4.5 Synchronization

We have established how simple chemical reactions can create an oscillator. The phase of such simple oscillators is set by initial conditions. In certain situations, e.g. for the pacemaker cells in the heart, the oscillators must act in concert. One way to synchronize a number of oscillators is to couple them to an external source, as in the light of the sun in case of circadian rhythms. In other cases, a collection of self–coupled oscillators may spontaneously synchronize as a collective. The following *Kuramoto model* provides an explanation of how such synchronization may happen.

Consider a set of oscillators, each parametrized by a phase angle θ_i, for $i = 1, 2, \cdots, N$. We shall assume that each oscillator advances at a uniform angular velocity ω_i, taken independently from a probability distribution function $p(\omega)$, such that

$$\dot{\theta}_i = \omega_i.$$

In a biological context the rate ω for a collection of cells (or organisms) may well depend on the concentration of chemicals within it. While these concentrations vary between individuals, it is likely that for a specific system the range of this variation is small, and the distribution is narrowly peaked around some central frequency Ω. Without loss of mathematical rigor we can set $\Omega = 0$, which is equivalent to measuring angles relative to a frame rotating at angular velocity Ω (i.e. after a shift $\theta_i \rightarrow \theta_i - \Omega t$).

To synchronize the oscillators we need a coupling between their phases. The simplest form of such coupling, pushing θ_i towards θ_j, and independent of a phase change by 2π, is $\sin(\theta_j - \theta_i)$. The coupled dynamics of phases of many such oscillators is now governed by

$$\dot{\theta}_i = \omega_i + \sum_{j=1}^{N} W_{ij} \sin(\theta_j - \theta_i), \tag{4.37}$$

where W_{ij} indicates the strength of the coupling to j from i. To make analytical progress, we shall assume that all interactions have the same value of K/N. (As each oscillator is coupled to N others, it makes sense to scale the interaction parameter by N.) In this case, we can re-write Eq. (4.37) as

$$
\begin{aligned}
\dot{\theta}_i &= \omega_i + K\Im\left[e^{-i\theta_i} \left(\frac{\sum_{j=1}^{N} e^{i\theta_j}}{N} \right) \right] \\
&= \omega_i + K\Im\left[m e^{i\phi} \right], \tag{4.38}
\end{aligned}
$$

where $\Im$ stands for the imaginary part, and we have indicated the average of all phase points (around the complex imaginary circle) by $m e^{i\phi}$. The *order parameter*

$$m = \left| \frac{\sum_{j=1}^{N} e^{i\theta_j}}{N} \right|, \tag{4.39}$$

is a measure of synchronization amongst the oscillators. If each oscillator follows its own period, perhaps somewhat altered by the others, the phases in Eq. (4.39) will shift with time

more or less independently, eventually coving the unit circle, in which case the average over them will be zero. If a finite fraction of the oscillators is locked to the central frequency Ω (thus appearing stationary in our rotating frame), their contributions will be time independent, and (if more or less in phase) add us to a finite value. Without loss of generality, we can set the overall phase of the sum to zero, $\phi = 0$, resulting in the self-consistent set of equations

$$\dot{\theta}_i = \omega_i - Km \sin \theta_i \,. \tag{4.40}$$

The solutions to this equation have two possible forms, mimicking the two populations of oscillators. The first set includes oscillators locked to the central frequency, hence with $\dot{\theta}_i = 0$. To satisfy Eq. (4.40), these oscillators acquire a "phase lag"

$$\sin \theta_i = \frac{\omega_i}{Km} \,. \tag{4.41}$$

Such locking is possible only if the natural frequency of the oscillator is sufficiently close to the central frequency, i.e. as long as $|\omega_i| < Km$. Oscillators with frequency difference $|\omega_i| > Km$ cannot be synchronized to the central frequency, and their phases vary over time according to

$$\dot{\theta}_i = \omega_i - Km \sin(\theta_i) \neq 0 \,. \tag{4.42}$$

We can self-consistently solve for m by summing over the phase contributions of the stationary oscillators (the moving ones do not contribute to m). Since the behavior of the locked oscillators depends only on their native frequency, we can use the probability density $p(\omega)$ to write

$$m = \frac{1}{N} \sum_{\text{locked oscillators } j} e^{i\theta_j} = \int_{-Km}^{Km} d\omega \, p(\omega) e^{i\theta(\omega)} \,. \tag{4.43}$$

We can change variables to $\theta = \arcsin(\omega/Km)$, and expand the narrow distribution to second order around its peak to simplify the self-consistency equation to

$$
\begin{aligned}
m &= \int_{-\pi/2}^{\pi/2} d\theta (Km \cos \theta) p(Km \sin \theta) e^{i\theta} \\
&= \int_{-\pi/2}^{\pi/2} d\theta (Km \cos \theta) \left[p(0) - \frac{(Km \sin \theta)^2}{2} |p''(0)| + \cdots \right] (\cos \theta + i \sin \theta) \\
&= Km \left[\frac{\pi}{2} p(0) - \frac{k^2 m^2 \pi}{8} |p''(0)| + \cdots \right] \,.
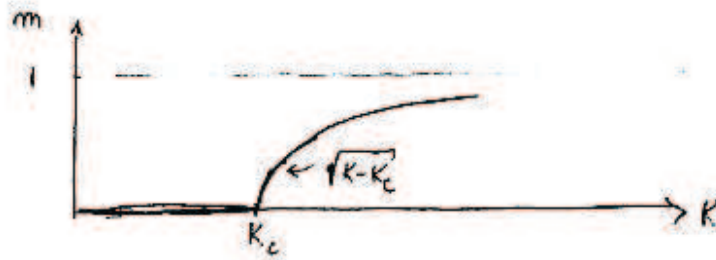\end{aligned}
\tag{4.44}
$$
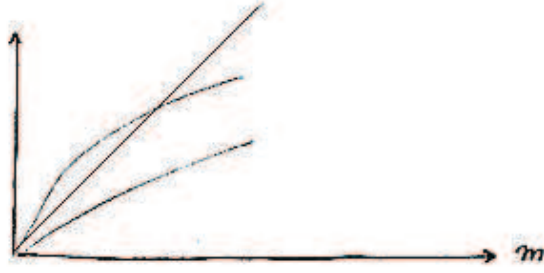
A non-zero solution for m is possible only for

$$K > K_c = \frac{2}{\pi p(0)}. \tag{4.45}$$

Below K_c, $m = 0$ is the only solution, and all oscillators are unlocked. For larger couplings the oscillators are synchronized and rotate together, while on reducing the coupling to its critical value the order parameter vanishes as

$$m \propto \sqrt{K - K_c}. \tag{4.46}$$

For example, if $p(\omega)$ can be approximated by a Gaussian distribution of width σ,

$$K_c = \sqrt{\frac{8}{\pi}}\sigma, \quad \text{and} \quad m \simeq \sqrt{2\pi\left(\frac{K}{K_c} - 1\right)}. \tag{4.47}$$

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 in 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,

85

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

$$\frac{\partial C_i}{\partial t} = F_i\left(\{C_j\}\right) + D_i \nabla^2 C_i\,. \tag{4.48}$$

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. (4.48).

Let us specifically ask if it is possible to have a stable fixed point $\{C_i^*\}$ as solution to Eqs. (4.48) *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

$$C_i(\vec{r}, t) = C_i^* + c_i(\vec{r}, t)\,, \quad \Rightarrow \quad \frac{\partial c_i}{\partial t} = \sum_j M_{ij} c_j + D_i \nabla^2 c_i\,, \quad \text{with} \quad M_{ij} = \left.\frac{\partial F_i}{\partial C_j}\right|_{C^*}\,. \tag{4.49}$$

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

$$c_i(\vec{r}, t) = \int d\vec{k}\, e^{i\vec{k}\cdot\vec{r}} \tilde{c}_i(\vec{k}, t)\,, \tag{4.50}$$

in terms of which Eq. (4.49) becomes

$$\frac{d\tilde{c}_i(\vec{k}, t)}{dt} = \sum_j \left(M_{ij} - \delta_{ij} D_i k^2\right)\,. \tag{4.51}$$

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

$$M(k) = \begin{pmatrix} M_{11} - D_1 k^2 & M_{12} \\ M_{21} & M_{22} - D_2 k^2 \end{pmatrix}\,. \tag{4.52}$$

The product of the two eigenvalues is given by the determinant of the above matrix as

$$\begin{aligned} \lambda_+(k)\lambda_-(k) &= \det M(k) \\ &= \left(M_{11} M_{22} - M_{12} M_{21}\right) - \left(M_{11} D_2 + M_{22} D_1\right) k^2 + D_1 D_2 k^4\,. \end{aligned} \tag{4.53}$$

At $k = 0$ (uniform state) both eigenvalues are by fiat negative, and thus $\det M(0)$ (the term within the first brackets above) is positive. It is possible that both eigenvalues remain negative at all wavevectors, as depicted by the curves marked by 1 and 2 in the Figure below. For the fixed point to become unstable to a perturbation at finite k, the larger eigenvalue, $\lambda_+(k)$, has to pass through zero and become positive. Note that since

$$\lambda_+(k) + \lambda_-(k) = \text{tr}M(k) = (M_{11} + M_{22}) - (D_1 + D_2)k^2 \,, \tag{4.54}$$

the other eigenvalue, $\lambda_-(k)$, has to become even more negative. Since both the first and last terms in Eq. (4.53) are positive, a change of sign for the eigenvalue is only possible if the middle term is large and positive, i.e.

$$(M_{11}D_2 + M_{22}D_1) > 0 \,, \quad \text{while} \quad (M_{11} + M_{22}) < 0 \,. \tag{4.55}$$

(The latter is required by the stability condition for $k = 0$.) If so, then Eq. (4.53) can describe a curve that crosses zero at two points, k_+ and k_-, with a maximum at an intermediate k_m. There will then be a band of unstable modes spanning wave-numbers from k_- to k_+ (curves labelled by 3 in the figure), and by setting this equation (and its derivative) to zero, it is easily checked that

$$k_+^2 + k_-^2 = 2k_m^2 = \frac{M_{11}D_2 + M_{22}D_1}{D_1 D_2} \,. \tag{4.56}$$

87
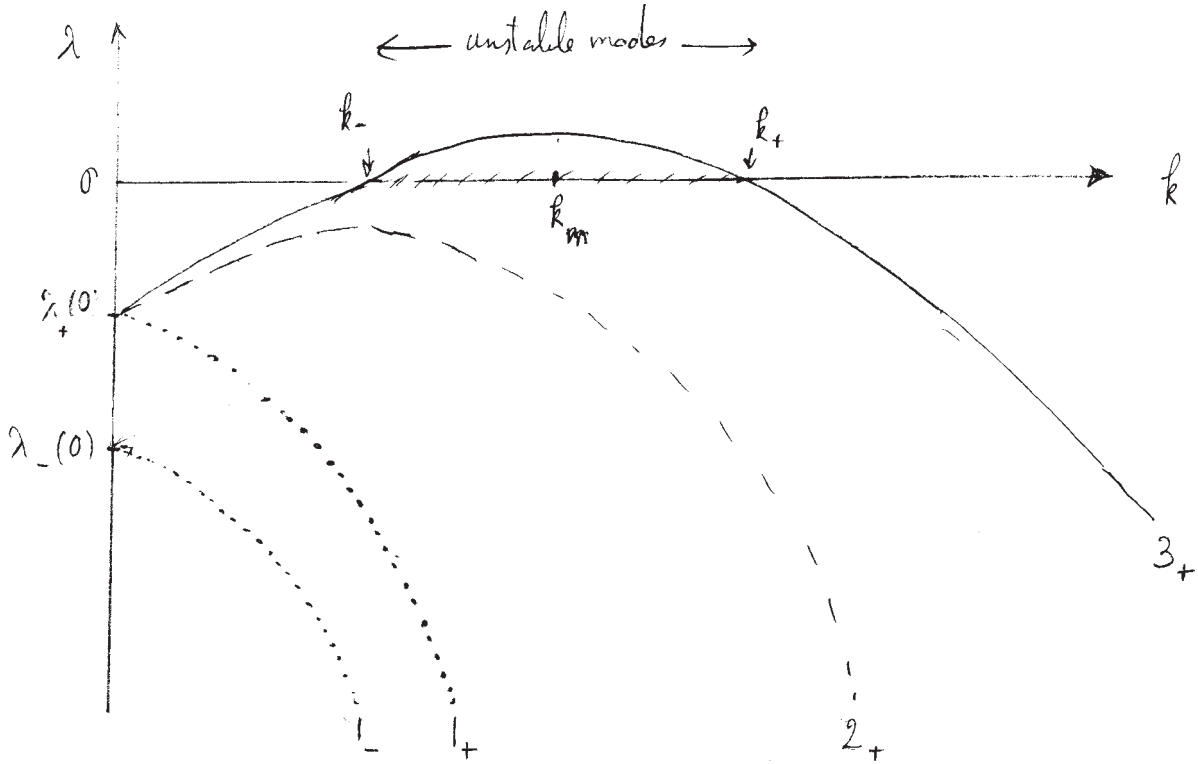
The value of the product in Eq. (4.53) must be negative at its maximum if $\lambda_+(k_m) > 0$ while $\lambda_-(k_m) < 0$, and thus we must require

$$
\begin{aligned}
\lambda_+(k_m)\lambda_-(k_m) &= \det M(0) - \frac{(M_{11}D_2 + M_{22}D_1)^2}{4D_1D_2} < 0 \\
&\Rightarrow \quad (M_{11}D_2 + M_{22}D_1) > 2\sqrt{D_1D_2 \det M(0)}\,.
\end{aligned}
\tag{4.57}
$$

Clearly the conditions in Eq. (4.55) cannot be simultaneously satisfied if both M_{11} and M_{22} are negative, or if both diffusion coefficients have the same value. Let us suppose that $M_{11} < 0$ and $M_{22} > 0$, in which case the requirement is

$$
|M_{11}|\frac{D_2}{D_1} < M_{22} < |M_{11}|\,, \quad \Rightarrow \quad D_1 > D_2\,.
\tag{4.58}
$$

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 competition of *long-range inhibition* and *short-range excitation*. In fact, 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. If $M_{12} < 0$, species 1 being both self and cross inhibitory, the instability occurs when the two components are out of phase; otherwise the two species will vary in phase. In the extreme limit of $D_2 = 0$ and $M_{22} < 0$ instability sets in for all wavenumbers with $k^2 > k_-^2 = \det M(0)/(M_{22}D_1)$. Of course, in all cases the instability wavelength must be large enough so that the assumptions implicit in the continuum formulation of reaction-diffusion equations remain valid.

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