Diffusion and cellular-level simulation

CS/CME/BioE/Biophys/BMI 279

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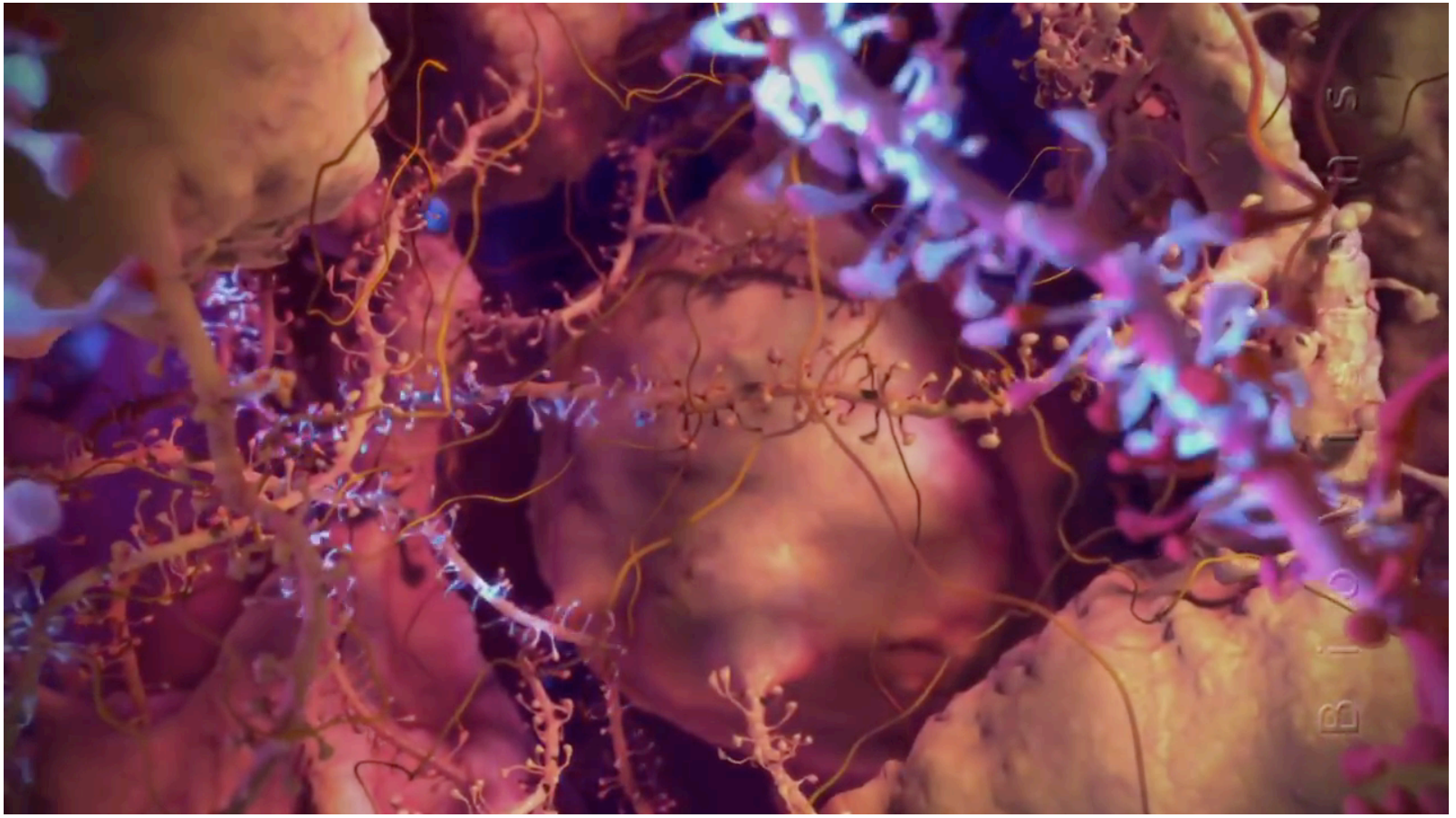
Outline

- How do molecules move around in a cell?
- Diffusion as a random walk (particle-based perspective)
- Continuum view of diffusion
- Simulating diffusion

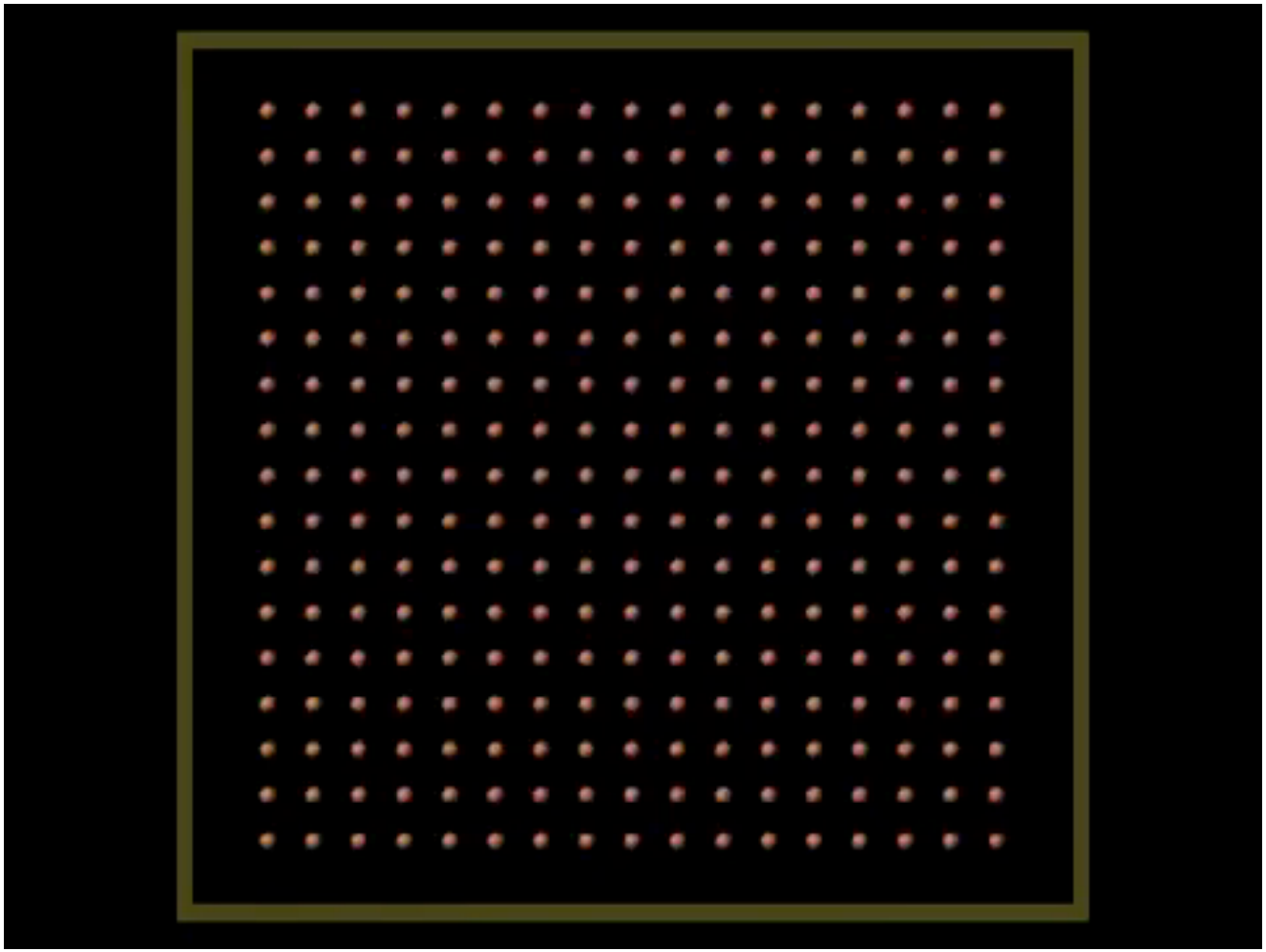
How do molecules move around in a cell?



From *Inner Life of the Cell* | *Protein Packing*, XVIVO and Biovisions @ Harvard

- The interior of the cell is crowded, and all the molecules jiggle about.
- Note that lots of molecules (e.g., water) aren't even shown in this movie.

Molecules jiggle about because other molecules keep bumping into them



https://www.youtube.com/watch?v=1jYabtziQZo

Diffusion

A single molecule would move with velocity along a straight path, but does not do so in a cell due to frequent "bumping" with other molecules in the cell

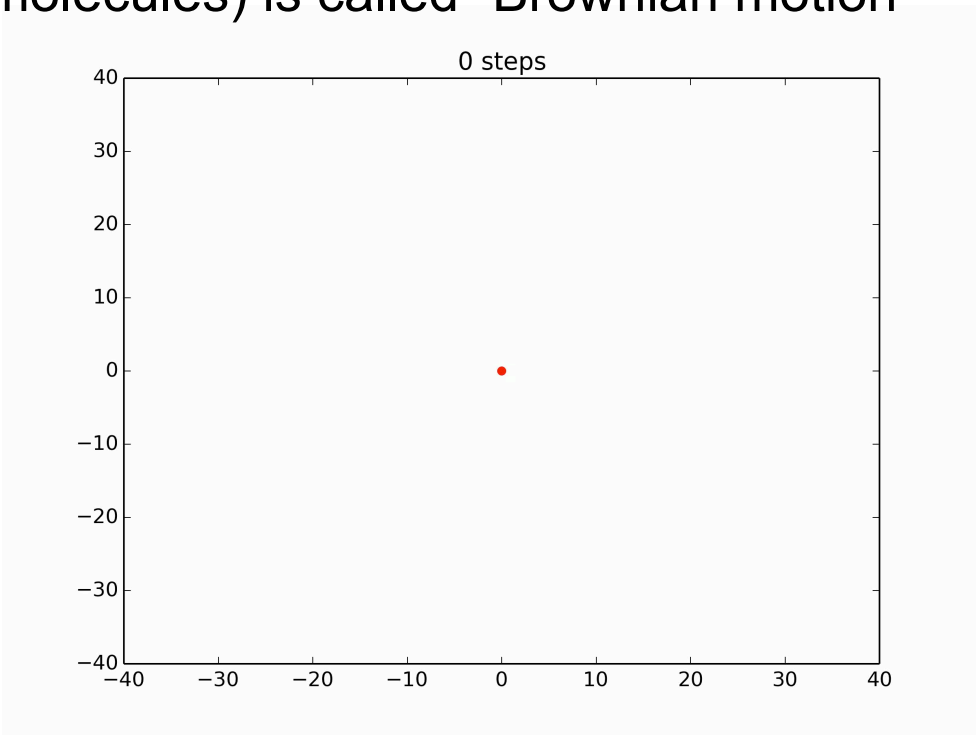
- This "jiggling about" by lots of molecules leads to diffusion
- Individual molecules follow a random walk, due to collisions with surrounding molecules
- Diffusion = many random walks by many molecules
  - Substance goes from region of high concentration to region of lower concentration
- Molecules can move around in complicated ways within cells. We will focus on the basic case of random, unconfined, undirected motion.

Diffusion as a random walk (particle-based perspective)

Particle = “molecule”

Random walk

- We can model the motion of a molecule as a random walk
  - At each time step, randomly pick a direction, and move one unit in that direction
  - This type of motion (when caused by random collisions with other molecules) is called “Brownian motion”



In the movie, only cardinal directions are chosen, but we could pick diagonal directions as well and still get Brownian motion

1, 2, or 3 dimensions

- In biological systems, a random walk can take place in:
  - 3 dimensions: a protein moving freely within the interior of a cell
  - 2 dimensions: a protein moving within a cell membrane
  - 1 dimension: a protein (e.g., transcription factor) moving along a strand of DNA

Consider the 1D case (for simplicity)

- A particle starts at $x_0 = 0$
- At each time step, it has 50% probability of moving one unit forward, and 50% probability of moving one unit backward
- Denote the sequence of positions as x_0, x_1, x_2, x_3, …
- Question: if you repeat this process many times and make a histogram of the position x_3, what will it look like? How about x_{100}?

Properties of 1D Brownian motion

- After 3 steps:
  - Probabilities:
    - $P(x_3 = -3) = 1/8$
    - $P(x_3 = -1) = 3/8$
    - $P(x_3 = 1) = 3/8$
    - $P(x_3 = 3) = 1/8$
  - Mean displacement: $E[x_3] = 0$
  - Mean-squared displacement: $E[x_3^2] = 3$
- After N steps:
  - Mean displacement: $E[x_N] = 0$
  - Mean-squared displacement: $E[x_N^2] = N$
  - More generally, if the particle moves a distance L at each time step, $E[x_N^2] = NL^2$
  - As N grows large, the distribution approaches a Gaussian (with mean 0 and variance NL^2)

Expected value is a weighted average, where the weights are the probabilities of each value being averaged. Ie E(x_3) = P(x_3) = 1/8*P(x_3 = -3) + 3/8*P(x_3 = -1) + 3/8*P(x_3 = 1) + 1/8P(x_3 = 3)

Diffusion as a function of time

- Instead of thinking of position as a function of *N*, we might think of it as a function of time.
  - Let *t* denote total time and Δ*t* denote time step. Then:

$$N = \frac{t}{\Delta t}$$

$$E\left[x(t)^2\right] = E\left[x_N{}^2\right] = NL^2 = \frac{t}{\Delta t}L^2$$

Here we represent the number of steps as the total simulation time, divided by the time-step for each iteration

  - In other words, the expected or mean squared displacement grows linearly with time

Diffusion constant

Smaller particles are not buffeted as much as large particles, as the collision-likelihood is lower for smaller particles

- To quantify speed of diffusion, we define the diffusion constant *D*:

$$D = \frac{L^2}{2\Delta t}$$

Note: L is average displacement per time step for each coordinate (x, y, or z)

- Then $E\left[x(t)^2\right] = 2Dt$

D relates squared displacement with time

- In 2D, the diffusion constant is defined such that

$$E\left[r(t)^2\right] = E\left[x(t)^2\right] + E\left[y(t)^2\right] = 4Dt$$

$r(t)$ is displacement from initial position at time t

- In 3D, $E\left[r(t)^2\right] = E\left[x(t)^2\right] + E\left[y(t)^2\right] + E\left[z(t)^2\right] = 6Dt$
- Larger molecules generally diffuse more slowly than small ones

An example

- Diffusion constants (D):
  - Sugar: 500 $(\mu m)^2/s$
  - Typical protein: 5 $(\mu m)^2/s$
- Cell size (radius R):
  - Bacterium (E. coli): 1 μm
  - Neutrophil: 10 μm
  - Nerve cell: 1000 μm
- Roughly how long does it take for sugar, introduced in one place in the cell, to spread everywhere?

$$t \approx \frac{R^2}{6D}$$

This represents the time it takes for a single molecule to traverse the cell from the center to the perimeter

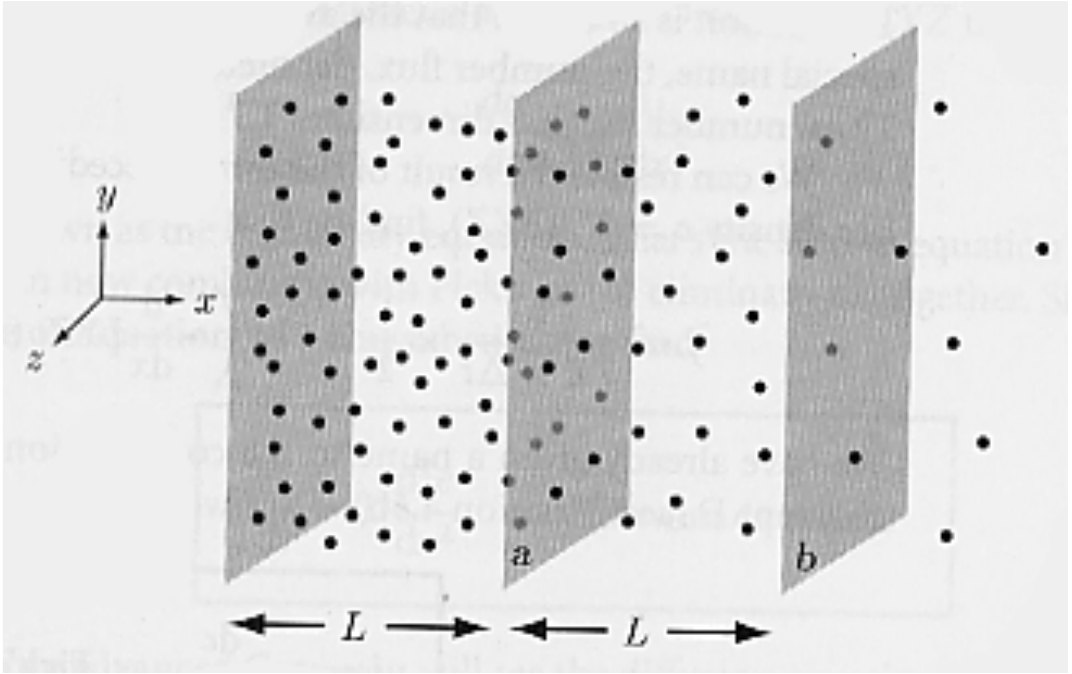
From Chris Burge
(see links on course website)

Continuum view of diffusion

Rather than defining the concentration based on the absolute number of molecules, examine the concentration instead as a representation of the number of molecules

Basic intuition

- Although we can't predict the motion of one particle, we can predict the average motion of a large number of particles
  - Particles will move from regions of high concentration to regions of low concentration

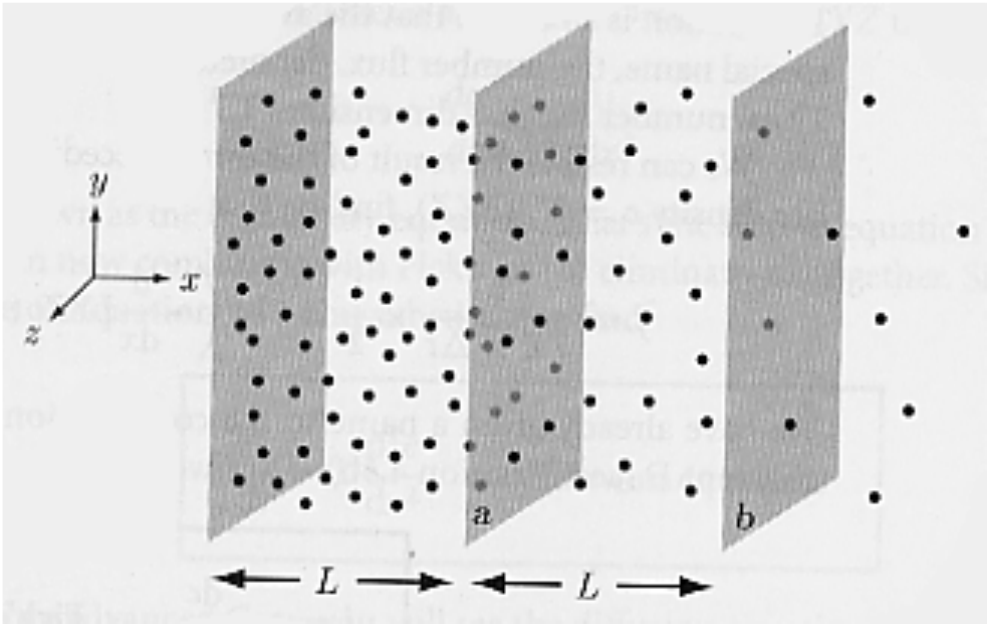


Here, we essentially are expanding the idea of random walks for concentration of atoms, rather than calculating/ tracking the location of every single atom

Flux is the number of particles passing from one slice/section to the next. Because flux is larger when there are more particles and lower when there are less particles. Slices with smaller concentration will tend to receive more-incoming particles and slices with relatively higher concentration will send out more particles

Fick's law (or Fick's 1st law)

- Suppose that particles are uniformly distributed in the *y* and *z* dimensions, and vary only in *x*
- Let *c* represent concentration (a function of *x*)
- Define the flux *J* as the rate at which particles diffuse across a boundary
- Then Fick's 1st law states that: $J = -D\frac{\partial c}{\partial x}$



Flux is dependent on diffusion constant, because it speaks to the speed at which the particles are moving. The negative sign is to account for the fact that particles move from high to low concentration (which we define as a positive flux, but have a negative slope (dc/dx))

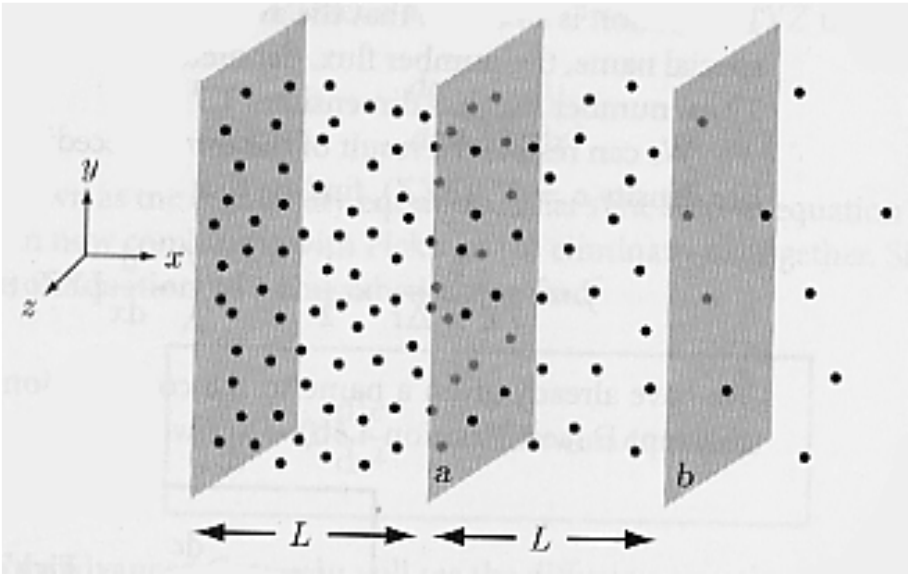
Note: Fick's "laws" are approximations assuming frequent collisions between particles (https://doi.org/10.1002/aic.14926)

How does concentration change with time?

- Now think of concentration and flux as a function of position *x* and time *t*
- The concentration at a particular position goes down with time if there is more flux away from that position than there is coming in to that position (in other words, if the flux at that position is increasing as one moves in the positive *x* direction)

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

dJ/dx is defined as positive if flux increasing with x. If dJ/dx is positive, then flux will be higher to the right of xi, than to the left. This means that more particles will be leaving the current position xi (moving to the right to xi+1) than the particles entering xi (moving from location xi-1 to xi). This will decrease the concentration at the current position (this is why we have the negative sign). Alternatively, if dJ/dx is negative, then the flux will be higher on the left of the current position, then the right. More particles will be entering from the left than leaving from the right, which means concentration will increase.

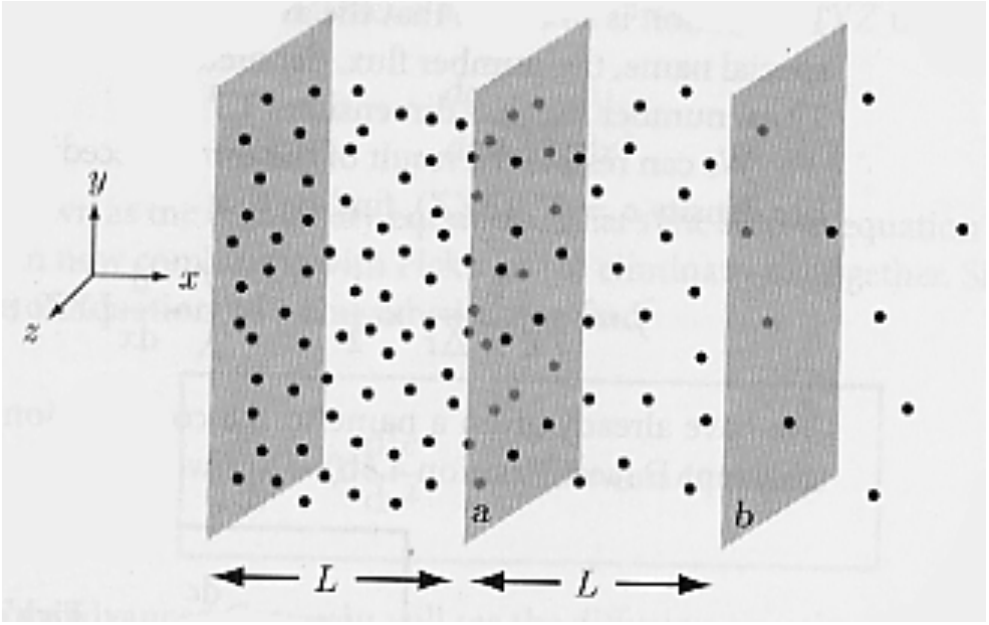


Diffusion Equation (or Fick's 2nd law)

- Combining these formulae gives us:

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = -\frac{\partial}{\partial x}\left(-D\frac{\partial c}{\partial x}\right) = D\frac{\partial^2 c}{\partial x^2}$$

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



Example

- 1D diffusion from a point:
  - Solution to the diffusion equation is a Gaussian whose variance grows linearly with time

In three dimensions …

- Now suppose concentration varies as a function of *x*, *y*, *z*, and *t*
- The diffusion equation generalizes to:

$$\frac{\partial c}{\partial t} = D\nabla^2 c = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial z^2}\right)$$

∇^2 is called the Laplacian operator

Laplacian operator means to take the second derivative with respect to each input dimension/coordinate

Simulating diffusion

Reaction-diffusion simulation

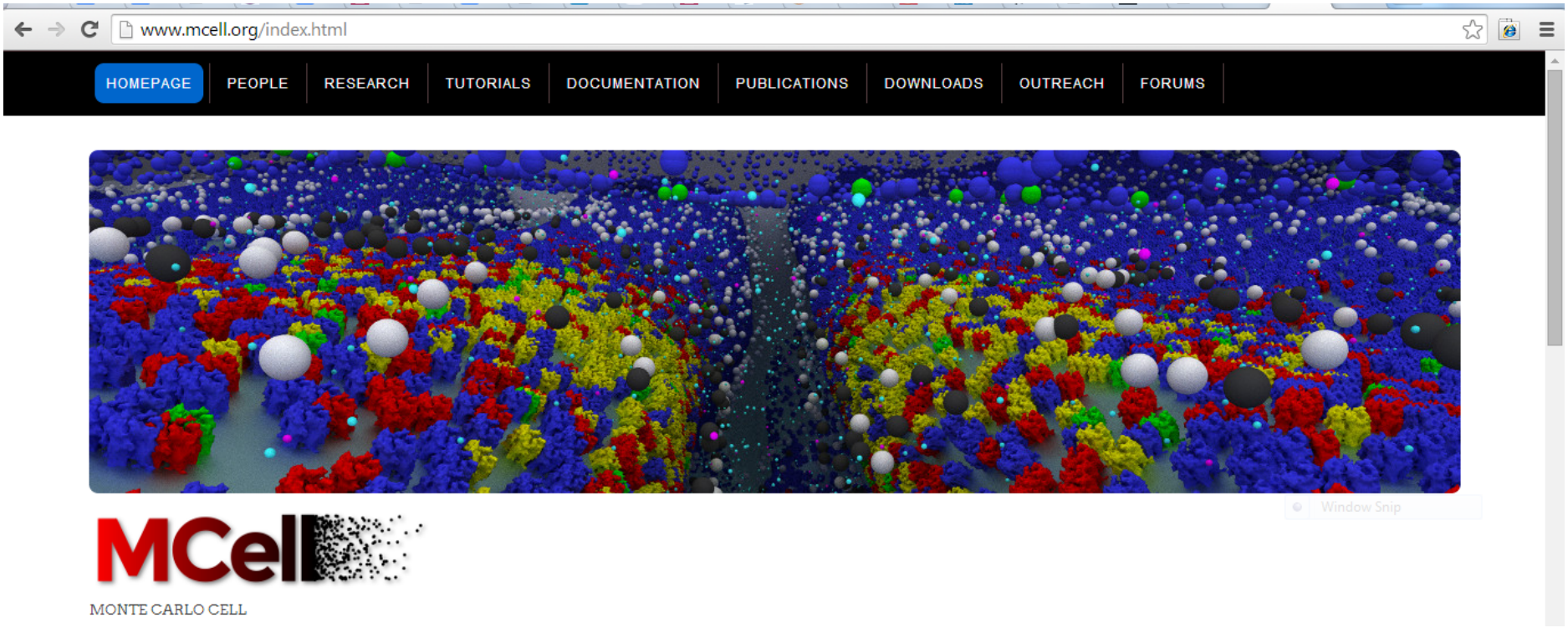
- A common way to model how molecules move within the cell involves *reaction-diffusion simulation*
- Basic rules:
  - Molecules move around by diffusion
  - When two molecules come close together, they have some probability of reacting to combine or modify one another
- Two implementation strategies:
  - Particle-based
  - Continuum models

Reaction:
- Two molecules becomes bound
- A bound complex splits and forms multiple molecules
- A molecule modifies another molecule

Track positions of individual molecules

Track concentration of molecules within a given region

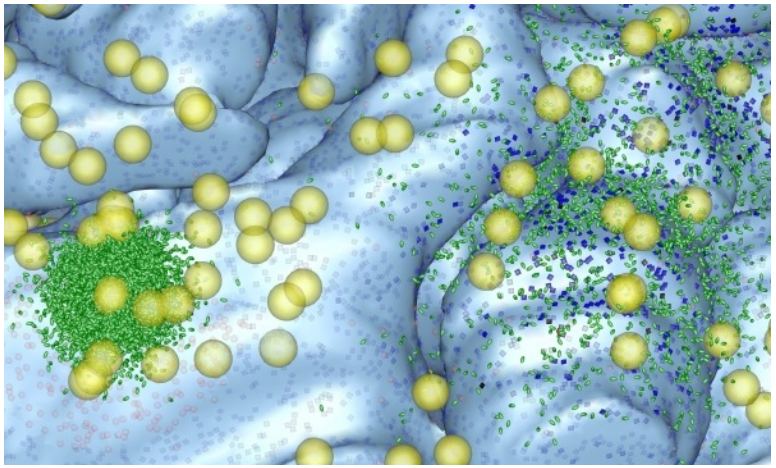
MCell: one of several particle-based simulation software packages



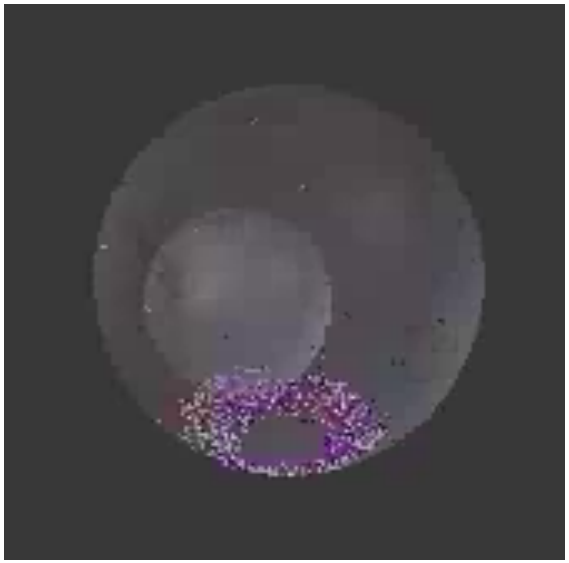
Other similar software packages: Smoldyn, Chemcell

How MCell works

- Particles representing molecules move according to a random walk, and react with one another probabilistically when they come into contact
  - MCell uses Monte Carlo algorithms
- Morphology of cell membranes (and other cellular structures) represented by a mesh



http://www.mcell.cnl.salk.edu/



Naomi Latorraca

MCell applications

- MCell has been widely used in neuroscience, to model phenomena such as synaptic transmission
- A common approach is to perform simulations under various assumptions and see which ones best match experimental data
  - See, for example, Coggan et al., Evidence for Ectopic Neurotransmission at a Neuronal Synapse, *Science* 309:446-451 (2005)

Showed the phenomenon of long-range diffusion of neurotransmitters based on modeling

Continuum approach

- Divide space into finite “voxels”
- Instead of tracking positions of molecules, track concentrations of each type of molecule in each voxel
- At each time step, update concentrations based on reactions of molecules within a voxel, and diffusion between neighboring voxels based on concentration differences (i.e., the diffusion equation)

Continuum approach

- Advantage: faster

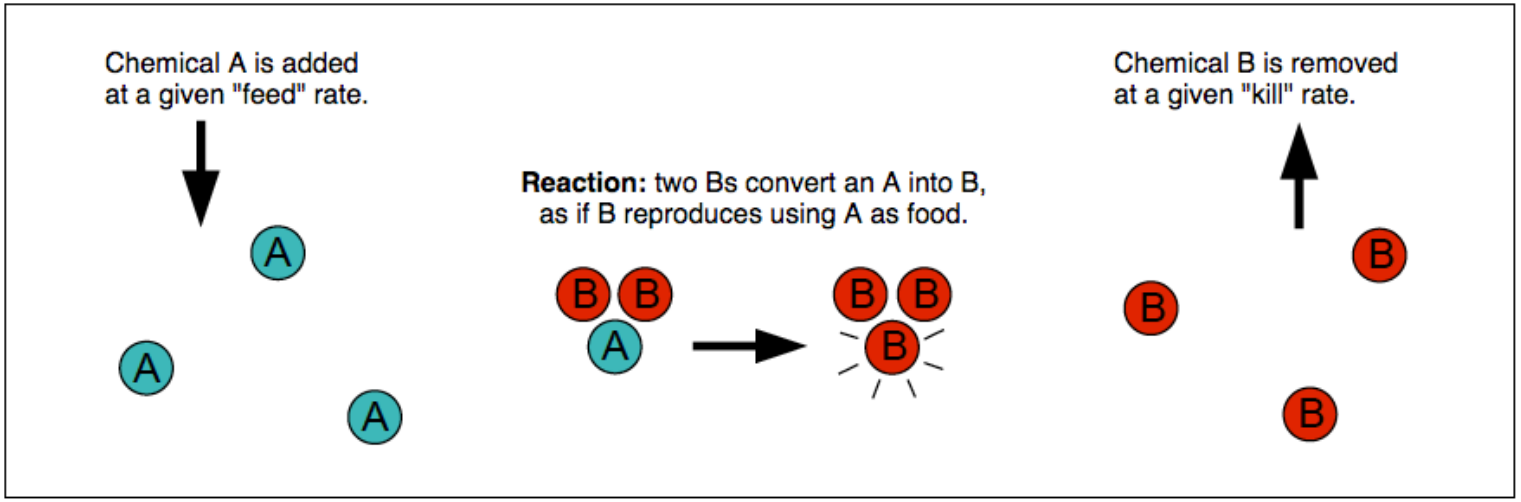
Don't need to keep track and update every single particle/ molecule, you can represent a large number of molecules within a given voxel as a single number. Voxel-based simulations are deterministic

- Disadvantage: less accurate for small numbers of molecules

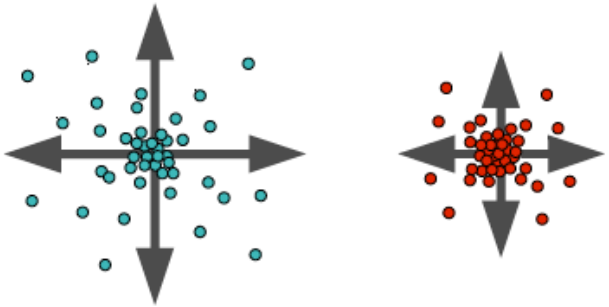
It's possible to have fractions of molecules in a given voxel in these models, which is not possible in practice

- Unlike the particle-based approach, the continuum approach is deterministic
- Example software: Simmune

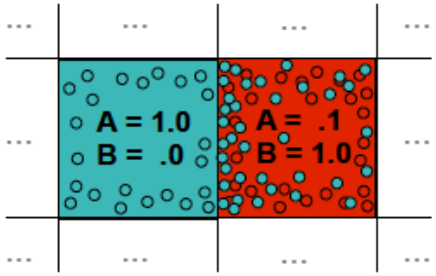
Example: Gray-Scott model



Diffusion: both chemicals diffuse so uneven concentrations spread out across the grid, but A diffuses faster than B.



The system is approximated by using two numbers at each grid cell for the local concentrations of A and B.

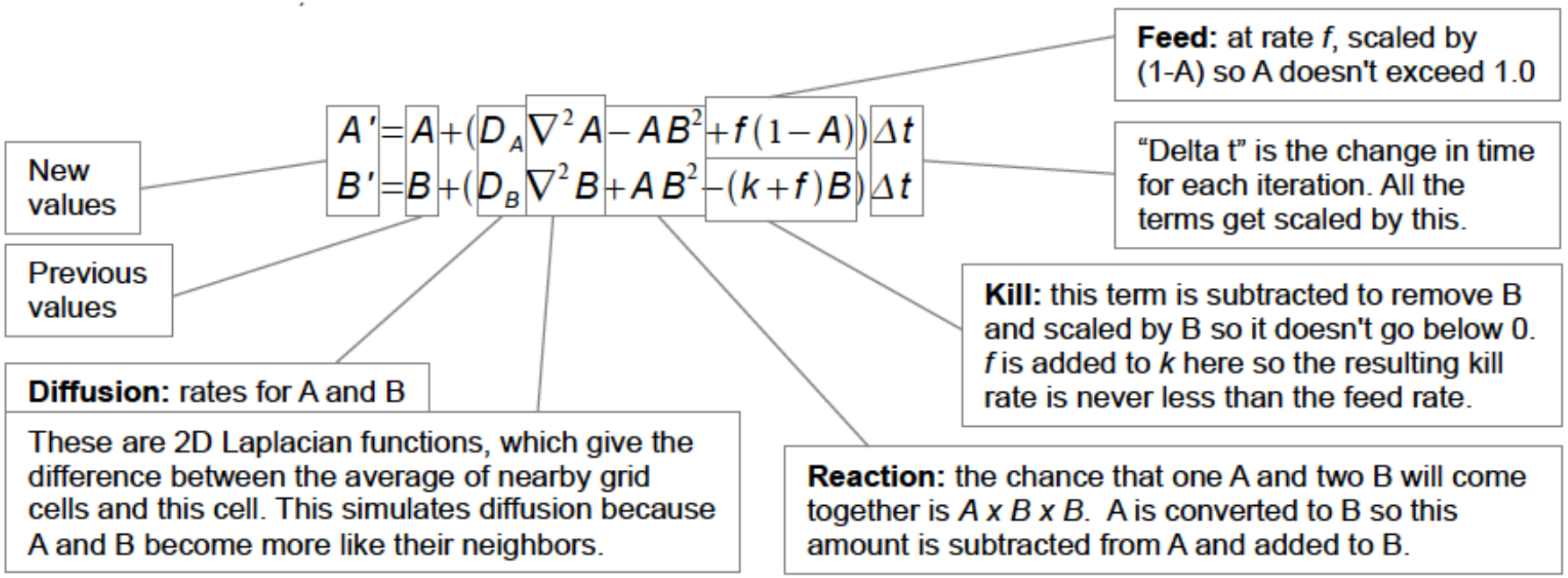


http://www.karlsims.com/rd.html

You're not responsible for these details

Gray-Scott model

The grid is repeatedly updated using the following equations to update the concentrations of A and B in each cell, and model the behaviors described above.



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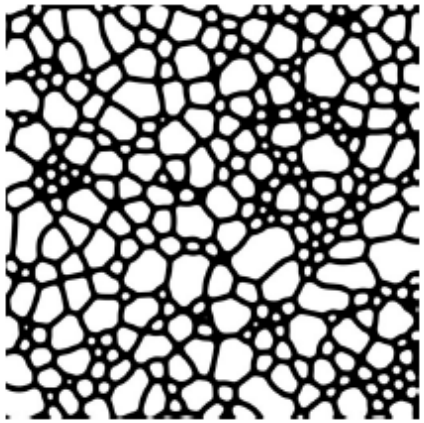
Gray-Scott model






All sorts of interesting patterns emerge as one varies the parameters

http://www.karlsims.com/rd.html

Gray-Scott model

- Demo: http://pmneila.github.io/jsexp/grayscott/

Alan Turing on morphogenesis

- Alan Turing proposed this as a model for pattern formation in animals
  - A. M. Turing, Philosophical Transactions of the Royal Society of London, Series B, Vol. 237:37-72, 1952

THE CHEMICAL BASIS OF MORPHOGENESIS

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

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system.

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