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On Oscillations in a Gene Network with Diffusion

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Abstract: We consider one system of partial derivative equations of the parabolic type as a model of a simple 3D gene network in the presence of diffusion of its three components. Using discretization of the phase portrait of this system, comparison theorems, and other methods of the qualitative theory of differential equations, we show uniqueness of the equilibrium solution to this system and find conditions of instability of this equilibrium. Then, we obtain sufficient conditions of existence of at least one oscillating functioning regime of this gene network. An estimate of lower and upper bounds for periods of these oscillations is given as well. In quite a similar way, these results on the existence of cycles in 3D gene networks can be extended to higher-dimensional systems of parabolic or other evolution equations in order to construct mathematical models of more complicated molecular–genetic systems.

Keywords: gene network models; phase portraits; systems of non-linear differential equations; reaction–diffusion equations; cycles; stability; invariant surfaces; invariant domains; Poincaré map; fixed point theorem

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1. Introduction

We study a system of three nonlinear evolution equations of the parabolic type as a model of interaction of three species that compete according to the "rock–paper–scissors" scheme. At the same time, this system describes the functioning of some of the simplest circular gene networks, called molecular repressilators (inhibitors) in the presence of diffusion of their components in ambient space.

During the long period of our collaboration with biologists, as in [1–3], we were especially interested in detecting equilibriums and oscillating regimes (cycles) of similar models without diffusion. In these studies, we had one more geometric problem that consists in localization of these cycles in the phase portraits of corresponding dynamical systems [4,5]. This was quite useful in biological interpretations of numerical experiments with these models.

For gene networks with diffusible components, we consider now their simplest case, when the domain Ω of the geometric variables x_1, x_2, x_3 coincides with $\mathbb{R}^3$. Surely, in more realistic models, such a domain should have a compact support and should be endowed with corresponding boundary conditions on $\partial\Omega$. Such a boundary value problem was studied in [6], where a two-dimensional system of parabolic equations with quadratic non-linearity as a reaction–diffusion model of two competitive biological species in a compact domain with the Neumann boundary conditions was considered; see also [7].

In any numerical experiment with these systems of differential equations, we should fix the values of their parameters. In most interesting cases, the methods of the qualitative theory of differential equations, such as comparison theorems [7], analysis of monotonicity of solutions [8], etc., help to describe the behavior of solutions to these systems for a wide range of values of these parameters. Here, in control of the behavior of these solutions to such problems, our main tool is decomposition of the phase portraits of the corresponding dynamical systems to smaller domains. In each of these domains, a qualitative description of these solutions is much simpler than in the whole phase portrait, even in the cases when the parameters in the equations are not fixed. This is especially important for mathematical modeling of biological processes, when one has to take into account synchronization and bifurcations of solutions [9–11], noise [12–14], and various amplification and chaotic phenomena [15–17].

Numerous applications of analogous evolution differential equations regarding problems of population dynamics, biochemical kinetics, and modeling of miscellaneous biological control systems and ensembles of corresponding oscillating processes have a very long history; see for example [18–20]. Our short-term plan is to extend the results of this paper to more complicated models of molecular–genetic systems, taking into account the diffusion of their components.

2. Materials and Methods

2.1. Mathematical Model

Here, we study a model of the simplest molecular repressilators realized in the form of the following system of reaction–diffusion parabolic equations:

$$\begin{aligned} \frac{\partial u_1}{\partial t} - c_1^2 \Delta u_1 &= k_1 \cdot (f_1(u_3) - u_1); \\ \frac{\partial u_2}{\partial t} - c_2^2 \Delta u_2 &= k_2 \cdot (f_2(u_1) - u_2); \\ \frac{\partial u_3}{\partial t} - c_3^2 \Delta u_3 &= k_3 \cdot (f_3(u_2) - u_3). \end{aligned} \tag{1}$$

Non-negative concentrations of its three components are denoted by $u_j(t, x_1, x_2, x_3)$, and the Laplace operator $\Delta = \dfrac{\partial^2}{\partial x_1^2} + \dfrac{\partial^2}{\partial x_2^2} + \dfrac{\partial^2}{\partial x_3^2}$ describes their diffusion in the space. Here and below, $j = 1, 2, 3$, and $j - 1 = 3$ for $j = 1$; positive constants c_j and k_j characterize the rates of diffusion and, respectively, the rates of natural degradations of these components. The velocities of their synthesis are given by positive smooth monotonically decreasing functions $f_j(u_{j-1})$ of non-negative arguments, $f_j(u_{j-1}) \to 0$ for $u_{j-1} \to \infty$; see [2,5]. Let $a_j := f_j(0) = \max f_j$.

Following [7,21], we describe the solutions to the systems of type (1) in terms of the trajectories of dynamical systems or nonlinear semi-groups generated by the differential operator of the second order

$$\begin{pmatrix} -c_1^2\Delta & 0 & 0 \\ 0 & -c_2^2\Delta & 0 \\ 0 & 0 & -c_3^2\Delta \end{pmatrix}.$$

Lemma 1. *The domain* $D^3 = [0, a_1] \times [0, a_2] \times [0, a_3] \subset \mathbb{R}_+^3$ *contains exactly one point* $P_0 = (u_1^0, u_2^0, u_3^0)$ *such that*

$$f_1(u_3^0) = u_1^0, \quad f_2(u_1^0) = u_2^0, \quad f_3(u_2^0) = u_3^0, \quad \text{and} \quad u_1^0 = f_1(f_3(f_2(u_1^0))). \tag{2}$$

Proof of Lemma 1. The last equality follows immediately from the previous ones. In the cases of some similar non-linear systems, it was noted in [4,5] that the left-hand side of the last equality of (2) grows monotonically, and the right-hand side decreases monotonically from $f_1(f_3(f_2(0)))$ to zero. Thus, the graphs of both sides have exactly one intersection point that determines the first coordinate u_1^0. The remaining coordinates of the sought after equilibrium point P_0 are determined uniquely from the second and third equations of (2). □

Hence, the constant functions $u_j(t, x_1, x_2, x_3) \equiv u_j(t, X) \equiv u_j^0$ describe an equilibrium in the gene network model; here, $\Delta u_j \equiv 0$, $\dfrac{\partial u_j}{\partial t} \equiv 0$ for all j, X, t.

In contrast with [6,7,22], we are particularly interested in the cases when the equilibrium point P_0 is not stable, since system (1) does not have oscillating solutions otherwise.

Thus, from now on, we assume that point P_0 is unstable. From time to time, we recall this assumption in the statements of our propositions. Some of them remain true in the case when point P_0 is stable as well. However, when trajectories are near such a stable equilibrium point where all biochemical processes stop, their behavior does not have substantial biological interpretation.

2.2. Combinatorial Structure of the Model

The main aim of this work is to describe the behavior of solutions of system (1) in the domain D^3. We start with one basic fact: if the initial data $u_j(0, x_1, x_2, x_3)$ of this system are contained in D^3, then the corresponding solution to this system remains in this domain for all positive t.

Lemma 2. *If* $0 \le u_j(0, x_1, x_2, x_3) \le a_j$, $j = 1, 2, 3$, *then for all* $t > 0$, *solutions to system* (1) *satisfy the inequalities* $0 \le u_j(t, x_1, x_2, x_3) \le a_j$.

Proof of Lemma 2. 1. Let $u_1(t_0, X^*) = 0$ for some $t_0 > 0$ and $X^* = (x_1^*, x_2^*, x_3^*) \in \mathbb{R}^3$, and let us assume that for all $t \le t_0$, the inequality $u_1(t_0, X^*) \ge 0$ holds. Then, at each such point X^*, we have $\Delta u_1(t_0, X^*) \ge 0$. Since $f_1(u_3) > 0$, at these points, we obtain $\dot{u}_1 = c_1^2 \Delta u_1 + k_1 f_1(u_3) > 0$. Thus, the function u_1 grows at these points. In a similar way, one can verify that the functions $u_2(t, X)$ and $u_3(t, X)$ grow with t on the faces $u_2 = 0$ and $u_3 = 0$ of the parallelepiped D^3, respectively.

2. Let $u_1(t_0, X^*) = a_1$ for some $t_0 > 0$ and $X^* = (x_1^*, x_2^*, x_3^*) \in \mathbb{R}^3$, and let us assume that for all $t \le t_0$, the inequality $u_1(t_0, X^*) \le a_1$ holds. Then, we have $\Delta u_1(t_0, X^*) \le 0$ at each such point X^*. In the right-hand side of the first equation of system (1), we obtain $f_1(u_3) - u_1 = f_1(u_3) - a_1 \le 0$; here, the equality holds for $u_3 = 0$ only. Then, for $u_3 > 0$, we have $\dfrac{\partial u_1}{\partial t} = c_1^2 \Delta u_1 + k_1(f_1(u_3) - a_1) < 0$; thus, the function u_1 decreases here with t. If $u_3 = 0$, then on the edge $\{u_1 = a_1;\ u_3 = 0\}$ of the parallelepiped D^3, the right-hand side of the third equation of system (1) is strictly positive, and according to the first part of this proof, $\Delta u_3 \ge 0$. Hence, on $\{u_1 = a_1;\ u_3 = 0\}$, we have $\dfrac{\partial u_3}{\partial t} > 0$, and trajectories of the points of this edge remain in D^3 as well. In the same way, the functions $u_2(t, X)$ and $u_3(t, X)$ decrease for the faces $u_2 = a_2$ and $u_3 = a_3$ of D^3, respectively. □

Corollary 1. *The parallelepiped* D^3 *is a* **positively invariant** *domain of system* (1).

This means that trajectories $(u_1(t), u_2(t), u_3(t))$ of the points of D^3 remain in this domain as $t \to +\infty$. Below, we call this domain invariant. Following [4], consider decomposition of the invariant domain D^3 by three planes $u_j = u_j^0$, which contain the equilibrium point P_0. This decomposition consists of eight smaller parallelepipeds (blocks), which we denote by binary multi-indices $[\varepsilon_1 \varepsilon_2 \varepsilon_3]$; here, $\varepsilon_j = 0$, if $u_j \le u_j^0$ for all points of a block, and $\varepsilon_j = 1$, if $u_j \ge u_j^0$ for all its points.

As in [5], we denote by W_1 the union of six blocks [001], [011], [010], [110], [100], [101]. It follows from Theorem 1 (see below) that the periodic trajectories (cycles) of system (1) are contained in the domain W_1 and do not intersect the remaining two blocks [000] and [111] of this decomposition of domain D^3. Thus, we do not consider these two blocks systematically.

For n-dimensional analogues of system (1), similar decompositions of the phase portraits to 2^n blocks can be described as well; see [23]. The main aim of these discretizations is construction of smaller invariant domains that contain cycles of corresponding systems of equations. Usually, these smaller domains are composed of $2n$ blocks. Section 2.4 below is devoted to such a construction in our 3D case.

2.3. Small Oscillations Near Equilibrium

Let us examine small oscillations of solutions to system (1) in a sufficiently small neighborhood

$$V_\delta(P_0) := (u_1^0 - \delta, u_1^0 + \delta) \times (u_2^0 - \delta, u_2^0 + \delta) \times (u_3^0 - \delta, u_3^0 + \delta) \subset Q^3$$

of its equilibrium solution $u_j(t, x_1, x_2, x_3) \equiv u_j^0$, $j = 1, 2, 3$. The linearization matrix of system (1) at point P_0 has the form

$$J(P_0) = \begin{pmatrix} -k_1 & 0 & -k_1 p_1 \\ -k_2 p_2 & -k_2 & 0 \\ 0 & -k_3 p_3 & -k_3 \end{pmatrix}; \tag{3}$$

here, the parameters $p_j = -\dfrac{df_j}{du_{j-1}} > 0$ are calculated at the equilibrium point P_0.

Let $U_j(t, x_1, x_2, x_3z) := u_j(t, x_1, x_2, x_3) - u_j^0$. Neglecting the second and the higher-order terms in Taylor's expansions of the right-hand sides of system (1) near point P_0, we obtain

$$f_j(u_{j-1}) - u_j = f_j(u_{j-1}^0) - p_j \cdot (u_{j-1} - u_{j-1}^0) - u_j^0 - (u_j - u_j^0).$$

Consider first the particular case $c_1 = c_2 = c_3 = c$. We assume also that the real parts of the eigenvalues of matrix $J(P_0)$ do not vanish, i.e., that the equilibrium point P_0 of system (1) is a hyperbolic one. Under this standard assumption, according to the classical Grobman–Hartman theorem [24,25], in some small neighborhood $V_\delta(P_0)$, the system (1) is topologically equivalent to its linearization

$$\begin{aligned} \frac{\partial U_1}{\partial t} - c^2 \Delta U_1 &= -p_1 k_1 U_3 - k_1 U_1; \\ \frac{\partial U_2}{\partial t} - c^2 \Delta U_2 &= -p_2 k_2 U_1 - k_2 U_2; \\ \frac{\partial U_3}{\partial t} - c^2 \Delta U_3 &= -p_3 k_3 U_2 - k_3 U_3. \end{aligned} \tag{4}$$

If the values of the parameters of system (1) vary and the real parts of some of these eigenvalues become zero, then variations of the phase portrait of this nonlinear system can be described by the Andronov–Hopf bifurcation theorem (see [26]), where the conditions of the birth of cycles are exposed.

Let $S = S(t, x_1, x_2, x_3) = \lambda_1 U_1 + \lambda_2 U_2 + \lambda_3 U_3$; the real coefficients λ_j are determined below from (6) in order to obtain the following equation

$$\begin{aligned} \frac{\partial S}{\partial t} = c^2 \Delta S - [U_1(\lambda_1 k_1 + p_2 k_2 \lambda_2) + U_2(k_2 \lambda_2 + p_3 k_3 \lambda_3) + U_3(\lambda_1 p_1 k_1 + \lambda_3 k_3)] = \\ c^2 \Delta S - K(U_1 \lambda_1 + U_2 \lambda_2 + U_3 \lambda_3). \end{aligned} \tag{5}$$

Here, $S = S(t, x_1, x_2, x_3) \underset{t \to +\infty}{\longrightarrow} 0$ for any initial data, and the plane $\lambda_1 U_1 + \lambda_2 U_2 + \lambda_3 U_3 = 0$ is invariant for system (4) in the space of the variables U_1, U_2, U_3.

Representation (5) follows from the proportionality conditions:

$$\frac{\lambda_1 k_1 + p_2 k_2 \lambda_2}{\lambda_1} = \frac{\lambda_2 k_2 + \lambda_3 p_3 k_3}{\lambda_2} = \frac{\lambda_3 k_3 + \lambda_1 k_1 p_1}{\lambda_3} = K. \tag{6}$$

Since these equations are homogeneous with respect to λ_j, we can restrict our considerations to the case $\lambda_1 = 1$. The structure of system (4) is symmetric with respect to the cyclic permutations of the variables, and we can assume also that $k_3 \geq k_1$, $k_3 \geq k_2$.

Proportions (6) are reduced to the equation

$$\mathcal{P}(\lambda_3) := \lambda_3^3 p_2 p_3 k_2 k_3 - \lambda_3^2 (k_3 - k_1)(k_3 - k_2) - \lambda_3 (2k_3 - k_1 - k_2) p_1 k_1 - p_1^2 k_1^2 = 0.$$

Then, $\mathcal{P}(0) < 0$, $\mathcal{P}'(0) < 0$, $\mathcal{P}''(0) < 0$; thus, the polynomial $\mathcal{P}$ has exactly one positive root $\lambda_3 = \lambda_+$, and $\lambda_2 = \dfrac{k_3 - k_1}{p_2 k_2} + \dfrac{p_1}{k_2 p_2 \lambda_+}$ is positive as well. Thus, all the coefficients in the definition of the linear combination $S(t, x_1, x_2, x_3)$ are positive, and the intersection of plane $\lambda_1 U_1 + \lambda_2 U_2 + \lambda_3 U_3 = 0$ with the neighborhood $V_\delta(P_0)$ is contained in the domain W_1.

Since we are interested in the instability of P_0; in the case of arbitrary positive coefficients k_j, we can use various instability criteria formulated in [7,27] (see also references therein) in the analysis of solutions to system (1) near the equilibrium. For example, it was shown in [21], Chapter 3, Theorem 15.3, that the equilibrium solution to such a system is not stable, if some eigenvalues of the corresponding matrix have a positive real part. In our 3D case, this instability happens when there is a pair of eigenvalues $\lambda_1 = \bar{\lambda}_2$ such that $\mathrm{Re}\lambda_1 = \mathrm{Re}\lambda_2 > 0$. The remaining eigenvalue λ_3 is negative.

Solutions to the linearized system (4) have very clear explicit representation in the particular case $k_1 = k_2 = k_3 = k$. Following the usual approach, we consider the functions $v_j(t, q_1, q_2, q_3) \equiv v_j(t, Q)$ defined by the Fourier transform:

$$U_j(t, X) = \frac{1}{(\sqrt{2\pi})^3} \int\limits_{\mathbb{R}^3} e^{-Q \cdot X i} v_j(t, Q) dQ, \quad j = 1, 2, 3.$$

Then, system (4) is reduced to a linear system of ordinary differential equations

$$\begin{aligned} &\frac{dv_1}{dt} + (c^2 |Q|^2 + k) v_1 + k p_1 v_3 = 0; \\ &\frac{dv_2}{dt} + (c^2 |Q|^2 + k) v_2 + k p_2 v_1 = 0; \\ &\frac{dv_3}{dt} + (c^2 |Q|^2 + k) v_3 + k p_3 v_2 = 0, \end{aligned} \tag{7}$$

or in the matrix form, $\dfrac{dV}{dt} = -AV$, where $A = (c^2|Q|^2 + k)E + M$, E is the unit matrix and

$$M = \begin{pmatrix} 0 & 0 & kp_1 \\ kp_2 & 0 & 0 \\ 0 & kp_3 & 0 \end{pmatrix}, \quad M^2 = \begin{pmatrix} 0 & k^2 p_1 p_3 & 0 \\ 0 & 0 & k^2 p_1 p_2 \\ k^2 p_2 p_3 & 0 & 0 \end{pmatrix}, \tag{8}$$
$$M^3 = k^3 p_1 p_2 p_3 E.$$

Let $b^3 := p_1 p_2 p_3$, $b > 0$. Since the matrices E and M commute, the solution to system (7) is expressed in the form

$$V(t, Q) = e^{-At} V(0, Q) = e^{-(c^2|Q|^2 + k)Et} e^{-Mt} V(0, Q).$$

It follows from (8) that $e^{-Mt} = \alpha''(t)E - \alpha'(t)M + \alpha(t)M^2$, where

$$\alpha(t) = \left(\frac{t^2}{2!} - \frac{t^5 b^3 k^3}{5!} + \frac{t^8 b^6 k^6}{8!} - \dots \right); \quad \alpha'''(t) = -b^3 k^3 \alpha(t);$$
$$\alpha(0) = \alpha'(0) = 0; \quad \alpha''(0) = 1.$$

Hence,

$$\alpha(t) = \frac{1}{3}\exp(-bkt) + \frac{1}{3}\exp\left(\frac{bkt}{2}\right)\left(-\cos\frac{bk\sqrt{3}t}{2} + \sin\frac{bk\sqrt{3}t}{2}\right).$$

Consequently, the inverse Fourier transform of the solution $e^{-At}V(0,Q)$ contains summands of the types $\exp(-k(b+1)t)\cdot B_1(t,X)$ and $\exp\left(\frac{k(b-2)t}{2}\right)\cdot B_2(t,X)$, where B_1, B_2 are bounded functions. It is well known that if all eigenvalues of the matrix $(-A)$ are strictly negative, then the solutions to system (7) describe the damping oscillations near the equilibrium P_0.

Let $\mathbb{B}(r)$ be an open ball centered at the origin $x_j = 0$ with radius r. Representation of $\alpha(t)$ in the matrix exponent e^{-Mt} above implies the following proposition.

Lemma 3. *If $c_1 = c_2 = c_3$, $k_1 = k_2 = k_3$, $q_1q_2q_3 > 8$ and the support of the initial data $v_j(0,Q)$ satisfies the condition $\operatorname{supp} v_j \subset \mathbb{B}\left(\sqrt{\frac{k(b-2)}{2c^2}}\right)$, then system (7) has unbounded solutions and point P_0 is unstable.*

In terms of the initial system (1), this means that these solutions leave the small neighborhood $V_\delta(P_0)$ and do not return there as $t \to \infty$. Before this moment, trajectories of all points of this neighborhood pass from block to block according to the arrows of the following *State Transition Diagram* (STD); see [4,5].

$$\begin{array}{ccccc} [001] & \longrightarrow & [011] & \longrightarrow & [010] \\ \uparrow & & & & \downarrow \\ [101] & \longleftarrow & [100] & \longleftarrow & [110] \end{array} \tag{9}$$

This expressive term was introduced in [23] in the modeling of some other biological control systems by piecewise linear ordinary differential equations.

In the general case of arbitrary positive coefficients k_j, the Vyshnegradskii criterion [28] implies that the characteristic polynomial

$$\lambda^3 + \lambda^2(k_1+k_2+k_3) + \lambda(k_1k_2+k_1k_3+k_2k_3) + k_1k_2k_3(1+p_1p_2p_3)$$

of the linearization matrix (3) has eigenvalues with positive real parts if and only if

$$k_1k_2k_3(1+p_1p_2p_3) > (k_1+k_2+k_3)\cdot(k_1k_2+k_1k_3+k_2k_3);$$

or after some reductions, if and only if

$$p_1p_2p_3 > 8 + \left(\sqrt{\frac{k_1}{k_2}} - \sqrt{\frac{k_2}{k_1}}\right)^2 + \left(\sqrt{\frac{k_1}{k_3}} - \sqrt{\frac{k_3}{k_1}}\right)^2 + \left(\sqrt{\frac{k_3}{k_2}} - \sqrt{\frac{k_2}{k_3}}\right)^2. \tag{10}$$

Thus, the more deviations $\left|\frac{k_j}{k_i} - 1\right|$, the stronger the instability conditions should be, and we obtain the following proposition.

Lemma 4. *For arbitrary values of the coefficients c_j, k_j, inequality (10) is equivalent to instability of the equilibrium point P_0.*

2.4. Construction of a Smaller Invariant Domain

The main result of this paper is based on the following technical proposition, which actually has a combinatorial nature.

Theorem 1. *If point P_0 is unstable, then the union W_1 of the six blocks listed in (9) is a positive invariant domain of system (1).*

Proof of Theorem 1. The proof of this theorem follows from Lemmas 5–10. Each of these Lemmas describes the behavior of the trajectories, respectively, in blocks [001], [011], [010], [110], [100], [101] according to the arrows of STD (9). □

Lemma 5. *If point P_0 is unstable and the initial data $u_j(0, X)$ of system (1) satisfy the conditions*

$$u_3^0 \le u_3(0, x_1, x_2, x_3) \le a_3; \quad 0 \le u_1(0, x_1, x_2, x_3) \le u_1^0; \quad 0 \le u_2(0, x_1, x_2, x_3) \le u_2^0,$$

then there exists $t_* = t_*(x_1, x_2, x_3) > 0$ such that solution $\{u_j(t_*, x_1, x_2, x_3)\}$ to this system satisfies the inequalities

$$u_3^0 \le u_3(t_*, x_1, x_2, x_3) \le a_3; \quad 0 \le u_1(t_*, x_1, x_2, x_3) \le u_1^0; \quad u_2^0 \le u_2(t_*, x_1, x_2, x_3) \le a_2. \tag{11}$$

Thus, if the initial data are in block [001], then the solution $\{u_1(t_*, X),\ u_2(t_*, X),\ u_3(t_*, X)\}$ eventually arrives at block [011].

Proof of Lemma 5. The first two pairs of inequalities (11) are proved exactly in the same way as the corresponding inequalities in Lemma 2.

Let $\Gamma_1 = [101] \cap [001] = \{u_1 = u_1^0; 0 \le u_2 \le u_2^0; u_3^0 \le u_3 \le a_3\}$ be a face of block [001]. The δ-neighborhood $V_\delta(\Gamma_1)$ of this face in [001] consists of the neighborhood $V_\delta(P_0)$ of point P_0 and three domains:

$$\begin{aligned}
\Gamma_{12} &:= (u_1^0 - \delta; u_1^0] \times [0; u_2^0 - \delta] \times [u_3^0; u_3^0 + \delta),\\
\Gamma_{13} &:= (u_1^0 - \delta; u_1^0] \times (u_2^0 - \delta; u_2^0] \times [u_3^0 + \delta; a_3],\\
\Gamma_{10} &:= (u_1^0 - \delta; u_1^0] \times [0; u_2^0 - \delta] \times [u_3^0 + \delta; a_3].
\end{aligned}$$

Let $[001) := [001] \setminus V_\delta(\Gamma_1)$. In the neighborhood $V_\delta(P_0)$, trajectories of all points pass from block to block according to the arrows of STD (9).

In the domain $\Gamma_{10} \cup \Gamma_{13}$, we have $k_1(f_1(u_3) - u_1) < -k_1\delta\dfrac{p_1}{2}$; thus, for some $m > 0$, the inequality $\dfrac{\partial u_1}{\partial t} < -m^2 < 0$ holds in this domain. Similarly, in Γ_{12}, we have $k_3(f_3(u_2) - u_3) > k_3\delta\dfrac{p_3}{2}$, and in this domain, we obtain $\dfrac{\partial u_3}{\partial t} > m^2 > 0$. Thus, trajectories of all points of the domain Γ_{12} pass to the domain $\Gamma_{10} \cup [001)$, and trajectories of all points of $\Gamma_{10} \cup \Gamma_{13}$ pass to the domain $[001)$.

Now, for trajectories of points of the remaining part $[001)$ of block [001], we obtain estimates

$$k_2 a_2 > \frac{\partial u_2}{\partial t} - c_2^2 \Delta u_2 = k_2(f_2(u_1) - u_2) > k_2\delta\frac{p_2}{2}. \tag{12}$$

For $t > 0$, solutions to the equations $\dfrac{\partial \mathcal{U}_2^-}{\partial t} - c_2^2\Delta\mathcal{U}_2^- = k_2\delta\dfrac{p_2}{2}$ and $\dfrac{\partial \mathcal{U}_2^+}{\partial t} - c_2^2\Delta\mathcal{U}_2^+ = k_2 a_2$ have the forms

$$\mathcal{U}_2^-(t, X) = k_2\delta\frac{p_2}{2}t + \left(2c_2\sqrt{\pi t}\right)^{-3}\int_{\mathbb{R}^3}\mathcal{U}_2^-(0, \xi)\cdot\exp\left[-\frac{|X - \xi|^2}{4c_2^2 t}\right]d\xi, \tag{13}$$

respectively,

$$\mathcal{U}_2^+(t, X) = k_2 a_2 t + \left(2c_2\sqrt{\pi t}\right)^{-3}\int_{\mathbb{R}^3}\mathcal{U}_2^+(0, \xi)\cdot\exp\left[-\frac{|X - \xi|^2}{4c_2^2 t}\right]d\xi, \tag{14}$$

and hence eventually grow monotonically with respect to t with positive velocity bounded from zero, here $\xi \in \mathbb{R}^3$.

Let $u_2(0, X) = \mathcal{U}_2^-(0, X) = \mathcal{U}_2^+(0, X)$. Then, the comparison theorems [29] imply that $\mathcal{U}_2^+(t, X) \geq u_2(t, X) \geq \mathcal{U}_2^-(t, X)$ for positive t.

Thus, trajectories of all points of $[001)$ eventually arrive at the face $\Gamma_2 = [001] \cap [011]$ where $u_2 = u_2^0$, and $0 \leq u_1 \leq u_1^0$; $u_3^0 \leq u_3 \leq a_3$. Hence, the Lemma is proved. □

Let $\widehat{\Gamma}_1 = \Gamma_1 \setminus (\Gamma_1 \cap V_\delta(P_0))$ and $\widehat{\Gamma}_2 = \Gamma_2 \setminus (\Gamma_2 \cap V_\delta(P_0))$ be truncated faces of block $[001]$ described above. The following topological proposition will be used in Theorem 2, Section 3.

Remark 1. *These truncated faces $\widehat{\Gamma}_1$, $\widehat{\Gamma}_2$, and their analogues $\widehat{\Gamma}_j$ described below are compact and homeomorphic to a closed two-dimensional disk.*

Corollary 2. *Trajectory of each point of $\widehat{\Gamma}_1$ arrives at the face $\widehat{\Gamma}_2$ in a time t_1 such that*

$$\frac{u_2^0}{k_2 a_2} \leq t_1 \leq \frac{2u_2^0}{k_2 \delta p_2}.$$

Let $\psi_1 : \widehat{\Gamma}_1 \to \widehat{\Gamma}_2$ be the corresponding shift along the trajectories of points of $\widehat{\Gamma}_1$.

The proofs of Lemmas 6–10 are quite analogous to that of Lemma 5. They are based on estimates and representations similar to (12)–(14) and on comparison theorems for solutions to parabolic equations; see [29]. The proofs of Lemmas 7 and 9 differ from that of Lemma 5 just by cyclic permutations of multi-indices in notations of the blocks and by cyclic permutations $u_1(t, x_1, x_2, x_3) \to u_2(t, x_1, x_2, x_3) \to u_3(t, x_1, x_2, x_3) \to u_1(t, x_1, x_2, x_3)$ of the functions u_j.

Lemma 6. *If point P_0 is unstable and the initial data $u_j(0, X)$ of system (1) satisfy the conditions*

$$0 \leq u_1(0, x_1, x_2, x_3) \leq u_1^0; \quad u_2^0 \leq u_2(0, x_1, x_2, x_3) \leq a_2; \quad u_3^0 \leq u_3(0, x_1, x_2, x_3) \leq a_3,$$

then there exists $t_* = t_*(x_1, x_2, x_3) > 0$, such that the solution to this system satisfies the inequalities

$$0 \leq u_1(t_*, x_1, x_2, x_3) \leq u_1^0; \quad u_2^0 \leq u_2(t_*, x_1, x_2, x_3) \leq a_2; \quad 0 \leq u_3(t_*, x_1, x_2, x_3) \leq u_3^0.$$

Or if the initial data are in block $[011]$, then the solution $\{u_1(t_*, X), u_2(t_*, X), u_3(t_*, X)\}$ eventually arrives at block $[010]$. Let

$$\Gamma_3 = [011] \cap [010] = \{0 \leq u_1 \leq u_1^0; u_2^0 \leq u_2 \leq a_2; u_3 = u_3^0\}$$

be the face of $[010]$ where these solutions arrive, and $\widehat{\Gamma}_3 = \Gamma_3 \setminus (\Gamma_3 \cap V_\delta(P_0))$.

Corollary 3. *The trajectory of each point of $\widehat{\Gamma}_2$ arrives at the face $\widehat{\Gamma}_3$ in a time t_2 such that*

$$\frac{a_3 - u_3^0}{k_3 a_3} \leq t_2 \leq \frac{2(a_3 - u_3^0)}{k_3 \delta p_3}.$$

Let $\psi_2 : \widehat{\Gamma}_2 \to \widehat{\Gamma}_3$ be the corresponding shift along these trajectories.

Lemma 7. *If point P_0 is unstable and the initial data $u_j(0, X)$ of system (1) satisfy the conditions*

$$u_2^0 \leq u_2(0, x_1, x_2, x_3) \leq a_2; \quad 0 \leq u_3(0, x_1, x_2, x_3) \leq u_3^0; \quad 0 \leq u_1(0, x_1, x_2, x_3) \leq u_1^0,$$

then there exists $t_* = t_*(x_1, x_2, x_3) > 0$, such that the solution to this system satisfies the inequalities

$$u_2^0 \leq u_2(t, x_1, x_2, x_3) \leq a_2; \quad 0 \leq u_3(t, x_1, x_2, x_3) \leq u_3^0; \quad u_1^0 \leq u_1(t, x_1, x_2, x_3) \leq a_1.$$

Or if the initial data are in block [010], then the solution $\{u_1(t_*, X), u_2(t_*, X), u_3(t_*, X)\}$ arrives eventually at block [110]. Let

$$\Gamma_4 = [010] \cap [110] = \{u_1 = u_1^0; u^0 \le u_2 \le a_2; 0 \le u_3 \le u_3^0\},$$
$$\widehat{\Gamma}_4 = \Gamma_4 \setminus (\Gamma_4 \cap V_\delta(P_0)),$$

and $\psi_3 : \widehat{\Gamma}_3 \to \widehat{\Gamma}_4$, as in the previous Lemma.

Corollary 4. *The trajectory of each point of $\widehat{\Gamma}_3$ arrives at the face $\widehat{\Gamma}_4$ in a time t_3 such that*

$$\frac{u_1^0}{k_1 a_1} \le t_3 \le \frac{2u_1^0}{k_1 \delta p_1}.$$

Lemma 8. *If point P_0 is unstable and the initial data $u_j(0, X)$ of system (1) satisfy the conditions*

$$0 \le u_3(0, x_1, x_2, x_3) \le u_3^0; \quad u_1^0 \le u_1(0, x_1, x_2, x_3) \le a_1; \quad u_2^0 \le u_2(0, x_1, x_2, x_3) \le a_2,$$

then there exists $t_* = t_*(x_1, x_2, x_3) > 0$, such that the solution to this system satisfies the inequalities

$$0 \le u_3(t, x_1, x_2, x_3) \le u_3^0; \quad u_1^0 \le u_1(t, x_1, x_2, x_3) \le a_1; \quad 0 \le u_2(t, x_1, x_2, x_3) \le u_2^0.$$

Or if the initial data are in block [110], then the solution arrives eventually to block [100]. Similarly, let $\Gamma_5 = [110] \cap [100] = \{u_1^0 \le u_1 \le a_1; u_2 = u_2^0; 0 \le u_3 \le u_3^0\}$, $\widehat{\Gamma}_5 = \Gamma_5 \setminus (\Gamma_5 \cap V_\delta(P_0))$, and $\psi_4 : \widehat{\Gamma}_4 \to \widehat{\Gamma}_5$, as above.

Corollary 5. *The trajectory of each points of $\widehat{\Gamma}_4$ arrives at the face $\widehat{\Gamma}_5$ in a time t_4 such that*

$$\frac{a_2 - u_2^0}{k_2 a_2} \le t_4 \le \frac{2(a_2 - u_2^0)}{k_2 \delta p_2}.$$

Lemma 9. *If point P_0 is unstable and the initial data $u_j(0, X)$ of system (1) satisfy the conditions*

$$u_1^0 \le u_1(0, x_1, x_2, x_3) \le a_1; \quad 0 \le u_2(0, x_1, x_2, x_3) \le u_2^0; \quad 0 \le u_3(0, x_1, x_2, x_3) \le u_3^0,$$

then there exists $t_* = t_*(x_1, x_2, x_3) > 0$, such that the solution to this system satisfies the inequalities

$$u_1^0 \le u_1(t, x_1, x_2, x_3) \le a_1; \quad 0 \le u_2(t, x_1, x_2, x_3) \le u_2^0; \quad u_3^0 \le u_3(t, x_1, x_2, x_3) \le a_3.$$

Or if the initial data are in block [100], then the solution eventually arrives at block [101]. Similarly, let $\Gamma_6 = [100] \cap [101] = \{u_1^0 \le u_1 \le a_1; 0 \le u_2 \le u_2^0; u_3 - u_3^0\}$, $\widehat{\Gamma}_6 = \Gamma_6 \setminus (\Gamma_6 \cap V_\delta(P_0))$, and $\psi_5 : \widehat{\Gamma}_5 \to \widehat{\Gamma}_6$, as above.

Corollary 6. *The trajectory of each point of $\widehat{\Gamma}_5$ arrives at the face $\widehat{\Gamma}_6$ in a time t_5 such that*

$$\frac{u_3^0}{k_3 a_3} \le t_5 \le \frac{2u_3^0}{k_3 \delta p_3}.$$

Lemma 10. *If point P_0 is unstable and the initial data $u_j(0, X)$ of system (1) satisfy the conditions*

$$0 \le u_2(0, x_1, x_2, x_3) \le u_2^0; \quad u_3^0 \le u_3(0, x_1, x_2, x_3) \le a_3; \quad u_1^0 \le u_1(0, x_1, x_2, x_3) \le a_1,$$

then there exists $t_* = t_*(x_1, x_2, x_3) > 0$, such that the solution to this system satisfies the inequalities

$$0 \le u_2(t, x_1, x_2, x_3) \le u_2^0; \quad u_3^0 \le u_3(t, x_1, x_2, x_3) \le a_3; \quad 0 \le u_1(t, x_1, x_2, x_3) \le u_1^0.$$

Or if the initial data are in block $[101]$, then the solution eventually arrives at block $[001]$. Finally, let $\psi_6 : \widehat{\Gamma}_6 \to \widehat{\Gamma}_1$ be the corresponding shift along the trajectories of points of the truncated face $\widehat{\Gamma}_6$.

Corollary 7. *The trajectory of each point of $\widehat{\Gamma}_6$ arrives at the face $\widehat{\Gamma}_1$ in a time t_6 such that*

$$\frac{a_1 - u_1^0}{k_1 a_1} \le t_6 \le \frac{2(a_1 - u_1^0)}{k_1 \delta p_1}.$$

Inequalities in the statements of Lemmas 6–10 are arranged in such an order that, by analogy with Lemma 5, only the last pair of these inequalities changes.

3. Main Results

The results of the previous Section 2.4 imply the following.

Proposition 1. *If point P_0 is unstable, then the domain W_1 is invariant, and the trajectories of its points travel through blocks according to the arrows of STD (9).*

Let $X = (x_1, x_2, x_3)$ be an arbitrary point of $\mathbb{R}^3$, and

$$0 \le u_1(0, x_1, x_2, x_3) \le u_1^0, \quad 0 \le u_2(0, x_1, x_2, x_3) \le u_2^0, \quad u_3^0 \le u_3(0, x_1, x_2, x_3) \le a_3.$$

The composition $\Psi = \psi_6 \circ \psi_5 \circ \psi_4 \circ \psi_3 \circ \psi_2 \circ \psi_1 : \widehat{\Gamma}_1 \to \widehat{\Gamma}_1$ of the shifts along the, trajectories defined above is the Poincaré map of the cycle which will be described now. It was noted above that the truncated face $\widehat{\Gamma}_1$ is compact and homeomorphic to a closed two-dimensional disk; see Remark 1. The domain $W_1 \setminus \left(W_1 \cap V_{\delta(P_0)}\right)$ is homeomorphic to a compact torus.

According to the Brouwer fixed point theorem, see for example [30], the map Ψ has at least one fixed point $P_* = P_*(u_1^*, u_2^*, u_3^*) \in \widehat{\Gamma}_1$, $\Psi(P_*) = P_*$. Clearly, the trajectory of this point P_* is periodic, and we obtain the following result.

Theorem 2. *If point P_0 is unstable and the initial data of system (1) are contained in W_1, then for any fixed $(x_1, x_2, x_3) \in \mathbb{R}^3$, this system has at least one periodic trajectory $\mathcal{C} = \{u_1(t, x_1, x_2, x_3); u_2(t, x_1, x_2, x_3); u_3(t, x_1, x_2, x_3)\}$, which passes from block to block according to the arrows of STD (9).*

By summing all inequalities in Corollaries 2–7, we obtain the following estimates for the periods of the cycles of the system.

Proposition 2. *For each cycle of system (1), its period T satisfies the inequalities*

$$\frac{1}{k_1} + \frac{1}{k_2} + \frac{1}{k_3} \le T \le \frac{2a_1}{p_1 \delta k_1} + \frac{2a_2}{p_2 \delta k_2} + \frac{2a_3}{p_3 \delta k_3}.$$

We have described a bounded invariant domain in the phase portrait of the system of three parabolic equations considered as a model of one simple gene network with diffusion of its components. Uniqueness of an equilibrium solution to this system is shown. We find sufficient conditions of instability of this equilibrium, which implies the existence of oscillations in this gene network model.

4. Discussion and Future Work

On the basis of the approach used in [23,31,32], with the help from the methods of the qualitative theory of differential equations, such as the Brouwer fixed point theorem, these three-dimensional results can be extended in a similar way to higher-dimensional nonlinear systems of parabolic equations considered as models of more complicated circular gene network models, circadian oscillators, etc.

For some of these models, periodic regimes of their functioning are not unique (see [2,5,33]); thus, the geometry and combinatorics of their phase portraits as well as the behavior of their solutions are much more complicated than in the three-dimensional case studied here. However, in these higher-dimensional cases, one can control the trajectories of the dynamical systems. For example, in the absence of diffusion, the phase portrait of one 18-dimensional dynamical system was decomposed in [5] to 262,144 blocks, as what occurred above in Section 2.2 for the 3D system of this type, and it was shown that that union of 36 blocks of this decomposition contains a cycle of corresponding dynamical systems, and the union of the other 12 blocks of that decomposition contains another cycle of this system.

Numerous series of numerical experiments with various multidimensional gene network models were fulfilled on cloud servers and on personal computers in order to illustrate the corresponding mathematical results on the detection of the cycles; see [1,4,5] and references therein.

Now, our main tasks are to extend these constructions in phase portraits and to extend the results regarding the description of the behavior of these trajectories to the cases of higher-dimensional gene network models with diffusion, in order to detect their cycles and to localize their positions in the phase portraits of these models.

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Abbreviations

The following abbreviation is used in this manuscript:

STD	State Transitions Diagram

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