Diffusion, Reaction, and Biological pattern formation
Morphogenesis and positional information

How do cells know what to do?
Fundamental questions

• How do proteins in a cell segregate to front or back?
• How does an embryo become differentiated into specialized parts?
• How does an initially uniform tissue become specialized into multiple parts based on chemical signal?
Chemical patterns inside cells

Back:
Rho
PTEN

Front:
Rac
PI3K,
PIP$_2$, PIP$_3$

What process(es) account for segregation of chemicals?
Patterns on a larger scale
Patterns in development

Drosophilla
Interpreting a chemical gradient?

Morphogen gradient: can it lead to multiple cell types?
Wolpert’s French Flag

How it was proposed to work

- Spatial gradients of “morphogens” create the subdivision
- Threshold concentrations of morphogen trigger gene expression in the cells in the tissue, leading to distinct expression.
Example: early morphogenesis in the fly (Drosophila)
Embryo initially has no major internal boundaries

Front (anterior)  back (posterior)
Stages

1
2
3
4
Stages

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Later: Patterns of gene products

What is the question?

• How can we account for spontaneous creation of such striped patterns of protein activity from the initial fertilized egg?

Reaction diffusion systems and Patterns
On its own, diffusion promotes uniformity

Diffusion

\[
\frac{\partial A}{\partial t} = D \frac{\partial^2 A}{\partial x^2}
\]

Units: \([D] = L^2/t\)
Linked to some reactions, it can CAUSE patterns to form spontaneously.

Reaction:
\[
\frac{\partial A}{\partial t} = f(A,B) \\
\frac{\partial B}{\partial t} = g(A,B)
\]

Diffusion:
\[
\frac{\partial A}{\partial t} = D \frac{\partial^2 A}{\partial x^2}
\]

Units: \([D] = L^2/t\)
Example: (Schnakenberg)

\[
\begin{align*}
\frac{\partial A}{\partial t} &= f(A,B) + D_A \frac{\partial^2 A}{\partial x^2} \\
\frac{\partial B}{\partial t} &= g(A,B) + D_B \frac{\partial^2 B}{\partial x^2}
\end{align*}
\]

\[S_1 \Leftrightarrow A\]
\[S_2 \xrightarrow{k_4} B\]
\[B + 2A \xrightarrow{k_3} 3A\]

\[f(A,B) = k_1 - k_2 A + k_3 A^2 B\]
\[g(A,B) = k_4 - k_3 A^2 B\]
Example: Shnakenberg RD system

Starting close to the HSS, the system evolves a spatial pattern that persists with time.
How does it work?


Derived conditions for diffusion-driven pattern formation in a reaction-diffusion system.
Why does it work? Basic idea

- Equations:
  \[
  \frac{\partial C_1}{\partial t} = R_1(C_1, C_2) + D_1 \frac{\partial^2 C_1}{\partial x_2^2}, \\
  \frac{\partial C_2}{\partial t} = R_2(C_1, C_2) + D_2 \frac{\partial^2 C_2}{\partial x_2^2}.
  \]

- BC’s: sealed domain (no flux, i.e. Neumann)
Reaction mixture is stable

- Assume a stable homogeneous steady state:

\[
R_1(\overline{C}_1, \overline{C}_2) = 0, \\
R_2(\overline{C}_1, \overline{C}_2) = 0.
\]
Consider small perturbations of the homogeneous steady state

- perturbations:

\[
\begin{align*}
C_1(x, t) &= \overline{C}_1 + C_1'(x, t) \\
C_2(x, t) &= \overline{C}_2 + C_2'(x, t)
\end{align*}
\]

- Substitute into PDEs and use Taylor expansions to linearize the equations
Linearized equations

\[ \frac{\partial C_1'}{\partial t} = a_{11} C_1' + a_{12} C_2' + D_1 \frac{\partial^2 C_1'}{\partial x'^2}, \]
\[ \frac{\partial C_2'}{\partial t} = a_{21} C_1' + a_{22} C_2' + D_2 \frac{\partial^2 C_2'}{\partial x'^2}, \]

- Where the coefficients are elements of the Jacobian matrix

\[ a_{11} = \left. \frac{\partial R_1}{\partial C_1} \right|_{\bar{c}_1, \bar{c}_2'}, \quad a_{12} = \left. \frac{\partial R_1}{\partial C_2} \right|_{\bar{c}_1, \bar{c}_2'}, \quad a_{21} = \left. \frac{\partial R_2}{\partial C_1} \right|_{\bar{c}_1, \bar{c}_2'}, \quad a_{22} = \left. \frac{\partial R_2}{\partial C_2} \right|_{\bar{c}_1, \bar{c}_2'} \]
Some requirements:

- Stability of the homogeneous steady state:

\[ a_{11} + a_{22} < 0, \]
\[ a_{11}a_{22} - a_{12}a_{21} > 0, \]
Eigenfunctions and eigenvalues

- Solutions to the linear equations are:

\[
\begin{pmatrix}
C'_1 \\
C'_2
\end{pmatrix} = \begin{pmatrix}
\alpha_1 \\
\alpha_2
\end{pmatrix} \cos qx e^{\alpha t}.
\]

Eigenfunctions chosen to satisfy both the PDE and BC’s (e.g. no flux at x=0, L):

\[ q = n\pi / L \]
Interpretation

- The form of the perturbations

$$\cos(qx) e^{\sigma t}$$

The value $q$ is the wave number (spatial periodicity) and $\sigma$ is the rate of growth.
If the rate of growth $\sigma$ is $>0$ then perturbations will grow.

$\cos(qx) e^{\sigma t}$
Dispersive waves

- In general, waves of different periodicity will grow or decay at different rates, so the growth rate $\sigma$ will depend on the wave number $q$. 
Condition for pattern formation:

- There exists some (range of) wavenumber values such that $\sigma > 0$
Substitute the perturbations into the linearized equations:

\[
\begin{pmatrix}
C'_1 \\
C'_2
\end{pmatrix}
= 
\begin{pmatrix}
\alpha_1 \\
\alpha_2
\end{pmatrix}
\cos qx \ e^{\sigma t}.
\]

What set of (algebraic) equation do you get?
Answer:

\[ \alpha_1 \sigma = a_{11} \alpha_1 + a_{12} \alpha_2 - D_1 q^2 \alpha_1, \]
\[ \alpha_2 \sigma = a_{21} \alpha_1 + a_{22} \alpha_2 - D_2 q^2 \alpha_2. \]
Rearrange terms

\[\alpha_1(\sigma - a_{11} + D_1 q^2) + \alpha_2(-a_{12}) = 0,\]
\[\alpha_1(-a_{21}) + (\sigma - a_{22} + D_2 q^2)\alpha_2 = 0,\]

This is a set of linear eqs in the alpha’s which has a unique (trivial) solution unless the system has a zero determinant.
Nontrivial perturbations

- Exist only if determinant $= 0$

$$\det \begin{pmatrix} \sigma - a_{11} + D_1 q^2 & -a_{12} \\ -a_{21} & \sigma - a_{22} + D_2 q^2 \end{pmatrix} = 0.$$ 

- Simplifying leads to a quadratic eqn for $\sigma$:

$$\left(\sigma - a_{11} + D_1 q^2\right)\left(\sigma - a_{22} + D_2 q^2\right) - a_{12}a_{21} = 0,$$
Characteristic equation for $\sigma$:

- Eqn $\sigma^2 - \beta \sigma + \gamma = 0$
- Where $\beta = - \frac{(-a_{22} + D_2 q^2 - a_{11} + D_1 q^2)}{(a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12}a_{21}}$
- $\gamma = \frac{(a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12}a_{21}}{(-a_{22} + D_2 q^2 - a_{11} + D_1 q^2)}$
Technical stuff

• It is easy to show that for $\sigma$ to be positive, $\gamma$ has to be negative.

• $\gamma = \left( a_{11} - D_1 q^2 \right) \left( a_{22} - D_2 q^2 \right) - a_{12} a_{21} < 0$

• Look for wave number values such that $\gamma < 0$
When is gamma negative?

- Gamma depends on $q^2$ quadratically

\[ [(a_{11} - D_1 q^2)(a_{22} - D_2 q^2)] \]
When is gamma negative?

\[ \gamma = \frac{a_{11}}{D_1} \frac{a_{22}}{D_2} q^2 \]

\[ \frac{(a_{11} - D_1 q^2)(a_{22} - D_2 q^2)}{q^2} - a_{12} a_{21} \]
Gamma first becomes negative at

\[ q_{\text{min}}^2 = \frac{1}{2} \left( \frac{a_{22}}{D_2} + \frac{a_{11}}{D_1} \right) \]
Condition for instability

• Use the criterion that

$$\gamma (q_{\text{min}}^2) < 0$$

• Obtain (details omitted)

\[
(a_{11}a_{22} - a_{12}a_{21}) - \frac{1}{4} \left( \frac{D_1a_{22} + D_2a_{11}}{D_1D_2} \right) < 0.
\]
Conditions:

\[ a_{11} + a_{22} < 0, \]
\[ a_{11}a_{22} - a_{12}a_{21} > 0, \]
\[ a_{11}D_2 + a_{22}D_1 > 2\sqrt{D_1D_2(a_{11}a_{22} - a_{12}a_{21})^{1/2}} > 0. \]
Interpretation

• (Detailed arguments omitted here.)

• Case 1: \( a_{12} < 0, \quad a_{21} > 0 \)

• Case 2: \( a_{12} > 0, \quad a_{21} < 0 \)

• In either case, need \( D_1 < D_2 \)
Turing (1952): “The chemical basis of morphogenesis”

With “appropriate” reaction kinetics, an RD system can form spatial patterns due to the effect of diffusion.

Pattern formation in biology

Hans Meinhardt

\[ \frac{\partial a}{\partial t} = \frac{\rho a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_0 \]

\[ \frac{\partial h}{\partial t} = \rho a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2} \]

Phyllotaxis (Wikipedia)

http://www.eb.tuebingen.mpg.de/departments/former-departments/h-meinhardt/home.html
Reaction-Diffusion systems and animal coat patterns

Is biological pattern all based on Turing mechanism?
Back to the fly

Drosophilla
Back to the fly:

• How can we account for spontaneous creation of such striped patterns of protein activity from the initial fertilized egg?
Turing system?

- For some years, it was imagined that this pattern was set up by an activator-inhibitor system. More recently, this has been overturned.
Bicoid synthesized from mRNA at one end, then redistributes to form gradient.

Front (anterior)  back (posterior)
“Reading the bicoid gradient”
“Reading the bicoid gradient”

Eric Wieschaus:

• "Cells make choices based on levels of bicoid. Nuclei can measure and make decisions based on those choices."

• “Discovery of bicoid helped emphasize the importance of quantitative aspects of developmental biology.”
Bicoid diffusion model

- Equation for the morphogen gradient

\[ \frac{\partial M}{\partial t} = D \nabla^2 M - \tau^{-1} M + s_0 \delta(x), \]
Bicoid gradient

• Variability from one embryo to the next – how is error in body plan avoided?
Bicoid

Other genes

Feedback interactions sharpen the gradients