Other models of morphogenesis: chemotaxis, juxtacrine signaling and mechanochemical theory

Lecture 27
Simple model of morphogenesis: butterfly wings

Diffusion-driven instability is neither sufficient nor necessary mechanism for the creation of biological structures.

Consider, for example, a model that was proposed by Murray for the formation of patterns on moth wings. The model describes a pair of morphogen $S$ and switch gene $g$:

$$\frac{\partial S}{\partial t} = D \left( \frac{\partial^2 S}{\partial r^2} + \frac{1}{r} \frac{\partial S}{\partial r} + \frac{1}{r^2} \frac{\partial^2 S}{\partial \theta^2} \right) - KS$$

$$\frac{\partial g}{\partial t} = K_s S + \frac{K_g g^2}{K_i + g} - K_g g$$

on a circular segment:

Gene $g$ possesses a bistable behavior that fixes in time the pattern of $S$ morphogen diffusion.

Self-organization does not mean that the emerging pattern is a result of amplification of random noise. Rather biological morphogenesis is a transformation of genetic program into biological structures made out of living cells by means of processes of self-organization. We begin our consideration of alternative morphogenetic scenarios with an example of a model where the pattern on butterfly wings is a consequence of “frozen” spatial distribution of a morphogen. The model describes two species: a morphogen and a bistable “switch” gene which is used to “fix” the spatial distribution of the morphogen. The morphogen is assumed to be released due to some other process at fixed time and fixed locations on the wing. As it diffuses, it constantly degrades. Therefore, after initial spreading over the surface of the wing the morphogen will be eventually destroyed. However, in those locations of the wing, there the morphogen concentration exceeded some threshold value, the non-diffusive gene $g$ will be “switched” into a high expression state thus memorizing the distribution of the morphogen even the last molecule of $S$ has been digested by proteases.
Chemotaxis: introducing active cell motion

In a realistic approach to modeling biological morphogenesis it is important to account for the cell motion.

\[
\frac{\partial n}{\partial t} + \nabla \cdot J = f(n,r)
\]

First we consider the situation where the flux is due to cell diffusion and chemotaxis:

\[
J = D_n \nabla n + \chi(\alpha) n \nabla a
\]

Here \( a \) is the concentration of attractant and \( \beta \) is the sensitivity of moving cells to the attractant. Consider the following model describing aggregating amoeba:

\[
\frac{\partial n}{\partial t} = r n \left( 1 - \frac{n}{n_i} \right) - \nabla \cdot \left( \chi n \nabla a \right) + D_n \Delta n
\]

\[
\frac{\partial a}{\partial t} = \alpha n - \beta a + D_a \Delta a
\]

This system has homogeneous stationary state \((n_i, \alpha/\beta n_i)\). To analyze its stability we first need to linearize the system around the steady state through introduction of new variables:

\[
\begin{align*}
    u &= n - n_i; \quad v = a - \alpha/\beta n_i; \\
    u' &= ru - \chi n_i \Delta v + D_n \Delta u \\
    v' &= \alpha u - \beta v + D_a \Delta v
\end{align*}
\]

Assuming 1D space, we look for solutions of this system in the form \( \exp(\lambda t + ikx) \). This results in the following characteristic equation:

\[
\begin{vmatrix}
    -\lambda + \alpha & \chi n_i k^2 \\
    -\beta - \lambda - k^2 D_n & -\beta - \lambda - k^2 D_a
\end{vmatrix} = 0
\]

Britton, Essential mathematical biology, 2003

Starting with this lecture we are going to consider models describing morphogenetic processes. This means that we are no longer simply interested in spatial distribution of molecules, which is the case in chemical pattern-formation, but rather in the spatial distribution of cells that form the biological structures. In this case, the types of motion are lot more complex than simple diffusion and convection. Cells actively travel through the tissue or substrate (bacteria). This motion is guided by two major beacons: chemical gradients and mechanical forces. In the first case it is called chemotaxis and in the other mechano- or haptotaxis.

We start with considering chemotactic motion of cells on the example of a model describing aggregating amoeba \( Dictyostelium discoideum \). Just like in the case of Turing instability, we perform linear stability analysis to find out if patterns will emerge out of spatially homogeneous state. Note the appearance of term with \( k^2 \) in a non-diagonal element of the characteristic matrix.
Instability in chemotactic systems

The coefficients of the characteristic equation are given by:

\[ B = k^2(D_n + D_a) + r + \beta \]
\[ C = k^2D_aD_n + k^2(\beta D_n + rD_a - \alpha\chi n_0) + r\beta \]

Note that the conditions of stability for the ODE stationary state are satisfied and \( B \) is always > 0. To achieve the instability we need \( C < 0 \). Similarly to the case of Turing instability we obtain the two conditions:

\[ \beta D_n + rD_a - \alpha\chi n_0 < 0 \]
\[ \frac{(\beta D_n + rD_a - \alpha\chi n_0)^2}{4D_aD_n} > r\beta \]

Plotting the dependence \( C(k^2) = 0 \) on the \((k^2, \chi)\) plane we obtain:

Note that for all \( \chi \) exceeding the critical value, the conditions of instability existence are satisfied.

This property relieves the condition of Turing instability requiring significant difference in diffusion coefficients.

We continue linear stability analysis as in the Turing case. Note that the system of adjoining ODEs was chosen in this model in such a way that the stationary state is stable (\( \text{Tr}A < 0, \det A > 0 \)). The two additional conditions we obtain look very similar to the Turing case, however in this case we have a chemotactic term which guarantees the existence of instability once strength of chemotactic response exceeds certain critical threshold. Thus we no longer need to request that the diffusion coefficients should be significantly different.
Formation of fish skin patterns through chemotaxis

In this model formation of skin patterns is considered as chromatophore cell migration in the attractive field of a morphogen which is a part of an activator-inhibitor couple:

\[
\frac{\partial n}{\partial t} + \nabla \cdot n\vec{v} = n(r_1 + r_2) - \nabla \cdot (\chi(u)n\nabla u) + D_n \Delta n
\]

\[
\frac{\partial u}{\partial t} = f(u,v) + D_u \Delta u - (r_1 + r_2)u
\]

\[
\frac{\partial v}{\partial t} = g(u,v) + D_v \Delta v - (r_1 + r_2)v
\]

Here additional to reaction and chemotaxis terms are introduced to describe the effect of growth of the domain. The main contribution of chemotaxis in this model is introduction of robust pattern formation which does not require tight parameter control.

Chemotaxis is a fascinating phenomenon and there exist a large number of papers on modeling chemotactic phenomena in a variety of systems from bacteria to higher eukaryotic cells. Here we will consider only one example which is in fact an extension of the modeling ideas inspired by Turing method. In this model the skin pattern of *Pomacanthus* angelfish is assumed to be formed by two types of cells – iridophores and melanophores. The cells can migrate in the skin tissue influenced by attraction to a chemical which is a part of an activator-inhibitor couple. While the nature of these mysterious morphogens and their detailed interaction is not considered similar to “classical” Turing-type approach, the behavior of cells follows fairly realistic pattern. One important conclusion of adding chemotaxis to Turing mechanism is provision of parametric robustness which cannot be observed in pure Turing systems. Also this model has one more element of note. The authors explicitly introduce the growth of fish by adding terms describing propagation of cells due to the growth. It is assumed that the fish grows with two different exponents r1 and r2 along the directions of a two-dimensional space.
In this approach it is assumed that the cells migrate in the viscoelastic ECM and there are mechanical forces acting between the cells and the ECM.

The model typically consists of three equations:

- **cell density** (conservation of the number of cells)
- **mechanical force balance** between the cells and the ECM
- **ECM density** (conservation of ECM)

General form of the cell density equation remains essentially the same:

\[
\frac{\partial n}{\partial t} + \nabla \cdot J = f(n,r)
\]

However, the fluxes in this case are different.

**Diffusion.** This flux remains to represent random dispersal of cells. However, it is argued that long-distance terms should be included:

\[
J_d = -D_1 \nabla n + D_2 \nabla (\Delta n)
\]

**Convection.** This flux describes passive motion of cells pushed by the ECM. It is proportional to the velocity of ECM displacement \( u(r,t) \):

\[
J_c = n \frac{\partial \vec{u}}{\partial t}
\]

**Mechanotaxis.** This flux models motion of cells up the gradient of ECM density. It is assumed that the cells move toward the area of more attachment sites, thus higher density of ECM:

\[
J_h = an \nabla \rho
\]
Mechanochemical forces and ECM

In general terms the cell-matrix mechanical force balance is given by the equation:
\[ \nabla \sigma + \rho \vec{F} = 0 \]

The conservation of ECM is given by the equation:

Finally the full system of all three equations looks like:

Proper derivation of the equation describing the balance between the cells and ECM is beyond the limits of this course. Here we only consider these equations for general information and will not use them actively in the following part of the course.
Juxtacrine patterning and lateral inhibition

Introduction of more biologically realistic mechanisms requires departure from the methods of partial differential equations. Here we consider an example of a cellular pattern formation caused by so-called "juxtacrine" signaling. One typical example of juxtacrine signaling is provided by delta-notch developmental pathway.

As the discrete nature of cells becomes more important for the biologically realistic modeling, the continuous description given by partial differential equations becomes less and less applicable. Here we consider an example where such problem arises. Juxtacrine signaling refers to the signaling between adjacent cells through the mediation of ligands that are attached to the surface of the cell. A typical example of such signaling is represented by a delta-notch pathway. Normally, juxtacrine signaling serves the purpose of lateral inhibition of the neighbors. This type of mechanism results in the formation of patterns (like shown on the slide) with very short wavelength – exactly two cells!
Model for juxtacrine signaling

Instead of partial differential equations this model (Wearing et al, Bull of Math Bio, v 62, p. 293, 2000) uses system of coupled ODE describing square cells on a rectangular lattice. The three variables involved are:

- \( a_i(t) \) – Delta (ligand)
- \( f_i(t) \) – free Notch receptors
- \( b_i(t) \) – bound Notch receptors

The values in brackets are computed as the average over the neighborhood of closest cells:

\[
\langle a_i \rangle = \frac{a_{i-1} + 2a_i + a_{i+1}}{4}
\]

In the model for the juxtacrine signaling by Wearing et al, the authors set aside partial differential equations and used instead coupled ODEs considering cells as regular square elements on the rectangular lattice. Note how they use interaction with the neighboring cells instead of using diffusion operator. Under the assumptions of this model, there is a feedback loop provided by the fact that there is increase or decrease in production of ligands and receptors caused by the engagement of the receptors on the cell surface. This feedback loop is capable of inducing spatial patterns.
Positive feedback and lateral induction

Depending on the strength of the positive feedback provided by the production functions Pf and Pa, it is possible to arrive at the stable spatial patterns with simple but non-trivial organization. As opposed to the lateral inhibition this mechanism was termed “lateral induction”:

The stability of the homogeneous stationary state of the N linked equations can be studied in practically the same way as in the case of Turing instability and chemotaxis. We leave all the math out to make the life easier. The outcome of this analysis shows that there exist the area in the parameter space given by the slopes of functions $P_a$ and $P_f$ which corresponds to a positive feedback and there formation of stable spatial patterns is possible.
What to take home

• Transition from the simplest models of morphogenesis to more realistic ones necessitates the explicit use of cells as the acting agents characterized by rates of birth, death and motility.

• There exist several types of cell motion that need to be described mathematically. The most developed areas are represented by chemotaxis and mechanotaxis.

• The apparatus of partial differential equations becomes restrictive when the dynamics of individual cells is important and is described realistically.