Diffusion and cellular-level simulation

CS/CME/BioE/Biophys/BMI 279

Oct. 21 and 26, 2021

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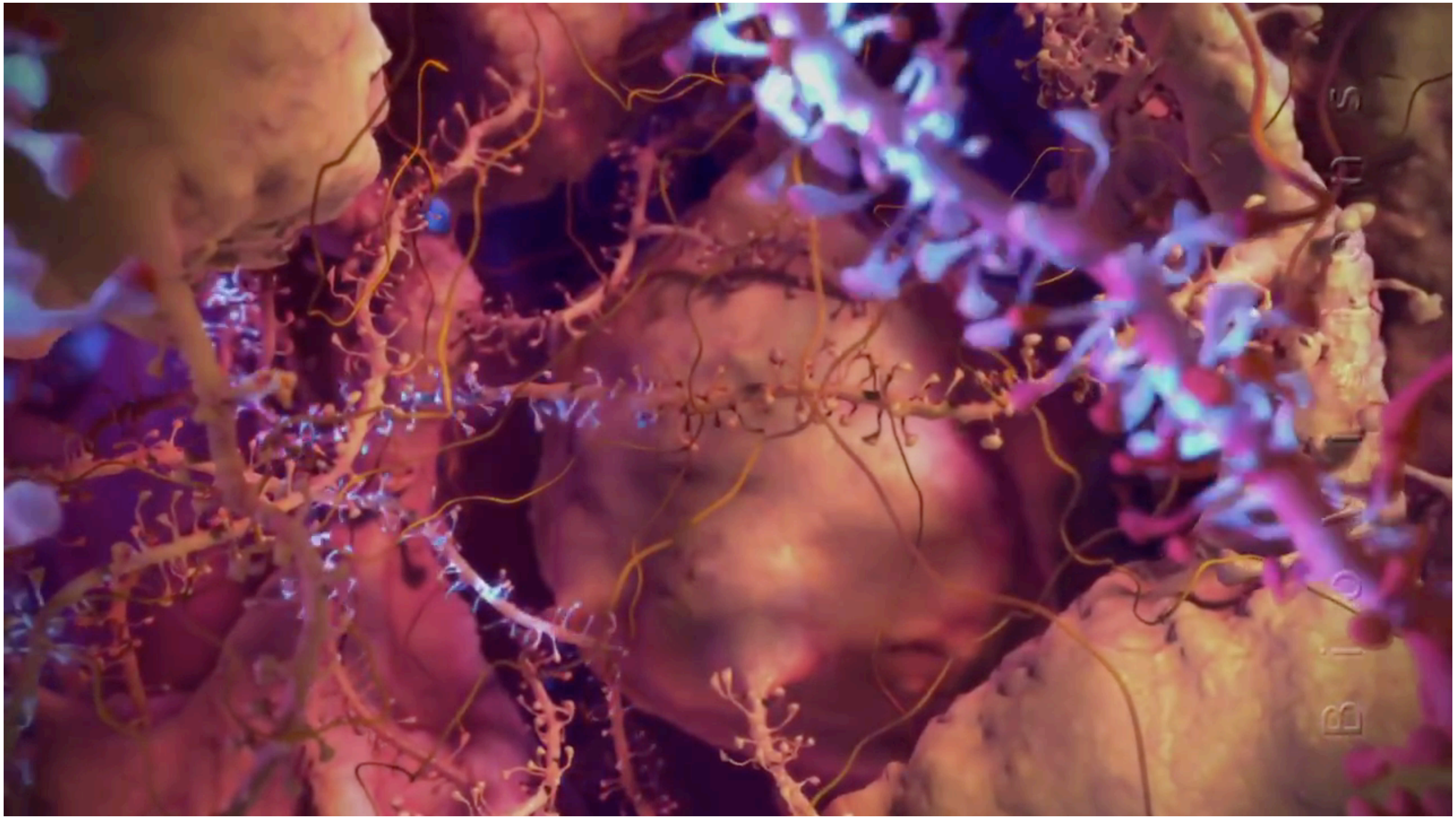
Outline

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

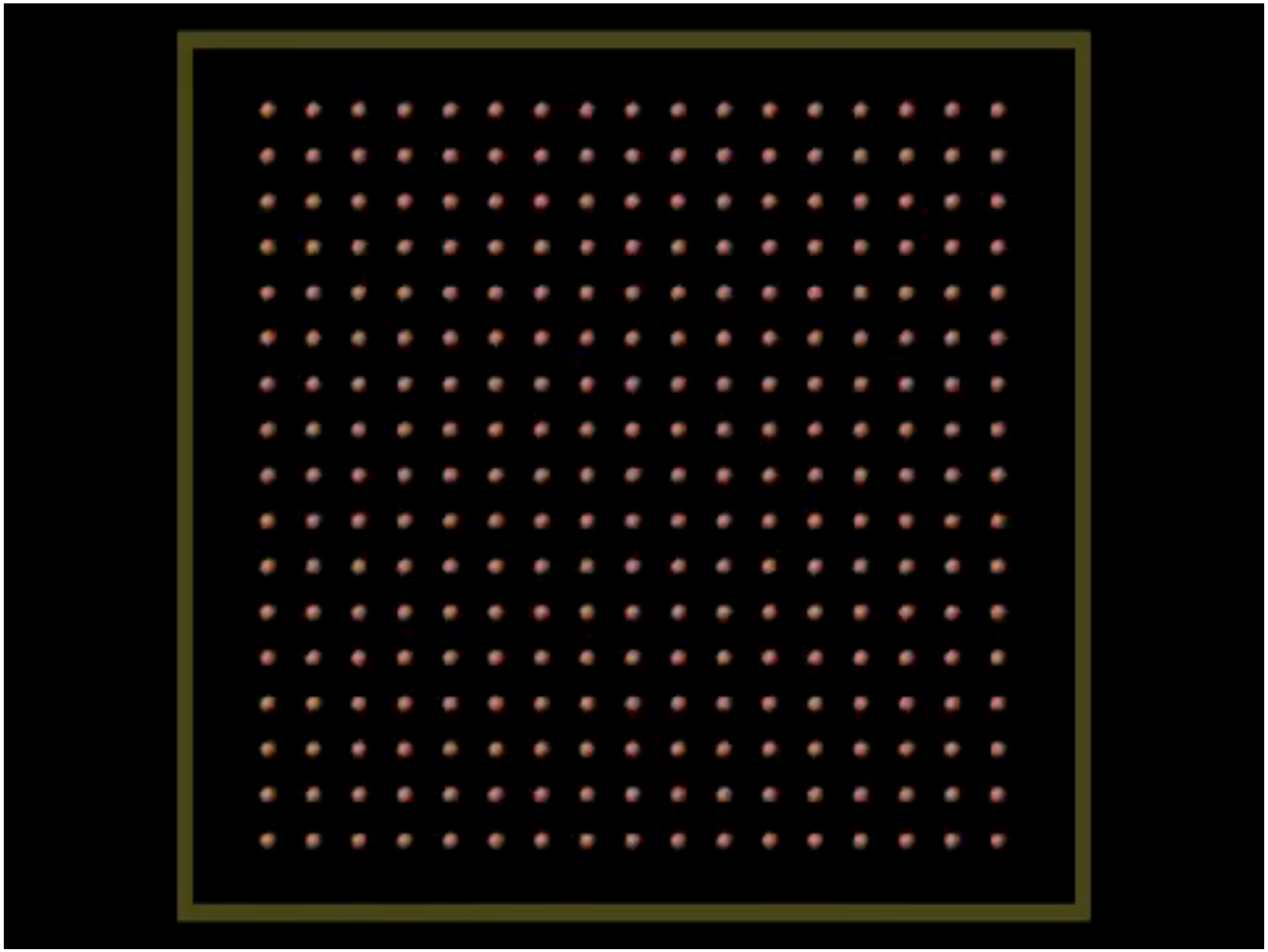
How do molecules move around in a cell?



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

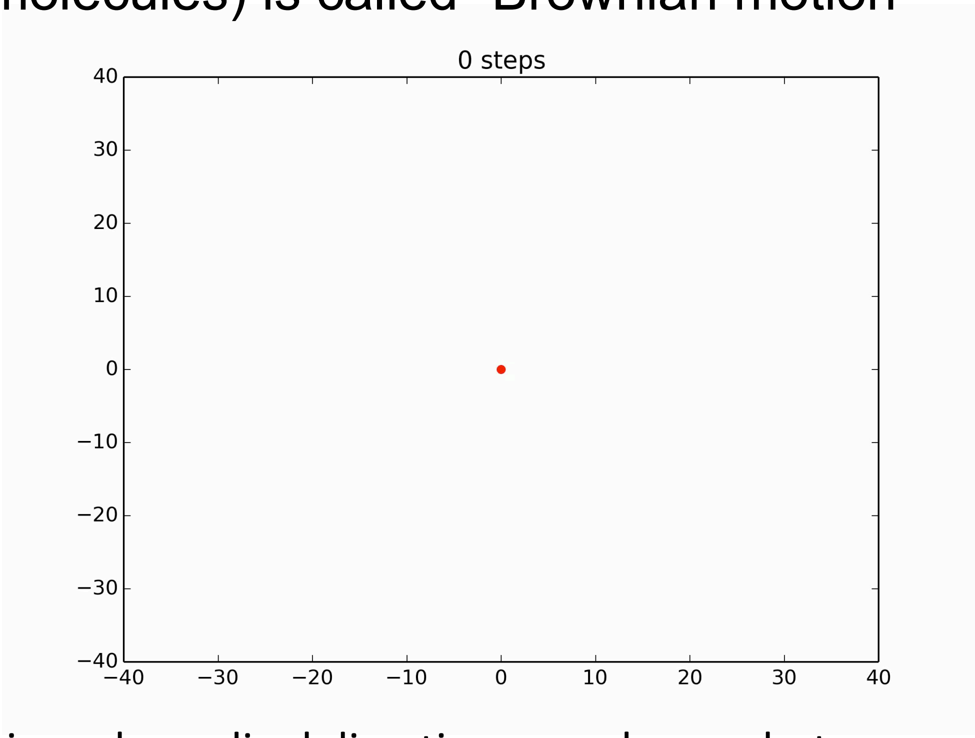
Diffusion

- 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

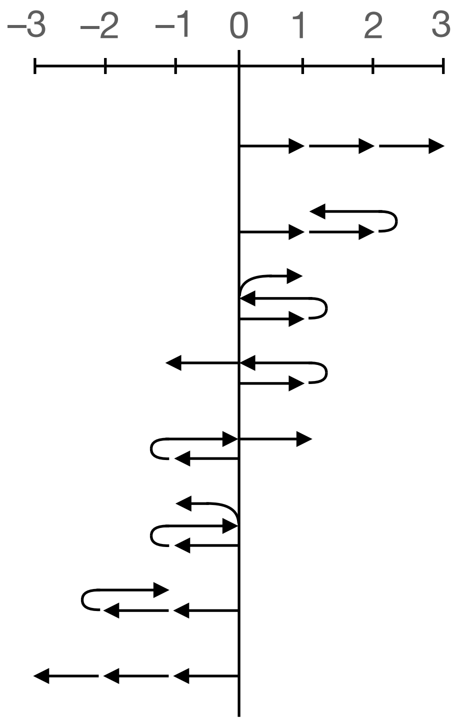
Consider the 1D case (for simplicity)

x_0 refers to the x at time step of 0

- 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}?
  - **Please think about this before the next class!**

Position after 3 time steps (x_3)

Here we have all the different possibilities of the position after 3 time steps



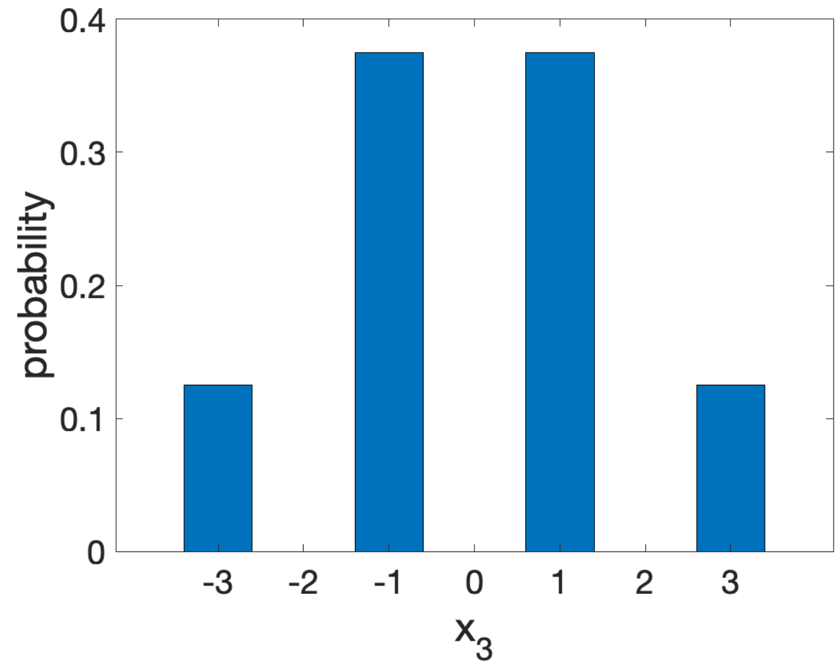
Position (x_3)	$(x_3)^2$
+3	+9
+1	+1
+1	+1
–1	+1
+1	+1
–1	+1
–1	+1
–3	+9
$E[x_3] = 0$	$E[x_3^2] = 3$

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

E[x_N] refers to “expectation” of x_n, which is also known as the mean

Position after 3 time steps (x_3)

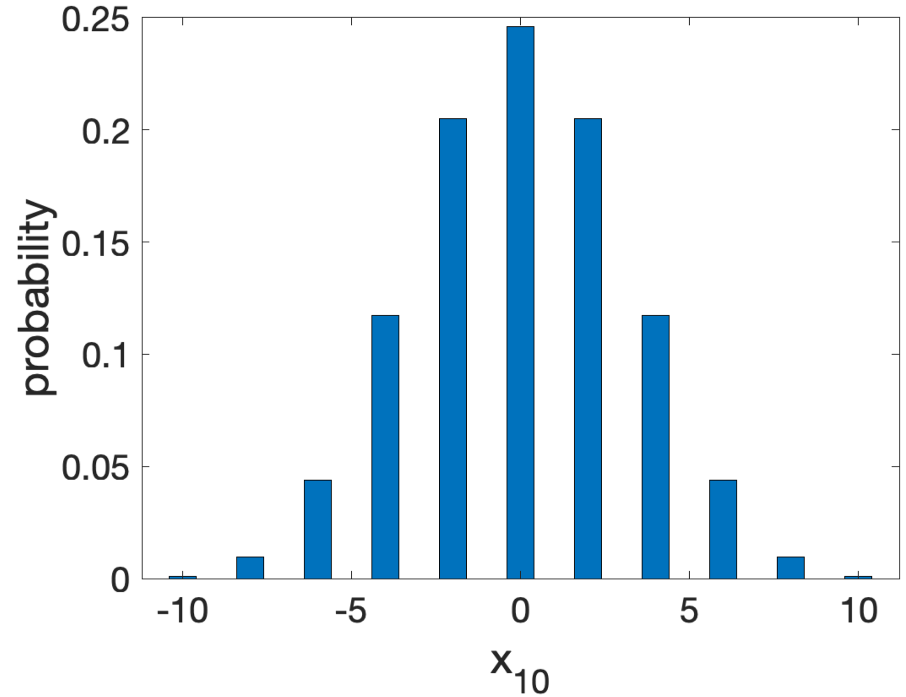
- Probabilities:
  - $P(x_3 = -3) = 1/8$
  - $P(x_3 = -1) = 3/8$
  - $P(x_3 = 1) = 3/8$
  - $P(x_3 = 3) = 1/8$



- 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: $E[x_{10}^2] = 10$



Here we can see the histogram starts looking like a normal/ gaussian distribution

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 Δt denote time step. Then:

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

L = distance moved per time step

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

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

Intuitively, this is because large molecules require more force to change its acceleration

Example values

- Diffusion coefficient (*D*):
  - Sugar: 500 $(\mu m)^2/s$
  - Typical protein: 5 $(\mu m)^2/s$
- 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

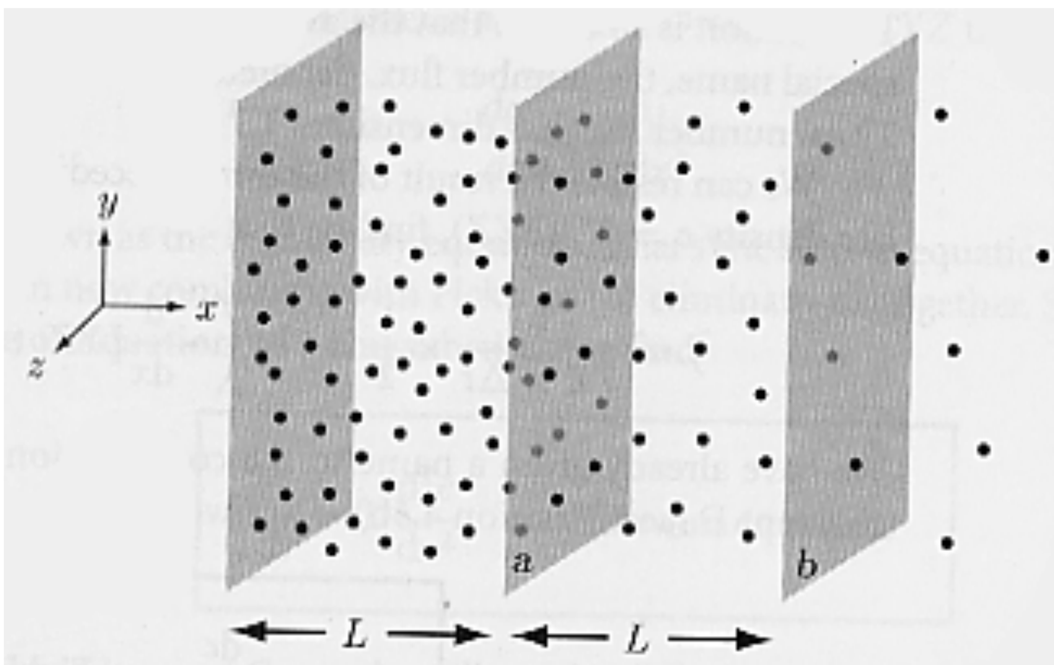
Most molecules diffuse around the cell, but in some cases, molecules are transported through active transporters and proteins

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

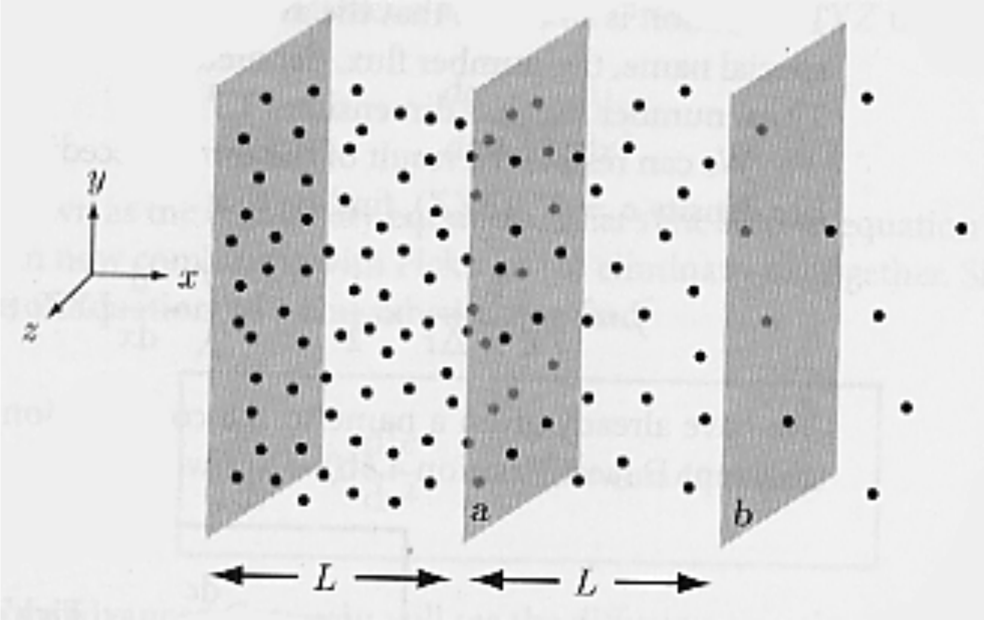


For simplicity in the next several slides, we'll consider that concentration varies along x axis, but not the y or z axes

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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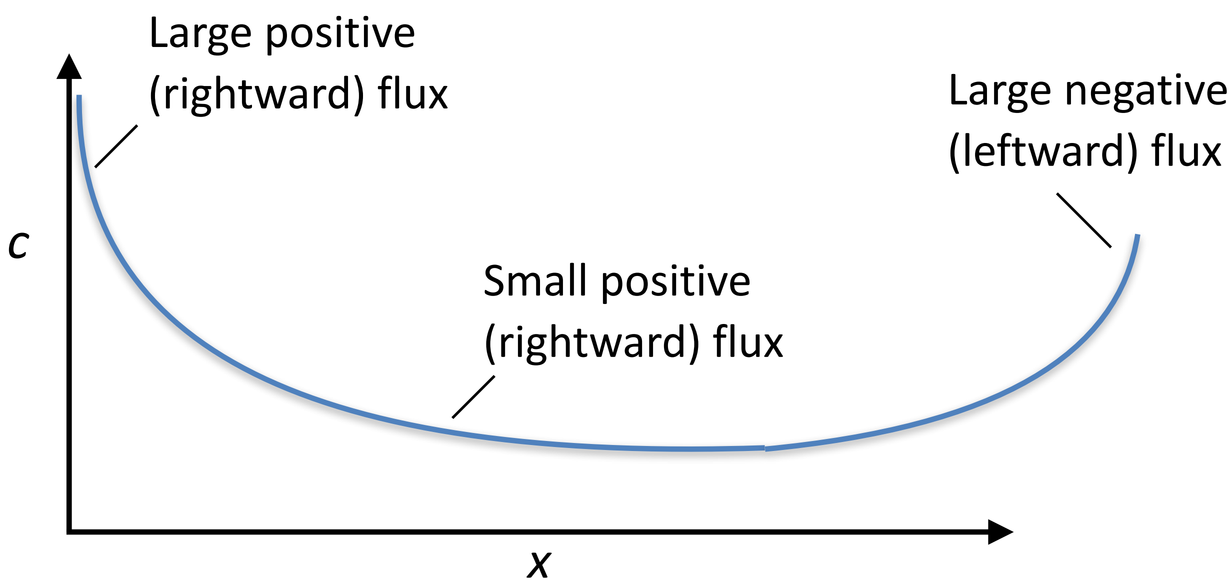
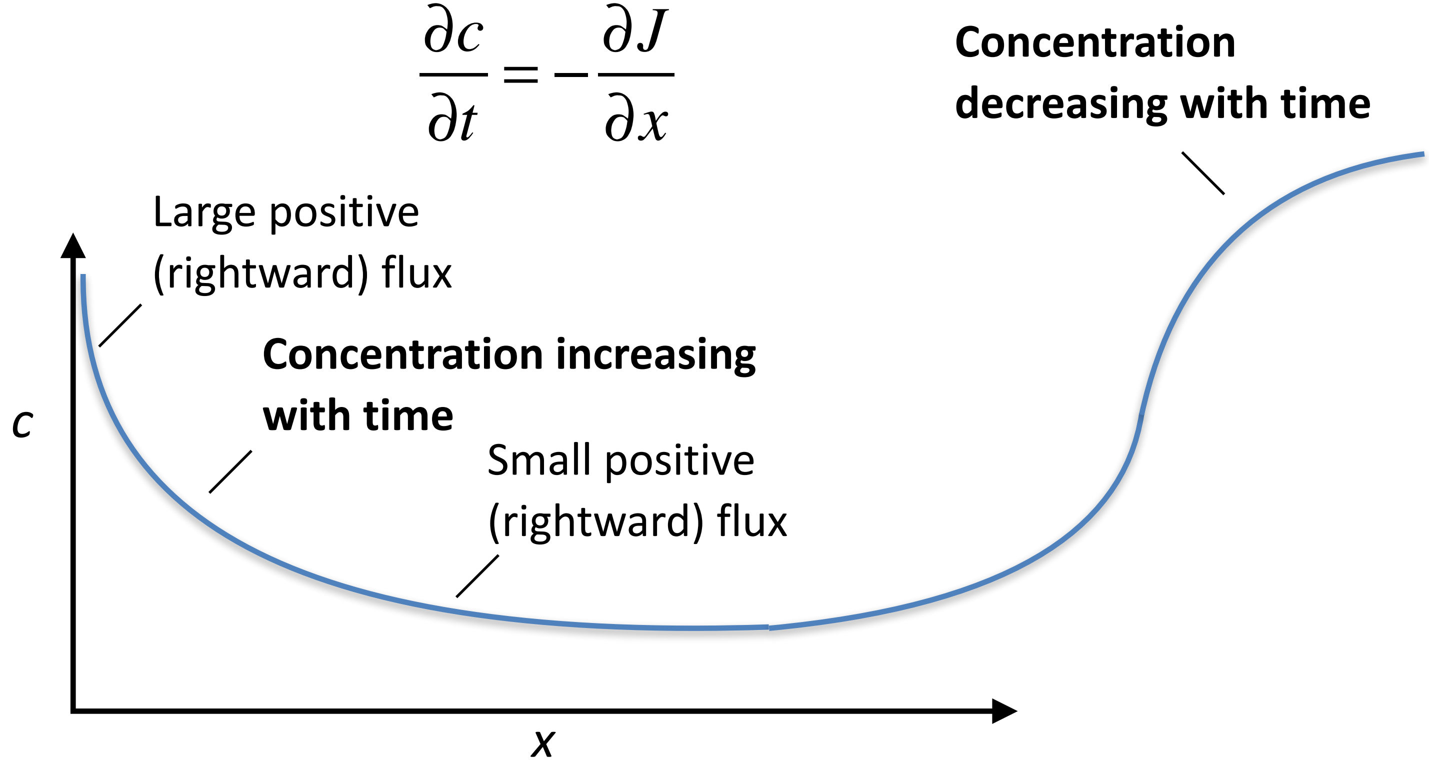
Flux is D times the change in concentration as a function of distance



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 up with time if there is less flux away from that position than there is coming in to that position (in other words, if the flux at that position is decreasing as one moves in the positive *x* direction)

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



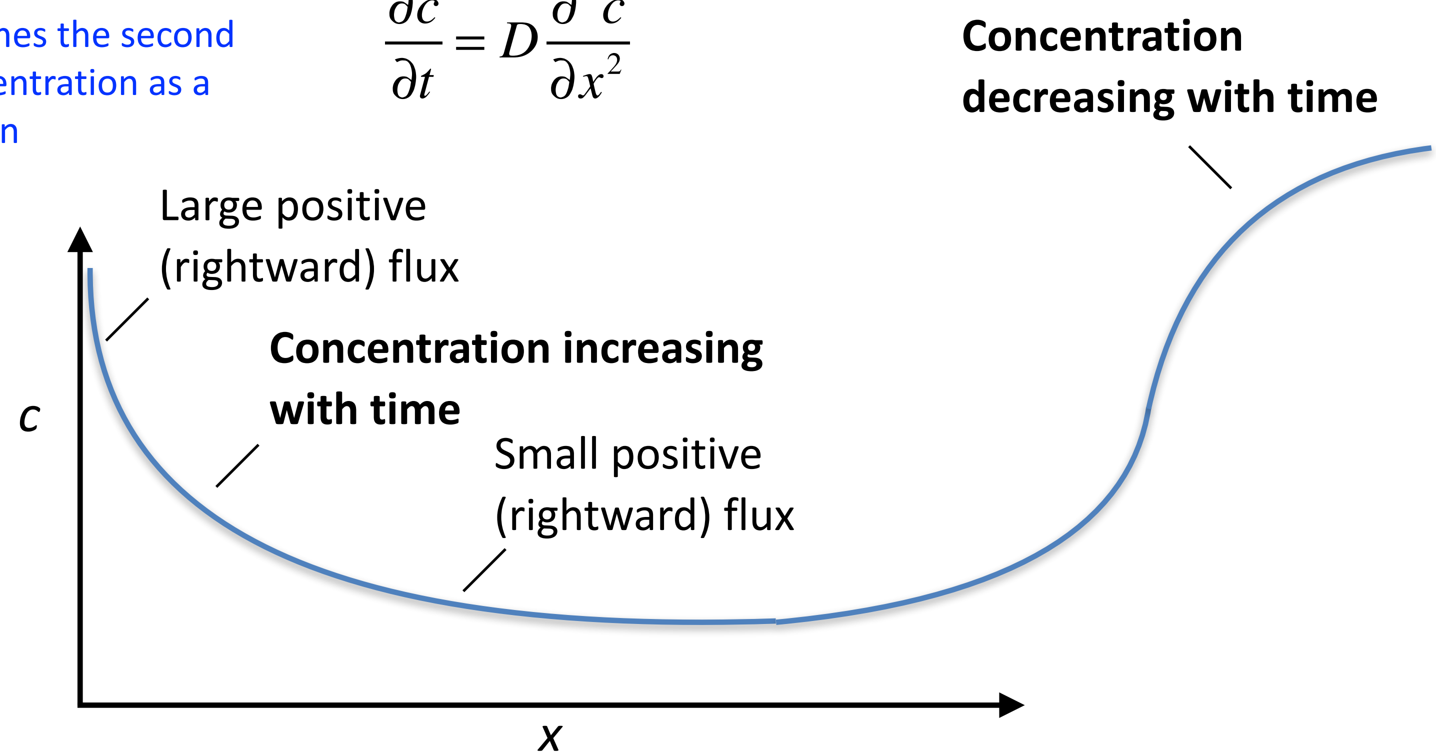
Diffusion Equation (or Fick's 2nd law)

- Combining these formulae gives us:

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

Change in concentration as a function of time is the D times the second derivative of concentration as a function of position

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



Example

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

An example mentioned in class is if you add dye to a bucket, the diffusion of the dye will spread initially, and then slowly as time increases.

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

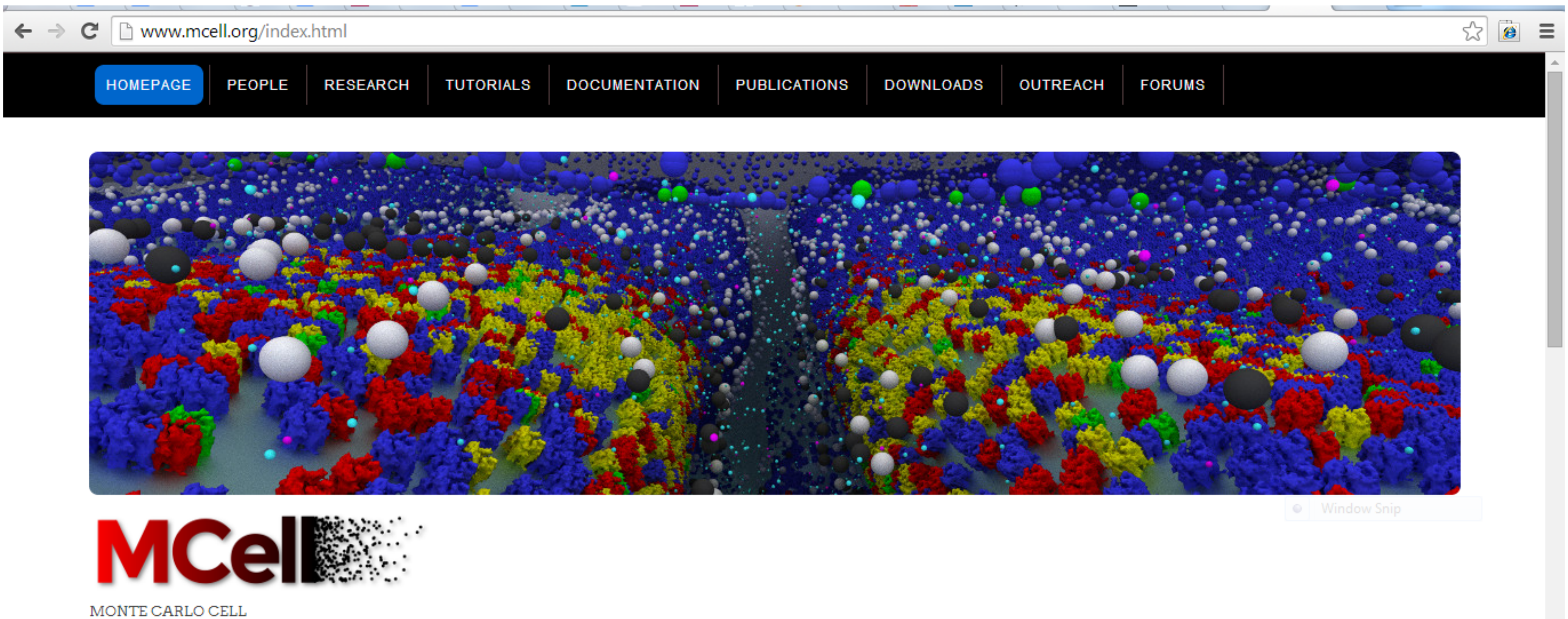
Reaction-diffusion simulation

- *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

An example of 2 molecules combining is if a drug bumps into its target protein, they might react and join together

- Two implementation strategies:
  - Particle-based
  - Continuum models

MCell: one of several particle-based simulation software packages

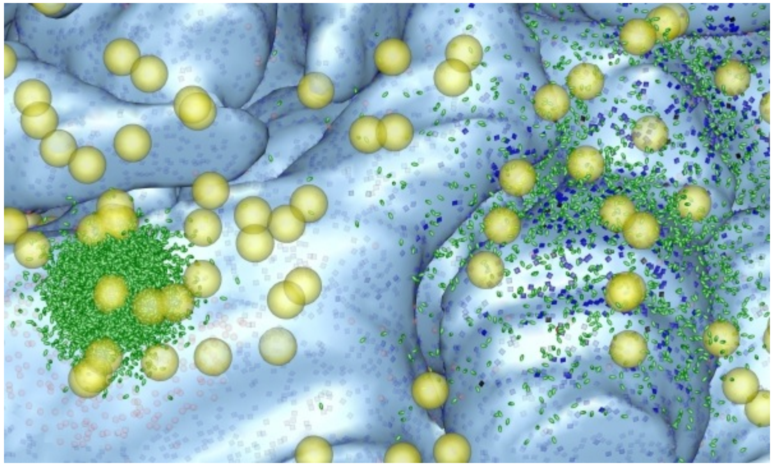


Other similar software packages: Smoldyn, Chemcell

How MCell works

When we talk about molecules, we are disregarding water and only referring to the biomolecules we care about.

- 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

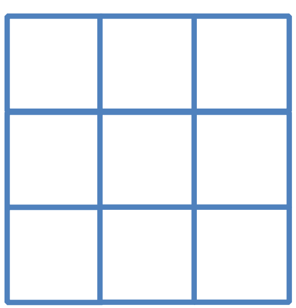
MCell applications

MCell is great for this, because neurotransmitters diffuse across the synapse between neighboring neurons

- 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)



The 2D grid is like pixels on a computer

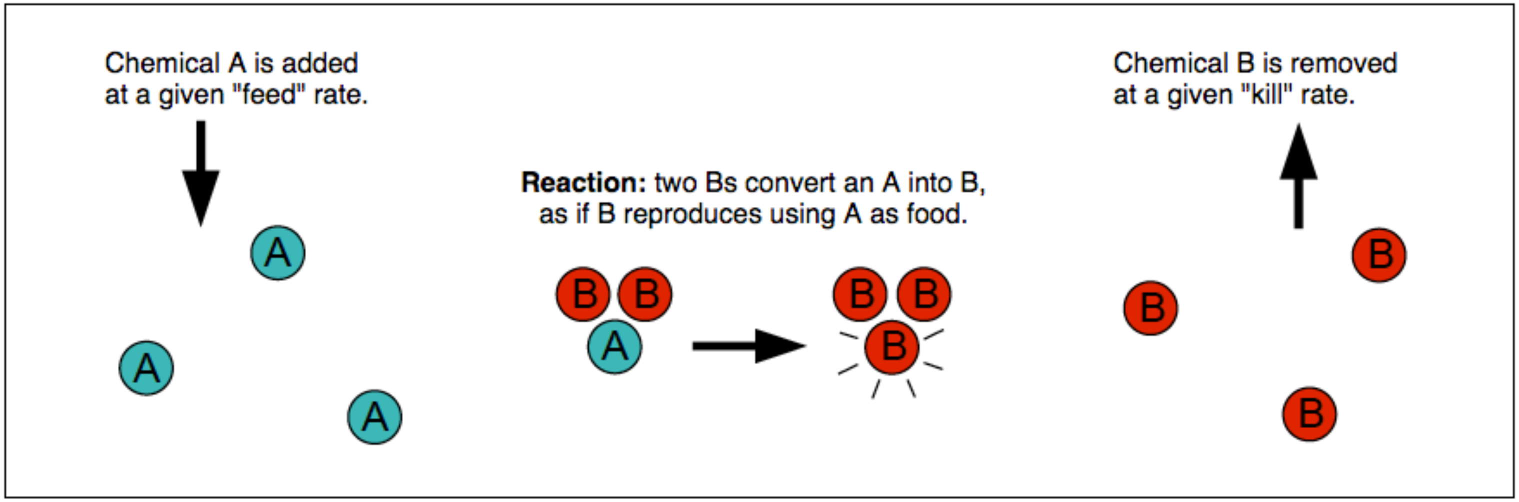
2D grid for illustrative purposes
In a 3D grid, the individual boxes are "voxels"

Continuum approach

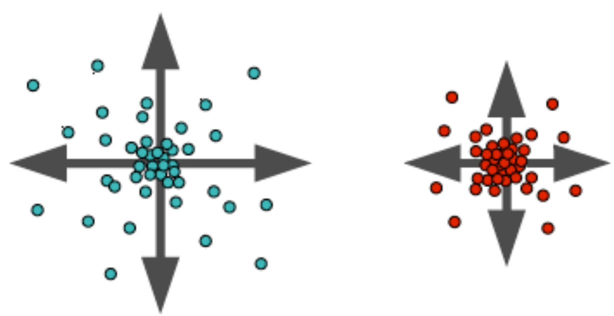
- Advantage: faster
- Disadvantage: less accurate for small numbers of molecules
- Unlike the particle-based approach, the continuum approach is deterministic
- Example software: Simmune

Deterministic means that we will always get the same output because we can neglect the randomness due to small numbers of molecules.

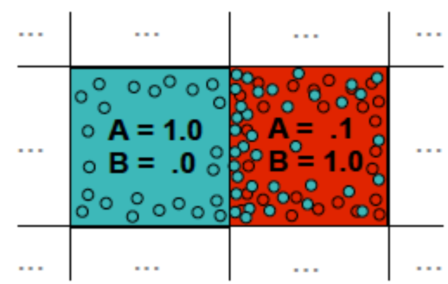
Example: Gray-Scott model



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.



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.

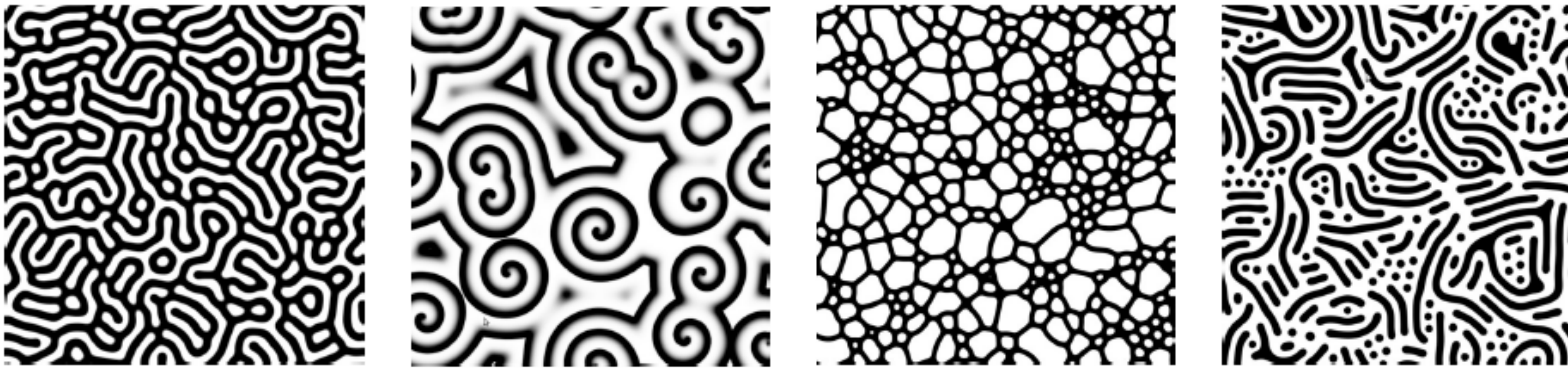
Kill: this term is subtracted to remove B and scaled by B so it doesn't go below 0. *f* is added to *k* here so the resulting kill rate is never less than the feed rate.

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

Some of these patterns resemble those on animals like zebras and giraffes

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

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

Alan Turing on morphogenesis

We still don't understand how patterns on animal skins, but to this day, researchers still use this model for work in this field

- 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

Please fill out the mid-quarter feedback survey

https://forms.gle/rXWfAtYf75S76dK4A

Deadline tonight! Please fill it out now, if you haven’t already.

I appreciate you feedback!

Gray-Scott model

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