Diffusion and cellular-level simulation

CS/CME/BioE/Biophys/BMI 279

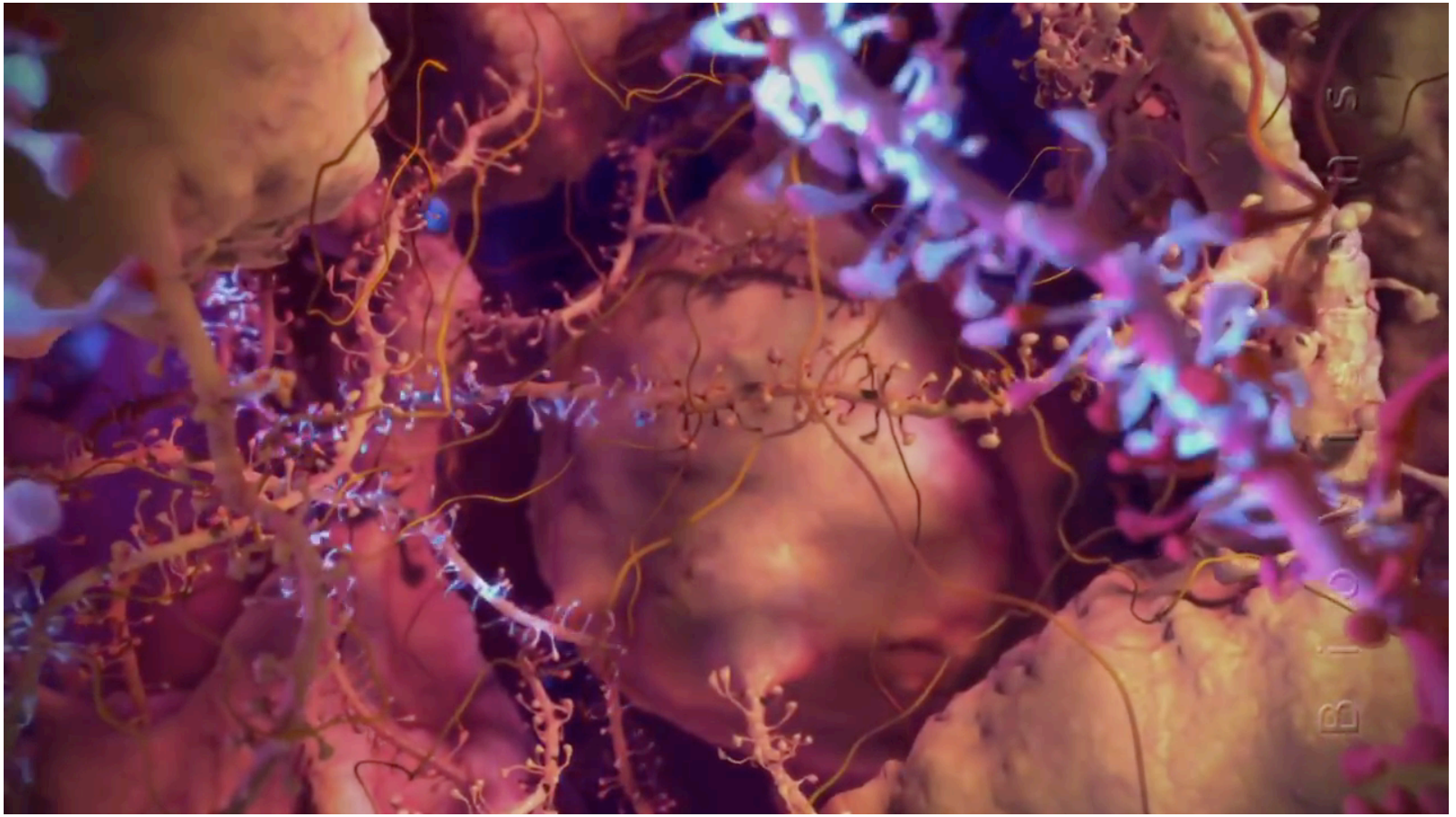
Oct. 15 and 20, 2020

Ron Dror

Outline

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

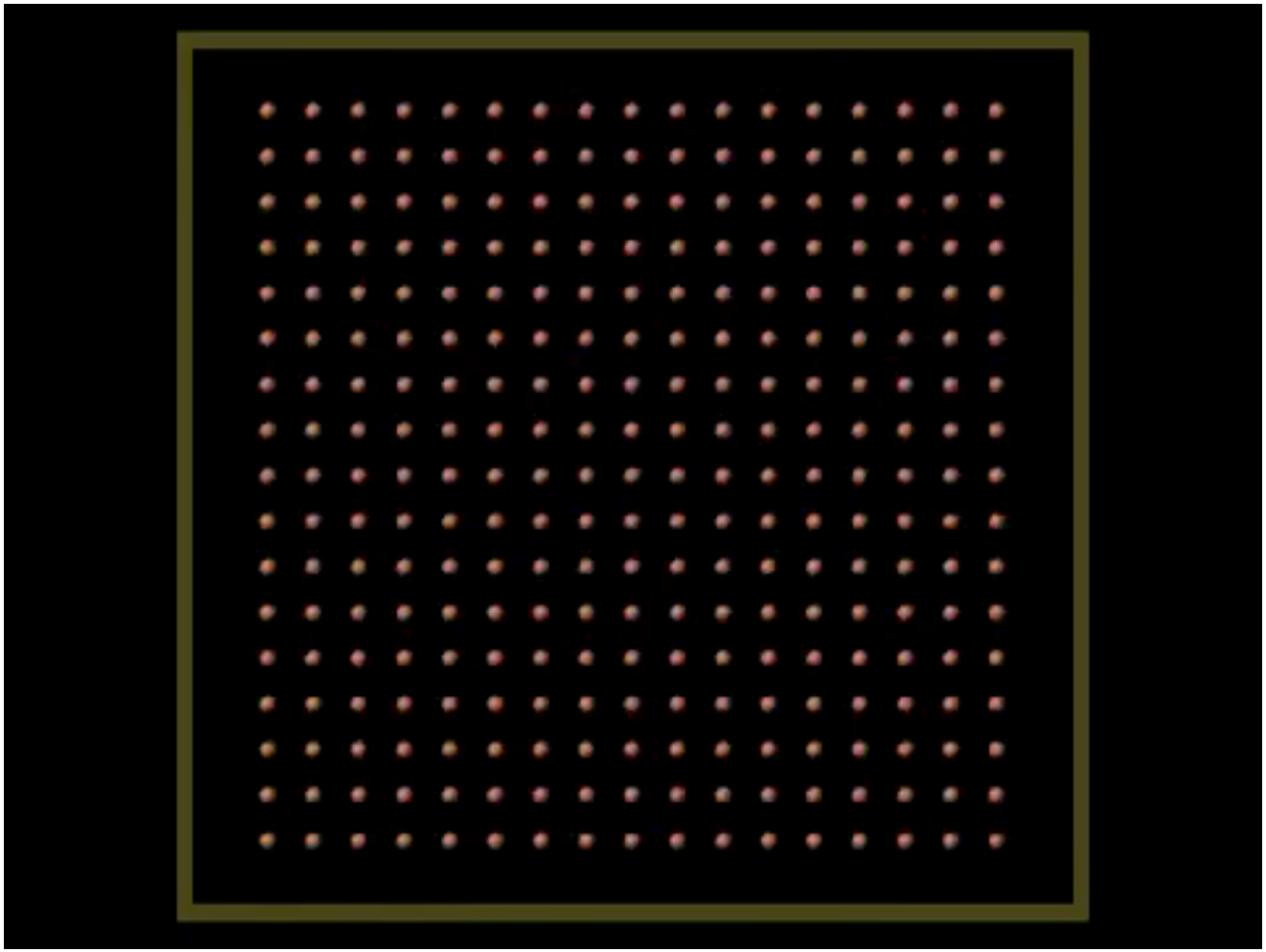
How do molecules move around in a cell?



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

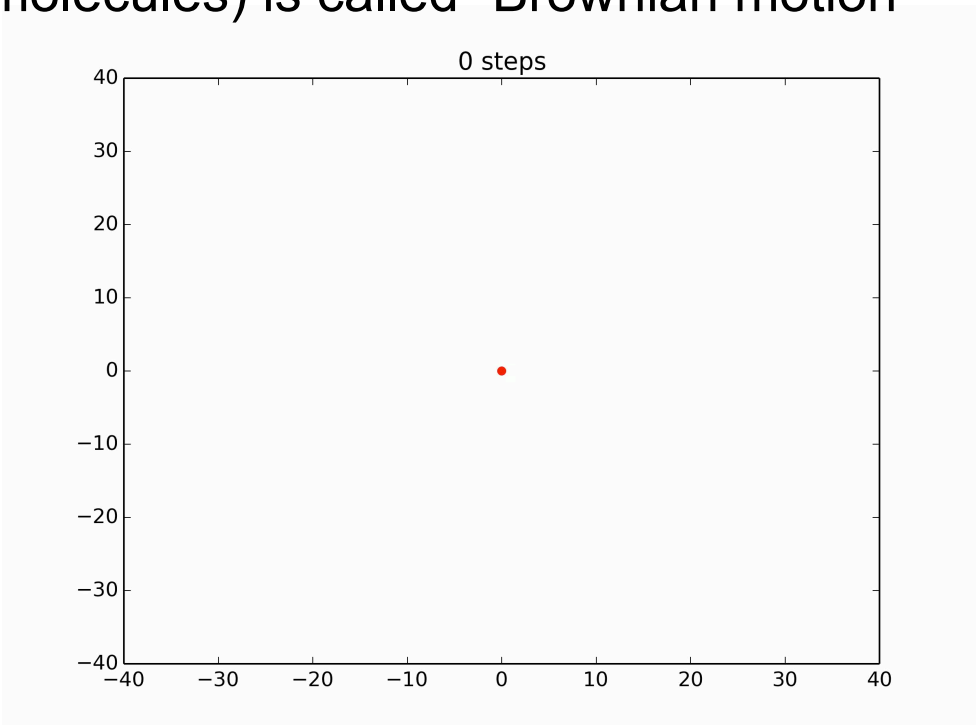
Diffusion

- 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
- We will focus on the basic case of random, unconfined, undirected motion. Certain molecules move around in more complicated ways within cells.

Diffusion as a random walk (particle-based perspective)

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

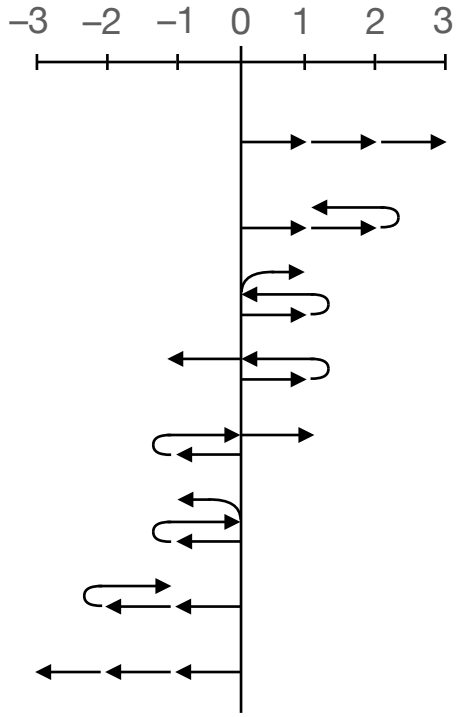
1, 2, or 3 dimensions

- 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}?

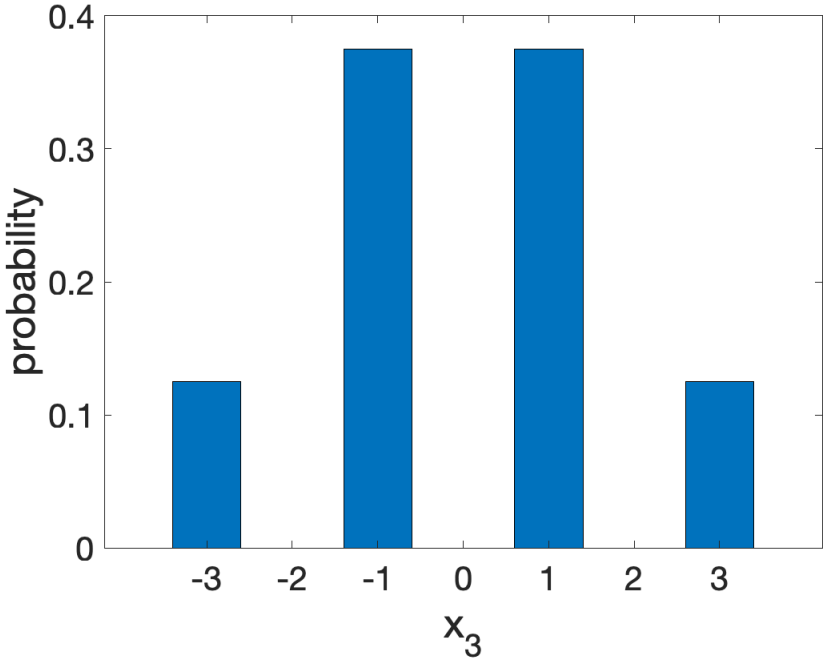
Position after 3 time steps (x_3)



Position (x_3)	$(x_3)^2$
+3	+9
+1	+1
+1	+1
–1	+1
+1	+1
–1	+1
–1	+1
–3	+9
$E[x_3] = 0$	$E[x_3^2] = 3$
After N steps: $E[x_N] = 0$	$E[x_N^2] = N$

Position after 3 time steps (x_3)

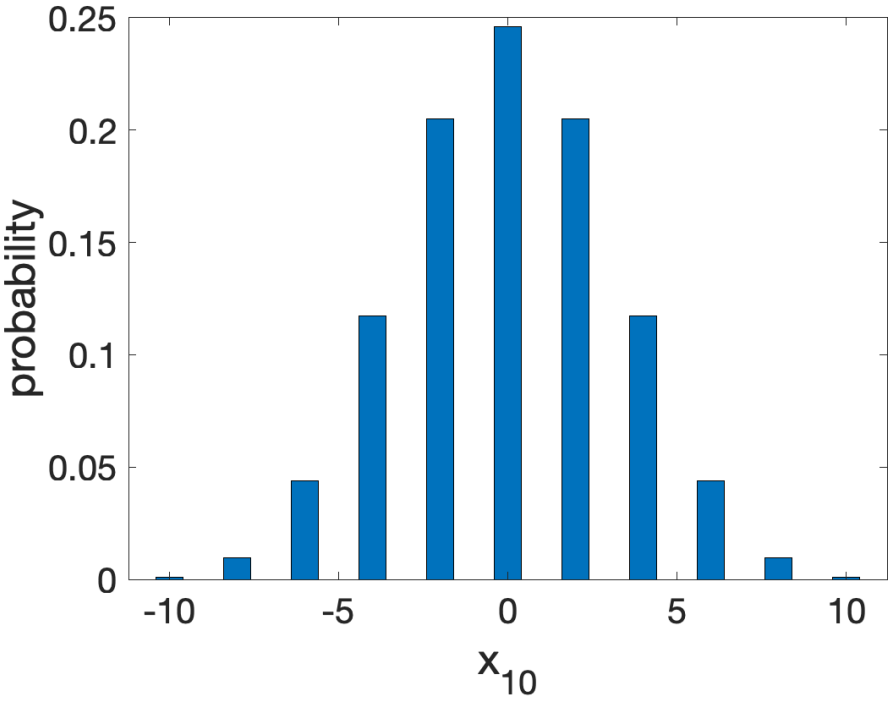
- Probabilities:
  - $P(x_3 = -3) = 1/8$
  - $P(x_3 = -1) = 3/8$
  - $P(x_3 = 1) = 3/8$
  - $P(x_3 = 3) = 1/8$



- Mean displacement:
  $E[x_3] = 0$
- Mean-squared displacement:
  $E[x_3^2] = 3$

Position after 10 time steps (x_{10})

- Mean displacement: $E[x_{10}] = 0$
- Mean-squared displacement: $E[x_{10}^2] = 10$



Properties of 1D Brownian motion

- 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)

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:

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

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

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

Diffusion constant

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

The constant 2 is just a convention

- 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

because larger molecule will experience smaller accelerations when colliding with other molecule (e.g. water)

Example values

- Diffusion constants (D):
  - Sugar: 500 $(\mu m)^2/s$
  - Typical protein: 5 $(\mu m)^2/s$
- Cell size:
  - Bacterium (E. coli): 1 μm radius
  - Human neutrophil: 10 μm radius
  - A human neuron can be 100 μm wide and, in extreme cases, over 1 m in length

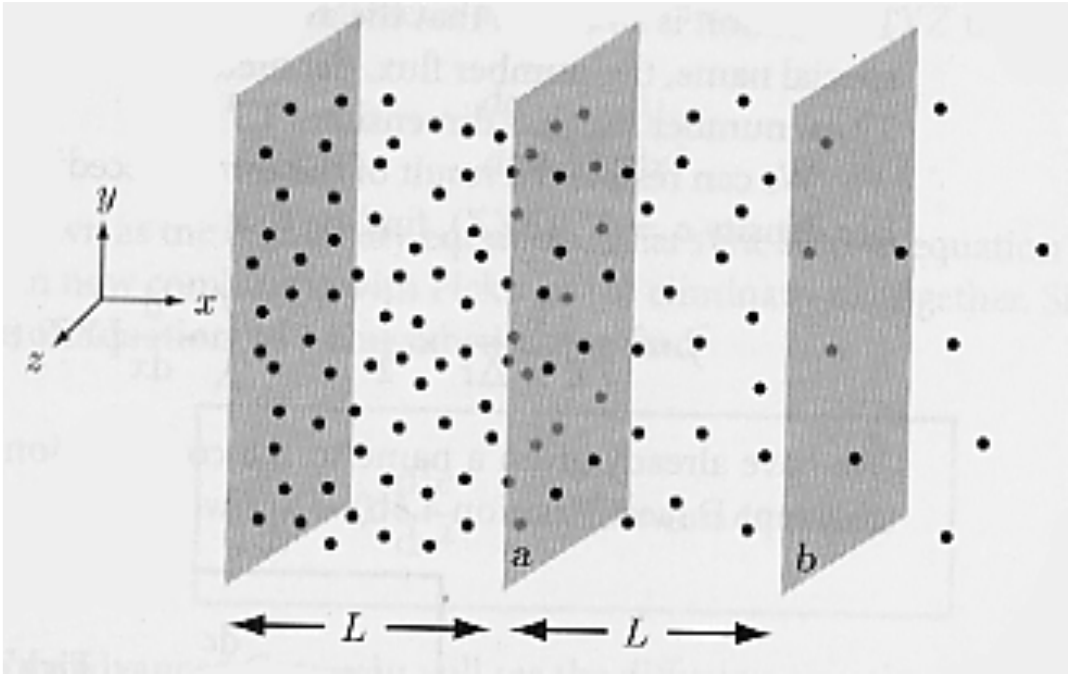
Sugar has a larger diffusion constant than protein because protein is much larger than sugar. In general, smaller molecule has larger diffusion constant.

From Chris Burge
(see links on course website)

Continuum view of diffusion

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

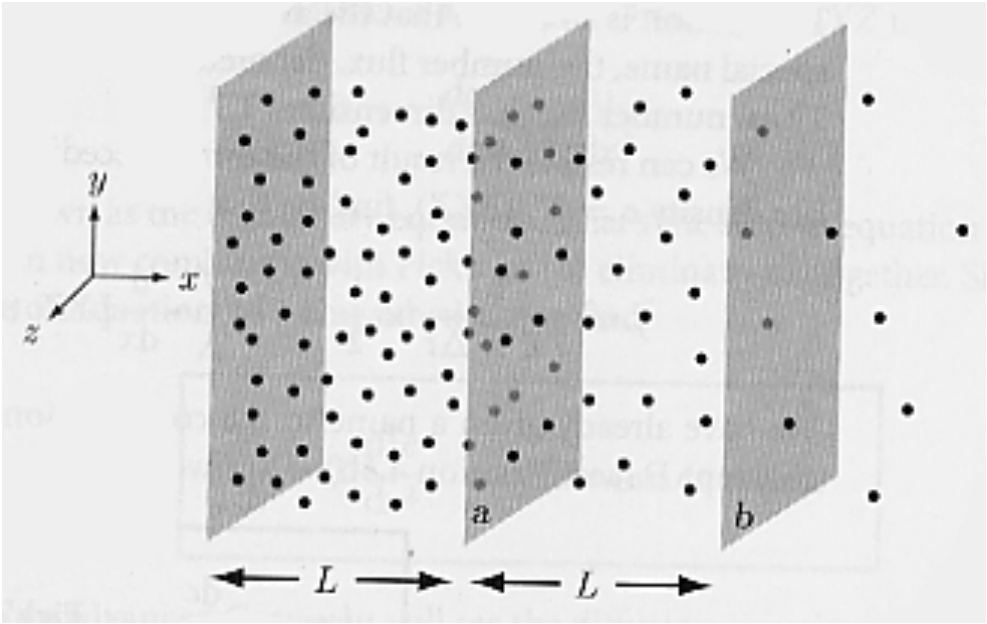


Individual particles have the same probability of moving to the left or to the right regardless of the overall concentration. However, there are a lot more particles in the higher concentration region. That's why in aggregate, we have more particles moving from regions of high concentration to the regions of low concentration

From Chris Burge

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



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

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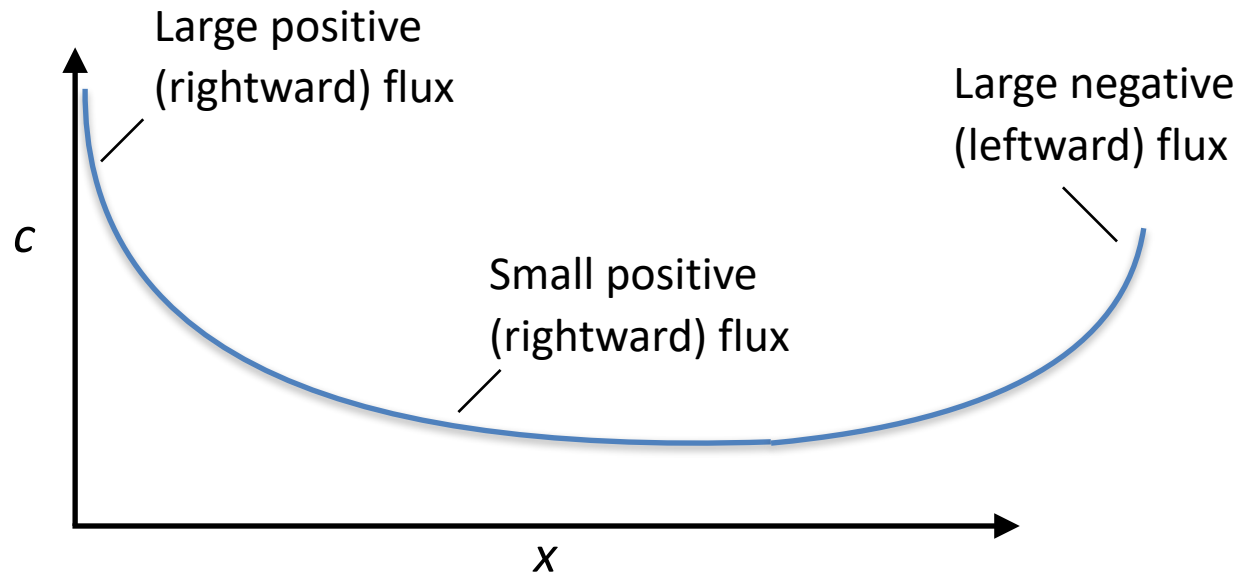
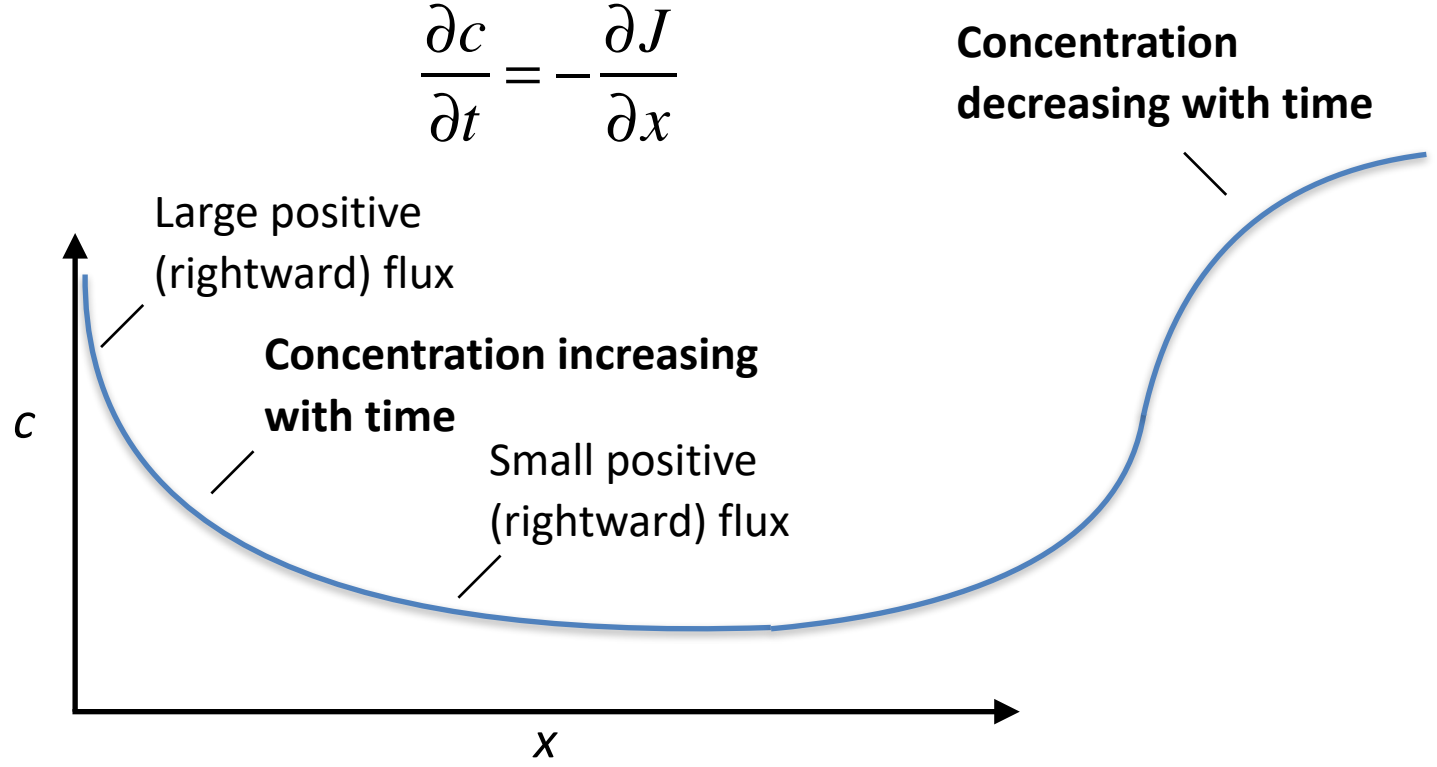


How does concentration change with time?

- 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)

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



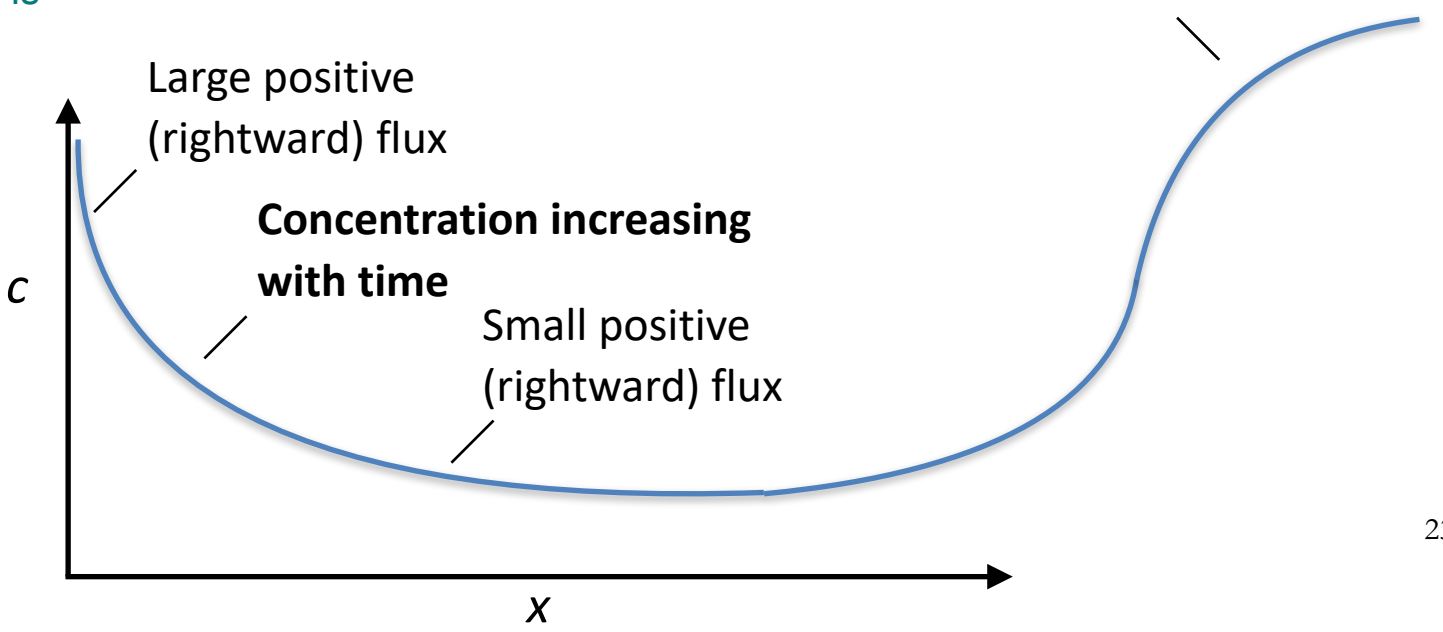
Diffusion Equation (or Fick's 2nd law)

- Combining these formulae gives us:

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

Positive second derivative means the slope is increasing as you move in x, while negative second derivate means the slope is decreasing

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



Example

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

The standard deviation (width/diameter) of the Gaussian grows proportionally to the square root of 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

Simulating diffusion

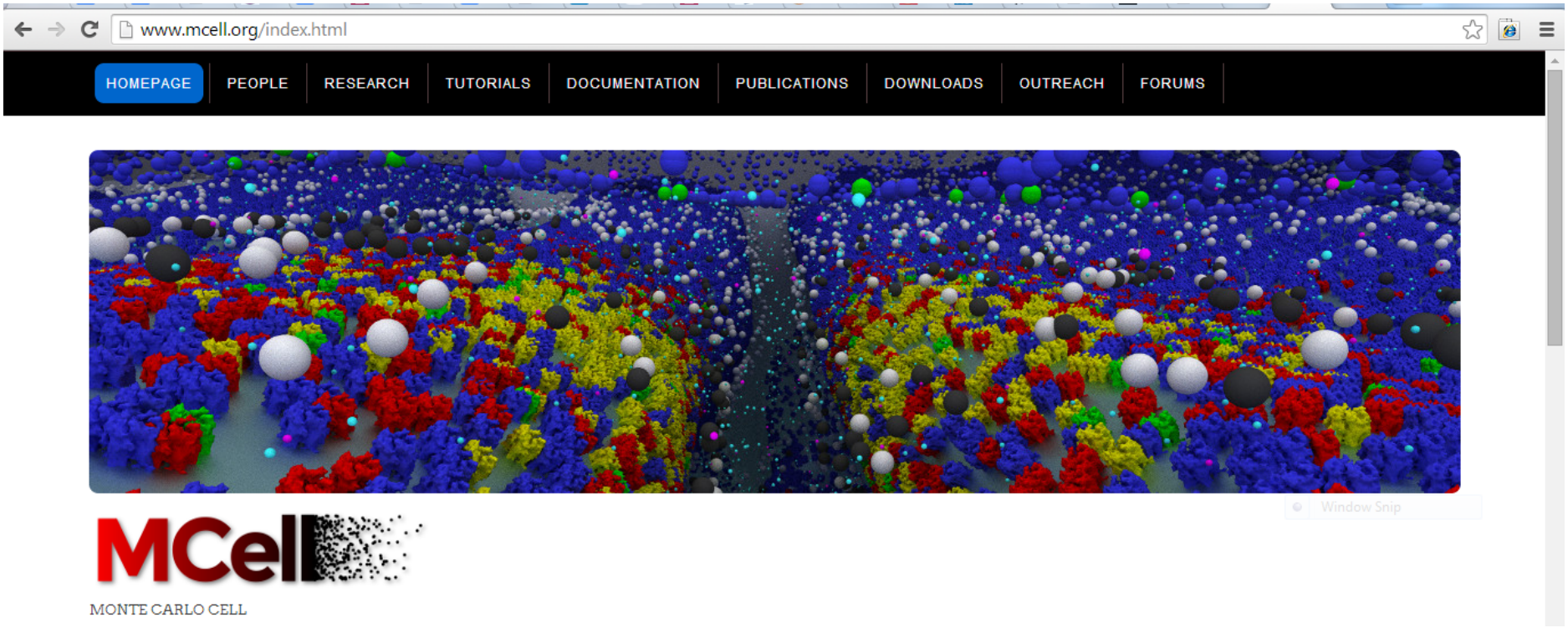
Reaction-diffusion simulation

- 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

Molecules diffuse independently of each other

"Reaction" is defined in a very general sense. Reaction takes place when 2 or more molecules come close together and do something to one another

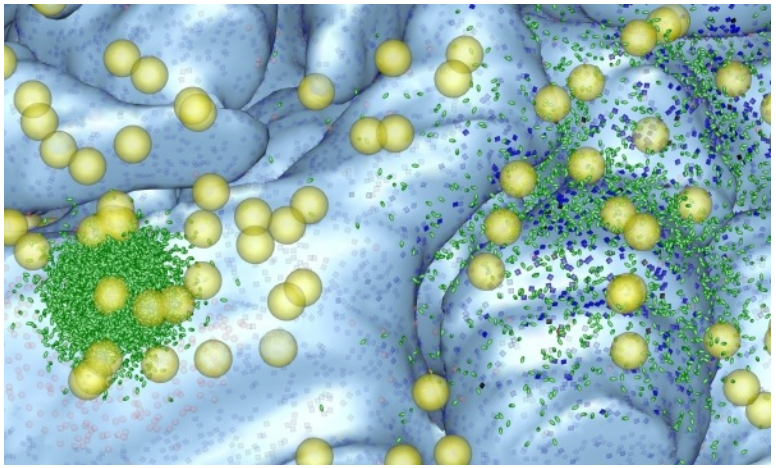
MCell: one of several particle-based simulation software packages



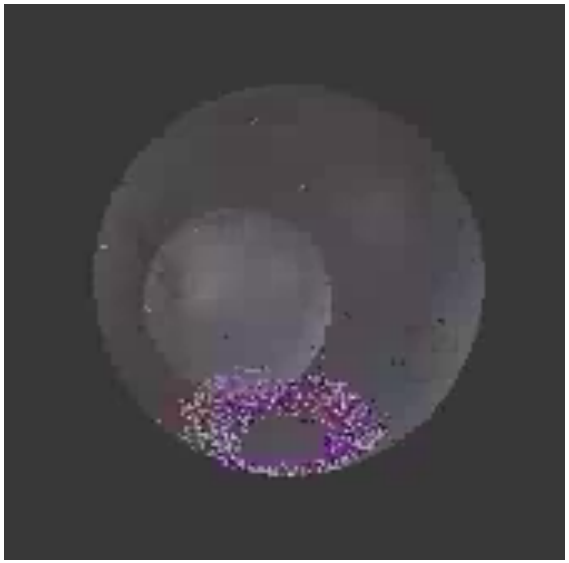
Other similar software packages: Smoldyn, Chemcell

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/



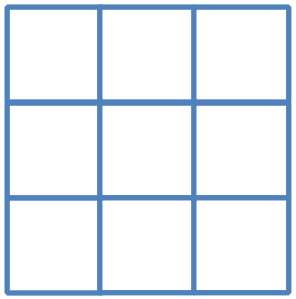
Naomi Latorraca

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)

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)

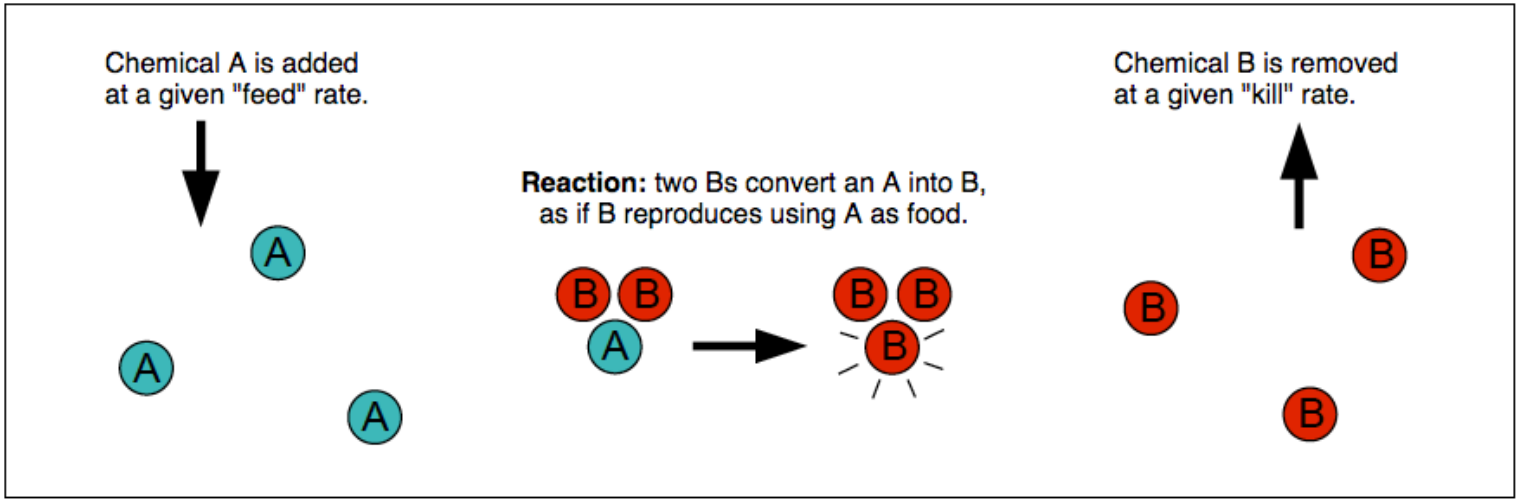


2D grid for illustrative purposes
In a 3D grid, the individual boxes are “voxels”

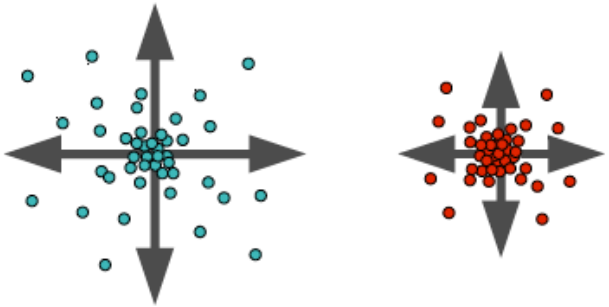
Continuum approach

- Advantage: faster because we are no longer representing every single molecule
- Disadvantage: less accurate for small numbers of molecules
- Unlike the particle-based approach, the continuum approach is deterministic
- Example software: Simmune

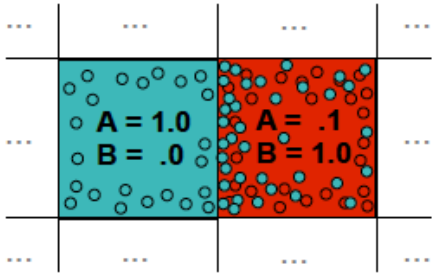
Example: Gray-Scott model



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.

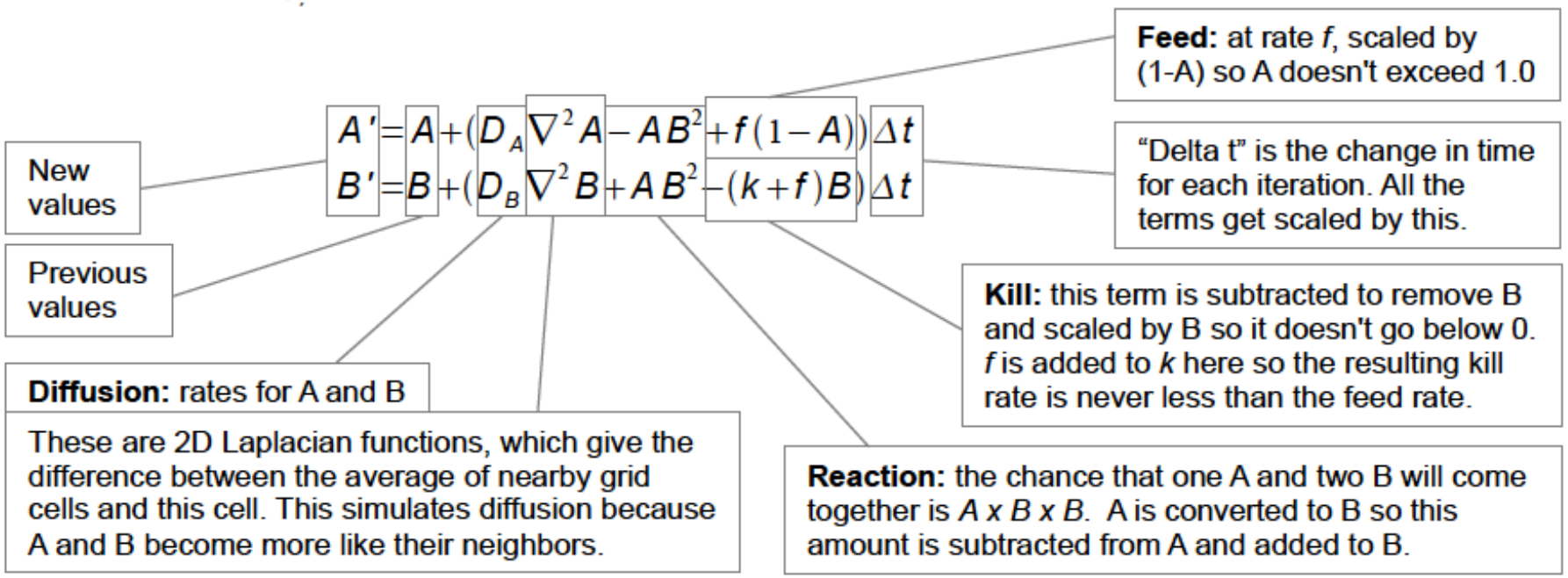


http://www.karlsims.com/rd.html

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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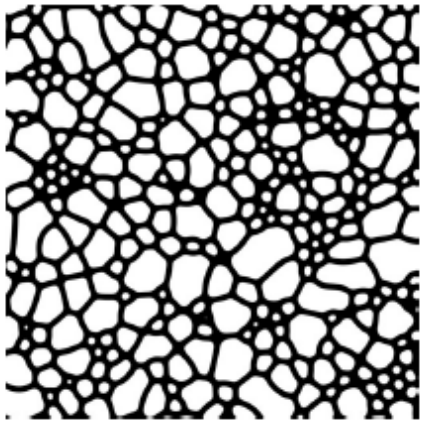
Gray-Scott model






All sorts of interesting patterns emerge as one varies the parameters

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

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*

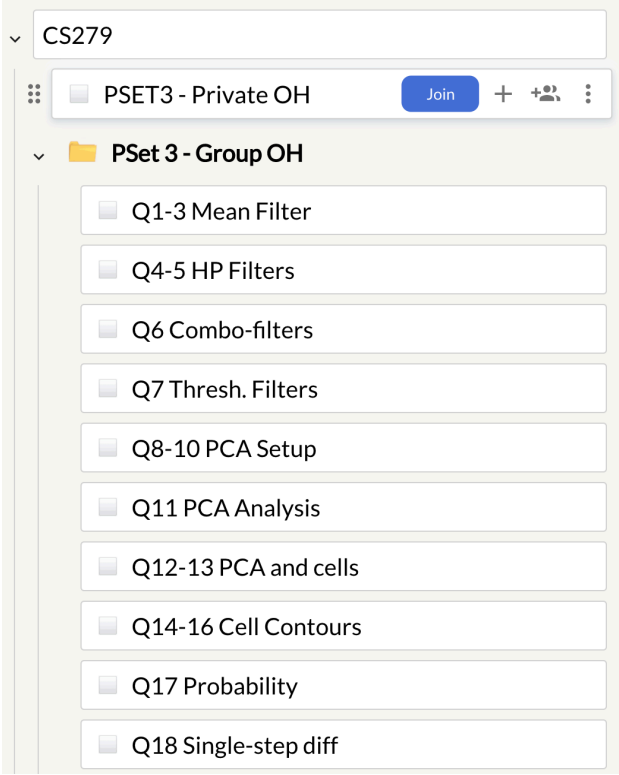
(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

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.

You're not responsible for this

Thanks for your feedback!

- Additional TA office hours
  - We'll be adding more office hours in the coming week, before the final project deadline, and before the final
- Office hours on Nooks instead of Zoom
  - https://nooks.in/goto/4UOr4UBTZzHqaJlV?pwd=Bizd8s
  - Please join a group room if at all possible
- Grading
  - We will be clearer about why points were deducted
  - Please explain your rationale; this will generally get you more credit



Gray-Scott model

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