Biological Physics - Biopatterning

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Biopatterning

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1.1 Introduction to Dynamical Systems

1.1.1 Elements of non-linear dynamical systems

We will focus on concrete examples in the context of gene expression, but let us first introduce some of the general framework and useful tools that have been developed in general for the study of non-linear dynamics. We follow here the monograph by Strogatz (**?**).

The dynamics of a general non-linear system can be described by a set of coupled differential equations

$$\begin{aligned} \dot{x}_1 &= f_1(x_1, ...x_n) \\ &\vdots \\ \dot{x}_n &= f_n(x_1, ...x_n). \end{aligned}$$

For example, damped harmonic motion with the second order (linear) DE

$$m\ddot{x} + b\dot{x} + kx = 0$$

can be written a set of coupled first-order equations as

$$\begin{aligned} \dot{x}_1 &= x_2 \\ \dot{x}_2 &= -\frac{k}{m}x_1 - \frac{b}{m}x_2. \end{aligned}$$

We examine first the one-variable system ("flow on the line"), then two-variable systems ("flow on the plane") where oscillations and limit cycles can exist. For reasons of time we do not touch here on three-variable system ("3-D flow") which is the minimal situation to exhibit chaotic dynamics. In general, an n-variable system requires n equations to represent it. Many very interesting biological systems can be simplified to two variables.

Flows on the line

We start with an examination of the possible *trajectories* of a system. That is, we plot the path in a 2n-dimensional space, where the dimensions are the n independent coordinates and their corresponding momenta. Here, we take a fairly loose view of this definition, and we will generally just use the independent coordinates and their time- derivatives. We begin by examining the one-dimensional flow, that is, the dynamics of a single first-order DE,

$$\dot{x} = f(x).$$

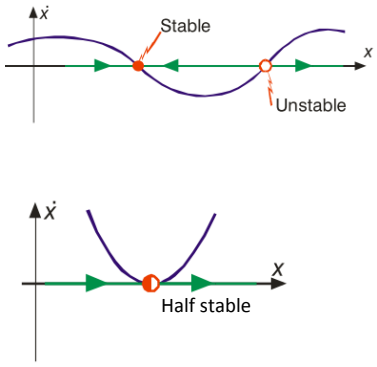


Fig. 1.1 Illustrations of the types of fixed points in 1-D systems. Note the notation: stable fixed points are denoted by filled circles; unstable fixed points by open circles, and half-stable points by half- filled circles, as shown in the examples. Note the notation: stable fixed points are denoted by filled circles; unstable fixed points by open circles, and half-stable points by half- filled circles, as shown in the examples.

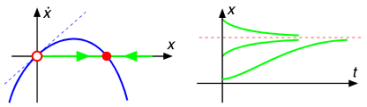


Fig. 1.2 Fixed points of the autocatalytic system.

Fixed points of a 1-D flow. The function f is single-valued for all x. The dynamics therefore take place along a line (the x axis). In the notation of Strogatz, the phase-plane plot represents a vector field on the line: the velocity vector $\dot{x}$ is shown for every x. The trajectory is a plot of $\dot{x}$ as a function of x. The time coordinate is thus implicit we could, for example, mark off time ticks along the curve given any starting value of x, and hence $\dot{x}$, but the main properties of the system are apparent directly from the phase-plane plot.

We can immediately identify two types of *fixed point*. These are values of x for which x is zero, so that the system is, momentarily at least, at rest.

- A *stable* fixed point results whenever $\dot{x}$ is zero and the slope of the $\dot{x}$ vs x curve $d\dot{x}/dx$ is negative. This ensures that for small fluctuations away from the fixed point, as shown in green arrows on the plot, the velocity $\dot{x}$ is in a sense to bring the system back to the fixed point. A stable fixed point is also known as a *sink* or an *attractor*.
- An *unstable* fixed point, on the other hand, has $d\dot{x}/dx > 0$, so that small fluctuations result in a motion directed away from the fixed point. Other names for an unstable fixed point include *source* or *repeller*.
- One other type of fixed point is possible, and is known as a half-stable point.

Example of Autocatalytic chemical reaction. Consider the reaction

$$\mathrm{A} + \mathrm{X} \underset{\mathrm{k_2}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} 2\mathrm{X}$$

which is a non-linear dynamical system. The presence of X stimulates further production of X hence the term "autocatalytic". (This is one model for the growth of amyloid plaques in the brain in diseases such as BSE and CJD: the presence of a small amount of plaque, X, catalyses the conversion of normal protein, A, to plaque.) There are two variables in the process: a, the concentration of reactant A, and x, the concentration of reactant X. If the concentration of A is always large, then it will be effectively constant. The problem then reduces to dynamics in one variable.

Given the rate constants for forward and reverse reactions, k_1 and k_2, the equation governing the dynamics is

$$\dot{x} = k_1 a x - k_2 x^2.$$

We can sketch the trajectory in the phase-plane, as shown. It is also straightforward to sketch the concentration vs time, as in the right hand panel. Since $\dot{x}$ is linearly proportional to x in the vicinity of the fixed points, the approach to equilibrium must be exponential.

Dynamic variables and control variables. In the example above, x and a are *dynamical variables*: that is, they are the

variables which change with time. The two other variables, k_1 and k_2, are control variables. In that particular case, varying the control variables did not change the general character of the dynamics, but only the details.

Consider now the system described by

$$\dot{x} = x^2 + a.$$

As a is increased from a negative value, the two equilibria one stable, and one unstable first approach each other, then merge to form a half-stable fixed point, and finally annihilate. The control parameter, or variable, a, thus determines the stability of the system.

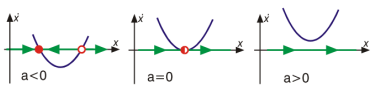


Fig. 1.3 In this example, a is control variable. Its value determines the stability of the system.

In general, complex dynamical systems have fewer control parameters than dynamical variables. We are interested in situations, such as that shown above, where a change in one or more of the control parameters leads to discontinuities i.e., qualitatively different dynamics, such as a change from stable to unstable behaviour. This is the basis of Catastrophe Theory. The key result from catastrophe theory is that the number of configurations of discontinuities depends on the number of control variables, and not on the number of dynamical variables.

In particular, if there are four or fewer control variables, there are only seven distinct types of catastrophe, and in none of these is more than two dynamical variables involved. In the next section we consider all cases up to two control parameters. For simplicity we restrict ourselves to a single dynamical variable, x, with little loss of generality.

Potential methods. The existence of stable, unstable and half-stable fixed points (i.e. equilibria) suggests another way of looking at the dynamics, in terms of an underlying potential, which we shall here denote by $V(x)$. Stable equilibria are local minima in $V(x)$, unstable equilibria are local maxima and half-stable fixed points are points of inflection.

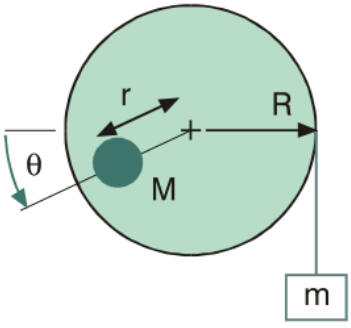


Fig. 1.4 Mechanical pulley example Here,a is control variable. Its value determines the stability of the system. In this weighted pulley, The gravitational potential is given by $V = mR\theta - Mr\sin\theta$, we can simplify notation $V = A\theta - B\sin\theta$. For small θ we can approximate this as $V \simeq (A-B)\theta + \frac{B}{6}\theta^3$. That has the same behavior as $V = \alpha\theta + \theta^3$, with $\alpha = 6(A-B)/B$. The system will thus be stable as long as $\alpha < 0$, i.e. $B > A$, i.e. $Mr > mR$.

In this course we are dealing with the evolution of arbitrary dynamical systems (as loosely interpreted), and hence there may not actually be a true potential energy. In mechanical systems there often is one. In terms of the equation $\dot{x} = f(x)$, we can define the potential to be

$$f(x) = -\frac{dV}{dx}.$$

For a first-order system (and hence one-dimensional motion) we have to imagine a particle with an inertia which is negligible in comparison with the damping force.

The negative sign implies that the force on a particle is always "downhill", towards lower potential. This can be shown simply by applying the chain rule to the time-derivative of the potential

and applying the definition of the potential:

$$\begin{aligned} \frac{dV}{dt} &= \frac{dV}{dx}\frac{dx}{dt} \\ &= -\left(\frac{dV}{dx}\right)^2 \leq 0. \end{aligned}$$

Thus $V(t)$ decreases along trajectories, and the particle always moves towards lower potential.

In summary, the potential has the following properties:

(1) $-dV/dx$ is force-like (i.e., is in the direction of motion).

(2) Equilibrium positions, x^* (fixed points) are given by $-dV/dx = 0$.

(3) The stability of the fixed point is determined by the sign of $-d^2V/dx^2|_{x^*}$.

Forms of the potential curve. The potential function can always be approximated by a Taylor series, so that

$$V(x) = a + bx + cx^2 + ...$$

We can ignore a, since it is just a constant and does not affect the dynamics. In the vicinity of a single fixed point (i.e. equilibrium) we can also eliminate b by shifting the coordinate system to put the fixed point at the origin (although b cannot be ignored for multiple fixed points). This leaves us with

$$V(x) = cx^2 + dx^3 + ex^4 + ...$$

We can now enumerate the possibilities.

(1) **Harmonic Potential.** This is the simplest possible form, and the only one possible for purely linear systems:

$$V(x) = \alpha x^2.$$

There is a single fixed point, $x^* = 0$, for all α. If $\alpha > 0$ then the fixed point is stable; if $\alpha < 0$ then it is unstable.

(2) **Asymmetric cubic potential: The saddle-node bifurcation.** The potential has the form

$$V(x) = \alpha x + x^3.$$

For $\alpha > 0$, no equilibrium position is possible. For $\alpha < 0$, then there is always one stable and one unstable equilibrium. Here we introduce the idea of *control space*. We can plot the location of the fixed point, x^* , as a function of the control parameter, α, as shown in Figure 1.5.
On the control space plot, the solid line denotes the location of the *stable* equilibrium, while the dashed line indicates the locus of the *unstable* equilibrium, both as a function of α.

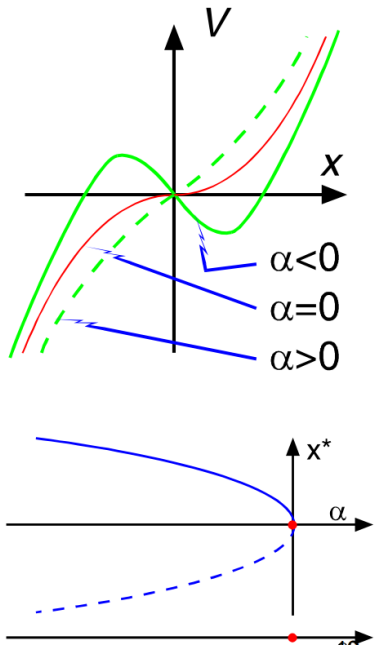


Fig. 1.5 cubic and linear potential

The form of the instability shown here is what Strogatz calls a saddle-node bifurcation, and sometimes known as a limit point instability or a fold.
The phase-plane trajectories for this system were shown earlier, for the system with $\dot{x} = x^2 + a$ (Figure 1.3). This is the origin of the term "saddle-node bifurcation" as a is decreased through zero the fixed point is first created, and then bifurcates into two: one stable and one unstable. See example in Figure 1.4.

(3) **Cubic potential with quadratic term: The transcritical bifurcation.** The potential this time includes a term in x^2 rather than a linear term as in the previous section.

$$V(x) = x^3 + \alpha x^2$$

The effect of this is to give a double root, and hence a fixed point, at the origin, regardless of the location of the third root.
The bifurcation diagram is shown in Figure 1.6. This is generally known as the transcritical bifurcation. One physical example of such a system is the laser.

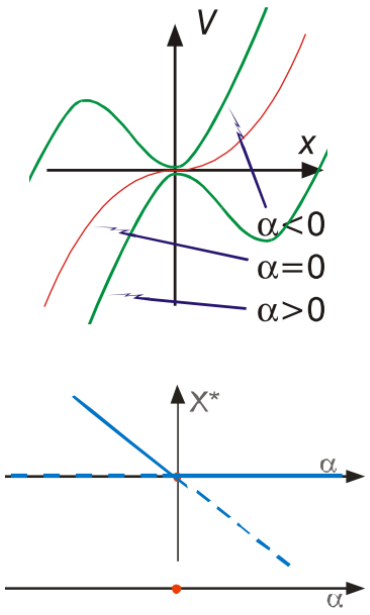


Fig. 1.6 cubic and quadratic potential

(4) **Symmetric quartic potential: The pitchfork bifurcation.** The potential is:

$$V(x) = x^4 + \alpha x^2.$$

Two cases:

- For $\alpha \geq 0$ there is just one stable equilibrium;
- For $\alpha < 0$ there is one unstable equilibrium and two stable equilibrium points.

Plotted in Figure 1.7 is the case of positive term on the 4^{th} power. In this case we refer to the Stable Symmetric Transition. It is also known as a Pitchfork Bifurcation (see Strogatz) from the shape of the bifurcation diagram, as shown at right. One example of this sort of potential is the Euler strut.
If we take the negative sign on the 4^{th} power, the additional quartic term may also act to destabilize the system, and the locus of the fixed points changes qualitatively (exercise).

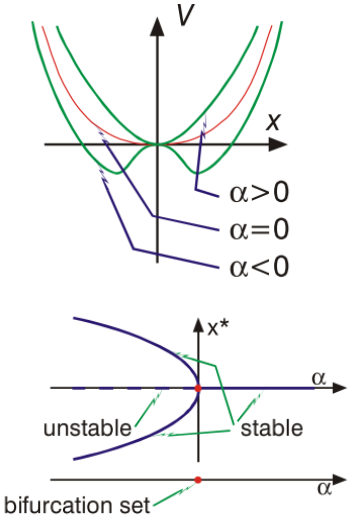


Fig. 1.7 symmetric quartic potential

(5) **Asymmetric quartic potential with two control parameters: the Cusp catastrophe.** We now consider an asymmetric potential, of the form

$$V(x) = \alpha x^2 + x^4 + \beta x$$

where the βx term introduces asymmetry to the symmetric quartic form of the previous case. We now have two control parameters, α and β. Depending on the sign of α, then, we get two different sorts of behaviour.

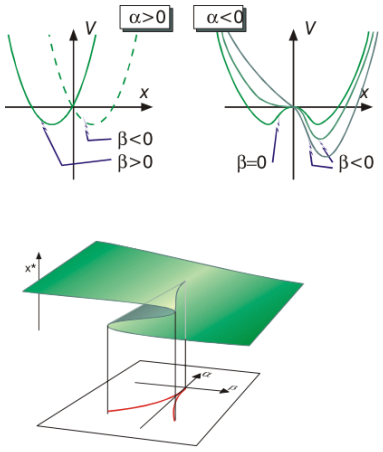


Fig. 1.8 asymmetric quartic potential

If $\alpha > 0$ then the linear term merely shifts the position of the fixed point, but does not qualitatively change the dynamics from that of a simple harmonic potential. If $\alpha < 0$ however, the linear term can eliminate the unstable fixed points and one of the stable fixed points as well.
The control space diagram the bifurcation set is now two dimensional. Consider the *equilibrium surface*, or a plot of the location of x^* against α and β. The bifurcation set is the set of points in the (α, β) plane dividing the plane into different regions of stability, and has a characteristic cusp shape, see Figure 1.9.
As we move from the shaded to the non-shaded region (i.e. across the bifurcation set), there is a sudden change in behaviour, with marked hysteresis when the path is reversed.

1.1.2 Two dimensional systems

Oscillations are not possible in one-variable systems, so that all the "fixed points" are static. In two variables, we have the possibility of periodic ("closed") trajectories, which are known as limit cycles, as we would predict from our knowledge of the harmonic oscillator a classic two-variable system. Near a fixed point, the general nonlinear differential equations can be approximated by a set of linear equations, so we can examine the behaviour near fixed points of any two-variable system by generalizing the harmonic oscillator equations.

Concepts for 2-variable systems: Phase space and nullclines

We have seen fixed points in one variable. This concept generalises to two variables, and their stability can be determined by linearising the system and looking at eigenvalues (real parts) of the matrix of partial derivatives. Two other important concepts in nonlinear systems are phasespace and nullclines.

For 2 coordinates, the phaseplane is a sketch of the system time evolution in $(x; y)$ coordinates. This is different from a sketch against time which is the way you often see data. Phaseplanes can provide much more useful info such as a global way of looking at your system.

Nullclines are curves that enable one to break the plane into regions of different qualitative behaviour. If 2 variables $\dot{x} = f(x, y)$, $\dot{y} = g(x, y)$, then nullclines are $f(x, y) = 0$ and $g(x, y) = 0$, and their crossing points are the fixed points.

Nature of stable solutions in 2-variable systems

Non-linear systems can, in the vicinity of a fixed point, be linearised. As shown in the lecture slides, linear systems have only

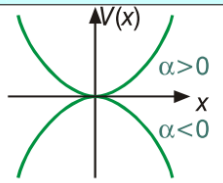
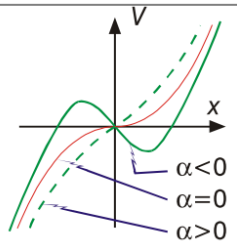
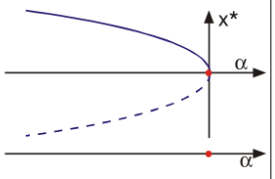
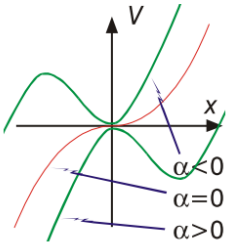
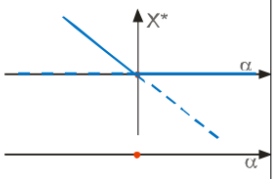
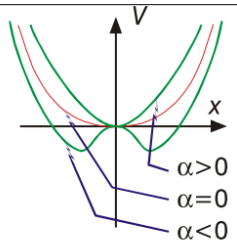
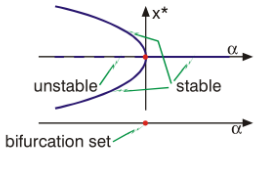
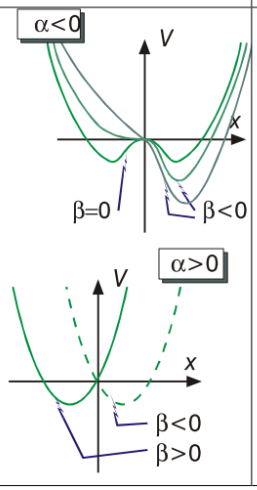
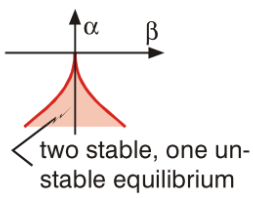
Name	f(x)	V(x)	Potential	Bifurcation diagram
Harmonic potential	$-2\alpha x$	αx^2		
Limit-point instability Saddle-node bifurcation Fold	$-\alpha - 3x^2$	$\alpha x + x^3$		
Transcritical Bifurcation	$-2\alpha x - 3x^2$	$\alpha x^2 + x^3$		
Pitchfork Bifurcation Stable symmetric transition	$-2\alpha x - 3x^2$	$\alpha x^2 \pm x^4$		
Cusp catastrophe	$2\alpha x + 4x^3 + \beta$	$\alpha x^2 + x^4 + \beta x$		

Fig. 1.9 summary of instabilities in one dimensional systems

five types of solution: spiral (stable or unstable; node (stable or unstable), and saddle point.
A non-linear system can also exhibit a different solution, known as 'limit cycle'. The "limit cycle is defined as an isolated, closed trajectory. That is, neighbouring trajectories are not closed. It is an attractor if neighbouring trajectories spiral towards it, or a repeller if they spiral away.

1.2 Biopatterning

In the following, we will explore how self-organizing patterns at a macroscopic scale emerge from the microscopic dynamics of the components of a biological system. How do zebra stripes emerge? Or the symmetric geometry of flowers? Or the ordering of lens-making cells in the eye? Biology exhibits an incredible number of examples of regular patterns that can occur in both space and time.

Generally speaking, pattern formation can be treated as a question in communication of spatial information. We can think of four different mechanisms that can lead to patterning: (i) Turing patterns, (ii) morphogen gradients, (iii) lateral inhibition and (iv) clock and wavefront mechanisms. Here, we will focus on patterns in space generated by the first three types of mechanisms.

1.3 Turing Patterns

Patterning can arise spontaneously in a system due to the presence of instabilities in the system. An example of this are Turing patterns. The occurrence of these patterns was hypothesized by Turing as a mechanism to explain the spontaneous emergence of morphogen patterns in development. Although it turned out that biological systems seem to rely on different mechanisms during morphogensis, it remains true that many patterns of gene expression can be driven by reaction-diffusion equations as those describing Turing pattern.

Let's imagine to have to molecules, X and Y, distributed in space, which can react with each other and diffuse. Their dynamics can be mathematically formalized with a system of partial differential equations:

$$\partial_t X = D_X \partial_x^2 X + f(X,Y) \tag{1.1}$$
$$\partial_t Y = D_Y \partial_x^2 Y + g(X,Y) \tag{1.2}$$

with initial conditions

$$X(x,0) = X_0(x) \tag{1.3}$$
$$Y(x,0) = Y_0(x) \tag{1.4}$$

and fixed boundary conditions.

For the sake of brevity, we will introduce a vector notation where

$$\vec{X} = \begin{bmatrix} X \\ Y \end{bmatrix}, \; F(\vec{X}) = \begin{bmatrix} F(X,Y) \\ G(X,Y) \end{bmatrix}, \; D = \begin{bmatrix} D_X & 0 \\ 0 & D_Y \end{bmatrix}$$

Let's assume that in the absence of diffusion the system has steady-state (X^*, Y^*) and let's examine the stability of the steady-state by moving slightly away. If

$$\vec{Z} = \begin{bmatrix} X - X^* \\ Y - Y^* \end{bmatrix}$$

then the time derivateve of $\vec{Z}$ is

$$\dot{\vec{Z}} = \begin{bmatrix} f(X - X^*, Y - Y^*) \\ g(X - X^*, Y - Y^*) \end{bmatrix}$$

We can linearize these equations (first term of the Taylor expansion) and we get:

$$\begin{bmatrix} f(X - X^*, Y - Y^*) \\ g(X - X^*, Y - Y^*) \end{bmatrix} = \begin{bmatrix} f(X^*, Y^*) \\ g(X^*, Y^*) \end{bmatrix} + A\vec{Z} = A\vec{Z},$$

where we exploied the fact that (X^*, Y^*) is steady-state and

$$A = \begin{bmatrix} \partial_X f & \partial_Y f \\ \partial_X g & \partial_Y g \end{bmatrix}$$

is the Jacobian of F. We then get

$$\dot{\vec{Z}} = A\vec{Z}.$$

The solution of this equation will of of the form

$$\vec{Z} = \sum_{n=1}^{2} w_i \vec{v}_i \exp(\lambda_i t)$$

where $\vec{v}_i$ are the eigenvectors of A with eigenvalues:

$$\lambda_i = \frac{Tr(A) \pm \sqrt{Tr(A)^2 - 4Det(A)}}{2}$$

and w_i depend on the initial conditions.

If at long time scales, $\vec{Z}$ tends to zero, then the steady-state will be stable. This happens if both eigenvalues are negative, which is equivalent to $Tr(A) < 0$ and $Det(A) > 0$.

If we add diffusion, the equation we want to solve is

$$\dot{\vec{Z}} = A\vec{Z} + D\partial_x^2 \vec{Z},$$

which admits solutions of the form:

$$\vec{Z} = Z_0 \exp(\lambda t) \exp(iqx).$$

These represent spatial waves with wave number q whose amplitude is either growing or shrinking with time.

By substituting the solution in the equation above, one obtains:

$$(A - q^2 D - \lambda I) Z_0 = 0,$$

where I is the identity matrix. The system is unstable if at least one of the eigenvalues in $A - q^2 D$ has a real positive part, which happens if $Det(A - q^2 D) < 0$.

For a diffusion driven instability to occur, we then have the condition

$$Det(A - q^2 D) = D_X D_Y q^4 - q^2 (D_Y \partial_X f + D_X \partial_Y g) + Det(A) < 0.$$

Both $D_X D_Y q^4$ and $Det(A)$ are positive. Therefore, we need to have

$$D_Y \partial_X f + D_X \partial_Y g > 0$$

and the critical case of pattern emerges when

$$D_X D_Y q^4 - q^2 (D_Y \partial_X f + D_X \partial_Y g) + Det(A) = 0.$$

We can determine the value of q corresponding to the minimum of $Det(A - q^2 D)$. This corresponds to the wave number that grows at the onset of instability. If we define $k = q^2$, then

$$\frac{d(Det(A - kD)}{dk} = 2 D_X D_Y k - (D_Y \partial_X f + D_X \partial_Y g) = 0$$

We find that

$$k_{min} = q^2_{min} = \frac{D_Y \partial_X f + D_X \partial_Y g}{2 D_X D_Y}$$

The second derivative of $Det(A - kD) = 2 D_X D_Y > 0$ proving that this is a minimum.

If we replace this solution back in the condition for instability, we get:

$$\frac{-(D_Y \partial_X f + D_X \partial_Y g)^2}{4 D_X D_Y} + Det(A) < 0$$

and therefore

$$4 D_X D_Y Det(A) - (D_Y \partial_X f + D_X \partial_Y g)^2 < 0.$$

If we define the relative diffusion $\delta = D_Y / D_X$ then the expression above can be written as

$$4 \delta Det(A) - (\delta \partial_X f + \partial_Y g)^2 < 0$$

The root of this equation defines the critical diffusion ratio for the onset of instability (pattern formation).

In the case of finite systems with fixed boundary conditions, only some modes are allowed. For instance, if the system is defined

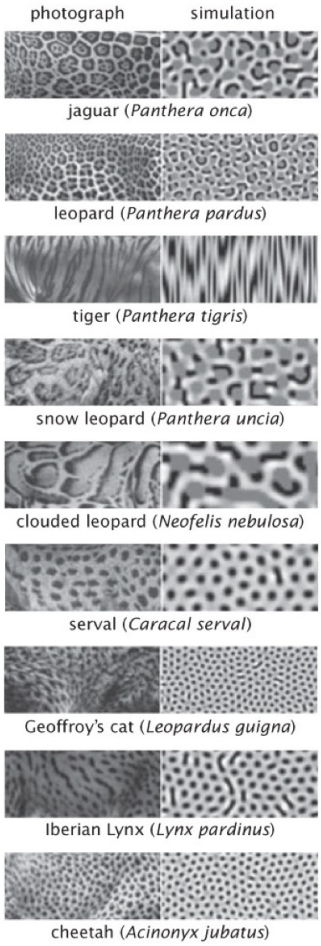


Figure 20.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fig. 1.10 Coat patterns in a variety of species (left) and corresponding simulated pattern (right).

over $[0, L]$, then the solution can be combinations of only wave numbers $q_n = \frac{2\pi n}{L}$ such that

$$\vec{Z} = \sum_n w_n \vec{v}_n \exp(\lambda_n t) \exp(i q_n x).$$

Any mode will be unstable if

$$D_X D_Y q_N^4 - q_n^2 (D_Y \partial_X f + D_X \partial_Y g) + Det(A) < 0.$$

There are several reasons why to molecules can have different diffusion coefficient: their size, their binding rate to other surrounding molecules, the ability to penetrate through certain compartments. Note that Turing patterns are not limited to small molecules diffusing around. Cell populations that migrate and interact can also give rise to Turing patterns.

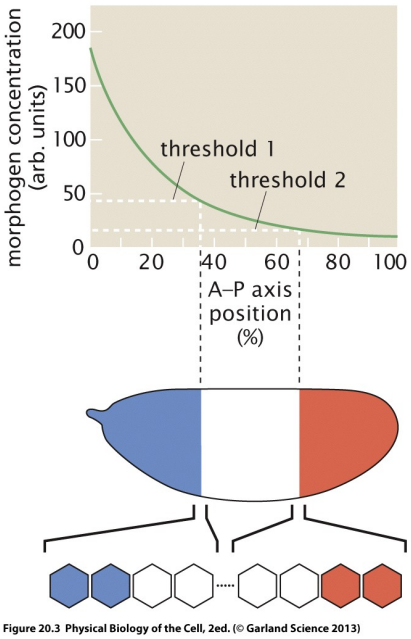


Fig. 1.11 Example of patterning driven by a morphogen gradient

1.4 Morphogen gradients

As we mentioned earlier, Turing patterns do not seem to be the mechanism by which pattern formation arises in development. In this case, cells decide their fate using positional information regarding the concentration of a morphogen (see Fig. 1.11 for a simple French flag pattern). The morphogen gradient that cells sense normally has a maternal origin. Interestingly, the resulting patterns are extremely robust to noise in morphogen concentration.

To start, let's consider a morphogen M that diffuses at rate D and degrades at rate α. The morphogen is introduced at time t at position $x = 0$ in concentration M_0. The equation describing its dynamic will be

$$\partial_t M = D\partial_X^2 M - \alpha M,$$

which has steady-state solution $M(x) = M_0 \exp(-x/\lambda)$, where $\lambda = \sqrt{D/\alpha}$.

If cell fate and patterning is determined by the concentration of the morphogen, similarly to the french flag model, than changes in initial concentrations would in this case affect the resulting patterning. For instance, if the boundary between two regions is determined by the position x_0 at which $M(x_0) = T$, then this position would shift by $\delta = \lambda \log \frac{M_0'}{M_0}$, if the initial concentration shifts from M_0 to M_0'.

Let's consider an alternative model where the morphogen pro-

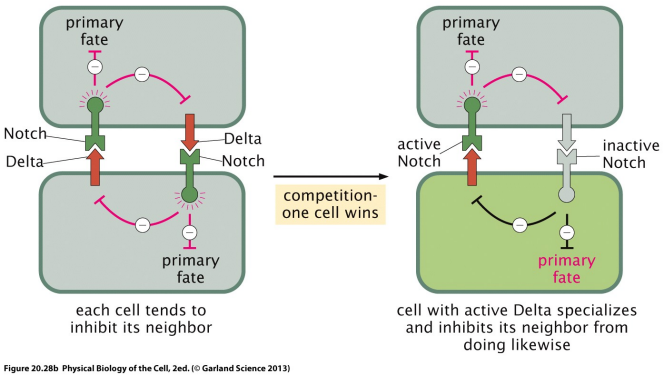


Fig. 1.12 Sketch of the feedback loop between Delta and Notch of two neighboring cells

motes its own degradation:

$$\partial_t M = D\partial_x^2 M - \alpha M^2.$$

The steady-state solution of this equation is

$$M(x) = \frac{6D}{\alpha(x+\epsilon)^2},$$

where $\epsilon = \sqrt{6D/\alpha M_0}$. In this case, as long as M_0 is very large, ϵ will be very small, and $M(x)$ will be almost independent of M_0.

1.5 Lateral inhibition: the Notch-Delta concept

Some biological tissues exhibit specific patterns where neighboring cells have "opposite" morphologies creating a checkboard pattern. Neither reaction-diffusion models nor morphogen gradients can give rise to such phenomenon. However, one can think of a mechanisms by which neighboring cells inhibit each other's gene expression program leading to opposite cell fate. Here, we will consider a well-studied example of such mechanism: the Notch-Delta system.

Notch is a mebrane-bound receptor that is activated by the ligand Delta supplied by a neighboring cell (Fig. 1.12). When the two interact, the activated Notch inhibits the production of the Delta ligand in its own cell. Therefore, the neighboring cell that initially supplied Delta will not have its own Notch receptors interacting with the Delta of the first cell, which will promote the production of Delta creating a positive feedback loop where the different gene expression in the two neighboring cells will be amplified.

To understand this mathematically, let's define N_1 and N_2 the Notch activity in cell 1 and 2, and D_1 and D_2 the Delta activity

in cell 1 and 2. Then, the dynamic of the system can be described by the following set of differential equations:

$$\begin{aligned} \dot{N}_1 &= F(D_2) - \gamma_N N_1 && (1.5)\\ \dot{D}_1 &= G(N_1) - \gamma_D D_1 && (1.6)\\ \dot{N}_2 &= F(D_1) - \gamma_N N_2 && (1.7)\\ \dot{D}_2 &= G(N_2) - \gamma_D D_2 && (1.8) \end{aligned}$$

where γ_N and γ_D represent the degradation rate of Notch and Delta, respectively, $F(D_i)$ represents the activation of Notch by the Delta of the neighboring cell, and $G(N_i)$ represents the suppression of Delta by the Notch of the same cell.

We can change render these equations dimensionless by dividing all the equations by γ_N:

$$\begin{aligned} \dot{N}_1 &= f(D_2) - N_1 && (1.9)\\ \dot{D}_1 &= v[g(N_1) - D_1] && (1.10)\\ \dot{N}_2 &= f(D_1) - N_2 && (1.11)\\ \dot{D}_2 &= v[g(N_2) - D_2] && (1.12) \end{aligned}$$

where $v = \gamma_D/\gamma_N$, $f = F/\gamma_N$ and $g = G/\gamma_D$.

Let's consider the limit when $v \gg 1$ (Delta decays very fast compared to Notch). This effectively means that we can separate time-scale so that the Delta time scale is much faster than that of Notch. Then one can approximate $D_1 \approx g(N_1)$ and $D_2 \approx g(N2)$ and get:

$$\begin{aligned} \dot{N}_1 &= f(g(N_2)) - N1 && (1.13)\\ \dot{N}_2 &= f(g(N_1)) - N2. && (1.14) \end{aligned}$$

To understand the dynamic, let's draw a phage protrait (fig. 1.13). The nullclines, defined as $N1 = f(g(N_2))$ and $N2 = f(g(N_1))$ are shown in red and blue. The points at which the nullclines intersect are the fixed points where the system is at equilibrium. The nullclines divide the phage protrait in different areas where we can determine whether N_1 or N_2 will decrease or increase (arrows in fig. 1.13). This shows that the stable equilibria are in the two extreme cases, where the two cells have opposite behavior.

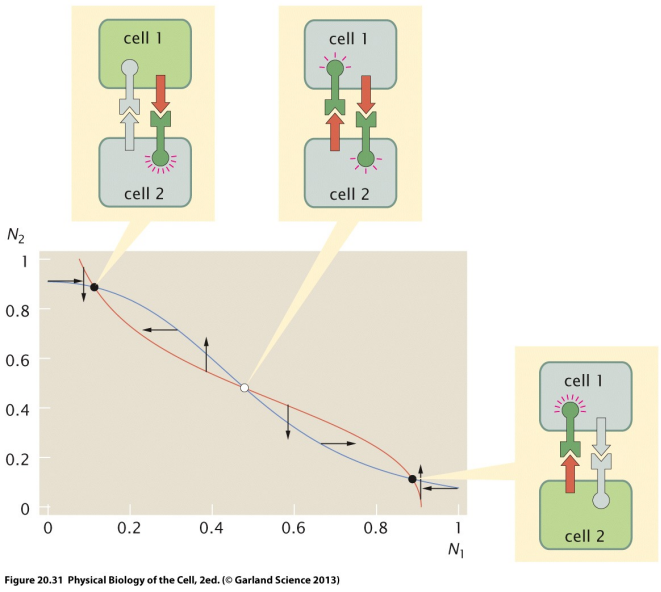


Fig. 1.13 Phase portrait of the Delta-Notch system