7 Pattern formation, diffusion-driven instability (Murray II: Ch. 2.1-2.4,3.1)

Biology is rich of patterns, some examples being

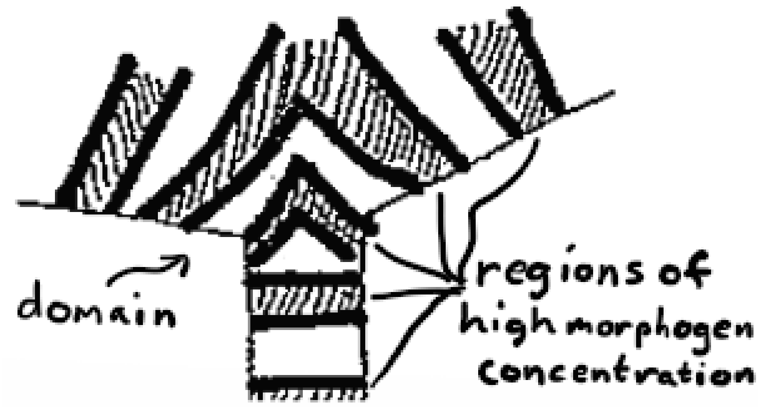
- Patterns in animal coating, snake skins, butterfly wings etc.
- Spatial organisation in initially homogeneous embryo to form an individual.
- Patterning principles of bacteria (forming complex patterns).
- Patchiness in ecology.

This lecture addresses formation of stationary patterns in reaction-diffusion systems. Wave-like spatio-temporal patterns are addressed in the next lecture.

7.1 Morphogenesis (MII 2.1)

The field of Morphogenesis concerns biological processes that determine biological shape and structure in an organism. These processes are in general poorly understood. It is clear that the processes must be genetically controlled, but the genes themselves cannot create the structure.

One possible mechanism for explaining the pattern formation of animal coating (and other morphogenesis) is the following: the genetic code gives the parameters for a reaction-diffusion process which show stationary non-homogeneous spatial patterns. The process describes the concentration of a morphogen at an early stage of the development of an organism. A morphogen is a chemical that is involved in morphogenesis, for example by creating black color in regions where morphogen concentration is high:



The mechanism that causes patterns in concentration to form from an initial close-to homogeneous concentration is the diffusion-driven instability (Turing instability, Turing 1952).

7.2 Diffusion-driven instability (MII 2.2)

Consider a reaction-diffusion model for coupled concentrations of two morphogens, an 'activator' $n_A(\boldsymbol{r}', t')$ and an 'inhibitor' $n_I(\boldsymbol{r}', t')$:

$$
\begin{aligned}
\frac{\partial n_A}{\partial t'} &= f_A(n_A, n_I) + D_A \nabla'^2 n_A \\
\frac{\partial n_I}{\partial t'} &= f_I(n_A, n_I) + D_I \nabla'^2 n_I
\end{aligned} ,
$$

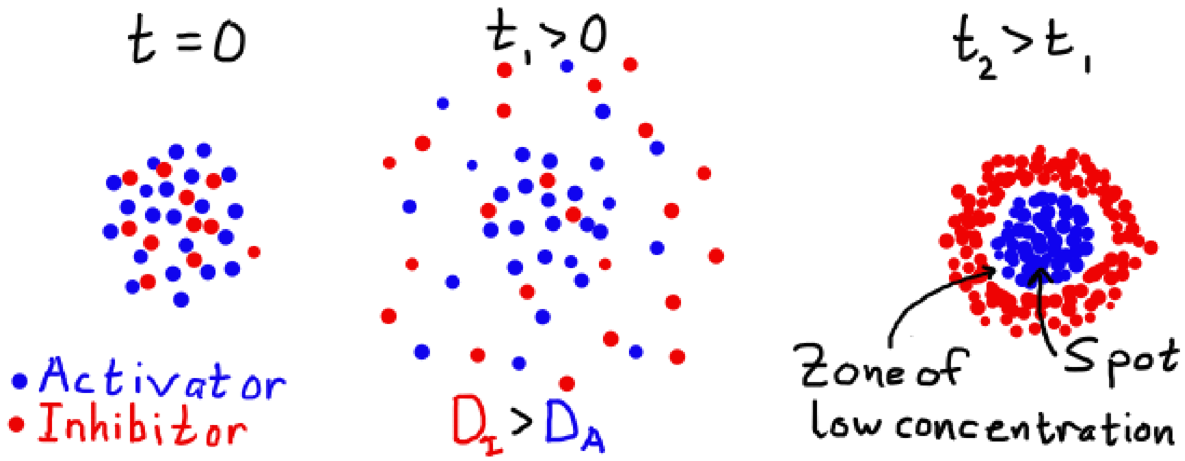
where $0 < D_A < D_I$, t' and $\boldsymbol{r}'$ are time and space in dimensional units, and $\boldsymbol{\nabla}' = (\frac{\partial}{\partial r'_1}, \ldots, \frac{\partial}{\partial r'_{\mathrm{dim}}})$ is the Del operator in dim dimensions.
Initial condition Assume that $n_{A,I}(\boldsymbol{r}', t' = 0)$ are given functions
Boundary condition Assume no flux through system boundary:

$$
\boldsymbol{\nabla}'_{\boldsymbol{e}} n_{A,I}(\boldsymbol{r}', t')|_{\boldsymbol{r}' \in \mathrm{boundary}} = 0 ,
$$

with $\boldsymbol{e}$ the unit vector normal to the system boundary and $\boldsymbol{\nabla}'_{\boldsymbol{e}} \equiv \boldsymbol{e} \cdot \boldsymbol{\nabla}'$ the directional derivative in direction $\boldsymbol{e}$. The no-flux boundary condition implies that the system is not influenced from the outside, i.e. emerging patterns are self-organising.

Basic mechanism Assume f_I, f_A chosen such that n_{A} (activator) stimulates production of n_{I} and n_{I}(inhibitor) slows production of n_{A}.

Assume that if the diffusion constants vanish, $D_\mathrm{A} = D_\mathrm{I} = 0$, the system tends to a linearly stable uniform steady state. Now, since $0 < D_\mathrm{A} < D_\mathrm{I}$ the inhibitor n_I spreads quicker than the activator n_A. Assume that a small spatial region initially has higher concentrations of n_A and n_I than its surroundings. Since $D_\mathrm{I} > D_\mathrm{A}$, n_I spreads faster and dominates and inhibits growth of the activator in the surroundings, but leaves an excess of n_A in the original area. As a result, we may obtain a concentration of n_A surrounded by n_I; a spot is formed:



Several random initial regions of higher concentration may lead to spotted patterns (or channels if activators spread quick enough). This mechanism allows for spatially heterogeneous, time-independent, stable solutions (patterns). This may be unexpected, because without the reaction term, diffusion smoothens concentrations, here it is responsible for patterns.

7.3 Stability to spatial perturbations (MII 2.3)

To investigate the diffusion-driven instability mathematically, we make a perturbation around a stable homogeneous steady state.

7.3.1 Homogeneous steady states

Change to vector notation and dimensionless units: $\boldsymbol{r} = \boldsymbol{r}'/L$ and $t = t'D_A/L^2$, where L is the linear size of the spatial domain:

$$\frac{\partial \boldsymbol{n}}{\partial t} = \boldsymbol{f}(\boldsymbol{n}) + \nabla^2 \mathbb{D}\boldsymbol{n}\,, \quad \mathbb{D} = \begin{pmatrix} 1 & 0 \\ 0 & d \end{pmatrix}. \tag{1}$$

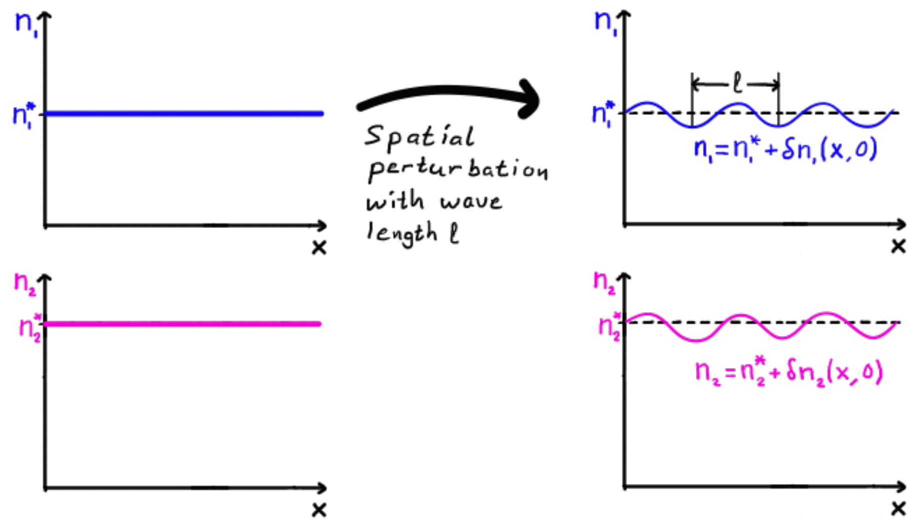
Here $\boldsymbol{n} = (n_A, n_I)L^{\rm dim}$, $\boldsymbol{f} = (f_A, f_I)L^{2+\rm dim}/D_A$ and $d = D_I/D_A > 1$. Interchanging n_A and n_I gives the case $d < 1$. Homogeneous solutions (no spatial dependence in $\boldsymbol{n}$) to Eq. (1) are governed by $\dot{\boldsymbol{n}} = \boldsymbol{f}(\boldsymbol{n})$. Relevant steady states are given by positive zeroes $\boldsymbol{n}^*$ such that $\boldsymbol{f}(\boldsymbol{n}^*) = 0$. Their linear stability is determined by the eigenvalues $\lambda_\pm^{(\mathbb{J})}$ of the stability matrix $\mathbb{J}(\boldsymbol{n}^*)$:

$$\mathbb{J}(\boldsymbol{n}^*) = \left.\begin{pmatrix} \frac{\partial f_1}{\partial n_1} & \frac{\partial f_1}{\partial n_2} \\ \frac{\partial f_2}{\partial n_1} & \frac{\partial f_2}{\partial n_2} \end{pmatrix}\right|_{\boldsymbol{n}=\boldsymbol{n}^*}, \quad \lambda_\pm^{(\mathbb{J})} = \frac{1}{2}\Big(\mathrm{tr}\mathbb{J} \pm \sqrt{(\mathrm{tr}\mathbb{J})^2 - 4\det\mathbb{J}}\Big). \quad (2)$$

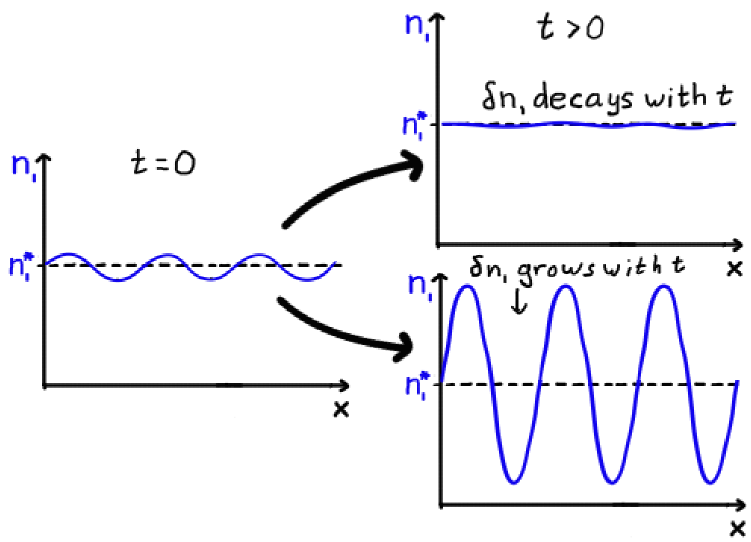
Since the steady state is stable, all eigenvalues have negative real part, i.e. $\mathrm{tr}\mathbb{J} < 0$ and $\det\mathbb{J} > 0$ must be satisfied for our steady state.

7.3.2 Small spatial perturbation

Assume $\boldsymbol{n}^*$ is stable and consider a small spatio-temporal perturbation $\delta\boldsymbol{n}(\boldsymbol{r}, t)$ to the homogeneous steady state, $\boldsymbol{n} = \boldsymbol{n}^* + \delta\boldsymbol{n}(\boldsymbol{r}, t)$. Example in one spatial dimension:



The perturbations δn_1 and δn_2 may grow or decay with time:



The stability could depend on the wave length ℓ: when $\ell \to \infty$ (homogeneous case) the system is stable.

Insert $\boldsymbol{n} = \boldsymbol{n}^* + \delta\boldsymbol{n}(\boldsymbol{r}, t)$ into Eq. (1), keeping only terms to first order in $\delta\boldsymbol{n}$:

$$\frac{\partial}{\partial t}(\boldsymbol{n}^* + \delta\boldsymbol{n}) = \boldsymbol{f}(\boldsymbol{n}^* + \delta\boldsymbol{n}) + \nabla^2\mathbb{D}(\boldsymbol{n}^* + \delta\boldsymbol{n}) \,,$$

$$\Rightarrow \frac{\partial}{\partial t}\delta\boldsymbol{n} = \mathbb{J}(\boldsymbol{n}^*)\delta\boldsymbol{n} + \nabla^2\mathbb{D}\delta\boldsymbol{n} \tag{3}$$

with $\mathbb{J}(\boldsymbol{n})$ being the stability matrix in Eq. (2).

Separation of variables This equation is separable, make ansatz $\delta\boldsymbol{n}(\boldsymbol{r}, t) = T(t)R(\boldsymbol{r})\delta\boldsymbol{n}_0$ with constant $\delta\boldsymbol{n}_0$

$$\frac{\partial}{\partial t}T(t)R(\boldsymbol{r})\delta\boldsymbol{n}_0 = T(t)R(\boldsymbol{r})\mathbb{J}(\boldsymbol{n}^*)\delta\boldsymbol{n}_0 + T(t)\nabla^2R(\boldsymbol{r})\mathbb{D}\delta\boldsymbol{n}_0$$

$$\Rightarrow \frac{1}{T(t)}\frac{\partial}{\partial t}T(t)\delta\boldsymbol{n}_0 = \mathbb{J}(\boldsymbol{n}^*)\delta\boldsymbol{n}_0 + \frac{\nabla^2R(\boldsymbol{r})}{R(\boldsymbol{r})}\mathbb{D}\delta\boldsymbol{n}_0 \,. \tag{4}$$

Since the right-hand side does not depend on t we must have

$$\frac{1}{T(t)}\frac{\partial}{\partial t}T(t) = \lambda = \text{const.} \quad \Rightarrow \quad T(t) = T(0)e^{\lambda t} \,.$$

Similarly we must have

$$\frac{\nabla^2R(\boldsymbol{r})}{R(\boldsymbol{r})} = -k^2 = \text{const.} \tag{5}$$

This is the Helmholz equation. The choice of the form $-k^2$ for the separation coefficient is natural for most zero-flux boundary conditions. Solutions $R(\boldsymbol{r})$ describe spatial waves with wave number k. Eq. (5) can be solved by separation of variables, 2D example: $R(\boldsymbol{r}) = X(x)Y(y) \Rightarrow R(\boldsymbol{r}) \sim e^{\mathrm{i}(k_x x + k_y y)}$. This solution is natural for rectangular domains, but for other shapes (circular etc.) it may be useful to first change coordinates before separation of the spatial variables.

7.3.3 Eigenvalue analysis

As the following analysis shows, we do not need to explicitly solve Eq. (5) to find the stability conditions due to spatial perturbations. Using $\partial T/\partial t = \lambda T$ and $\nabla^2 R = -k^2 R$ in Eq. (4), we find an equation relating the constants λ, and k

$$\lambda \delta \boldsymbol{n}_0 = \mathbb{J}(\boldsymbol{n}^*)\delta \boldsymbol{n}_0 - k^2 \mathbb{D}\delta \boldsymbol{n}_0 = [\underbrace{\mathbb{J}(\boldsymbol{n}^*) - k^2\mathbb{D}}_{\mathbb{K}(k)}]\delta \boldsymbol{n}_0$$

This is the equation for the eigenvalues $\lambda(k)$ and eigenvectors $\delta\boldsymbol{n}_0(k)$ of the matrix $\mathbb{K}(k)$. The eigenvalues are given by

$$\det[\lambda\mathbb{I} - \mathbb{K}] = 0 \quad \Rightarrow \quad \lambda^2 - \mathrm{tr}\mathbb{K}\,\lambda + \det\mathbb{K} = 0\,.$$

with solutions $\lambda_\pm(k)$. Since $\mathrm{tr}\mathbb{K}$ is negative for all values of k:

$$\mathrm{tr}\mathbb{K} = \underbrace{\mathrm{tr}\mathbb{J}}_{<0} - \mathrm{k}^2\mathrm{tr}\mathbb{D} < 0\,.$$

one eigenvalue $\lambda_-(k)$ has negative real part. For the second eigenvalue $\lambda_+(k)$ to be positive, corresponding to unstable perturbations, we search for values of k such that $\det\mathbb{K}(k) < 0$. Write

$$\det\mathbb{K} = \det(\mathbb{J} - k^2\mathbb{D}) = dk^4 - (dJ_{11} + J_{22})k^2 + \det\mathbb{J}\,. \tag{6}$$

Find range of k such that $\det\mathbb{K}(k) < 0$ by solving $\det\mathbb{K} = 0$ in Eq. (6)

$$k_\pm^2 = \frac{1}{2d}\left(dJ_{11} + J_{22} \pm \sqrt{(dJ_{11} + J_{22})^2 - 4d\det\mathbb{J}}\right)\,. \tag{7}$$

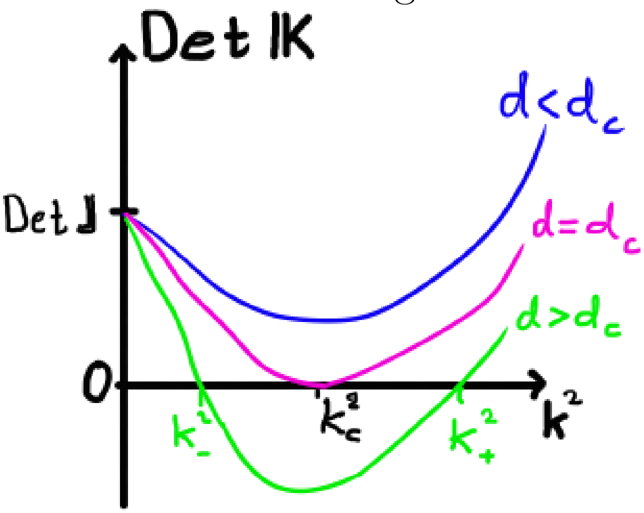
For $k_\pm^2$ to be real in Eq. (7), the square root must be real:

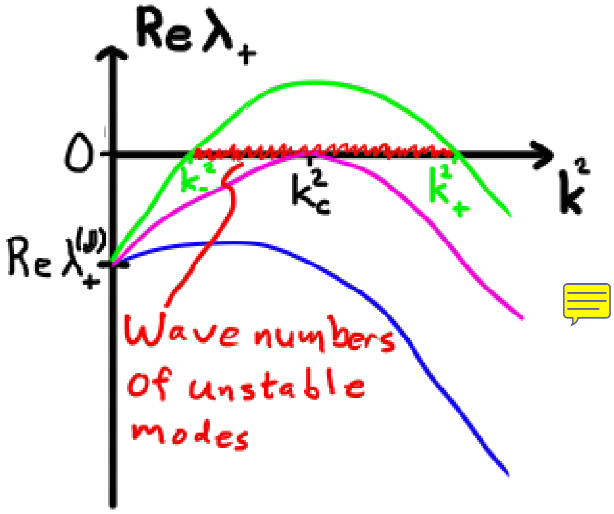
$$(dJ_{11}+J_{22})^2 - 4d\det\mathbb{J} \geq 0\,. \tag{8}$$

For $k_\pm^2$ to be positive in Eq. (7) (so that $k_\pm$ real) use that $\det\mathbb{J}>0$ $\Rightarrow$ the square root is smaller than $dJ_{11}+J_{22}$, i.e. $k_\pm^2 \geq 0$ if

$$dJ_{11}+J_{22} > 0\,. \tag{9}$$

When $k=0$ in Eq. (6), $\det\mathbb{K}=\det\mathbb{J}>0$ and for large k, $\det\mathbb{K}\sim dk^4>0$. If Eqs. (8) and (9) are satisfied, then $\det\mathbb{K}$ has two crossings with zero and it is negative for $k_- < k < k_+$:





In this range, the maximal eigenvalue λ_+ of $\mathbb{K}$ is positive. A bifurcation occurs at $d=d_\mathrm{c}$ where $k_+=k_-\equiv k_\mathrm{c}$. For $d>d_\mathrm{c}$ the homogeneous steady state is unstable to spatial perturbations in the range $k_-<k<k_+$. The condition $k_+=k_-$ in Eq. (7) is obtained by setting the discriminant to zero:

$$(d_\mathrm{c}J_{11}+J_{22})^2 - 4d_\mathrm{c}\det\mathbb{J} = 0$$

The largest solution ($d_\mathrm{c}>1$) defines d_c. At this bifurcation point

$$k_\mathrm{c}^2 = \frac{1}{2d_\mathrm{c}}\left(d_\mathrm{c}J_{11}+J_{22}\right)\,.$$

Note that $J_{ij}=\partial f_i/\partial n_j \propto L^2\partial f_{A|I}/\partial n_{A|I} \Rightarrow k_\pm \propto L$ in Eq. (7), i.e. the range of wave numbers $k_-<k<k_+$ giving rise to instabilities takes smaller values and becomes narrower if the system size L is decreased. Consequently, a small system can only have few waves (if any), and they must have low wave numbers.

7.3.4 Summary of conditions to have Turing instability

Conditions for the homogeneous steady state to be stable:

$$\mathrm{tr}\mathbb{J} < 0 \text{ and } \det\mathbb{J} > 0 .$$

Conditions for system to be unstable for a range of wave numbers ($\det\mathbb{K} < 0$) is given by Eqs. (8) and (9) (remove equality in Eq. (8) since it corresponds to a marginal case)

$$dJ_{11} + J_{22} > 0 \text{ and } \frac{(dJ_{11}+J_{22})^2}{4d} > \det\mathbb{J} .$$

Here $\mathbb{J}$ is evaluated at the stable homogeneous steady state:

$$\mathbb{J} = \begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix} = \left.\begin{pmatrix} \frac{\partial f_1}{\partial n_1} & \frac{\partial f_1}{\partial n_2} \\ \frac{\partial f_2}{\partial n_1} & \frac{\partial f_2}{\partial n_2} \end{pmatrix}\right|_{\boldsymbol{n}=\boldsymbol{n}^*} .$$

From these conditions it follows that $d \neq 1$ (hence $d > 1$ as assumed earlier) and that the signs of the elements of $\mathbb{J}$ take one of the forms

$$\begin{pmatrix} + & + \\ - & - \end{pmatrix} , \begin{pmatrix} + & - \\ + & - \end{pmatrix} .$$

If the conditions above are fulfilled there exist a range of wave numbers for which the system is unstable. But depending on the boundary conditions we do not yet know if any of these ($k_- < k < k_+$) are allowed solutions.

7.4 Boundary conditions

We have found the following solutions to Eq. (3):

$$\delta\boldsymbol{n}_k(\boldsymbol{r},t) = e^{\lambda(k)t}R_k(\boldsymbol{r})\delta\boldsymbol{n}_0(k) ,$$

where $\lambda(k)$ are eigenvalues and eigenvectors to $\mathbb{K}(k)$, and $R_k(\boldsymbol{r})$ are solutions to the Helmholz equation $\nabla^2 R_k(\boldsymbol{r}) + k^2 R_k(\boldsymbol{r}) = 0$. Now we want to apply the initial condition $\delta\boldsymbol{n}(\boldsymbol{r}, t = 0)$ and the boundary condition

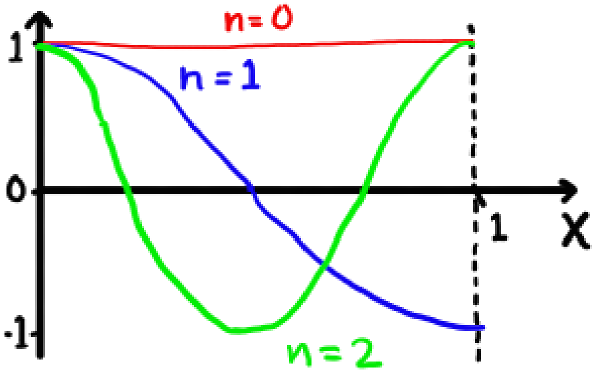
$$\boldsymbol{\nabla}_{\boldsymbol{e}}\delta\boldsymbol{n}|_{\boldsymbol{r}\in\text{boundary}} = 0 . \quad (\text{from } \boldsymbol{\nabla}_{\boldsymbol{e}}(\boldsymbol{n}^* + \delta\boldsymbol{n})|_{\boldsymbol{r}\in\text{boundary}} = 0)$$

7.4.1 Example: One-dimensional box between $0 \leq x \leq 1$

The solutions to Helmholz equation with no-flux boundary condition,

$$-\frac{\partial}{\partial x}R_k(x=0) = \frac{\partial}{\partial x}R_k(x=1) = 0\,,$$

are $R_k(x) = \cos(kx)$ with $k = 0, \pi, 2\pi, \ldots$.



Thus only discrete values of k are allowed: $k = n\pi$ with $n = 0, 1, 2, \ldots$ Note that the upper bound is $x = 1$ because x was scaled with system size L in the dedimensionalization.

7.4.2 Example: Two-dimensional box with unit side length

$$R_{k_{n,m}}(x,y) = \cos(\underbrace{n\pi}_{k_x} x)\cos(\underbrace{m\pi}_{k_y} y)$$

Solutions are labelled by $k_{n,m} = |\boldsymbol{k}| = \pi\sqrt{n^2+m^2}$ with integer n, m.

General boundary conditions on a finite domain Other shapes of the system boundary give more complicated solutions, but still only discrete values of k are allowed (assuming a finite domain). In general the solution satisfying the boundary condition is

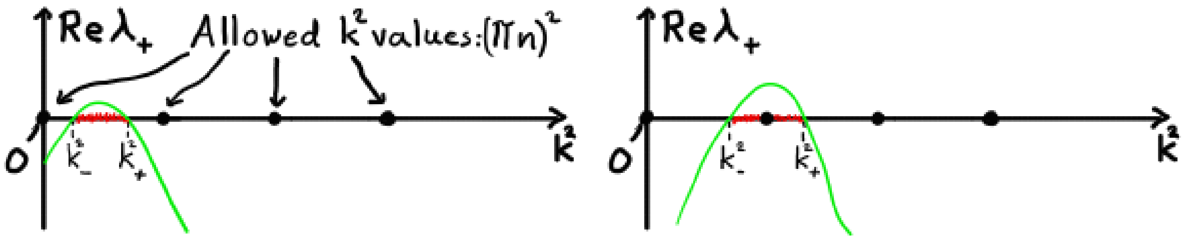
$$\delta\boldsymbol{n}(\boldsymbol{r},t) = \sum_k c_k e^{\lambda(k)t} R_k(\boldsymbol{r})\delta\boldsymbol{n}_0(k)\,,$$

where the sum runs over all allowed values of k and where the coefficients c_k are chosen so that the initial condition $\delta\boldsymbol{n}(\boldsymbol{r},0)$ is satisfied.

If any k with $k_- < k < k_+$ has non-zero c_k, the system is linearly unstable and spatial perturbations to the homogeneous stable state grow. When perturbations grow large, the system is assumed to be stabilized by non-linear contributions that determine the final pattern in the system. This pattern is related to the pattern created by the linear contribution, but not necessarily the same. Thus, the final pattern depends on a combination of the initial condition, the linear perturbation theory, and the non-linear effects of the system. If no k in $k_- < k < k_+$ has non-zero c_k, the system decays back to the spatially homogeneous solution after a small perturbation.

7.4.3 One-dimensional box revisited

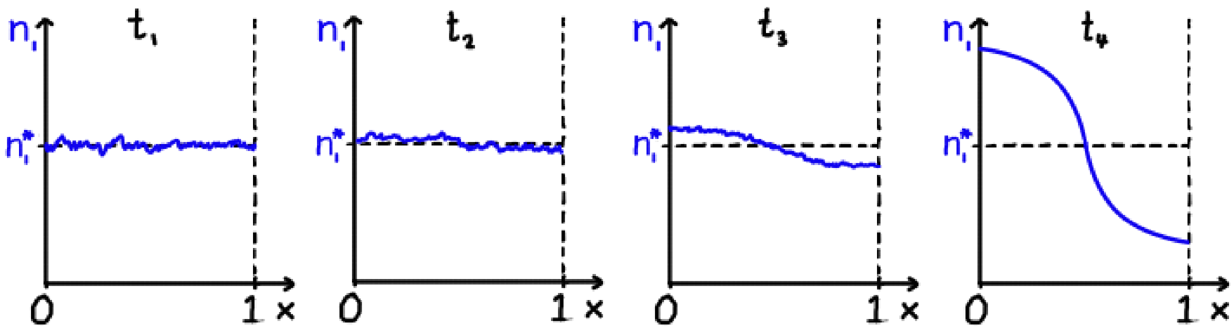
As seen above, solutions satisfying the boundary conditions in 1D are $R_k(x) = \cos(kx)$, where k takes discrete values $k = n\pi$ with $n = 0, 1, 2, \ldots$. Does any of these correspond to an unstable mode? $k = 0$ never leads to instability (stable homogeneous solution). What about $k = \pi$? As observed above, $k_+ \sim \sqrt{J_{ij}} \sim L$, so if the system size L is small enough then $k_+ < k = \pi$ and no allowed k-values exist between k_- and $k_+ \Rightarrow$ no instability possible (left panel below).



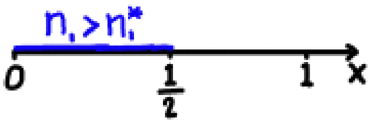
Increasing L so that exactly one mode, $k = \pi$, lies in $k_- < k < k_+$ (right panel above) we have

$$\boldsymbol{n} = \boldsymbol{n}^* + \delta\boldsymbol{n}\,,\ \text{with } \delta\boldsymbol{n} \sim e^{\lambda_+(\pi)t}\cos(\pi x)\delta\boldsymbol{n}_0^+(\pi)$$

where $\lambda_+(\pi)$ and $\boldsymbol{n}_0^+(\pi)$ are the positive eigenvalue and corresponding eigenvector of $\mathbb{K}$ when $k = \pi$. A small random perturbation decays in all modes except $k = \pi$ where it grows, illustrated below at successive times $t_1 < t_2 < t_3 < t_4$ (assume first component of $\delta\boldsymbol{n}_0^+(\pi)$ is positive)

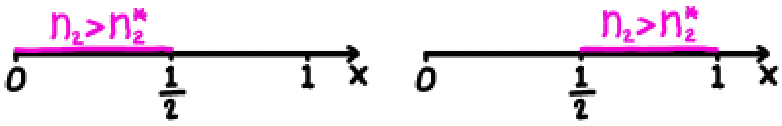


A pattern develops in n_1:

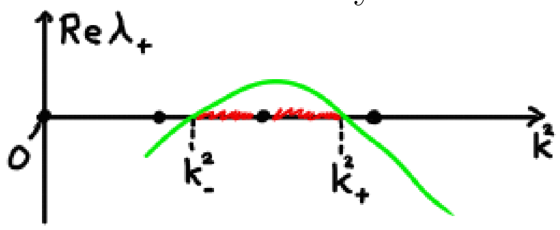


Similarly a pattern for n_2 emerges (which depends on the relative sign of the components in the eigenvector $\delta \boldsymbol{n}_0^+(\pi)$):

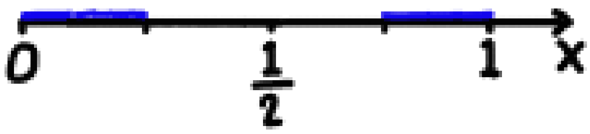
Same sign Opposite sign



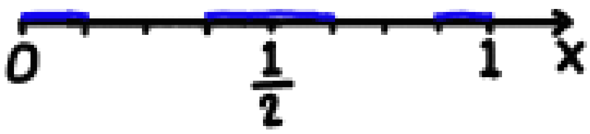
Now assume that only the mode $n = 2$ lies in $k_- < k < k_+$:



The corresponding pattern is ($n = 2$):

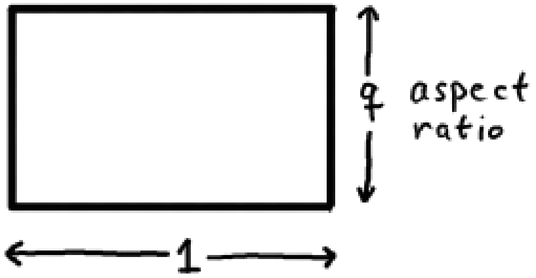


and so forth ($n = 4$):



7.5 Two-dimensional patterns (MII 2.4, 3.1)

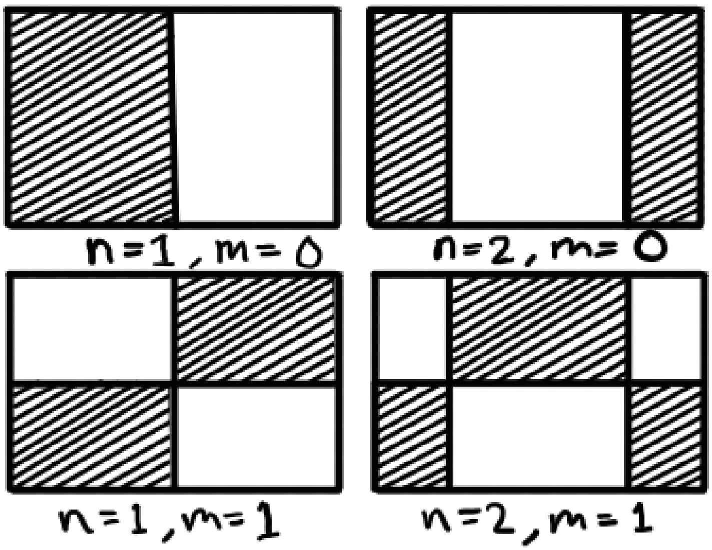
Two-dimensional rectangular boundary



Allowed solutions for the boundary conditions of this geometry are

$$R_{k_{n,m}}(x,y) = \cos(\underbrace{n\pi}_{k_x} x)\cos\left(\underbrace{\frac{m\pi}{q}}_{k_y} y\right).$$

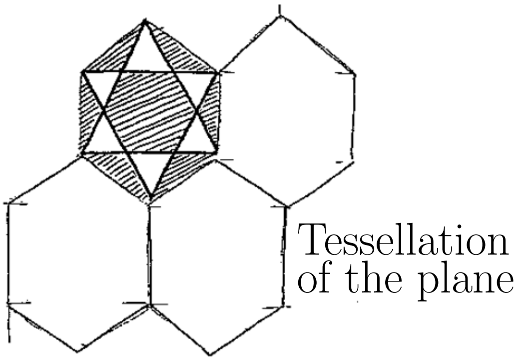
To have a Turing instability, we must have $k_- < \pi\sqrt{n^2 + (m/q)^2} < k_+$. Some patterns corresponding to a single wave vector $\boldsymbol{k} = (k_x, k_y) = \pi(n, m/q)$ in this range are (shaded regions corresponds to $n_1 > n_1^*$):

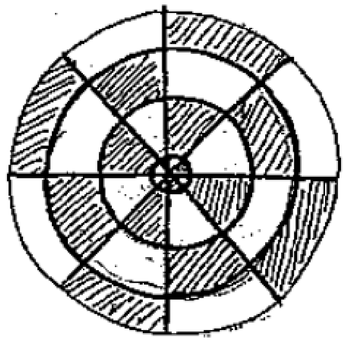


Less simple domains require the solution of the Helmholz equation (5)

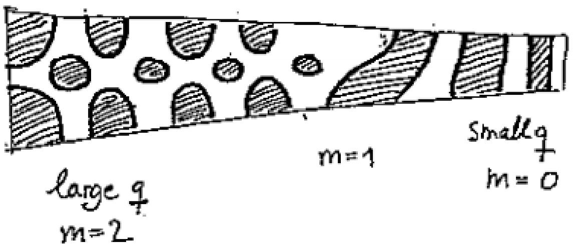
$$\nabla^2 R(\boldsymbol{r}) = -k^2 R(\boldsymbol{r}), \qquad \boldsymbol{\nabla}_{\boldsymbol{e}} R(\boldsymbol{r})|_{\boldsymbol{r}\in\text{boundary}} = 0. \tag{10}$$

Some symmetric domains have explicit solutions, such as the left panel below:

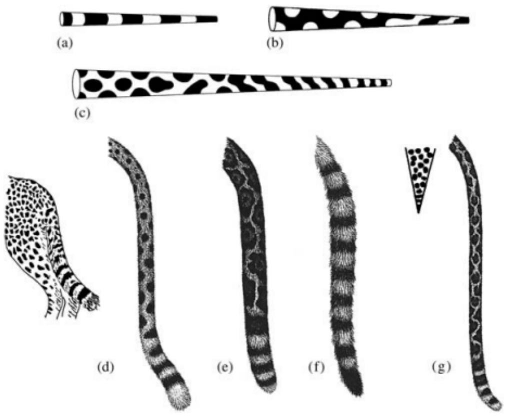




However, for most domains solutions must be found numerically, as for the circular domain (right panel above).
The linear stability theory outlined in this Lecture works well when the unstable modes have small wave numbers (large wave length). For example, consider shapes of tails or legs of animals:



As the aspect ratio q becomes smaller, the possible values of m that fits the range $k_- < \pi\sqrt{n^2 + (m/q)^2} < k_+$ becomes smaller. The resulting patterns have small wave numbers and remind of coating on spotted animals: striped tails. The following figure compares the patterns obtained from simulations of reaction diffusion equations on three domains (a)–(c) to typical tail markings of members of the cat family (d)–(g):



[Figure taken from Murray, *Mathematical Biology II* (2003)]

If you need more training, you can have a look at the training question on instabilities in activator inhibitor systems.