Spatial modeling

Lecture 6 of Introduction to Biological Modeling
Nov. 3, 2010

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Last week - stochasticity

- Sources
- Amount
- Amplifying
- Reducing
- Modeling

Reading

Takahashi, Arjunan, and Tomita, "Space in systems biology of signaling pathways – towards molecular crowding in silico" *FEBS Letters* 579:1783-1788, 2005.

Cellular organization

Physics of spatial organization

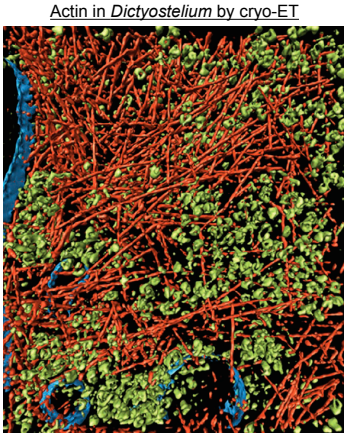
Spatial modeling

Examples

Summary

Nanometer scale organization

Actin in *Dictyostelium* by cryo-ET



Intracellular crowding

- 15 - 30% volume is occupied
- proteins, ribosomes, RNA
- globular, complexes, filaments

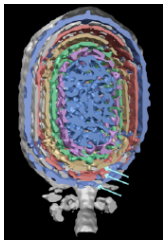
- accelerates protein folding
- accelerates most reaction rates
- slows diffusion

- hard to investigate directly

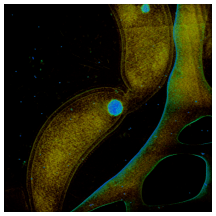
Credit: Medalia *et al. Science* 298:1209, 2002.

Organization in viruses and bacteria

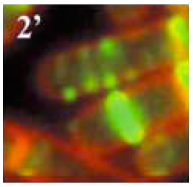
DNA in bacteriophage



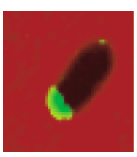
Ni storage organelles in *Caulobacter crescentus*



FtsZ cytoskeletal polymer in *E. coli*

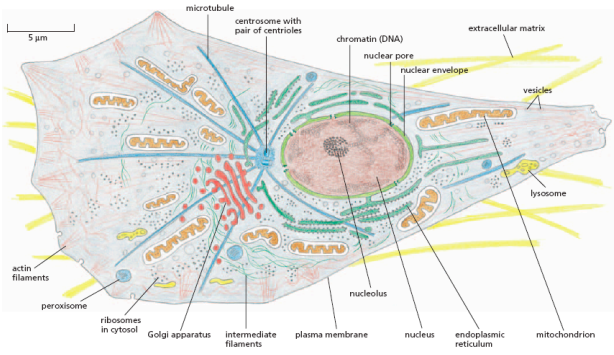


Chemotaxis receptors in *E. coli*



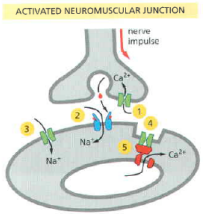
Credit: Comolli *et al. Virology* 371:267, 2008; Courtesy of Luis Comolli; Ben-Yehuda, Sigal and Losick, *Cell*, 109:257, 2002; courtesy of Judith Armitage.

Organization in eukaryotes

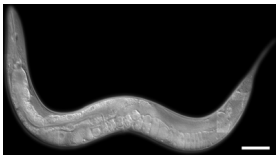


Credit: Alberts *et al. Molecular Biology of the Cell, 5th ed.* 2008.

Multicellular organization



C. elegans



Credits: Alberts *et al. Molecular Biology of the Cell, 5th ed.* 2008; http://www.nematode.net/Species.Summaries/Caenorhabditis.elegans/index.php

Cell biology is *extremely* spatially organized.
A well-mixed cell is a dead cell.

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A well-mixed cell is a dead cell.

But, nearly all modeling research assumes well-mixed systems.

So, when does space matter?

Cell biology is *extremely* spatially organized.
A well-mixed cell is a dead cell.

But, nearly all modeling research assumes well-mixed systems.

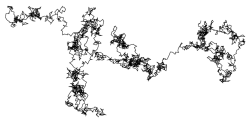
So, when does space matter?
- when you are studying spatial phenomena
- when you want a truly accurate model
- when spatial aspects affect system behavior

Organization questions

Questions about spatial organization
- What are the underlying causes?
- How is it maintained?
- What are some consequences?
- How can I model it?

Diffusion

Brownian motion - driven by collisions with water and surrounding molecules

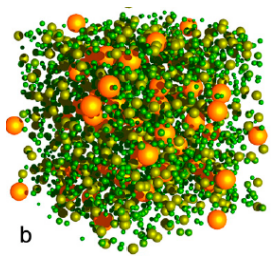


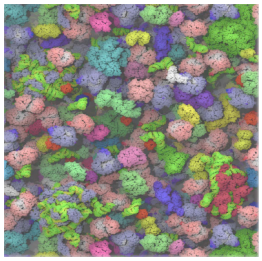
average instantaneous velocity = $\sqrt{\frac{k_B T}{m}}$

k_B = Boltzmann's constant
T = absolute temperature
m = molecule mass

Intracellular diffusion modeling

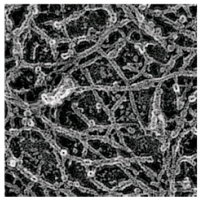
Diffusion simulations in virtual cytoplasms



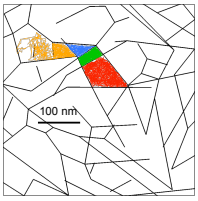


Credits: Ridgway *et al. Biophys. J.* 94:3748, 2008; McGuffee and Elcock, PLoS Comp. Biol. 6:e1000694, 2010;

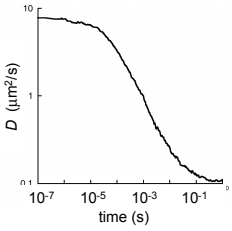
Hop diffusion



EM picture of filaments underlying membrane



Simulated lipid diffusion

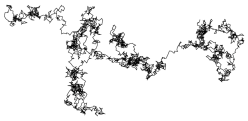


time scale	diffusion
ns to μs	same as without obstructions
μs to ms	anomolous (*D* changes over time)
ms to s	slow normal diffusion

Image: Morone, et al. *J. Chem. Biol.* 174:851-862, 2006.

Diffusion

Brownian motion - driven by collisions with water and surrounding molecules



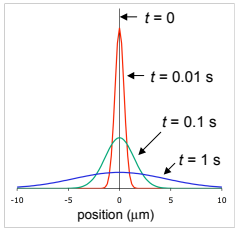
average instantaneous velocity = $\sqrt{\frac{k_B T}{m}}$
(~30 mph for lysozyme
= 13 μm/μs)

k_B = Boltzmann's constant
T = absolute temperature
m = molecule mass

In *ideal* Brownian motion, which is a good approximation
- trajectory is infinitely detailed
- instantaneous speed is infinite
- one collision implies an infinite number of collisions
- trajectory is a two-dimensional fractal
- hard to simulate, hard to visualize, but mathematically convenient

Diffusion

Concentration / probability density spreads over time



Spread is

$\sigma = \sqrt{2Dt}$

$t = \frac{\sigma^2}{2D}$

if D = 10 μm²/s

t	σ
1 ms	0.14 μm
1 s	4.5 μm
10 s	14 μm

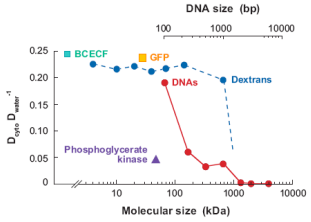
~ 1 second for diffusion across a cell

Diffusion coefficients

Stokes-Einstein equation for diffusion coefficient: $D = \frac{k_B T}{6\pi\eta R}$

η = viscosity
R = molecule radius

diffusion in water: $D \approx \frac{2616}{\sqrt[3]{m}}$ μm²/s, m is mass in Daltons



diffusion in cells is slower than in water
÷ 4 for eukaryotes
÷ 15 for bacteria
÷ 1000 for eukaryotic membranes
÷ 4000 for bacterial membranes

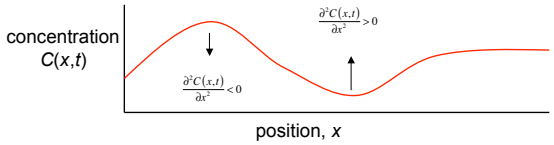
example:
for 50 kDa protein
D ~ 71 μm²/s in water
D ~ 18 μm²/s in a eukaryote

Credit: Dix and Verkman, *Ann. Rev. Biophys.* 37:247, 2008; Andrews, *Methods in Molecular Biology*, in press, 2010

Diffusion differential equation

Diffusion equation (Fick's law)

1-D: $\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2}$



Diffusion differential equation

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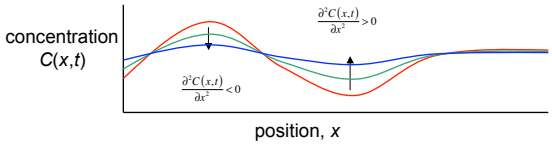


Two diffusion equation solutions

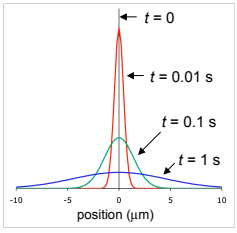
$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2}$$

1. A point spreads as a Gaussian

$$C(x,0) = \delta(x) = \begin{cases} \infty & x = 0 \\ 0 & x \neq 0 \end{cases}$$

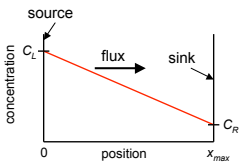
$$C(x,t) = \frac{C_0}{\sigma\sqrt{2\pi}}\exp\left(-\frac{x^2}{2\sigma^2}\right)$$

$$\sigma = \sqrt{2Dt}$$



2. In 1-D, steady state has no curvature

$$C(x,\infty) = ax + b$$



boundary conditions

$$C(0,t) = C_L$$

$$C(x_{max},t) = C_R$$

$$C(x,\infty) = \frac{C_R - C_L}{x_{max}}x + C_L$$

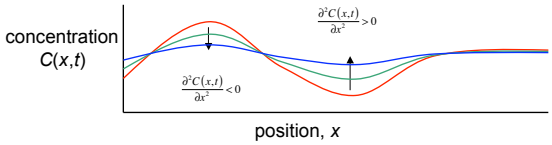
Diffusion differential equation

Diffusion equation (Fick's law)

1-D: $\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2}$

3-D: $\frac{\partial C(x,y,z,t)}{\partial t} = D\left[\frac{\partial^2 C(x,y,z,t)}{\partial x^2} + \frac{\partial^2 C(x,y,z,t)}{\partial y^2} + \frac{\partial^2 C(x,y,z,t)}{\partial z^2}\right]$

general: $\frac{\partial C(\mathbf{x},t)}{\partial t} = D\nabla^2 C(\mathbf{x},t)$



Reaction-diffusion equation

$$A + B \underset{k_r}{\overset{k_f}{\rightleftharpoons}} C$$

$$\frac{\partial[A]}{\partial t} = D_A\nabla^2[A] - k_f[A][B] + k_r[C]$$

$$\frac{\partial[B]}{\partial t} = D_B\nabla^2[B] - k_f[A][B] + k_r[C]$$

$$\frac{\partial[C]}{\partial t} = D_C\nabla^2[C] + k_f[A][B] - k_r[C]$$

diffusion terms | reaction terms

$$= \mathbf{N}\cdot\mathbf{r} = \sum_{reactions} n_{i,j}r_j$$

stoichiometric matrix

fwd rev

$$\mathbf{N} = \begin{bmatrix} -1 & 1 \\ -1 & 1 \\ 1 & -1 \end{bmatrix} \begin{matrix} A \\ B \\ C \end{matrix}$$

rate vector

$$\mathbf{r} = \begin{bmatrix} k_f[A][B] \\ k_r[C] \end{bmatrix} \begin{matrix} \text{fwd} \\ \text{rev} \end{matrix}$$

reaction-diffusion equation

$$\frac{\partial c_i}{\partial t} = D_i\nabla^2 c_i + \sum_{reactions} n_{i,j}r_j$$

When does space matter?

Spatial organization can arise if diffusion is slower than reactions

Diffusion $\tau = \frac{\Delta x^2}{2D}$ Δx = characteristic size, D = diffusion coefficient

Unimolecular reaction

$A \xrightarrow{k} B$ $\tau = \frac{1}{k}$

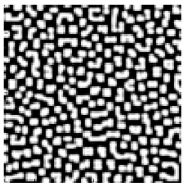
Bimolecular reaction

$A + B \xrightarrow{k} C$ $\tau = \frac{[A]+[B]}{k[A][B]}$

Spontaneous pattern formation

Turing (1951)
- proposed idea of morphogens: chemicals that create patterns, which biological development works from.
- Based work on reaction-diffusion equation.

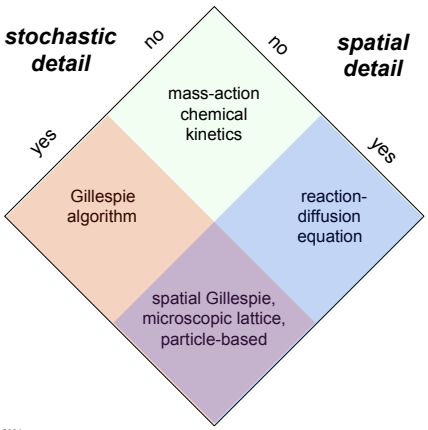
Gierer and Meinhardt (1972)
- Expanded Turing's work for pattern formation:
- Positive feedback at spots causes *short-range activation*
- Depletion or diffusion causes *long-range inhibition*, between spots



Taxonomy of biochemical simulation methods

low detail
less accurate
fewer parameters
easier

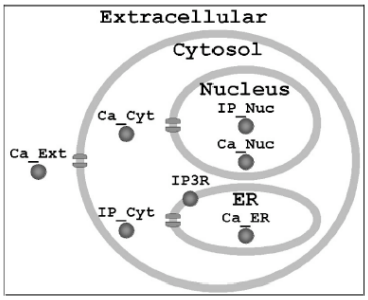
high detail
more accurate
more parameters
harder



Reviews: Andrews and Arkin, *Current Biol.* 16:R523, 2006;
Andrews, Dinh, Arkin, *Encyclopedia of Complexity and Systems Science*, 9:8730, 2009.

Compartment-based spatial models

Not truly spatial models, but often adequate



Supported by most simulators

- Copasi
- SBW (and SBML)
- Virtual Cell

Credit: Schaff et al. Chaos, 11:115, 2001.

Deterministic simulations

Deterministic spatial simulations

Based on the *reaction-diffusion partial differential equation*:

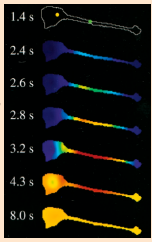
$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C \quad \rightarrow \quad \frac{\partial [C]}{\partial t} = D\nabla^2[C] + k_1[A][B] - k_2[C]$$

For simulation, space is partitioned into a fine grid.

Virtual Cell is a deterministic spatial simulator.

http://www.nrcam.uchc.edu/

A Virtual Cell simulation of Ca^{2+} wave propagation in a neuron.



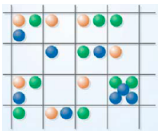
Benefits
- Computationally efficient
- Well-developed algorithms
- Good software

Drawbacks
- Not stochastic
- No single-molecule detail

Figure: Fink *et al. Biophys. J.* 79:163, 2000

Spatial Gillespie method

Method
Coarse lattice
Sub-volumes have discrete numbers of molecules
Simulated with the Gillespie algorithm



Benefits
- Can use existing PDE models
- Reasonably computationally efficient

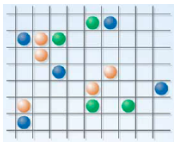
Drawbacks
- Mediocre spatial resolution
- Lattice can cause artifacts
- Difficult to represent membrane geometries

Software
- MesoRD
- GMP
- SmartCell

Figure: Takahashi, Arjunan, Tomita, *FEBS Lett.* 579:1783, 2005.

Microscopic lattice method

Method
Very fine lattice
Up to one molecule per site
Molecules hop between sites to diffuse



Benefits
- Good spatial resolution
- Good for macromolecular crowding

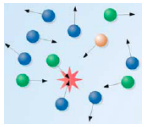
Drawbacks
- Very computationally intensive
- Lattice artifacts

Software
Spatiocyte
GridCell

Figure: Takahashi, Arjunan, Tomita, *FEBS Lett.* 579:1783, 2005

Particle-based biochemical simulations

Method
Space is continuous
Molecules are point-like particles
Molecules can react when they collide



Benefits
- Excellent spatial resolution (~ 5 nm)
- Realistic membrane geometries
- No lattice artifacts

Drawbacks
- Computationally intensive

Software
•• Smoldyn
• MCell
• ChemCell

Figure: Takahashi, Arjunan, Tomita, *FEBS Lett.* 579:1783, 2005.

Summary: Length and time scales, and modeling

$\tau = \frac{\Delta x^2}{2D}$

Biology

single proteins | protein complexes | intracellular organization | bacterium | eukaryotic cell

1 nm | 10 nm | 100 nm | 1 μm | 10 μm | 100 μm *

200 ns | 20 μs | 2 ms | 200 ms | 20 s | 33 min

Spatial simulations

molecular dynamics | Brownian dynamics | Micro-scopic lattice | particle-based | Spatial Gillespie | Reaction-diffusion equations →

Non-spatial simulations

Gillespie algorithm | ODE →

* Scales assume D = 2.5 μm²/s.

Summary: Length and time scales, and modeling

$\tau = \frac{\Delta x^2}{2D}$

Biology — my interest

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Spatial simulations

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Non-spatial simulations

Gillespie algorithm | ODE →

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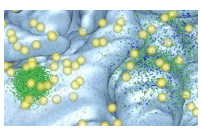
Cellular organization
Physics of spatial organization
Spatial modeling
- Smoldyn
Examples
Summary

Spatial stochastic simulators

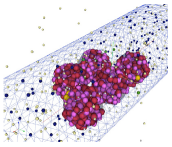
MCell
- oldest
- most used
- best graphics
www.mcell.psc.edu
www.mcell.cnl.salk.edu

ChemCell
- simplest
www.sandia.gov/~sjplimp/chemcell

Smoldyn
- newest
- most accurate
- fastest
- most features
www.smoldyn.org



Model of a chick ciliary ganglion somatic spine mat



Model of a *Synechococcus* carboxysome organelle

Model of *E. coli* chemotaxis

Figures: Coggan *et al. Science* 309:446, 2005; Plimpton and Slepoy, *J. Phys.: Conf. Ser.* 16:305, 2005; modified from Lipkow, Odde, *Cell Mol. Bioeng.* 1:84, 2008.

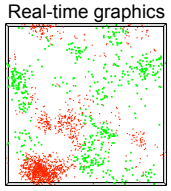
Smoldyn workflow

Text configuration file

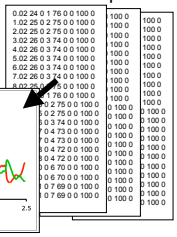
```
# Predator-prey simulation

graphics opengl
graphic_iter 5

dim 3
species rabbit fox
max_mol 100000
molperbox 1

boundaries 0 -100 100 p
boundaries 1 -100 100 p
boundaries 2 -10 10 p

time_start 0
time_stop 20
time_step 0.001

color rabbit 1 0 0
color fox 0 1 0
display_size rabbit 3
display_size fox 4

difc all 100
reaction r1 rabbit -> rabbit + rabbit 10
reaction r2 rabbit + fox -> fox + fox 8000
reaction r3 fox -> 0 10

mol 1000 rabbit u u u
mol 1000 fox u u u

output_files lotvoltout.txt
cmd i 0 5 0.01 molcount lotvoltout.txt

end_file
```

Smoldyn

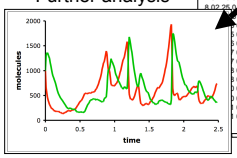
Real-time graphics



Text output



Further analysis

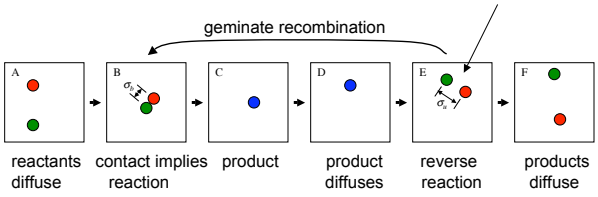


Algorithms: Reversible bimolecular reactions

Reversible reaction: $A + B \underset{k_r}{\overset{k_f}{\rightleftharpoons}} C$

Algorithm

Separate reaction products by *unbinding radius*, σ_u



I solved the binding and unbinding radii (σ_b and σ_u) to yield correct reaction rates (k_f and k_r) and geminate recombination probabilities.

Refs: Andrews and Bray, *Phys. Biol.* 1:137, 2004; Andrews, *Phys. Biol.* 2:111, 2005.

Reaction rate validation

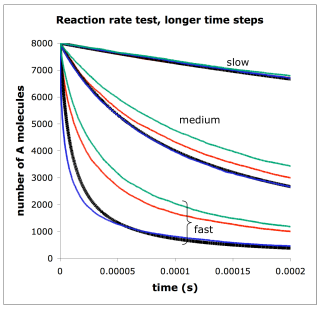
Reaction: $A + B \xrightarrow{k} C$

k values

"slow"	5.9e5 $M^{-1}s^{-1}$
"medium"	5.9e6 $M^{-1}s^{-1}$
"fast"	5.9e7 $M^{-1}s^{-1}$

Results

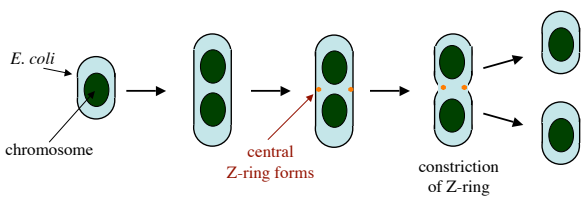
- mass action theory
- ChemCell
- MCell
- Smoldyn



- Smoldyn is nearly exact; ChemCell and MCell simulate reactions too slowly
- ChemCell and MCell get *less* accurate with shorter time steps
- The Smoldyn "error" is actually an approximation in mass action theory

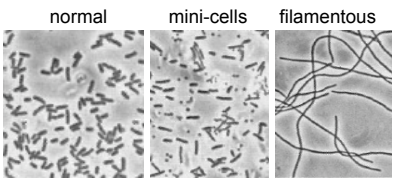
Figure: Andrews, Addy, Brent, Arkin, *PLoS Comp. Biol.* 2010.

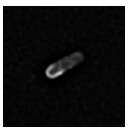
Bacterial cell division



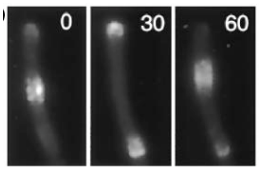
How does the cell locate its center?

E. coli Min system



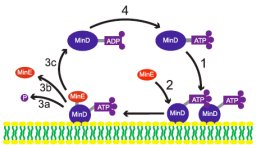


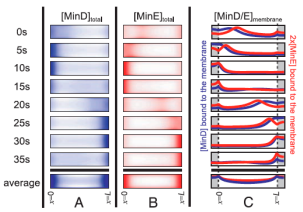
- Min mutants are mini-cells or filamentous
- Min proteins oscillate from pole to pole
- In long cells, get two peaks



Figures: de Boer, Crossley, and Rothfield, *Cell* 56:641, 1989; Shih, Le, and Rothfield, *Proc. Natl. Acad. Sci. USA* 100:7865, 2003.

Huang, Meir, Wingreen model of Min system



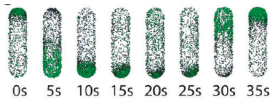


- Based on reaction-diffusion equations
- Min concentration is always low in the middle
- The cell decides that the middle is where Min is not
- Min inhibits Z-ring formation

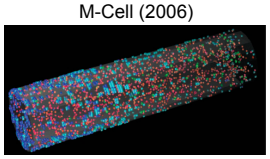
Figures: Huang, Meir, Wingreen, *Proc. Natl. Acad. Sci. USA* 100:12724, 2003.

Lots of "me too" Min models

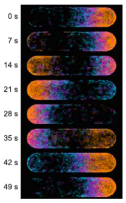
Meso-RD (2005)



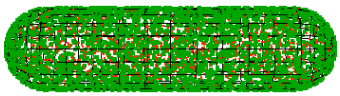
M-Cell (2006)



E-cell (2010)



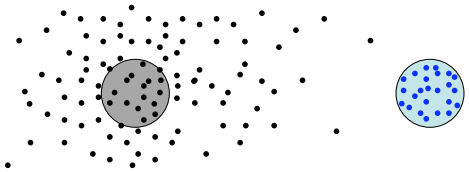
Smoldyn (unpublished)



Credits: Hattne, Fange, and Elf, *Bioinformatics*, 21:2923, 2005; Kerr *et al.* Proc. Natl. Acad. Sci. USA, 103:347, 2006; Arjunan and Tomita, *Syst. Synth. Biol.* 4:35, 2010.

Example: signaling between yeast cells

Yeast cells come in two mating types (i.e. "genders"):



*MAT*α - secretes α-factor (detects **a**-factor)

signal sender

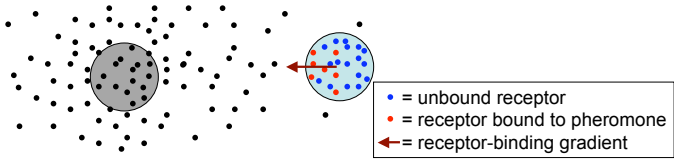
*MAT***a** - receptors bind α-factor (secretes **a**-factor)

signal receiver

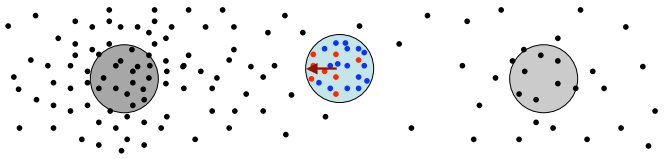
Background: mate location and selection

receiver (*MAT***a**) cells

(1) use the pheromone gradient to determine the direction to a sender cell



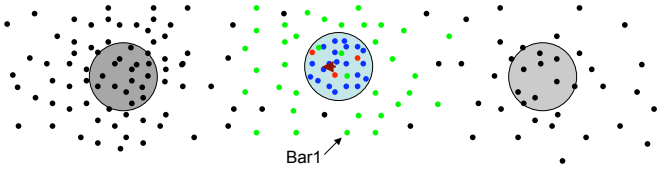
(2) mate with the strongest-emitting sender cell



A paradox: *MAT***a** cells destroy α-factor with Bar1

Because mate selection ability is limited by pheromone detection, it seems that receiver (*MAT***a**) cells would detect as much pheromone as possible.

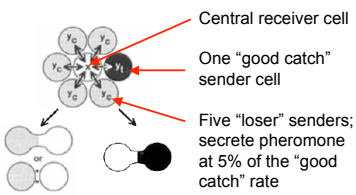
However, *receiver* cells also secrete the *α-factor protease* Bar1.



Why would a receiver cell shield itself from an incoming signal?

Simulation of cell mating partner selection

Competition mating assay



Simulation

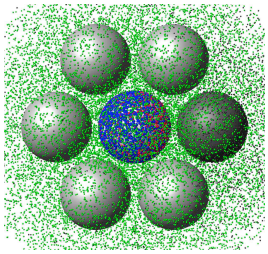
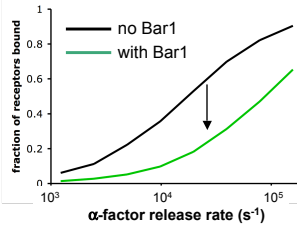


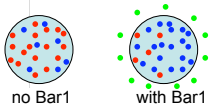
Figure: Jackson and Hartwell, *Cell* 63:1039, 1990.

Effect of Bar1: decreases sensitivity

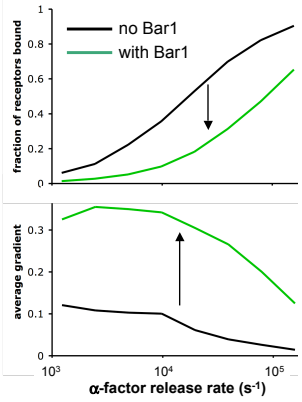


Bar1 decreases sensitivity

It takes more α-factor to achieve the same fraction of bound receptors

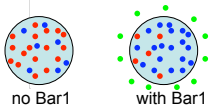


Effect of Bar1: increases detected gradient



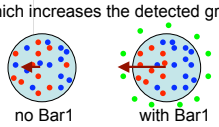
Bar1 decreases sensitivity

Fewer receptors bind α-factor for any given release rate

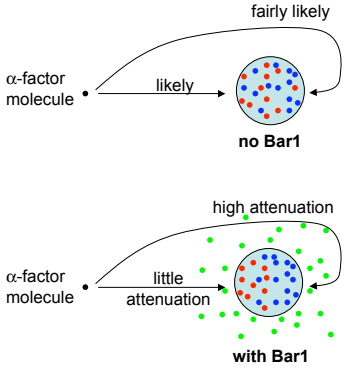


Bar1 increases detected gradient

Bar1 shields the far side of the receiver (*MAT***a**) cell more than the close side, which increases the detected gradient.

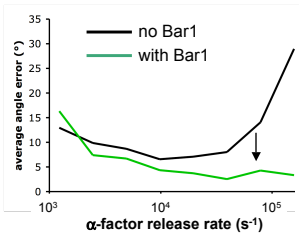


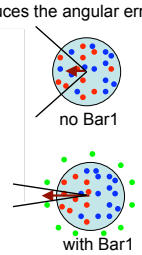
How Bar1 increases detected gradient



Result: Bar1 decreases angle error

With Bar1, the larger gradient reduces the angular error.





Conclusion

Bar1 improves mating partner selection by sharpening the α-factor signal. This agrees with experimental results.

Summary

Cellular organization

Physics of spatial organization
- Brownian motion
- Diffusion
- Reaction-diffusion equation

Spatial modeling
- Compartments
- Reaction-diffusion, spatial Gillespie, lattice, particle-based
- Smoldyn

Examples
- Min system
- yeast pheromone signaling

Homework

Next week is on modeling mechanics and/or cancer

Mechanics reading

Alberts and Odell, "In silico reconstitution of *Listeria* propulsion exhibits nano-saltation" PLoS Biology 2:e412, 2004.

Cancer reading

?