Spatial modeling

Lecture 6 of Introduction to Biological Modeling
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Steve Andrews
Brent lab, Basic Sciences Division, FHCRC

Last week - stochasticity

• Sources
• Amount
• Amplifying
• Reducing
• Modeling

Reading

Cellular organization
Physics of spatial organization
Spatial modeling
Examples
Summary

Nanometer scale organization

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

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

Organization in eukaryotes

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 = \( \sqrt{\frac{k_B T}{m}} \) (\(~30~\text{mph for lysozyme} = 13~\mu\text{m/\mu s}\) )

\( k_B \) = Boltzmann’s constant
\( T \) = absolute temperature
\( m \) = molecule mass

**Intracellular diffusion modeling**

Diffusion simulations in virtual cytoplasms

**Hop diffusion**

EM picture of filaments underlying membrane

Simulated lipid diffusion

- time scale
  - ns to \( \mu \)s
  - \( \mu \)s to ms
  - ms to s

- diffusion
  - same as without obstructions
  - anomalous (\( D \) changes over time)
  - slow normal diffusion

**Diffusion**

Brownian motion - driven by collisions with water and surrounding molecules

average instantaneous velocity = \( \sqrt{\frac{k_B T}{m}} \) (\(~30~\text{mph for lysozyme} = 13~\mu\text{m/\mu s}\) )

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 coefficients**

Stokes-Einstein equation for diffusion coefficient:

\[ D = \frac{k_B T}{6 \pi \eta R} \]

\( \eta \) = viscosity
\( R \) = molecule radius

Diffusion in water:

\[ D \approx \frac{2616}{m} \mu\text{m}^2/\text{s} \]

\( m \) = mass in Daltons

Diffusion in cells is slower than in water

- \(~4\) for eukaryotes
- \(~15\) for bacteria
- \(\approx 1000\) for eukaryotic membranes
- \(\approx 4000\) for bacterial membranes

Example:

- for 50 kDa protein
  - \( D \approx 71 \mu\text{m}^2/\text{s} \) in water
  - \( D \approx 18 \mu\text{m}^2/\text{s} \) in a eukaryote
1. A point spreads as a Gaussian:

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

\[ \sigma = \sqrt{2Dt} \]

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

\[ C(x) = \frac{C_m}{2} (1 + \text{erf} \left( \frac{x}{2\sqrt{D}t} \right)) \]

boundary conditions:

\[ C(0) = C_0 \quad \text{and} \quad C(\infty) = \frac{C_m}{2} \]

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:

\[ \frac{\partial C(x,t)}{\partial t} = D \nabla^2 C(x,t) \]

When does space matter?

Spatial organization can arise if diffusion is slower than reactions.

- Diffusion: \[ \tau = \frac{\Delta x^2}{2D} \]
  - \( \Delta x \) is characteristic size
  - \( D \) is diffusion coefficient

- Unimolecular reaction: \[ \tau = \frac{1}{k} \]
  - \( k \) is the reaction rate constant

- Bimolecular reaction: \[ \tau = \frac{[A] + [B]}{k[A][B]} \]

\[ A + B \rightarrow C \]
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

Deterministic simulations

Based on the reaction-diffusion partial differential equation:

\[ \frac{d[A]}{dt} = D \nabla^2 [A] + k_1[A][B] - k_2[A] \]

For simulation, space is partitioned into a fine grid.

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

Compartment-based spatial models

Not truly spatial models, but often adequate

Supported by most simulators
- Copasi
- SBW (and SBML)
- Virtual Cell

Virtual Cell is a deterministic spatial simulator.

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

**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

**Summary: Length and time scales, and modeling**

<table>
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<tr>
<th>Biology</th>
<th>1 nm</th>
<th>10 nm</th>
<th>100 nm</th>
<th>1 µm</th>
<th>10 µm</th>
<th>100 µm</th>
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<tr>
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<td>2 ms</td>
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<tr>
<td>eukaryotic cell</td>
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</tbody>
</table>

\[ \tau = \frac{2D}{\Delta x^2} \]

**Spatial simulations**
- Molecular Brownian dynamics
- Microscopic lattice
- Particle-based
- Gillespie
- Reaction-diffusion equations

**Non-spatial simulations**
- Gillespie algorithm
- ODE

* Scales assume \( D = 2.5 \mu m^2/s \).

**Spatial stochastic simulators**

- **MCell**
  - Oldest
  - Most used
  - Best graphics
  - Website: [www.mcell.psc.edu](http://www.mcell.psc.edu)

- **ChemCell**
  - Simplest
  - Website: [www.sandia.gov/~sjplimp/chemcell](http://www.sandia.gov/~sjplimp/chemcell)

- **Smoldyn**
  - Newest
  - Most accurate
  - Fastest
  - Most features
  - Website: [www.smoldyn.org](http://www.smoldyn.org)

**Examples**
- Model of a chick ciliary ganglion somatic spine mat
- Model of a Synechococcus carboxysome organelle
- Model of E. coli chemotaxis

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

Reversible reaction: \[ A + B \xrightarrow{k_f} C \]

**Algorithm**

- Separate reaction products by unbinding radius, \( \sigma_u \)

I solved the binding and unbinding radii (\( \sigma_b \) and \( \sigma_u \)) to yield correct reaction rates (\( k_b \) and \( k_f \)) and geminate recombination probabilities.

**Smoldyn workflow**

Text configuration file

```plaintext
bind_file

graphics openpl

graphics_file 3

difc all 100

display_size fox 4

display_size rabbit 3

color fox 0 1 0

color rabbit 1 0 0

time_step 0.001

time_start 0

boundaries 2 -10 10 p

boundaries 1 -100 100 p

boundaries 0 -100 100 p

molperbox 1

max_mol 100000

species rabbit fox

dim 3

graphic_iter 5

graphics opengl
```

**Real-time graphics**

**Text output**

```plaintext
cmd 1 0 5 0.01 molcount lotvoltout.txt
output_files lotvoltout.txt
mol 1000 fox u u u
reaction r3 fox -> 0 10
reaction r2 rabbit + fox -> fox + fox 8000
reaction r1 rabbit -> rabbit + rabbit 10

difc all 100

display_size fox 4

display_size rabbit 3

color fox 0 1 0

color rabbit 1 0 0

time_step 0.001

time_start 0

boundaries 2 -10 10 p

boundaries 1 -100 100 p

boundaries 0 -100 100 p

molperbox 1

max_mol 100000

species rabbit fox

dim 3

graphic_iter 5

graphics opengl
```

**Further analysis**

**In long cells, get two peaks**

**Min proteins oscillate from pole to pole**

**Min mutants are mini-cells or filamentous**

**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

**Bacterial cell division**

- **E. coli**
  - chromosome
  - central Z-ring forms
  - constriction of Z-ring

- How does the cell locate its center?

**E. coli Min system**

- **normal**
- **mini-cells**
- **filamentous**

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

**Cellular organization**

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

**References**

**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:**


**Example: signaling between yeast cells**

Yeast cells come in two mating types (i.e., “genders”):

- **MATa** - secretes α-factor (detects a-factor)
- **MATa** - receptors bind α-factor (secretes a-factor)

**signal sender**

**signal receiver**

**A paradox: MATa cells destroy α-factor with Bar1**

Because mate selection ability is limited by pheromone detection, it seems that receiver (MATa) 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?**

**Background: mate location and selection**

1. Use the pheromone gradient to determine the direction to a sender cell
2. Mate with the strongest-emitting sender cell

**Simulation of cell mating partner selection**

**Competition mating assay**

- Central receiver cell
- One “good catch” sender cell
- Five “loser” senders; secrete pheromone at 5% of the “good catch” rate

**Simulation**

**Lots of “me too” Min models**

- Meso-RD (2005)
- M-Cell (2006)
- E-cell (2010)
- Smoldyn (unpublished)

**Credits:**


**Example:**

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

How Bar1 increases detected gradient

Bar1 decreases sensitivity. Fewer receptors bind α-factor for any given release rate.

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

Cancer reading
?