Introduction: Cellular-level simulation

CS/CME/Biophys/BMI 371

March 8, 2018

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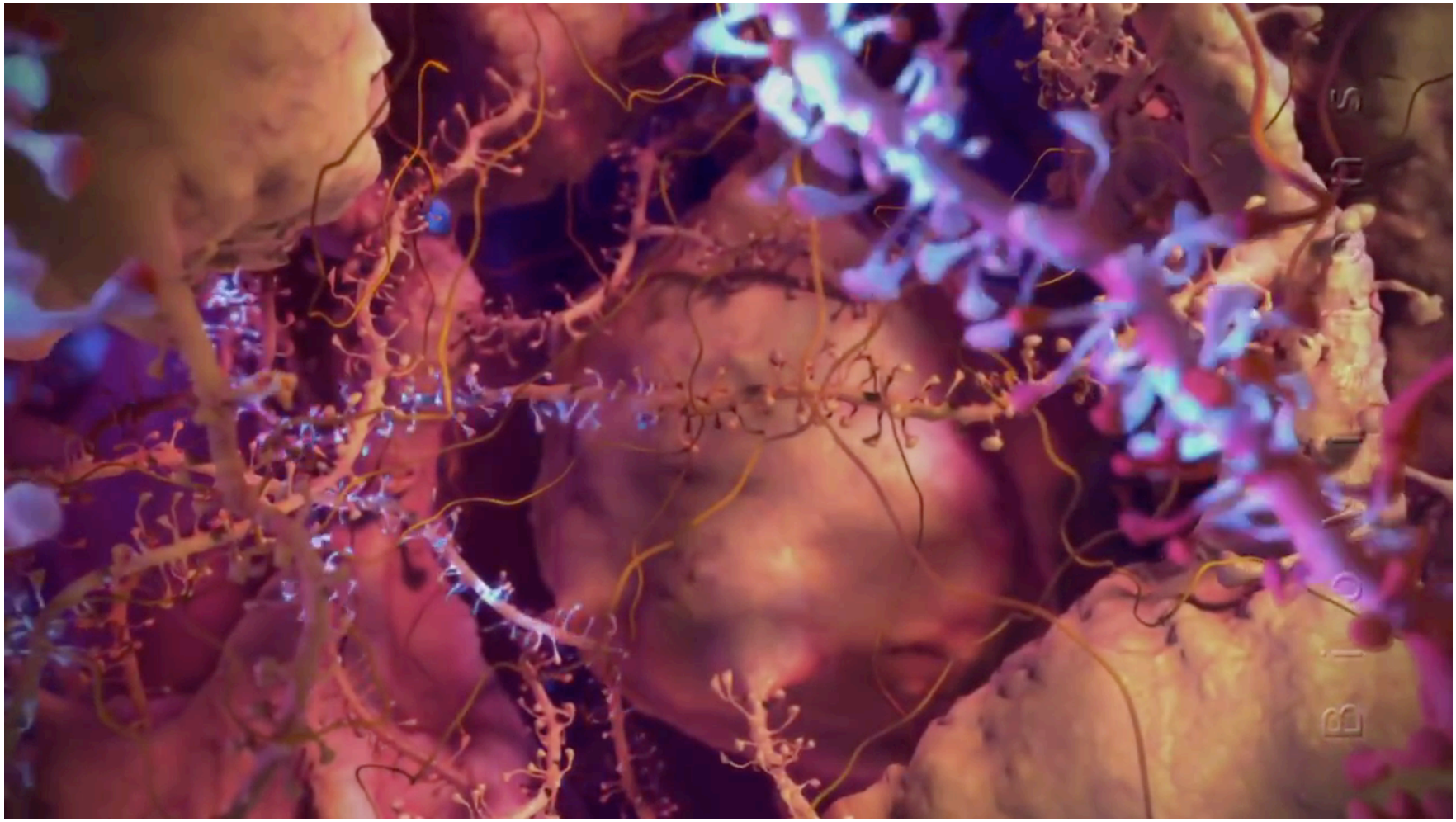
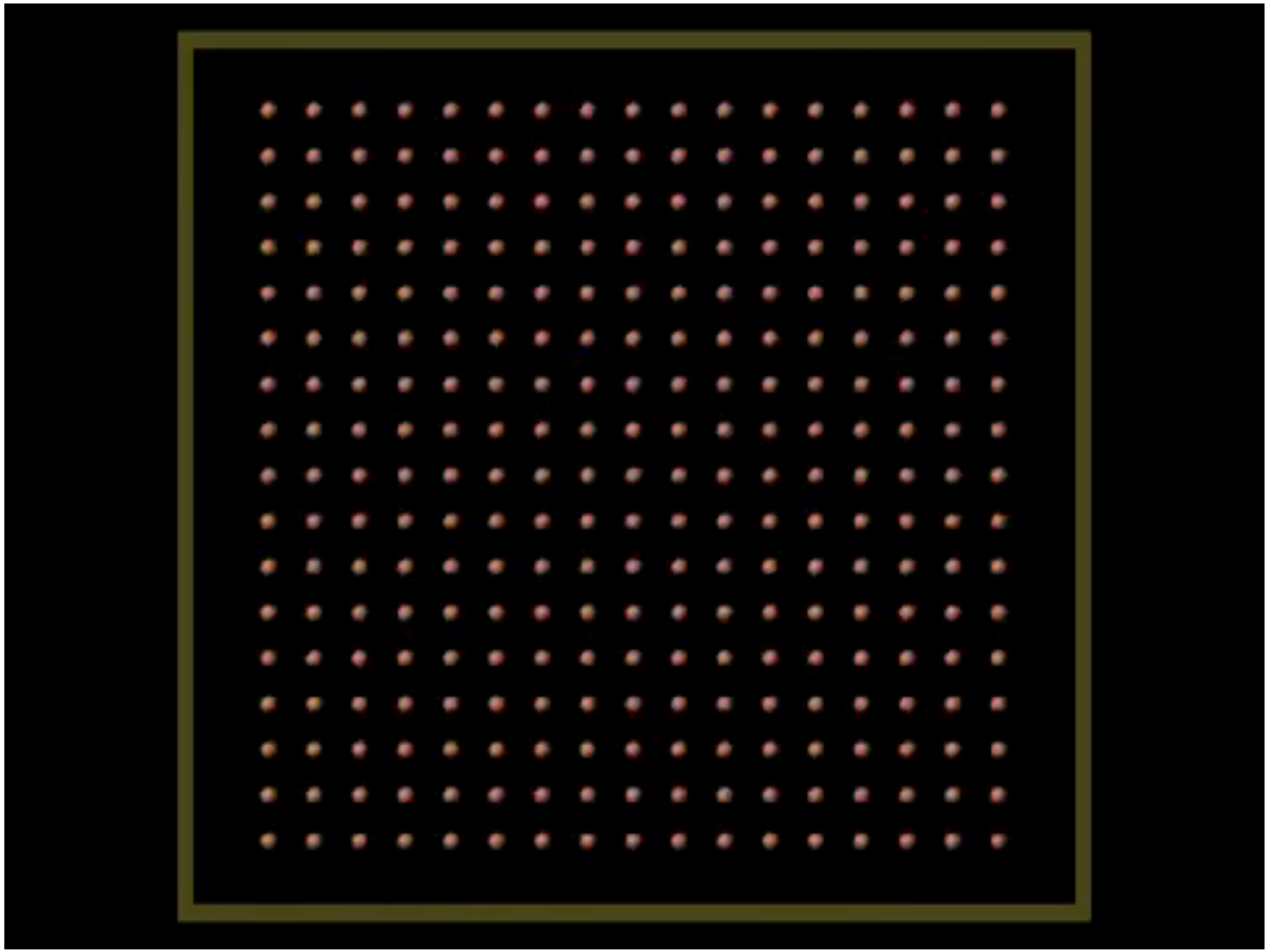


From *Inner Life of the Cell* | *Protein Packing*, XVIVO and Biovisions @ Harvard

- 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

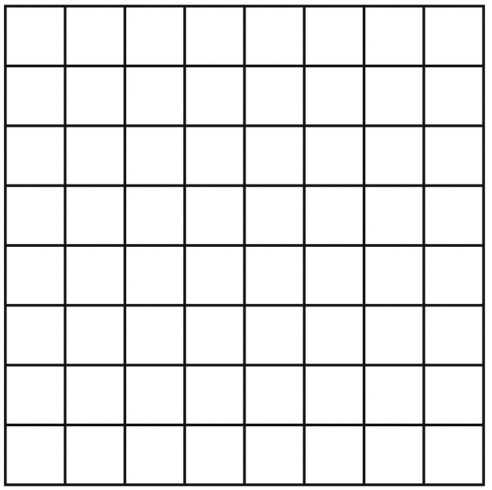
- This “jiggling about” by lots of molecules leads to diffusion
- Individual molecules follow a random walk, due to collisions with surrounding molecules
- Diffusion = many random walks by many molecules
  - Substance goes from region of high concentration to region of lower concentration

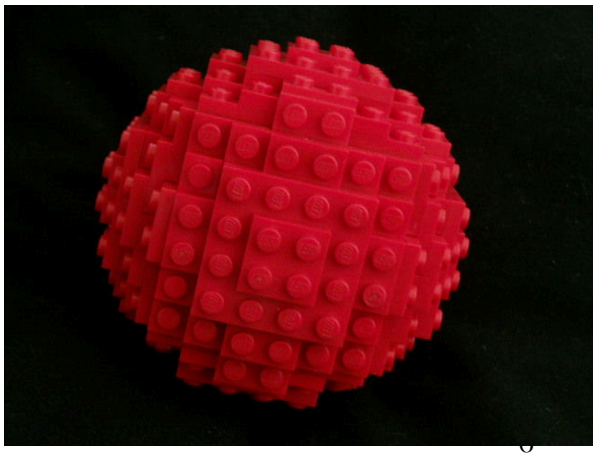
Reaction-diffusion simulation

- 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
- Several implementation strategies:
  - Particle-based (Represent molecules by particles, and track the motion of each one)
  - Continuum models
  - In some (limited) cases, one can solve the partial differential equations analytically

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
- One of the papers we’ll cover uses this approach (via the Virtual Cell platform), together with analytical solutions, to study the effect of cell shape on cell signaling

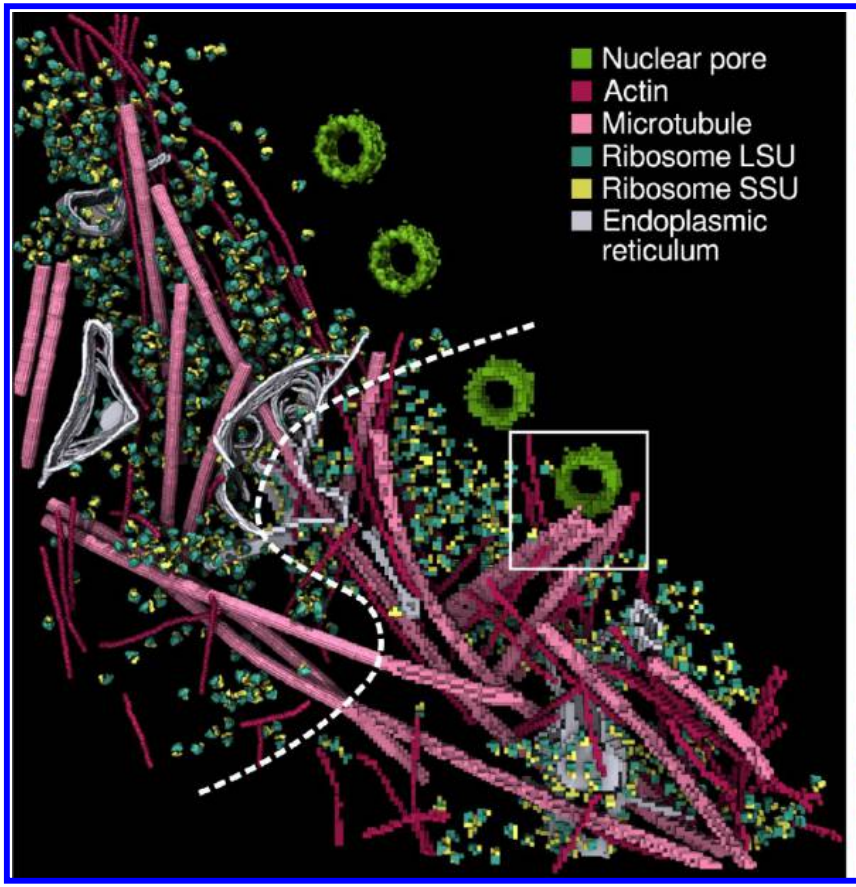




http://www.instructables.com/id/How-to-Make-a-Lego-Ball/

Increasing the realism of cellular-level simulations

- The second paper uses cryo-electron tomography (a variant of cryo-EM) to recover complicated cellular geometries for simulation
- The software employed (Lattice Microbes) uses a voxelized approach, but with “stochastic dynamics”
  - It can represent the exact number of particles (e.g., molecules) of a given type in each voxel, giving improved accuracy when the number of particles is very small
  - It captures the randomness in how particles move



Earnest et al., *J. Phys. Chem. B* 121:3871-3881, 2017

Background information

- Review paper (Models at the single cell level, 2010)
  - http://onlinelibrary.wiley.com/doi/10.1002/wsbm.49/full
- Slides from CS/CME/Biophys/BMI 279:
  - http://web.stanford.edu/class/cs279/lectures/lecture12.pdf