Lecture 7: Turing Patterns in biology

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Contents

Turing Patterns

Consider simple system with two components u(x.t) & v(x.t):

$$\frac{\partial u}{\partial t} = D_1 \nabla^2 u + f(u, v)$$

$$\frac{\partial v}{\partial t} = D_2 \nabla^2 v + g(u, v)$$

Turing instability if and only if:

$$\left.\begin{array}{ll} \text{I} & f_u + g_v < 0 \\ \text{II} & f_u g_v - f_v g_u > 0 \end{array}\right\}$$

System would have a STABLE steady state WHITOUT Diffusion

$$\left.\begin{array}{ll} \text{III} & D_1 g_v + D_2 f_u > 2\sqrt{D_1 D_2 (f_u g_v - f_v g_u)} \end{array}\right\}$$

But this uniform steady state is UNSTABLE in a system WITH Diffusion

Remark: I & III implies $D_1 \neq D_2$ (required but NOT sufficient!!)

Biochemical Implementation of the Turing Mechanism

Conditions for the Diffusion-driven Instability

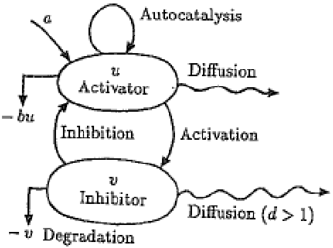
Conditions

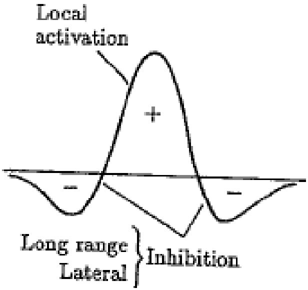
I.	$f_u + g_v < 0$	diagonal entries opposite signs
II.	$f_u g_v - f_v g_u > 0$	off-diagonal entries opposite signs
III.	$D_2 f_u + D_1 g_v > 0$	$D_1 \neq D_2$ different diffusion speeds

Activator - Inhibitor Systems

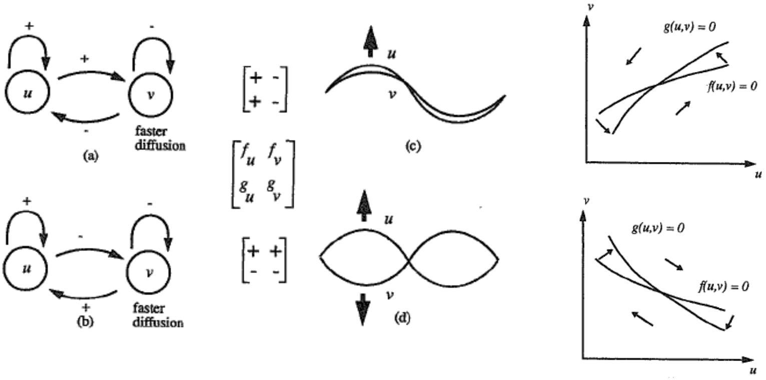
$$J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} = \begin{pmatrix} + & + \\ - & - \end{pmatrix} \quad \text{or} \quad J = \begin{pmatrix} + & - \\ + & - \end{pmatrix}$$

Activator-Inhibitor Systems



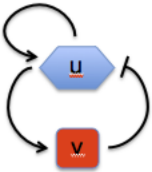


Activator-Inhibitor Systems

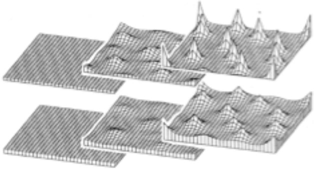


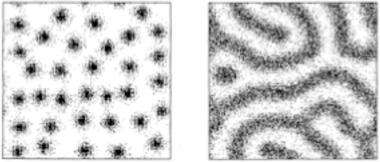
Activator-Inhibitor (Gierer-Meinhardt, 1972)

$$\frac{\partial u}{\partial t} = D_1 \nabla^2 u + \alpha - \beta u + \frac{\gamma u^2}{v}$$
$$\frac{\partial v}{\partial t} = D_2 \nabla^2 v + \delta u^2 - \eta v$$



- u: slow diffusion, short range activation
- v: fast diffusion, long range inhibition





A.J. Koch, H. Meinhardt, Rev Mod Phys 66 (1994)

Schnakenberg Model (Gierer-Meinhardt, 1972)

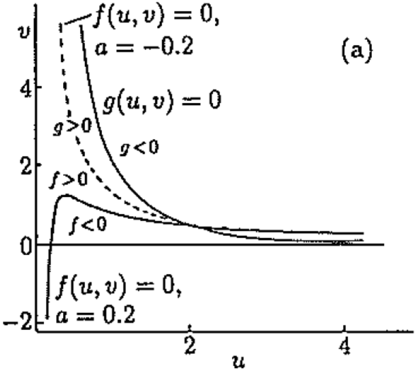
$$\frac{\partial u}{\partial t} = \Delta u + f(u,v)$$
$$\frac{\partial u}{\partial t} = d\Delta v + g(u,v)$$

with

$$f(u,v) = k_1 - k_2 u + k_3 u^2 v$$
$$g(u,v) = k_4 - k_3 u^2 v$$

u: slow difffusion

v: fast difffusion, $d > 1$

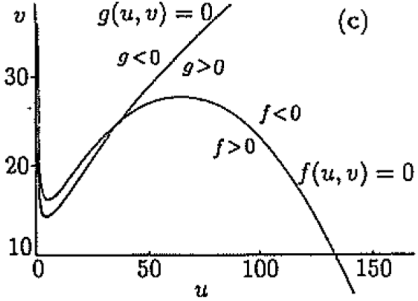


Substrate-Inhibition System, 1975

An empirical system that was studied experimentally by Thomas

$$
\begin{aligned}
f(u,v) &= k_1 - k_2 u - H(u,v) \\
g(u,v) &= k_3 - k_4 v - H(u,v) \\
H(u,v) &= \frac{k_5 uv}{k_6 + k_7 u + k_8 u^2} \quad (1)
\end{aligned}
$$

Here u and v are respectively the concentrations of the substrate oxygen and the enzyme uricase.



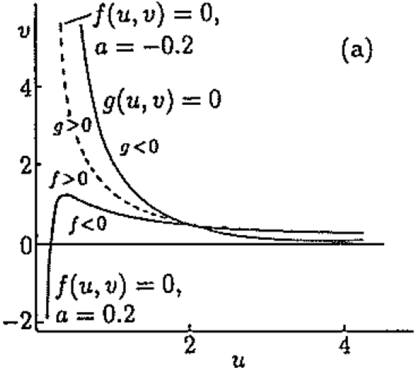
A detailed analysis of a reaction diffusion mechanism

Schnakenberg Model (Gierer-Meinhardt, 1972)

The simplest Turing system is the Schnakenberg reaction

$$\begin{aligned} u_t &= \gamma f(u,v) + u_{xx} \\ &= \gamma(a - u + u^2 v) + u_{xx} \\ v_t &= \gamma g(u,v) + d v_{\underline{xx}} \quad \text{diffusion term} \\ &= \gamma(b - u^2 v) + d v_{xx} \end{aligned}$$

r d a b



Steady State

The steady state (u_0, v_0) is given by

$$u_0 = a + b \quad v_0 = \frac{b}{(a+b)^2}$$

with $b > 0, \quad a + b > 0.$

As previously discussed, for Turing patterns we require

$$\begin{aligned} tr(J) = f_u + g_v &\quad < \quad 0 \\ det(J) = f_u g_v - f_v g_u &\quad > \quad 0 \\ df_u + g_v &\quad > \quad 0 \\ (df_u + g_v)^2 - 4d(f_u g_v - f_v g_u) &\quad > \quad 0 \end{aligned}$$

Turing Space

Conditions for Turing Patterns:

$$
\begin{aligned}
&tr(J) = f_u + g_v < 0 \\
&det(J) = f_u g_v - f_v g_u > 0 \\
&d f_u + g_v > 0 \\
&(d f_u + g_v)^2 - 4d(f_u g_v - f_v g_u) > 0
\end{aligned}
$$

At the steady state $u_0 = a + b$, $v_0 = \frac{b}{(a+b)^2}$ with $b > 0$, $a + b > 0$:

$$
\begin{aligned}
f_u &= \frac{b-a}{a+b}; \quad f_v = (a+b)^2 > 0 \\
g_u &= \frac{-2b}{a+b} < 0; \quad g_v = -(a+b)^2 < 0
\end{aligned}
$$

Turing Space

u, v what are these?

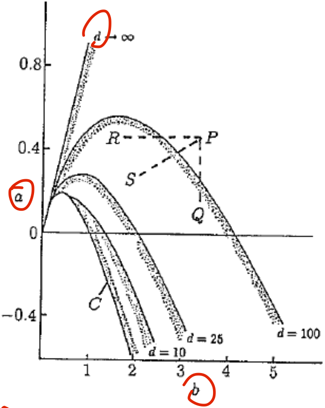
must be non-zero.

a,b production rate

Taking all conditions together we obtain (after some tedious algebra) the pattern formation space in the (a,b,d) domain:

$$i. \quad 0 < b - a < (a+b)^3 < d(b-a)$$

$$ii. \quad (d(b-a) - (a+b)^3)^2 > 4d(a+b)^4$$



Turing space : AUC

AUC ↑ as d ↑

Eigenvalue Problem

On the domain $x \in (0, p)$ with $p > 0$ we then have

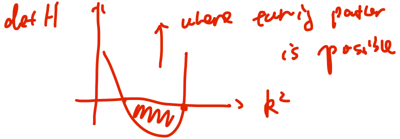
$$W_{xx} + k^2 W = 0, \qquad W_x = 0 \quad \text{for} \quad x \in [0, p] \tag{2}$$

which is solved by

$$W_n(x) = A_n \cos\left(\underline{n\pi x/p}\right), \qquad n = \pm 1, \pm 2, \ldots \tag{3}$$

where the A_n are arbitrary constants.

Unstable Wavenumbers



lower bound

$$\gamma L(a,b,d) = k_1^2 < k^2 = \left(\frac{n\pi}{p}\right)^2 < k_2^2 = \gamma M(a,b,d)$$

$$\begin{aligned} L &= \frac{(d(b-a)-(a+b)^3)}{2d(a+b)} \\ &- \frac{\sqrt{(d(b-a)-(a+b)^3)^2 - 4d(a+b)^4}}{2d(a+b)} \\ M &= \frac{(d(b-a)-(a+b)^3)}{2d(a+b)} \\ &+ \frac{\sqrt{(d(b-a)-(a+b)^3)^2 - 4d(a+b)^4}}{2d(a+b)} \end{aligned}$$

Unstable Wavelengths

The range of unstable modes W_n have wavelengths $\omega = \frac{2\pi}{k}$ bounded by ω_1 and ω_2

$$\frac{4\pi^2}{\gamma L(a,b,d)} = \omega_1^2 < \omega^2 = \left(\frac{2p}{n}\right)^2 < \omega_2^2 = \frac{4\pi^2}{\gamma M(a,b,d)}$$

The importance of γ

check whether $\left\{\frac{\pi}{p}\right\}$ is in the system

k_1 k_2

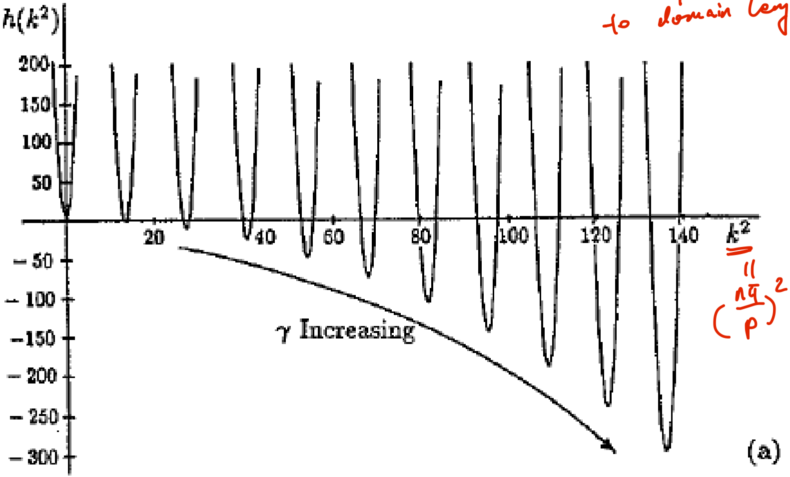
$$\gamma L(a,b,d) = k_1^2 < k^2 = \left(\frac{n\pi}{p}\right)^2 < k_2^2 = \gamma M(a,b,d)$$

$$\frac{4\pi^2}{\gamma L(a,b,d)} = \omega_1^2 < \omega^2 = \left(\frac{2p}{n}\right)^2 < \omega_2^2 = \frac{4\pi^2}{\gamma M(a,b,d)}$$

The smallest wavenumber is π/p, that is $n = 1$. For fixed a, b, d, if γ is sufficiently small there is no allowable k in the range and thus no mode W_n which can be driven unstable.

Unstable Modes: impact of γ

γ is proportional to domain length

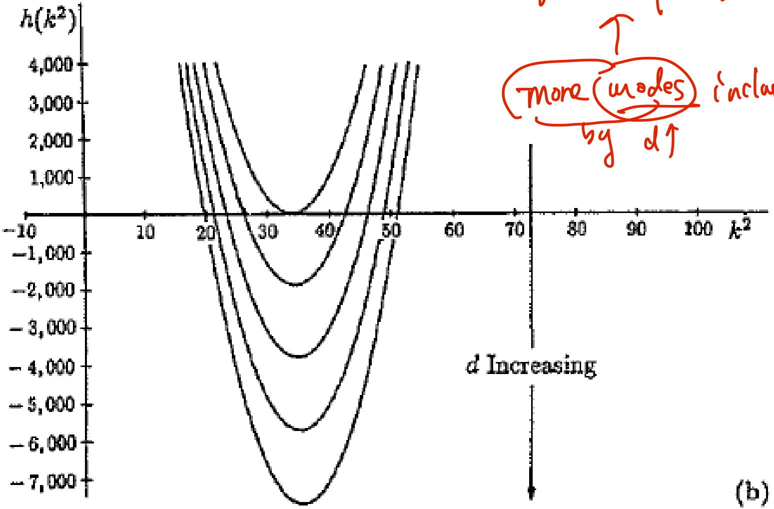


$$k^2 = \left(\frac{n\pi}{p}\right)^2 .$$

Unstable Modes: impact of d

more complexity .

More modes included by $d\uparrow$



Non-dimensional general Models

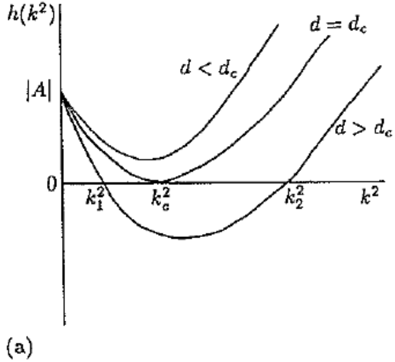
All such reaction diffusion systems can be non-dimensionalized and scaled to take the general form

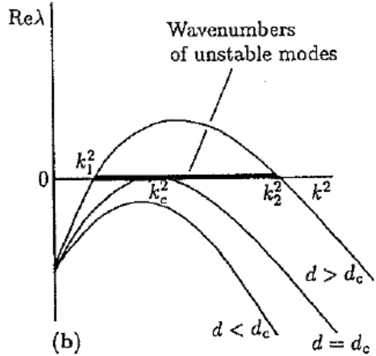
$$\begin{aligned} \dot{u} &= \gamma f(u,v) + \Delta u \\ \dot{v} &= \gamma g(u,v) + d\Delta v \end{aligned}$$

where d is the ratio of diffusion coefficients and γ can have the following interpretations

- $\gamma^{1/2}$ is proportional to the linear size of the spatial domain in one dimension. In two dimensions γ is proportional to the area.
- γ represents the relative strength of the reaction terms. An increase in γ may thus represent an increase in activity of some rate-limiting step in the reaction sequence.
- An increase in γ can also be thought of as equivalent to a decrease in the diffusion coefficient ratio d.

Wavenumbers with diffusion-driven instability





Spatially heterogenous solution

outside [,] we will get invalid in stedy state

$[k_1 \frac{p}{\pi}, \; k_2 \frac{p}{\pi}]$

temporal

$$w(x,t) \sim \boxed{\sum_{n_1}^{n_2}} C_n \exp\left(\lambda\left(\frac{n^2\pi^2}{p^2}\right) \underline{t}\right) \cos\left(\frac{n\pi x}{p}\right)$$

n_1 is the smallest integer greater than or equal to $\frac{pk_1}{\pi}$,
n_2 is the largest integer less than or equal to $\frac{pk_2}{\pi}$,

C_n are the constants which are determined by a Fourier series analysis of the initial conditions of w. The C_n are non-zero because biological initial conditions are inevitably stochastic.

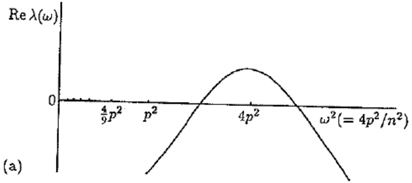
How to get the $\boxed{\text{spatial}}$ osilation?

Spatially heterogenous solution

If domain size admits only the wavenumber $n = 1$, then we have

$$w(x,t) \quad \sim \quad C_{1,0} \exp\left(\lambda\left(\frac{\pi^2}{p^2}\right)t\right)\cos\left(\frac{n\pi x}{p}\right)$$

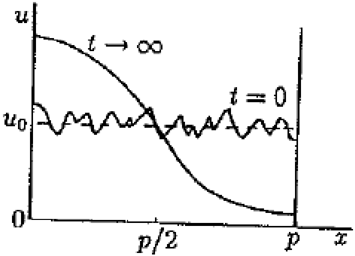
All other modes decay exponentially with time. C_1 can be determined from the initial conditions.

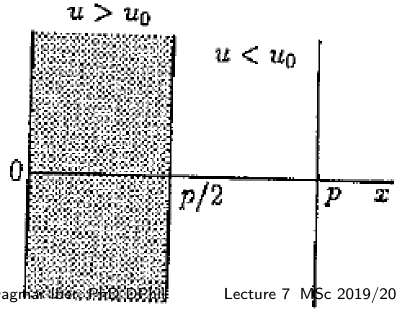


Patterning

We then have for the concentration of morphogen u

$$u(x,t) \quad \sim \quad u_0 + C_{1,0} \exp\left(\lambda\left(\frac{\pi^2}{p^2}\right)t\right)\cos\left(\frac{n\pi x}{p}\right)$$



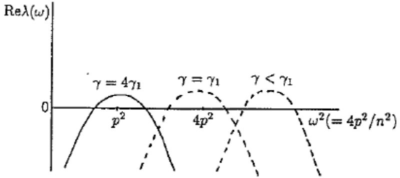


Increase domain size

If we double the domain size $\gamma = \gamma_1$ increases to $\gamma = 4\gamma_1$

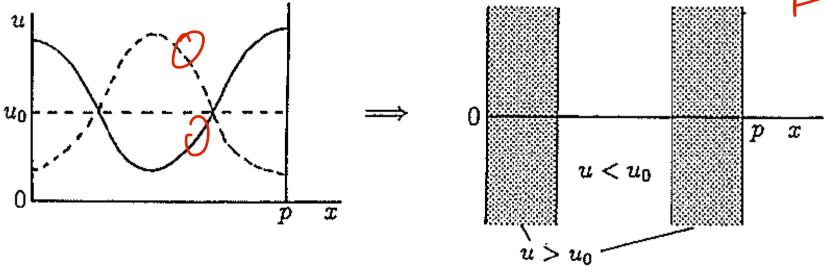
$$\frac{4\pi^2}{\gamma L(a,b,d)} > \omega^2 > \frac{4\pi^2}{\gamma M(a,b,d)}$$

The wavelength of the unstable mode is now $\omega = p$, i.e. $n = 2$.



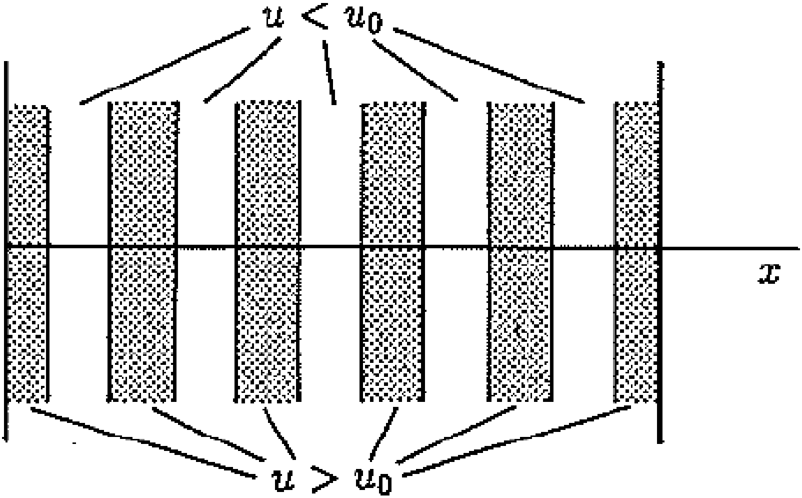
Patterning on doubled domain

can have ... or —— | | | | is also possible.



Note that with zero flux boundary conditions there are two possible solutions that depend only on the initial conditions!!

Patterning on large domain: $n = 10$



Patterning on complex domains

Patterning on 2D domains

Consider the 2-dim domain $x \in [0, p]$ $y \in [0, q]$ with $p, q > 0$ with rectangular boundary ∂B. The spatial eigenvalue problem is now

$$\frac{\partial^2 W}{\partial x^2} + \frac{\partial^2 W}{\partial y^2} + k^2 W = 0, \qquad \left.\frac{\partial W}{\partial x}\right|_{0,p} = 0, \quad \left.\frac{\partial W}{\partial y}\right|_{0,q} = 0$$

or in short-hand notation

$$\Delta W + k^2 W = 0, \qquad (\vec{n} \cdot \nabla) W = 0 \quad \text{for} \quad (x, y) \quad \text{on} \quad \partial B.$$

Patterning on 2D domains

$$\frac{\partial^2 W}{\partial x^2} + \frac{\partial^2 W}{\partial y^2} + k^2 W = 0, \qquad \left.\frac{\partial W}{\partial x}\right|_{0,p} = 0, \quad \left.\frac{\partial W}{\partial y}\right|_{0,q} = 0$$

The eigenfunctions are then

$$\begin{aligned} W_n(x) &= C_{n,m} \cos\frac{n\pi x}{p} \cos\frac{m\pi y}{q}, \qquad n, m = \pm 1, \pm 2, \ldots \\ k^2 &= \pi^2 \left(\frac{n^2}{p^2} + \frac{m^2}{q^2}\right) \end{aligned} \tag{4}$$

where the $C_{n,m}$ are arbitrary constants.

Spatially heterogenous solution

$$
\begin{aligned}
w(x,t) \quad &\sim \quad \sum_{n,m} C_{n,m} \exp\left(\overset{\text{Real}}{\lambda\left(k^2\right)}\, t\right) \overbrace{\cos\left(\frac{n\pi x}{p}\right) \cos\left(\frac{m\pi y}{q}\right)}^{\text{i part separated by euler formula.}} \\
\gamma L(a,b,d) \quad &= \quad k_1^2 < k^2 = \pi^2 \left(\frac{n^2}{p^2} + \frac{m^2}{q^2}\right) < k_2^2 = \gamma M(a,b,d)
\end{aligned}
$$

where the summation is over all pairs (n,m) that satisfy the inequality.

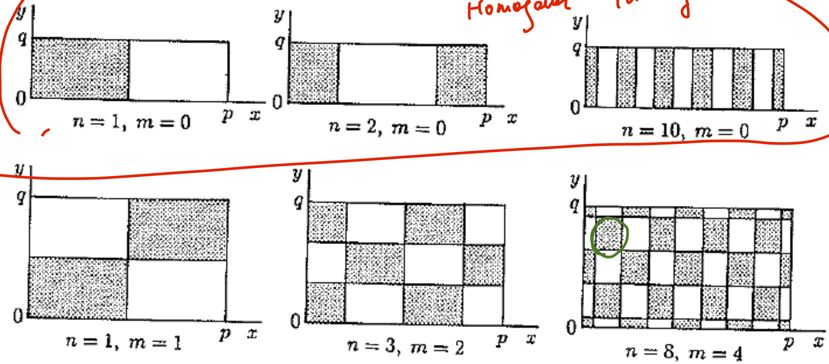
Typical 2-dimensional patterns

Bone no.

possible explanation for different

the stability can be accounted by change of modes

Homogeneous in y



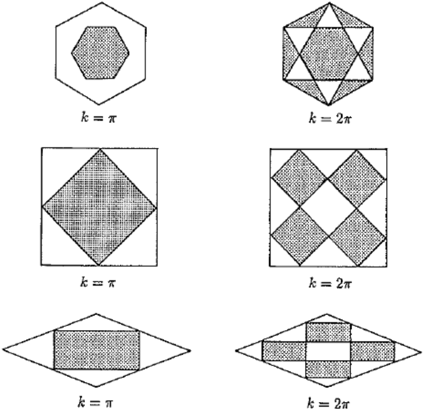
$$\left(\frac{n\pi}{p} + \frac{m\pi}{p}\right)^2$$

Other geometries

For other geometries the analysis quickly becomes complicated. Even for circular domains the eigenvalues have to be determined numerically.

There are some elementary solutions for symmetric domains which tesselate the plane, namely squares, hexagons, rhombi, and, by subdivision, traingles.

Other geometries



Patterning Question

Consider an animal that is either spotted or striped: what pattern has its tail?

Turing Pattern on growing domains

Reaction-diffusion equation on a growing domain

$$\left.\frac{\partial c_i}{\partial t}\right|_{\boldsymbol{x}} + \nabla \cdot (c_i \boldsymbol{u}) = D_i \Delta c_i + R(c_i). \tag{5}$$

$|_{\boldsymbol{x}}$ indicates that the time derivative is performed while keeping $\boldsymbol{x}$ constant.

The terms $\boldsymbol{u} \cdot \nabla c_i$ and $c_i \nabla \cdot \boldsymbol{u}$ describe advection and dilution, respectively.

If the domain is incompressible, i.e. $\nabla \cdot \boldsymbol{u} = 0$, the equations further simplify.

Prescribed Growth

In 'prescribed growth models' an initial domain and a spatio-temporal velocity or displacement field are defined. The domain with initial coordinate vectors $\boldsymbol{X}$ is then moved according to this velocity field $\boldsymbol{u}(\boldsymbol{X}, t)$, i.e.

$$\frac{\partial \boldsymbol{X}(t)}{\partial t} = \left.\frac{\partial \boldsymbol{x}}{\partial t}\right|_{\boldsymbol{X}} = \boldsymbol{u}(\boldsymbol{X}, t) \tag{6}$$

Model-based Displacement Fields

The velocity field $\boldsymbol{u}(\boldsymbol{X}, t)$ can be captured in a functional form that represents either the observed growth and/or signaling kinetics.

In the simplest implementation the displacement may be applied only normal to the boundary, i.e.

$$\boldsymbol{u} = \mu \boldsymbol{n}, \tag{7}$$

where $\boldsymbol{n}$ is the normal vector to the boundary and μ is the local growth rate.

Model-based Displacement Fields

Growth processes often depend on signaling networks that evolve on the tissue domain.

The displacement field $\boldsymbol{u}(\boldsymbol{X}, t)$ may thus dependent on the local concentration of some growth or signaling factor.

We then have

$$\boldsymbol{u} = \mu(c)\boldsymbol{n}, \tag{8}$$

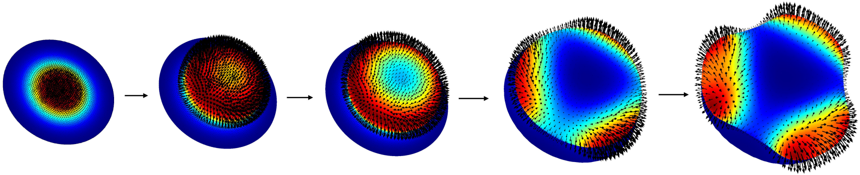
where c is the local concentration of the signaling factor.

Example: Schnakenberg Turing Model

$$
\begin{aligned}
\frac{\partial c_1}{\partial t} + \nabla \cdot (c_1 \boldsymbol{u}) &= \Delta c_1 + \gamma(a - c_1 + c_1^2 c_2) \\
\frac{\partial c_2}{\partial t} + \nabla \cdot (c_2 \boldsymbol{u}) &= d\Delta c_2 + \gamma(b - c_1^2 c_2); \qquad (9)
\end{aligned}
$$

a, b, γ, and d are constant parameters in the Turing model.

'Prescribed' Domain Growth under Control of a Signaling Model.



The figure shows as an example a 2D sheet that deforms within a 3D domain according to the strength of the signaling field normal to its surface, i.e. $\boldsymbol{u} = \mu c_1^2 c_2 \boldsymbol{n}$, where c_1 and c_2 are the two variables that are governed by the Schnakenberg-type Turing model.

Thanks!!

Thanks for your attention!

Slides for this talk will be available at:
`http://www.bsse.ethz.ch/cobi/education`