Investigation of a reaction-diffusion system, related to retinal patterning

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Abstract. In this paper we study a one-dimensional spatially-continuous reaction-diffusion system, related to patterning of \textit{Drosophila}'s retina. We search for conditions of stability or diffusion-driven (Turing) instability of a homogeneous prepattern steady state.

1. Introduction
\textit{Drosophila}'s retina is a regular hexagonal structure. It is formed in the wake of a moving morphogenetic front, called the morphogenetic furrow \cite{1,2} A mathematical model, explaining formation of this regular structure, is still lacking.

In the paper \cite{3} a one-dimensional mathematical spatially-discrete model was proposed, which reflected some peculiarities of formation of the real regular structure. In this model the morphogenetic front propagates through a discrete lattice. In the papers \cite{4–6} this model was modified and transferred to the two-dimensional space. The model is based on a spatially-discrete reaction-diffusion equations. However, this model suffers from grave shortcomings. For example, it makes use of a smaller hexagonal matrix composed of tissue cells. In reality, however, the cells do not form a topologically hexagonal matrix. It is also unclear whether the eventual regular structure is related to the cellular matrix. Besides, in the framework of the model it is assumed that a part of the regular structure has been formed from the very beginning. Therefore, the question of how the structure arises remains open. Hence the model does not explain formation of the whole regular structure properly.

We suppose that some progress can be made in the framework of a spatially-continuous model. In this framework mechanisms of patterning due to moving pattern-forming fronts depend on stability or instability of an unexcited prepattern steady state \cite{7,8}. In this paper we study a one-dimensional spatially-continuous reaction-diffusion system, related to patterning of the retina. We search for conditions of stability or diffusion-driven (Turing) instability, see, e. g., \cite{9}, of a homogeneous prepattern steady state.

2. Model
We consider the system of reaction-diffusion equations for the activator $a$ and inhibitor $u$

$$
\frac{\partial a}{\partial t} = f(a, u) + D_a \frac{\partial^2 a}{\partial x^2}, \quad \frac{\partial a}{\partial x} \bigg|_{x=0} = \frac{\partial a}{\partial x} \bigg|_{x=l} = 0,
$$
$$
\frac{\partial u}{\partial t} = g(a, u) + D_u \frac{\partial^2 u}{\partial x^2}, \quad \frac{\partial u}{\partial x} \bigg|_{x=0} = \frac{\partial u}{\partial x} \bigg|_{x=l} = 0,
$$
(1)
where reactions are given by
\[
\begin{align*}
  f(a,u) &= P_a \theta_{n_a} \left( \frac{a}{a^*} \right) - \gamma_a a + G \left[ 1 - \theta_{m_u} \left( \frac{u}{u^*} \right) \right], \\
  g(a,u) &= P_u \theta_{n_u} \left( \frac{a}{a^*} \right) - \gamma_u u,
\end{align*}
\]

$D_a$ and $D_u$ are diffusion coefficients, $\gamma_a$ and $\gamma_u$ are degradation rates, $a_{a,u}$ and $u_{a,u}$ are activation levels, $P_{a,u}$ are production rates, $\theta_n(x) = \frac{x^n}{x^n + 1}$ is the Hill function, $G$ is an activation rate.

The change of variables gives dimensionless parameters $x^* = \frac{x}{l}$, $t^* = \left( \frac{D_a}{l^2} \right) t$, $D^*_a = D_a / D_a \equiv 1$, $D^*_u = D_u / D_a \equiv d$, $\gamma^*_a = (l^2 / D_a) \gamma_a$, $P^*_{a,u} = (l^2 / D_a) P_{a,u}$, $G^* = (l^2 / D_a) G$, where $l$ is a characteristic length. Hereafter we omit the asterisks in the designations. The system (1) becomes
\[
\begin{align*}
  \partial_t a &= f(a,u) + \partial_{xx} a, \quad \partial_x a|_{x=0} = \partial_x a|_{x=l} = 0, \\
  \partial_t u &= g(a,u) + d \partial_{xx} u, \quad \partial_x u|_{x=0} = \partial_x u|_{x=l} = 0,
\end{align*}
\]

where $d$ is the diffusion coefficient ratio.

3. Linear stability analysis

3.1. Conditions for stability of a homogeneous steady state solution in the absence of diffusion

In sections 3.1 and 3.2 we recall main facts from the Turing theory of pattern formation, see, e.g., [9].

Homogeneous states are described by the system of equations
\[
\begin{align*}
  \partial_t a &= f(a,u), \\
  \partial_t u &= g(a,u).
\end{align*}
\]

A steady state solution $(a_0, u_0)$ of the system (3) is given by the equations $f(a_0, u_0) = 0$ and $g(a_0, u_0) = 0$. Linearization of the system (3) around the solution $(a_0, u_0)$ gives the system
\[
\partial_t \mathbf{w} = A \mathbf{w},
\]

where $\mathbf{w} = (a - a_0, u - u_0)$, and
\[
A = \begin{pmatrix} \partial_a f & \partial_u f \\ \partial_a g & \partial_u g \end{pmatrix}_{a=a_0, u=u_0} = \begin{pmatrix} f_a & f_u \\ g_a & g_u \end{pmatrix}.
\]

The solution of the system (4) is
\[
\mathbf{w}(t) = \sum_{i=1}^{2} c_i e^{\lambda_i t} \varphi_i,
\]

where $\lambda_i$ and $\varphi_i$ are the eigenvalues and eigenvectors of the matrix $A$, respectively, $c_i$ are indeterminate coefficients. The eigenvalues $\lambda_{1,2}$ are the roots of the characteristic equation
\[
|\lambda E - A| \equiv \lambda^2 - (\text{tr} A) \lambda + |A| = 0,
\]
where $E$ is the identity matrix, and are given by
\[
\lambda_{1,2} = \frac{f_a + g_u \pm \sqrt{(f_a - g_u)^2 + 4f_au}}{2}.
\]
The steady state solution of the system (4) is linearly stable, if for any eigenvalue $\text{Re} \lambda_i < 0$, i.e.,
\[
\text{tr} A = f_a + g_u < 0, \quad |A| = f_ag_u - f_ug_a > 0.
\]
(6)

### 3.2. Conditions for instability of the homogeneous steady state solution

Linearization of the system (2) around the homogeneous steady state solution $(a_0, u_0)$ gives the system
\[
\partial_t w = A w + D\partial_{xx}w,
\]
(7)
where
\[
D = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix}.
\]
The solution of the system (7) is
\[
\psi(x, t) = \sum_{n=0}^{\infty} \sum_{i=1}^{2} c_{n,i} e^{\lambda_i(k_n^2)t} \varphi_{n,i} \psi_n(x),
\]
where
\[
k_n^2 = \left( \frac{\pi n}{l} \right)^2 \quad \text{and} \quad \psi_n(x) = \cos(k_n x)
\]
are the eigenvalues and eigenfunctions of the Sturm–Liouville problem
\[
-\partial_{xx} \psi = k^2 \psi, \quad x \in (0, l), \quad \psi'(0) = 0, \quad \psi'(l) = 0,
\]
respectively, $k$ is the wave number, $\lambda_i(k_n^2)$ and $\varphi_{n,i}$ are the eigenvalues and eigenvectors of the matrix $A - k_n^2 D$, respectively, $c_{n,i}$ are indeterminate coefficients. The eigenvalues $\lambda_{1,2} \equiv \lambda_{1,2}(k^2)$ are the roots of the characteristic equation
\[
|\lambda E - A + k^2 D| = \lambda^2 + p(k^2)\lambda + q(k^2) = 0,
\]
(8)
with
\[
p(k^2) = -\text{tr} (A - k^2 D) = -\text{tr} A + (1 + d)k^2,
\]
\[
q(k^2) = |A - k^2 D| = dk^4 - (df_a + g_u)k^2 + |A|.
\]
Note that Eq. (8) becomes Eq. (5) when $k = 0$.

Linear stability and instability of the homogeneous steady state solution of the system (7) depends on the roots $\lambda \equiv \lambda(k^2)$ of the characteristic equation. The solution $(a_0, u_0)$ of the system (7) is unstable, if the condition $\text{Re} \lambda(k^2) > 0$ is met for some $k \neq 0$. The first condition (6) implies $p(k^2) > 0$. Therefore, the condition $\text{Re} \lambda(k^2) > 0$ is met if $q(k^2) < 0$ for some $k \neq 0$.

Since $|A| > 0$, the sufficient conditions for $\text{Re} \lambda(k^2) > 0$ are
\[
df_a + g_u > 0, \quad (df_a + g_u)^2 > 4d|A|.
\]
(9)
If $g_u < 0$, the first of the conditions (6) and (9) imply the conditions
\[
d > 1, \quad f_a > 0, \quad g_u < 0.
\]
(10)
If the conditions (6), (9), (10) are met (i.e., the solution \((a_0, u_0)\) is unstable), the interval of unstable wave numbers \(k\) is given by

\[
k_1^2 < k^2 < k_2^2,
\]

where

\[
k_{1,2}^2 = \frac{df_a + g_u \mp \sqrt{(df_a - g_u)^2 + 4df_ag_a}}{2d}
\]

are the roots of the equation \(q(k^2) = 0\).

### 3.3. Application of the linear stability analysis to the model

In this section we apply the Turing theory to the system (2). One obtains

\[
A \equiv \begin{pmatrix}
f_a & f_u \\
g_a & g_u
\end{pmatrix} = \begin{pmatrix}
Q_a \theta'_{n_a} \left( \frac{a}{a_a} \right) - \gamma_a & -G_u \theta'_{m_u} \left( \frac{u}{u_u} \right) \\
Q_u \theta'_{n_u} \left( \frac{u}{u_u} \right) & -\gamma_u
\end{pmatrix},
\]

where \(Q_a = P_a/a_a\), \(G_u = G/u_u\), \(Q_u = P_u/a_u\). We study the system for the small positive activation rate: \(0 < G \ll 1\). In this case the system has the unique positive homogeneous steady state solution \((a_0, u_0) = (O(G), O(G^n_u))\) as \(G \to 0\), and, therefore,

\[
A = \begin{pmatrix}
-\gamma_a & 0 \\
0 & -\gamma_u
\end{pmatrix} + \begin{pmatrix}
Q_a \delta_{n_u} + (1 - \delta_{n_{u,1}}) O(G) & -G_u \delta_{m_u} + (1 - \delta_{m_{u,1}}) O(G^n_u) \\
Q_u \delta_{n_u} + (1 - \delta_{n_{u,1}}) O(G) & 0
\end{pmatrix}
\]

as \(G \to 0\),

where \(\delta_{n,m}\) is the Kronecker symbol.

Biologically relevant Hill coefficients are \(n_a > 1\), \(n_u > 1\) and \(m_u > 1\). These values result in the matrix

\[
A \approx \begin{pmatrix}
-\gamma_a & 0 \\
0 & -\gamma_u
\end{pmatrix}.
\]

In this case the conditions (9), (10) are not met, and, therefore, the homogeneous steady state solution \((a_0, u_0)\) is linearly stable.

We do not consider here the cases when at least one of the Hill coefficients is equal to one and at least one of the coefficients is greater than one.

If \(n_a = n_u = m_u = 1\), one obtains

\[
A = \begin{pmatrix}
f_a & f_u \\
g_a & g_u
\end{pmatrix} = \begin{pmatrix}
Q_a - \gamma_a & -G_u \\
Q_u & -\gamma_u
\end{pmatrix}
\]

The eigenvalues \(\lambda_i\) take the form

\[
\lambda_{1,2} = \frac{(Q_a - \gamma_a) - \gamma_u \pm \sqrt{((Q_a - \gamma_a) + \gamma_u)^2 - 4G_uQ_u}}{2}
\]

The steady state solution \((a_0, u_0)\) of the system (4) is linearly stable, if for any eigenvalue \(\text{Re} \lambda_i < 0\), i.e.,

\[
(Q_a - \gamma_a) < \gamma_u, \quad (Q_a - \gamma_a) \gamma_u < G_uQ_u.
\]

(12)
The homogeneous steady state solution \((a_0, u_0)\) of the system (7) is unstable, if

\[
\gamma_a < Q_a, \quad \gamma_u < d (Q_a - \gamma_a),
\]

\[
(d (Q_a - \gamma_a) - \gamma_u)^2 > 4d |A| \equiv 4d (G_u Q_u - (Q_a - \gamma_a) \gamma_u).
\]

(13)

The set of solutions of the system of the inequalities (12), (13) is not empty. This is clear if the system is recast in the form

\[
\frac{1}{d} < \frac{Q_a - \gamma_a}{\gamma_u} < 1, \quad \frac{Q_a - \gamma_a}{\gamma_u} < \frac{G_u Q_u}{\gamma_a^2}, \quad \frac{4}{d} \left( \frac{G_u Q_u}{\gamma_a^2} - \frac{Q_a - \gamma_a}{\gamma_u} \right) < \left( \frac{Q_a - \gamma_a}{\gamma_u} - \frac{1}{d} \right)^2.
\]

If the conditions (12), (13) are met (i.e., the solution \((a_0, u_0)\) is unstable), the interval of unstable wave numbers \(k\) is given by (11), and the boundaries \(k_{1,2}\) of the interval are given by

\[
k_{1,2}^2 = \frac{d (Q_a - \gamma_a) - \gamma_u \pm \sqrt{d (Q_a - \gamma_a) + \gamma_u}^2 - 4d G_u Q_u}{2d}.
\]

Hence, if \(n_a = n_u = m_u = 1\), the homogeneous steady state solution \((a_0, u_0)\) is unstable.

4. Concluding remarks

The object of the study was the one-dimensional spatially-continuous reaction-diffusion system, related to patterning of the retina. We have found that in the case of biologically relevant Hill coefficients a homogeneous prepattern steady state is stable with respect to local perturbations. We can conclude that a possible mechanism of patterning is when the moving morphogenetic front transforms the homogeneous prepattern steady state into an unstable one.

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