ETH zürich

Lecture 2: Diffusion-based Patterning

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MSc Computational Biology 2019/20

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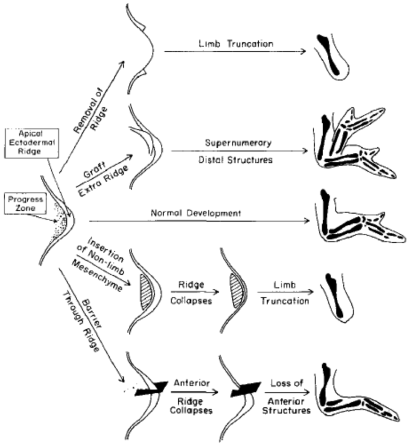
Contents

Embryonic Patterning

Diffuse Signals determine Embryonic Patterning



Tabin, Cell, 1991

- AER required for outgrowth
- ZPA contains factor that leads to digit duplication
- Limb mesenchyme necessary to sustain outgrowth
- Impermeable barrier restricts patterning mainly to the posterior side (Summerbell, 1979)

Source Duplications

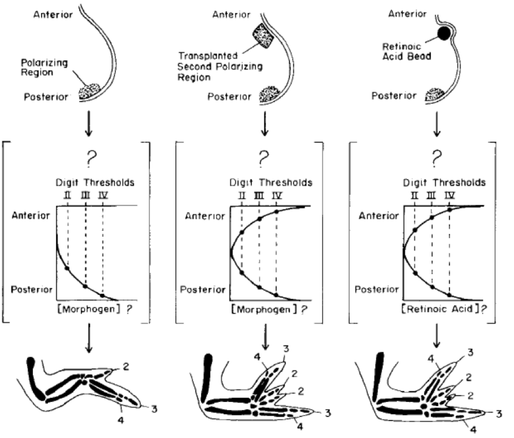
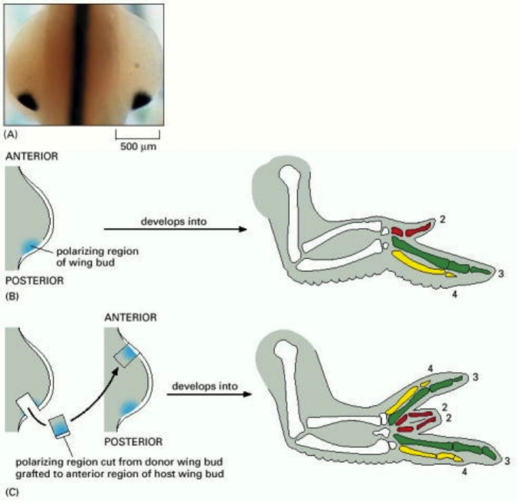


Figure 4. The Morphogen Model for Polarizing Activity in the Limb Bud

A normal limb may pattern its anterior–posterior axis by producing in the posterior polarizing region a diffusible compound whose gradient decreases anteriorily. As the concentration falls through certain threshold levels, the limb bud tissue is instructed to form particular digits. Grafting a second polarizing region at the anterior margin would create a second source of the morphogen, changing the concentration profile of the postulated morphogen such that each threshold would be reached twice in a symmetrical pattern. Implanting a retinoic acid bead has the same effect on limb pattern as a transplanted polarizing region, consistent with retinoic acid being or inducing the expression of the proposed morphogen.

Patterning by Diffusable Reagents

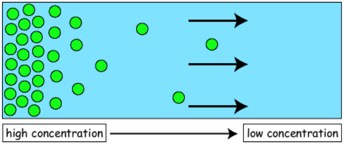


The Diffusion Equation

The Diffusion Equation - Derivation

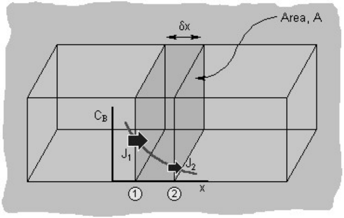
The Diffusion Equation in 1D

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}; \quad 0 \leq x \leq L$$



Fick's First Law

$$J = -D\frac{\partial c}{\partial x}$$

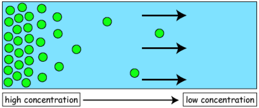


Fick's Second Law

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = D\frac{\partial^2 c}{\partial x^2}$$

Fick’s First Law

Diffusion flux: continuum limit of random walk.
Random Walk: half of the particles $N(x, t)$ move to the left, half to the right.



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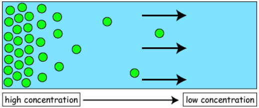
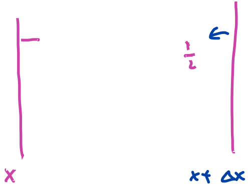


Net Movement to the right in spatial interval $[x, x + \Delta x]$:

$$-\frac{1}{2}\left[N(x + \Delta x, t) - N(x, t)\right]$$



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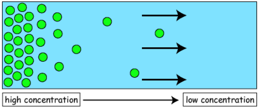


Net Movement to the right in spatial interval $[x, x+\Delta x]$:

$$-\frac{1}{2}\left[N(x+\Delta x,t)-N(x,t)\right]$$

Flux: net movement of particles across some area element of area a, normal to the random walk during a time interval Δt:

$$J=-\frac{1}{2}\left[\frac{N(x+\Delta x,t)-N(x,t)}{a\Delta t}\right]$$

Fick's First Law

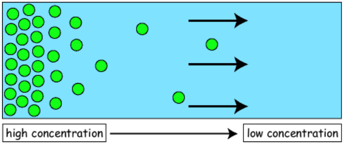
$$J = -\frac{1}{2}\left[\frac{N(x+\Delta x, t) - N(x,t)}{a\Delta t}\right]$$

Fick's First Law

$$
\begin{aligned}
J &= -\frac{1}{2}\left[\frac{N(x+\Delta x, t) - N(x,t)}{a\Delta t}\right] \\
&= \underbrace{-\frac{1}{2}\frac{(\Delta x)^2}{\Delta t}}_{D}\left[\frac{N(x+\Delta x, t) - N(x,t)}{a(\Delta x)^2}\right]
\end{aligned}
$$

Fick's First Law

$$
\begin{aligned}
J &= -\frac{1}{2}\left[\frac{N(x+\Delta x,t)-N(x,t)}{a\Delta t}\right] \\
&= -\underbrace{\frac{1}{2}\frac{(\Delta x)^2}{\Delta t}}_{D}\left[\frac{N(x+\Delta x,t)-N(x,t)}{a(\Delta x)^2}\right] \\
&= -D\left[\frac{c(x+\Delta x,t)-c(x,t)}{\Delta x}\right]
\end{aligned}
$$



Concentration $c = \frac{N(x,t)}{a\Delta x}$
Diffusion coefficient in 1D:
$D = \frac{(\Delta x)^2}{2\Delta t}$

Fick's First Law

$$
\begin{aligned}
J &= -\frac{1}{2}\left[\frac{N(x+\Delta x,t)-N(x,t)}{a\Delta t}\right] \\
&= -\underbrace{\frac{1}{2}\frac{(\Delta x)^2}{\Delta t}}_{D}\left[\frac{N(x+\Delta x,t)-N(x,t)}{a(\Delta x)^2}\right] \\
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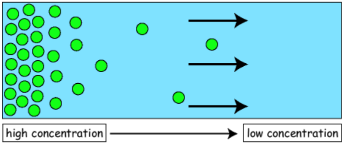
\end{aligned}
$$



Concentration $c = \frac{N(x,t)}{a\Delta x}$

Diffusion coefficient in 1D:

$D = \frac{(\Delta x)^2}{2\Delta t}$

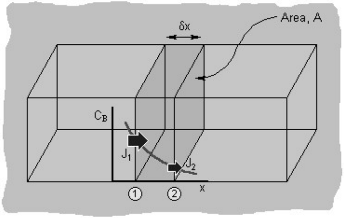
Fick's First Law

$$J = -D\frac{\partial c}{\partial x}$$

Fick's Second Law

Fick's Second Law follows from the conservation of mass:

$$\frac{\Delta c}{\Delta t} = -\frac{J(x + \Delta x, t) - J(x, t)}{\Delta x}$$



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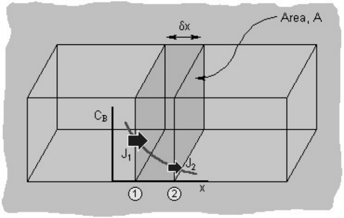

Fick's Second Law

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right)$$

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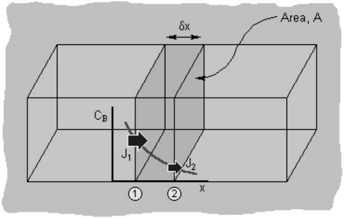
$$\frac{\Delta c}{\Delta t} = -\frac{J(x+\Delta x, t) - J(x, t)}{\Delta x}$$



Fick's Second Law

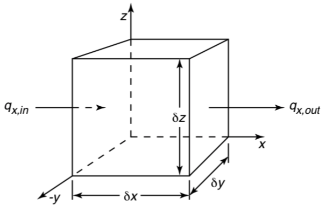
$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right)$$

If $D = const$,

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

Fluxes in 3D

In 3D, the net particle movement can be described by a movement in 6 different directions along 3 orthogonal axes:



$$
\begin{aligned}
J &= -\frac{1}{6}\begin{pmatrix} \frac{N(x+\Delta x,t)}{\Delta y\Delta z\Delta t} - \frac{N(x,t)}{\Delta y\Delta z\Delta t} \\ \frac{N(y+\Delta y,t)}{\Delta x\Delta z\Delta t} - \frac{N(y,t)}{\Delta x\Delta z\Delta t} \\ \frac{N(z+\Delta z,t)}{\Delta x\Delta y\Delta t} - \frac{N(z,t)}{\Delta x\Delta y\Delta t} \end{pmatrix} \\
&= -\frac{(\Delta l)^2}{6\Delta t}\begin{pmatrix} \frac{N(x+\Delta x,t)}{\Delta x^2\Delta y\Delta z} - \frac{N(x,t)}{\Delta x^2\Delta y\Delta z} \\ \frac{N(y+\Delta y,t)}{\Delta x\Delta y^2\Delta z} - \frac{N(y,t)}{\Delta x\Delta y^2\Delta z} \\ \frac{N(z+\Delta z,t)}{\Delta x\Delta y\Delta z^2} - \frac{N(z,t)}{\Delta x\Delta y\Delta z^2} \end{pmatrix} \\
&= -D\begin{pmatrix} \frac{c(x+\Delta x,t)-c(x,t)}{\Delta x} \\ \frac{c(y+\Delta y,t)-c(x,t)}{\Delta y} \\ \frac{c(z+\Delta z,t)-c(x,t)}{\Delta z} \end{pmatrix}
\end{aligned}
$$

Concentration $c = \frac{N(x,t)}{\Delta x\Delta y\Delta z}$

Diffusion coefficient in 1D:
$D = \frac{(\Delta l)^2}{6\Delta t}$ with
$\Delta l = \Delta x = \Delta y = \Delta z$.

The Diffusion Equation in 3D

Fick's First Law

$$J = -D\left(\frac{\partial c}{\partial x}\vec{e_x} + \frac{\partial c}{\partial y}\vec{e_y} + \frac{\partial c}{\partial z}\vec{e_z}\right) = -D\begin{pmatrix} \frac{\partial c}{\partial x} \\ \frac{\partial c}{\partial y} \\ \frac{\partial c}{\partial z} \end{pmatrix} = -D\nabla c$$

Fick's Second Law

$$\frac{\partial c}{\partial t} = -\nabla \cdot J = -\begin{pmatrix} \frac{\partial}{\partial x} \\ \frac{\partial}{\partial y} \\ \frac{\partial}{\partial z} \end{pmatrix}^T \cdot \begin{pmatrix} -D & \begin{matrix} \frac{\partial c}{\partial x} \\ \frac{\partial c}{\partial y} \\ \frac{\partial c}{\partial z} \end{matrix} \end{pmatrix} = -\nabla \cdot (-D\nabla c)$$

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right) = D\Delta c, \qquad \text{if} \quad D = const.$$

Solving the Diffusion Equation

Solving the Diffusion Equation

Diffusion Equation

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \\
\text{Boundary Condition (BC):} \quad & c(t,0) = c(t,\pi) = 0 \\
\text{Initial Condition (IC):} \quad & c(0,x) = \sin(x).
\end{aligned}
$$

Solving the Diffusion Equation

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$$

We can remove the diffusion coefficient D by adjusting the time scale to $\tau = D \cdot t$ such that $\frac{\partial c}{\partial \tau} = \frac{\partial^2 c}{\partial x^2}$. We therefore consider in the following

$$
\text{PDE:} \qquad \frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2}.
$$

Solving the Diffusion Equation - Separation of Variables

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2}$$

Ansatz: $c(t, x) = T(t)\, X(x)$:

$$\frac{\partial (T(t)\, X(x))}{\partial t} = \frac{\partial^2 (T(t) X(x))}{\partial x^2}$$

Solving the Diffusion Equation - Separation of Variables

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2}$$

Ansatz: $c\,(t, x) = T\,(t)\,X\,(x)$:

$$\frac{\partial(T\,(t)\,X\,(x))}{\partial t} = \frac{\partial^2(T\,(t)X\,(x))}{\partial x^2}$$

$$\frac{T'\,(t)}{T\,(t)} = \lambda = \frac{X''\,(x)}{X\,(x)}$$

Temporal & Spatial Solutions

$$\frac{T'(t)}{T(t)} = \lambda = \frac{X''(x)}{X(x)}$$

The solution of the temporal part reads:

$$T(t) = T(0)e^{\lambda t}$$

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$$\frac{T'(t)}{T(t)} = \lambda = \frac{X''(x)}{X(x)}$$

The solution of the temporal part reads:

$$T(t) = T(0)e^{\lambda t}$$

The solution of the spatial part reads:

$$X(x) = C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x}$$

If $\lambda < 0$, then the exponent is complex.

General Solution

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2}$$

$$c\left(t,x\right) = T\left(t\right)X\left(x\right) = T(0)e^{\lambda t}\left(C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x}\right)$$

We now need to take care of the boundary and initial conditions.

Boundary Conditions

Substituting the general solution

$$c\left(t,x\right)=T\left(t\right)X\left(x\right)=T(0)e^{\lambda t}\left(C_1 e^{\sqrt{\lambda}x}+C_2 e^{-\sqrt{\lambda}x}\right)$$

into the BC

$$c(t,0)=c(t,\pi) \quad = \quad 0,$$

we see that these can only be met if $\lambda < 0$.

Boundary Conditions

Substituting the general solution

$$c\,(t,x) = T\,(t)\,X\,(x) = T(0)e^{\lambda t}\left(C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x}\right)$$

into the BC

$$c(t,0) = c(t,\pi) \;\; = \;\; 0,$$

we see that these can only be met if $\lambda < 0$.

To ensure $\lambda < 0$, λ must satisfy

$$\lambda = -n^2 \qquad n = 1, 2, \ldots$$

Boundary Conditions

For

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the exponent is complex, i.e. $\lambda \in \mathcal{C}$.

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$$\sqrt{\lambda} = i\sqrt{-\lambda} = i\omega,$$

with $\omega \in \mathcal{R}$, and note that

$$e^{i\omega x} = \cos(\omega x) + i \sin(\omega x),$$

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such that

$$\begin{aligned} X(x) &= C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x} \\ &= C_1(\cos(\omega x) + i\sin(\omega x)) + C_2(\cos(-\omega x) + i\sin(-\omega x)) \end{aligned}$$

Boundary Conditions

For

$$\lambda = -n^2 \qquad n = 1, 2, \dots$$

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Boundary Conditions

$$c\,(t,x) = \underbrace{T(0)e^{\lambda t}}_{T(t)}\underbrace{(\cos(\omega x)\,(C_1 + C_2) + i\sin(\omega x))(C_1 - C_2))}_{X(x)}$$

To meet the boundary conditions,

$$c(t,0) = c(t,\pi) \quad = \quad 0,$$

we require $(C_1 + C_2) = 0$, such that

$$X\,(x) = 2iC_1 \sin(\omega x)\,.$$

Superposition principle

According to the superposition principle, the solution that respects the boundary conditions reads:

$$c\left(t,x\right)=\sum_{n=1}^{\infty}A_{n}e^{-n^{2}t}\sin\left(nx\right).$$

$A_n = 2iC_1 T(0)$.

Initial Conditions

Substituting the general solution into the IC ...

$$c\,(0,x) = \sin\,(x) \stackrel{!}{=} \sum_{n=1}^{\infty} A_n \sin\,(nx)$$

... immediately leads to the choice:

$$A_n = \begin{cases} 1, & \text{if } n = 1 \\ 0, & \text{else} \end{cases}$$

The solution reads:

$$c\,(t,x) = e^{-t} \sin\,(x)\,.$$

Comparison to Numerical Solution

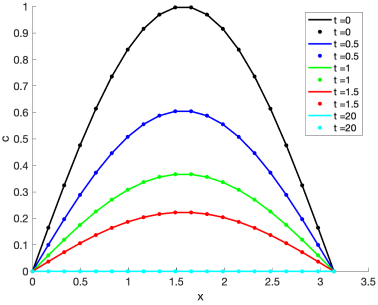
PDE: $$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$$

BC: $$c(t,0) = 0,$$ $$c(t,L) = 0$$

IC: $$c(0,x) = sin(x)$$

Analytical Solution (dots):

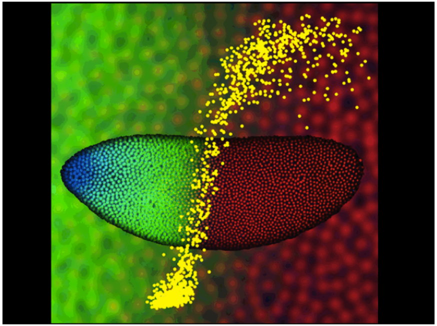
$$c\left(t,x\right) = e^{-Dt}\sin\left(x\right).$$



Morphogen Gradient Formation

Morphogen Gradients

- What is a morphogen gradient?
- Can diffusion create gradients?
- Robustness of morphogen gradients



A simple 1D diffusion model

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}; \quad 0 \leq x \leq L$$

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$$IC: \; c(x,0) = 0 \quad x > 0$$

A simple 1D diffusion model

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}; \quad 0 \leq x \leq L$$

$$IC: \ c(x,0) = 0 \quad x > 0$$

$$BC: \ c(0) = c_0 \qquad c(L) = 0$$

A simple 1D diffusion model

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}; \quad 0 \leq x \leq L$$

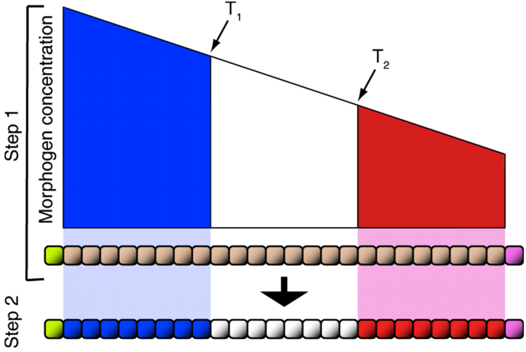
$$IC: \; c(x,0) = 0 \quad x > 0$$

$$BC: \; c(0) = c_0 \qquad c(L) = 0$$

Steady-state solution:

$$c(x) = c_0 \frac{L-x}{L}$$

French Flag Model (Wolpert)



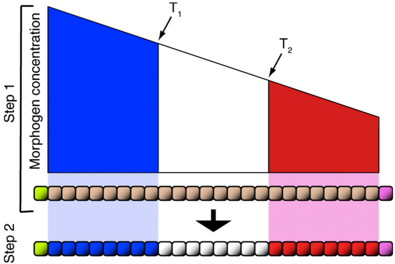
Jaeger et al (2008) Development

Just simply calculation

The French Flag Model (Lewis Wolpert)

The French Flag represents the effect of different morphogen concentrations on cell differentiation

- a morphogen affects cell states based on concentration
- these states are represented by the different colours of the French flag
  - high concentrations ⇒ blue gene
  - lower concentrations ⇒ white gene
  - below the lowest concentration threshold ⇒ red genes, i.e. default state in cells



Time-Dependent Solution

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \\
\text{BC:} \quad & c(t,0) = c_0, \qquad c(t,L) = 0 \\
\text{IC:} \quad & c(0,0) = c_0; \qquad c(0,x) = 0 \quad \forall \quad x > 0.
\end{aligned} \tag{1}
$$

The general solution is again

$$
c\,(t,x) = T\,(t)\,X\,(x) = T(0)e^{D\lambda t}\left(C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x}\right).
$$

Boundary Conditions

$$c\,(t,x) = T\,(t)\,X\,(x) = T(0)e^{D\lambda t}\left(C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x}\right)$$

To meet the boundary condition $c(t,0) = c_0$, we would require

$$c\,(t,0) = T(0)e^{D\lambda t}\,(C_1 + C_2) = c_0.$$

This does not work as the LHS is time-dependent, while the RHS is not.

We need a different approach to deal with inhomogeneous boundary conditions.

Inhomogeneous boundary conditions

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \\
\text{BC:} \quad & c(t,0) = c_0, \qquad c(t,L) = 0 \\
\text{IC:} \quad & c(0,0) = c_0; \qquad c(0,x) = 0 \quad \forall \quad x > 0.
\end{aligned} \tag{2}
$$

We have previously determined the steady-state solution:

$$c_s(x) = c_0 \frac{L - x}{L}$$

We now generate a new function $u(x,t) = c(x,t) - c_s(x)$.

Inhomogeneous boundary conditions

With $u(x,t) = c(x,t) - c_s(x)$,

$$\text{PDE:} \qquad \frac{\partial u}{\partial t} = \frac{\partial (c - c_s)}{\partial t} = D\frac{\partial^2 (c - c_s)}{\partial x^2} = D\frac{\partial^2 u}{\partial x^2}$$

Inhomogeneous boundary conditions

With $u(x,t) = c(x,t) - c_s(x)$,

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial u}{\partial t} = \frac{\partial (c - c_s)}{\partial t} = D\frac{\partial^2 (c - c_s)}{\partial x^2} = D\frac{\partial^2 u}{\partial x^2} \\
\text{BC:} \quad & u(t,0) = c(t,0) - c_s(0) = c_0 - c_0 = 0 \\
& u(t,L) = c(t,L) - c_s(L) = 0
\end{aligned}
$$

Inhomogeneous boundary conditions

With $u(x,t) = c(x,t) - c_s(x)$,

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial u}{\partial t} = \frac{\partial (c - c_s)}{\partial t} = D\frac{\partial^2 (c - c_s)}{\partial x^2} = D\frac{\partial^2 u}{\partial x^2} \\
\text{BC:} \quad & u(t,0) = c(t,0) - c_s(0) = c_0 - c_0 = 0 \\
& u(t,L) = c(t,L) - c_s(L) = 0 \\
\text{IC:} \quad & u(0,0) = c(0,0) - c_s(0) = 0 \\
& u(0,x) = c(0,x) - c_s(0,x) = -c_0\frac{L-x}{L} \quad \forall \quad x > 0.
\end{aligned}
$$

We already know how to solve the PDE for u, which has homogenous boundary conditions.

Homogenous Boundary Conditions

We have as general solution,

$$u\left(t,x\right) = T(0)e^{D\lambda t}\left(C_1 e^{\sqrt{\lambda}x} + C_2 e^{-\sqrt{\lambda}x}\right)$$

with

$$\lambda = -n^2 \qquad n = 1, 2, \ldots$$

Substituting $\sqrt{\lambda} = i\sqrt{-\lambda} = i\omega$, we obtain

$$X\left(x\right) \;=\; \cos\left(\omega x\right)\left(C_1 + C_2\right) + i\sin\left(\omega x\right))(C_1 - C_2).$$

To meet the boundary conditions, we require $\left(C_1 + C_2\right) = 0$ and $\omega = \frac{n\pi}{L}$, such that

$$X\left(x\right) = 2iC_1 \sin\left(\frac{n\pi x}{L}\right).$$

Superposition principle

According to the superposition principle, the solution that respects the boundary conditions reads:

$$u\left(t,x\right)=\sum_{n=1}^{\infty}A_n e^{-D\frac{n^2\pi^2}{L^2}t}\sin\left(\frac{n\pi x}{L}\right);\qquad A_n=2iC_1\,T(0).$$

Initial Conditions

Substituting the general solution into the IC ...

$$u(0,0) \;=\; 0 \overset{!}{=} \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi \cdot 0}{L}\right) = 0$$

Initial Conditions

Substituting the general solution into the IC ...

$$
\begin{aligned}
u(0,0) &= 0 \overset{!}{=} \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi \cdot 0}{L}\right) = 0 \\
u(0,x) &= -c_0 \frac{L-x}{L} = f(x) \overset{!}{=} \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right) \quad \forall \quad x > 0
\end{aligned}
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Substituting the general solution into the IC ...

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\end{aligned}
$$

We now multiply both sides with $\sin\left(\frac{m\pi x}{L}\right)$ and integrate from 0 to L

$$
\int_0^L f(x) \sin\left(\frac{m\pi x}{L}\right) dx = \int_0^L \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right) \sin\left(\frac{m\pi x}{L}\right) dx
$$

Orthogonal Functions

Orthogonal functions belong to a function space which is a vector space that has a bilinear form. When the function space has an interval as the domain, the bilinear form may be the integral of the product of functions over the interval:

$$\langle f, g \rangle = \int \overline{f(x)} g(x)\, dx. \tag{3}$$

The functions f and g are orthogonal when this integral is zero, i.e.

$$\langle f,\ g \rangle = 0 \tag{4}$$

whenever $f \neq g$. As with a basis of vectors in a finite-dimensional space, orthogonal functions can form an infinite basis for a function space.

Orthogonal Functions

The sine functions $\sin(nx)$ and $\sin(mx)$ are orthogonal on the interval $(-\pi, \pi)$ when $m \neq n$. For then,

$$2\sin(mx)\sin(nx) = \cos((m-n)x) - \cos((m+n)x),$$

and the integral of the product of the two sine functions vanishes,

$$\int_{-\pi}^{\pi} \sin(nx)\sin(mx)dx = \begin{cases} 1, & \text{if } n = m \\ 0, & \text{if } n \neq m \end{cases}.$$

Initial Conditions

$$\int_0^L f(x)\sin\left(\frac{m\pi x}{L}\right)dx \quad = \quad \int_0^L \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right)\sin\left(\frac{m\pi x}{L}\right)dx$$

$$\int_0^L \sin\left(\frac{n\pi x}{L}\right)\sin\left(\frac{m\pi x}{L}\right)dx = 0, \qquad \forall\, m \neq n.$$

$$\int_0^L \sin^2\left(\frac{n\pi x}{L}\right)dx = \left[\frac{x}{2} - \frac{sin(2x)}{4}\right]_0^L = \frac{L}{2}.$$

Coefficients A_n

$$A_n \quad = \quad \frac{2}{L}\int_0^L f(x)\sin\left(\frac{n\pi x}{L}\right)dx.$$

Coefficients A_n

$$A_n = \frac{2}{L}\int_0^L -c_0\left(\frac{L-x}{L}\right)\sin\left(\frac{n\pi x}{L}\right)dx.$$

Coefficients A_n

$$
\begin{aligned}
A_n &= \frac{2}{L}\int_0^L -c_0\left(\frac{L-x}{L}\right)\sin\left(\frac{n\pi x}{L}\right)dx. \\
&= -\frac{2c_0}{L^2}\left(L\int_0^L \sin\left(\frac{n\pi x}{L}\right)dx - \int_0^L x\sin\left(\frac{n\pi x}{L}\right)dx\right).
\end{aligned}
$$

Coefficients A_n

$$
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&= -\frac{2c_0}{L^2}\frac{L}{n\pi}\left(L\underbrace{\left[-\cos\left(\frac{n\pi x}{L}\right)\right]_0^L}_{=0} - \left[-x\cos\left(\frac{n\pi x}{L}\right)+\sin\left(\frac{n\pi x}{L}\right)\right]_0^L\right)
\end{aligned}
$$

Coefficients A_n

$$
\begin{aligned}
A_n &= \frac{2}{L}\int_0^L -c_0\left(\frac{L-x}{L}\right)\sin\left(\frac{n\pi x}{L}\right)dx. \\
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&= \frac{2c_0}{L^2}\frac{L}{n\pi}\left(\left[-x\cos\left(\frac{n\pi x}{L}\right)\right]_0^L\right)
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&= -\frac{2c_0}{L^2}\frac{L}{n\pi}\left(\underbrace{L\left[-\cos\left(\frac{n\pi x}{L}\right)\right]_0^L}_{=0} - \left[-x\cos\left(\frac{n\pi x}{L}\right) + \sin\left(\frac{n\pi x}{L}\right)\right]_0^L\right) \\
&= \frac{2c_0}{L^2}\frac{L}{n\pi}\left(\left[-x\cos\left(\frac{n\pi x}{L}\right)\right]_0^L\right) \\
&= \frac{2c_0}{L^2}\frac{L}{n\pi}(-L) = -\frac{2c_0}{n\pi}.
\end{aligned}
$$

Solution

The solution then reads:

$$u(t,x) = \sum_{n=1}^{\infty} -\frac{2c_0}{n\pi} e^{-D\frac{n^2\pi^2}{L^2}t} \sin\left(\frac{n\pi x}{L}\right).$$

and thus

$$c(t,x) = c_s(t,x) + u(t,x) = c_0\left(\frac{L-x}{L}\right) - \sum_{n=1}^{\infty} \frac{2c_0}{n\pi} e^{-D\frac{n^2\pi^2}{L^2}t} \sin\left(\frac{n\pi x}{L}\right).$$

Comparison to Numerical Solution

PDE: $$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$$

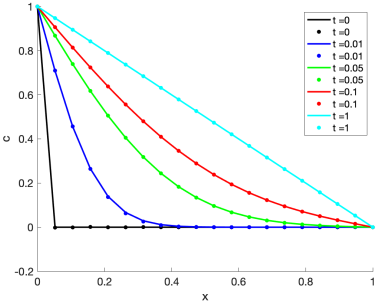
BC: $$c(t,0) = c_0,$$

$$c(t,L) = 0$$

IC: $$c(0,0) = c_0;$$

$$c(0,x) = 0 \quad \forall \quad x > 0.$$

.



Analytical Solution (dots):

$$c\left(t,x\right) = c_s\left(t,x\right) + u\left(t,x\right) = c_0\left(\frac{L-x}{L}\right) - \sum_{n=1}^{\infty}\frac{2c_0}{n\pi}e^{-D\frac{n^2\pi^2}{L^2}t}\sin\left(\frac{n\pi x}{L}\right).$$

Time to steady state

$$c\left(t,x\right)=c_s\left(t,x\right)+u\left(t,x\right)=c_0\left(\frac{L-x}{L}\right)-\sum_{n=1}^{\infty}\frac{2c_0}{n\pi}e^{-D\frac{n^2\pi^2}{L^2}t}\sin\left(\frac{n\pi x}{L}\right).$$

The solution reaches steady state exponentially fast with rate

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

Characteristic time to steady state:

$$t_{char}=\frac{1}{k}=\frac{L^2}{Dn^2\pi^2}.$$

The time to steady state thus depends on domain length L relative to the diffusion coefficient D.

Time to steady state

$$c\left(t,x\right) = c_s\left(t,x\right) + u\left(t,x\right) = c_0\left(\frac{L-x}{L}\right) - \sum_{n=1}^{\infty} \frac{2c_0}{n\pi} e^{-D\frac{n^2\pi^2}{L^2}t} \sin\left(\frac{n\pi x}{L}\right).$$

The solution reaches steady state exponentially fast with rate

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

Characteristic time to steady state:

$$t_{char} = \frac{1}{k} = \frac{L^2}{Dn^2\pi^2}.$$

The time to steady state thus depends on domain length L relative to the diffusion coefficient D. Higher modes n reach steady state faster.

Physiological Time to steady state

Typical diffusion coefficient: $D \in [0.1, 10]\ \mu\text{m}^2\text{s}^{-1}$.
Typical size of patterning domain: $L \in [50, 500]\ \mu\text{m}$.

Characteristic time to steady state:

$$t_{char} = \frac{1}{k} = \frac{L^2}{Dn^2\pi^2} \leq \frac{500^2}{0.1\pi^2} = 2.5 \cdot 10^5 s = 70\,\text{hours} \approx 3\,\text{days}.$$

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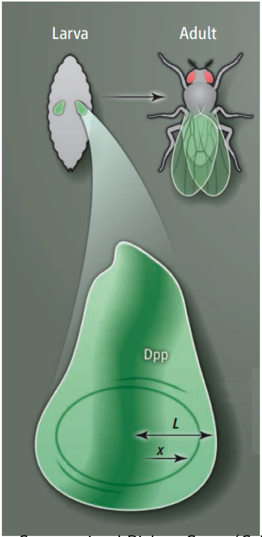
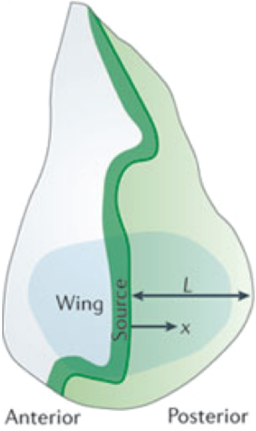
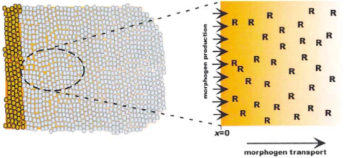
Developmental patterning processes typically progress within hours to days.

Whether gradients are in steady state must therefore be assessed in the individual cases.

The Dpp Gradient in the *Drosophila* wing disc

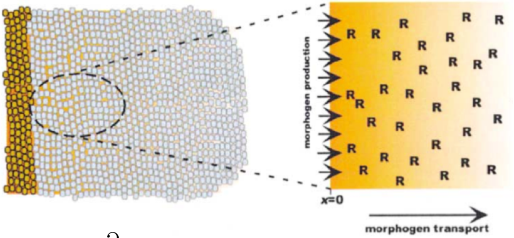






Dpp is secreted continously from the stripe at the AP boundary into the domain.

The problem with a constant morphogen influx

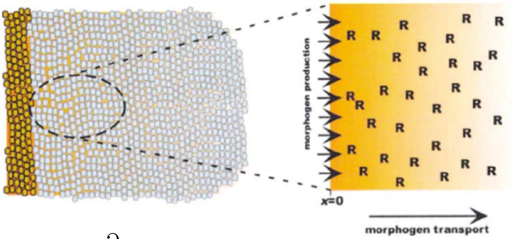


$$\frac{\partial c}{\partial t} = D\Delta c; \quad 0 \leq x \leq L$$

$$IC: \; c(x,0) = 0$$

$$BC: \; \left.\frac{\partial c}{\partial x}\right|_{x=0} = -j; \qquad \left.\frac{\partial c}{\partial x}\right|_{x=L} = 0$$

The problem with a constant morphogen influx



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Steady-state solution:

$$c_s(x) = ax + b.$$

The two BCs

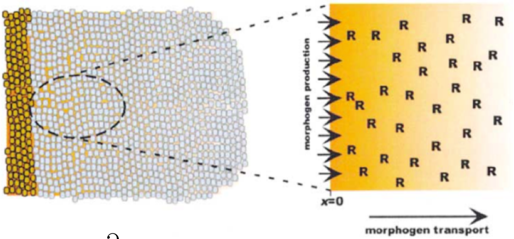
$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = a = -j.$$

$$\left.\frac{\partial c}{\partial x}\right|_{x=L} = a = 0$$

require different values for a.

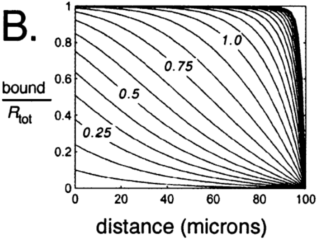
Accordingly, there is
no steady-state solution.

The problem with a constant morphogen influx



$$\frac{\partial c}{\partial t} = D\Delta c; \quad 0 \leq x \leq L$$

However, no "useful" steady state gradients:



$$BC: \left.\frac{\partial c}{\partial x}\right|_{x=0} = -j \qquad c(x=L,t)=0$$

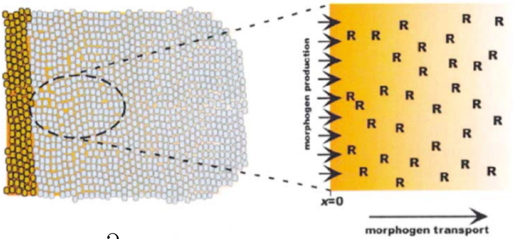
Lander et al (2002) Dev Cell

has a steady state solution $c_s(x) = ax + b$
with $a = -j$, $b = L \cdot j$

linear with

$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2}$

The problem with a constant morphogen influx



$$\frac{\partial c}{\partial t} = D\Delta c; \quad 0 \leq x \leq L$$

$$BC: \left.\frac{\partial c}{\partial x}\right|_{x=0} = -j \qquad c(x = L, t) = 0$$

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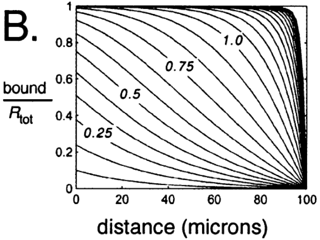
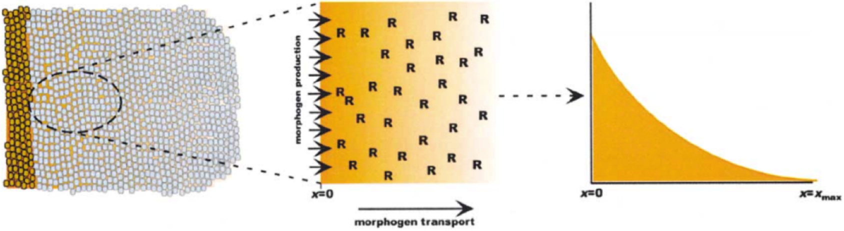


Lander et al (2002) Dev Cell

Can diffusion create "useful" gradients?

The importance of degradation



$$\frac{\partial c}{\partial t} = D\Delta c - kc; \quad 0 \leq x \leq 1$$

$$IC \quad : \quad c(x,0) = 0 \qquad BC : \left.\frac{\partial c}{\partial x}\right|_{x=0} = -j \qquad \left.\frac{\partial c}{\partial x}\right|_{x=1} = 0$$

Steady-state solution

$$\frac{\partial c}{\partial t} = D\Delta c - kc = 0; \quad 0 \leq x \leq 1$$

General steady-state solution:

$$c(x) = a\exp(\mu x) + b\exp(-\mu x); \qquad \mu = 1/\lambda = \sqrt{\frac{k}{D}}$$

Boundary Conditions:

$$\left.\frac{\partial c}{\partial x}\right|_{x=0} = \mu(a-b) = -j$$

$$\left.\frac{\partial c}{\partial x}\right|_{x=1} = \mu(a\exp(\mu) + b\exp(-\mu)) = 0$$

Coefficients:

$$b = -\frac{j}{\mu}\frac{1}{\exp(-2\mu) - 1}$$

$$a = b\exp(-2\mu)$$

The importance of degradation

$$
\begin{aligned}
\frac{\partial c}{\partial t} &= D\Delta c - kc; \quad 0 \leq x \leq 1 \\
IC &: \quad c(x,0) = 0 \qquad BC: \left.\frac{\partial c}{\partial x}\right|_{x=0} = -j \qquad \left.\frac{\partial c}{\partial x}\right|_{x=L} = 0
\end{aligned}
$$

Steady-state solution:

$$
c(x) = \frac{j}{\mu}\frac{\exp\mu(2-x) + \exp(\mu x)}{\exp(2\mu) - 1}; \qquad \mu = 1/\lambda = \sqrt{\frac{k}{D}}
$$

If we include degradation, we again obtain a steady state solution.

Time-Dependent Solution

$$\text{PDE:} \qquad \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc$$

Ansatz: Separation of Variables: $c(t,x) = T(t)\,X(x)$

$$\begin{aligned}
\frac{\partial(T(t)\,X(x))}{\partial t} &= D\frac{\partial^2(T(t)\,X(x))}{\partial x^2} - k(T(t)\,X(x)) \\
X(x)\,\frac{\partial T(t)}{\partial t} &= T(t)\,D\frac{\partial^2 X(x)}{\partial x^2} - k(T(t)\,X(x)) \\
\frac{T'(t)}{T(t)} + k &= \sigma = D\frac{X''(x)}{X(x)}
\end{aligned}$$

Temporal & Spatial Solutions

$$\frac{T'(t)}{T(t)} + k = \sigma = D\frac{X''(x)}{X(x)}$$

The solution of the temporal part reads:

$$T(t) = T(0)e^{(\sigma - k)t}$$

The solution of the spatial part reads:

$$X(x) = C_1 e^{\sqrt{\sigma/D}x} + C_2 e^{-\sqrt{\sigma/D}x}$$

If $\lambda < 0$, then the exponent is complex.

General Solution

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc$$

$$c\left(t,x\right) = T\left(t\right)X\left(x\right) = T(0)e^{(\sigma-k)t}\left(C_1 e^{\sqrt{\sigma/D}x} + C_2 e^{-\sqrt{\sigma/D}x}\right)$$

We now need to take care of the boundary and initial conditions.

Inhomogeneous boundary conditions

$$\text{PDE:} \quad \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc$$

$$\text{BC:} \quad \left.\frac{\partial c}{\partial x}\right|_{x=0} = -j \qquad \left.\frac{\partial c}{\partial x}\right|_{x=L} = 0$$

$$\text{IC:} \quad c(x,0) = 0.$$

We have previously determined the steady-state solution:

$$c_s(x) = \frac{j}{\mu}\frac{\exp\mu(2-x) + \exp(\mu x)}{\exp(2\mu) - 1}; \qquad \mu = 1/\lambda = \sqrt{\frac{k}{D}}$$

We now generate a new function $u(x,t) = c(x,t) - c_s(x)$.

Transformation to Homogeneous BCs

With $u(x,t) = c(x,t) - c_s(x)$,

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial u}{\partial t} = \frac{\partial (c - c_s)}{\partial t} = D\frac{\partial^2 (c - c_s)}{\partial x^2} - k(c - c_s) \\
& \qquad = D\frac{\partial^2 u}{\partial x^2} - ku \\
\text{BC:} \quad & \left.\frac{\partial u}{\partial x}\right|_{x=0} = \left.\frac{\partial c}{\partial x}\right|_{x=0} - \left.\frac{\partial c_s}{\partial x}\right|_{x=0} = 0 \\
& \left.\frac{\partial u}{\partial x}\right|_{x=L} = \left.\frac{\partial c}{\partial x}\right|_{x=L} - \left.\frac{\partial c_s}{\partial x}\right|_{x=L} = 0 \\
\text{IC:} \quad & u(x,0) = c(x,0) - c_s(x) \\
& \qquad = -\frac{j}{\mu}\frac{\exp \mu(2 - x) + \exp(\mu x)}{\exp(2\mu) - 1}.
\end{aligned}
$$

Homogenous Boundary Conditions

We now solve the PDE for u with homogenous boundary conditions.

We have as general solution,

$$u\left(t,x\right)=T\left(t\right)X\left(x\right)=T(0)e^{(\sigma-k)t}\left(C_1e^{\sqrt{\sigma/D}x}+C_2e^{-\sqrt{\sigma/D}x}\right).$$

As $c(x,t)=c_s+u(x,t)$, we require $u\left(t,x\right)\to 0$ as $t\to\infty$ and thus

$$\sigma<k.$$

Homogenous Boundary Conditions

$$u(t,x) = T(t)\,X(x) = T(0)e^{(\sigma-k)t}\left(C_1 e^{\sqrt{\sigma/D}x} + C_2 e^{-\sqrt{\sigma/D}x}\right).$$

Substituting $\sqrt{\sigma/D} = i\sqrt{-\sigma/D} = i\omega$, we obtain

$$X(x) \;=\; \cos(\omega x)\,(C_1 + C_2) + i\sin(\omega x))(C_1 - C_2).$$

To meet the homogenous boundary conditions at $x = 0$ and $x = L$, we require $(C_1 - C_2) = 0$ and $\omega = \frac{n\pi}{L}$, such that

$$X(x) = 2C_1\cos\left(\frac{n\pi x}{L}\right).$$

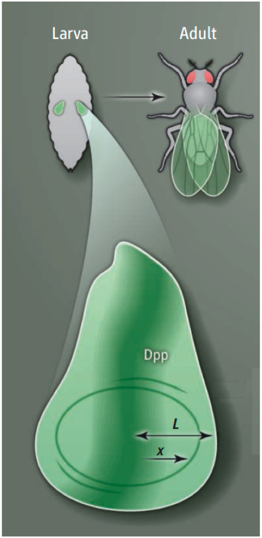
Superposition principle

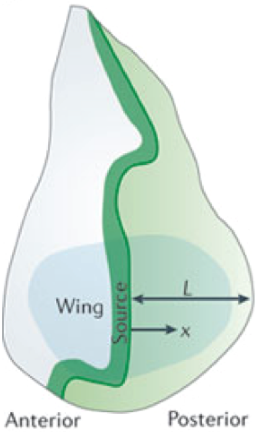
From $\sqrt{-\sigma/D} = \omega$, we further obtain $\sigma = -D\omega^2 = -D\frac{n^2\pi^2}{L^2}$.

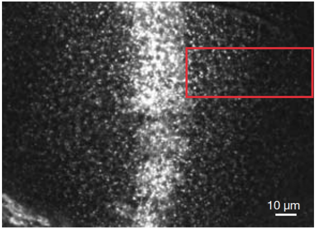
According to the superposition principle, the solution that respects the boundary conditions reads:

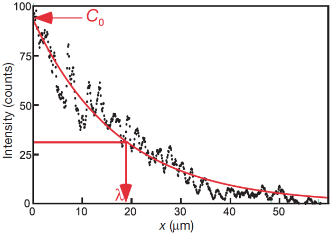
$$u(t,x) = \sum_{n=1}^{\infty} A_n e^{-\left(D\frac{n^2\pi^2}{L^2}+k\right)t} \cos\left(\frac{n\pi x}{L}\right); \qquad A_n = 2C_1 T(0).$$

The Dpp Gradient is of exponential shape









Initial Conditions

Substituting the general solution into the IC ...

$$u(x,0) \quad = \quad \frac{j}{\mu}\frac{\exp\mu(2-x)+\exp(\mu x)}{\exp(2\mu)-1} = f(x) \stackrel{!}{=} \sum_{n=1}^{\infty} A_n \cos\left(\frac{n\pi x}{L}\right)$$

As before,

$$A_n = \frac{2}{L}\int_0^L f(x)\cos\left(\frac{n\pi x}{L}\right) dx.$$

Time to steady state

The solution reaches steady state exponentially fast with rate

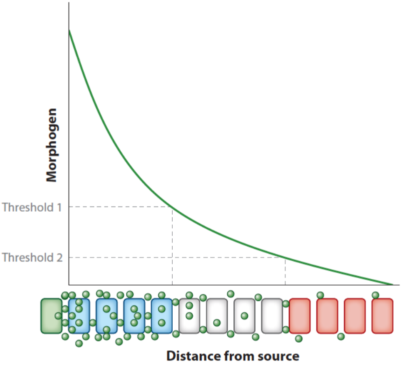
$$\delta = \frac{Dn^2\pi^2}{L^2} + k.$$

Characteristic time to steady state:

$$t_{char} = \frac{1}{\delta} = \frac{L^2}{Dn^2\pi^2 + kL^2}.$$

The time to steady state thus depends on domain length L relative to the diffusion coefficient D AND the degradation rate k.

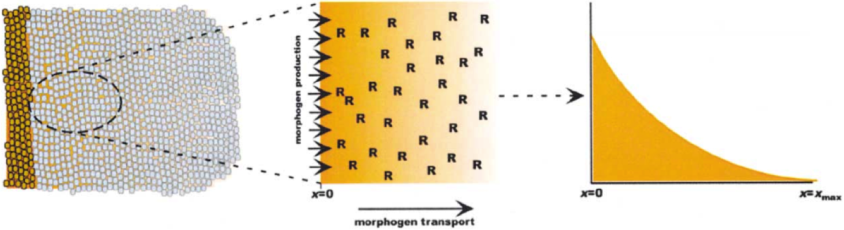
The modified French Flag Model in Patterning



The French Flag model can still be used also with an exponential gradient:

$$c = c_0 \exp\left(-x/\lambda\right)$$

Degradation & fixed boundary conditions



Steady-state solution:

$$PDE: \quad \frac{\partial c}{\partial t} = D\Delta c - kc; \quad 0 \leq x \leq L$$

$$IC: \quad c(x,0) = 0$$

$$BC: \quad c(0,t) = c_0 \qquad c(L) = 0$$

$$c(x) = c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)}$$

$$\lambda = \sqrt{\frac{D}{k}}$$

Time-Dependent Solution

$$
\begin{aligned}
\text{PDE:} \quad & \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc \\
\text{BC:} \quad & c(t,0) = c_0, \qquad c(t,L) = 0 \\
\text{IC:} \quad & c(0,0) = c_0; \qquad c(0,x) = 0 \quad \forall \quad x > 0. \qquad (5)
\end{aligned}
$$

Ansatz: Separation of Variables: $c(t,x) = T(t)\,X(x)$

$$
\begin{aligned}
\frac{\partial (T(t)\,X(x))}{\partial t} &= D\frac{\partial^2 (T(t)\,X(x))}{\partial x^2} - k(T(t)\,X(x)) \\
X(x)\,\frac{\partial T(t)}{\partial t} &= T(t)\,D\frac{\partial^2 X(x)}{\partial x^2} - k(T(t)\,X(x)) \\
\frac{T'(t)}{T(t)} + k &= \sigma = D\frac{X''(x)}{X(x)}
\end{aligned}
$$

Temporal & Spatial Solutions

$$\frac{T'(t)}{T(t)} + k = \sigma = D\frac{X''(x)}{X(x)}$$

The solution of the temporal part reads:

$$T(t) = T(0)e^{(\sigma - k)t}$$

The solution of the spatial part reads:

$$X(x) = C_1 e^{\sqrt{\sigma/D}x} + C_2 e^{-\sqrt{\sigma/D}x}$$

If $\lambda < 0$, then the exponent is complex.

General Solution

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc$$

$$c(t,x) = T(t)\,X(x) = T(0)e^{(\sigma-k)t}\left(C_1 e^{\sqrt{\sigma/D}x} + C_2 e^{-\sqrt{\sigma/D}x}\right)$$

We now need to take care of the boundary and initial conditions.

Inhomogeneous boundary conditions

$$\begin{aligned}
\text{PDE:} \quad & \frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc \\
\text{BC:} \quad & c(t,0) = c_0, \qquad c(t,L) = 0 \\
\text{IC:} \quad & c(0,0) = c_0; \qquad c(0,x) = 0 \quad \forall \quad x > 0. \qquad (6)
\end{aligned}$$

We have previously determined the steady-state solution:

$$\begin{aligned}
c_s(x) &= c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)} \\
\lambda &= \sqrt{\frac{D}{k}}
\end{aligned}$$

We now generate a new function $u(x,t) = c(x,t) - c_s(x)$.

Transformation to Homogeneous BCs

With $u(x,t) = c(x,t) - c_s(x)$,

$$\begin{aligned}
\text{PDE:} \qquad & \frac{\partial u}{\partial t} = \frac{\partial (c - c_s)}{\partial t} = D\frac{\partial^2 (c - c_s)}{\partial x^2} - k(c - c_s) \\
& \qquad = D\frac{\partial^2 u}{\partial x^2} - ku \\
\text{BC:} \qquad & u(t,0) = c(t,0) - c_s(0) = c_0 - c_0 = 0 \\
& u(t,L) = c(t,L) - c_s(L) = 0 \\
\text{IC:} \qquad & u(0,0) = c(0,0) - c_s(0) = 0 \\
& u(0,x) = c(0,x) - c_s(0,x) \\
& \qquad = -c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)} = f(x) \quad \forall \quad x > 0.
\end{aligned}$$

We now solve the PDE for u with homogenous boundary conditions.

Homogenous Boundary Conditions

We have as general solution,

$$u\left(t,x\right)=T\left(t\right)X\left(x\right)=T(0)e^{(\sigma-k)t}\left(C_1e^{\sqrt{\sigma/D}x}+C_2e^{-\sqrt{\sigma/D}x}\right).$$

As $c(x,t)=c_s+u(x,t)$, we require $u\left(t,x\right)\rightarrow 0$ as $t\rightarrow\infty$ and thus

$$\sigma<k.$$

Homogenous Boundary Conditions

$$u(t,x) = T(t)X(x) = T(0)e^{(\sigma-k)t}\left(C_1 e^{\sqrt{\sigma/D}x} + C_2 e^{-\sqrt{\sigma/D}x}\right).$$

Substituting $\sqrt{\sigma/D} = i\sqrt{-\sigma/D} = i\omega$, we obtain

$$X(x) = \cos(\omega x)(C_1 + C_2) + i\sin(\omega x))(C_1 - C_2).$$

To meet the homogenous boundary conditions as $x = 0$ and $x = L$, we require $(C_1 + C_2) = 0$ and $\omega = \frac{n\pi}{L}$, such that

$$X(x) = 2iC_1 \sin\left(\frac{n\pi x}{L}\right).$$

Superposition principle

From $\sqrt{-\sigma/D} = \omega$, we further obtain $\sigma = -D\omega^2 = -D\frac{n^2\pi^2}{L^2}$.

According to the superposition principle, the solution that respects the boundary conditions reads:

$$u\left(t,x\right) = \sum_{n=1}^{\infty} A_n e^{-\left(D\frac{n^2\pi^2}{L^2}+k\right)t} \sin\left(\frac{n\pi x}{L}\right); \qquad A_n = 2iC_1 T(0).$$

Initial Conditions

Substituting the general solution into the IC ...

$$
\begin{aligned}
u(0,0) &= 0 \stackrel{!}{=} \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi \cdot 0}{L}\right) = 0 \\
u(0,x) &= -c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)} = f(x) \stackrel{!}{=} \sum_{n=1}^{\infty} A_n \sin\left(\frac{n\pi x}{L}\right) \quad \forall \quad x > 0
\end{aligned}
$$

As before,

$$
A_n = \frac{2}{L} \int_0^L f(x) \sin\left(\frac{n\pi x}{L}\right) dx.
$$

Coefficients A_n

$$
\begin{aligned}
A_n &= \frac{2}{L}\int_0^L \left(-c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)} \sin\left(\frac{n\pi x}{L}\right)\right) dx. \\
&= \frac{-2c_0}{L\sinh\left(\frac{L}{\lambda}\right)} \int_0^L \left(\sinh\left(\frac{L-x}{\lambda}\right) \sin\left(\frac{n\pi x}{L}\right)\right) dx. \\
&= \frac{-2c_0}{L\sinh\left(\frac{L}{\lambda}\right)} I
\end{aligned}
$$

We now need to determine the integral I.

Determination of Integral

$$
\begin{aligned}
I &= \int_0^L \left(\sinh\left(\frac{L-x}{\lambda}\right)\sin\left(\frac{n\pi x}{L}\right)\right)dx. \\
&= -\frac{L}{n\pi}\left[\sinh\left(\frac{L-x}{\lambda}\right)\cos\left(\frac{n\pi x}{L}\right)\right]_0^L \\
&\quad -\frac{L}{\lambda n\pi}\int_0^L \left(\cosh\left(\frac{L-x}{\lambda}\right)\cos\left(\frac{n\pi x}{L}\right)\right)dx. \qquad (7)
\end{aligned}
$$

Determination of Integral

$$
\begin{aligned}
I_2 &= \int_0^L \left(\cosh\left(\frac{L-x}{\lambda}\right)\cos\left(\frac{n\pi x}{L}\right)\right) dx \\
&= \frac{L}{n\pi}\left[\cosh\left(\frac{L-x}{\lambda}\right)\sin\left(\frac{n\pi x}{L}\right)\right]_0^L \\
&\quad + \frac{L}{\lambda n\pi}\int_0^L \left(\sinh\left(\frac{L-x}{\lambda}\right)\sin\left(\frac{n\pi x}{L}\right)\right) dx. \qquad (8)
\end{aligned}
$$

Determination of Integral

$$
\begin{aligned}
I &= \int_0^L \left(\sinh\left(\frac{L-x}{\lambda}\right)\sin\left(\frac{n\pi x}{L}\right)\right)dx \\
&= \frac{L}{n\pi}\sinh\left(\frac{L}{\lambda}\right) \\
&\quad -\left(\frac{L}{\lambda n\pi}\right)^2 \int_0^L \left(\sinh\left(\frac{L-x}{\lambda}\right)\sin\left(\frac{n\pi x}{L}\right)\right)dx
\end{aligned}
$$

After rearrangements we obtain

$$
I = \frac{\frac{L}{n\pi}\sinh\left(\frac{L}{\lambda}\right)}{\left(1+\left(\frac{L}{\lambda n\pi x}\right)^2\right)}
$$

Coefficients A_n

$$
\begin{aligned}
A_n &= \frac{-2c_0}{L\sinh\left(\frac{L}{\lambda}\right)} I \\
&= \frac{-2c_0}{L\sinh\left(\frac{L}{\lambda}\right)} \frac{\frac{L}{n\pi}\sinh\left(\frac{L}{\lambda}\right)}{\left(1+\left(\frac{L}{\lambda n\pi}\right)^2\right)} \\
&= \frac{-2c_0}{n\pi\left(1+\left(\frac{L}{\lambda n\pi}\right)^2\right)} \\
&= \frac{-2c_0 n\pi}{(n\pi)^2+\left(\frac{L}{\lambda}\right)^2}
\end{aligned}
$$

Solution

The solution then reads:

$$u\left(t,x\right)=-\sum_{n=1}^{\infty}\frac{2c_0 n\pi}{(n\pi)^2+\left(\frac{L}{\lambda}\right)^2}\exp\left(-\left(D\frac{n^2\pi^2}{L^2}+k\right)t\right)\sin\left(\frac{n\pi x}{L}\right).$$

and

$$c\left(t,x\right)=c_s\left(t,x\right)+u\left(t,x\right)$$

We see that the solution reaches steady state exponentially fast with rate

$$\frac{Dn^2\pi^2}{L^2}+k.$$

Comparison to Numerical Solution

PDE: $$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc$$

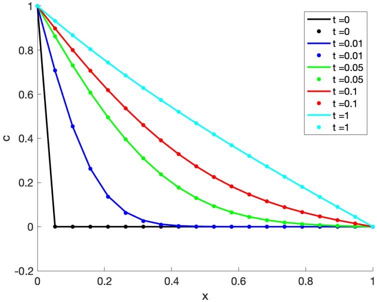
BC: $$c(t,0) = c_0,$$

$$c(t,L) = 0$$

IC: $$c(0,0) = c_0;$$

$$c(0,x) = 0 \quad \forall \quad x > 0.$$

.



Analytical Solution (dots):

$$c(t,x) = c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)} - \sum_{n=1}^{\infty} \frac{-2c_0 n\pi}{(n\pi)^2 + \left(\frac{L}{\lambda}\right)^2} \exp\left(-\left(D\frac{n^2\pi^2}{L^2} + k\right)t\right) \sin\left(\frac{n\pi x}{L}\right).$$

Time to steady state

$$
\begin{aligned}
c(t,x) \quad &= \quad c_0 \frac{\sinh\left(\frac{L-x}{\lambda}\right)}{\sinh\left(\frac{L}{\lambda}\right)} \\
&\quad - \sum_{n=1}^{\infty} \frac{-2c_0 n\pi}{(n\pi)^2 + \left(\frac{L}{\lambda}\right)^2} \exp\left(-\left(D\frac{n^2\pi^2}{L^2} + k\right)t\right) \sin\left(\frac{n\pi x}{L}\right).
\end{aligned}
$$

The solution reaches steady state exponentially fast with rate

$$\delta = \frac{Dn^2\pi^2}{L^2} + k.$$

Characteristic time to steady state:

$$t_{char} = \frac{1}{\delta} = \frac{L^2}{Dn^2\pi^2 + kL^2}.$$

The time to steady state thus depends on domain length L relative to the diffusion coefficient D AND the degradation rate k.

Estimate of Time to steady state

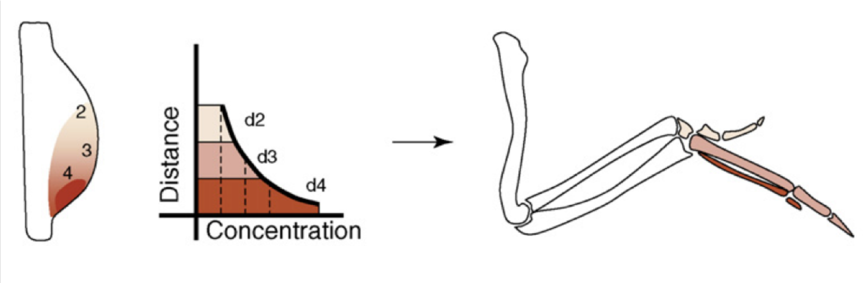
Typical diffusion coefficient: $D \in [0.1, 10]\ \mu\mathrm{m}^2\mathrm{s}^{-1}$.
Typical size of patterning domain: $L \in [50, 500]\ \mu\mathrm{m}$.
Typical protein degradation rate: $k \in [10^{-5}, 1]\ \mathrm{s}^{-1}$.

Characteristic time to steady state:

$$t_{char} = \frac{1}{\delta} = \frac{L^2}{Dn^2\pi^2 + kL^2} \leq \frac{500^2}{0.1\pi^2 + 10^{-5} \cdot 500^2} = 10^5 s \approx 1 day.$$

Developmental patterning processes typically progress within hours to days. Gradients will be dynamic (pre-steady state) ONLY if the degradation rate is low.

The modified French Flag Model in Limb Patterning



What model for Morphogen Gradients?

$$\begin{aligned} 1D\ Domain: &\quad 0 \leq x \leq L \\ PDE: &\quad \frac{\partial c}{\partial t} = D\Delta c - f(c) \\ IC: &\quad c(x > 0, 0) = 0 \end{aligned}$$

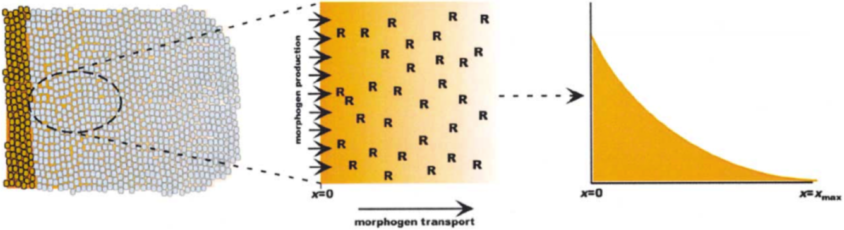
Degradation Term $f(c)$

- none $\Rightarrow$ linear gradient
- linear $\Rightarrow$ exponential gradient
- non-linear $\Rightarrow$ powerlaw gradient

Boundary Conditions

- Fixed concentration at both boundaries, i.e. $c(0,t) = c_0$ & $c(L) = 0$
- Fixed concentration at source, zero concentration at infinity, $c(0,t) = c_0$ & $c(x \to \infty) = 0$
- Flux boundary conditions, i.e. $\left.\frac{\partial c}{\partial x}\right|_{x=0} = -j$ & $\left.\frac{\partial c}{\partial x}\right|_{x=L} = 0$

STANDARD MODEL: boundary at infinity



Steady-state solution:

$$PDE: \quad \frac{\partial c}{\partial t} = D\Delta c - kc; \quad 0 \leq x \leq \infty$$

$$IC: \quad c(x,0) = 0$$

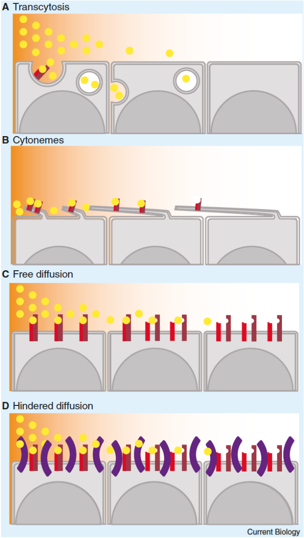
$$BC: \quad c(0,t) = c_0 \qquad c(x \to \infty) = 0$$

$$c(x) = c_0 \exp\left(-\frac{x}{\lambda}\right)$$

$$\lambda = \sqrt{\frac{D}{k}}$$

Alternative Transport Mechanisms

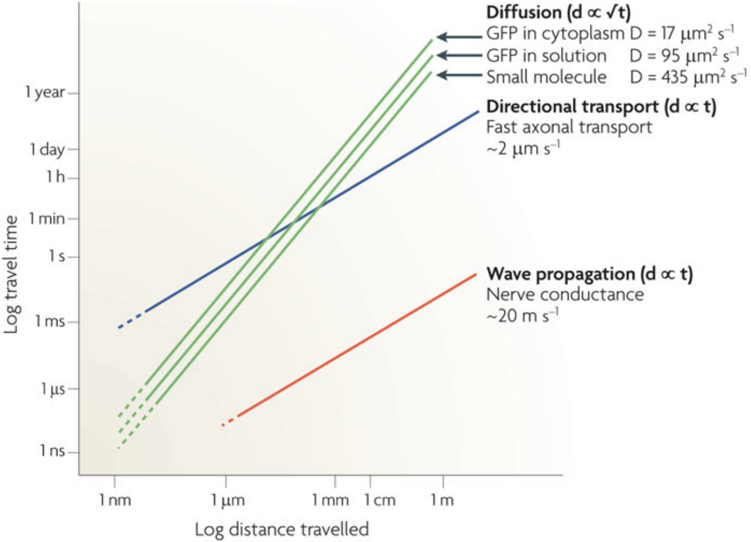
Transport Mechanisms



Experiments show that the majority of Dpp ligand in the *Drosophila* wing disc can be found inside rather than outside the cell. This has led to the suggestion of non-diffusive transport mechanisms:

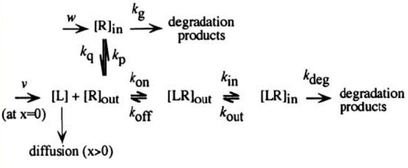
1. **Transcytosis:** Morphogens have been suggested to move by transcytosis. However, such transport would be much slower than transport by diffusion.
2. **Cell Lineage Transport**

Speed of Transport Processes



Diffusion-coupled Intracellular Gradients

Experiments show that the majority of Dpp ligand in the *Drosophila* wing disc can be found inside rather than outside the cell. However, this does not contradict a spreading mechanism by diffusion, but rather emphasizes the strength of morphogen internalization.



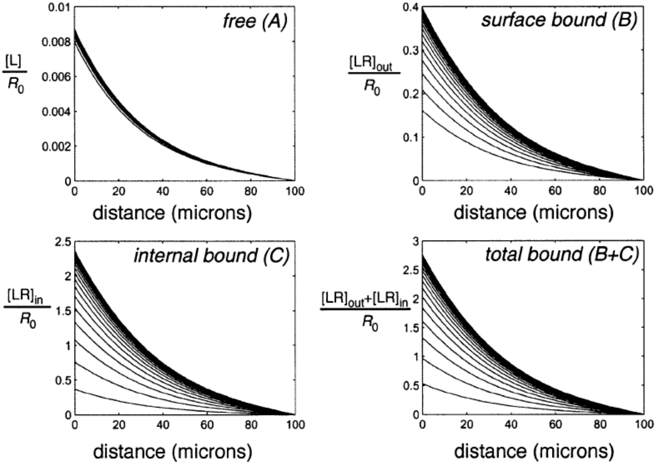
$$\partial A/\partial t = D' \partial^2 A/\partial x^2 - k_{on} R_0 A D + k_{off} B \quad (3)$$
$$\partial B/\partial t = k_{on} R_0 A D - (k_{off} + k_{in}) B + k_{out} C \quad (4)$$
$$\partial C/\partial t = k_{in} B - (k_{out} + k_{deg}) C \quad (5)$$
$$\partial D/\partial t = k_{off} B + k_q E - (k_{on} R_0 A + k_p) D \quad (6)$$
$$\partial E/\partial t = k_g k_p / k_q + k_p D - (k_q + k_g) E \quad (7)$$

A, B, C, D, and E correspond to $[L]$, $[LR]_{out}$, $[LR]_{in}$, $[R]_{out}$, and $[R]_{in}$, respectively, normalized to R_0; $R_0 = w k_q / (k_g k_p)$

C. Diffusion, Reversible Binding, Reversible Internalization, Degradation

Lander et al (2002) Dev Cell

Intracellular Gradients



Lander et al (2002) Dev Cell

Thanks!!

Thanks for your attention!

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