Diffusion and cellular-level simulation

CS/CME/BioE/Biophys/BMI 279

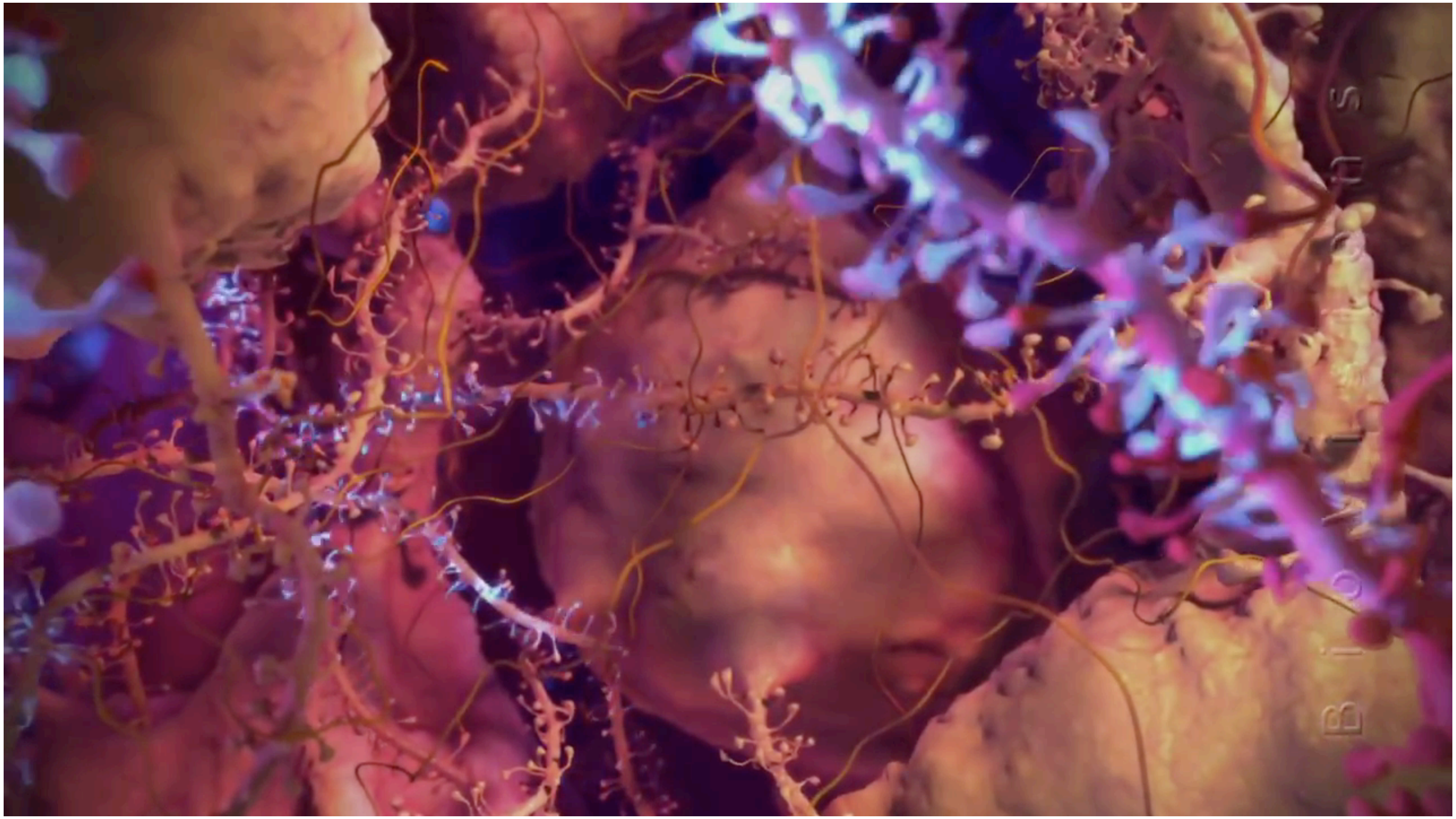
Nov. 2 and 9, 2023

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

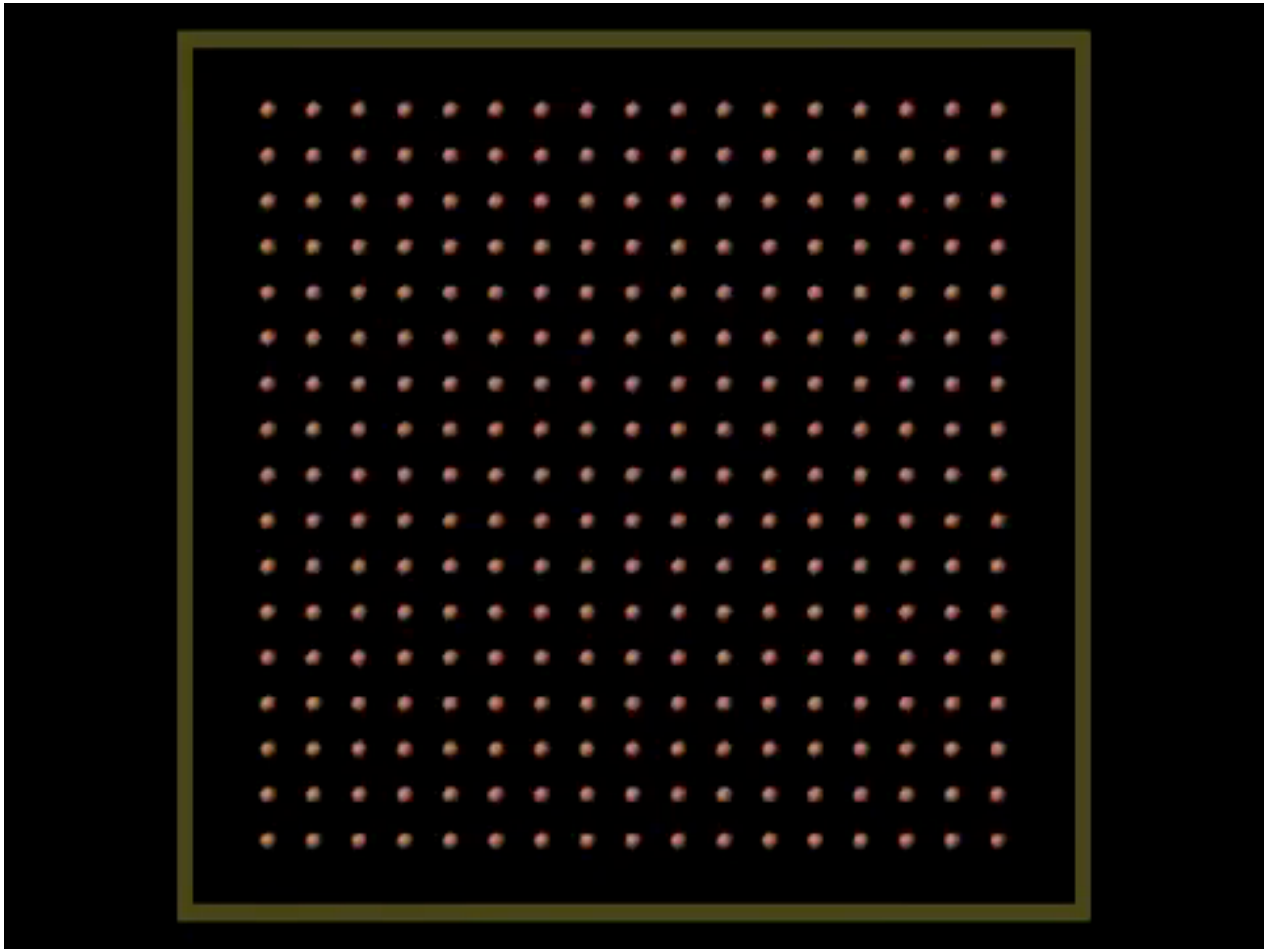
How do molecules move around in a cell?



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

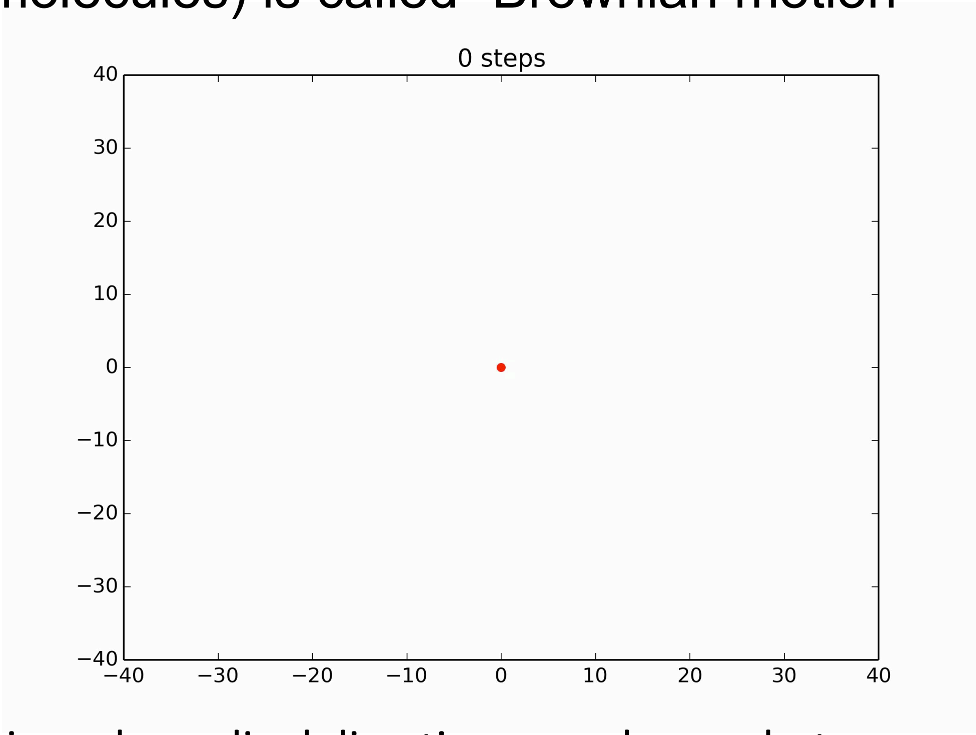
Diffusion

- 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

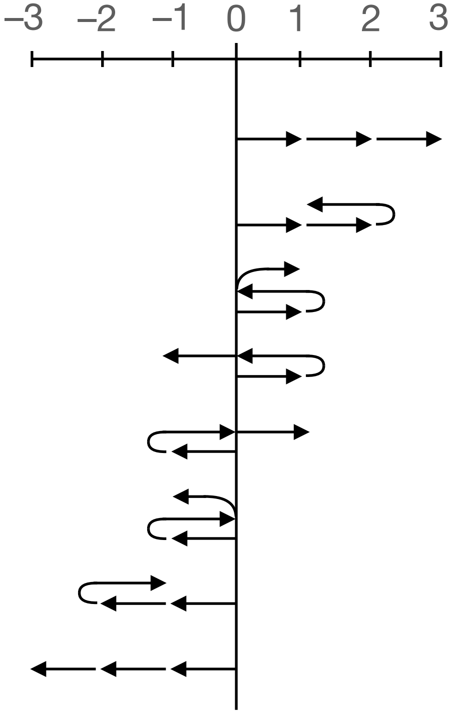
1, 2, or 3 dimensions

- 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 and x_{10} or x_{100}?

Position after 3 time steps (x_3)

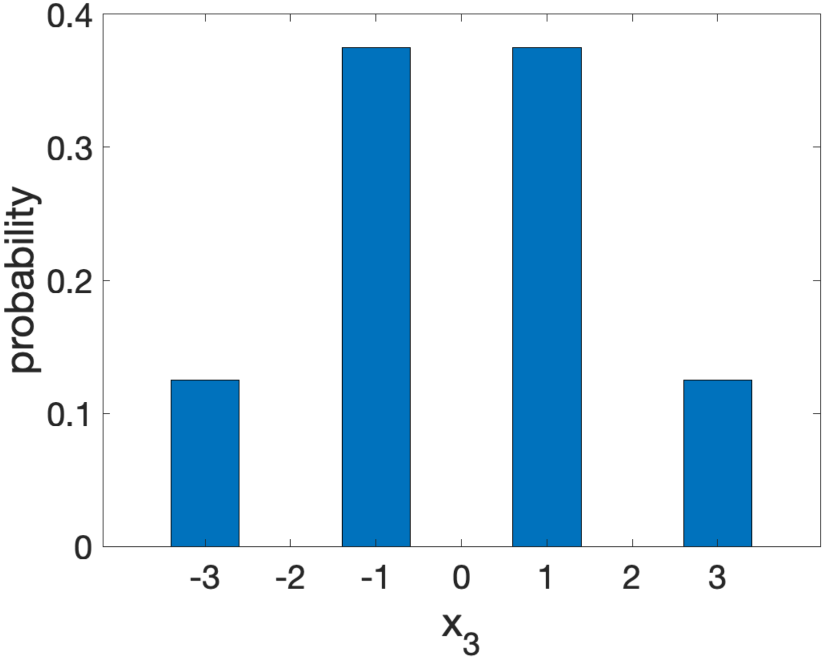


Position (x_3)	$(x_3)^2$
+3	+9
+1	+1
+1	+1
–1	+1
+1	+1
–1	+1
–1	+1
–3	+9
$E[x_3] = 0$	$E[x_3^2] = 3$

After N steps: $E[x_N] = 0$ $E[x_N^2] = N$

Position after 3 time steps (x_3)

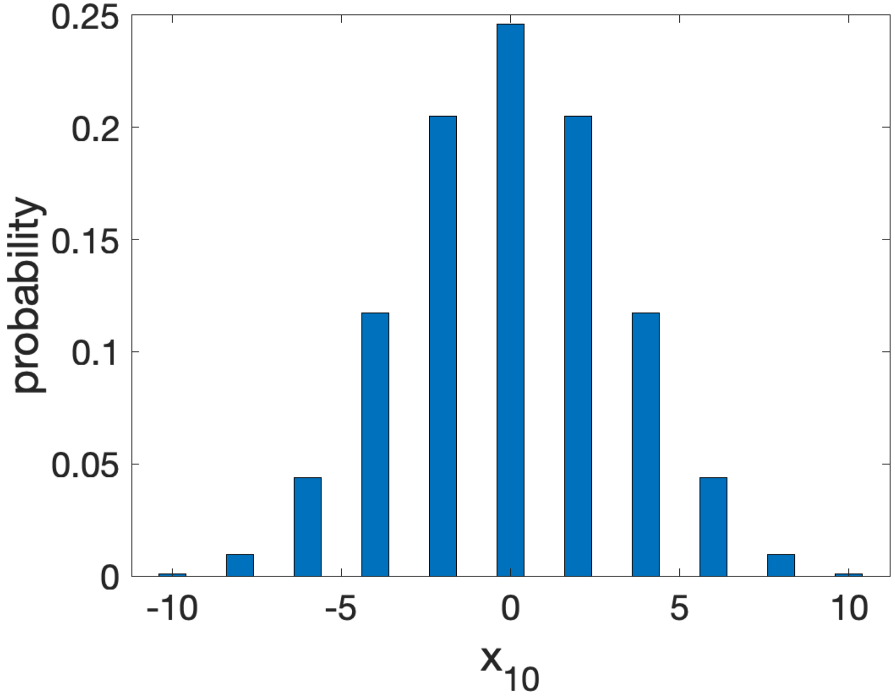
- Probabilities:
  - $P(x_3 = –3) = 1/8$
  - $P(x_3 = –1) = 3/8$
  - $P(x_3 = 1) = 3/8$
  - $P(x_3 = 3) = 1/8$



- 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 elapsed time and Δ*t* denote length of each 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 coefficient

- To quantify speed of diffusion, we define the diffusion coefficient *D*: $D = \frac{L^2}{2\Delta t}$

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

- Then $E\left[x(t)^2\right] = 2Dt$
- In 2D, the diffusion coefficient 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, $E\left[r(t)^2\right] = E\left[x(t)^2\right] + E\left[y(t)^2\right] + E\left[z(t)^2\right] = 6Dt$

Quick review: diffusion (particle-based perspective)

- Molecules in a cell typically follow a “random walk” (Brownian motion): their motion of direction keeps changing, because they’re continually colliding with other molecules
- The diffusion coefficient (*D*) of a molecule quantifies the speed of this motion
  - The square of the distance between a molecule’s position at time *t* and its position at time 0 is, on average, 6*Dt* (for Brownian motion in three dimensions)

Example values

- Diffusion coefficient (*D*):
  - Sugar: 500 (μm)^2/s
  - Typical protein: 5 (μm)^2/s
  - Note: Larger molecules generally diffuse more slowly than small ones
- Cell size:
  - Bacterium (E. coli): 1 μm radius
  - Human neutrophil (white blood cell): 10 μm radius
  - A human neuron can be 100 μm wide and, in extreme cases, over 1 m in length

From Chris Burge
(see links on course website)

Continuum view of diffusion

Basic intuition

- Although we can’t predict the motion of one particle (i.e., the path it will follow), 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

Concentration as a function of position

- Suppose that the concentration of a particular type of particle (e.g., a molecule) is constant in the *y* and *z* dimensions, and varies only in *x*
- Let *c* represent concentration (a function of *x*)

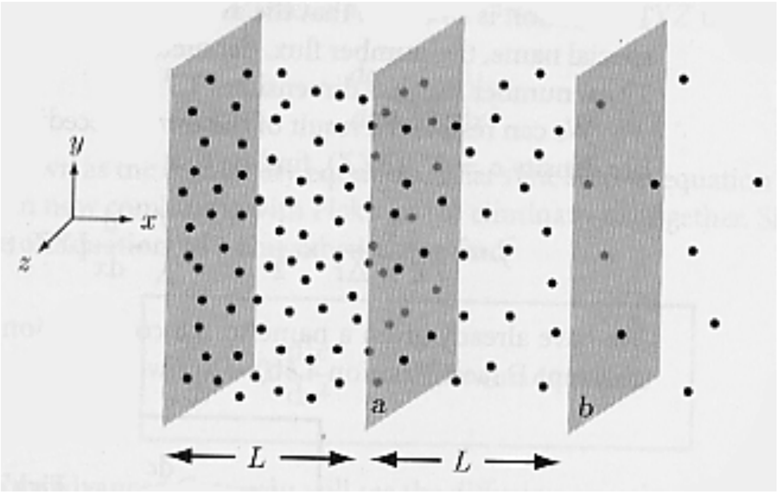
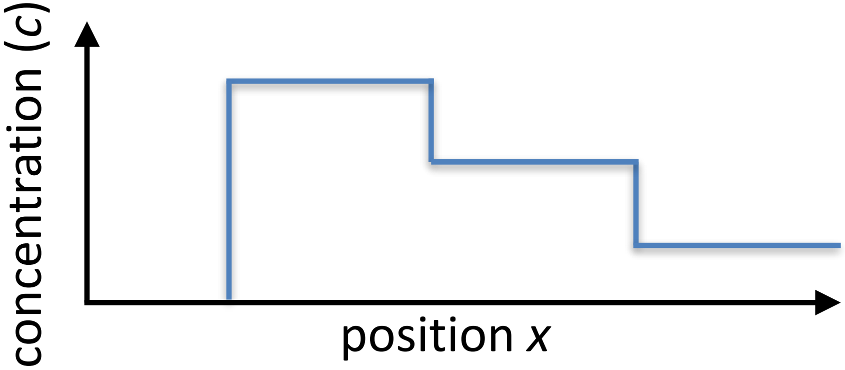
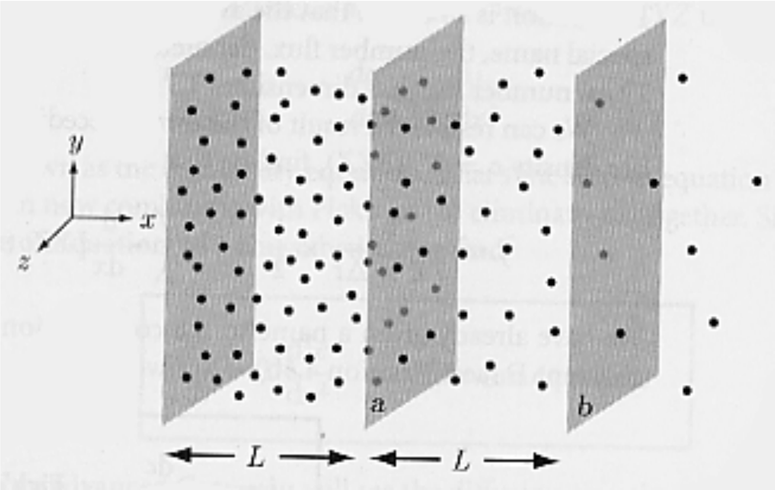


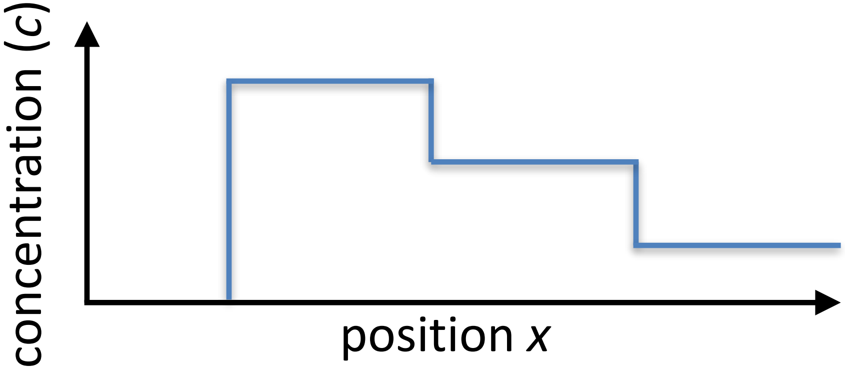
Illustration from Chris Burge



Flux

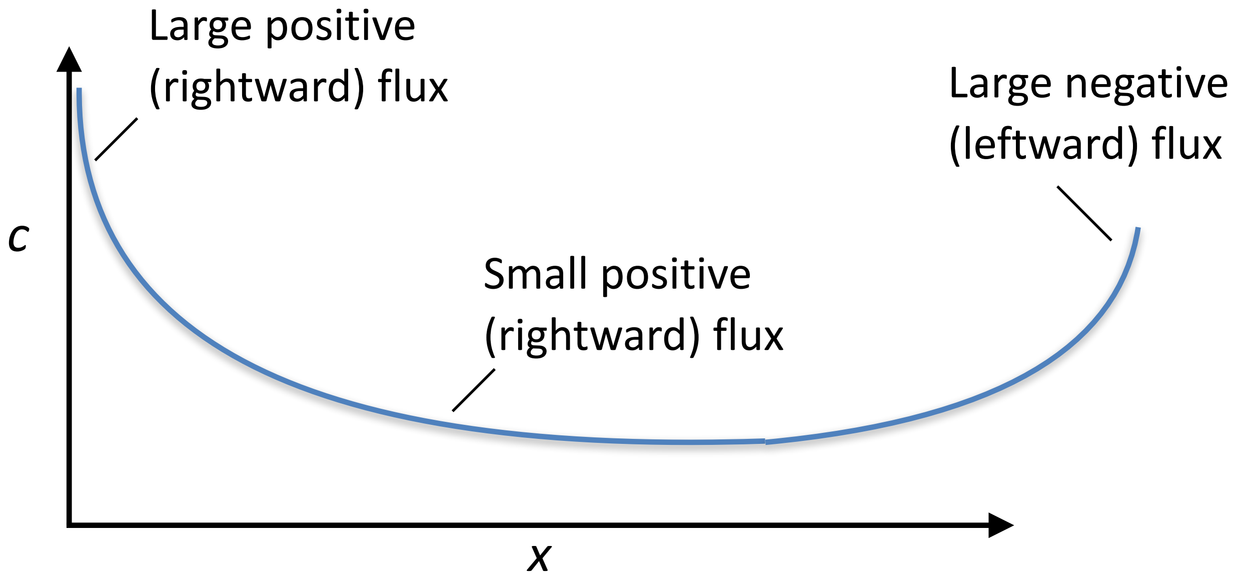
- Define the flux *J* as the rate at which particles diffuse across a boundary
  - That is, the flux at position x = *P* is the net rate at which particles go from the left of *P* to the right of *P*
  - This flux will be positive if particle concentration to the left of *P* is higher than concentration to the right of *P*, and negative if concentration to the left of *P* is lower than concentration to the right of *P*





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

- Let *c* represent concentration as a function of *x*
- Let *J* represent the net rate at which particles diffuse across a boundary. *J* is also a function of *x*.
- Fick's 1st law states that: $J = -D\frac{\partial c}{\partial x}$

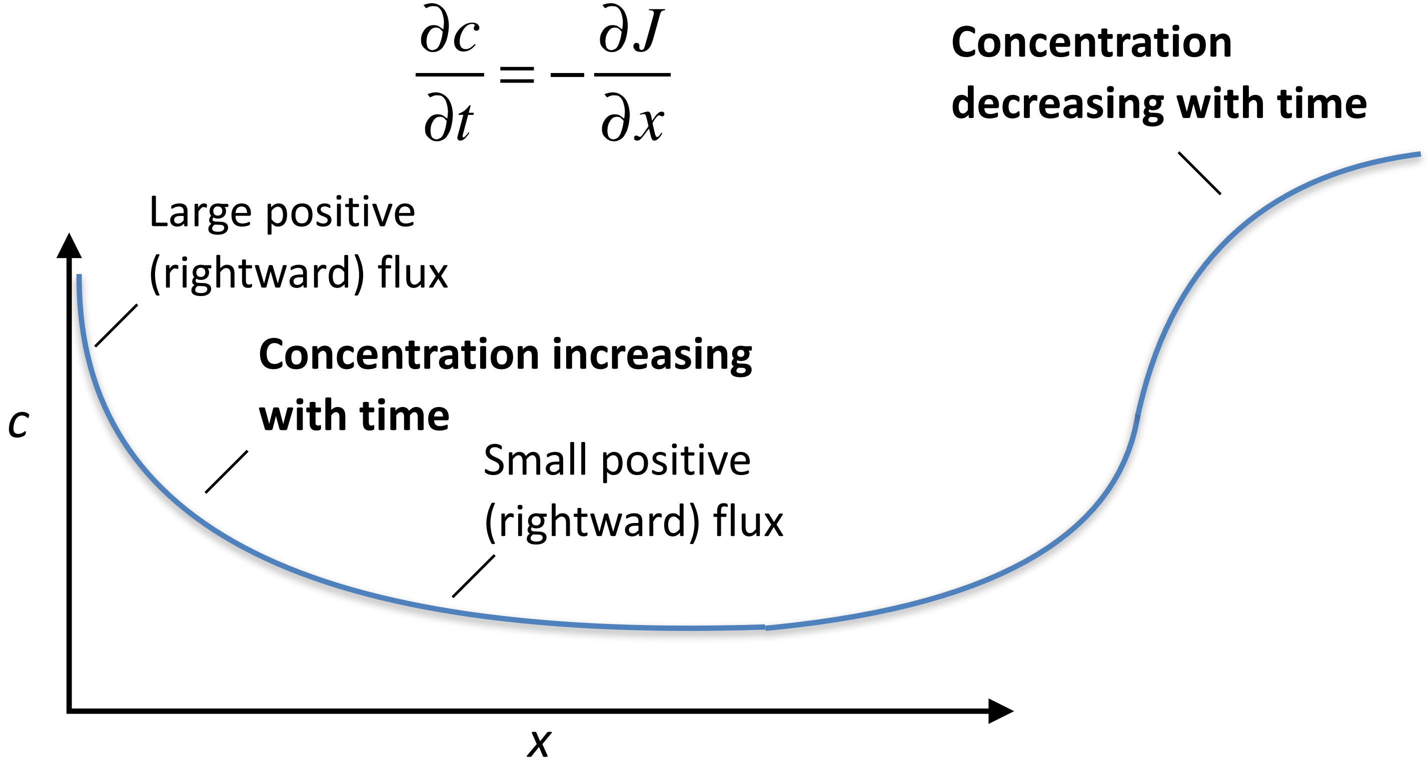


Note: Fick's "laws" are approximations assuming frequent collisions between particles (https://doi.org/10.1002/aic.14926)

How does concentration change with time?

- Now think of concentration and flux as functions of both position *x* and time *t*
- The concentration at a particular position goes up with time if there are more particles coming into that position than going away from it — in math terms, if the flux at that position is decreasing as one moves in the positive *x* direction

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



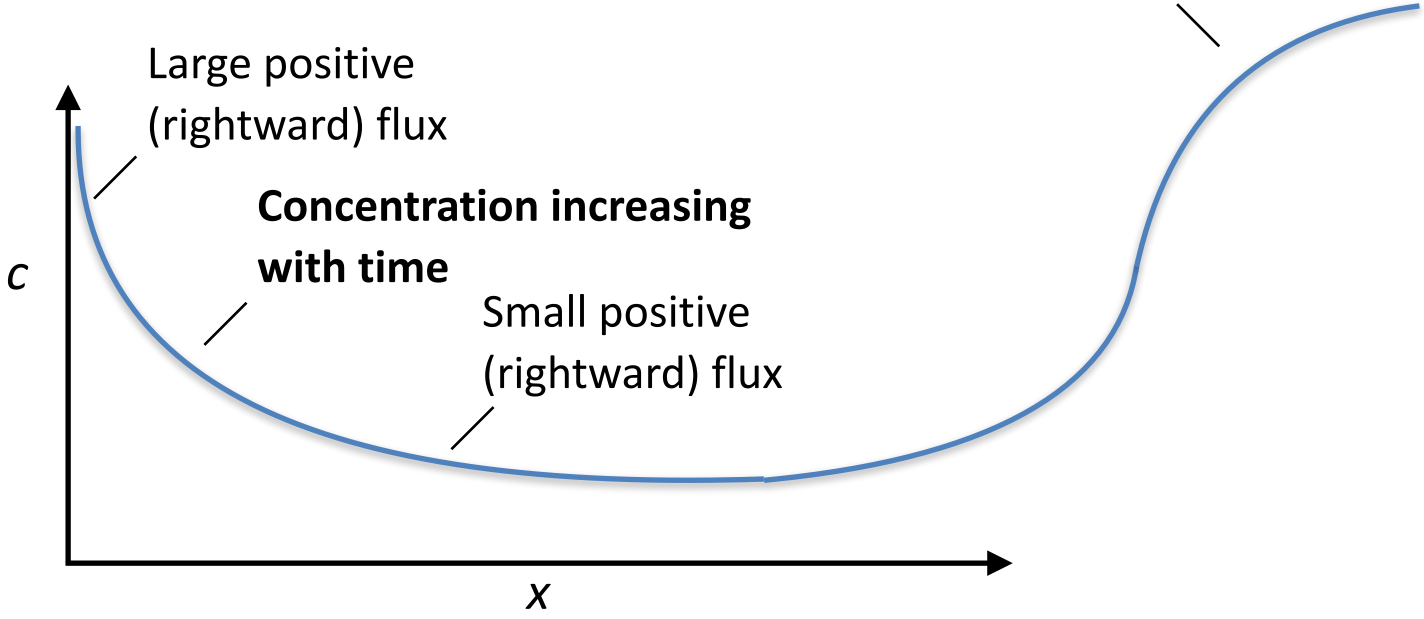
Concentration decreasing with time
Large positive (rightward) flux
Concentration increasing with time
Small positive (rightward) flux
c
x

Diffusion Equation (or Fick's 2nd law)

- Combining these formulae gives us:

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

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



Concentration decreasing with time

Large positive (rightward) flux

Concentration increasing with time

Small positive (rightward) flux

Example

- 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:

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

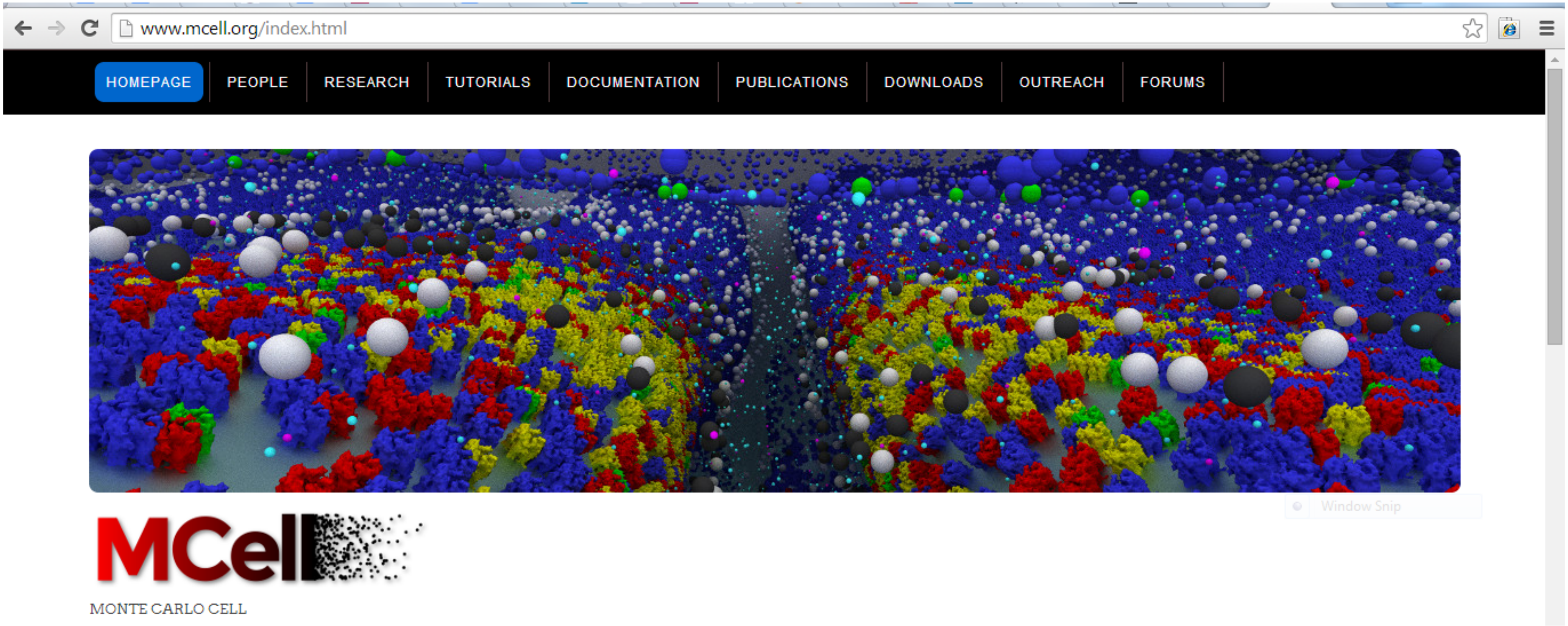
∇^2 is called the Laplacian operator

Simulating diffusion

Reaction-diffusion simulation

- *Reaction-diffusion simulation* is a common way to model how molecules move within the cell
- 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

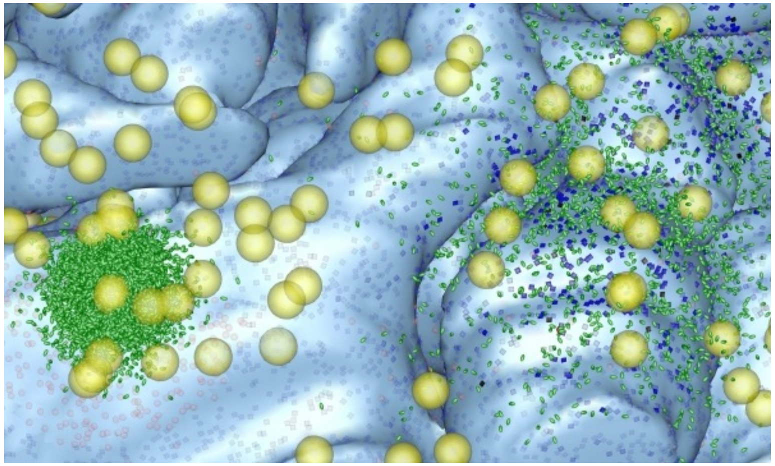
MCell: one of several particle-based simulation software packages



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
- Shape of cell membranes (and other cellular structures) represented by a mesh



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

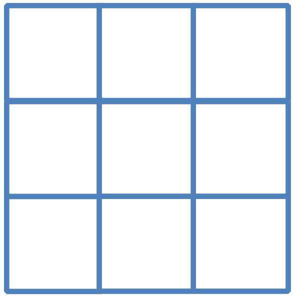
Naomi Latorraca

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)

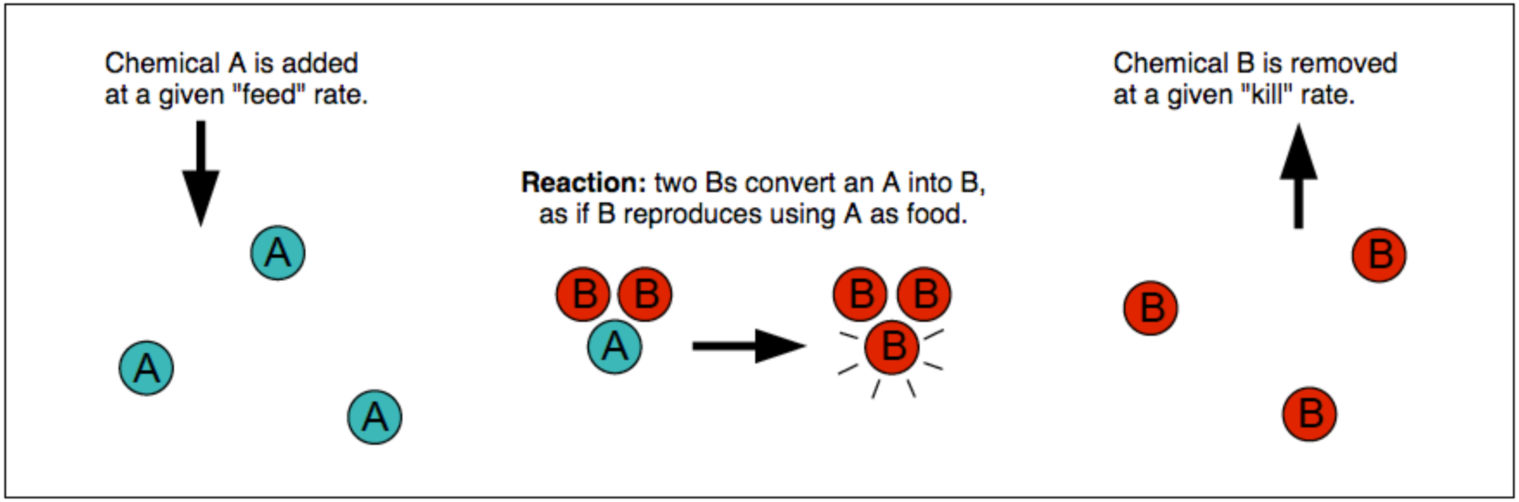


2D grid for illustrative purposes
In a 3D grid, the individual boxes are “voxels”

Continuum approach

- Advantage: faster
- 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

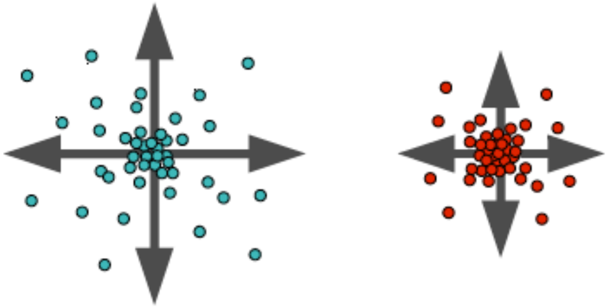


Chemical A is added at a given "feed" rate.

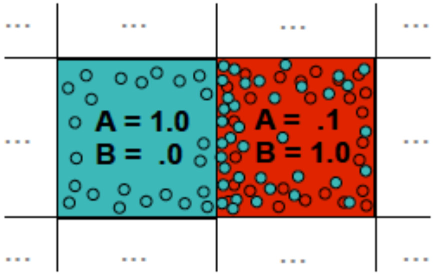
Reaction: two Bs convert an A into B, as if B reproduces using A as food.

Chemical B is removed at a given "kill" rate.

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



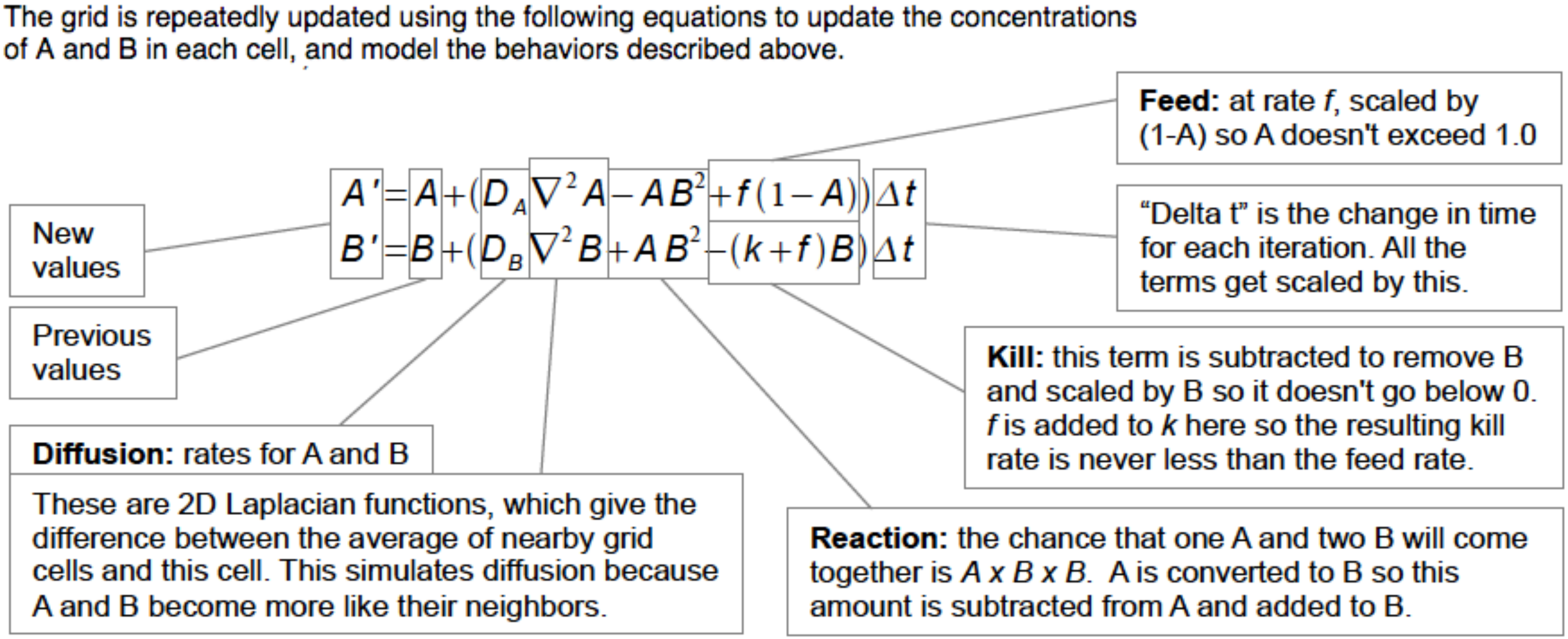
The system is approximated by using two numbers at each grid cell for the local concentrations of A and B.



You’re not responsible for these details

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

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.

$$A' = A + (D_A \nabla^2 A - AB^2 + f(1-A))\Delta t$$

$$B' = B + (D_B \nabla^2 B + AB^2 - (k+f)B)\Delta t$$

New values

Previous values

Diffusion: rates for A and B

These are 2D Laplacian functions, which give the difference between the average of nearby grid cells and this cell. This simulates diffusion because A and B become more like their neighbors.

Feed: at rate *f*, scaled by (1-A) so A doesn't exceed 1.0

"Delta t" is the change in time for each iteration. All the terms get scaled by this.

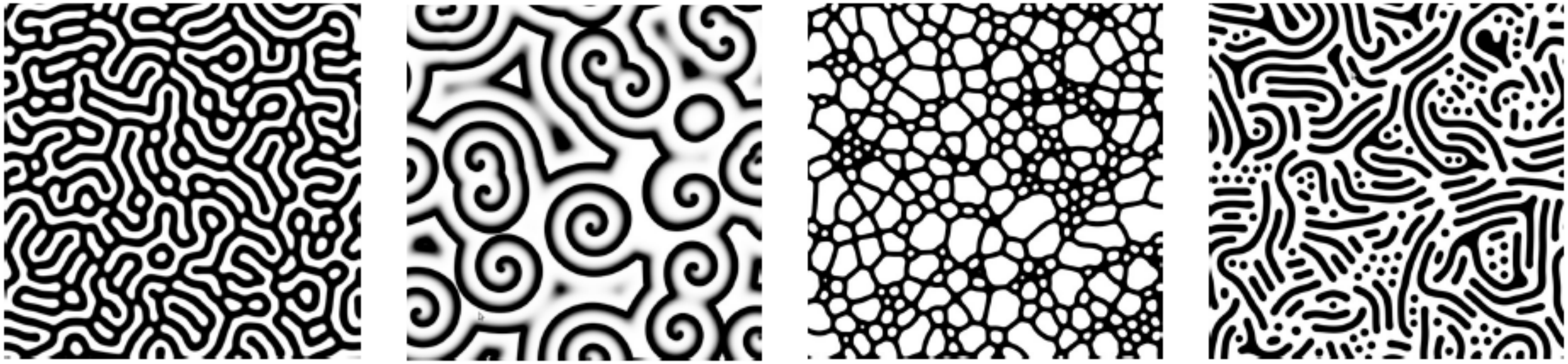
Kill: this term is subtracted to remove B and scaled by B so it doesn't go below 0. *f* is added to *k* here so the resulting kill rate is never less than the feed rate.

Reaction: the chance that one A and two B will come together is *A x B x B*. A is converted to B so this amount is subtracted from A and added to B.

You’re not responsible for these details

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

Gray-Scott model

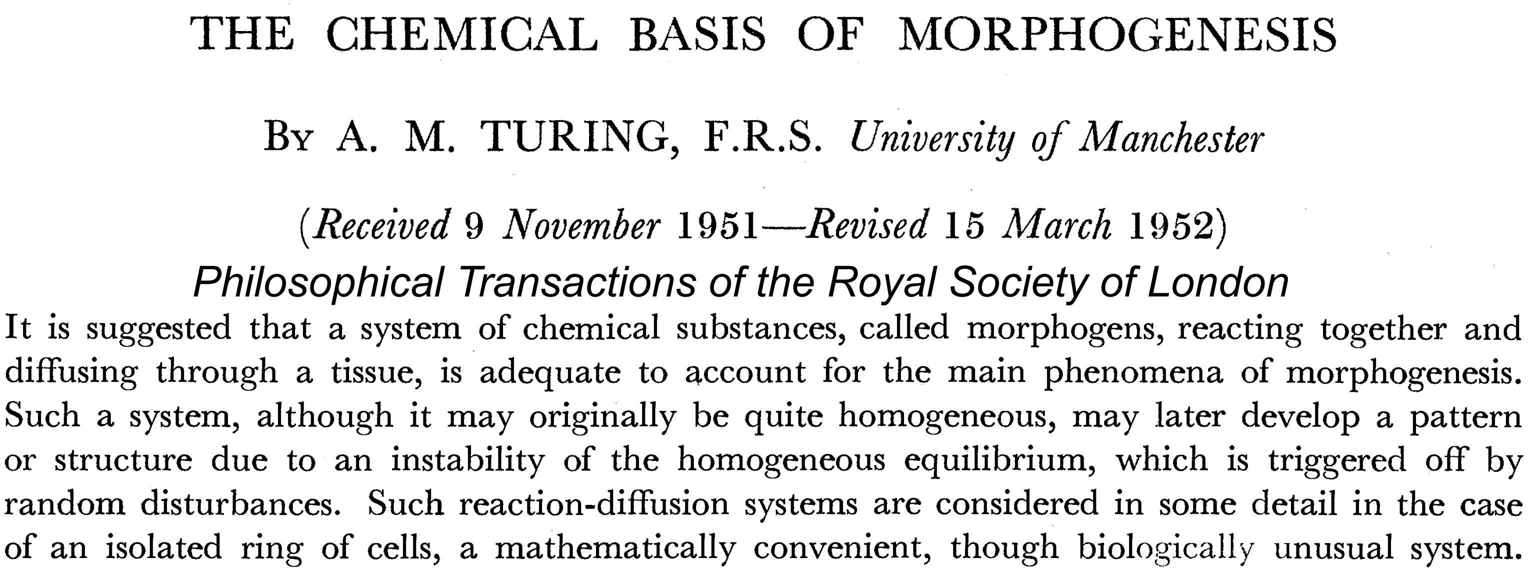


All sorts of interesting patterns emerge as one varies the parameters

Try it out at https://pmneila.github.io/jsexp/grayscott/

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

Alan Turing proposed a similar reaction-diffusion model for pattern formation in animals



THE CHEMICAL BASIS OF MORPHOGENESIS

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

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

Philosophical Transactions of the Royal Society of London

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.

Gray-Scott model

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

Assignment 3

- Due in one week. If you haven’t started, please do.
- We noticed a glitch in the video recording of Coding Tutorial 1. It will be fixed by tomorrow.
- Coding Tutorial 2 (covering additional material) will also take place tomorrow.