

General framework and useful tools

The dynamics of a general non-linear system can be described by a set of coupled differential equations:

$$\begin{aligned}\dot{x}_1 &= f_1(x_1, \dots, x_n) \\ &\vdots \\ \dot{x}_n &= f_n(x_1, \dots, x_n).\end{aligned}$$

For example, damped harmonic motion with the second order (linear) DE: $m\ddot{x} + b\dot{x} + kx = 0$

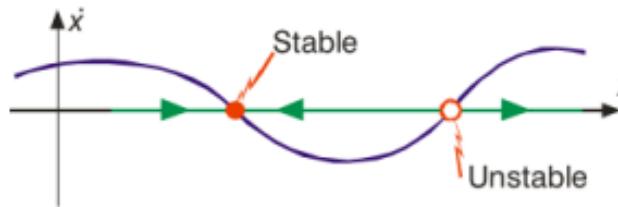
can be written a set of coupled first-order equations as:

$$\begin{aligned}\dot{x}_1 &= x_2 \\ \dot{x}_2 &= -\frac{k}{m}x_1 - \frac{b}{m}x_2.\end{aligned}$$

We examine, in turn, the one-variable system (“flow on the line”), the two-variable system (“flow on the plane”) and the three-variable system (“3-D flow”). In general, an n -variable system requires n equations to represent it.

Flow on the line

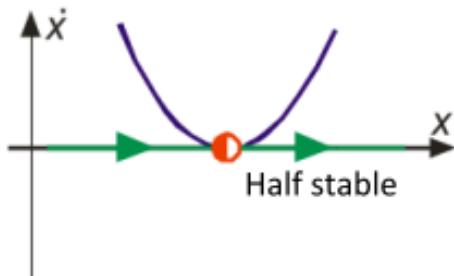
We begin by examining one-dimensional flow, that is, the dynamics of a single first-order DE, $\dot{x} = f(x)$.



Fixed points of a 1-D flow

The function f is single-valued for all x . The dynamics therefore take place along a line (the x axis).

In the notation of Strogatz, the phase-plane plot represents a vector field on the line: the velocity vector \dot{x} is shown for every x .



The trajectory is a plot of \dot{x} as a function of x . The time coordinate is thus implicit: we could, for example, mark off time ticks along the curve given any starting value of x , and hence \dot{x} , but the main properties of the system are apparent directly from the phase-plane plot.

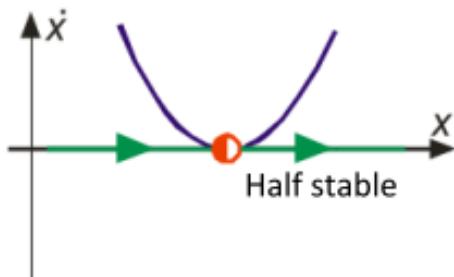
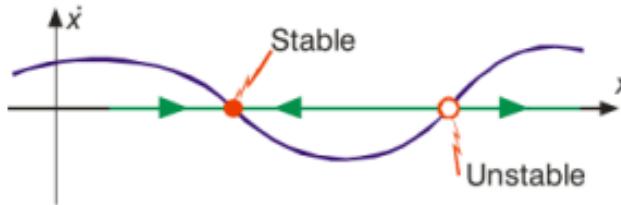
Flow on the line - cont

$$\dot{x} = f(x).$$

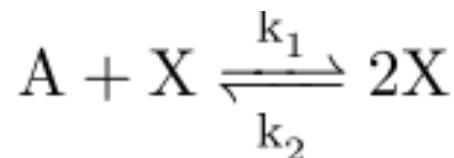
Fixed points of a 1-D flow

We can immediately identify two types of fixed point. These are values of x for which \dot{x} is zero, so that the system is, momentarily at least, at rest.

- A stable fixed point results whenever \dot{x} is zero and the slope of the \dot{x} vs x curve $d(\dot{x})/dx$ is negative. This ensures that for small fluctuations away from the fixed point, as shown in green arrows on the plot, the velocity \dot{x} is in a sense to bring the system back to the fixed point. **A stable fixed point is also known as a sink or an attractor.**
- An unstable fixed point, on the other hand, has $d(\dot{x})/dx > 0$, so that small fluctuations result in a motion directed away from the fixed point. **Other names for an unstable fixed point include source or repeller.**
- One other type of fixed point is possible, and is known as a half-stable point.



Example of Autocatalytic chemical reaction



This is a non-linear dynamical system. The presence of X stimulates further production of X hence the term “autocatalytic”.

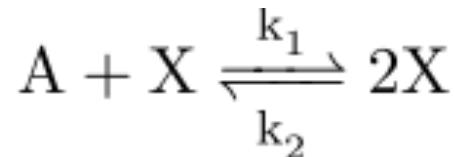
This is one model for the growth of amyloid plaques in the brain in diseases such as BSE and CJD: the presence of a small amount of plaque, X, catalyses the conversion of normal protein, A, to plaque.

There are two variables in the process: a , the concentration of reactant A, and x , the concentration of reactant X. If the concentration of A is always large, then it will be effectively constant. The problem then reduces to dynamics in one variable.

Given the rate constants for forward and reverse reactions, k_1 and k_2 , the equation governing the dynamics is

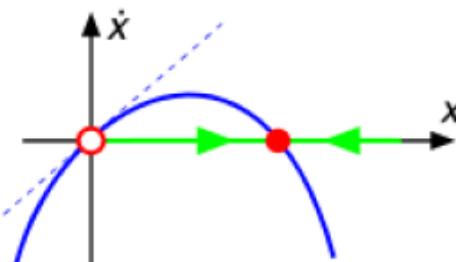
$$\dot{x} = k_1ax - k_2x^2.$$

Example of Autocatalytic chemical reaction-cont

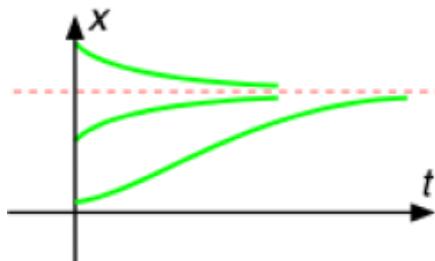


$$\dot{x} = k_1 ax - k_2 x^2.$$

The trajectory in the phase-plane can be plotted:



It is also straightforward to sketch the concentration vs time:



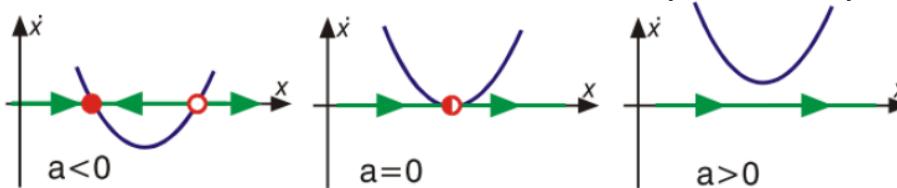
Since \dot{x} is linearly proportional to x in the vicinity of the fixed points, the approach to equilibrium must be exponential.

Here, x and a are dynamical variables: that is, they are the variables which change with time. The two other variables, k_1 and k_2 , are control variables.

In this particular case, varying the control variables does not change the general character of the dynamics, but only the details.

Control variables

Consider now the system described by $\dot{x} = x^2 + a$. As a is increased from a negative value, the two equilibria (one stable, and one unstable) first approach each other, then merge to form a half-stable fixed point, and finally annihilate. The control parameter, or variable, a , thus determines the stability of the system.



We are interested in situations, such as that shown above, where a change in one or more of the control parameters leads to discontinuities, i.e. qualitatively different dynamics, such as a change from stable to unstable behaviour.

This is the basis of Catastrophe Theory. The key result from catastrophe theory is that the number of configurations of discontinuities depends on the number of control variables, and not on the number of dynamical variables.

In particular, if there are four or fewer control variables, there are only seven distinct types of catastrophe, and in none of these is more than two dynamical variables involved.

Now we consider all cases up to two control parameters. For simplicity we restrict ourselves to a single dynamical variable, x , with little loss of generality.

Dynamics from an effective potential

We can look at the dynamics in terms of an underlying potential, which we shall here denote by $V(x)$. Stable equilibria are local minima in $V(x)$, unstable equilibria are local maxima and half-stable fixed points are points of inflection.

We are dealing with the evolution of arbitrary dynamical systems (as loosely interpreted), and hence there may not actually be a true potential energy (in mechanical systems there often is one).

In terms of the equation $\dot{x} = f(x)$, we can define the potential to be: $f(x) = -\frac{dV}{dx}$.

For a first-order system (and hence one-dimensional motion) we have to imagine a particle with an inertia which is negligible in comparison with the damping force.

The negative sign implies that the force on a particle is always “downhill”, towards lower potential. This can be shown simply by applying the chain rule to the time-derivative of the potential and applying the definition of the potential:

$$\begin{aligned}\frac{dV}{dt} &= \frac{dV}{dx} \frac{dx}{dt} \\ &= -\left(\frac{dV}{dx}\right)^2 \leq 0.\end{aligned}$$

Dynamics from an effective potential - cont

Thus $V(t)$ decreases along trajectories (in example of a particle, it always moves towards lower potential).

In summary, the potential has the following properties:

- (1) $-dV/dx$ is force-like (i.e., is in the direction of motion).
- (2) Equilibrium positions, x^* (fixed points) are given by $-dV/dx = 0$.
- (3) The stability of the fixed point is determined by the sign of $-d^2V/dx^2 |_{x^*}$.

Forms of the potential curve

The potential function can always be approximated by a Taylor series, so that
 $V(x) = a + bx + cx^2 + \dots$

We can ignore a , since it is just a constant and does not affect the dynamics.

In the vicinity of a single fixed point (i.e. equilibrium) we can also eliminate b by shifting the coordinate system to put the fixed point at the origin (although b cannot be ignored for multiple fixed points). This leaves us with
 $V(x) = cx^2 + dx^3 + ex^4 + \dots$

We can now enumerate the possibilities.

Potentials give rise to specific instabilities

(1) Harmonic Potential. This is the simplest possible form, and the only one possible for purely linear systems:

$$V(x) = \alpha x^2.$$

There is a single fixed point, $x^* = 0$, for all α . If $\alpha > 0$ then the fixed point is stable; if $\alpha < 0$ then it is unstable.

(2) Asymmetric cubic potential: The saddle-node bifurcation.

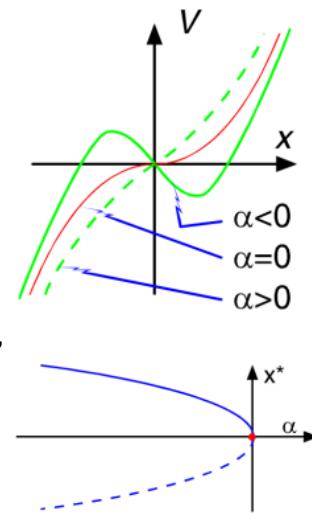
The potential has the form

$$V(x) = \alpha x + x^3.$$

For $\alpha > 0$, no equilibrium position is possible. For $\alpha < 0$, then there is always one stable and one unstable equilibrium. Here we introduce the idea of control space. We can plot the location of the fixed point, x^* , as a function of the control parameter, α :

On the control space plot, the solid line denotes the location of the stable equilibrium, while the dashed line indicates the locus of the unstable equilibrium, both as a function of α .

The form of the instability shown here is what Strogatz calls a saddle-node bifurcation, and sometimes known as a limit point instability or a fold. The phase-plane trajectories for this system were shown earlier, for the system with $\dot{x} = x^2 + a$. This is the origin of the term “saddle-node bifurcation” as a is decreased through zero the fixed point is first created, and then bifurcates into two: one stable and one unstable.



Potentials give rise to specific instabilities - cont

(3) Cubic potential with quadratic term: The transcritical bifurcation.

The potential this time includes a term in x^2 rather than a linear term as in the previous section.

$$V(x) = x^3 + \alpha x^2$$

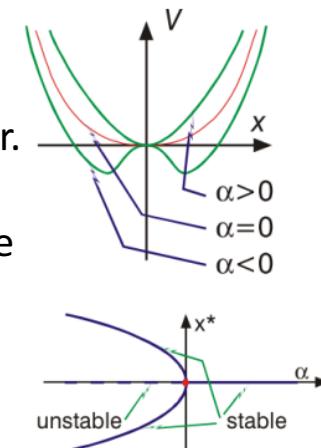
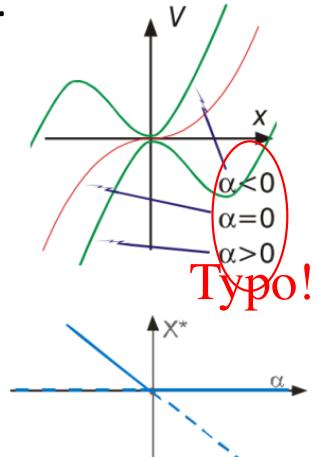
The effect of this is to give a double root, and hence a fixed point, at the origin, regardless of the location of the third root. This is generally known as the transcritical bifurcation. One physical example of such a system is the laser.

(4) Symmetric quartic potential: The pitchfork bifurcation. The potential is:

$$V(x) = x^4 + \alpha x^2.$$

- Two cases:
- For $\alpha \geq 0$ there is just one stable equilibrium;
 - For $\alpha < 0$ there is one unstable equilibrium and two stable equilibrium points.

Plotted on the side here is the case of positive term on the 4th power. In this case we refer to the Stable Symmetric Transition. It is also known as a Pitchfork Bifurcation (see Strogatz) from the shape of the bifurcation diagram, as shown at right. One example of this sort of potential is the Euler strut. If we take the negative sign on the 4th power, the additional quartic term may also act to destabilize the system, and the locus of the fixed points changes qualitatively (exercise).



Potentials give rise to specific instabilities - cont

(5) Asymmetric quartic potential with two control parameters:

the Cusp catastrophe.

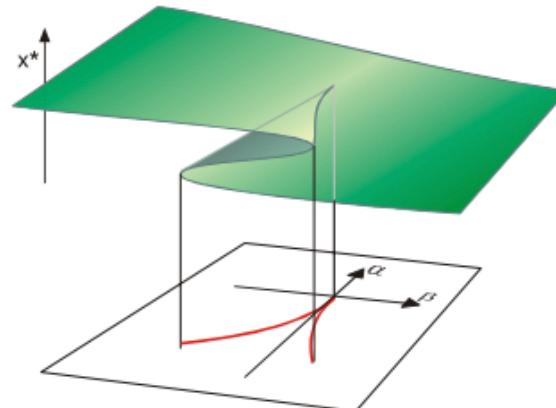
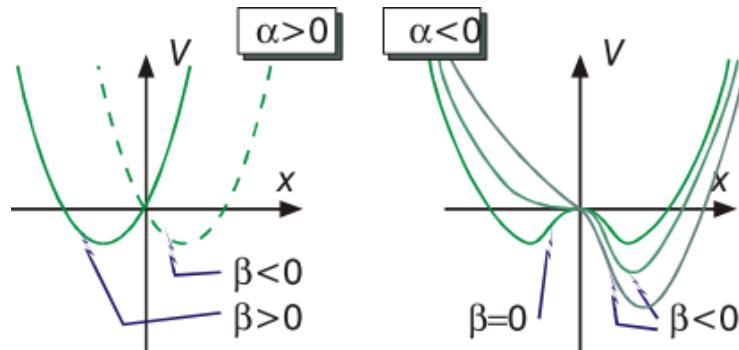
We now consider an asymmetric potential, of the form

$$V(x) = \alpha x^2 + x^4 + \beta x$$

where the βx term introduces asymmetry to the symmetric quartic form of the previous case. We now have two control parameters, α and β . Depending on the sign of α , then, we get two different sorts of behaviour.

If $\alpha > 0$ then the linear term merely shifts the position of the fixed point, but does not qualitatively change the dynamics from that of a simple harmonic potential.

If $\alpha < 0$ however, the linear term can eliminate the unstable fixed points and one of the stable fixed points as well.

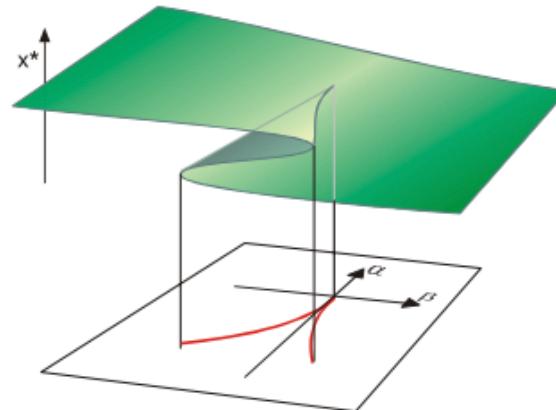
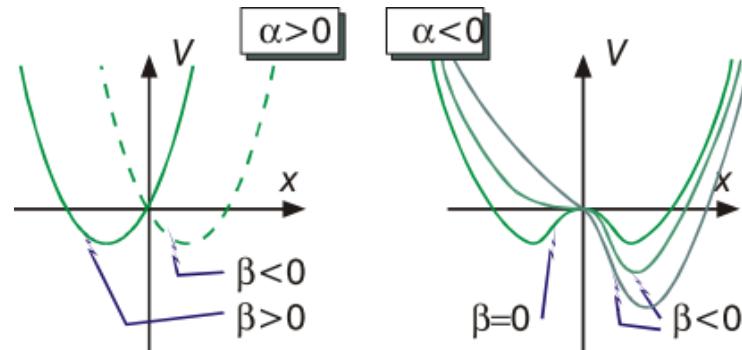


Potentials give rise to specific instabilities - cont

(5) -cont. Asymmetric quartic potential with two control parameters:
the Cusp catastrophe.

The control space diagram is now two dimensional. Consider the equilibrium surface, or a plot of the location of x^* against α and β . The bifurcation set is the set of points in the (α, β) plane dividing the plane into different regions of stability, and has a characteristic cusp shape.

As we move from the shaded to the non-shaded region (i.e. across the bifurcation set), there is a sudden change in behaviour, with marked hysteresis when the path is reversed.

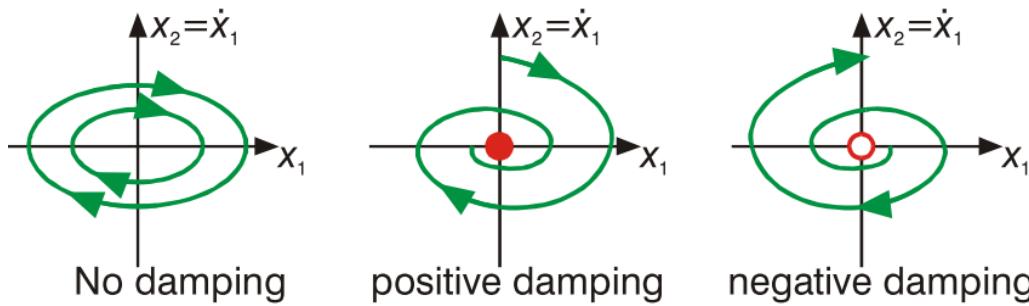


Name	$f(x)$	$V(x)$	Potential	Bifurcation diagram
Harmonic potential	$-2\alpha x$	αx^2		
Limit-point instability				
Saddle-node bifurcation	$-\alpha - 3x^2$	$\alpha x + x^3$		
Fold				
Transcritical Bifurcation	$-2\alpha x - 3x^2$	$\alpha x^2 + x^3$		
Pitchfork Bifurcation				
Stable symmetric transition	$-2\alpha x - 3x^2$	$\alpha x^2 \pm x^4$		
Cusp catastrophe	$2\alpha x + 4x^3 + \beta$	$\alpha x^2 + x^4 + \beta x$		

Two dimensional systems – e.g. harmonic oscillator $m\ddot{x} + b\dot{x} + kx = 0$

$$\dot{x}_1 = \quad x_2$$

$$\dot{x}_2 = -\frac{k}{m}x_1 - \frac{b}{m}x_2$$



We have seen fixed points. Their stability can be determined by linearising the system and looking at eigenvalues (real parts) of the matrix of partial derivatives. Two other important concepts in nonlinear systems are phasespace and nullclines.

Phase space

For 2 coordinates, the phaseplane is a sketch of the system time evolution in $(x; y)$ coordinates. This is different from a sketch against time which is the way you often see data. Phaseplanes can provide much more useful info, such as a global way of looking at your system.

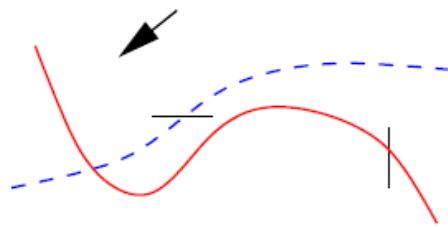
Nullclines

The latter are curves that enable one to break the plane into regions of different qualitative behaviour.

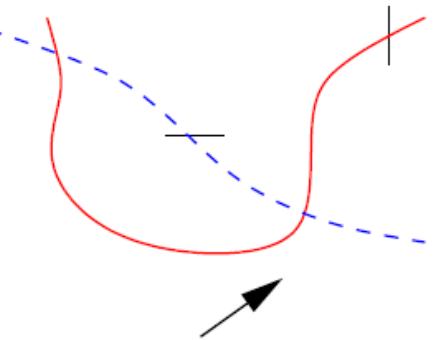
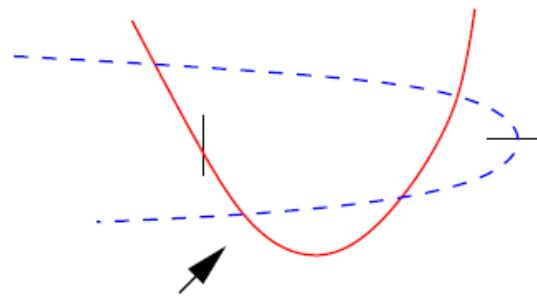
If 2 variables $x' = f(x, y)$, $y' = g(x, y)$, then nullclines are $f(x, y) = 0$ and $g(x, y) = 0$, and their crossing points are the fixed points.

Notice that x' and y' have defined sign in the regions identified by the nullclines, so a lot of the system behaviour can be determined at a glance.
e.g. could fill in these phase planes with qualitative trajectories, and determine the stability or instability of the fixed points.

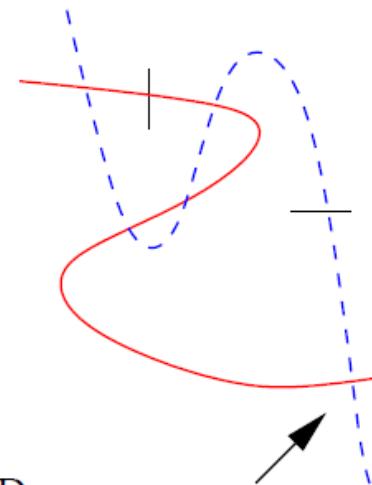
A



B



C



D

Turing's only paper on Biology

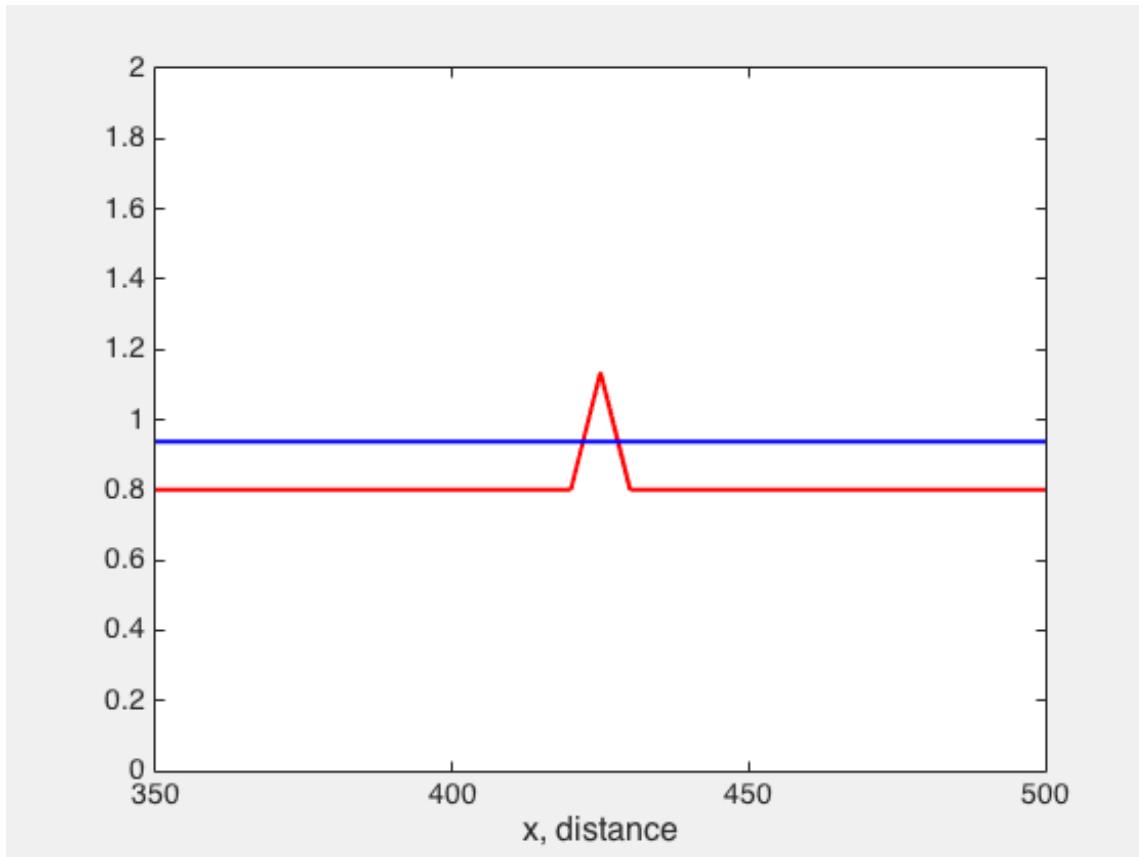
THE CHEMICAL BASIS OF MORPHOGENESIS

BY A. M. TURING, F.R.S. *University of Manchester*

(Received 9 November 1951—Revised 15 March 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system. The investigation is chiefly concerned with the onset of instability. It is found that there are six essentially different forms which this may take. In the most interesting form stationary waves appear on the ring. It is suggested that this might account, for instance, for the tentacle patterns on *Hydra* and for whorled leaves. A system of reactions and diffusion on a sphere is also considered. Such a system appears to account for gastrulation. Another reaction system in two dimensions gives rise to patterns reminiscent of dappling. It is also suggested that stationary waves in two dimensions could account for the phenomena of phyllotaxis.

Turing Patterns



Activator X (red), Inhibitor Y (blue)

- Chemical species (morphogens) X and Y diffusing extracellularly and undergoing reactions characterised by f and g
- Look for instability and see what conditions this imposes on f and g
- $D_X = D_Y = 0$ system stable spatially homogenous
- For some combinations of f,g and D_X, D_Y same fixed point unstable and pattern formation possible

Reaction Diffusion Equations

Consider the following system of 2-component system ordinary differential equations

$$\begin{aligned}\frac{\partial X}{\partial t} &= D_X \frac{\partial^2 X}{\partial x^2} + f(X, Y) \\ \frac{\partial Y}{\partial t} &= D_Y \frac{\partial^2 Y}{\partial x^2} + g(X, Y)\end{aligned}$$

with initial conditions

$$\begin{aligned}X(x, 0) &= X_0(x) \\ Y(x, 0) &= Y_0(x)\end{aligned}$$

We are generally dealing with patterns formed in finite domains with no-flux boundary conditions and we can choose this or fixed values $X = X_b$, $Y = Y_b$.

Perturbations from Steady State

Rewrite in vector notation

$$\vec{X} = \begin{pmatrix} X \\ Y \end{pmatrix} \quad F(\vec{X}) = \begin{pmatrix} f(X, Y) \\ g(X, Y) \end{pmatrix} \quad D = \begin{bmatrix} D_X & 0 \\ 0 & D_Y \end{bmatrix}$$

$$\dot{\vec{X}} = F(\vec{X}) + D \frac{\partial^2 \vec{X}}{\partial x^2}$$

In the **absence of diffusion**

$$\vec{X} = \begin{pmatrix} X \\ Y \end{pmatrix} \quad \dot{\vec{X}} = \begin{pmatrix} f(X, Y) \\ g(X, Y) \end{pmatrix}$$

which has steady states (X^*, Y^*) . We can examine the stability of these steady states by looking at response of the system to perturbations of the steady state

$$\vec{Z} = \begin{pmatrix} X - X^* \\ Y - Y^* \end{pmatrix}$$

Linearized Equations

The time derivative of the response is given by

$$\dot{\vec{Z}} = \begin{pmatrix} \dot{X} - \dot{X}^* \\ \dot{Y} - \dot{Y}^* \end{pmatrix} = \begin{pmatrix} f(X - X^*, Y - Y^*) \\ g(X - X^*, Y - Y^*) \end{pmatrix}$$

Finding the Jacobian matrix

$$A = \begin{bmatrix} f_X & f_Y \\ g_X & g_Y \end{bmatrix}_{(X^*, Y^*)}$$

and linearizing the set of equations in the vicinity of the steady state (X^*, Y^*) gives

$$\dot{\vec{Z}} = A\vec{Z}$$

Stability Requirements

Solutions to $\dot{\vec{Z}} = A\vec{Z}$ are of the form

$$\vec{Z}(x, t) = \sum_{n=1}^2 w_i \vec{v}_i \exp(\lambda_i t)$$

where \vec{v}_i are the eigenvectors of A with eigenvalues

$$\lambda_i = \frac{Tr(A) \pm \sqrt{Tr(A)^2 - 4\text{Det}(A)}}{2}$$

and the values w_i are set by the initial conditions. The steady state of the system is linearly stable to perturbations if \vec{Z} tends to zero as at long time scales. For this requirement to be fulfilled both eigenvalues must be negative which imposes the following requirements on matrix A

$$Tr(A) < 0 \quad \text{and} \quad \text{Det}(A) > 0$$

With Diffusion

The linearized system in the presence of diffusion is given by

$$\dot{\vec{Z}} = A\vec{Z} + D \frac{\partial^2 \vec{Z}}{\partial x^2}$$

and we look for solutions of the form

$$\vec{Z} = Z_0 \exp(\lambda t) \exp(iqx)$$

i.e. the perturbations are spatial waves with wave number q whose amplitude is either growing or shrinking in time depending on the sign of λ . Substituting this into the equation above gives

$$(A - q^2 D - \lambda I) Z_0 = 0$$

The system is unstable if at least one of the eigenvalues in the matrix $A - q^2 D$ has a positive real part. This corresponds to the determinant $\text{Det}(A - q^2 D) < 0$.

Diffusion-Driven Instability

For diffusion-driven instability we have the following condition

$$\text{Det}(A - q^2 D) = h(q^2) = D_X D_Y q^4 - q^2(D_Y f_X + D_X g_Y) + \det(A) < 0$$

Two of these terms are positive :

$D_X D_Y q^4$ [physical considerations], $\det(A)$ [previous analysis] and therefore we require that

$$D_Y f_X + D_X g_Y > 0.$$

The critical case for emergence of patterns occurs for

$$h(q^2) = D_X D_Y q^4 - q^2(D_Y f_X + D_X g_Y) + \det(A) = 0.$$

Diffusion-Driven Instability II

We can calculate the value for q for which the function h is minimal which represents the wave number which grows at the onset of instability.

$$\frac{dh(q^2)}{d(k^2)} = 2D_X D_Y q^2 - (D_Y f_X + D_X g_Y) = 0$$

$$\frac{d^2 h(q^2)}{d(k^2)^2} = 2D_X D_Y > 0$$

$$q_{min}^2 = \frac{D_Y f_X + D_X g_Y}{2D_X D_Y}$$

Substituting this back into the function h and setting this to less than zero gives

$$-(D_Y f_X + D_X g_Y)^2 + 4D_X D_Y \text{Det}(A) < 0.$$

The root of this equation defines the critical diffusion constant ratio for the onset of instability (pattern formation).

Finite System Size and Admissible Modes

Consider again

$$\dot{\vec{Z}} = A\vec{Z} + D \frac{\partial^2 \vec{Z}}{\partial x^2}$$

on the interval $[0, L]$ and with zero flux boundary conditions.

Solutions are combinations of waves with discrete wave numbers

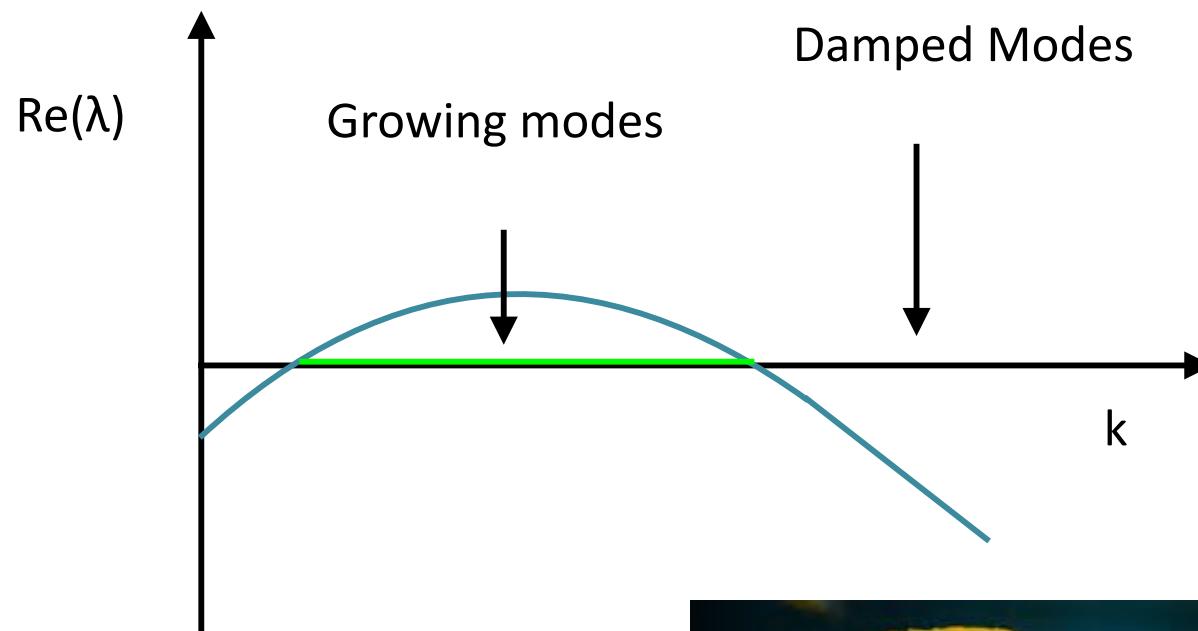
$q_n = \frac{2\pi n}{L}$ and of the form

$$\vec{Z}(x, t) = \sum_n w_n \vec{v}_n \exp(\lambda_n t) \exp(i q_n x)$$

Any given mode will be unstable in the presence of diffusion if

$$D_X D_Y q_n^4 - q_n^2 (D_Y f_X + D_X g_Y) + \det(A) < 0$$

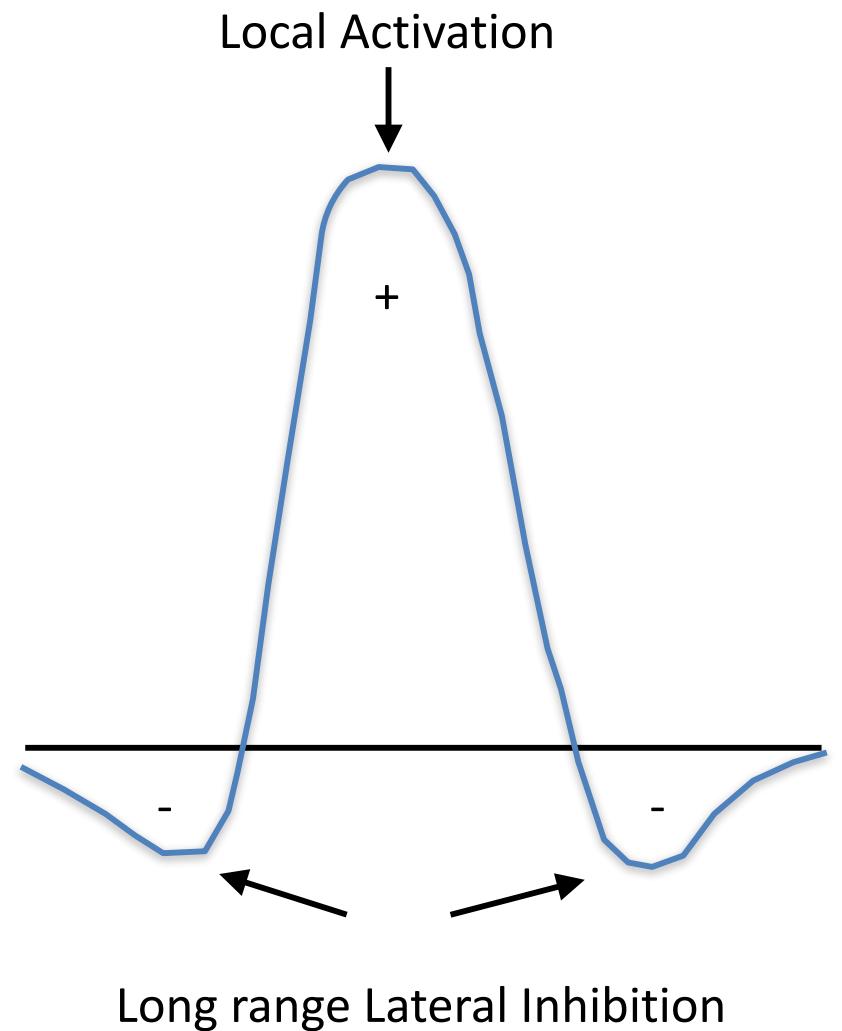
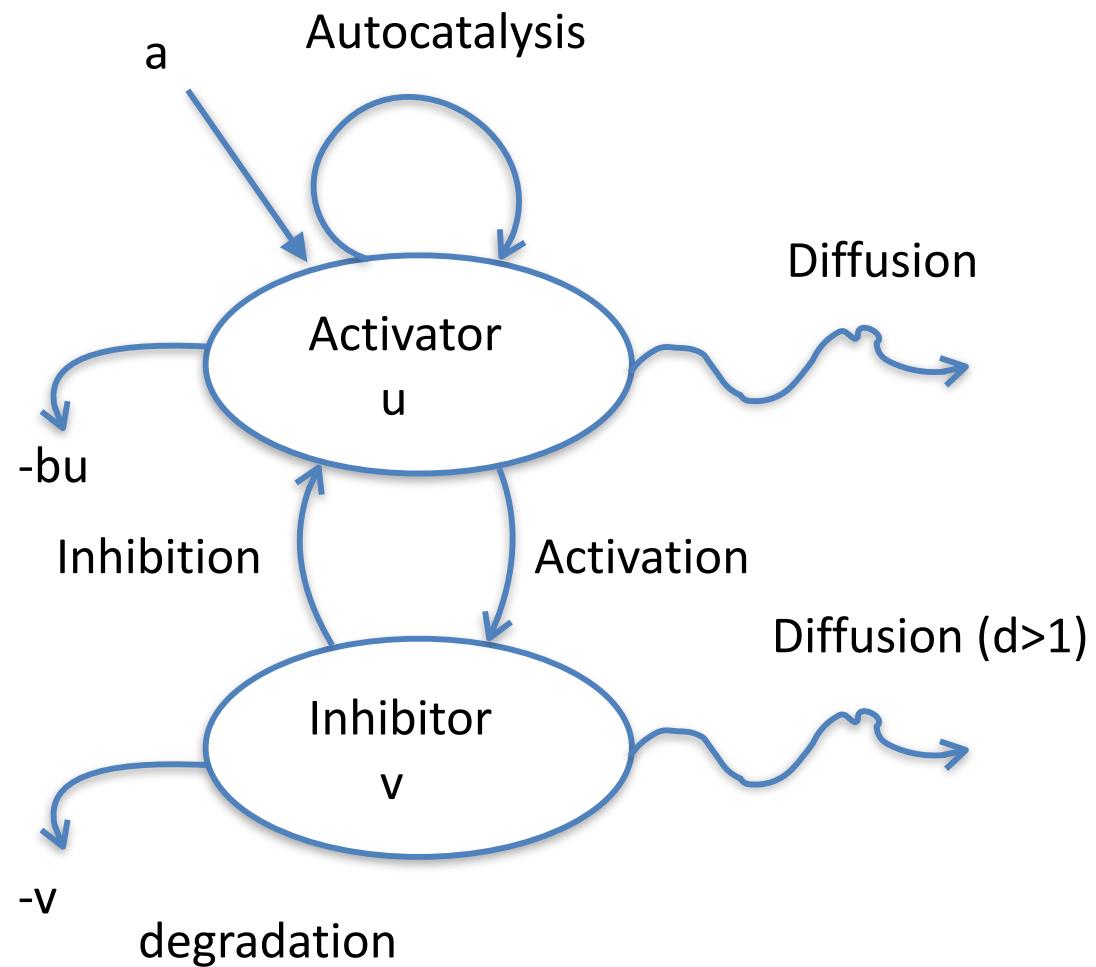
Mode Selection



Formation of stable spatial patterns



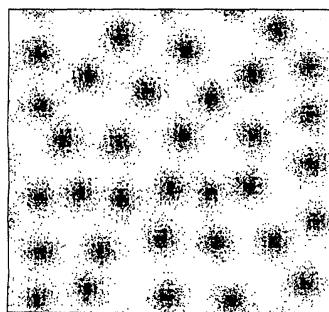
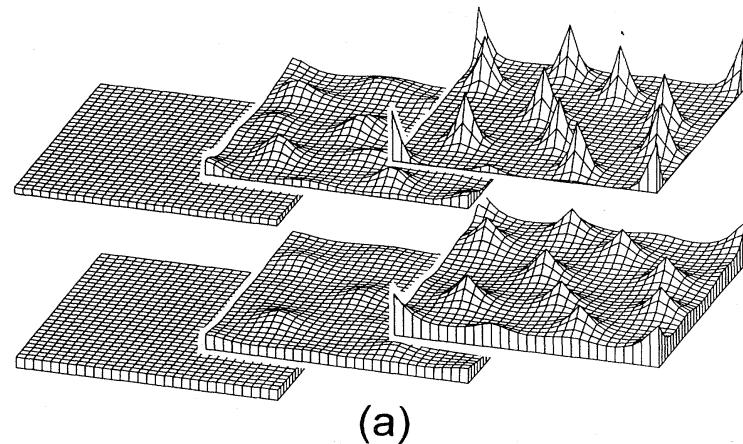
Activator-Inhibitor Systems



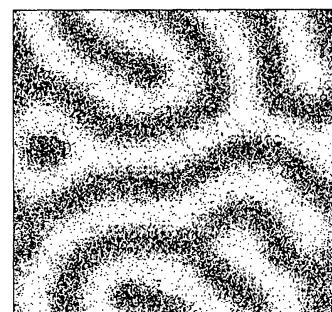
Gierer-Meinhardt (1972)

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

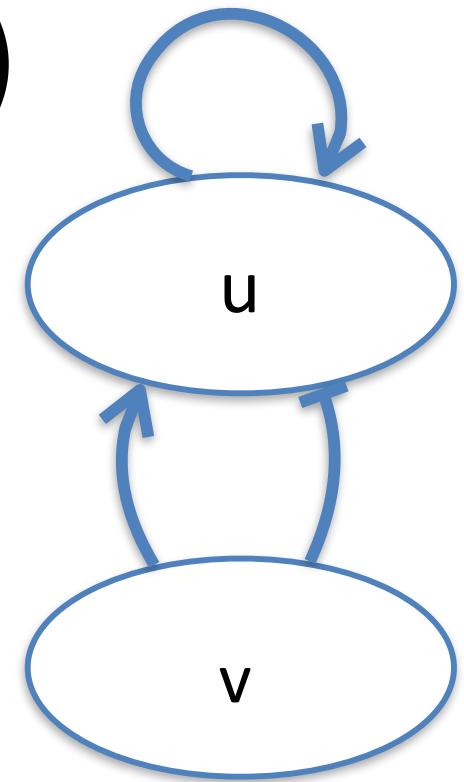
$$\frac{\partial v}{\partial t} = D_2 \nabla^2 v + \delta u^2 - \eta v$$



(b)



(c)



Activator u and rapidly diffusing inhibitor v

Patterns produced by activator inhibitor model

Koch and Meinhardt, Biological Pattern Formation : from Basic Mechanisms to Complex Structures
Rev. Modern Physics 66, 1481-1507 (1994)

Coat patterns versus simulations by Reaction diffusion type equation

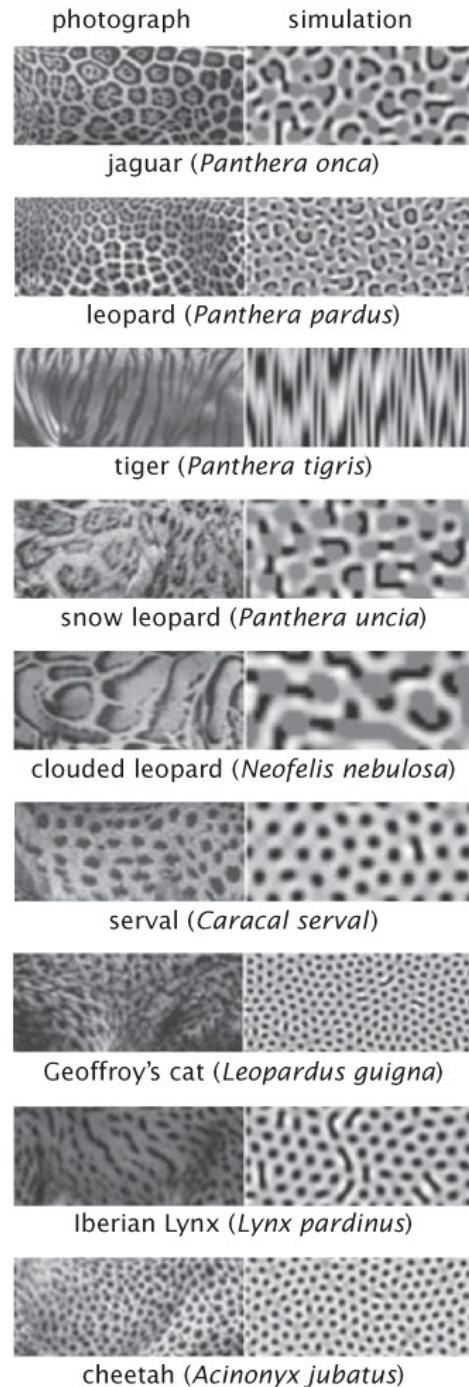


Figure 20.13 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

How differences in Diffusion Coefficients for X and Y Can Arise

Size Differences

Stokes-Einstein: (r – radius, η - viscosity)

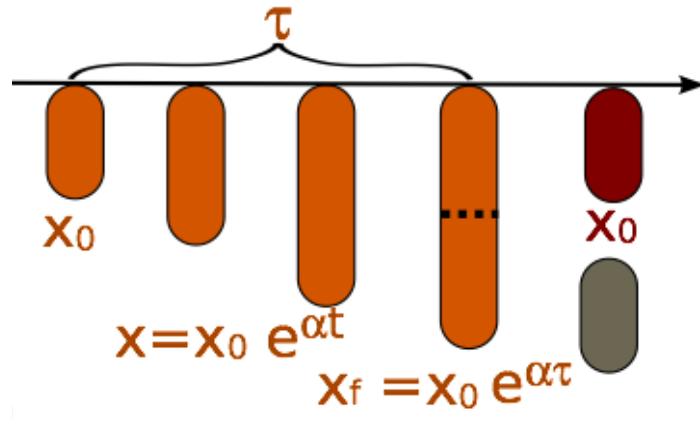
$$D = \frac{k_B T}{6\pi\eta r}$$

Binding Differences:

Activator A and Inhibitor Y diffuse at the same rate but the activator is involved in a binding reaction to an immobile receptor R. Effective diffusion constant.

$$D = 1/(1+k)$$

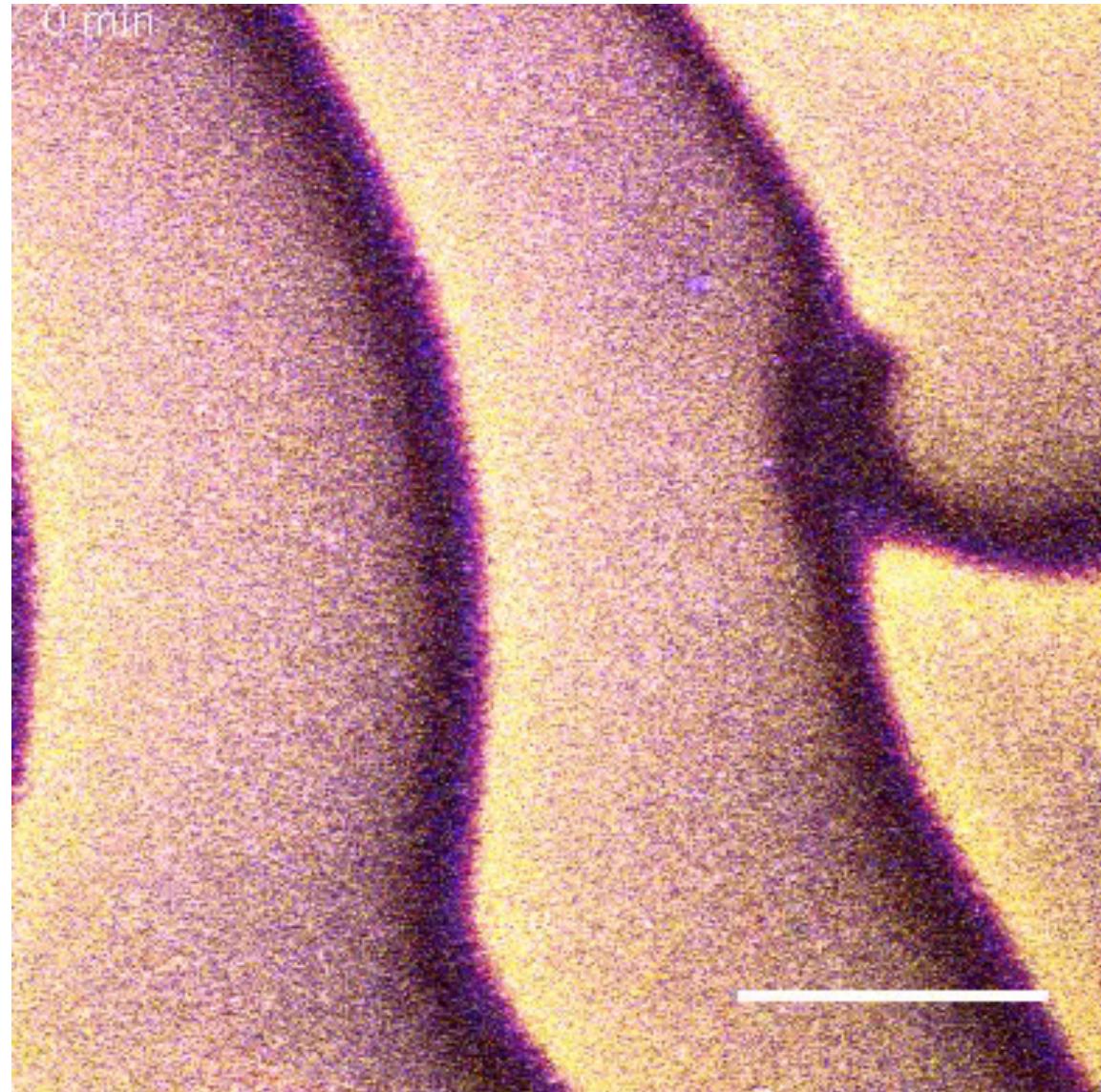
How does a cell know where to Divide?



- Formation of FtsZ ring divides the cell
- MinC Prevents Formation of FtsZ ring
- MinD binds the cell membrane and Recruits MinC
- MinE binds to MinD and expels it from the membrane

In Vitro Experiments

In vitro, protein waves emerge from the self-organization of these Min Proteins. For wave propagation, the proteins need to cycle through states of collective membrane binding and unbinding (ATP present, supported lipid bilayer).



*“Min protein patterns emerge from rapid rebinding and membrane interaction of MinE”, Loose et al
Nature Structural & Molecular Biology 18, 577–583 (2011)*

Dynamics

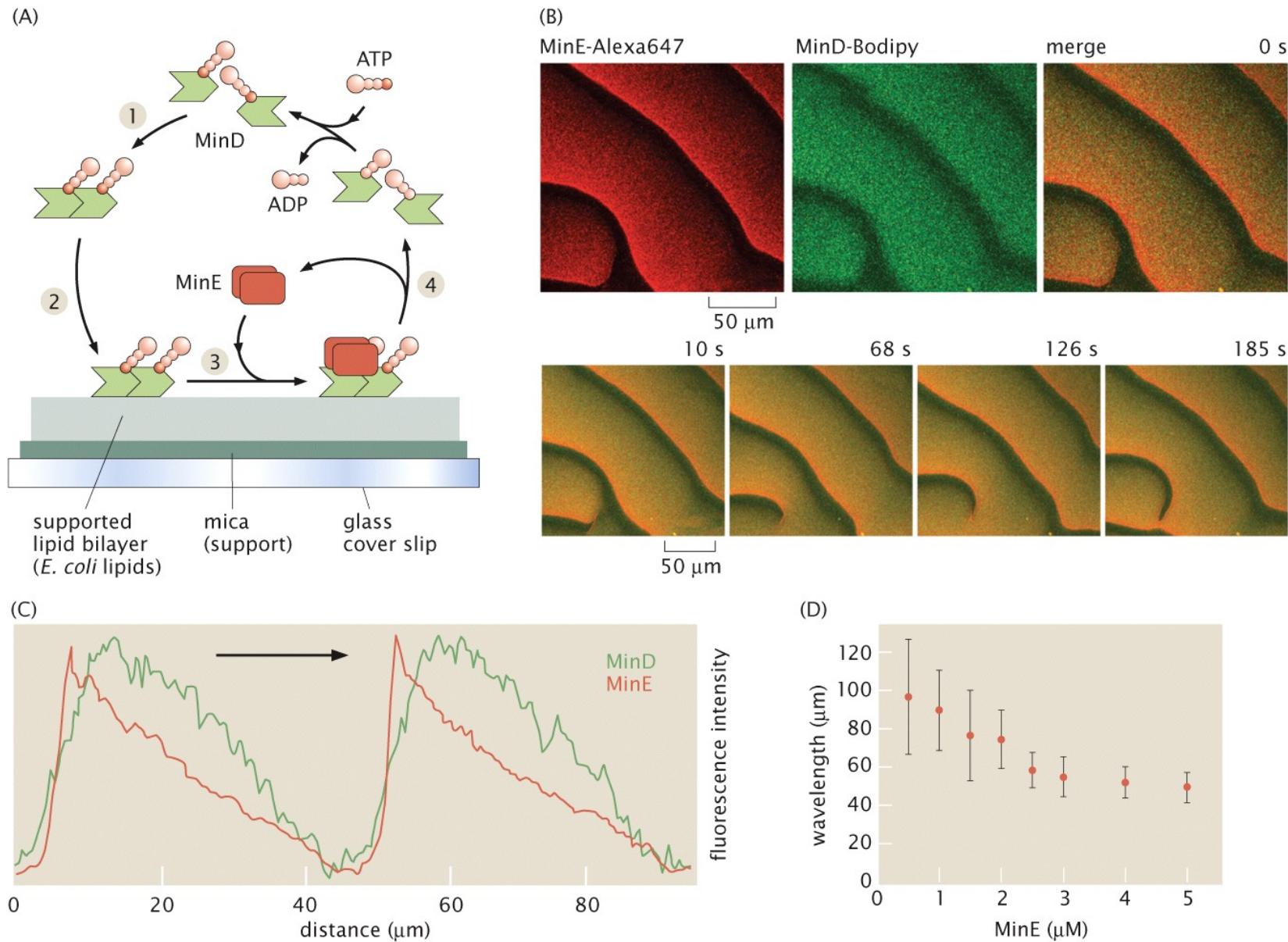
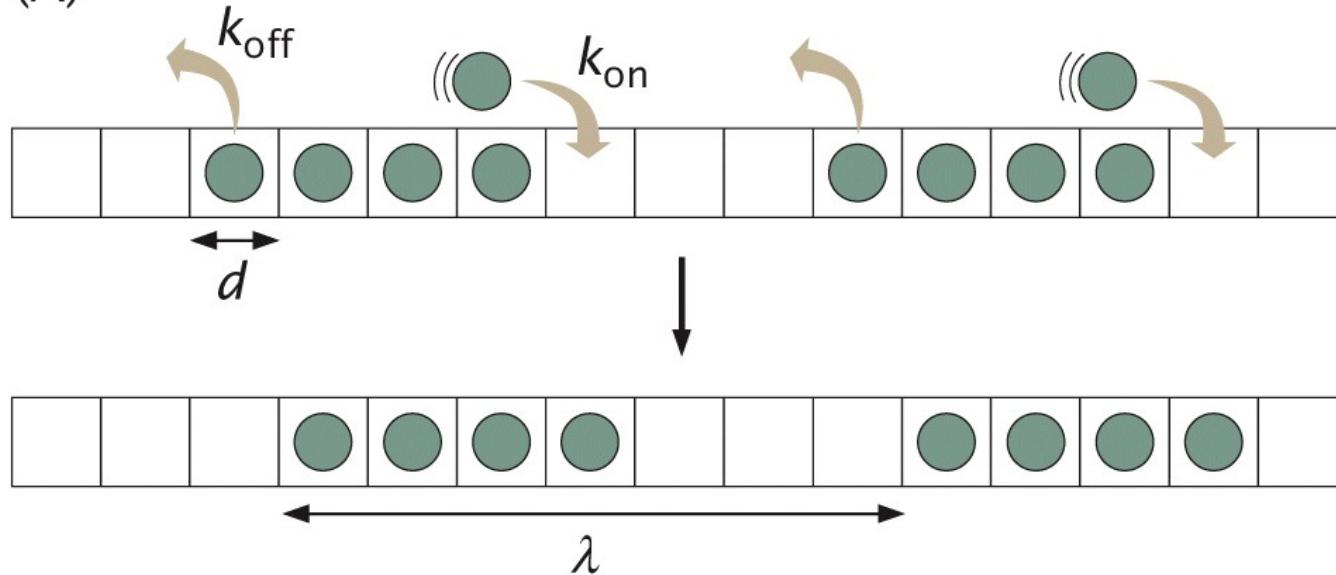


Figure 20.14 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

(A)



(B)

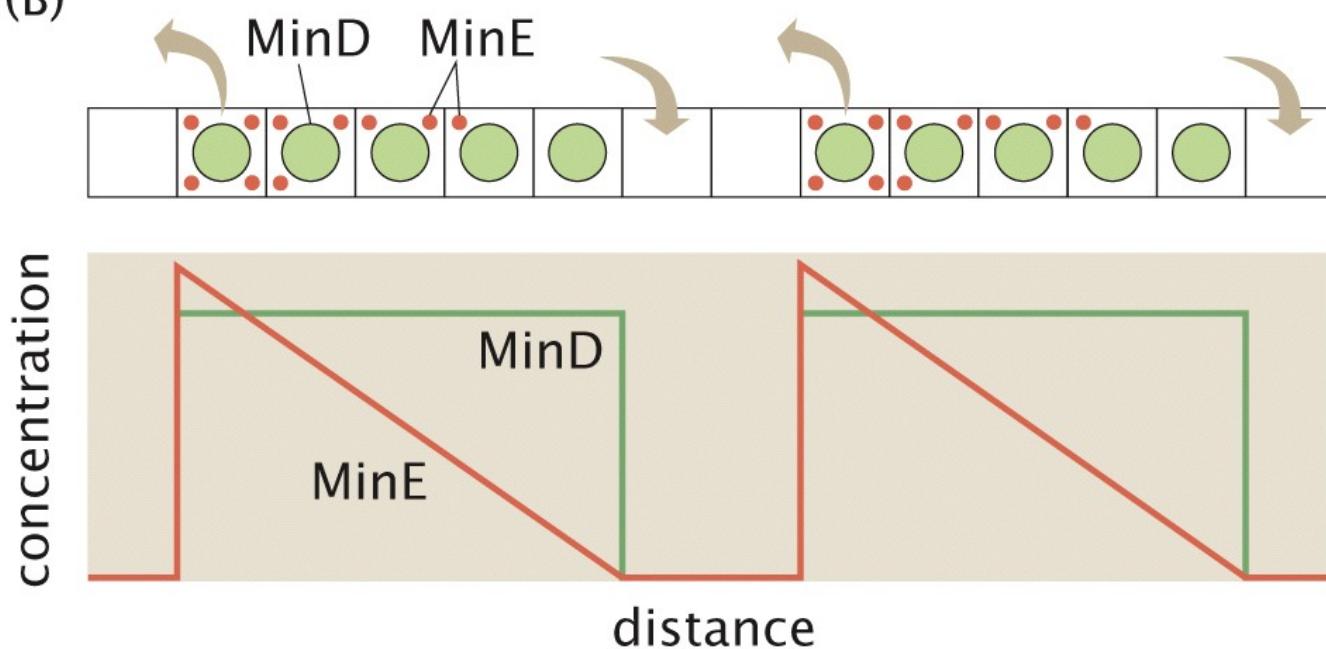
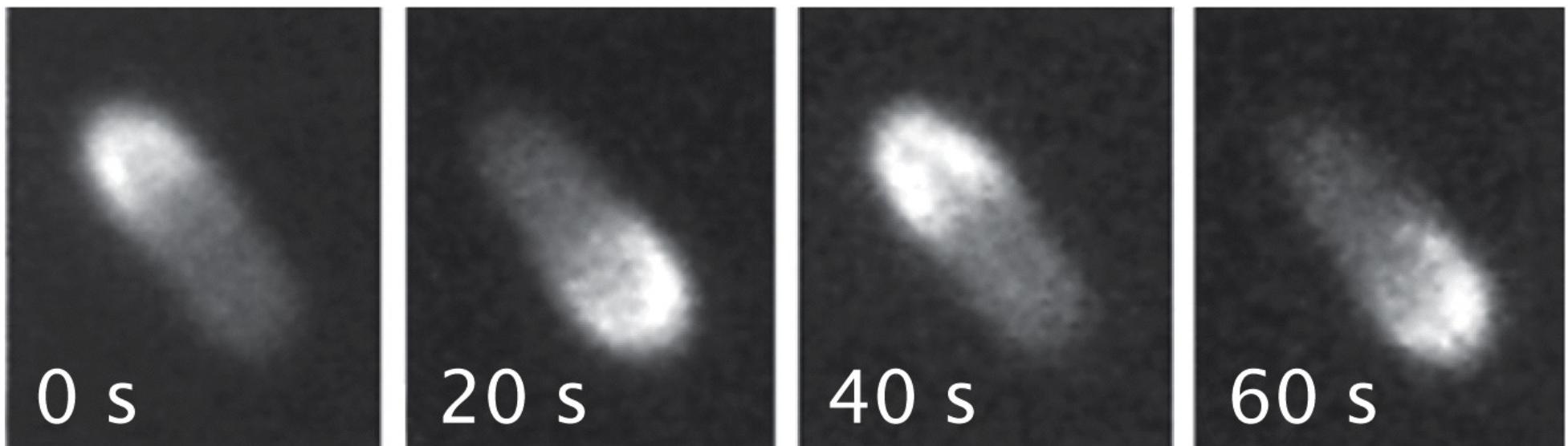
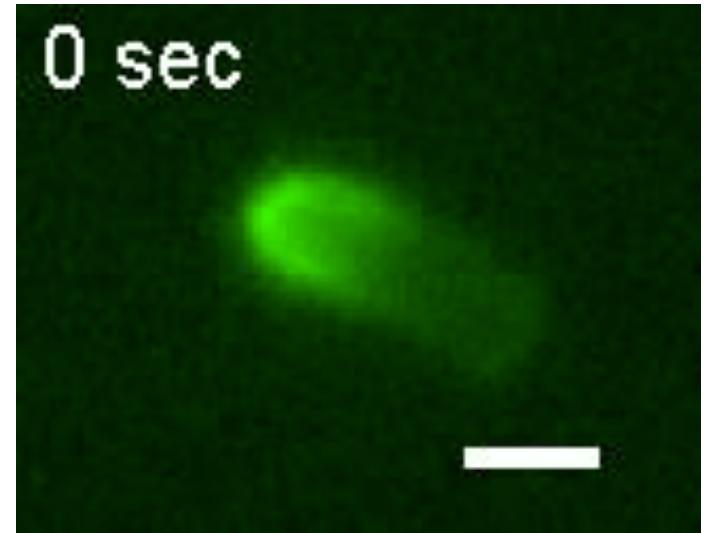


Figure 20.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Min Oscillations in Live Cells

Fluorescently
Labeled MinD



1 μm

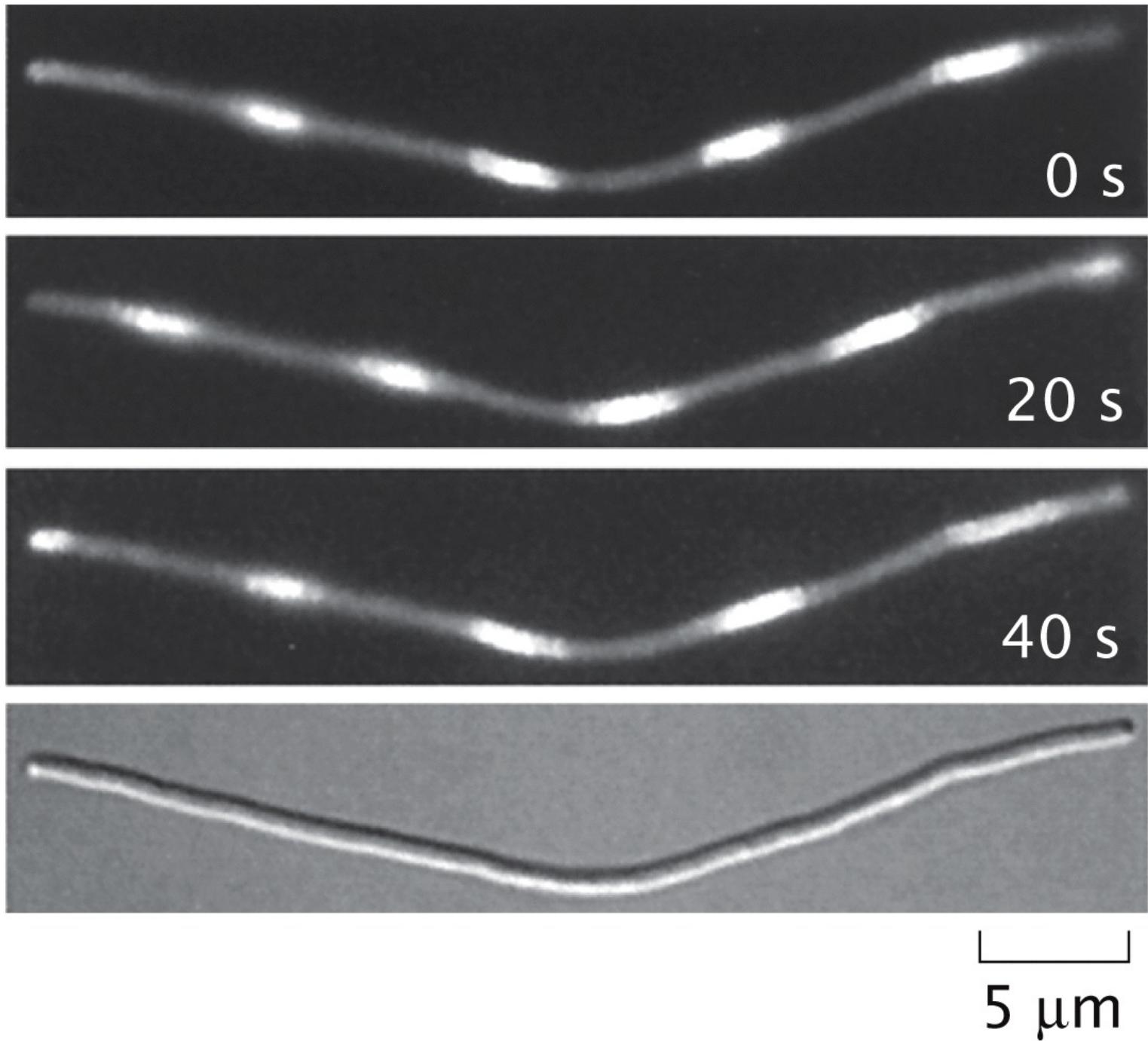
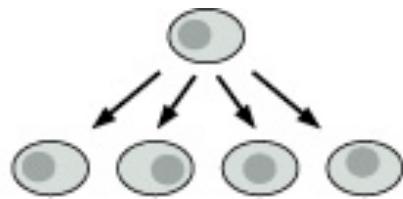
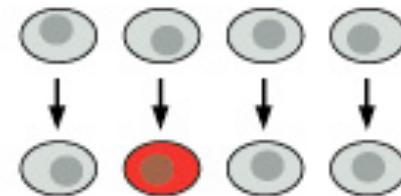


Figure 20.16b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

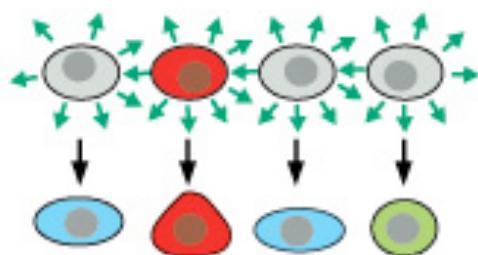
Assembling a Multi-cellular organism



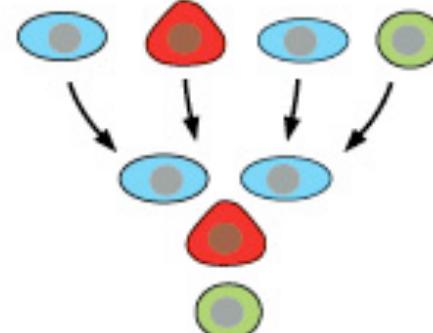
CELL PROLIFERATION



CELL SPECIALIZATION



CELL INTERACTION



CELL MOVEMENT

Figure 21–1. Molecular Biology of the Cell, 4th Edition.
(Multicellularity Chapter in Newer Editions)

Gene Regulation

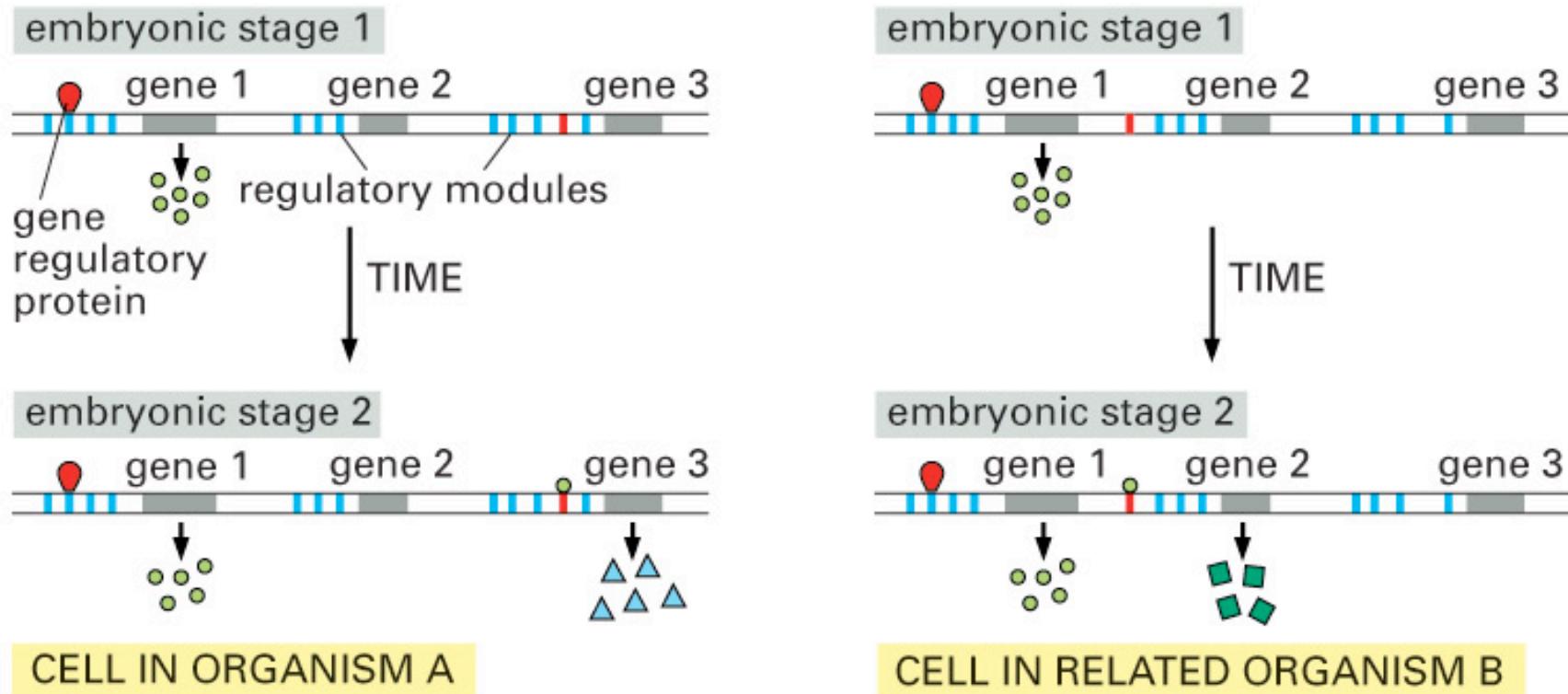
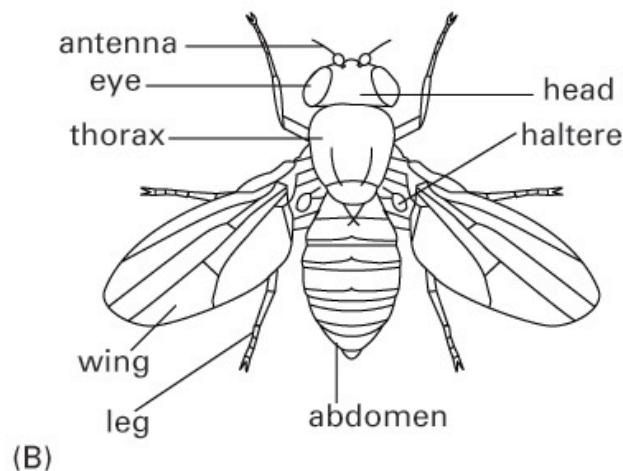


Figure 21–4. Molecular Biology of the Cell, 4th Edition.

Fly Development



(A)



(B)

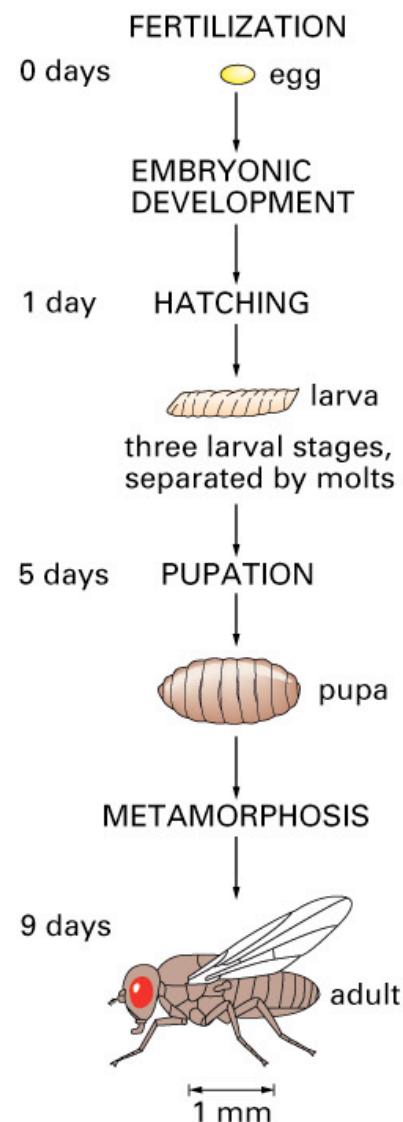


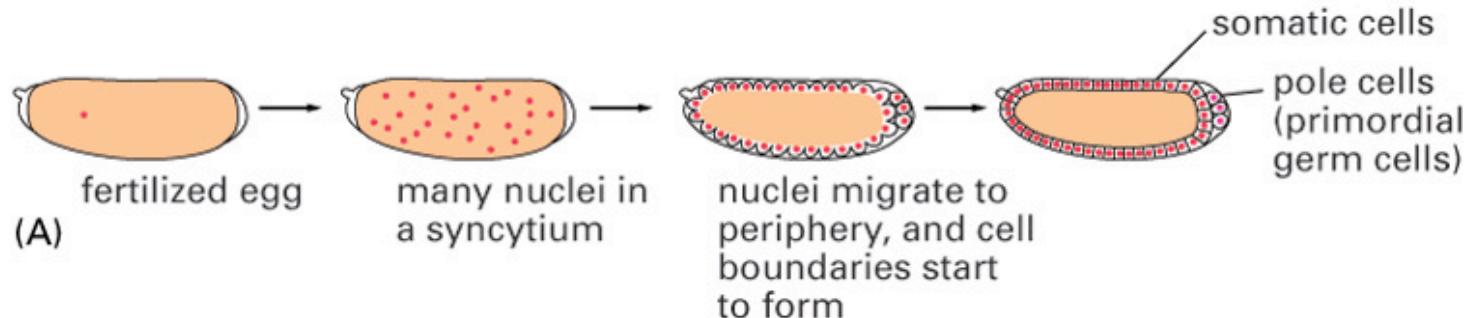
Figure 21–23. Molecular Biology of the Cell, 4th Edition.

Figure 21–24. Molecular Biology of the Cell, 4th Edition.

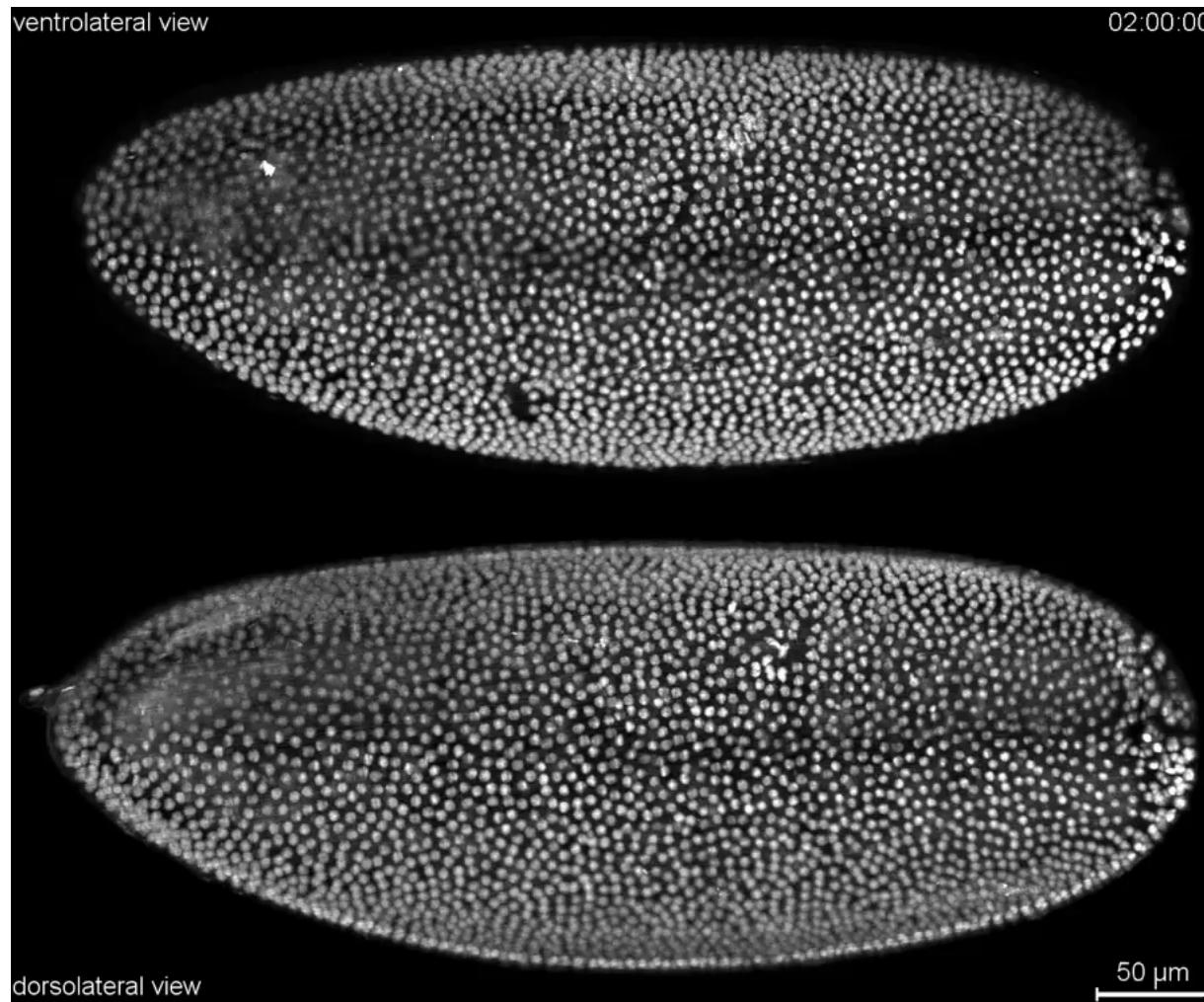
Early Embryo



Laser confocal images of stained chromatin (W. Baker and G. Schubiger)



Fly Development



Tomer et al, Nature Methods 9, 755–763 (2012)

Early Embryo

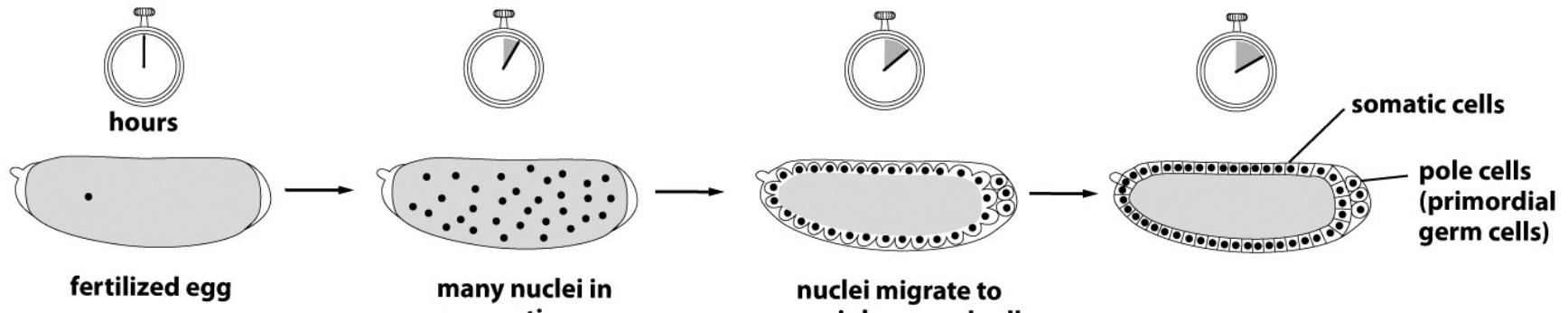


Figure 3.22 Physical Biology of the Cell (© Garland Science 2009)

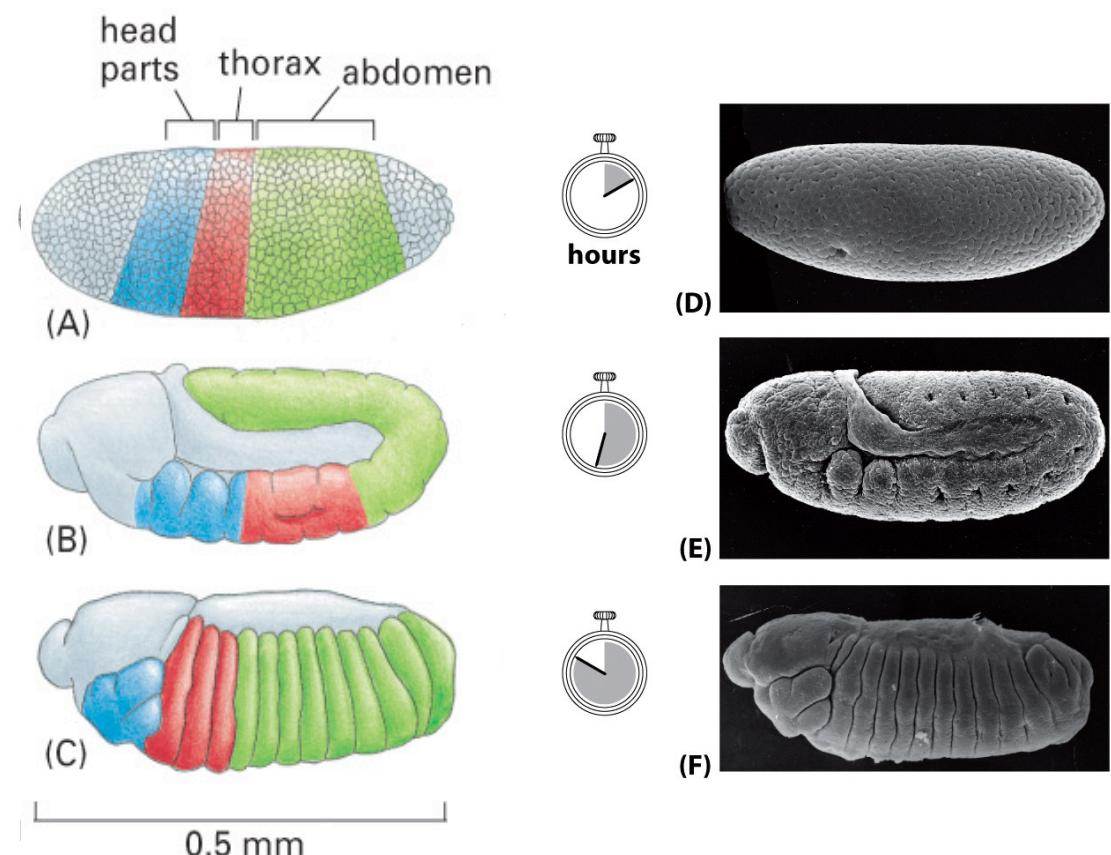


Figure 3.23 Physical Biology of the Cell (© Garland Science 2009)

Positional Information

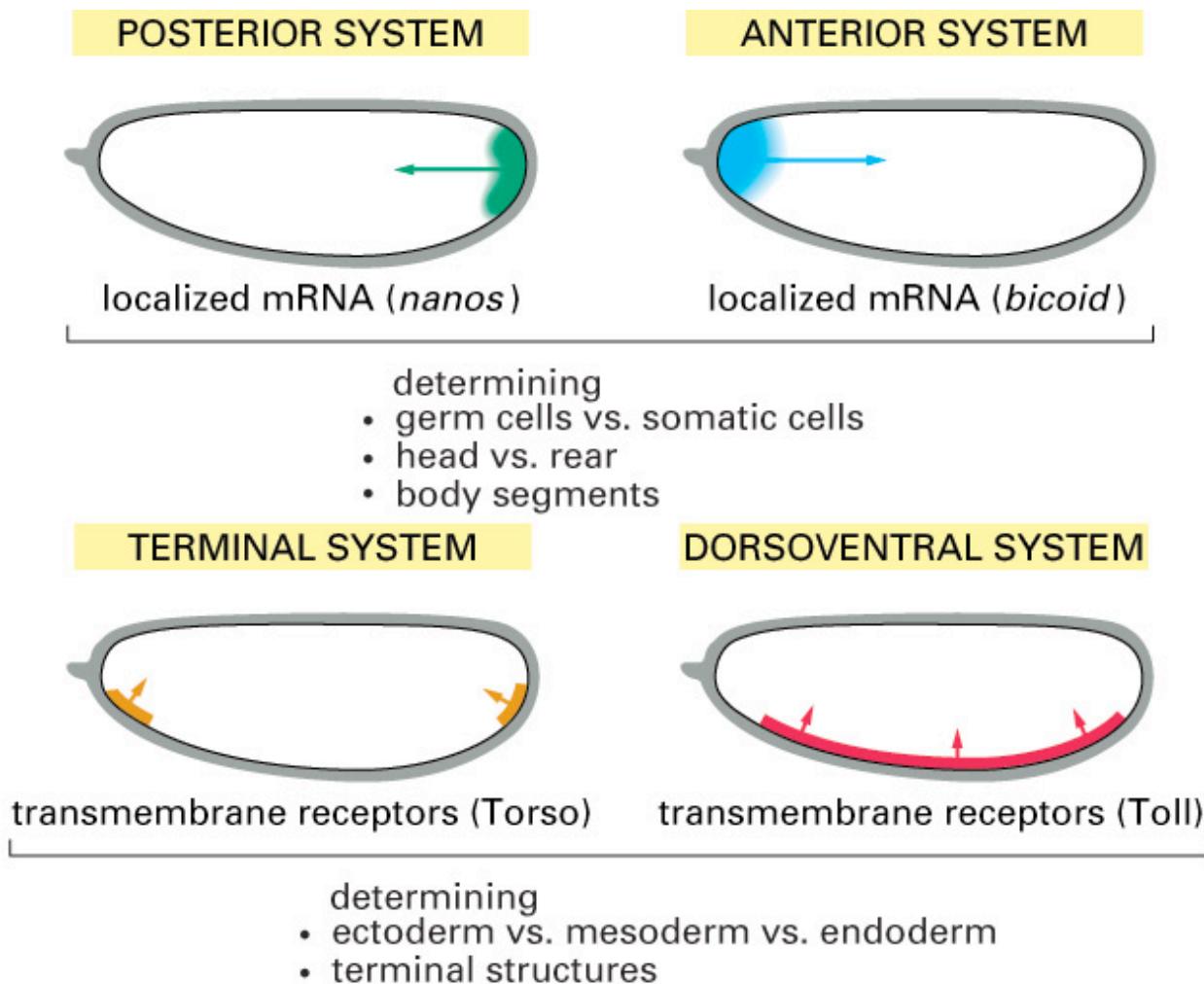


Figure 21–31. Molecular Biology of the Cell, 4th Edition.

Regulatory Proteins in the Drosophila Embryo and their patterning

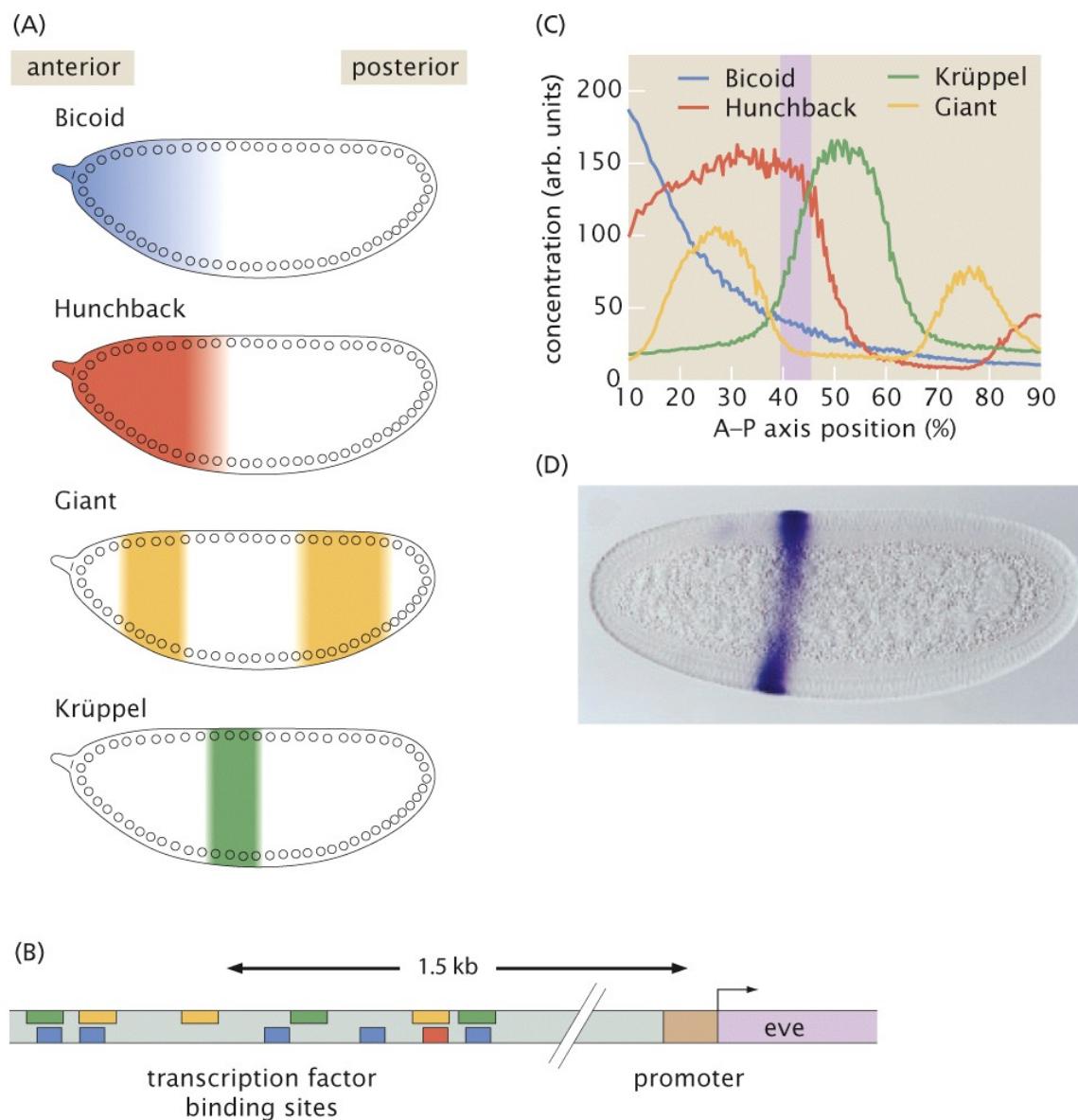


Figure 19.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Anterior-Posterior (AP) Axis Patterns of Gene Expression

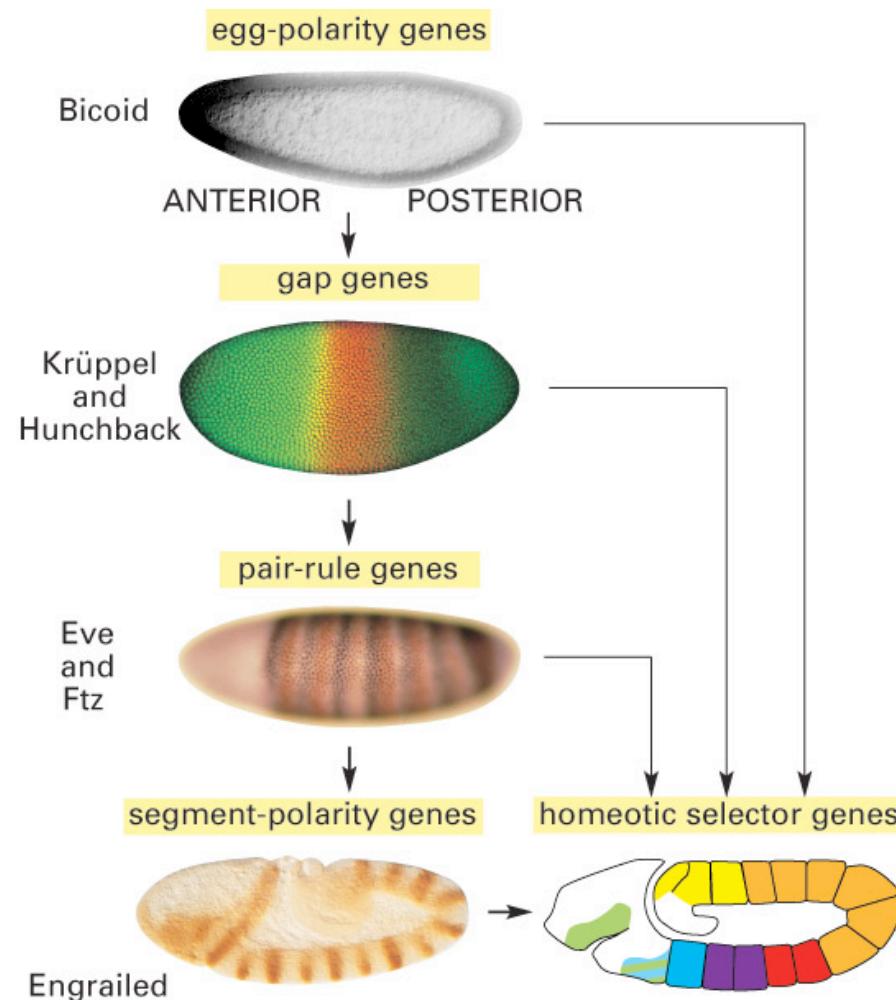
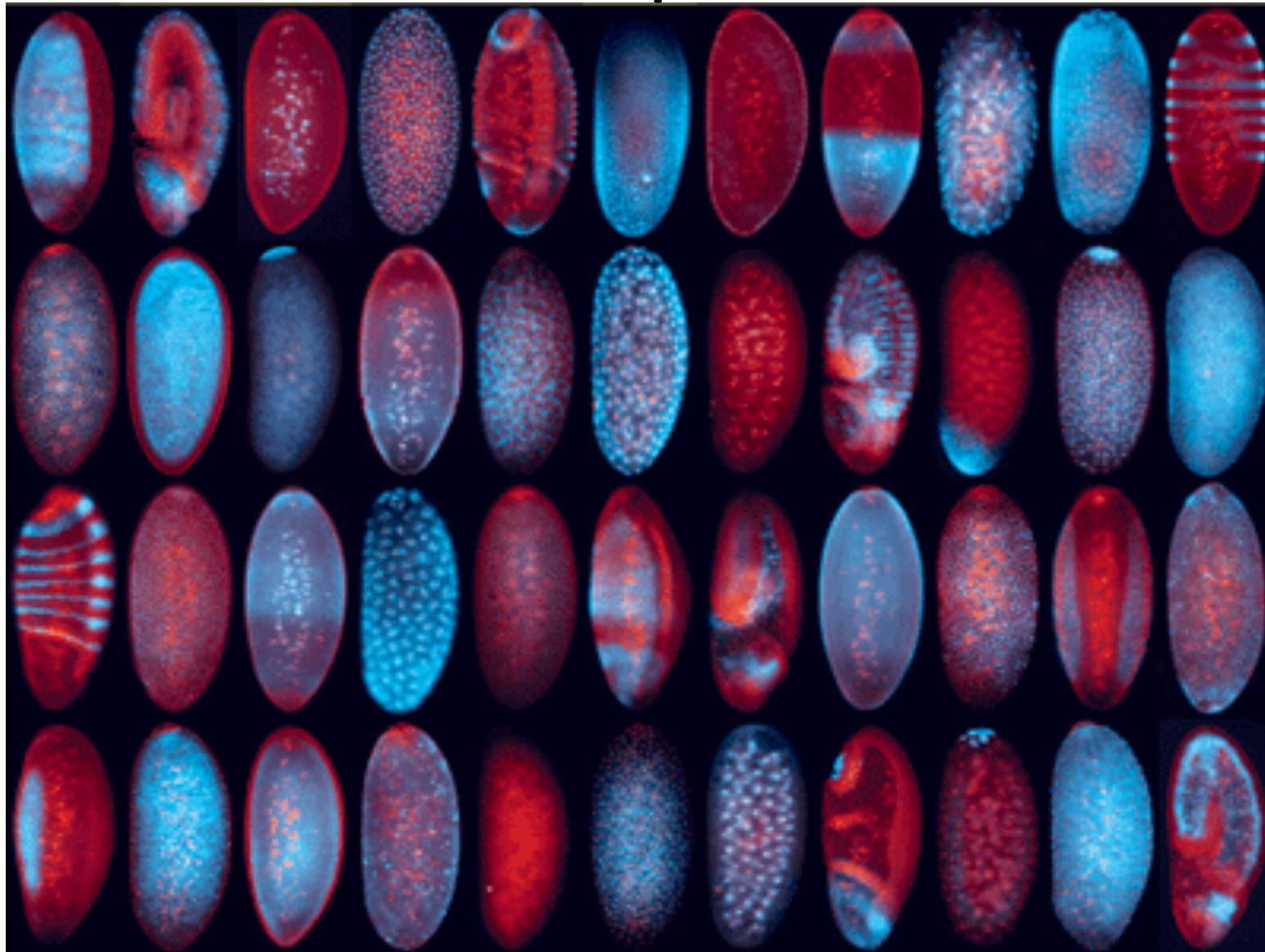


Figure 21–37. Molecular Biology of the Cell, 4th Edition.

Patterns of Expression During Fly Development



<http://fly-fish.ccbr.utoronto.ca/>

French Flag Model

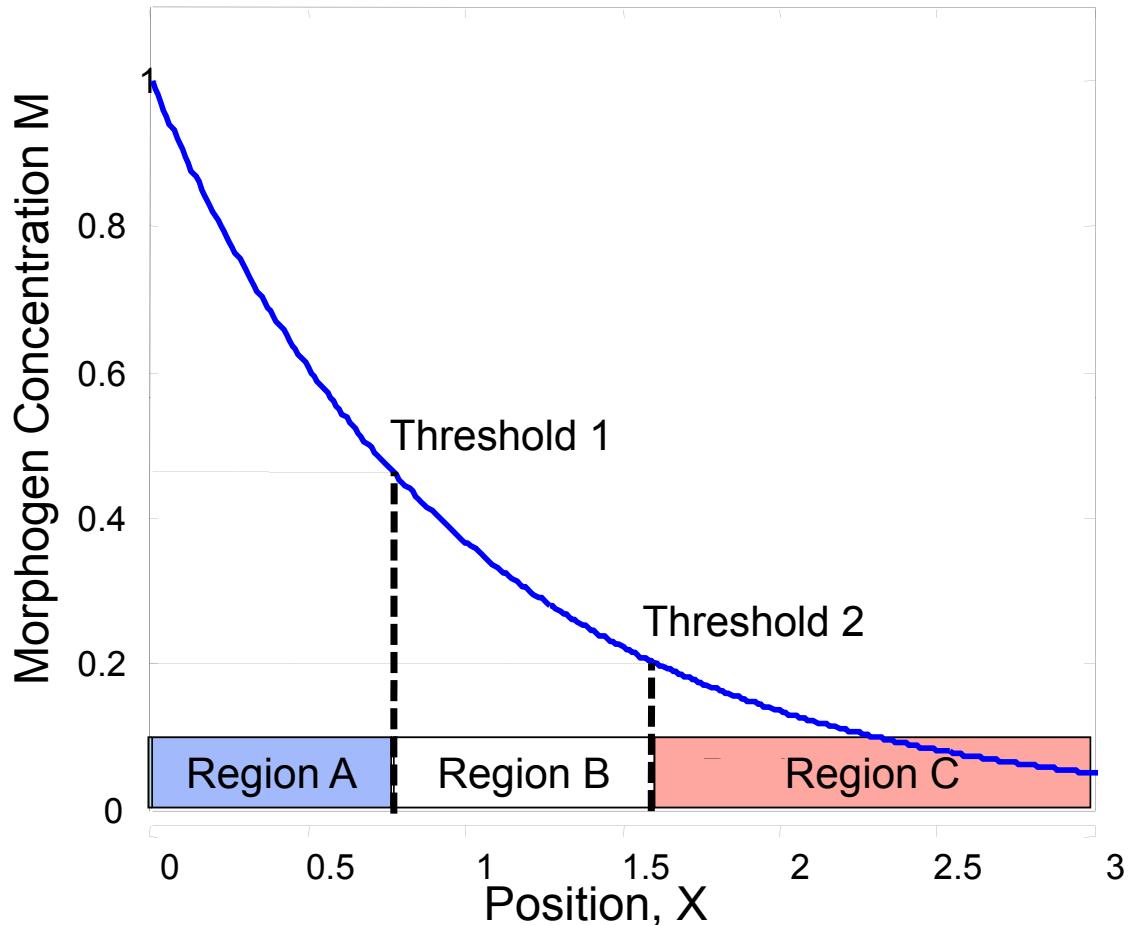
$M(x)$ decays with distance x

Cell sense
concentration
ranges

High ($M > T_1$)
Medium ($T_2 < M < T_1$)
Low ($M < T_2$)

Assume
Fates

A
B
C



“An Introduction to Systems Biology”, Uri Alon , Fig 8.1

Cell Fate Development is Robust with Respect Morphogen Concentration Fluctuations

- Experimentally patterning has been shown to be robust to genetic and environmental perturbations
- Production Rates of Proteins Highly Variable
- How does a change in morphogen concentration affect pattern formation?
- Experiments with a two-fold reduction in morphogen production gives very little change in sizes/positions of regions
- How is this achieved?

Exponential Morphogen Profile

- Morphogen M produced at position $x=0$, degraded at rate α , diffuses with diffusion constant D
- The diffusion-degradation equation of M at a position x is

$$\frac{\partial M}{\partial t} = D \frac{\partial^2 M}{\partial x^2} - \alpha M.$$

- At steady state : $\partial M / \partial t = 0$, $M(0,t) = M_0$, $M(\infty,t) = 0$

$$M(x) = M_0 e^{-x/\sqrt{D/\alpha}} = M_0 e^{-x/\lambda}.$$

- Decay length λ

Exponential Morphogen Profile

Boundary between two regions
when $M(x_0) = T$

$$x_0 = \lambda \ln \frac{M_0}{T}.$$

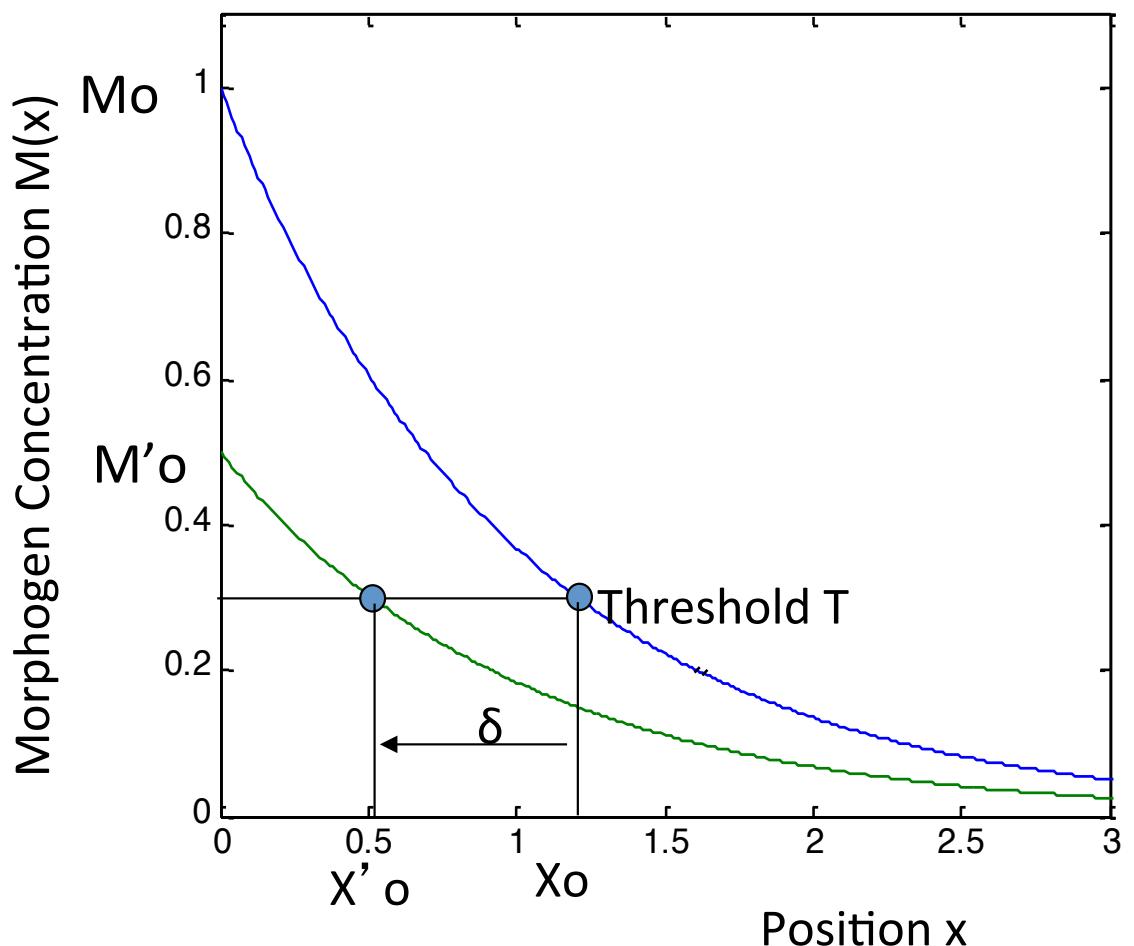
New Source concentration $M'0$

$$x'_0 = \lambda \ln \frac{M'_0}{T}.$$

Difference

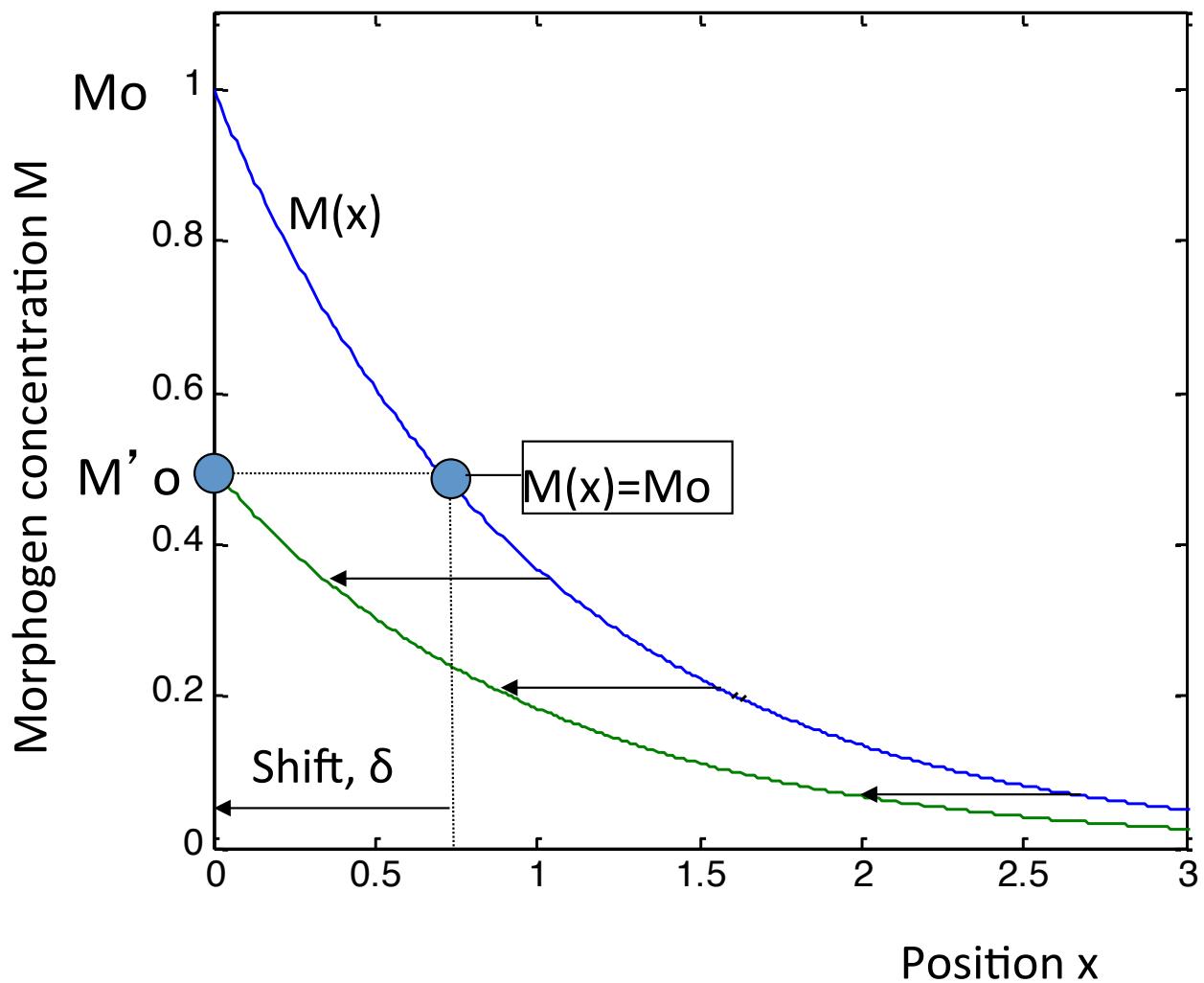
$$\delta = x'_0 - x_0 = \lambda \ln \frac{M'_0}{M_0},$$

Twofold reduction leads to a shift
of $\sim 0.7 \lambda$, enough to lose a region



Exponential Morphogen Profile

- Spatially uniform shift at all positions x
- Would like a robust model (minimize boundary shift δ)
- Increased decay rate would give smaller λ but would limit the spatial extent of the pattern
- Need rapid decay of the morphogen near source that becomes less rapid further away



Self Enhanced Morphogen Degradation

- Diffusion-degradation process with quadratic degradation

$$\frac{\partial M}{\partial t} = D \frac{\partial^2 M}{\partial x^2} - \alpha M^2.$$

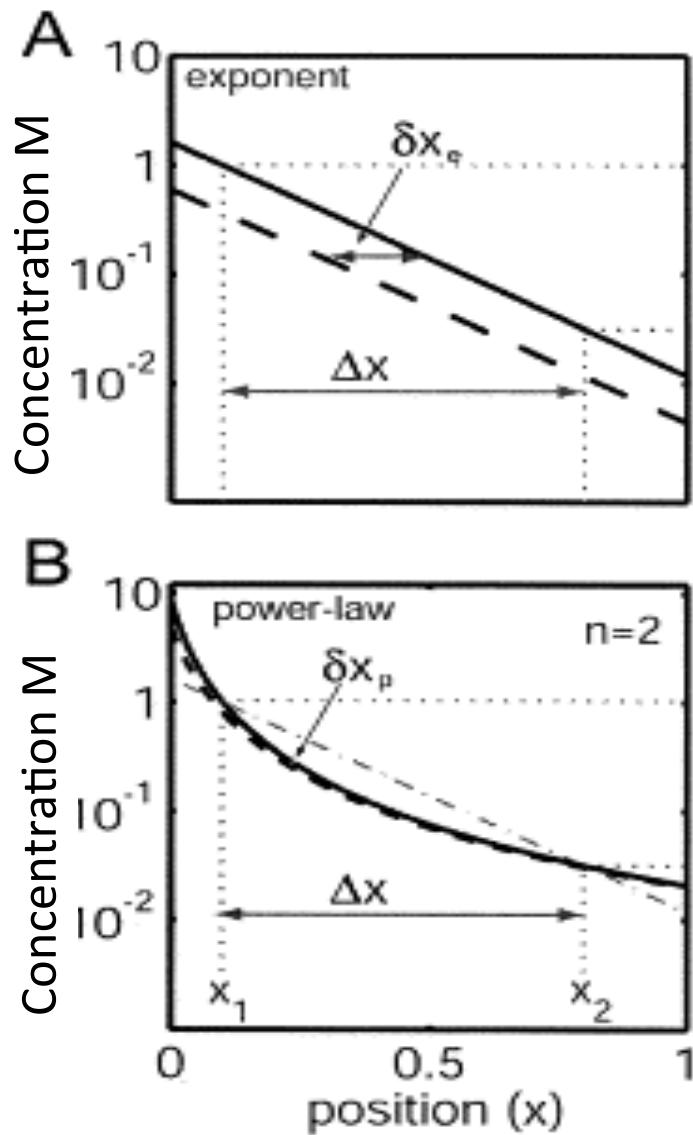
- At steady state : $\partial M / \partial t = 0, M(0,t) = M_0, M(\infty,t) = 0$

$$D \frac{d^2 M}{dx^2} - \alpha M^2 = 0.$$

- Power law solution

$$M(x) = \frac{6D}{\alpha(x + \varepsilon)^2}, \quad \varepsilon = \sqrt{\frac{6D}{\alpha M_0}}.$$

Morphogen Profile Comparison



$$M(x) = M_0 e^{-x/\lambda},$$

$$\ln M(x) = \ln M_0 - \frac{1}{\lambda} x.$$

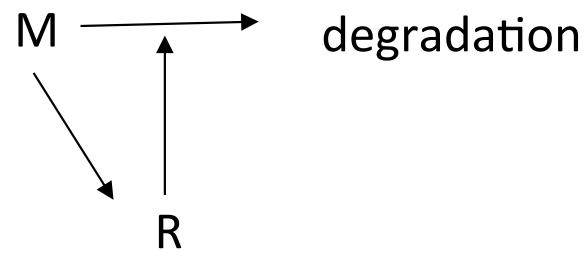
Limit M_0 very large such that ε very small
 $M(x)$ independent of M_0 :

$$M(x) = \frac{6D}{\alpha x^2},$$

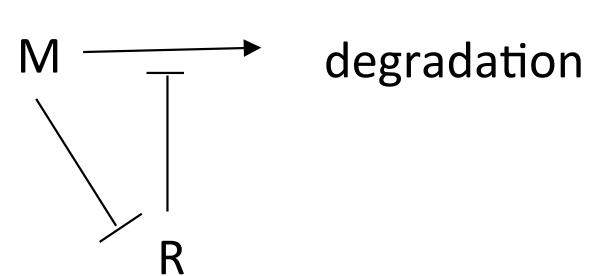
$$\ln M(x) = \ln 6D - \ln \alpha - 2 \ln x.$$

Network Motifs

a)



b)

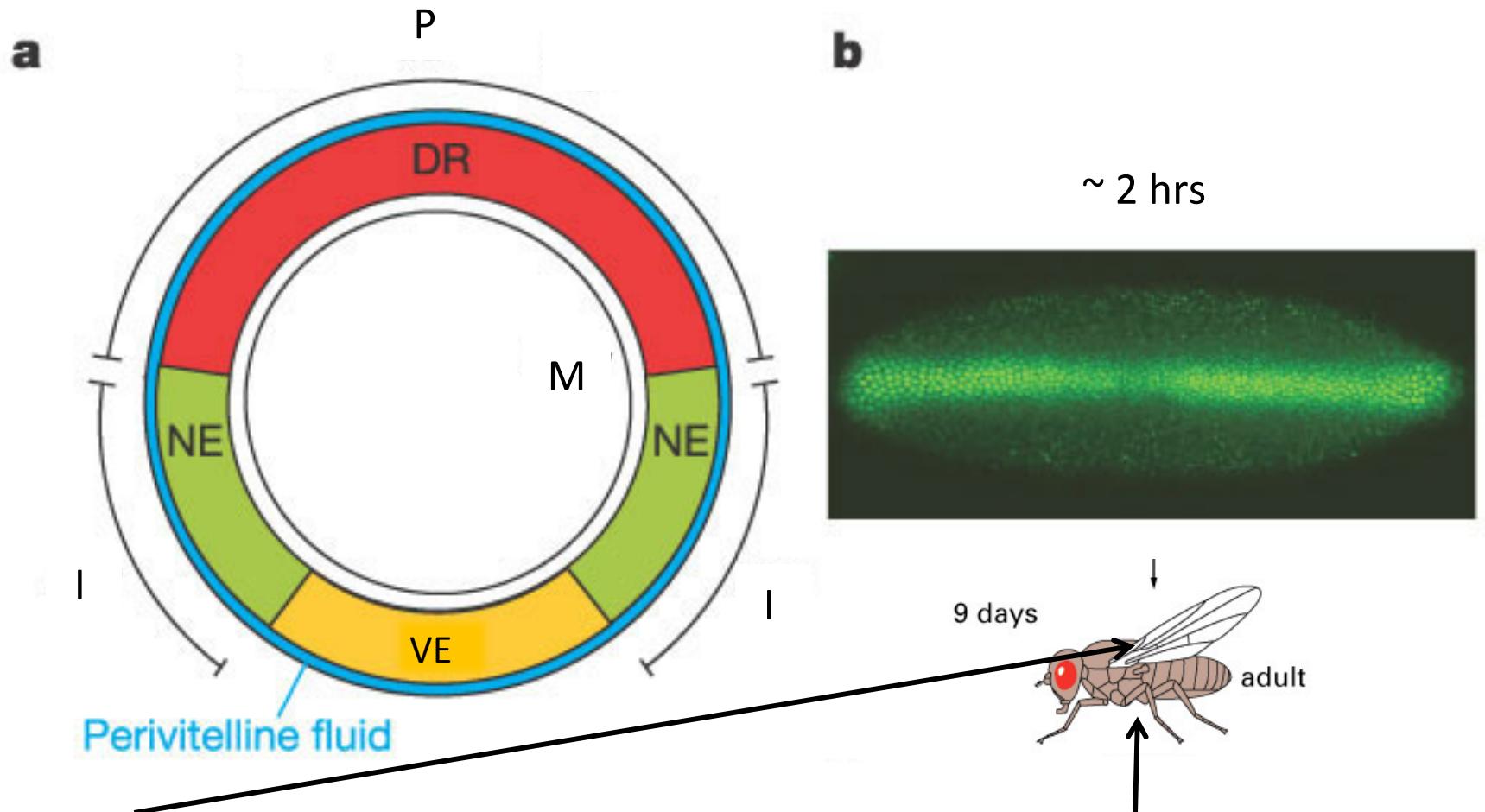


Two network motifs that provide self enhanced degradation of morphogen M.

(a) M binds receptor R and activates signaling pathways that increase R expression. M bound to R is taken up by the cells (endocytosis) and M is degraded.

(b) M binds R and activates signaling pathways that repress R expression binds and sequesters an extra-cellular protein that degrades M (a protease), thus R effectively inhibits M degradation.

Patterning of the Drosophila Embryo ~ 2hr from start of development

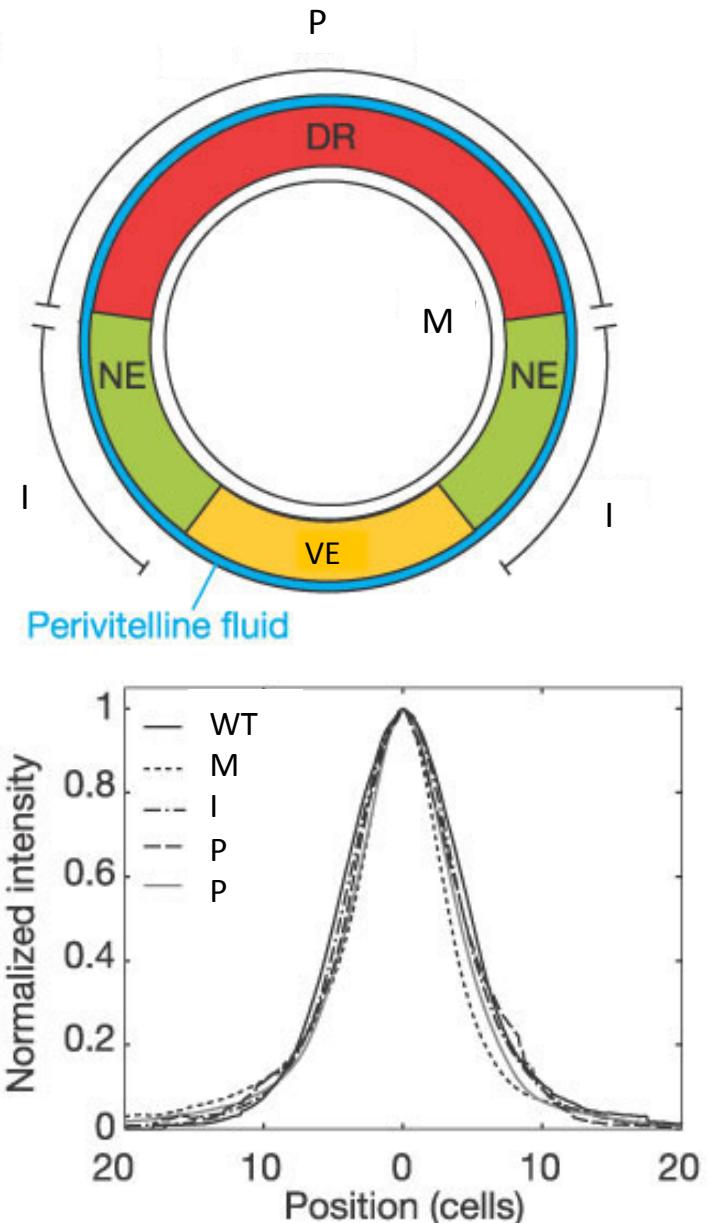


DR – Dorsal (Back), NE – Neuroectoderm, VE – Ventral (Underbelly)

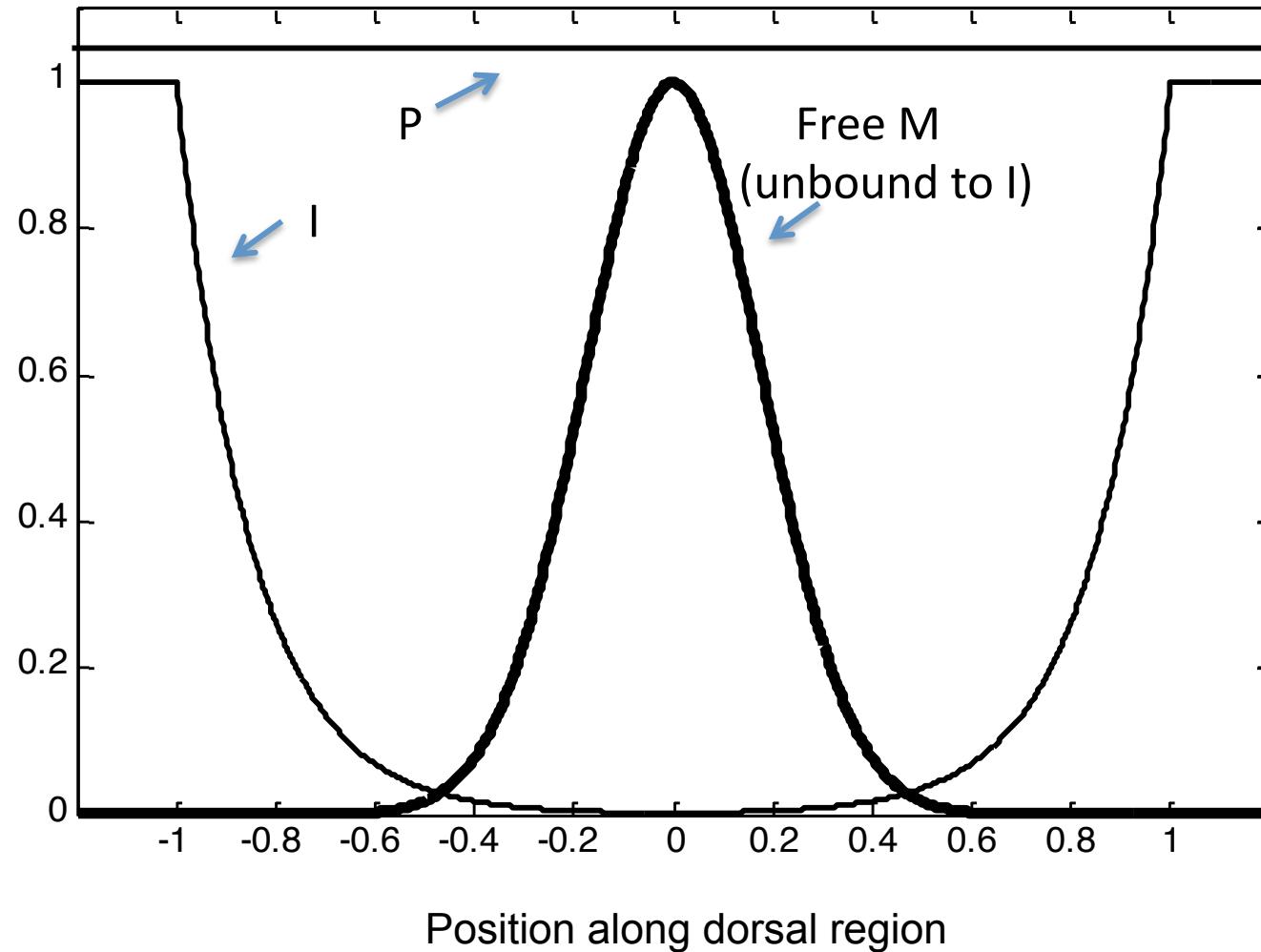
P – Protease, I – Inhibitor

Patterning of the Dorsal Region

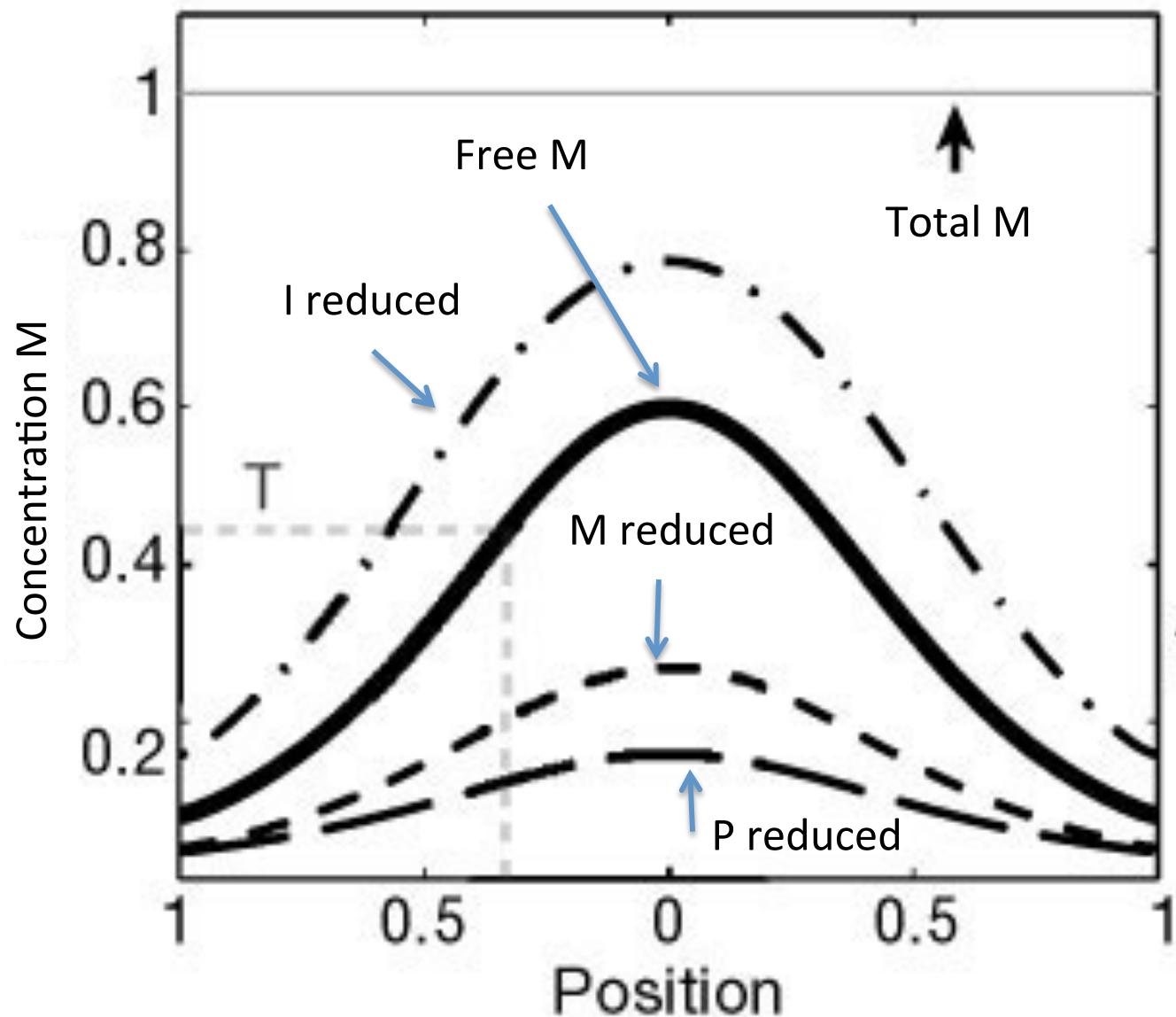
- Inhibitor protein I is produced by NE cells and inhibits the action of M by forming complex MI;
- The Protease P is produced by DR cells and cleaves I in MI complex releasing M (I is degraded, M is not)
- The morphogen M is produced by all cell types in the embryo, its concentration gradient specifies different cell fates. M degrades very slowly.
- I,P,M diffuse in the perivitelline fluid



Model for Patterning Dorsal Region



Distribution of M is not Robust



Model for DR sub-patterning

(1) Free I is degraded by P at a rate α_I and I binds M to form a stable complex [IM]=C at a rate k

$$\frac{\partial I}{\partial t} = D_I \frac{\partial^2 I}{\partial x^2} - kIM - \alpha_I PI$$

(2) [IM] is degraded by P at a rate α_C

$$\frac{\partial C}{\partial t} = D_C \frac{\partial^2 C}{\partial x^2} + kIM - \alpha_C PC$$

(3) M binds I at rate k and is released when C is degraded by P

$$\frac{\partial M}{\partial t} = D_M \frac{\partial^2 M}{\partial x^2} - kIM + \alpha_C PC$$

Robust patterning of M for : $D_C \gg D_M$ & $\alpha_C \gg \alpha_I$

Robust Solutions

Steady State Equations with $D_M = 0, \alpha_I = 0$

$$\frac{\partial I}{\partial t} = D_I \frac{\partial^2 I}{\partial x^2} - kIM = 0$$

$$D_C \frac{\partial^2 C}{\partial x^2} = 0$$

$$\frac{\partial C}{\partial t} = D_C \frac{\partial^2 C}{\partial x^2} + kIM - \alpha_C PC = 0$$

$$C(x) = ax + C_0$$



$$\frac{\partial M}{\partial t} = -kIM + \alpha_C PC = 0$$

$$kIM = \alpha_C PC_0$$

$$\frac{\partial^2 M^{-1}}{\partial x^2} = \frac{k}{D_I}$$

Robust Solutions

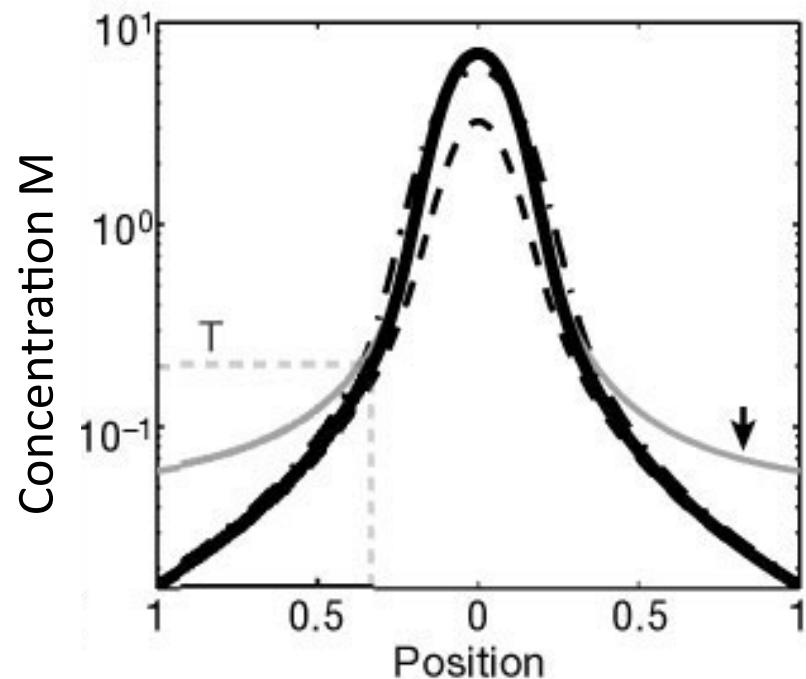
- Solution ($A = 2D_l/k$, $\varepsilon = \sqrt{A/M_{\text{tot}}}$)

$$M = \frac{A}{x^2 + \varepsilon^2}$$

- When M_{tot} is sufficiently large:

$$M \approx \frac{A}{x^2}$$

- Profile M effectively power law, and not dependent on the concentration of P, I or M.
- Profile is robust to changes in these parameters in this regime



Patterning by contact: Delta-Notch concept

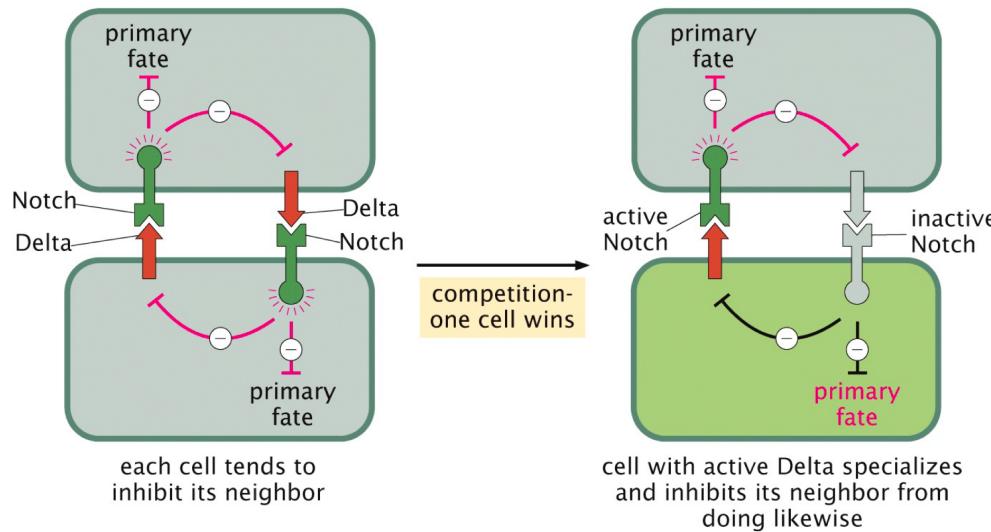


Figure 20.28b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

$$\begin{aligned}\dot{N}_1 &= F(D_2) - \gamma_N N_1 \\ \dot{D}_1 &= G(N_1) - \gamma_D D_1 \\ \dot{N}_2 &= F(D_1) - \gamma_N N_2 \\ \dot{D}_2 &= G(N_2) - \gamma_D D_2\end{aligned}$$

If Delta decays much faster than Notch:

$$\begin{aligned}\dot{N}_1 &= f(g(N_2)) - N_1 \\ \dot{N}_2 &= f(g(N_1)) - N_2.\end{aligned}$$

Patterning by contact: Delta-Notch concept

$$\begin{aligned}\dot{N}_1 &= f(g(N_2)) - N_1 \\ \dot{N}_2 &= f(g(N_1)) - N_2.\end{aligned}$$

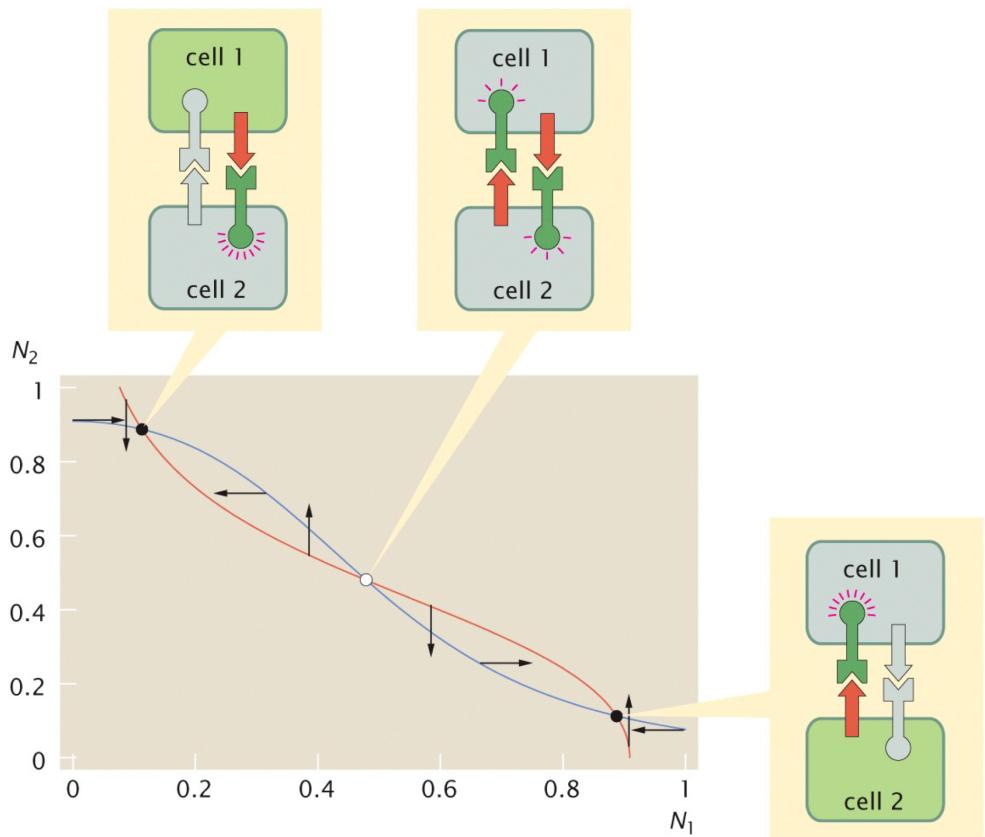


Figure 20.31 Physical Biology of the Cell, 2ed. (© Garland Science 2013)