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========== **MATHEMATICAL MODELING** ==========

Modeling of Bacterial Communication in the Extended Range of Population Dynamics

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Abstract. ”Quorum sensing” as a special kind of communication in bacterial populations can be analyzed by means of methods and techniques of mathematical modeling and computer simulation. In the present study, a modification of a deterministic mathematical model of bacterial quorum sensing is proposed, taking into account the law of multiphase population dynamics. The mathematical model is formalized by an initial-boundary value problem for a system of semilinear reaction-diffusion partial differential equations. The equations include generation terms in view of changes in the biomass density. The model describes space-time dynamics of concentrations of special substances (signaling agents and Lactonase enzymes) that characterize the quorum sensing in Gram-negative bacteria. The problem is solved by means of the finite element method using the COMSOL Multiphysics platform. Computational experiments are performed to estimate concentrations of key substances characterizing quorum sensing for *Pseudomonas putida* bacterial strains in an expanded range of population dynamics.

Key words: *bacterial communication, quorum sensing, reaction-diffusion model, bacterial dynamics, finite element modeling, simulation of chemical compounds distributions.*

INTRODUCTION

Currently, there are revolutionary changes taking place in science about the behavior of biological organisms of the microworld. One of the modern and urgent problems is the study of the complex biotic and abiotic interactions occurring within biological communities, in particular, bacterial colonies. From this concept, it is possible to analyze the process of bacterial communication based on various mechanisms, among the most important of which is “quorum sensing”. Quorum sensing refers to the ability of some species of bacteria (and other microbes) to regulate their numbers and respond collectively to external influences. It has been established that the communication process is controlled by the expression of specialized sets of genes due to the secretion of signaling molecules that initiate the transfer of information between bacteria [1–3].

Quorum sensing has been found and extensively studied in many Gram-negative bacteria, including deadly pathogens. In particular, *Pseudomonas aeruginosa* is a gram-negative, rod-shaped aerobic bacterium that, due to quorum sensing, is capable of causing hospital-acquired pneumonia, in particular when using ventilators. Its closest relative, *Pseudomonas putida*, although it has been recognized as a microorganism safe for humans, in some cases, can act as a pathogen for immunocompromised people (like newborns and cancer patients) or as a matrix for the transfer of more harmful bacteria, such as *P. aeruginosa* [4].

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More precisely, quorum sensing is responsible for the development of tolerance of many bacterial species to antibiotics, as well as for the formation of surface and spatial compact structures (biofilms, bacterial mats, fruiting bodies, etc.) that pose a threat to human health and life. Therefore, the collective behavior of bacteria has become an important object of interdisciplinary research. Along with biology and chemistry, methods and techniques of mathematical biology and *in silico* studies are used to examine this complex phenomenon.

Many models have been proposed to formalize quorum sensing as a complex phenomenon. If we classify the known models from a biological point of view, then we can distinguish separate categories based on which mechanisms are regulated using the quorum sense: bioluminescence (*Vibrio fischeri*) [5, 6], antibiotic resistance (*P. aeruginosa*) [7], mobility (*P. syringae*) [8], competence (*Streptococcus pneumoniae*) [9], virulence (*Escherichia coli*) [10], formation of biofilms and bacterial mats (*P. aeruginosa*) [11]. At the same time, from the mathematical point of view, a significant part of which can be attributed to the class of mathematical deterministic models described by the differential apparatus, whereas the other part is represented by discrete models with elements of uncertainty, which can be implemented using network theory, agent modeling, Monte Carlo modeling, etc. [8], [12–15].

In the pioneering works attributed to the deterministic direction, the apparatus of ordinary differential equations has been applied [12]. Later, numerous modifications of this approach were outlined, based on consideration of the molecular mechanisms of quorum sensing, quorum regulation during biofilm formation, the emergence of bioluminescence, the formation of a response to antibiotics, and the enhancement of virulence factors [13, 16–18].

Among differential approaches, let us mention the study [14] which describes a novel model of quorum sensing in Gram-negative bacterial single cells. A generic model is based on the law of mass action from chemistry and formalized by ordinary differential equations for the mass of signaling molecules inside and outside the cell. Later, numerous works have extended this model to describe quorum sensing as a regulation mechanism of luminescence in *V. fischeri* [6], to take into account negative feedback between concentrations of signaling molecules and degrading enzymes [18] and delay effect [17] in *P. putida.*

However, the mean field approximation provides only a very rough idealization for considering processes, since the spatial some inhomogeneity may be a determining factor for them. In nature, many bacterial genera are not living in well-stirred cultures but attach on surfaces, form dense structures like biofilms, fruit bodies or bacterial mats. This yields that modeling of bacterial communication needs to take into account the spatial distribution of bacterial cells and, as a result, the heterogeneous distribution of chemical compounds characterizing quorum sensing. Apart from modeling using cellular automata and agent-based approaches (discrete grid- and particle-based models respectively) [19–21], ordinary differential equations can be transferred into spatial systems, by combination with diffusion or other mechanisms leading to a spread in space. Mathematically, this may lead to reaction-diffusion equations.

Building a generic reaction-diffusion approach for modeling such a complex phenomenon as quorum sensing meets serious difficulties. In this way, various model approaches are being developed to describe specific cases of bacterial quorum mechanisms underlying different phenomena. In [14] the extended model by spatial structure also has been introduced to model communication between the cells via diffusion. The hybrid model governed by an ordinary differential equation for mass of signaling molecules within the cytoplasm and a partial differential equation for the density of signaling molecules outside of the cell at defined position for the system of individual cells has been suggested. The apparatus of partial differential equations has been employed in [22, 23] to model the biofilm formation and growth phenomenon activated by quorum sensing. Moreover, the model formalized by PDE has been proposed to describe quorum-sensing-dependent production of extracellular polymeric substances in [24]. The study [25] has proposed a mathematical model of quorum

quenching in batch cultures and biofilms, which is formalized by a system of partial differential equations, and a communication degradation model as a possible therapy by changing the inhibition period, which makes it possible to manipulate quorum recognition for *P. aeruginosa* bacterial strains.

The development of the reaction-diffusion approach for mathematical modeling of bacterial quorum sensing has been reported in the series of our studies [26–30]. This concept is based on the quorum sensing model for single cells proposed in the approach mentioned above [14] and its further original modifications developed in the studies [26]. The main feature of this model consists in the application of reaction-diffusion approximation to modeling of the space-time distributions of the concentrations of specific chemical substances characterizing quorum sensing and quorum quenching in bacteria that it has been repeatedly tested for bacteria of *Pseudomonas* genus. Various modifications have been introduced, taking into account the negative feedback under activation of special degrading enzymes, the presence of a delay effect and memory effects, variations and dynamic regimes, and the external addition of chemical substances.

The basic reaction-diffusion model of bacterial quorum sensing is given by an initial-boundary value problem for a system of partial differential equations of the diffusion type. The model allows us to evaluate the concentrations of substances characterizing the quorum sensing in the phase of active bacterial population growth followed by relaxation of its number to a certain level. In addition, this model can be modified to the case when bacterial communication is considered under the conditions of their continuous (flowing) cultivation, in which a new nutrient medium is added (to prevent nutrient depletion), and part of the medium with the cells of microorganisms and metabolic products are removed.

However, the law of bacterial population dynamics may include not only the growth phase, but also the phase of degradation and/or subsequent relaxation under 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 regime [31–34]. Therefore, it is of some scientific interest to introduce into consideration the modification of the bacterial communication model in light of the extended range of vital activity of bacteria.

Mostly, all modifications of the bacterial communication model presented earlier in [27–30] have been implemented by means of the finite difference method. At the same time, modern software systems of finite element analysis (the so-called FEA systems), e.g. COMSOL Multiphysics, ANSYS, NASTRAN, etc., allow us to solve problems effectively and without routine programming procedures using standard differential formulations. In this regard, the second aspect of the present study is the use of a finite element modeling system for the computer implementation of the bacterial communication model.

Thus, the current study was designed to develop the bacterial communication model by means of introducing the law of multiphase population dynamics and conduct computational experiments using COMSOL Multiphysics software.

The paper is organized as follows. We will first formulate the brief biological setup. The next section will be devoted to the mathematical problem statement of the bacterial communication model. Further we will report computing tools of COMSOL Multiphysics used for the numerical implementation of the model. Then, we will focus on computer simulations of space-time distributions of key characteristics of quorum sensing in Gram-negative bacteria for the example of *P. putida* bacterial species. Here, performing a full cycle of mathematical modeling and computer simulation to solve the multidisciplinary problem also underlines the main significance of the present study. Finally, we will summarize the main findings arising from this study.

FORMALIZATION OF THE BIOLOGICAL SYSTEM

Let us introduce the main variables that characterize the state of the biological system. To do this, we will present a formalized description of the process of bacterial communication, without pretending to grasp all the details of the biological foundations of this multifaceted and complex phenomenon.

Since in different bacterial species the quorum sensing is realized using different mechanisms, to be precise, suppose that a class of Gram-negative bacteria, in particular *Pseudomonas putida*, should be considered. *P. putida* is an interesting object of modeling and *in silico* studies, both from a biological point of view and in terms of setting up and conducting computational experiments. For many years, this type of bacteria belonged to non-pathogenic microorganisms that live mainly in soils.

However, recent studies show [4, 35] that *P. putida* can be a matrix for the transfer of dangerous infections caused by more virulent species of bacteria. As an example, the bacterium *Pseudomonas aeruginosa* induces the development of nosocomial pneumonia when using ventilators for immunocompromised patients (infected with COVID-19, cancer patients, newborns, etc.). The mechanism of "quorum sensing" in *P. putida* species is quite well studied experimentally, which makes it possible to numerically assess the characteristic parameters of a biosystem when it is studied using computing technologies.

A simplified diagram illustrating the principle of quorum-sensing is shown in Figure 1.

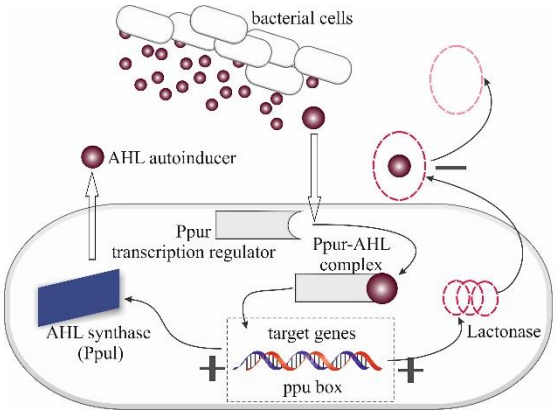


Fig. 1. The sketch of the quorum sensing regulatory network in *P. putida*.

Bacterial quorum-sensing is realized by the generation and propagation of special signaling molecules or autoinducers. Many Gram-negative bacteria use the so-called "N-acyl homoserine lactones" (or in short notation, AHL) as the autoinducers. This phenomenon allows a colony of bacteria to respond to external factors due to genes regulations.

The architecture of the quorum sensing regulation process for *P. putida* can be classified as Lux-type system for which the others functional elements of the biological system are follows [1, 36]. AHL-synthases (PpuL) are proteins of LuxI family associated to the production of AHL-autoinducers. Transcription regulators (PpuR) are referred to as proteins of LuxR family, which play the relevant role in quorum-sensing coordinating the expression of a variety of genes. PpuR transcription regulator requires its cognate AHLs for activity. In these terms, the AHL, produced by bacteria, penetrates through cell membranes, then diffuses and activates the regulatory proteins when the concentration of AHL reaches an intracellular threshold. As a result, the process of a DNA-binding protein increases AHL due to positive feedback.

There is also a process of degradation of AHL or quorum quenching caused by special enzymes, for example, Lactonase enzymes specific to *P. putida* bacterial strains. Quorum quenching can be associated with the occurrence of negative feedback in the dynamic system. Generated Lactonase leads to a fast decrease of the concentration of signaling molecules.

Moreover, during the "evolution" of the bacterial population, natural degradation of the signaling substance AHL and Lactonase enzyme can occur. The entire process has an iterative character.

MATHEMATICAL MODEL

The bacterial communication model describes the dynamics of changes in the concentrations of AHL and Lactonase enzyme taking into account the processes of their diffusion, generation, natural degradation, and degradation of AHL by Lactonase [26]. The mathematical formulation of the model is given by the initial boundary value problem for the system of semilinear reaction-diffusion equations, which (for one-dimensional case) can be written as follows:

$$\begin{cases} \dfrac{\partial u}{\partial t} = D_{AHL}\dfrac{\partial^2 u}{\partial x^2} - \gamma_{AHL}u - \gamma_{L\to AHL}Lu + F_1 \\ \dfrac{\partial L}{\partial t} = D_L\dfrac{\partial^2 L}{\partial x^2} - \gamma_L L + F_2 \end{cases}, \quad 0 < x < l, \quad 0 < t \le \bar{t}, \tag{1}$$

$$u(x,0) = u_0,\ L(x,0) = L_0, \quad 0 < x < l, \tag{2}$$

$$\left.\frac{\partial u}{\partial \mathbf{n}}\right|_{\Gamma} = 0,\ \left.\frac{\partial L}{\partial \mathbf{n}}\right|_{\Gamma} = 0, \quad 0 < t \le \bar{t}, \tag{3}$$

where $u(x, t)$ is the concentration of AHL in mol/l; $L(x, t)$ is the concentration of the Lactonase enzyme in mol/l; l is the linear size of a solution domain in μm; Γ is the boundary of the solution domain; $\bar{t}$ is the observation time in h; D_{AHL}, D_L, γ_{AHL}, γ_L, $\gamma_{L\to AHL}$ are positive parameters (in more detail see Table 1) responsible for the processes of diffusion and degradation of chemical compounds.

To specify the mathematical problem statement (1)–(3), we impose for simplicity the Neumann boundary conditions (3), assuming that the bacterial colonies are far enough from the boundaries and that the edge effects do not affect the distribution of the main substances characterizing the quorum sensing. Indeed, the boundary conditions can be considered in a more complex way, depending on the ratio of the colony size and solution area as well as conditions of bacterial cultivation. Some remarks concerning the existence and uniqueness of solutions obtained for similar class of problems can be found in [26]. The study is based on fundamental results reported in [37].

The system (1) includes the generation terms F_1 and F_2 which specify the density of bacterial biomass and the position of each bacterial colony x_c^j (where j is the number of the corresponding colony) in the solution domain. In the basic mathematical model of bacterial communication, these terms are determined by the Hill's function and the normal distribution of the bacterial biomass density by means of *a priori* assessment of the maximum attainable bacterial density:

$$F_s(x,u) = f_s(u)\sum_{j=1}^{M}\exp\left(-\frac{\left(x - x_c^j\right)^2}{2\sigma^2}\right), \quad s = 1,2, \tag{4}$$

$$f_1(u) = \alpha_{AHL} + \beta_{AHL}\frac{u^n}{u_{th}^n + u^n}, \quad f_2(u) = \beta_L\frac{u^n}{\left(u_{th} + \varepsilon\right)^n + u^n}, \tag{5}$$

where α_{AHL}, β_{AHL}, β_L, u_{th}, ε, σ, n are the positive parameters detailed in Table 1, M is the

total number of bacterial colonies.

The use of the Hill's law to formalize the production term f_1 of AHL has been proposed in [14]. This function involves a background production of AHL (α_{AHL} corresponds to the constitutive production rate) and a term for the positive feedback loop with an increased production rate of β_{AHL}. It is activated if a certain threshold u_{th} between low and increased activity is exceeded. The degree of polymerization n indicates the average number of monomeric units in a polymer molecule. Further, this approach has been applied in a number of studies representing various modifications of the single-cell-based model [18, 38], including the models with the lactonase production [26].

It should be pointed out that the production of Lactonase inside the cells depends on the AHL concentration. There is no background production for Lactonase compared to the rate α_{AHL} for AHL. Hence, if the AHL concentration reaches a certain threshold u_{th}, then also the production of Lactonase transitions in a state of increased activity but with a delay compared to AHL. We formalize that phenomenon by increasing the initial value of the AHL threshold u_{th} by ε, i.e. an increased production of Lactonase will not start until the threshold $u_{th}+\varepsilon$ is reached.

The model (1)–(5) allows one to evaluate the substances concentrations in the phase of active bacterial growth followed by relaxation to a certain level. This corresponds to the conditions of their flow cultivation, when new nutrient is added, and part of the medium with the cells of microorganisms and metabolic products are removed. However, the law of bacterial population dynamics may include not only the growth phases and the stationary phase, but also the phase of degradation or the long-term stationary phase due to the influence of various factors: the separation of daughter bacterial colonies, antibiotic action, bacterial growth in batch culture, lack of nutrients, the action of chemicals compounds, the radiation exposure, changes in the temperature, etc. [31–33, 39]. The typical diagram of the bacterial growth curve is demonstrated in Figure 2, where various scenarios for the final phase corresponding specific modes of bacterial evolution are shown.

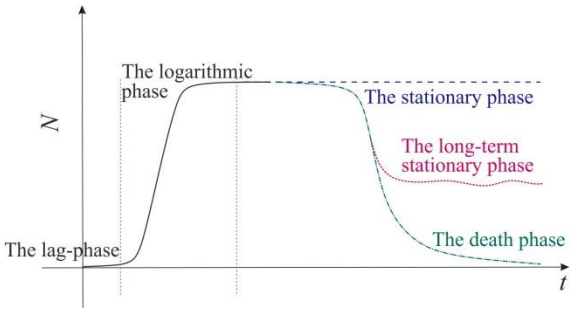


Fig. 2. Different phases of bacterial growth curve.

Since the extended range of population dynamics of microorganisms can include lag-phase, exponential phase, stationary phase, and death (mortality) phase, we can introduce the correspondent time dependence of bacterial density $N(t)$ into equation (3) of the basic model of bacterial quorum sensing:

$$F_s(x,t,u) = N(t)\, f_s(u) \sum_{j=1}^{M} \exp\left(-\frac{\left(x - x_c^j\right)^2}{2\sigma^2} \right), \quad s = 1,2, \tag{6}$$

where $N(t)$ is the normalized function defining the dynamics of a bacterial population density.

To provide the visual comparison of applied approaches (the basic model and the proposed modification), the corresponding functional diagrams of the biosystem are shown in

Figure 3. Here N_{max} corresponds to the equilibrium value of the bacterial population density which is observed in the stationary phase of population dynamics.

In order to formalize the generalized dependence for the density of the bacterial population (which can be used to vary the behavior in the final phase), we assume the following approximation. Let the function of bacterial density $N(t)$ describes the processes of increasing and decreasing (up to a certain threshold value) of bacterial biomass according to the following relations:

$$N(t)=\begin{cases}\left[1+\exp\left(-\mu\left(t-b_1\right)\right)\right]^{-1} & \text{if} \quad t\le t_N\\ a+b\left[1+\exp\left(\mu\left(t-b_2\right)\right)\right]^{-1} & \text{if} \quad t>t_N\end{cases} \tag{7}$$

where a, b are the dimensionless parameters which allow us to specify the "decrease level" of the bacterial density $N(t)$ in the long-term stationary phase; b_1, b_2 are the temporal approximation parameters in h; μ is the parameter related to the velocity of the population density growth in 1/h; t_N is the start time of degradation of bacterial population in h.

a) **b**)

Fig. 3. Functional diagrams of the basic (**a**) and modified (**b**) mathematical models of bacterial quorum sensing.

The example of graphic visualization of the dimensionless function $N(t)$ is demonstrated in Figure 4. In the example, a set of parameters are defined as follows: $\mu = 0.5$ 1/h, $a = b = 0.5$, $b_1 = 10$ h, $b_2 = 50$ h, $t_N = 30$ h.

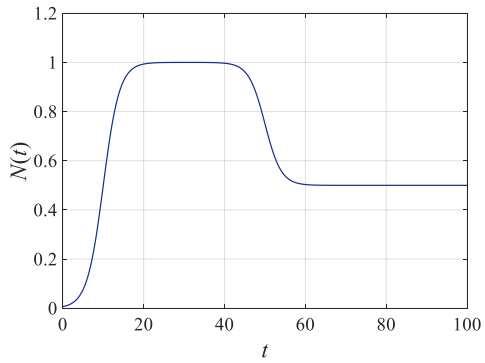


Fig. 4. Dynamics of changes in the normalized density of bacterial biomass during the observation time.

COMPUTATIONAL EXPERIMENTS AND DISCUSSION OF THE RESULTS

To numerical simulation based on the considered model, we use computing tools of the COMSOL Multiphysics platform (license agreement No 20/15/230) [40]. COMSOL Multiphysics is universal computer aid engineering software which allows one to solve differential problems using the finite element method without routine programming procedures.

In order to conduct computational experiments, we initialize the parameters of the mathematical model. Names of model parameters, descriptions, specified values, and units for equations (1)–(5) are listed in Table 1.

Table 1. Variables and parameters of the mathematical model

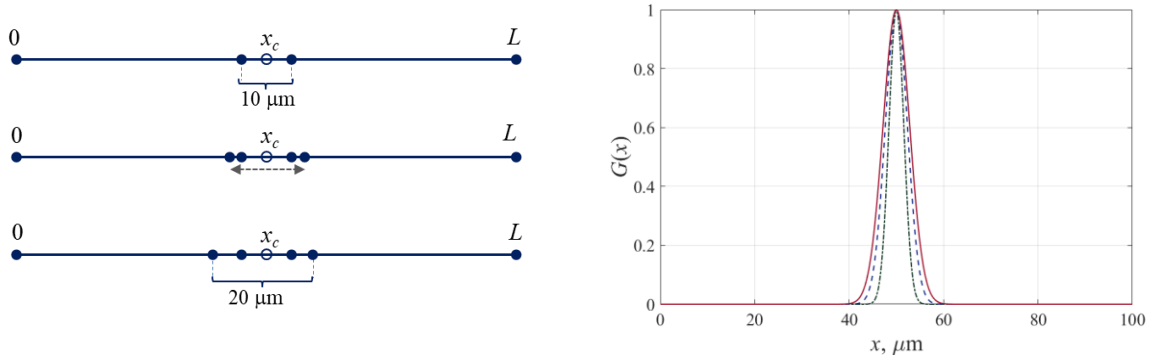
Parameter	Description	Value and unit
l	Linear dimension of the object	100 μm
D_{AHL}	Diffusion rate of AHL	100 μm^2/h
D_L	Diffusion rate of Lactonase	1 μm^2/h
γ_{AHL}	Abiotic degradation rate of AHL	0.05 1/h
$\gamma_{L\to AHL}$	Abiotic degradation rate of AHL by Lactonase	$1.5\cdot10^{-4}$ l/(mol·h)·
γ_L	Abiotic degradation rate of Lactonase	0.005 1/h
α_{AHL}	Low production rate of AHL	$1.058\cdot10^{-7}$ mol/(l/h)
β_{AHL}	Increased production rate of AHL	$1.058\cdot10^{-6}$ mol/(l/h)
β_L	Production rate of Lactonase	$5.05\cdot10^{3}$ mol/(l/h)
u_{th}	Threshold of AHL concentration between low and increased activity	70 nmol/l
n	Power parameter	2.5
ε	Threshold shift for Lactonase production	$5\cdot10^{-9}$ mol/l
u_0	Initial value of the AHL concentration	$5\cdot10^{-9}$ mol/l
L_0	Initial value of the Lactonase concentration	$1\cdot10^{-15}$ mol/l

The numerical values of the model parameters for the *P. putida* bacterial species were set using the data estimated using experimental finding and discussed in [41]. To specify the parameters of α_{AHL}, β_{AHL}, β_L, we assume that the maximum level of the bacterial density reaches the value of $4.6\cdot10^{11}$ cells/l in stationary phase. In general, the observation time $\bar{t}$ as well as parameters for the normalized function of bacterial population density (7) can be varied.

For instance, we consider one bacterial colony located at the fixed position $x_c = 50$ μm. We assume that the bacterial colony grows uniformly and the linear size increases from 10 μm to 20 μm during the period (0, 30) hours. The simplified diagram of sequential stages is displayed in Figure 5,a. Also, we suppose that at the same time the parameter σ related to "source" density distribution increases simultaneously. The form of normal distribution

$$G(x) = \exp\left(-\frac{(x - x_c)^2}{2\sigma^2}\right)$$

written in relations (4) is shown in Figure 5,b. The parameter σ can be numerically estimated using the "3-sigma rule" as $\sigma = R/3$ μm.



a) **b**)

Fig. 5. The diagram of the successive stages of growth of a bacterial colony (**a**) and the used normal distributions $G(x)$ for source functions (**b**).

First, to check the consistency of the model, let us perform a qualitative comparison the simulation results with the experimental data for *P. putida* under conditions of distributed bacterial biomass [41]. Let us consider that the bacterial population growth curve includes only lag-, log-, and stationary phases under the conditions of continues cultivation as reported in [41]. The corresponding normalized function $N(t)$ is shown in Figure 6. In particular, the least squares approximation results in the following parameters for the first equation in (7): $\mu = 0.38$ 1/h and $b_1 = 13.11$ h.

The results of numerical simulations of the bacterial quorum characteristics are presented in the context of the implementation of the modified model. The computer simulation results for AHL and Lactonase concentrations are displayed in Figure 7.

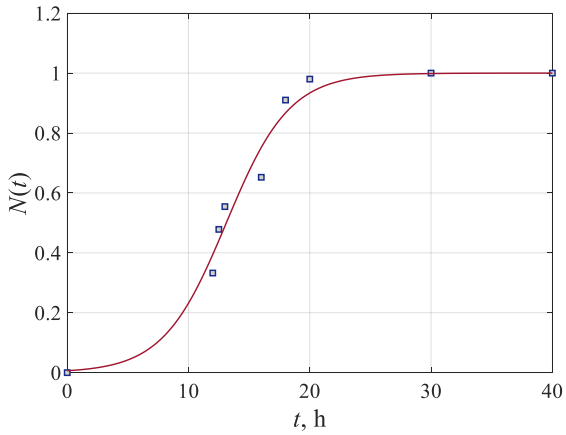


Fig. 6. The numerical approximation of the normalized bacterial density (continuous curve) related to the experimental data (discrete points) [41].

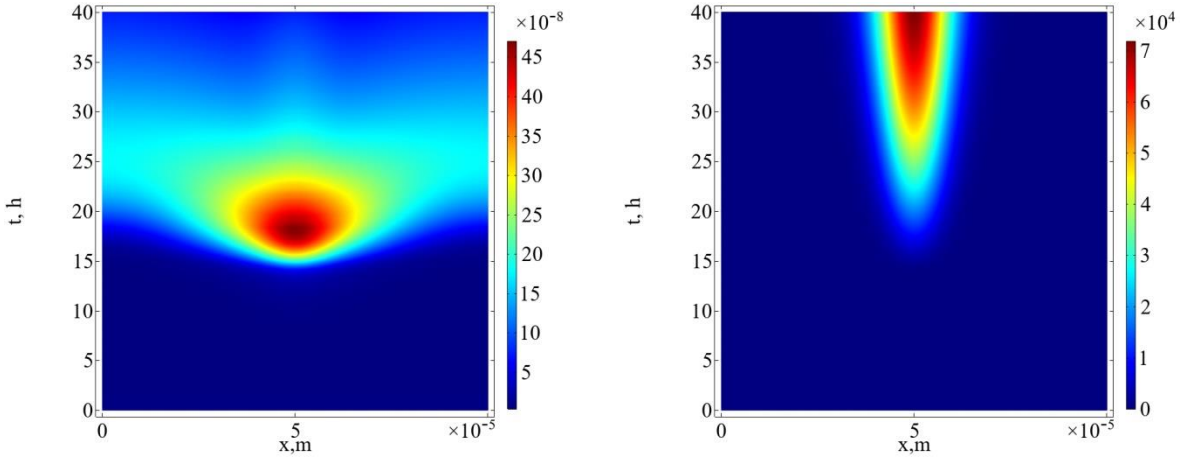


Fig. 7. The simulated space-time distributions of the AHL concentration (**a**) and the lactonase concentration (**b**).

Figure 8 demonstrates time-dependent profiles of the AHL concentration calculated by the model (1)–(7) compared with the experimental data obtained in [41].

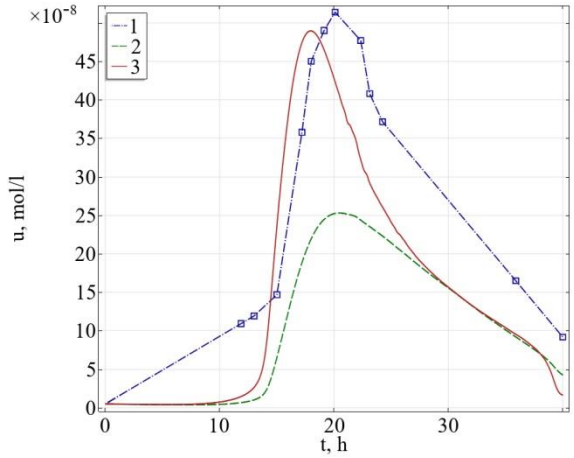


Fig. 8. The calculated time-dependent profiles of the AHL concentration compared to experimental data (1) obtained for continuous culture of *P. putida* [41] (the curve (2) corresponds to the average value in solution domain whereas the curve (3) presents the maximum level).

The assessment of the characteristic of the AHL concentration leads to the following. The absolute value of the maximum of the AHL concentration corresponds to the ~$5.1 \cdot 10^{-7}$ mol/l in the experiment and in simulation results we have ~$4.9 \cdot 10^{-7}$ mol/l that demonstrates an acceptable agreement in the order of the estimated values. The behavior of the characteristics qualitatively corresponds to the experimental data: we can observe a sharp increase in the AHL concentration (that means an increase in the quorum level) and a further decrease due to the generation and action of Lactonase enzymes. Notice that the original study [41] represents results of AHL computations in comparison with the experimental data that also indicates good agreement. But previously, the model was formalized using ordinary differential equations. In our case we deal with the space-time modeling of key characteristics of bacterial quorum sensing.

Furthermore, we can perform simulations of AHL and Lactonase concentrations in the extended range of population dynamics that may be associated with the various modes of evolution of bacterial populations. Figure 9 demonstrates the dynamics of the changes in the AHL concentration calculated at the central position $x_c = l/2$ of computational domain for two different modes of bacterial cultivation.

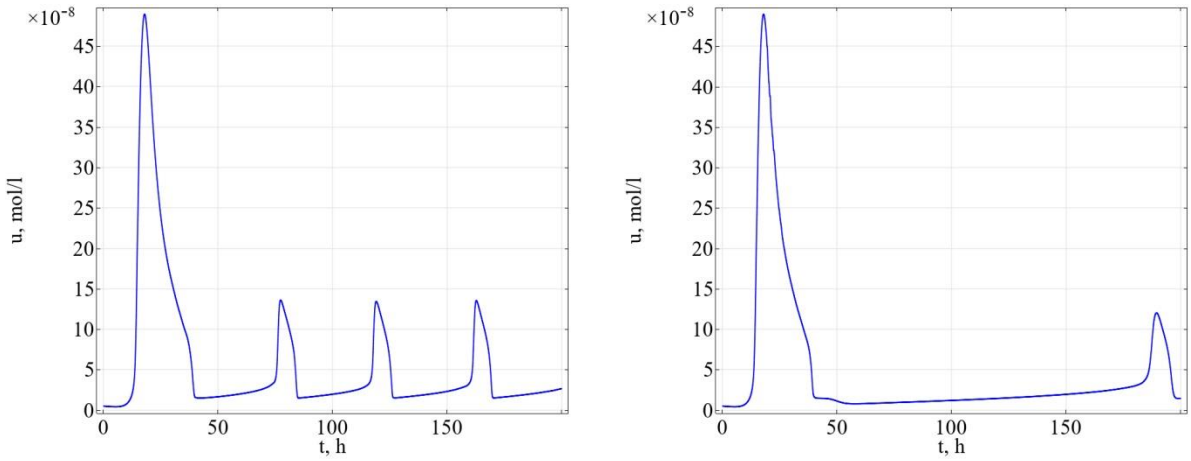
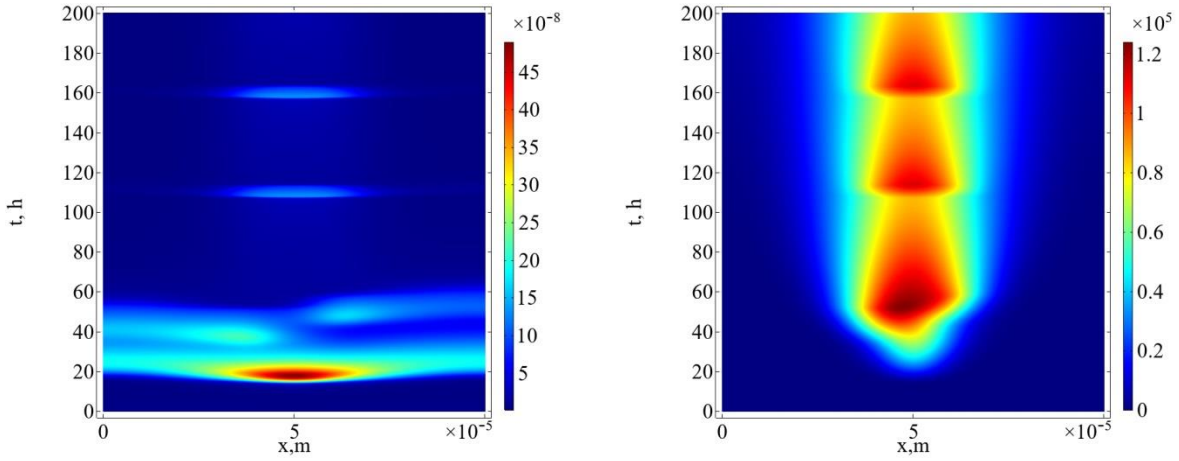


Fig. 9. Time-dependent profiles of the AHL concentration for the conditions of flow bacterial cultivation (**a**) and 50 % degradation of bacterial population (**b**).

These results suggest that under conditions of continuous cultivation the AHL concentration will be significantly reduced due to its inhibition by Lactonase. However, if the microbial activity is maintained, further periodic changes in the AHL concentration is observed due to a live bacterial colony. By about 80 hours, the colony is able to produce signaling molecules, maintaining a 30 % quorum level from the maximum reached value (as shown in Figure 9 a).

Further, let us assume that the living conditions of bacteria have changed, and the growth curve will include a long stationary phase corresponding to 50 % degradation of the population. Here we specify the following parameters for the function of bacterial biomass density (7): $a = b = 0.5$, $\mu = 0.4$ 1/h, $b_1 = 15$, $b_2 = 50$ h, $t_N = 30$ h. Figure 9 b) demonstrates the time-dependent profile of the AHL concentration calculated for this case. Our observations indicate that the population reduced by half for a long time (~150 hours) restores the quorum level. Note that the AHL concentration value corresponds to the $\sim 12 \cdot 10^{-8}$ mol/l which is quite considerable compared to the AHL concentration value $\sim 13.5 \cdot 10^{-8}$ mol/l for continues culture. This means that if the living conditions of bacteria and nutrient medium will be acceptable normalized, the concentration level of AHL will be restored to some “baseline” value even at a lower value of bacterial density. A population inhibited by 90 % will continue to produce signaling molecules at a very low level and this value will reach $\sim 10^{-8}$ mol/l by 200 hours. It should be pointed out that we can observe two competing processes which are an increase in the AHL concentration with a decrease in the Lactonase concentration due to negative feedback as well as a decrease in the AHL concentration with a drop in the population density at $t > 30$ hours. In this particular case, for the AHL concentration the population decline is the dominant factor compared to the growth due to decrease in the Lactonase concentration.

Finally, let us demonstrate visualization of quorum sensing characteristics computed for several bacterial colonies located in the computational domain. We initialized three bacterial colonies in symmetrical positions. Let us assume that the parent colony is set in the center of the computational domain $x_c^1 = 50$ μm at the start time, after 20 hours a daughter colony separates at a position of $x_c^2 = 40$ μm, and after another 10 hours another daughter colony separates at a position of $x_c^3 = 60$ μm. Here we suppose the 10 % strategy of degradation of population density $N(t)$. Figure 10 illustrates the space-time distributions of the concentrations of chemical substances characterizing bacterial quorum sensing.



a) **b**)

Fig. 10. The space-time distributions of the AHL concentration (**a**) and the lactonase concentration (**b**) for several bacterial colonies at 10 % degradation of bacterial population.

In this case, we can conclude that generally the distributions of AHL and Lactonase concentrations indicate a behavior similar to the previous version of the model implementation. In this case, the separation of daughter colonies does not significantly change the overall quorum level, since at the time of their separation; the Lactonase concentration is so relevant that it does not increase the activity of daughter colonies. Further maintenance of the vital activity of bacteria, the general level of the quorum also changes periodically, reaching the same value at the peak value (~$13 \cdot 10^{-8}$ mol/l) as in the case of the functioning of only one population.

It is readily seen that more refined and adequate mathematical models of bacterial quorum sensing should include not only a formalization of changes in the bacterial density but also scenarios for the growth of the bacterial biomass. This stimulates insights for further investigations.

CONCLUDING REMARKS

Thus, the study presents the result of the development and implementation of a modified reaction-diffusion model of bacterial communication, taking into account the extended range of bacterial population dynamics. The formalization of the multiphase character of population dynamics is introduced into the model based on a modification of the generational terms given the possible processes of increasing and decreasing bacterial population density to a certain threshold value.

The COMSOL Multiphysics as a finite element analysis software provides efficient tools for implementing the bacterial quorum sensing model described by partial differential equations. Computational experiments were conducted on the example of the bacterial species *P. putida*. Our findings indicate that in the degradation phase of bacterial evolution the level of intercellular communication decreases naturally with a decrease in population density. Primarily, the decrease in the quorum level is caused by the action of the Lactonase enzyme. However, when the living conditions of bacteria are restored and the population density is relaxed to a certain non-zero level, there are mutually competing processes of increasing and decreasing the AHL concentration, leading to fluctuations of this substance. Moreover, the level of AHL the “bursts” is quite high for a significantly degraded population.

The development of the bacterial communication model is necessary to be continued, taking into account the spatial-temporal distribution of bacterial biomass in a numerical assessment of the concentrations of AHL and Lactonase which characterize the quorum sensing phenomenon in Gram-negative bacteria.

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Моделирование процесса коммуникации бактерий в расширенном диапазоне популяционной динамики

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Аннотация. «Чувство кворума», представляющее один из видов бактериальной коммуникации, может быть исследовано с использованием средств и методов математического и компьютерного моделирования. В настоящей работе предложена модификация детерминированной математической модели бактериального чувства кворума с учетом закона многофазной динамики популяций. Математическая модель формализована в виде начально-краевой задачи для системы полулинейных уравнений в частных производных типа «реакция-диффузия». Динамика изменения плотности биомассы учтена в генерационных слагаемых модельных уравнений. Модель описывает изменение концентрации специальных химических субстанций – сигнального вещества и фермента лактоназы, характеризующих чувство кворума у грамотрицательных бактерий. Задача решается методом конечных элементов с использованием платформы COMSOL Multiphysics. Проведены вычислительные эксперименты по оценке концентраций ключевых веществ, характеризующих чувство кворума, для бактериального вида *Pseudomonas putida* в расширенном диапазоне динамики популяции.

Ключевые слова: *бактериальная коммуникация, чувство кворума, модель реакции-диффузии, бактериальная динамика, конечно-элементное моделирование, моделирование распределения химических соединений.*