ETH zürich

Lecture 5: Turing Pattern

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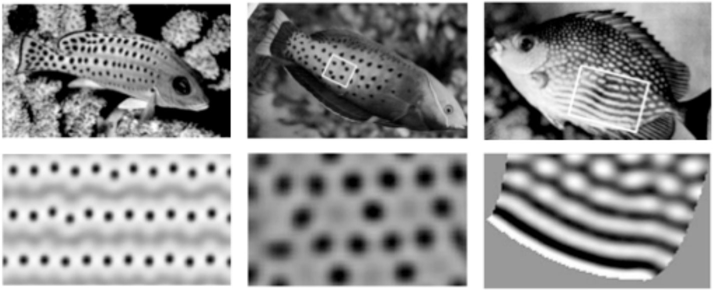
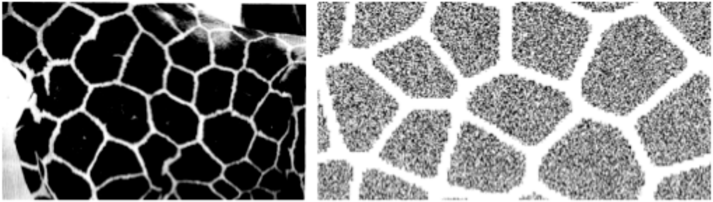
Bring the symmetry in a "deterministic" manner.
from a noisy init. condition.

Patterning Examples.





The Turing Patterning Mechanism

Turing instability

Diffusion-driven instability (Turing instability)

occurs when a steady state, linearly stable in the absence of diffusion, goes unstable when diffusion is present.

Diffusion Driven Instability

Consider a 2-component system

$$
\begin{aligned}
\dot{u} &= f(u,v) + D_1 \Delta u \qquad x \in \Omega \\
\dot{v} &= g(u,v) + D_2 \Delta v \qquad t \in [0,\infty)
\end{aligned}
$$

In the absence of diffusion $\Rightarrow$ stable state.

with initial conditions

$$
\begin{aligned}
u(x,0) &= u_0(x) \\
v(x,0) &= v_0(x).
\end{aligned}
$$

As boundary conditions we can chose zero-flux conditions or a fixed value $u = u_B$, $v = v_B$ on the boundary $\partial\Omega$.

Patterns are stable, steady (in time), spatially non-uniform solutions of this set of equations.

Vector Notation

Let

$$\vec{u} = \begin{pmatrix} u \\ v \end{pmatrix} \qquad \dot{\vec{u}} = F(\vec{u}) + D\Delta\vec{u}$$

$$F(\vec{u}) = \begin{pmatrix} f(u,v) \\ g(u,v) \end{pmatrix} \qquad D = \begin{bmatrix} D_1 & 0 \\ 0 & D_2 \end{bmatrix}$$

with boundary condition

$$(\vec{n} \cdot \nabla) \begin{pmatrix} u \\ v \end{pmatrix} = 0 \quad \text{on} \quad \partial\Omega \quad \text{or} \quad \vec{u} = \vec{u}_B \quad \text{on} \quad \partial\Omega.$$

$\vec{n}$ is the unit outward normal to $\partial\Omega$.

Stability of Steady State

Suppose

$$\vec{u} = \begin{pmatrix} u \\ v \end{pmatrix} \qquad \dot{\vec{u}} = \begin{pmatrix} f(u,v) \\ g(u,v) \end{pmatrix}$$

has steady states (u^*, v^*). w.r.t. time

The stability of the steady states can be determined by studying the long-term behaviour of perturbations of the steady state

$$\vec{w} = \begin{pmatrix} u - u^* \\ v - v^* \end{pmatrix}.$$

Linearization around the steady state

write f and g using Talyor expansion near the steadystate.

$$\dot{\vec{w}} = \begin{pmatrix} (u \dot{-} u^*) \\ (v \dot{-} v^*) \end{pmatrix} = \begin{pmatrix} f(u-u^*, v-v^*) \\ g(u-u^*, v-v^*) \end{pmatrix}$$

Determine the Jacobian

$$f(u,v) = f(u^*,v^*) + \frac{d}{du}(u-u^*) + \frac{d}{dv}(v-v^*)$$

$$J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix}$$

and linearize the set of equations around the steady state (u^*, v^*) to obtain

$$\dot{\vec{w}} = J\vec{w}.$$

Conditions for linear stability

See linear instability in other lectures.

$$\dot{\vec{w}} = J\vec{w}$$

can be solved to yield

same as $\dot{x} = \alpha x$

$$\vec{w}(x,t) = \sum_{i=1}^{i=2} \alpha_i \vec{v}_i \exp(\lambda_i t), \quad \lambda_i = \frac{tr(J) \pm \sqrt{tr(J)^2 - 4\det(J)}}{2}$$

where $\vec{v}_i$ and λ_i are the eigenvectors and eigenvalues of J. The α_i follow from the initial condition.

The steady state is linearly $\boxed{\text{stable}}$ if, $\vec{w} \to \vec{0}$ as $t \to \infty$. This requires that both eigenvalues are negative, and thus

exponential

$\lambda_i < 0$

only in the case of 2×2

$$tr(J) < 0 \qquad \det(J) > 0.$$

Linearized Set of Equations with Diffusion

In the presence of diffusion the linearized system reads

$$\dot{\vec{w}} = J\vec{w} \boxed{+ D\Delta\vec{w}.}$$

added part

We look for a separable solution of the form

$$\dot{\vec{w}} = J\vec{w} + D\Delta\vec{w} \quad \Leftrightarrow \quad \vec{w}(x,t) = \Phi(t)W(x)$$

Separable Solution

Time-dependent Solution

$$\dot{\Phi} = J\Phi \quad \Rightarrow \quad \Phi(t) = \sum_i \alpha_i \vec{v_i} \exp\left(\lambda_i t\right)$$

where λ_i represents the eigenvalues and $\vec{v_i}$ the eigenvectors of J.

Spatial Solution

$$0 = JW + D\Delta W \quad \Rightarrow \quad W(x) = \sum_i \alpha_i \vec{v_i} \exp\left(ikx\right)$$

k is referred to as wavenumber.

Spatio-temporal solution

Ansatz:

$$\vec{w}(x,t) = \Phi(t) W(x) = \sum_i \overbrace{\alpha_i \vec{v}_i \exp\left(\lambda t + ikx\right)}^{w_i \vec{v_i}}$$

$$\dot{\vec{w}} = J\vec{w} + D\Delta\vec{w} \qquad \sum \lambda_i w_i \vec{v_i}$$

$$\lambda\vec{w} = J\vec{w} - k^2 D\vec{w} \qquad \forall x$$

This is true for

We can rewrite this as

$$(H - \lambda I)\vec{w} = 0 \qquad H = J - k^2 D.$$

As we want a non-zero solution for $\vec{w}$, we require $\det\left(H\right) = 0$.

Eigenvalues of J

$D = \begin{bmatrix} D_1 & 0 \\ 0 & D_2 \end{bmatrix}$

$$(H - \lambda I)\vec{w} = 0 \qquad H = J - k^2 D \quad \det(H) = 0$$

We then have

$$\lambda^2 - tr(H)\lambda + \det(H) = 0$$

$$tr(H) = tr(J) - k^2 \underline{(D_1 + D_2)} < 0$$

$$\det(H) = D_1 D_2 k^4 - (D_2 f_u + D_1 g_v)k^2 + \det(J)$$

To obtain a diffusion-driven instability we require $\underline{\det(H) < 0}$. Since $D_1 D^2 k^4 > 0$ and $\det(J) > 0$, we require

$$\underbrace{D_2 f_u + D_1 g_v}_{\Downarrow\ D_1 \neq D_2} > D_1 D_2 k^2 + \underbrace{\det(J)/k^2}_{0} > 0.$$

f_u and g_v is different in direction

Dispersion Relation

For patterns to emerge we require

$$\det(H) = h(k^2) = D_1 D_2 k^4 - (D_2 f_u + D_1 g_v) k^2 + \det(J) < 0.$$

We thus want $h_{min} < 0$. The critical case occurs for for k. (wave number)

$$h_c(k^2) = D_1 D_2 k^4 - (D_2 f_u + D_1 g_v) k^2 + \det(J) = 0$$

h is minimal when

$$\frac{dh(k^2)}{d(k^2)} = 2 D_1 D_2 k^2 - (D_2 f_u + D_1 g_v) = 0; \quad \frac{d^2 h(k^2)}{d(k^2)^2} = 2 D_1 D_2 > 0$$

$$k^2_{min} = \frac{(D_2 f_u + D_1 g_v)}{2 D_1 D_2}.$$

Critical ratio of diffusion coefficients

We need

$$h_{min}(k^2) = D_1 D_2 k_{min}^4 - (D_2 f_u + D_1 g_v) k_{min}^2 + \det(J) < 0$$

$$k_{min}^2 = \frac{(D_2 f_u + D_1 g_v)}{2 D_1 D_2}$$

$$h_{min}(k^2) = -\frac{(D_2 f_u + D_1 g_v)^2}{4 D_1 D_2} + \det(J) < 0$$

This defines a critical diffusion coefficient ratio as the appropriate root of

$$-(D_2 f_u + D_1 g_v)^2 + 4 D_1 D_2 \det(J) < 0.$$

Range of wavenumbers

The range of wavenumbers for which $h(k^2) < 0$ follows by setting $h(k^2) = 0$

$$h(k^2) = D_1 D_2 k^4 - (D_2 f_u + D_1 g_v) k^2 + \det(J) = 0$$

$$k_{1,2}^2 = \frac{(D_2 f_u + D_1 g_v)}{2 D_1 D_2} \pm \frac{1}{2 D_1 D_2} \sqrt{(D_2 f_u + D_1 g_v)^2 - 4 D_1 D_2 (f_u g_v - f_v g_u)}.$$

Zero-flux boundary conditions

$e^{ikx} = \cos(kx) + i\sin(kx)$

With zero-flux boundary conditions, i.e.

$$(\vec{n}\cdot\nabla)\vec{w} = 0 \quad \text{on} \quad \partial\Omega.$$

we have

$$0 = JW + D\Delta W \quad \text{in} \quad \Omega \qquad \underline{(\vec{n}\cdot\nabla)\vec{W} = 0} \quad \text{on} \quad \partial\Omega$$

Thus if $\Omega = [0, L]$

$\sin(kL) = 0$

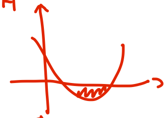
$kL = n\pi$

spatial $$\underline{W(x)} = \sum_n \alpha_n \cos\left(\frac{n\pi x}{L}\right), \qquad k^2 = \frac{n^2\pi^2}{L^2}.$$

by BC

Admissible Modes

det H



depending on D

k

Range of "k" that we can take

turn it upside

Consider

$$\dot{\vec{w}} = J\vec{w} + D\Delta\vec{w}$$

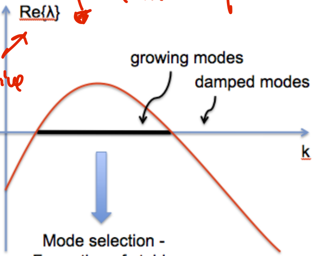
with $\Omega = [0, L]$ and zero-flux boundary conditions. We then have

coming from init.

$$\vec{w}(x,t) = \sum_n \alpha_n \vec{v}_n \exp\left(\lambda(k^2)t\right)\cos\left(\frac{n\pi x}{L}\right)$$

with $k^2 = \frac{n^2\pi^2}{L^2}$.

positive real part

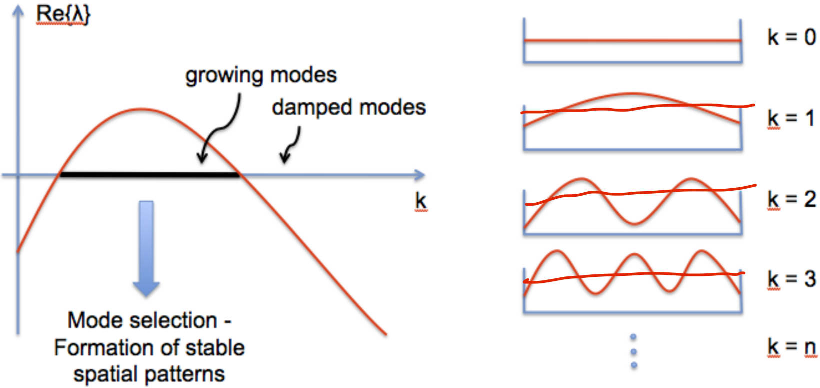


selected by the noisy init. cond.

Self-organizing Pattern

in the infinite domain

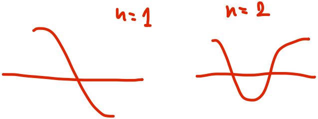
from BC

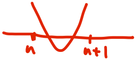


Which mode will dominate?

Mode Selection

in the case of small domain
vice verse. larger the domain, more
n





=> no k ?

Mode Selection

Of the growing modes the one closest to the peak of the dispersion curve grows fastest.

$$\frac{\partial \lambda}{\partial k^2} = 0 \quad \Rightarrow \quad \max(Re\lambda) = Re\lambda(k_m^2)$$

Strictly k_m may not be an allowable mode in a finite domain situation. In this case it is the possible mode closest to the analytically determined k_m.

Summary

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:

$$\left.\begin{array}{ll} \text{I} & f_u + g_v < 0 \end{array}\right\}$$ System would have a STABLE steady state WHITOUT Diffusion

$$\left.\begin{array}{ll} \text{II} & f_u g_v - f_v g_u > 0 \\ \text{III} & D_1 g_v + D_2 f_u > 2\sqrt{D_1 D_2 (f_u g_v - f_v g_u)} \end{array}\right\}$$ 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

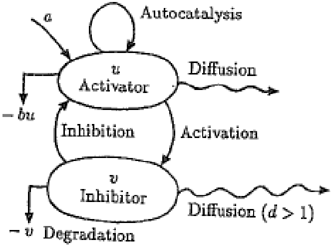
Conditions

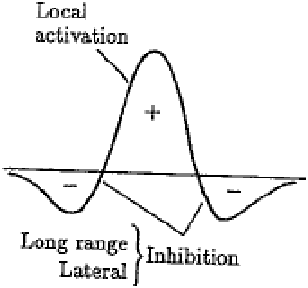
$$
\begin{array}{lll}
I. & f_u + g_v < 0 & \text{diagonal entries opposite signs} \\
II. & f_u g_v - f_v g_u > 0 & \text{off-diagonal entries opposite signs} \\
III. & D_2 f_u + D_1 g_v > 0 & D_1 \neq D_2 \quad \text{different diffusion speeds}
\end{array}
$$

Activator - Inhibitor Systems

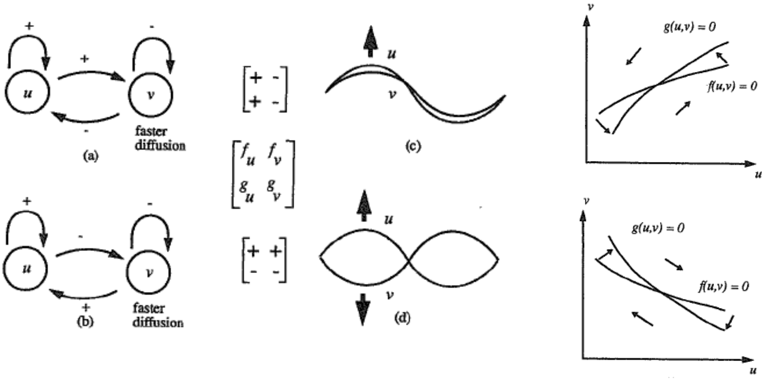
$$
J = \begin{pmatrix} f_u & f_v \\ g_u & g_v \end{pmatrix} = \begin{pmatrix} + & + \\ - & - \end{pmatrix} \quad \text{or} \quad J = \begin{pmatrix} + & - \\ + & - \end{pmatrix}
$$

Activator-Inhibitor Systems



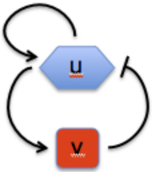


Activator-Inhibitor Systems

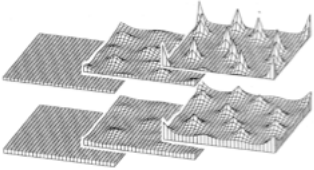


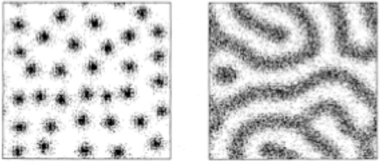
Activator-Inhibitor (Gierer-Meinhardt, 1972)

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



- 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)

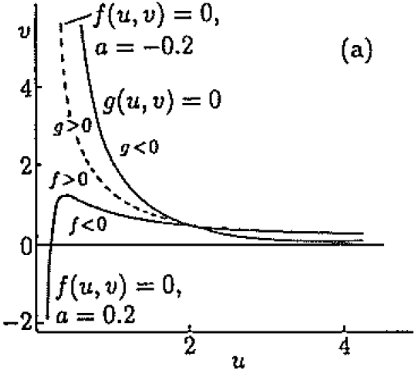
$$
\begin{aligned}
\frac{\partial u}{\partial t} &= \Delta u + f(u,v) \\
\frac{\partial u}{\partial t} &= d\Delta v + g(u,v)
\end{aligned}
$$

with

$$
\begin{aligned}
f(u,v) &= k_1 - k_2 u + k_3 u^2 v \\
g(u,v) &= k_4 - k_3 u^2 v
\end{aligned}
$$

u: slow difffusion

v: fast difffusion, $d > 1$

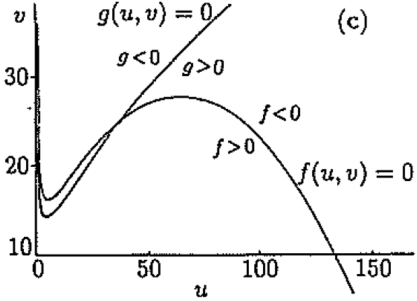


Substrate-Inhibition System, 1975

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.

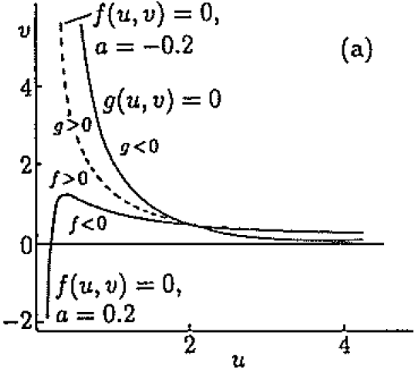


A detailed analysis of a reaction diffusion mechanism

Schnakenberg Model (Gierer-Meinhardt, 1972)

The simplest Turing system is the Schnakenberg reaction

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



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

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

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 $b > 0$, $a + b > 0$:

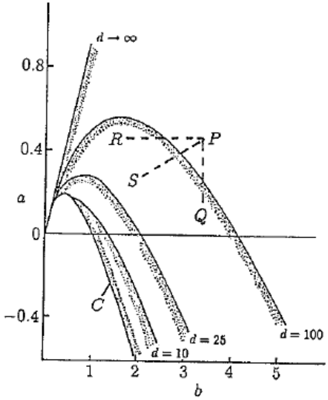
$$
\begin{aligned}
f_u &= \frac{b-a}{a+b}; \quad f_v = (a+b)^2 > 0 \\
g_u &= \frac{-2b}{a+b} < 0; \quad g_v = -(a+b)^2 < 0
\end{aligned}
$$

Turing Space

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

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

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



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

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

where the A_n are arbitrary constants.

Unstable Wavenumbers

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

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

Unstable Wavelengths

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

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

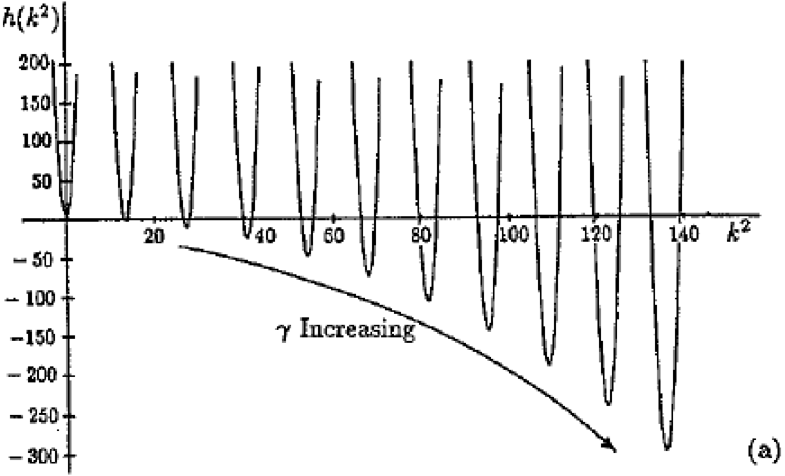
The importance of γ

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

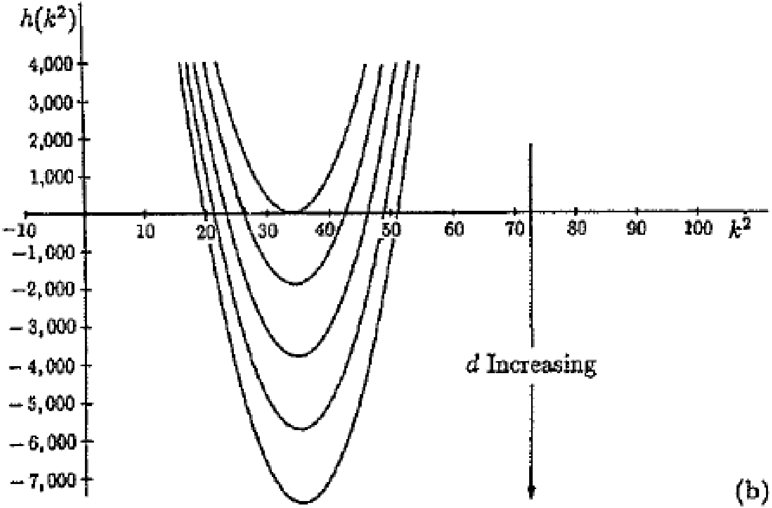
$$\frac{4\pi^2}{\gamma L(a,b,d)} = \omega_1^2 < \omega^2 = \left(\frac{2p}{n}\right)^2 < \omega_2^2 = \frac{4\pi^2}{\gamma M(a,b,d)}$$

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



Unstable Modes: impact of d



Non-dimensional general Models

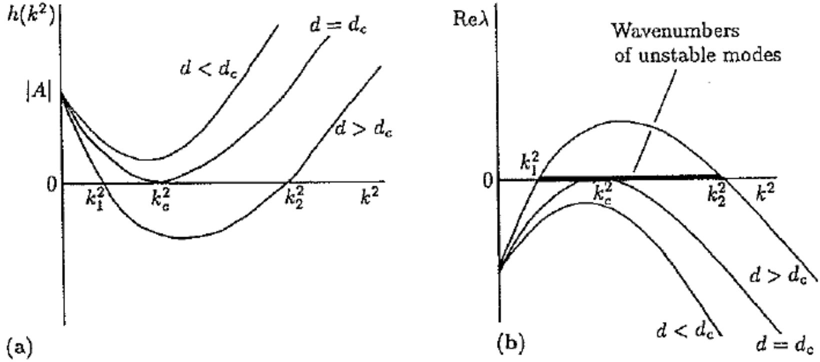
All such reaction diffusion systems can be non-dimensionalized and scaled to take the general form

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

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

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

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 $\frac{pk_2}{\pi}$,

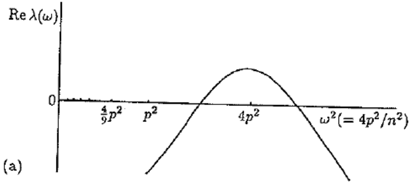
C_n are the constants which are determined by a Fourier series analysis of the initial conditions of w. The C_n are non-zero because biological initial conditions are inevitably stochastic.

Spatially heterogenous solution

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

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

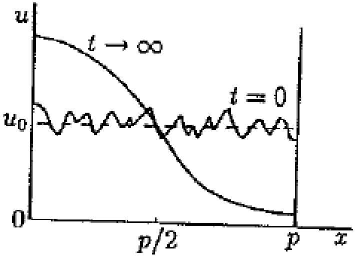
All other modes decay exponentially with time. C_1 can be determined from the initial conditions.

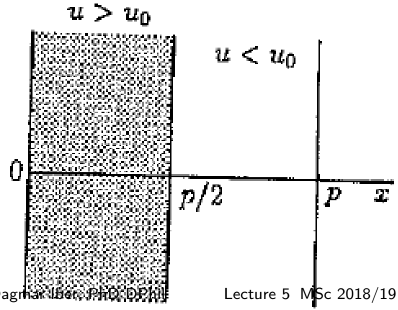


Patterning

We then have for the concentration of morphogen u

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



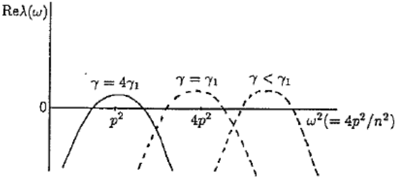


Increase domain size

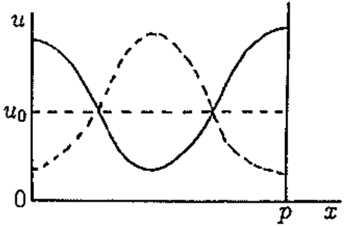
If we double the domain size $\gamma = \gamma_1$ increases to $\gamma = 4\gamma_1$

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

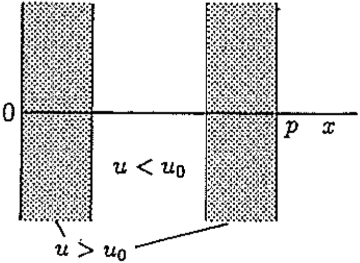
The wavelength of the unstable mode is now $\omega = p$, i.e. $n = 2$.



Patterning on doubled domain

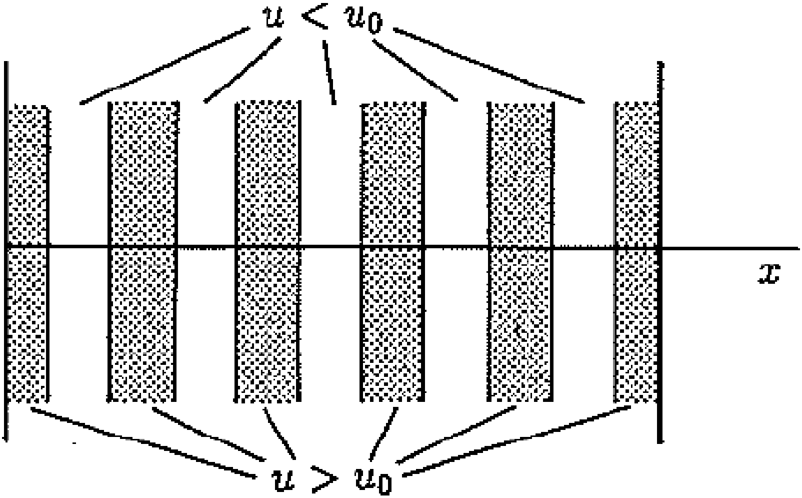


$\Longrightarrow$



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

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

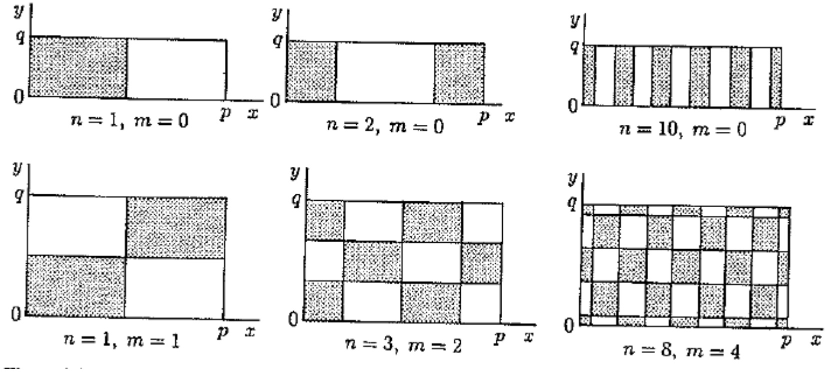
where the $C_{n,m}$ are arbitrary constants.

Spatially heterogenous solution

$$
\begin{aligned}
w(x,t) &\sim \sum_{n,m} C_{n,m} \exp\left(\lambda\left(k^2\right)t\right)\cos\left(\frac{n\pi x}{p}\right)\cos\left(\frac{m\pi y}{q}\right)\\
\gamma L(a,b,d) &= k_1^2 < k^2 = \pi^2\left(\frac{n^2}{p^2}+\frac{m^2}{q^2}\right) < k_2^2 = \gamma M(a,b,d)
\end{aligned}
$$

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

Typical 2-dimensional patterns

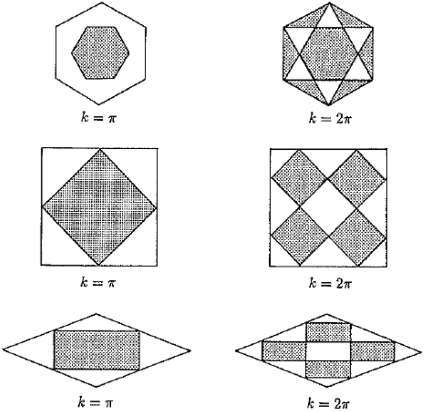


Other geometries

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?

Thanks!!

Thanks for your attention!

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