4.6 Turing patterns

So far we explored variations of a set of variables in time, ignoring dependencies on space. In fact cells actively compartmentalize different molecules to different locations. Genetic information is localized to the nucleus and has to be carried out to the rest of the cell by diffusion of various molecules (mRNA or proteins). Even in the absence of physical barriers, chemical reactions can give rise to interesting patterns of spatio-temporal concentration variations. Since diffusion is the most common mechanism for transport of molecules in space, we shall examine the following set of *reaction–diffusion* equations

$$\frac{\partial C_i}{\partial t} = F_i\left(\{C_j\}\right) + D_i \nabla^2 C_i \,. \tag{4.52}$$

Here, D_i is the diffusion coefficient for molecular species i (with concentration C_i) and the reactions are described by local non-linear terms included in $\{C_i\}$. Intrigued by the question of how biological patterns (e.g. body shapes, or colorations of animal coats) occur in the first place, Turing postulated a set of *morphogens* whose concentrations evolve as in Eqs. (4.52).

Let us specifically ask if it is possible to have a stable fixed point $\{C_i^*\}$ as solution to Eqs. (4.52) *if spatial variations are forbidden* (as in a very well mixed bag with very large $\{D_i\}$), but which becomes unstable if spatial variations are permitted. To answer this question, let us linearize the reaction-diffusion equations around the fixed point as

$$C_i(\vec{r},t) = C_i^* + c_i(\vec{r},t)\,, \quad \Rightarrow \quad \frac{\partial c_i}{\partial t} = \sum_j M_{ij} c_j + D_i \nabla^2 c_i\,, \quad \text{with} \quad M_{ij} = \left.\frac{\partial F_i}{\partial C_j}\right|_{C^*} . \tag{4.53}$$

Stability of the uniform solution implies that all eigenvalues of the matrix M_{ij} are negative. To examine the stability with respect to spatial variations we introduce Fourier transforms

$$c_i(\vec{r},t) = \int d\vec{k} e^{i\vec{k}\cdot\vec{r}} \tilde{c}_i(\vec{k},t)\,, \tag{4.54}$$

in terms of which Eq. (4.53) becomes

$$\frac{d\tilde{c}_i(\vec{k},t)}{dt} = \sum_j \left(M_{ij} - \delta_{ij} D_i k^2\right) c_j(\vec{k},t)\,. \tag{4.55}$$

The original question can now be recast as whether the matrix $M_{ij}(k) = M_{ij} - \delta_{ij} D_i k^2$ can have a positive eigenvalue at a finite wave-vector $\vec{k}$. The answer is clearly negative if only one chemical species is present, in which case $\lambda(k) = \lambda(0) - Dk^2$ is obviously more negative (hence more stable) at finite $\vec{k}$. However, Turing showed that even with two morphogens it is possible to find a finite wave-length instability.

Let us examine the 2×2 linear-stability matrix

$$M(k) = \begin{pmatrix} M_{11} - D_1 k^2 & M_{12} \\ M_{21} & M_{22} - D_2 k^2 \end{pmatrix} . \tag{4.56}$$

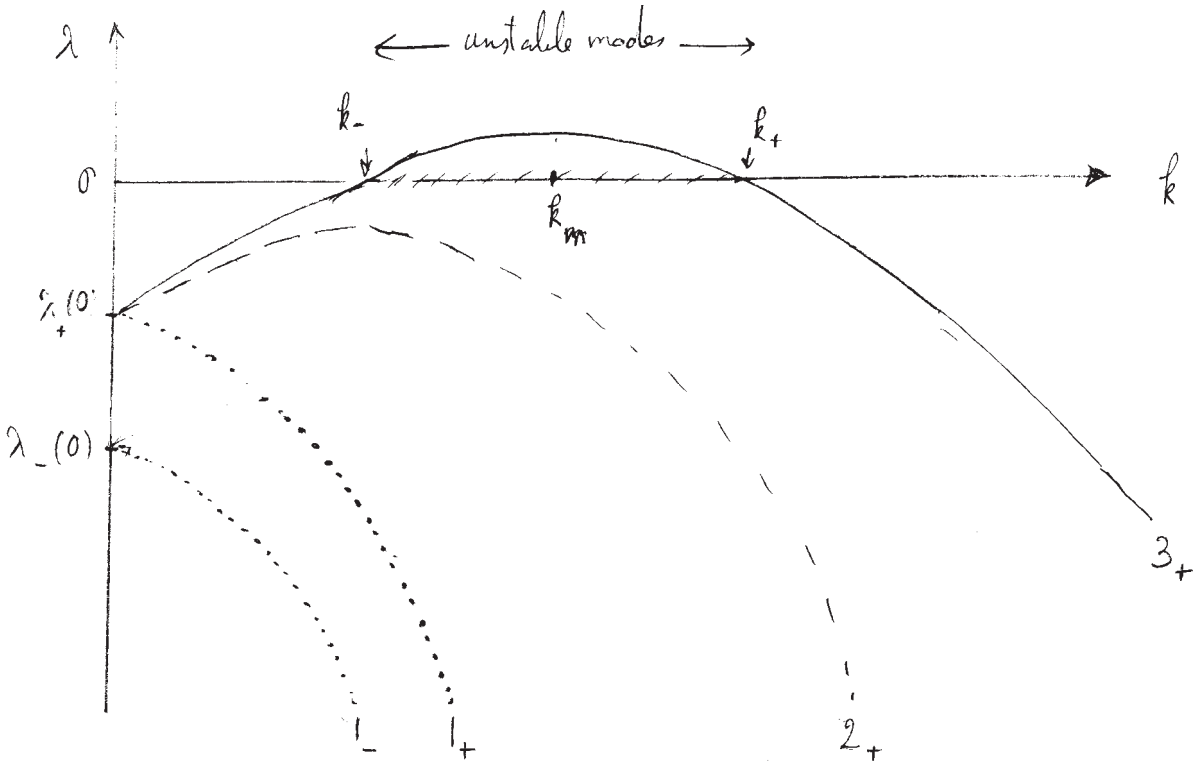
Let us denote the two eigenvalues of the matrix by $\lambda_\pm(k)$, and consider their variation with k, noting that their sum, given by

$$\lambda_+(k) + \lambda_-(k) = \mathrm{tr}M(k) = (M_{11} + M_{22}) - (D_1 + D_2)k^2\,, \tag{4.57}$$

becomes progressively more negative upon increasing k.

1. Given the assumption of stability of the uniform state, the two eigenvlaues are negative for $k = 0$. The simplest possibility, indicated by $(1_1, 1_+)$ in the figure, is that they monotonically decrease with k and there is no instability.

2. The larger eigenvalue $\lambda_+(k)$ can potentially increase with k (the conditions for this will be discussed later) at the expense of further decrease in $\lambda_k(k)$ to ensure the required decrease in the sum dictated by Eq. (4.57). The eigenvalues must eventually decrease at large k, behaving asymptotically as $-D_1k^2$ and $-D_2k^2$. As long as the maximum of $\lambda_+(k)$ remains negative (as in the curve labelled 2_+) there is again no instability.



3. The most interesting case is when the maximum occurs at a positive $\lambda_+(k)$ signaling a band of unstable modes as in the curve labelled 3_+. Perturbing a uniform initial state is thus expected to result, through diffusion of C_1 and C_2, to growing non-uniformities at the band of unstable wavelength. Nonlinearities are expected to prevent unbounded growth of perturbations, leading to finite patters that will likely carry signatures of the initial instability.

To examine the conditions necessary for formation of patterns, let us consider the product of the two eigenvalues, given by the determinant of the matrix $M(k)$ as

$$\begin{aligned}\lambda_+(k)\lambda_-(k) &= \det M(k) \\ &= (M_{11}M_{22} - M_{12}M_{21}) - (M_{11}D_2 + M_{22}D_1)\, k^2 + D_1D_2k^4\,. \end{aligned} \quad (4.58)$$

Within the unstable band ($\lambda_+(k) > 0$ and $\lambda_-(k) < 0$) the product must be negative. The first term in the brackets above, $\det M(0) = \lambda_+(0)\lambda_-(0)$ is positive as at $k = 0$ (uniform state) both eigenvalues are by fiat negative. The last term $D_1D_2k^4$ is also manifestly positive, and thus the only possible route to instability is if the middle term is large and positive, i.e.

$$(M_{11}D_2 + M_{22}D_1) > 0\,, \quad \text{while} \quad (M_{11} + M_{22}) < 0\,. \quad (4.59)$$

(The latter is required by the stability condition for $k = 0$.) If so, then Eq. (4.58) can potentially account for a curve that crosses zero at two points, k_+ and k_-, with a maximum at an intermediate k_m. The band of unstable modes will then span wave-numbers from k_- to k_+ (ala curve labelled by 3_+ in the figure). By setting this equation (and its derivative) to zero, it is easily checked that

$$k_+^2 + k_-^2 = 2k_m^2 = \frac{M_{11}D_2 + M_{22}D_1}{D_1D_2}\,. \quad (4.60)$$

Of course,the instability wavelength must be large enough so that the assumptions implicit in the continuum formulation of reaction-diffusion equations remain valid.

Clearly the conditions in Eq. (4.59) cannot be simultaneously satisfied if both M_{11} and M_{22} are negative, or if both diffusion coefficients have the same value. Without loss of generality, we can choose $M_{11} > 0$ and $M_{22} < 0$, in which case the necessary requirement for instability from Eq. (4.59) can be recast as

$$|M_{22}|\,\frac{D_1}{D_2} < M_{11} < |M_{22}|\,, \quad \Rightarrow \quad \frac{D_2}{D_1} > \frac{|M_{22}|}{M_{11}} > 1\,. \quad (4.61)$$

The negative diagonal term thus corresponds to the faster diffusing component. Since negative terms are usually associated with inhibition, the above conclusion can be summarized somewhat imprecisely by the statement that finite wavelength instabilities arise from a combination of *long-range inhibition and short-range excitation.* Since $M_{11}M_{22}$ is now negative, the additional requirement $\det M(0) = M_{11}M_{22} - M_{12}M_{21} > 0$, implies that the off-diagonal terms M_{12} and M_{21} must have opposite signs, with a product larger than $-M_{11}M_{22}$. If both elements of the top row are positive, the species 1 being both self and cross excitatory, the instability occurs when the two components are out of phase; otherwise the two species will vary in phase.

While necessary, the conditions in Eq. (4.61) is not sufficient for instability, as the value of the product in Eq. (4.58) must be negative at its maximum if $\lambda_+(k_m) > 0$ while $\lambda_-(k_m) < 0$, and thus we must require

$$\begin{aligned}\lambda_+(k_m)\lambda_-(k_m) &= \det M(0) - \frac{(M_{11}D_2 + M_{22}D_1)^2}{4D_1D_2} < 0 \\ \Rightarrow \qquad & (M_{11}D_2 + M_{22}D_1) > 2\sqrt{D_1D_2 \det M(0)}\,, \end{aligned} \quad (4.62)$$

which is a much more restrictive condition on the ratio D_2/D_1. For example, in case of the matrix

$$M(k) = \begin{pmatrix} 1 - D_1 k^2 & 1 \\ -3 & -2 - D_2 k^2 \end{pmatrix} , \tag{4.63}$$

the condition in Eq. (4.61) requires $D_2/D_1 > 2$, while Eq. (4.62) is satisfied for $D_2/D_1 > 4 + 2\sqrt{3} \approx 7.5$. The milder condition may in fact be sufficient to lead to transient "quasi-patterns" in the presence of noise[3].

Let us generalize Eq. (4.52)

$$\frac{\partial C_i}{\partial t} = F_i\left(\{C_j\}\right) + D_i \nabla^2 C_i + \eta(\vec{x}, t) , \tag{4.64}$$

to include a stochastic term $\eta(\vec{x}, t)$. For microscopic systems the noise could be due to thermal fluctuations, in macroscopic systems it could be due to variations in the environment. For chemical reactions, the intrinsic stochasticity of rate equations leads to typical $\sqrt{N}$ fluctuations for a finite number N of molecules. For simplicity we assume that the stochastic fluctuations are described by white noise with co-variance

$$\langle \eta(\vec{x}, t)\eta(\vec{x}', t')\rangle = 2N\delta(t - t')\delta^d(\vec{x} - \vec{x}') . \tag{4.65}$$

The noisy version of Eq. (4.55) is now

$$\frac{d\tilde{c}_i(\vec{k}, t)}{dt} = \sum_j \left(M_{ij} - \delta_{ij} D_i k^2\right) c_j(\vec{k}, t) + \tilde{\eta}(\vec{k}, t) , \tag{4.66}$$

with

$$\langle \eta(\vec{k}, t)\eta(\vec{k}', t')\rangle = \frac{2N}{(2\pi)^d}\delta(t - t')\delta^d(\vec{k} + \vec{k}') . \tag{4.67}$$

For a single (stable) variable c, it is easy to show that in steady state $\langle|\tilde{c}(\vec{k})|^2\rangle \propto N/\lambda(\vec{k})$. For the many variable case in Eq. (4.66) the power-spectrum of fluctuations in steady state is inversely proportional to $\det M(k)$ in Eq. (4.58). It is now easy to see that the peak in the power spectrum for the transient noisy fluctuations in concentration moves from $\vec{k} = 0$ to a finite wave-number k_m when $D_2/D_1 > |M_{22}|/M_{11}$.

4.7 Oscillatory patterns

There are also examples, such as for the Belousov?Zhabotinsky reaction, in which the fully mixed system simply oscillates, but otherwise forms oscillating patterns including spirals. There are other examples of "active membranes" is biology, such as cardiac tissue in which similar patterns are observed. Can we follow the reasoning of Turing to justify the appearance of oscillating patterns of *finite wavelength* from a collection of reaction diffusion equations as in Eqs.(4.52)?

[3]See "Fluctuation-driven Turing patterns," by T. Butler and N. Goldenfeld, in Phys. Rev. E **84**, 011112 (2011).

In this case, the $k = 0$ state corresponds to an oscillatory instability described by a pair of complex conjugate eigenvalues, $\lambda_\pm = \epsilon \pm i\omega$, with positive real part ($\epsilon > 0$). For a two component system, with diffusivities D_1 and D_2 since $\mathrm{tr}M(k) = \mathrm{tr}M(0) - k^2(D_1 + D_2)$, the real part is monotonically decreased to $\epsilon(k) = \epsilon - k^2(D_1 + D_2)/2$. Maximal instability still corresponds to $k = 0$, and no finite wavelength is selected. Thus, at least three components are needed to generate finite wavelength patterns in this context. A possible set of equations are:

$$\begin{aligned}
\frac{\partial c_+}{\partial t} &= F_+(c_+, c_-, c_0) + D_+\nabla^2 c_+ &&= \epsilon c_+ - \omega c_- + \gamma c_0 + D_+\nabla^2 c_+ + \cdots \\
\frac{\partial c_-}{\partial t} &= F_+(c_+, c_-, c_0) + D_-\nabla^2 c_- &&= \omega c_+ - \epsilon c_- + \gamma c_0 + D_-\nabla^2 c_- + \cdots \\
\frac{\partial c_0}{\partial t} &= -F_+ - F_- + D_0\nabla^2 c_0 &&= (\omega - \epsilon)c_+ - (\omega + \epsilon)c_- - 2\gamma c_0 + D_0\nabla^2 c_0 + \cdots .
\end{aligned} \tag{4.68}$$

Note that to illustrate a different point, the selected equations are chosen so as to conserve the total number $\int(c_+ + c_- + c_0)$. The stability matrix is then given by

$$M(k) = \begin{bmatrix} \epsilon - D_+k^2 & \omega & \gamma \\ -\omega & \epsilon - D_-k^2 & \gamma \\ \omega - \epsilon & -\omega - \epsilon & -2\gamma - D_0k^2 \end{bmatrix} . \tag{4.69}$$

At $k = 0$, the three eigenvalues of the matrix are $\lambda_0 = 0$ (a consequence of the conservation condition), and $\lambda_\pm = \epsilon - \gamma \pm i\sqrt{\omega^2 - \gamma^2}$. The coupling to γ thus reduces both the real and imaginary parts of the oscillatory unstable eigenvalues(compared to Eqs.(4.37)), but the character of the instability is not modified if γ is smaller than both ϵ and ω. The sum of the eigenvalues is still reduced at finite k by $-k^2(D_+ + D_- + D_0)$. However, it is still possible that (as in the case of the Turing system) the reduction of the $\lambda_0(k)$ compensates for an initial increase in the reals parts of $\lambda_\pm(k)$. A particular example (for $\epsilon = 2$, $\omega = 3$, $\gamma = 1$, $D_+ = D_- = 1/20$, and $D_0 = 2$) is plotted below, demonstrating maximal instability at a finite wavelength.