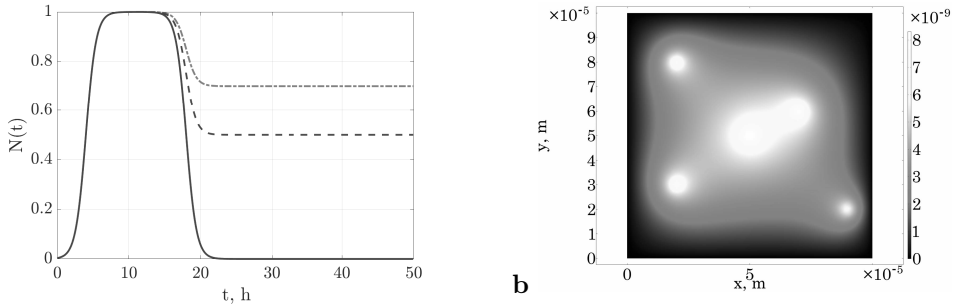

Fig. 1: The time dependence of normalized values of bacterial population density under variation of degradation strategies: $a = 0.7$, $b = 0.3$ (dot-dashed line), $a = b = 0.5$ (dashed line), and $a = 0$, $b = 1$ (solid line) — a and the distribution of AHL concentration $u(x, y)$ calculated for $t = 18$ h and $a = b = 0.5$ — b.

respectively. This fact can be explained by the simultaneous decrease in the Lactonase concentration. Due to the presence of negative feedback between these compounds, as a consequence, we do not observe the proportional changes in the AHL concentration. Finally, to reduce essentially the level of quorum sensing, one needs to apply "an aggressive" strategy providing almost zero population growth as shown in Figure 2c. The time of quorum quenching is estimated to be 28 h. Note also that the mechanisms of the space-time strategies of bacterial degradation remain to be elucidated in further studies.

Conclusion

Thus, the modified 2D quorum sensing model permits one to examine main characteristics responsible for the communication level in the biosystem during all phases of

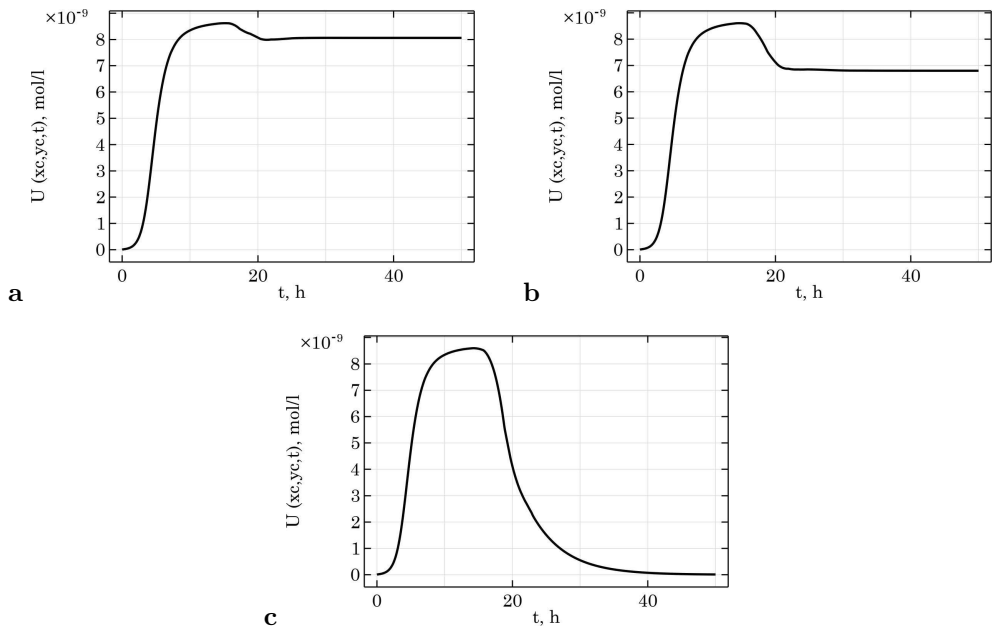

Fig. 2: The time dependencies of AHL concentrations corresponding to inhibition strategies with 70% — a, 50% — b alive population, and zero population growth — c.

bacterial growth. The proposed modification is based on the formalization of the multiphase character of population dynamics, which is included in generating terms of the system of PDEs. The computer implementation was performed by means of the finite element method using the COMSOL Multiphysics software. Computational experiments were conducted on the example of the bacterial species *P. putida*. The obtained data allowed us to specify the time of bacterial quorum quenching and the "level" of quorum under variation of parameters of mortality intensity.

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Шуай И., Масловская А. Г., Куттлер К. Двумерная реакционно-диффузионная модель характеристик чувства кворума в полном жизненном цикле развития бактерий. *Дальневосточный математический журнал.* 2022. Т. 22. № 2. С. 232–237.

АННОТАЦИЯ

Работа посвящена развитию двумерной реакционно-диффузионной модели процесса коммуникации бактерий посредством чувства кворума, наблюдаемого в течение всех фаз динамики бактериальной популяции. Математическая модель описывается начально-краевой задачей для системы полулинейных дифференциальных уравнений в частных производных, модифицированной с учетом многофазного характера динамики популяции. Модель реализована методом конечных элементов с использованием платформы COMSOL Multiphysics. Результаты моделирования химических субстанций, характеризующих чувство кворума, представлены на примере бактериального вида *P. putida* при варьировании параметров интенсивности смертности.

Ключевые слова: *реакционно-диффузионная модель чувства кворума, бактериальный рост, конечно-элементное моделирование, моделирование химических соединений.*