1 Morphogenesis

Morphogenesis requires, among other things, robust cell fate determination in accordance with the position of the cells in a tissue or embryo. Decisions regarding proliferation, differentiation, adhesion, migration etc. relies on chemical signals which are regulated by interactions within and across cells. Positional information is often gained by sensing concentration of chemical gradients. For instance, consider an embryo with maternal mRNA localized on one end, which transcribes morphogen M at rate α. The morphogen diffuses in the extra cellular matrix (diffusion constant D), and degrades with rate $1/\tau$, where τ is the average lifetime of the morphogen molecule. The morphogen concentration ρ at position x, at time t is given by,

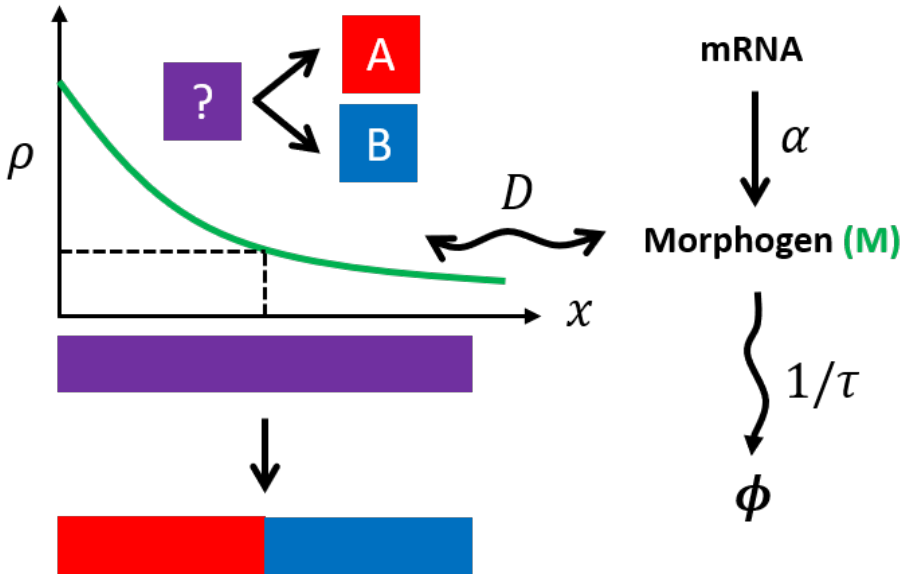

Figure 1: Cells in embryonic tissue can differentiate into distinct identities with an external morphogen gradient as the chemical cue

$$\frac{d\rho(x,t)}{dt} = \alpha\delta_{x,0} + D\nabla^2\rho - \rho/\tau \tag{1}$$

For $x \neq 0$, $t \to \infty$, at steady state,

$$\rho = D\tau\frac{\partial^2\rho}{\partial x^2} \tag{2}$$

A solution of the form $\rho = ae^{-x/\lambda_m}$ satisfies this equation, where $\lambda_m = \sqrt{D\tau}$ is the length-scale of the Morphogen gradient. At steady state, the current at $x = 0$ is equal to the production rate α. The current is given by,

$$j = -D\frac{\partial\rho}{\partial x} = \frac{Da}{\lambda_m}e^{-x/\lambda_m}\Big|_0 \tag{3}$$

resulting in $a = \alpha\sqrt{D/\tau}$. At steady state,

$$\frac{\partial}{\partial x}\left(D\frac{\partial\rho}{\partial x}\right) = 0 \tag{4}$$

$$D\frac{\partial\rho}{\partial x} = C \tag{5}$$

where C is a constant current independent of spatial position x. At $x = 0$, $C = a\sqrt{D/\tau}$, which is also the current at every point in space. This is an example of a non-equilibrium steady state. A scenario where

is no production or degradation, diffusion would simply homogenize the density over space resulting in an equilibrium steady state ($C = 0$).

Let's assume that cells which experience low Morphogen concentration $M < M_\Delta$ are unaffected by it and differentiate into cell type B, while through some signaling mechanisms the Morphogen can bias the other cells to differentiate into cell type A. In the presence of morphogen, the tissue, initially homogeneous, undergoes segmentation and the cells have gained 1 bit of information.

2 Diffusion

At the microscopic level, diffusion can be modeled as random walk process. Let's assume that the random walker can hop Δx to the left or right with equal probability $p = 1/2$. The density of random walkers at x at time $t + \Delta t$ is given by,

$$\rho(x, t + \Delta t) = \frac{1}{2}\left(\rho(x - \Delta x, t) + \rho(x + \Delta x, t)\right) \tag{6}$$

Subtracting $\rho(x, t)$ on both sides and dividing by Δt,

$$\frac{\rho(x + \Delta x, t) - \rho(x, t)}{\Delta t} = \frac{1}{2\Delta t}\left((\rho(x + \Delta x, t) - \rho(x, t)) - (\rho(x, t) - \rho(x - \Delta x, t))\right) \tag{7}$$

$$\frac{\rho(x + \Delta x, t) - \rho(x, t)}{\Delta t} = \frac{1}{2\Delta t}\left(\left.\frac{\partial \rho}{\partial x}\right|_{x+\Delta x} \Delta x - \left.\frac{\partial \rho}{\partial x}\right|_{x} \Delta x\right) \tag{8}$$

$$\frac{\rho(x + \Delta x, t) - \rho(x, t)}{\Delta t} = \frac{\Delta x^2}{2\Delta t}\left(\frac{\partial^2 \rho}{\partial x^2}\right) \tag{9}$$

In the limit $\Delta t \to 0$, and $D = \Delta x^2/2\Delta t$

$$\frac{d\rho}{dt} = D\frac{\partial^2 \rho}{\partial x^2} \tag{10}$$

Note that the diffusion constant D has the dimension L^2T^{-1}. Hence, a random walker would take time $\tau \sim \lambda^2/D$ to explore length-scale λ. The evolution equation ensures that at steady state, the curvature of the density profile is zero.

Fourier transform enable us to write the density $\rho(x, t)$ as an integral of sinusoidal modes with distinct wavelength ($\lambda \sim 1/k$), where the amplitude associated with each mode is given by $\phi(k)$. k is the wavenumber or inverse-wavelength of the modes.

$$\phi(k) = \int_{-\infty}^{+\infty} \rho(x) e^{ikx} dx \tag{11}$$

Taking Fourier transform of both sides in 2,

$$\int_{-\infty}^{\infty} \frac{d\rho}{dt} e^{ikx} dx = D \int_{-\infty}^{+\infty} \frac{\partial^2 \rho}{\partial x^2} e^{ikx} dx \tag{12}$$

Applying chain rule of integration

$$\frac{d\phi}{dt} = De^{ikx}\frac{\partial \rho}{\partial x}\bigg|_{-\infty}^{+\infty} - iDk \int_{-\infty}^{\infty} e^{ikx}\frac{\partial \rho}{\partial x} dx \tag{13}$$

Imposing $\partial\rho/\partial x \to 0$ at the boundaries $x \to \pm\infty$,

$$\frac{d\phi}{dt} = -iDke^{ikx}\rho\bigg|_{-\infty}^{+\infty} - Dk^2 \int_{-\infty}^{+\infty} \rho e^{ikx} dx \tag{14}$$

Imposing $\rho \to 0$ at the boundaries $x \to \pm\infty$,

$$\frac{d\phi}{dt} = -Dk^2\phi \tag{15}$$

$$\phi = \phi_o e^{-Dk^2 t} \tag{16}$$

where ϕ_o is the Fourier transform of the random walker density profile at time $t = 0$, $\rho(x, 0) = \rho_o(x)$. Modes with shorter wavelength $\gg 1$ decays faster, where the decay timescale $\tau_k \sim 1/Dk^2 \sim \lambda^2/D$. This is consistent with our intuitive understanding of the Diffusion process, as we would expect small variations in the density profile to be homogenized before the larger variations are erased out.

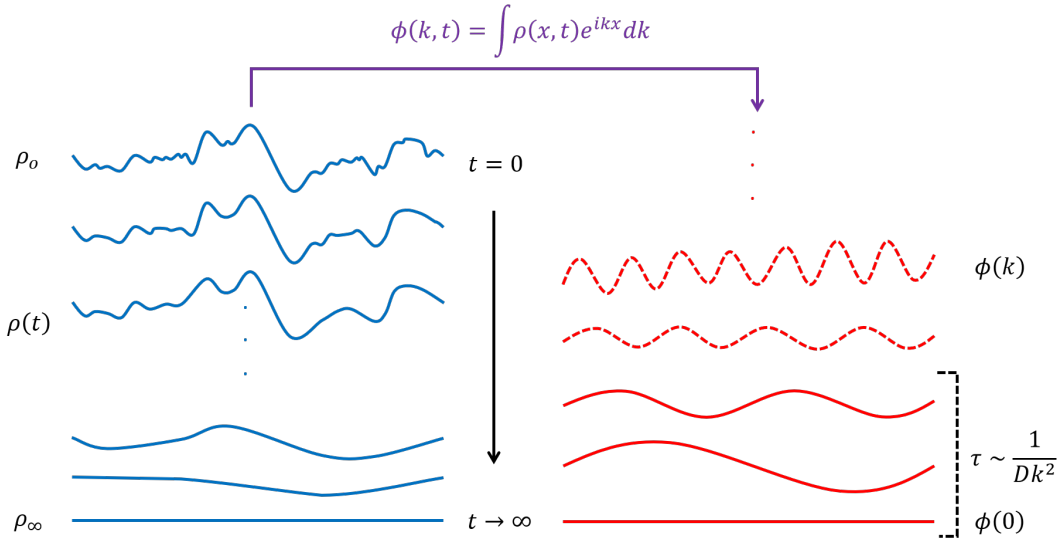

Figure 2: Diffusion reduces variation in density profiles. This can also be equivalently viewed as the amplitudes associated with fourier modes decaying. Modes associated with wavenumber k or wavelength $\lambda(\sim 1/k)$ continue to persist until the characteristic timescale $\tau \sim 1/Dk^2$.

3 Turing Instability

Alan Turing demonstrated a powerful and counter-intuitive pattern formation mechanism demonstrating spontaneous symmetry breaking via diffusion [Chemical Basis of Morphogenesis (1952)]. Let's assume a particular cell in a tissue, where there are two chemical species U and V with concentrations u and v respectively.

$$\frac{du}{dt} = f(u, v) \tag{17}$$

$$\frac{dv}{dt} = g(u, v) \tag{18}$$

We are interested in a system that is stable by itself, but demonstrates instability when diffusive coupling is introduced. Assuming the fixed point for the system is given by (u_*, v_*), the evolution of perturbations near the fixed point $u = u_* + \delta u, v = v_* + \delta v$ is given by,

$$\frac{d(\delta u)}{dt} = f(u_*, v_*) + \left.\frac{\partial f}{\partial u}\right|_{(u_*, v_*)} \delta u + \left.\frac{\partial f}{\partial v}\right|_{(u_*, v_*)} \delta v + O(2) \tag{19}$$

$$\frac{d(\delta v)}{dt} = g(u_*, v_*) + \left.\frac{\partial g}{\partial u}\right|_{(u_*, v_*)} \delta u + \left.\frac{\partial g}{\partial v}\right|_{(u_*, v_*)} \delta v + O(2) \tag{20}$$

Since (u_*, v_*) is a fixed point, $f(u_*, v_*) = 0$, $g(u_*, v_*) = 0$. After ignoring higher order terms, we obtain,

$$\frac{d}{dt}\begin{bmatrix}\delta u \\ \delta v\end{bmatrix} = \begin{bmatrix}f_u & f_v \\ g_u & g_v\end{bmatrix}\begin{bmatrix}\delta u \\ \delta v\end{bmatrix} \tag{21}$$

where the subscript for terms in the Jacobian Matrix indicates the variable with respect to which the derivative is estimated. The characteristic polynomial is given by,

$$\lambda^2 - (f_u + g_v)\lambda + (f_u g_v - f_v g_u) = 0 \tag{22}$$

For the system to be stable, both the eigenvalue has to be negative, implying $\lambda_1 + \lambda_2 < 0$ and $\lambda_1\lambda_2 > 0$. This gives us the first two conditions,

$$f_u + g_v < 0 \tag{23}$$

$$f_u g_v - f_u g_v > 0 \tag{24}$$

Assuming these conditions are met, let's assume that the chemicals U and V can diffuse between cells, with

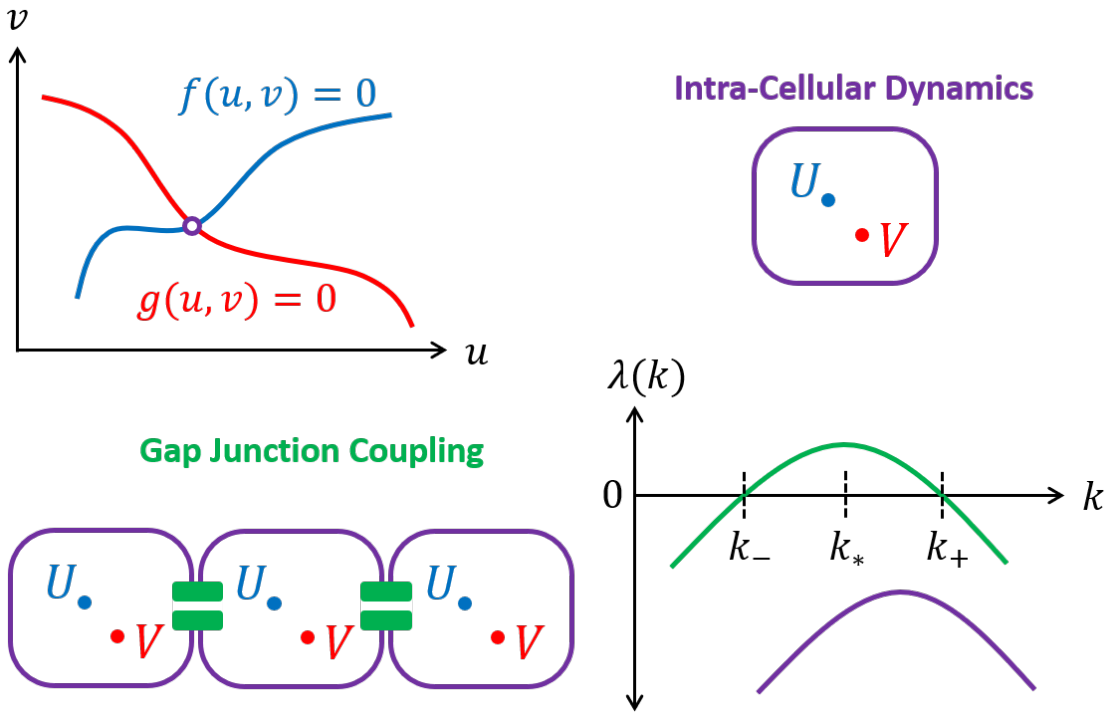

Figure 3: Conditions for stability derived from generic dynamics of two interacting chemical species. We examine the conditions under which diffusion is expected to induce instability.

diffusion rates being D_u and D_v respectively.

$$\frac{du}{dt} = f(u, v) + D_u\nabla^2 u \tag{25}$$

$$\frac{dv}{dt} = g(u, v) + D_v\nabla^2 v \tag{26}$$

The Fourier transform of the evolution equation of small perturbation around the fixed point is given by,

$$\frac{d}{dt}\begin{bmatrix}\phi \\ \psi\end{bmatrix} = \begin{bmatrix}f_u - D_u k^2 & f_v \\ g_u & g_v - D_v k^2\end{bmatrix}\begin{bmatrix}\phi \\ \psi\end{bmatrix} \tag{27}$$

Say the characteristic polynomial is $\lambda^2 - b\lambda + c = 0$. For the system to have instabilities, we require $\lambda_1 > 0, \lambda_2 < 0$ implying $c = \lambda_1\lambda_2 < 0$. This gives us the condition,

$$\Delta(q) = (D_u D_v)\, q^2 - (D_u g_v + D_v f_u)\, q + (f_u g_v - f_v g_u) < 0 \tag{28}$$

where $q = K^2 (> 0)$. We want the minima of this parabola to exist for positive q, and the value of the function to be negative near the minima. Hence, the minima of the parabola $\Delta(q)$ is

$$q_* = \frac{(D_u g_v + D_v f_u)}{2 D_u D_v} > 0 \tag{29}$$

This gives us the third condition,

$$D_u g_v + D_v f_u > 0 \tag{30}$$

Finally, for an instability $\min_q(\lambda_1\lambda_2) = \Delta(q_*) < 0$ for at least some range of $q \in [q_-, q_+]$. This gives us the fourth and final condition,

$$(D_u g_v + D_v f_u)^2 > 4 D_u D_v (f_u g_v - f_v g_u) \tag{31}$$

Assuming these four conditions, the sinusoidal modes in the range $k \in [k_- k_+] (k_\pm = \sqrt{q_\pm})$ would locally grow exponentially, while the rest of the modes decay. The most significant contribution corresponds to the mode $k_* = \sqrt{q_*}$ and this would result in periodic patterns with an arbitrary phase.

4 Reaction-Diffusion Systems

Lets examine the conditions and figure out the nature of interactions of the chemical species U and V. Let's assume that $f_u > 0$. Condition 1 (23) implies that $g_v < 0$. Let's further assume that $g_u > 0$. Condition 2 (24) implies that $f_v < 0$. This corresponds to a system where U activates itself and V, while V inhibits itself and U. Condition 3 (30) implies

$$\frac{D_v}{D_u} > -\frac{g_v}{f_u} > 1 \tag{32}$$

The inequality follow from Condition 1. The activator-inhibitor system can spontaneously generate patterns,

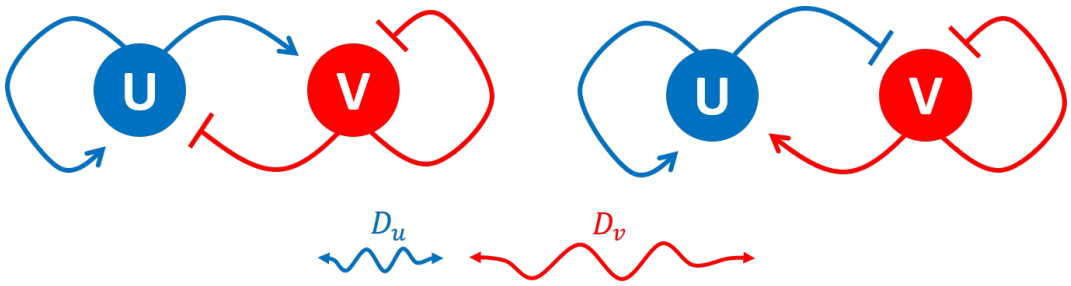

Figure 4: Two motifs that exhibit Turing Patterns. Left motif comprises of an activator U and inhibitor V, while the right motif consists of U being activated while V being inhibited. Inhibitor/Inhibited Molecules are required to diffuse faster to disrupt the stability.

given arbitrarily small perturbations to an unstable homogeneous state, provided the inhibitor diffuses faster than the activator. An example of this system is the Gierer-Meinhardt Model [Kybernetiks, 12, 30-39 (1972)],

$$\frac{da}{dt} = \frac{\rho a^2}{h} - \mu_a a + D_a \nabla^2 a \tag{33}$$

$$\frac{dh}{dt} = \sigma a^2 - \mu_h h + D_h \nabla^2 h \tag{34}$$

If we instead assume that $g_u < 0$, Condition 2 would imply that $f_v > 0$. This results in a system where

U activates itself and inhibits V, while V inhibits itself and activates U. An example of this system is the Schnakenberg Model [J. Theor. Biol, 81(3), 389-400 (1979)],

$$\frac{da}{dt} = \rho s a^2 - \mu_a a + D_a \nabla^2 a + \rho_o \tag{35}$$

$$\frac{ds}{dt} = \delta - \rho s a^2 - \mu_\delta s + D_s \nabla^2 s \tag{36}$$

For most practical purposes, it might be necessary to impose $D_v \gg D_u$. This usually results in Condition 4 (31) being satisfied as well.

The dynamical system and diffusion, both of which individually results in a homogeneous density profile, when combined, results in a spontaneous symmetry breaking giving rise to complex patterns. Unlike the first case where an external Morphogen results in patterning, Turing mechanisms generate spontaneous patterns. The gain in positional information is purely a consequence of internal interactions and the resulting emergent dynamics. This exemplifies the notion that the information necessary to unfold an organism during development is not just stored in the genome, but also banks on the reliability of emergent phenomena as the consequence of the interactions of gene products and environment.