# Morphogenesis
## How the Leopard Got Its Spots
### Mathematical Modeling Week 8
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Morphogenesis is the study of how spatial patterns and forms develop in organisms, especially embryos. In a developing embryo, how do some cells "know" that they should become brain tissue, other cells "know" they should become kidneys, or heart muscle, whatever. How can they do that? It's just a bunch of dumb chemicals!

Let's consider a very specific example, namely how certain animals develop highly regular coloring patterns in their coats—leopards have very regular spots, tigers have nice evenly-spaced stripes, etc. The general theory is that individual skin cells are influenced to produce different color hair or fur in response to the local concentration of one or more *morphogens*, that is, chemicals that influence morphogenesis. The tiger gets stripes of different colors because the concentration of a certain morphogen in its developing skin varies in a regular spatial pattern.

But of course this only defers the question. How does the pattern develop in the first place? In 1952 mathematician Alan Turing (the same Turing of "Turing Machine" and the "Turing Test" fame) wrote a landmark paper in which he proposed a mechanism by which "dumb" chemicals could arrange themselves into regular spatial patterns. It's closely related to the idea of diffusion-driven instability in coupled diffusion equations.

Consider two chemical species, A and B, with concentrations $u(x, t)$ and $v(x, t)$, respectively. Chemical A is an *activator*, in that it auto-catalyzes its own production. Chemical B is the *inhibitor*, in that it inhibits the production of A. Both chemicals diffuse passively in the region $0 < x < H$, with diffusivity $\kappa_1$ for A, $\kappa_2$ for B. The general form of the coupled system is

$$\frac{\partial u}{\partial t} - \kappa_1 \frac{\partial^2 u}{\partial x^2} = f(u, v)$$
$$\frac{\partial v}{\partial t} - \kappa_2 \frac{\partial^2 v}{\partial x^2} = g(u, v)$$

for some functions $f$ and $g$ that embody how A and B interact. These functions depend on the specific reactions being modelled.

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One such model of an activator-inhibitor pair is given by (after re-scaling)

$$\frac{\partial u}{\partial t} - \frac{\partial^2 u}{\partial x^2} = \frac{u^2}{v} - bu \tag{1}$$

$$\frac{\partial v}{\partial t} - \kappa \frac{\partial^2 v}{\partial x^2} = u^2 - v \tag{2}$$

where we've taken diffusivity one for chemical A. Here $b$ is some constant. The $u^2/v$ term in equation (1) is the auto-catalytic term for the production of $u$, while larger values of $v$ tend to inhibit the creation of A. The $-bu$ term might account for some natural decay in the concentration of $A$. In equation (2) we see that B tends to inhibit its own growth as well (via the $-v$ term), but A tends to promote the production of B via the $u^2$ term.

It turns out that the solutions to this system with Neumann boundary conditions can, with the right choice of $\kappa$ and $b$, approach a steady-state in which $u$ and $v$ are NOT spatially constant, but rather vary regularly. This is actually quite surprising, since diffusion typically results in flat, featureless steady-state solutions.

Here's a brief account of why such things can occur. The system (1)-(2) with zero Neumann boundary conditions has constant solution $u(x,t) = 1/b, v(x,t) = 1/b^2$; in fact, this is the only non-trivial constant solution. Now as we've seen, diffusive equations typically approach some kind of steady-state, and it wouldn't be at all surprising if the solutions here approach these constant solutions. And in fact, this usually happens, but for certain choices of $\kappa$ and $b$ it doesn't.

Here's why: first, linearize the system (1)-(2) around the solution $u = 1/b, v = 1/b^2$. Specifically, suppose $u = 1/b + \bar{u}, v = 1/b^2 + \bar{v}$ for some functions $\bar{u}$ and $\bar{v}$ which we assume are "small". Note $\bar{u}$ and $\bar{v}$ measure deviation from the steady-state solution. Insert $u = 1/b + \bar{u}, u = 1/b^2 + \bar{v}$ into the system (1)-(2) and drop quadratic (really small) terms. What you come up with is the coupled linear system

$$\frac{\partial \bar{u}}{\partial t} - \frac{\partial^2 \bar{u}}{\partial x^2} = b\bar{u} - b^2\bar{v} \tag{3}$$

$$\frac{\partial \bar{v}}{\partial t} - \kappa \frac{\partial^2 \bar{v}}{\partial x^2} = \frac{2}{b}\bar{u} - \bar{v}. \tag{4}$$

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Now you may recall (also from DE 2) that any function $h(x)$ defined on some interval $0 < x < H$ can be decomposed into a sum of sine and/or cosines of appropriate frequencies. In particular, such a function can be written as

$$h(x) = \sum_{k=1}^{\infty} c_k \cos(k\pi x/H)$$

where the $c_k$ are constants given by

$$c_k = \frac{2}{H} \int_0^H h(x) \cos(k\pi x/H)\, dx$$

for $k \geq 1$ (and $c_0 = \frac{1}{H} \int_0^H h(x) \cos(k\pi x/H)\, dx$). This is called the *Fourier Series* for $h(x)$. In what follows below I'll write Fourier Series as $h(x) = \sum_{\omega} c_\omega \cos(\omega x)$ where $\omega = k\pi/H$ for $k = 0, 1, 2, \ldots$.

In the present case, we're going to contemplate the possibility of decomposing $\bar{u}$ and $\bar{v}$ into a Fourier Series with respect to $x$. However, since $u$ and $v$ depend on $t$, the coefficients $c_k$ will themselves depend on $t$. We will write

$$\bar{u}(x, t) = \sum_{\omega} \phi_\omega(t) \cos(\omega x), \quad \bar{v}(x, t) = \sum_{\omega} \psi_\omega(t) \cos(\omega x)$$

where $\omega = k\pi/H$ for integers $k \geq 0$. The $\phi_\omega(t)$ and $\psi_\omega(t)$ are the coefficients in the Fourier-cosine expansion of $\bar{u}$ and $\bar{v}$ at time $t$. Note also that $\bar{u}$ and $\bar{v}$ as defined satisfy zero Neumann condition at $x = 0$ and $x = H$. If you plug these guesses at $\bar{u}$ and $\bar{v}$ into the linearized system (3)-(4) you obtain (after cancelling off the cosines) a linear system of ODE equations for $\phi_\omega$ and $\psi_\omega$ of the form

$$\phi_\omega' = (b - \omega^2)\phi_\omega - b^2 \psi_\omega \tag{5}$$

$$\psi_\omega' = \frac{2}{b}\phi_\omega - (1 + \kappa\omega^2)\psi_\omega. \tag{6}$$

This is really an infinite collection of linear systems of ODE's, one for each frequency $\omega$.

The solutions to the system will consist of exponential functions, e.g., $\phi_\omega(t) = c_1 e^{\lambda_1 t} + c_2 e^{\lambda_2 t}$ where $\lambda_1$ and $\lambda_2$ are the eigenvalues of the matrix
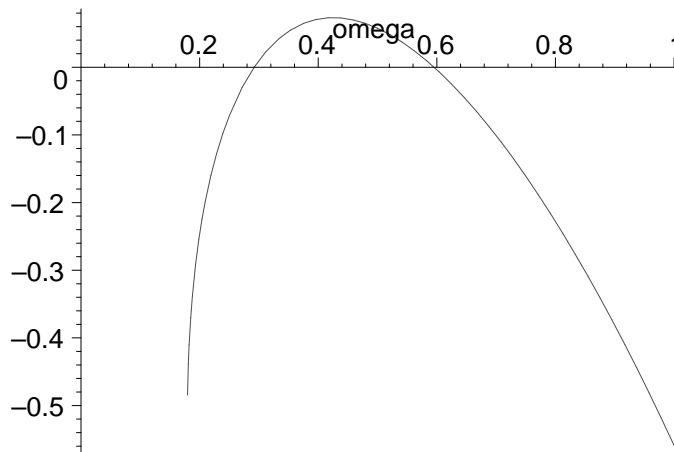
$$M = \begin{bmatrix} b - \omega^2 & -b^2 \\ 2/b & -(1 + \kappa\omega^2) \end{bmatrix}$$

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defined by the right side of equations (5)-(6) and $c_1$ and $c_2$ are constants. The function $\psi_\omega(t)$ will have a similar form.

If either eigenvalue $\lambda_1$ or $\lambda_2$ is positive for some particular $\omega$ then that portion $e^{\lambda_j t} \cos(\omega x)$ of the solution in the linearized equations will grow exponentially. This means that the equilibrium solution $u = 1/b, v = 1/b^2$ to the original nonlinear system (1)-(2) is unstable. More precisely, those Fourier frequencies for which the eigenvalues are positive are unstable near the equilibrium, and so those frequencies $\omega$ are "pushed away" from the equilibrium.

And in fact, we find that for certain ranges of $\omega, b$, and $\kappa$ at least one of the eigenvalues is positive. For example, with $b = 0.9$ and $\kappa = 15$ we find that one of the eigenvalues is positive for $\omega \in (0.28, 0.87)$. In particular, if $\omega = 0.51$ then one eigenvalue is about 0.29. As a result, that portion of the solution $\bar{u}$ or $\bar{v}$ to the linearized equations (3)-(4) that looks like a multiple of $\cos(0.51x)$ grows in time, and the corresponding portion of the solution to the nonlinear equations will tend to move away from the equilibrium.
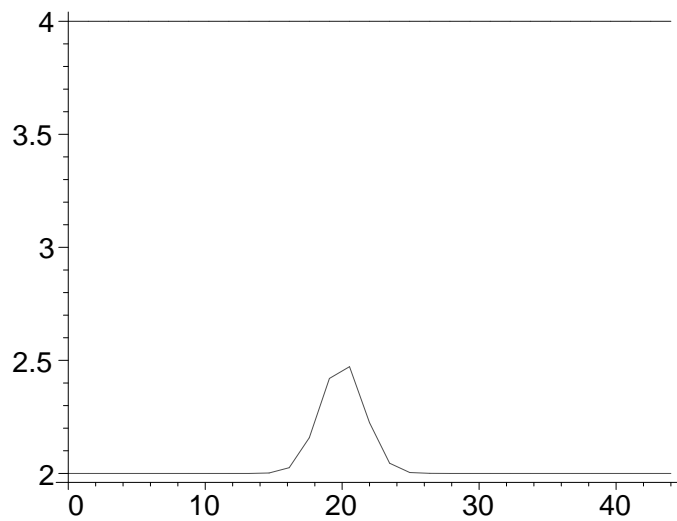
Here is an example using $b = 0.5$ and $\kappa = 16.56$ (these produce instability) on a domain $0 < x < 44$. First, below is a plot of the largest (most positive) eigenvalue of the matrix $M$ as a function of $\omega$.
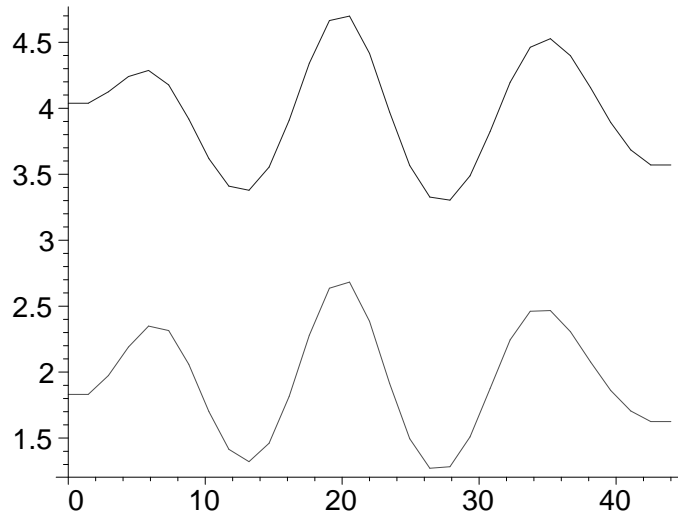


The eigenvalues are positive for $\omega \in (0.3, 0.6)$. Any corresponding terms $\cos(\omega x)$ in the solution will tend to be amplified away from the equilibrium solution, and so the equilibrium solution should contain strong frequencies in this range.. The range $0.3 < \omega < 0.6$ corresponds to wavelengths of about

$2\pi/0.6$ to $2\pi/0.3$, i.e., 10.5 to 21, roughly.

Here's the actual solution for certain initial conditions. The equilibrium solution is $u(x,t) \equiv 2, v(x,t) \equiv 4$. The initial condition for inhibitor is $v(x,0) = 4$ (equilibrium value) and for the activator we have $u(x,0) = 2 + 0.5e^{-(x-20)^2/10}$, a small perturbation off of equilibrium. A plot of the initial conditions looks like



But at time $t = 30$ the solution has settled down (almost!) to the solution

a regular pattern of alternating high and low concentrations of the morphogens.

For more information on this stuff, look at J.D. Murray's book *Mathematical Biology*, Springer-Verlag, 1989.