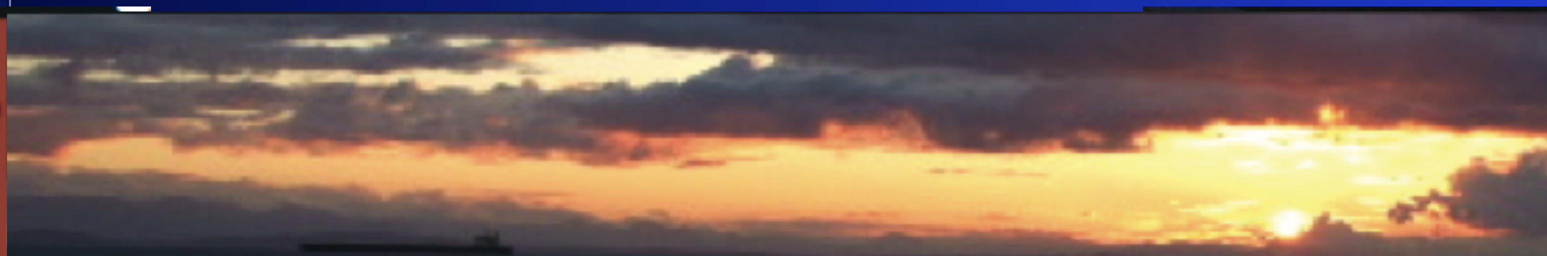
Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Diffusion, Reaction, and Biological pattern formation



mprime

PIMS

www.math.ubc.ca/~keshet/MCB2012/

Morphogenesis and positional information

How do cells know what to do?

Fundamental questions

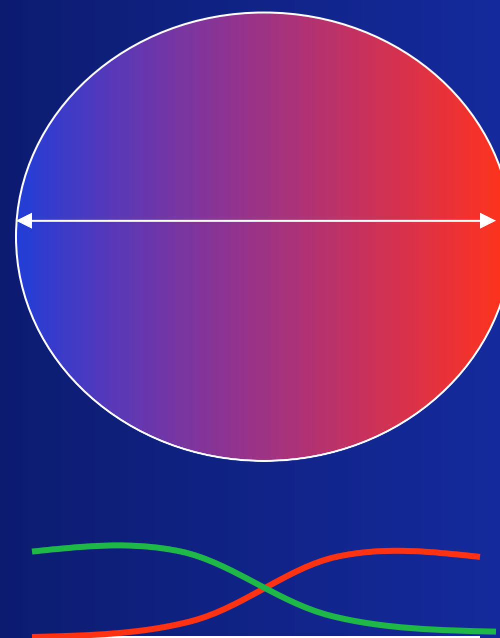
- How do proteins in a cell segregate to front or back?
- How does an embryo become differentiated into specialized parts?
- How does an initially uniform tissue become specialized into multiple parts based on chemical signal?

Chemical patterns inside cells

Back:

Rho

PTEN



Front:

Rac

PI3K,

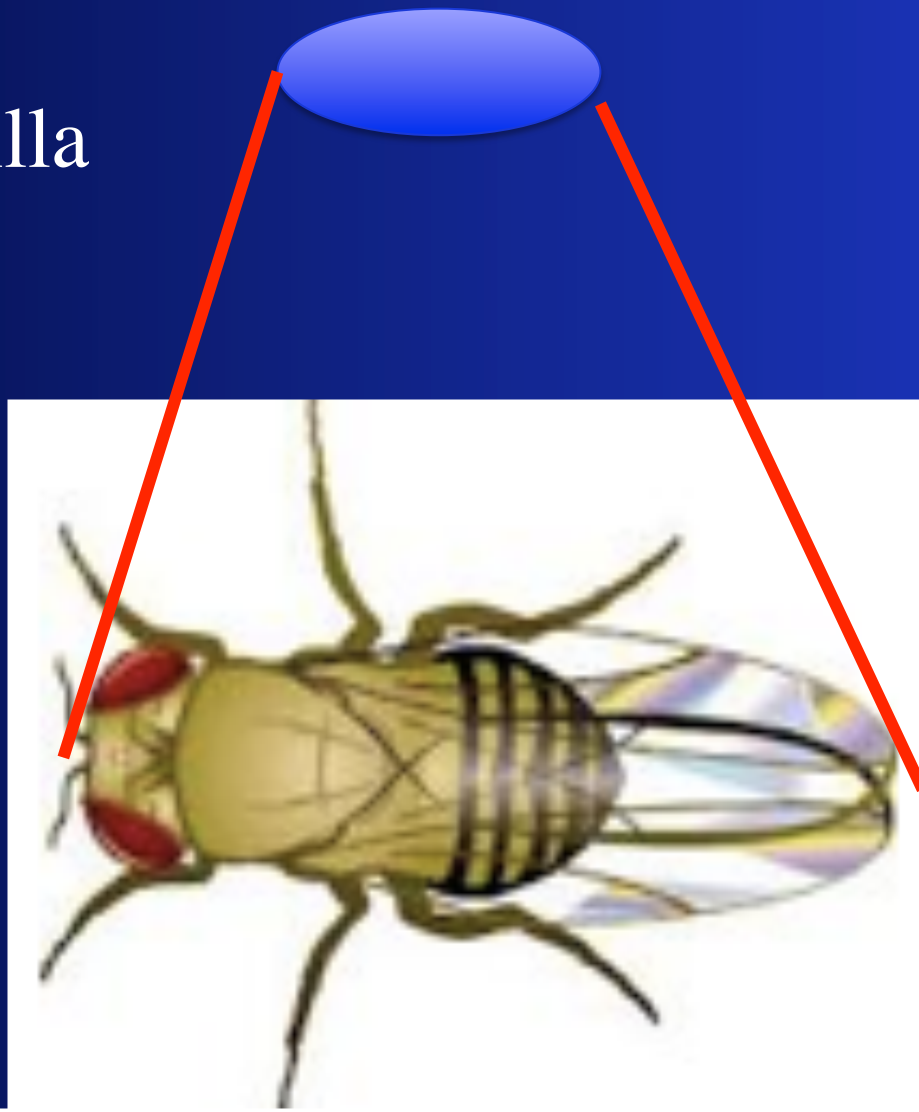
PIP_2, PIP_3

What process(es) account for segregation of chemicals?

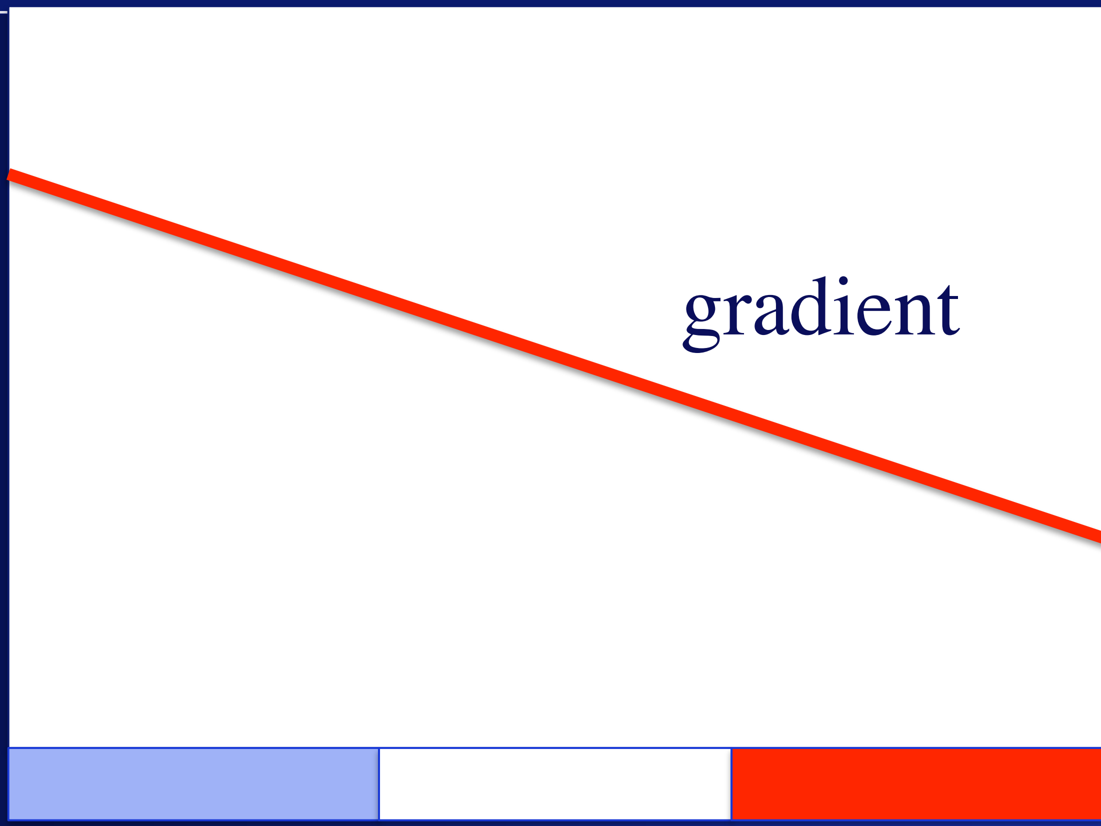
Patterns on a larger scale

Patterns in development

Drosophilla

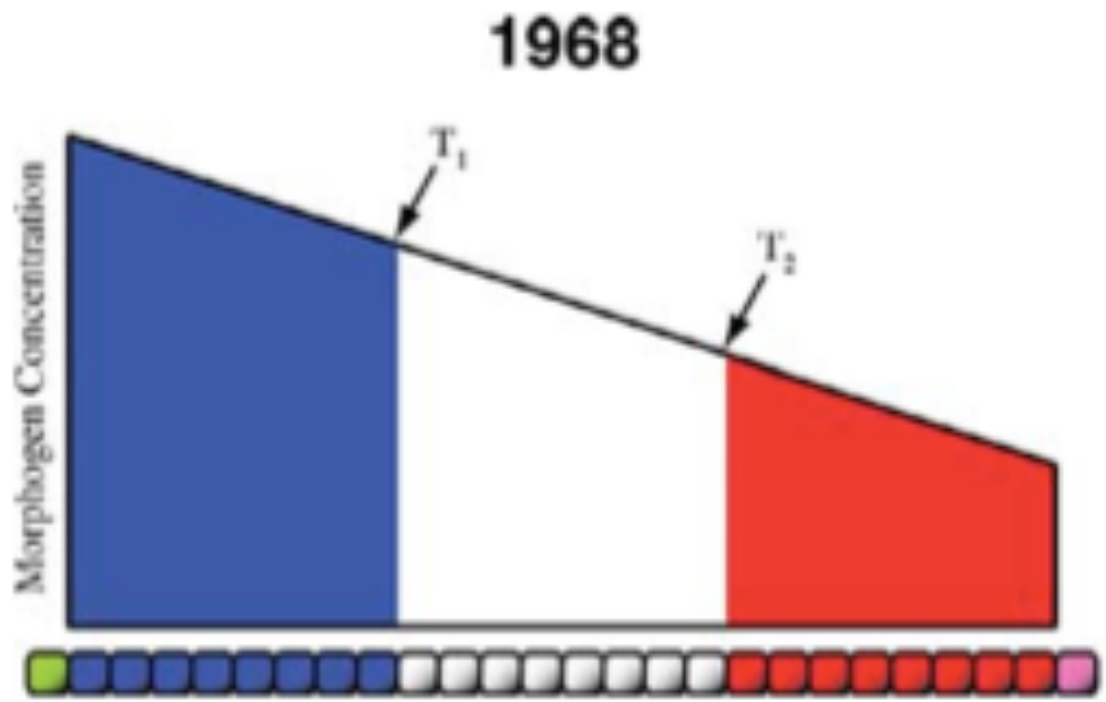


Interpreting a chemical gradient?



Morphogen gradient:
can it lead to multiple cell types?

Wolpert's French Flag

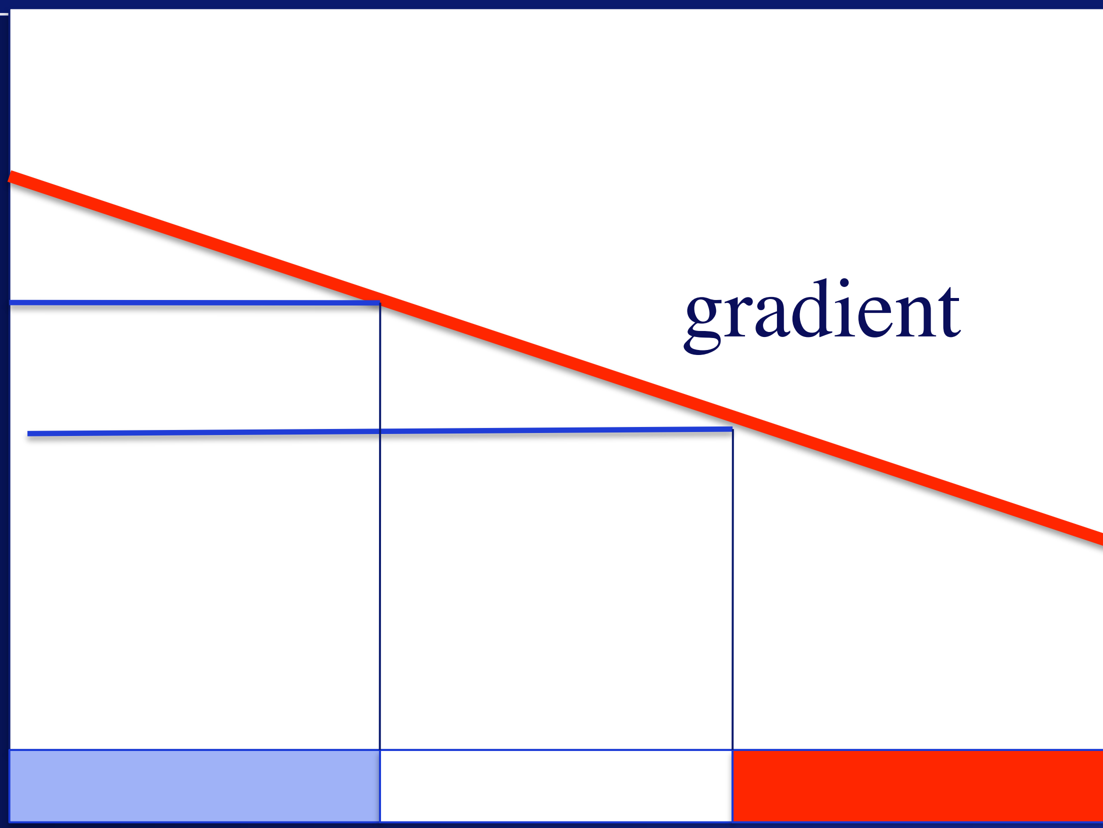


Citation: Jaeger J, Martinez-Arias A (2009) Getting the measure of positional information. PLoS Biol 7(3): e1000081. doi:10.1371/journal.pbio.1000081

How it was proposed to work

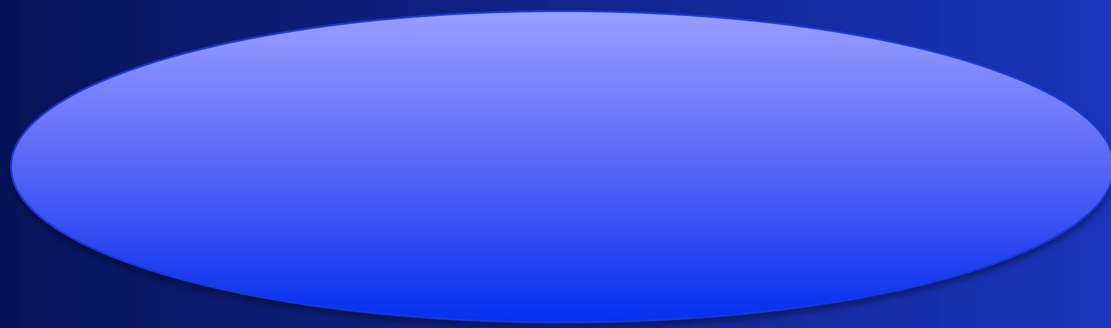
- Spatial gradients of “morphogens” create the subdivision
- Threshold concentrations of morphogen trigger gene expression in the cells in the tissue, leading to distinct expression.

Thresholds



Example: early morphogenesis in the fly (Drosophila)

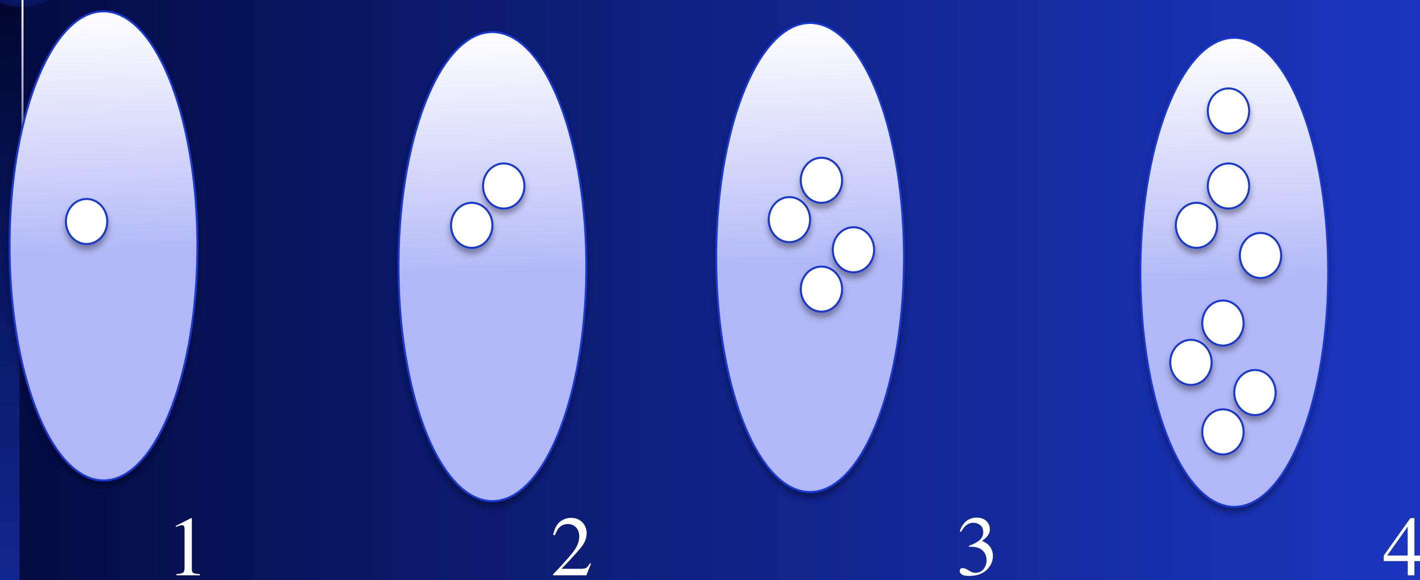
Embryo initially has no major internal boundaries



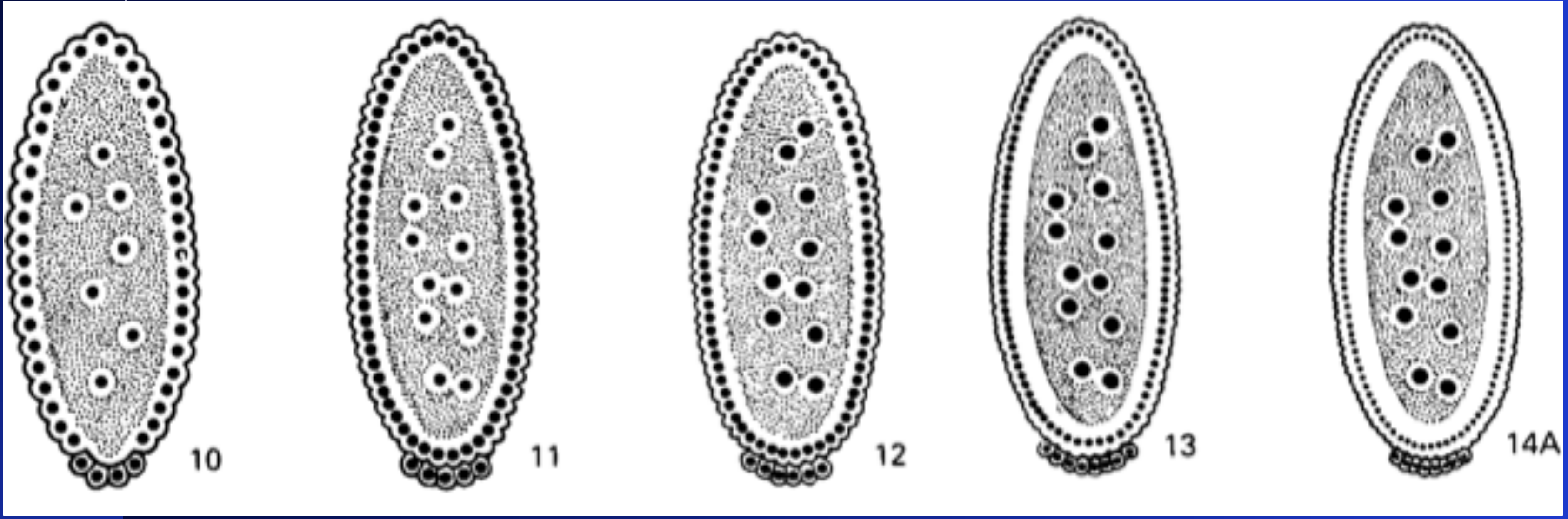
Front
(anterior)

back
(posterior)

Stages



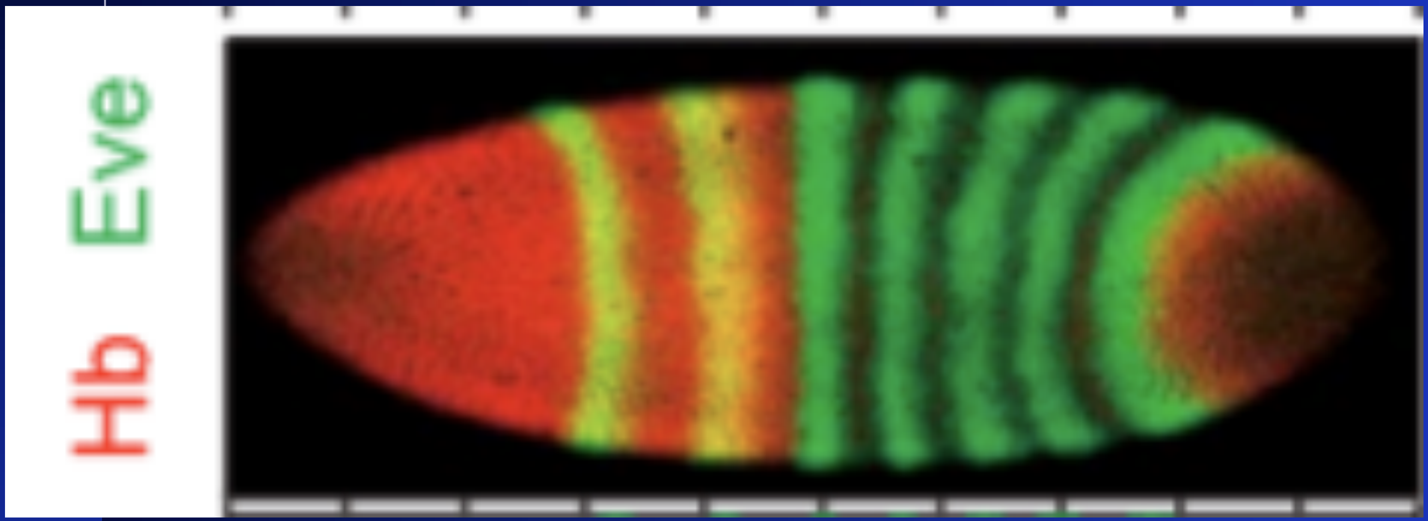
Stages



VICTORIA E. FOE AND BRUCE M. ALBERTS

J. Cell Sci. **61**, 31–70 (1983)

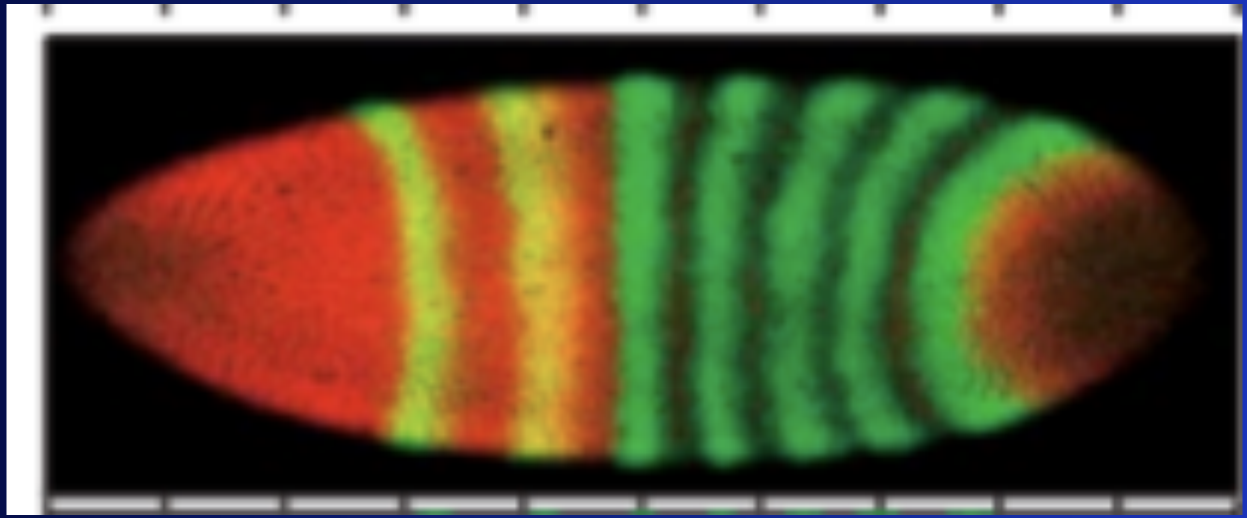
Later: Patterns of gene products



Bergmann S, Sandler O, Sberro H, Shnider S, Schejter E, et al. (2007) Pre-steady-state decoding of the Bicoid morphogen gradient. PLoS Biol 5(2): e46. doi:10.1371/ journal.pbio. 0050046

What is the question?

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



Bergmann S, Sandler O, Sberro H, Shnider S, Schejter E, et al. (2007) Pre-steady-state decoding of the Bicoid morphogen gradient. PLoS Biol 5(2): e46. doi:10.1371/ journal.pbio.0050046

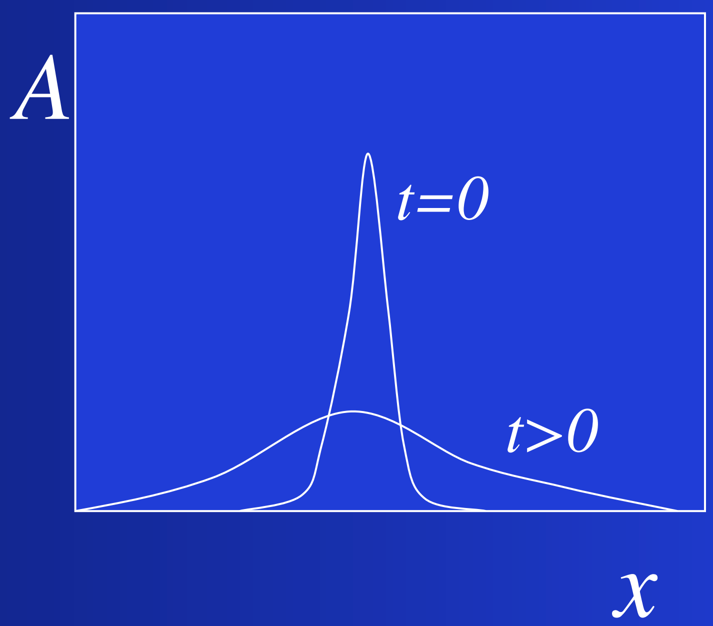
Reaction diffusion systems and Patterns

On its own, diffusion promotes uniformity

Diffusion

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

Units: $[D] = L^2/t$

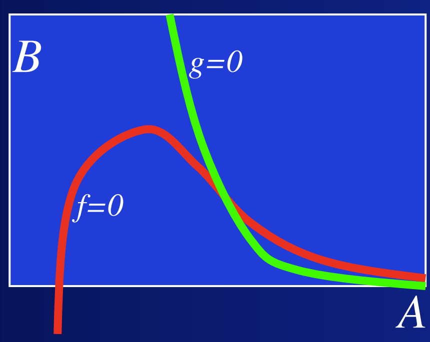


Linked to some reactions, it can CAUSE patterns to form spontaneously

Reaction

$$\frac{\partial A}{\partial t} = f(A,B)$$

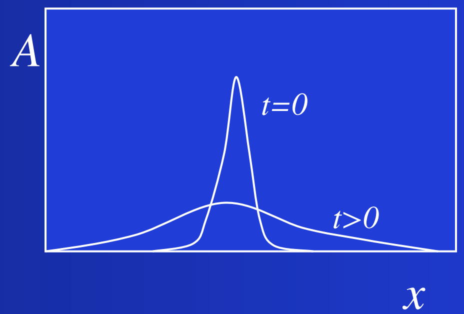
$$\frac{\partial B}{\partial t} = g(A,B)$$



+

Diffusion

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



Units: $[D] = L^2/t$

Example: (Schnakenberg)

$$\frac{\partial A}{\partial t} = f(A,B) + D_A \frac{\partial^2 A}{\partial x^2}$$

$$\frac{\partial B}{\partial t} = g(A,B) + D_B \frac{\partial^2 B}{\partial x^2}$$

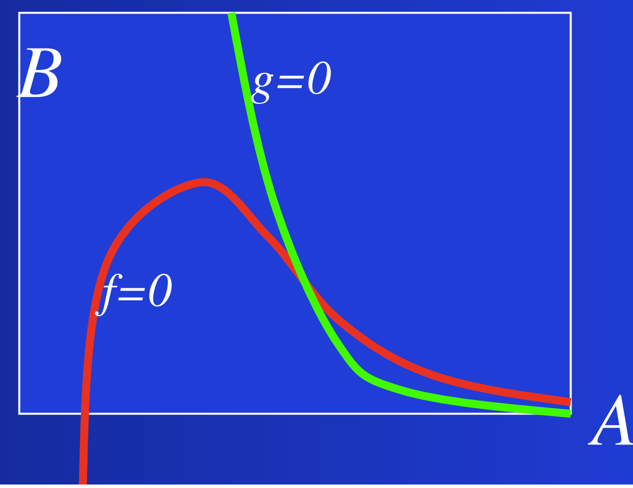
$$S_1 \Leftrightarrow A$$

$$S_2 \xrightarrow{k4} B$$

$$B + 2A \xrightarrow{k3} 3A$$

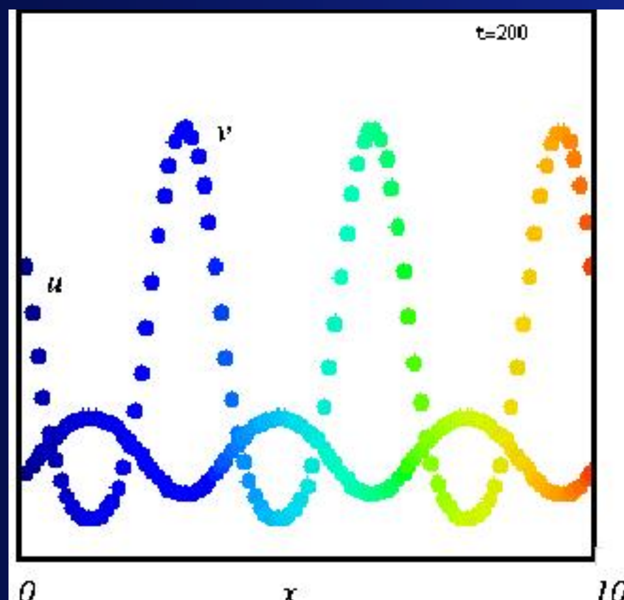
$$f(A,B) = k_1 - k_2 A + k_3 A^2 B$$

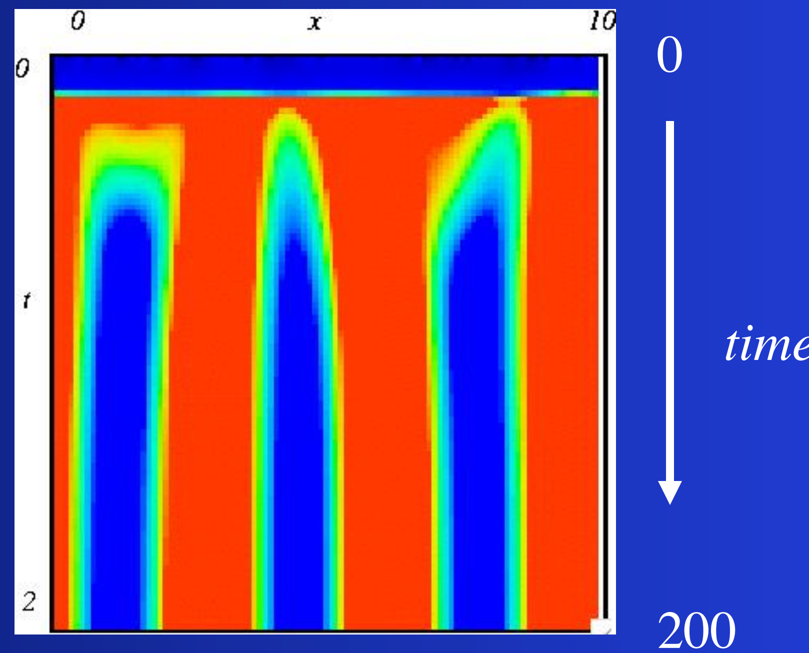
$$g(A,B) = k_4 - k_3 A^2 B$$



Example: Shnakenberg RD system

A





Starting close to the HSS, the system evolves a spatial pattern that persists with time.

How does it work?

A.M. Turing, *The Chemical Basis of Morphogenesis*, Phil. Trans. R. Soc. London B237, pp.37-72, 1952

Derived conditions for diffusion-driven pattern formation in a reaction-diffusion system.

Why does it work? Basic idea

- Equations:

$$\frac{\partial C_1}{\partial t} = R_1(C_1, C_2) + D_1 \frac{\partial^2 C_1}{\partial x_2},$$

$$\frac{\partial C_2}{\partial t} = R_2(C_1, C_2) + D_2 \frac{\partial^2 C_2}{\partial x^2}.$$

- 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:

$$C_1(x, t) = \bar{C}_1 + C_1'(x, t)$$
$$C_2(x, t) = \bar{C}_2 + C_2'(x, t)$$

- 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

$$a_{11} = \left.\frac{\partial R_1}{\partial C_1}\right|_{\bar{C}_1, \bar{C}_2}, \qquad a_{12} = \left.\frac{\partial R_1}{\partial C_2}\right|_{\bar{C}_1, \bar{C}_2},$$

$$a_{21} = \left.\frac{\partial R_2}{\partial C_1}\right|_{\bar{C}_1, \bar{C}_2}, \qquad a_{22} = \left.\frac{\partial R_2}{\partial C_2}\right|_{\bar{C}_1, \bar{C}_2},$$

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:

$$\begin{pmatrix} C_1' \\ C_2' \end{pmatrix} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} \cos qx \, e^{\sigma t}.$$

Eigenfunction Eigenvalue

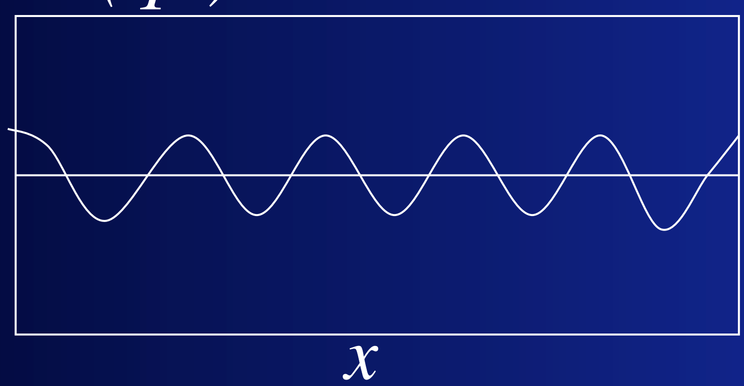
Eigenfunctions chosen to satisfy both the PDE and BC's (e.g. no flux at x=0, L): $q = n\pi / L$

Interpretation

- The form of the perturbations

$$\begin{pmatrix} C_1' \\ C_2' \end{pmatrix} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} \cos qx \, e^{\sigma t}.$$

$Cos(qx)\,\mathrm{e}^{\sigma t}$

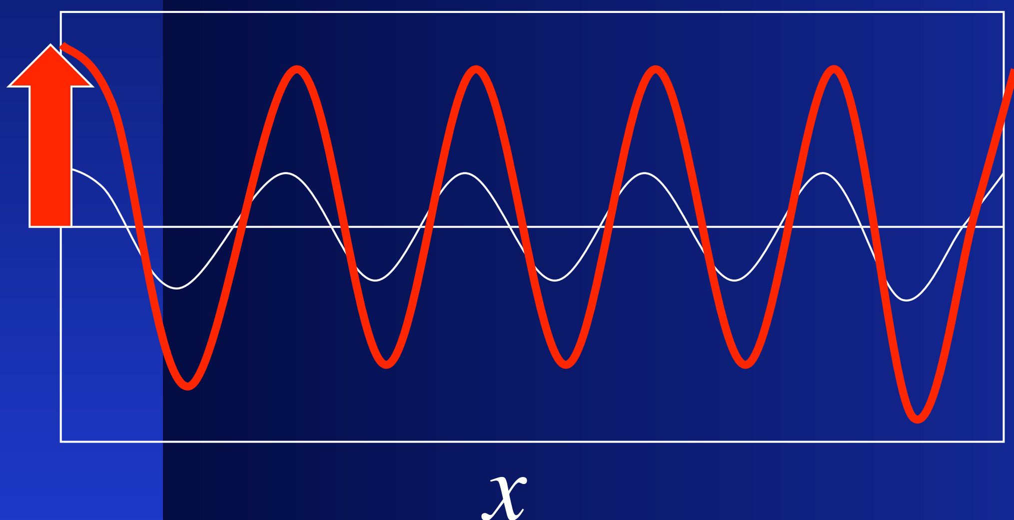


The value q is the wave number (spatial periodicity) and σ is the rate of growth

Spatial instability → pattern formation

If the rate of growth σ is >0 then perturbations will grow

$Cos(qx)\,e^{\sigma t}$



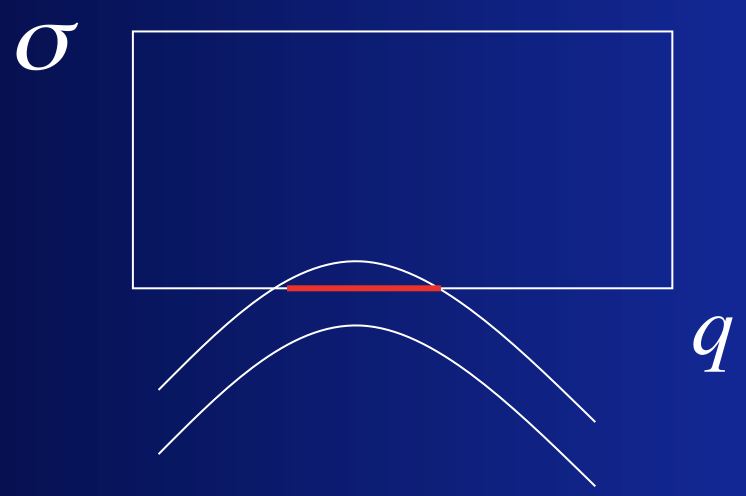
$$\begin{pmatrix} C_1' \\ C_2' \end{pmatrix} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} \cos qx\, e^{\sigma t}.$$

Dispersive waves

- In general, waves of different periodicity will grow or decay at different rates, so the growth rate σ will depend on the wave number q.

Condition for pattern formation:

- There exists some (range of) wavenumber values such $\sigma > 0$



Substitute the perturbations

$$\begin{pmatrix} C_1' \\ C_2' \end{pmatrix} = \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix} \cos qx \, e^{\sigma t}.$$

into the linearized equations

$$\frac{\partial C_1'}{\partial t} = a_{11} C_1' + a_{12} C_2' + D_1 \frac{\partial^2 C_1'}{\partial x^2},$$

$$\frac{\partial C_2'}{\partial t} = a_{21} C_1' + a_{22} C_2' + D_2 \frac{\partial^2 C_2'}{\partial x^2},$$

What set of (algebraic) equation do you get ?

Answer:

$$\alpha_1\sigma = a_{11}\alpha_1 + a_{12}\alpha_2 - D_1q^2\alpha_1,$$
$$\alpha_2\sigma = a_{21}\alpha_1 + a_{22}\alpha_2 - D_2q^2\alpha_2.$$

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 σ:

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

Characteristic equation for σ:

- Eqn $\sigma^2 - \beta\sigma + \gamma = 0$

- Where $\beta = -(-a_{22} + D_2 q^2 - a_{11} + D_1 q^2)$
- $\gamma = (a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12} a_{21}$

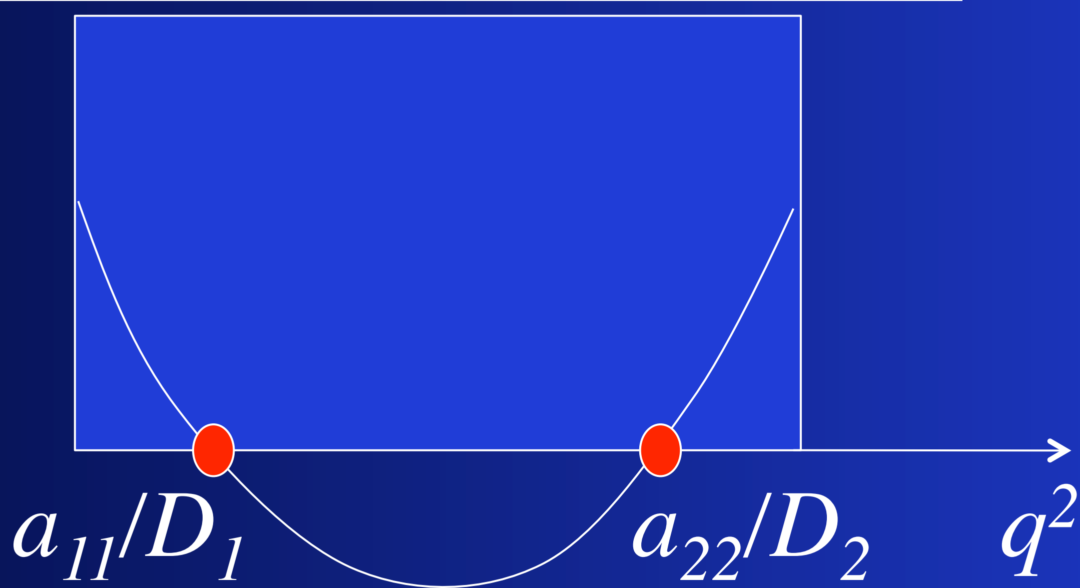
Technical stuff

- It is easy to show that for σ to be positive, γ has to be negative.
- $\gamma = (a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12} a_{21} < 0$
- Look for wave number values such that $\gamma < 0$

When is gamma negative?

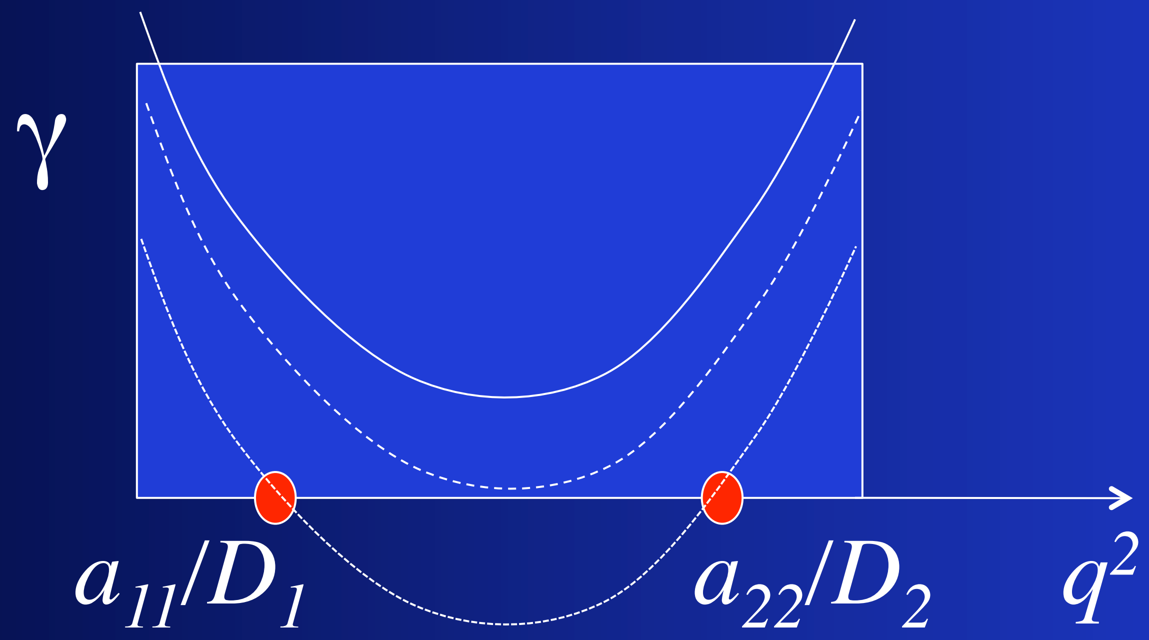
- Gamma depends on q^2 quadratically

$$[(a_{11} - D_1 q^2)(a_{22} - D_2 q^2)$$



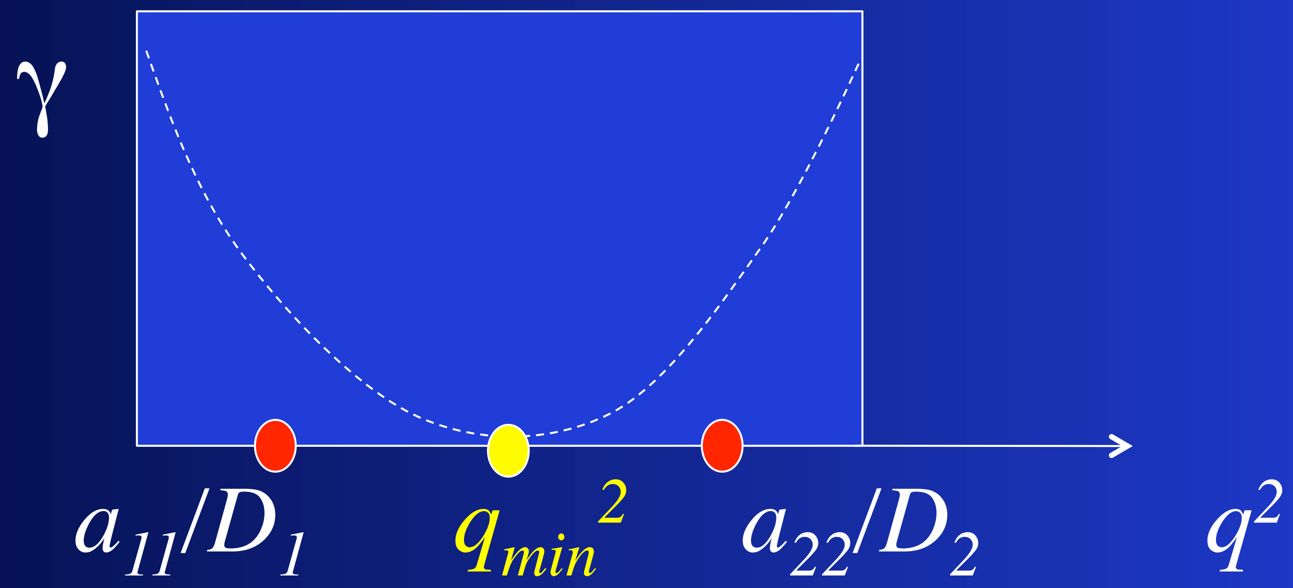
When is gamma negative?

- γ = $(a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12}a_{21}$



Gamma first becomes negative at

$$q_{\min}^2 = \frac{1}{2}\left(\frac{a_{22}}{D_2} + \frac{a_{11}}{D_1}\right)$$



Condition for instability

- Use the criterion that

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

- Obtain (details omitted)

$$(a_{11}a_{22} - a_{12}a_{21}) - \frac{1}{4}\left(\frac{D_1 a_{22} + D_2 a_{11}}{D_1 D_2}\right) < 0.$$

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

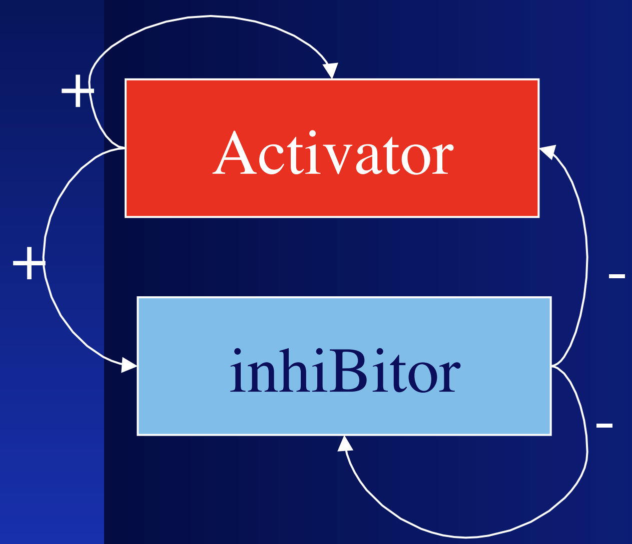
- (Detailed arguments omitted here.)
- Case 1: $a_{12} < 0, \qquad a_{21} > 0$
- Case 2: $a_{12} > 0, \qquad a_{21} < 0$
- In either case, need $D_1 < D_2$

Turing (1952): "The chemical basis of morphogenesis"

Diffusion

Reaction *(f,g)*

$D_A << D_B$



$$\frac{\partial A}{\partial t} = f(A,B) + D_A \frac{\partial^2 A}{\partial x^2}$$

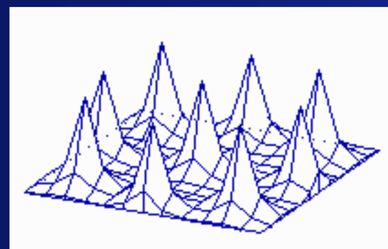
$$\frac{\partial B}{\partial t} = g(A,B) + D_B \frac{\partial^2 B}{\partial x^2}$$

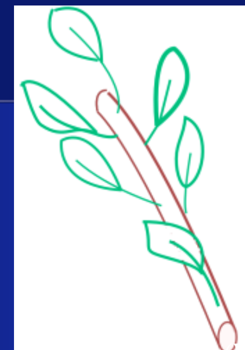
With "appropriate" reaction kinetics, an RD system can form spatial patterns due to the effect of diffusion.

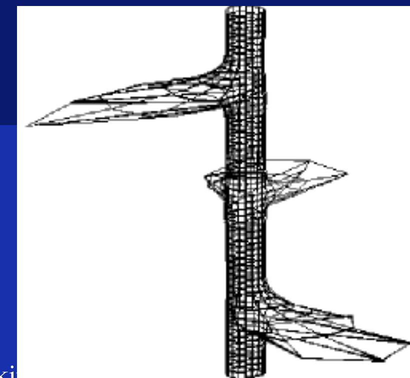
A.M. Turing, *(1952)* Phil. Trans. R. Soc. London B237, pp.37-72, 1952

Pattern formation in biology

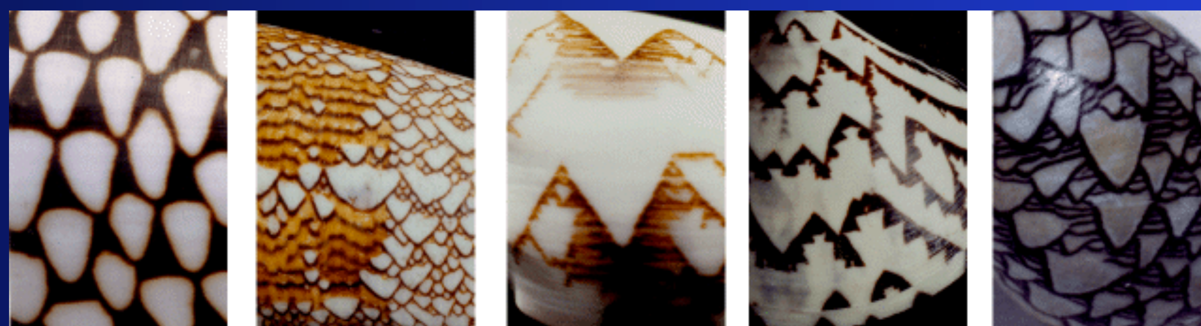
Hans Meinhardt





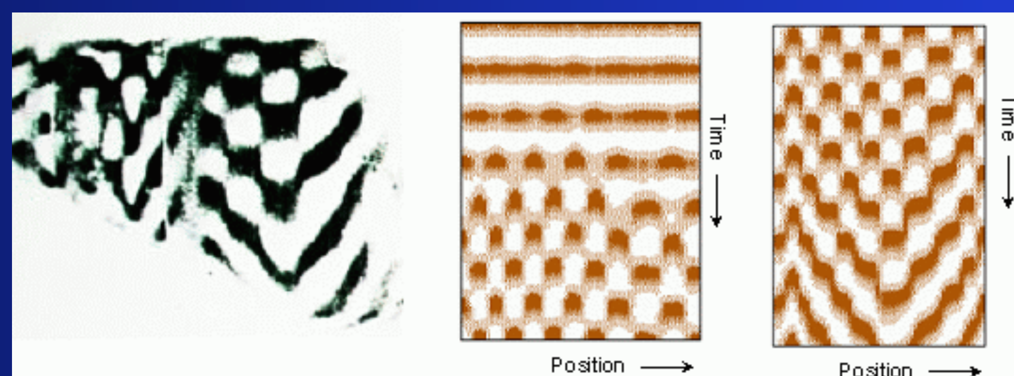


Phyllotaxis (Wikipedia)



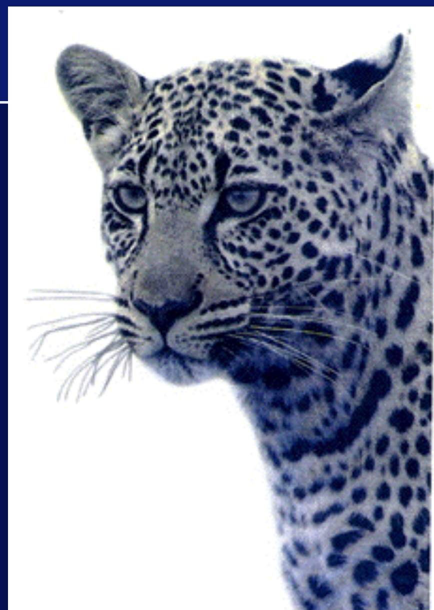
$$\frac{\partial a}{\partial t} = \frac{\rho\, a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_o$$

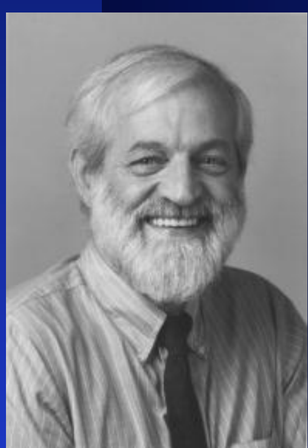
$$\frac{\partial h}{\partial t} = \rho\, a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2}$$

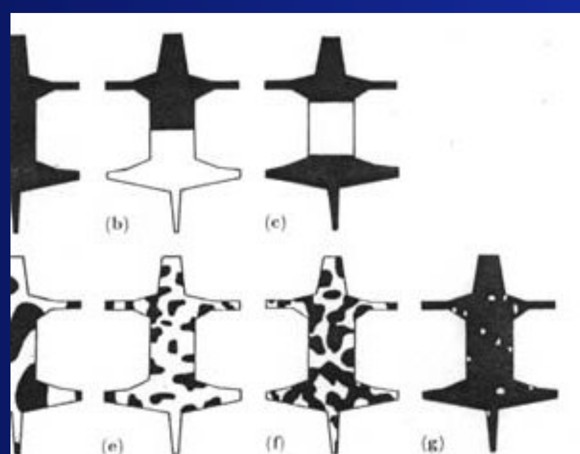


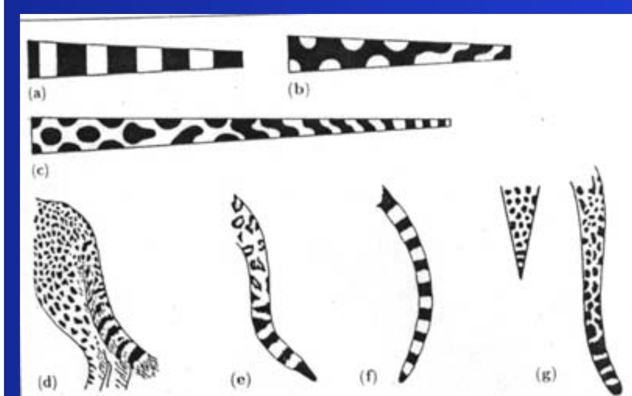
http://www.eb.tuebingen.mpg.de/departments/former-departments/h-meinhardt/home.html

Reaction-Diffusion systems and animal coat patterns







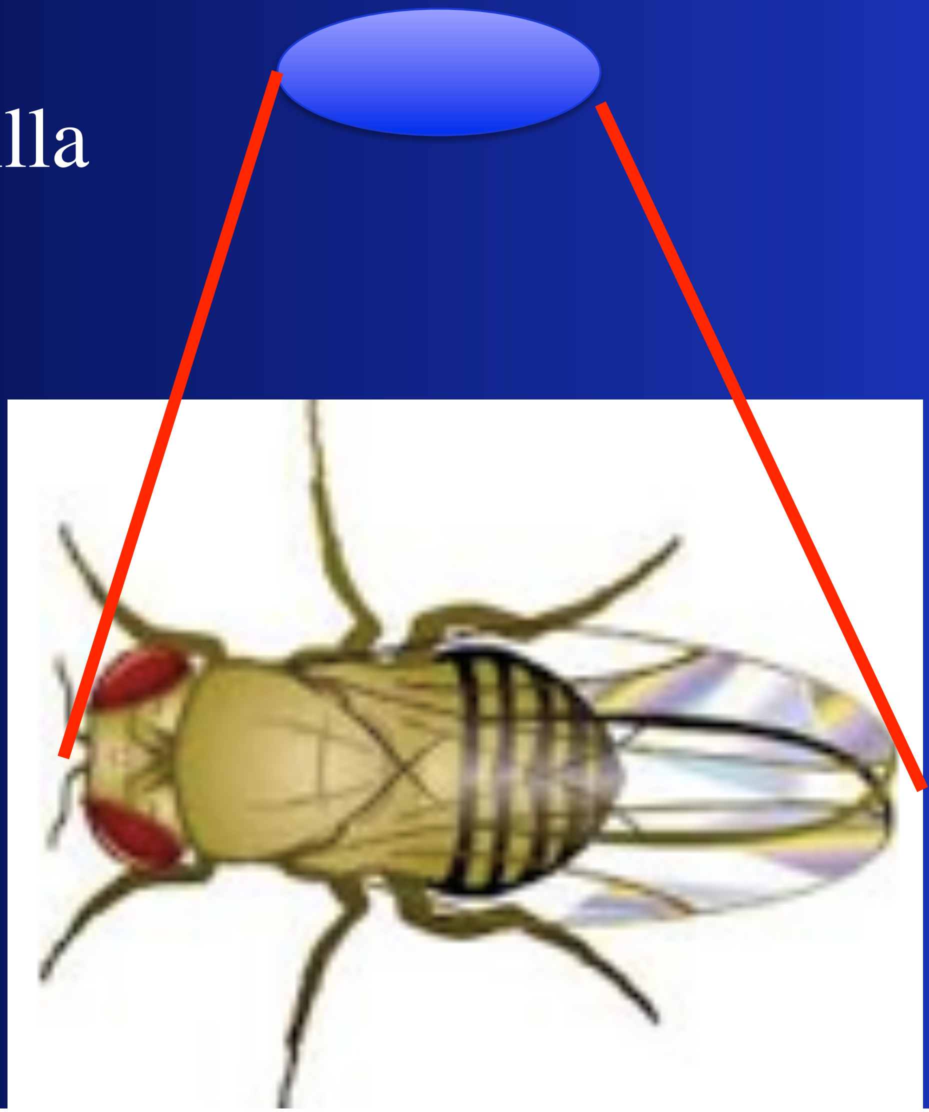


J.D Murray, A pre-**pattern** formation mechanism for **animal coat** markings, J. Theor. Biol. 88: 161-199, 1981

Is biological pattern all based on Turing mechanism?

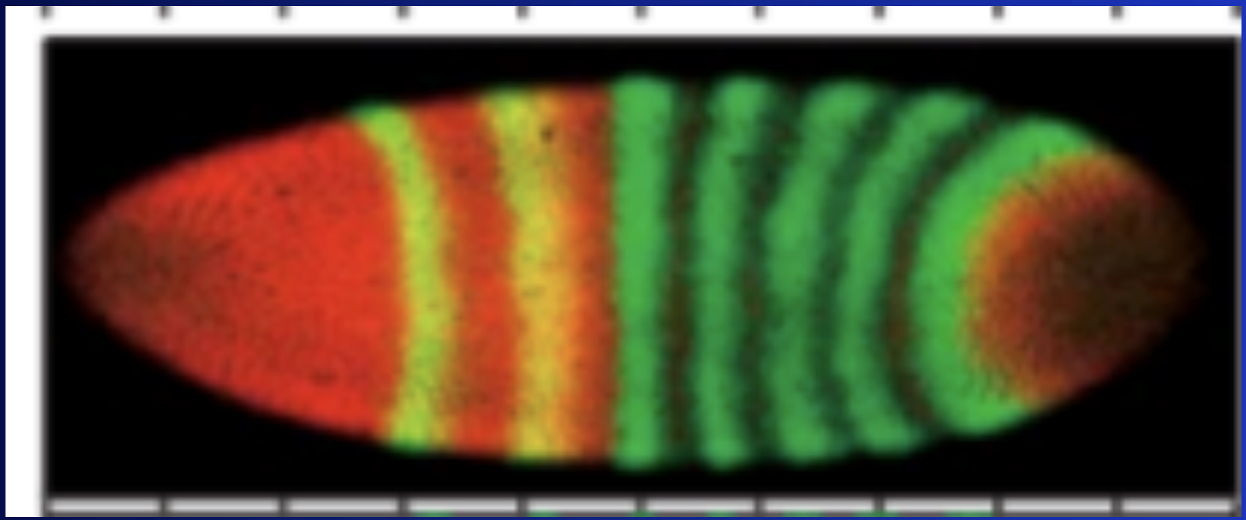
Back to the fly

Drosophilla



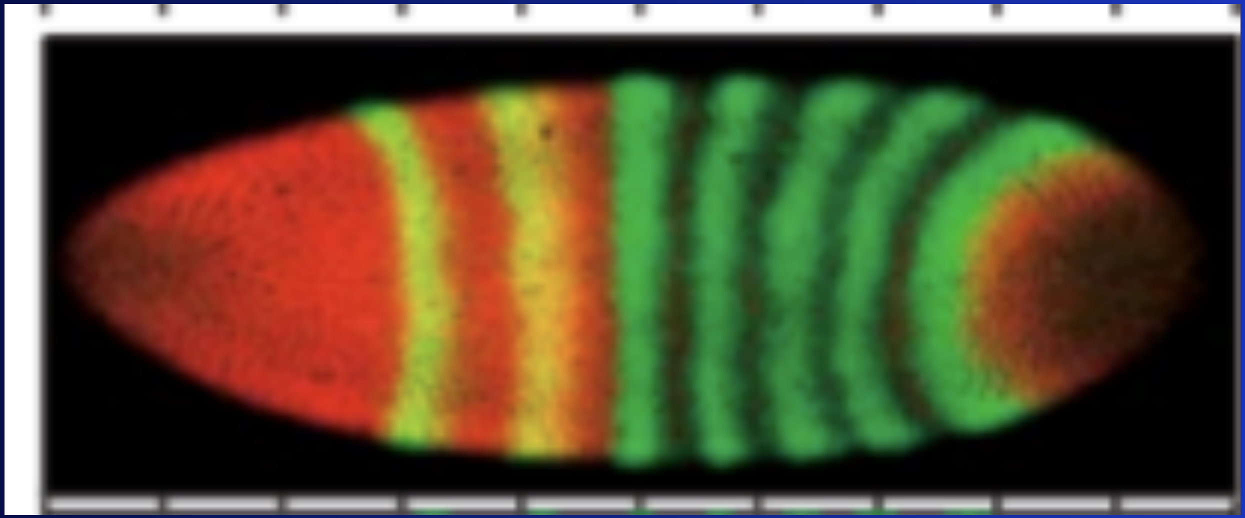
Back to the fly:

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

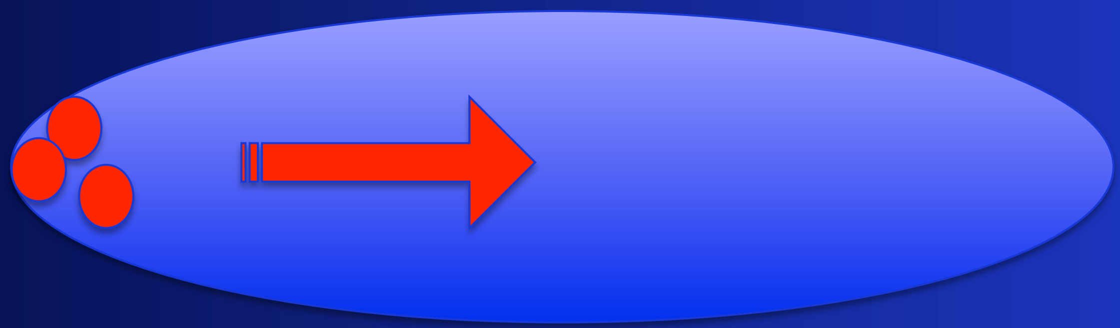


Turing system?

- 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

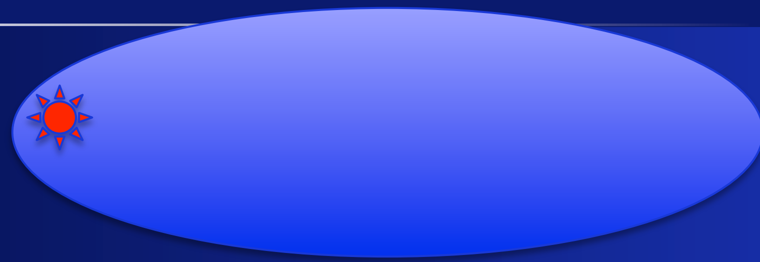


Front
(anterior)

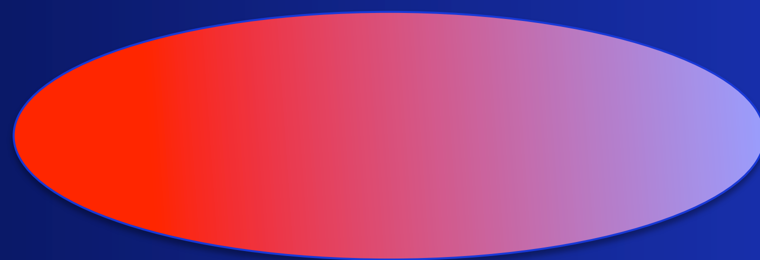
back
(posterior)

Bicoid

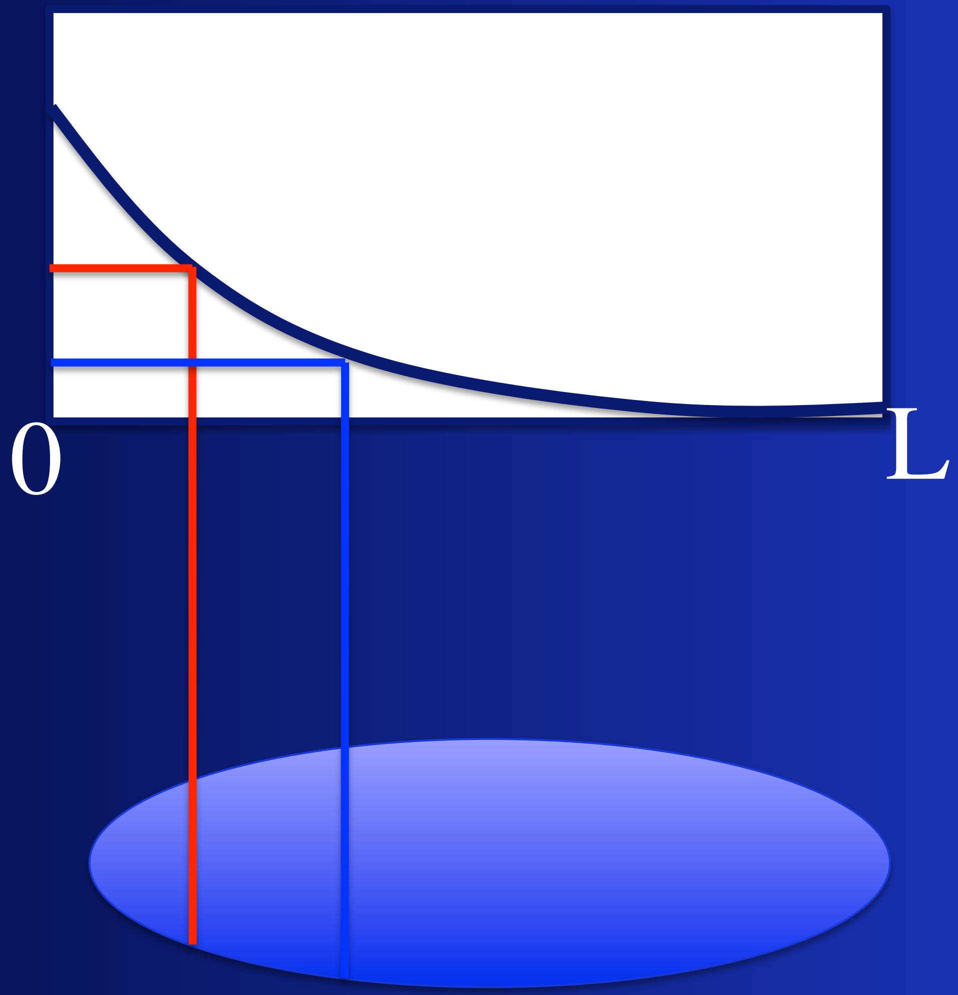
RNA



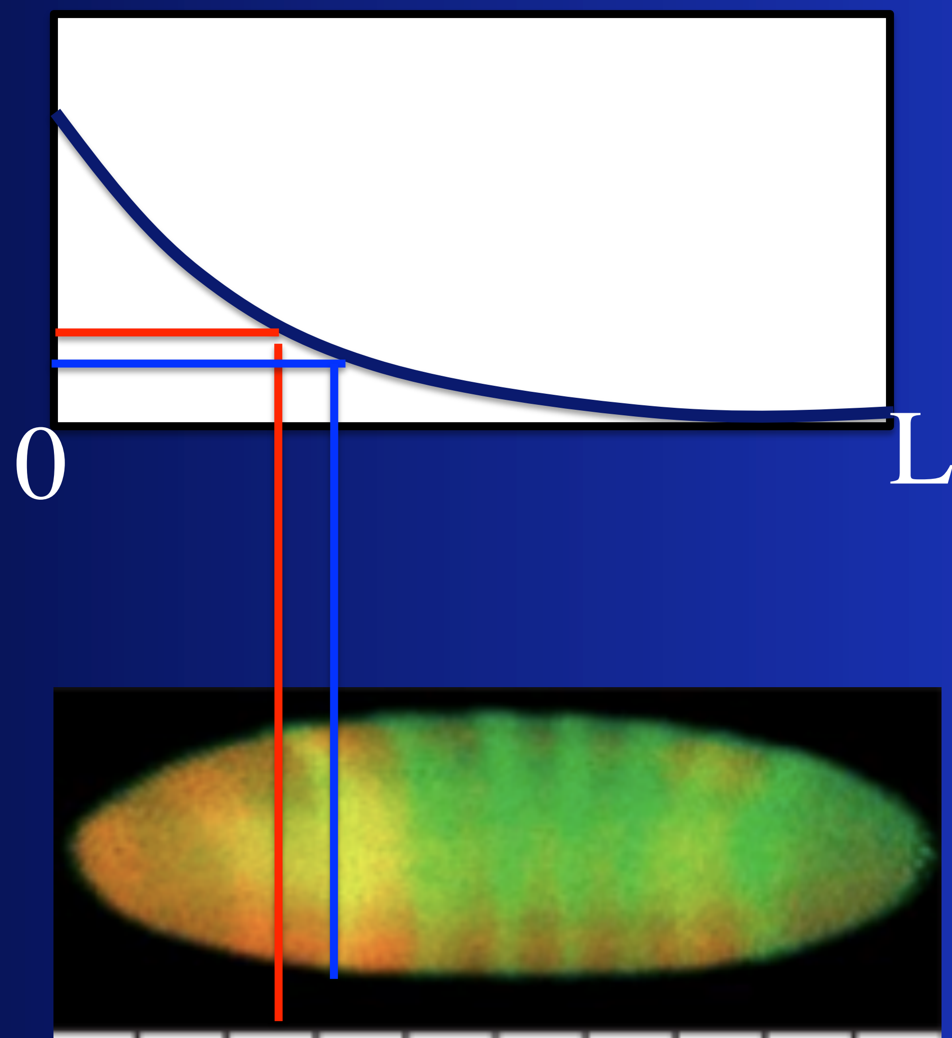
Protein



“Reading the bicoid gradient”



"Reading the bicoid gradient"



. PLoS Biol 5(2): e46. doi:10.1371/ journal.pbio.0050046

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."

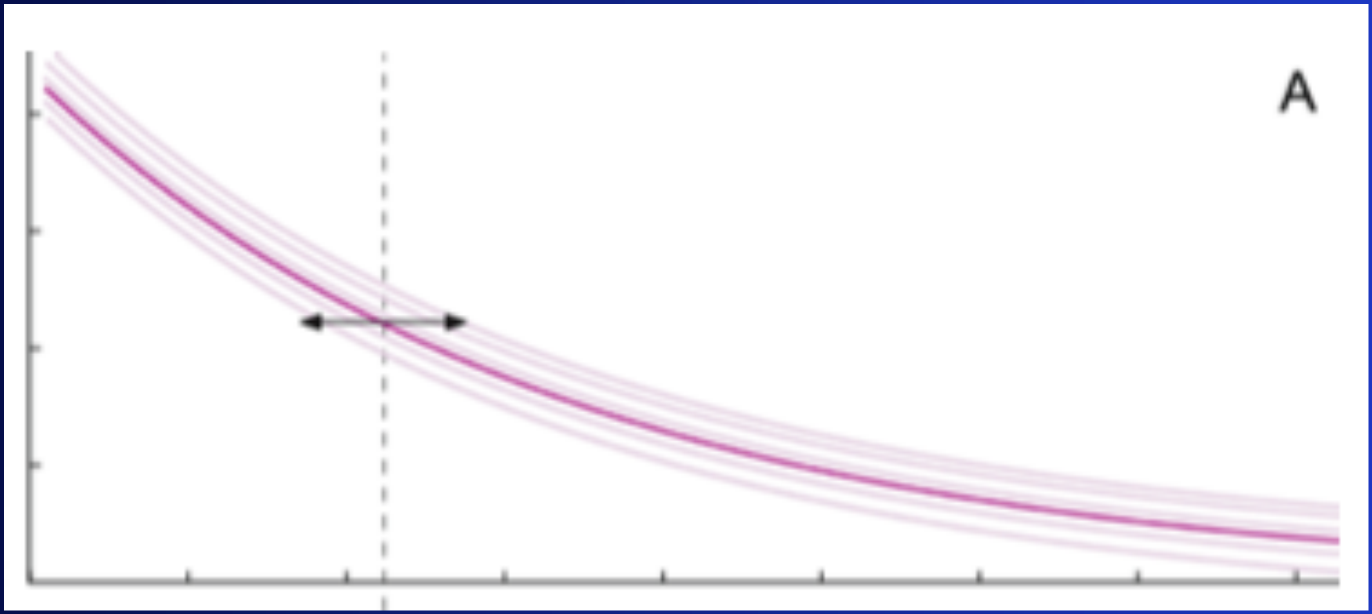
Bicoid diffusion model

- Equation for the morphogen gradient

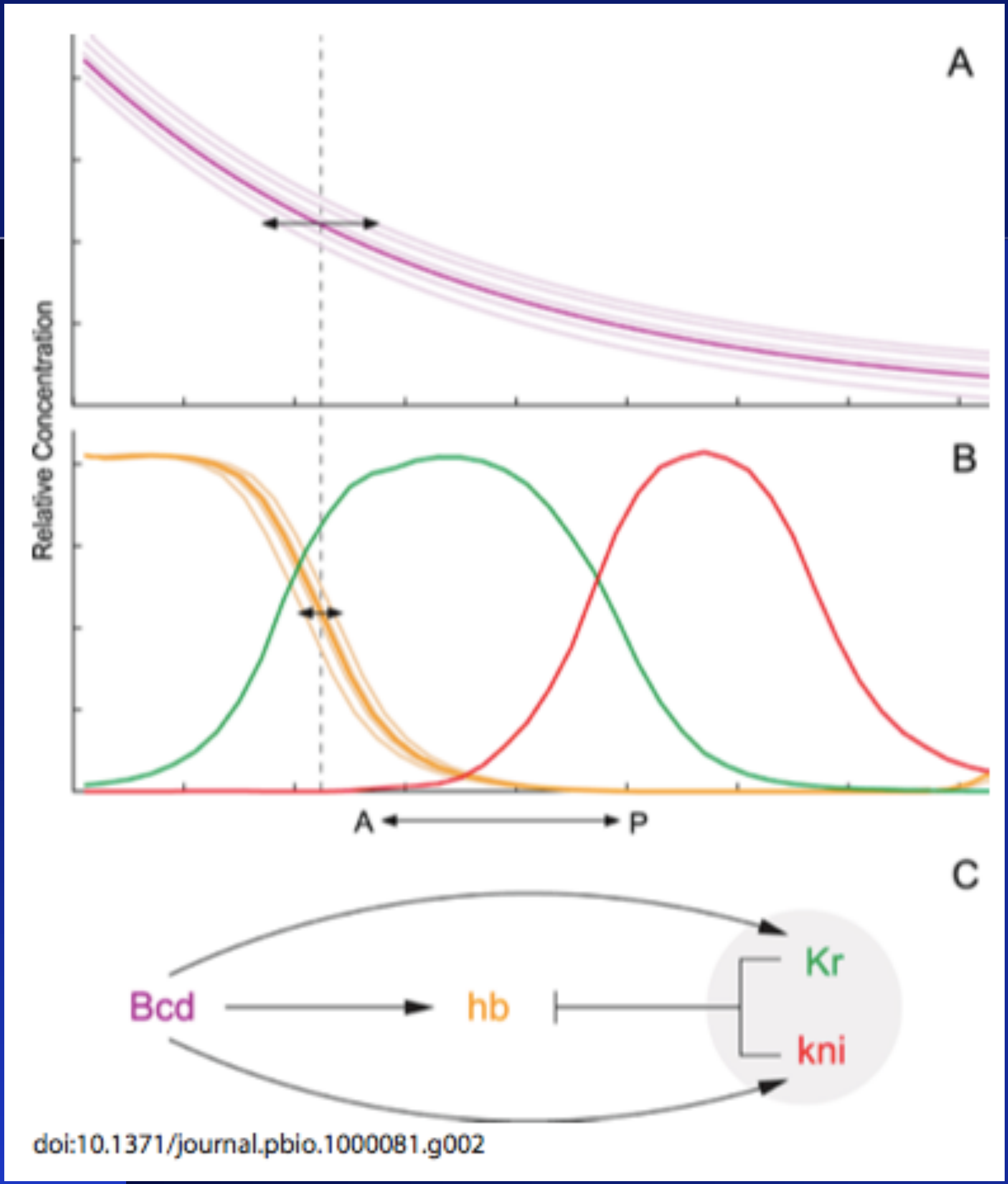
$$\frac{\partial M}{\partial t} = D\nabla^2 M - \tau^{-1} M + s_0 \delta(x),$$

Bicoid gradient

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



Citation: Jaeger J, Martinez-Arias A (2009) Getting the measure of positional information. PLoS Biol 7(3): e1000081. doi:10.1371/journal.pbio.1000081



Bicoid

Other genes

Feedback interactions sharpen the gradients

Citation: Jaeger J, Martinez-Arias A (2009) Getting the measure of positional information. PLoS Biol 7(3): e1000081. doi:10.1371/journal.pbio.1000081