

Computer modeling in biochemistry and cell biology & “What do professors do all day?”

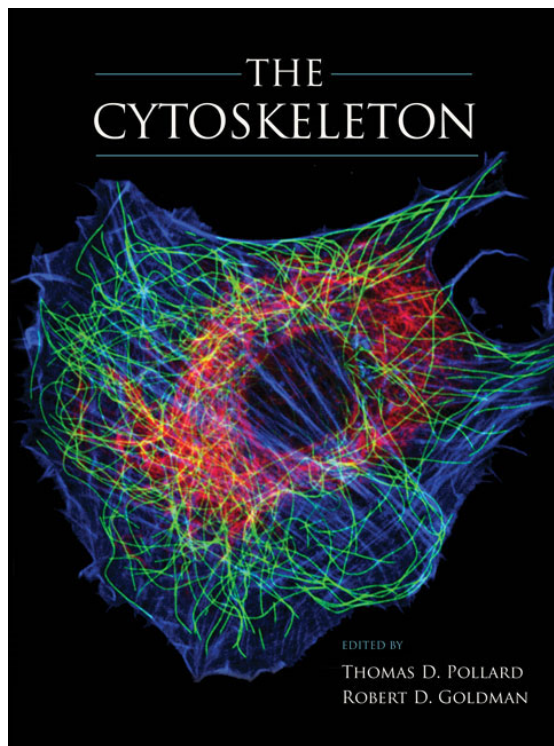
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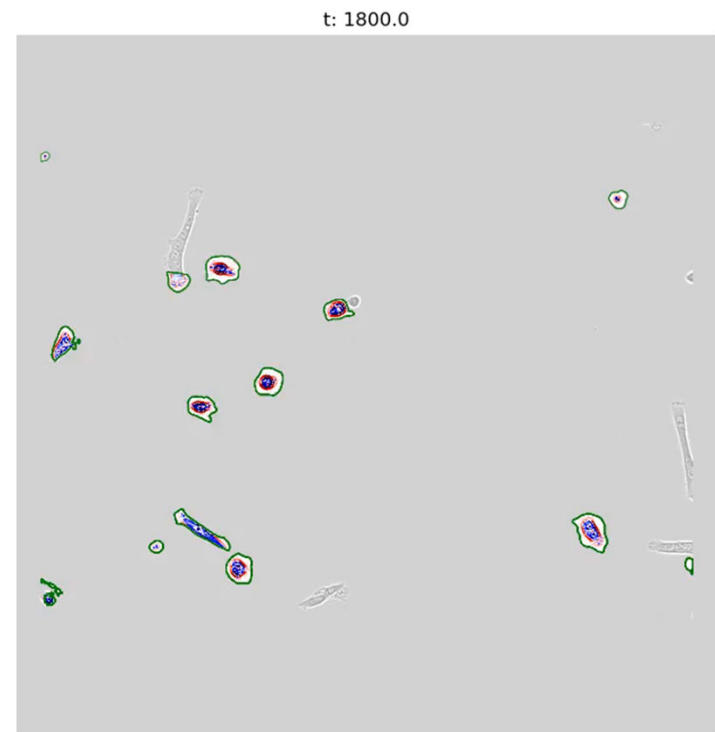
OHSU Center for Spatial Systems Biomedicine

Cells are like magic

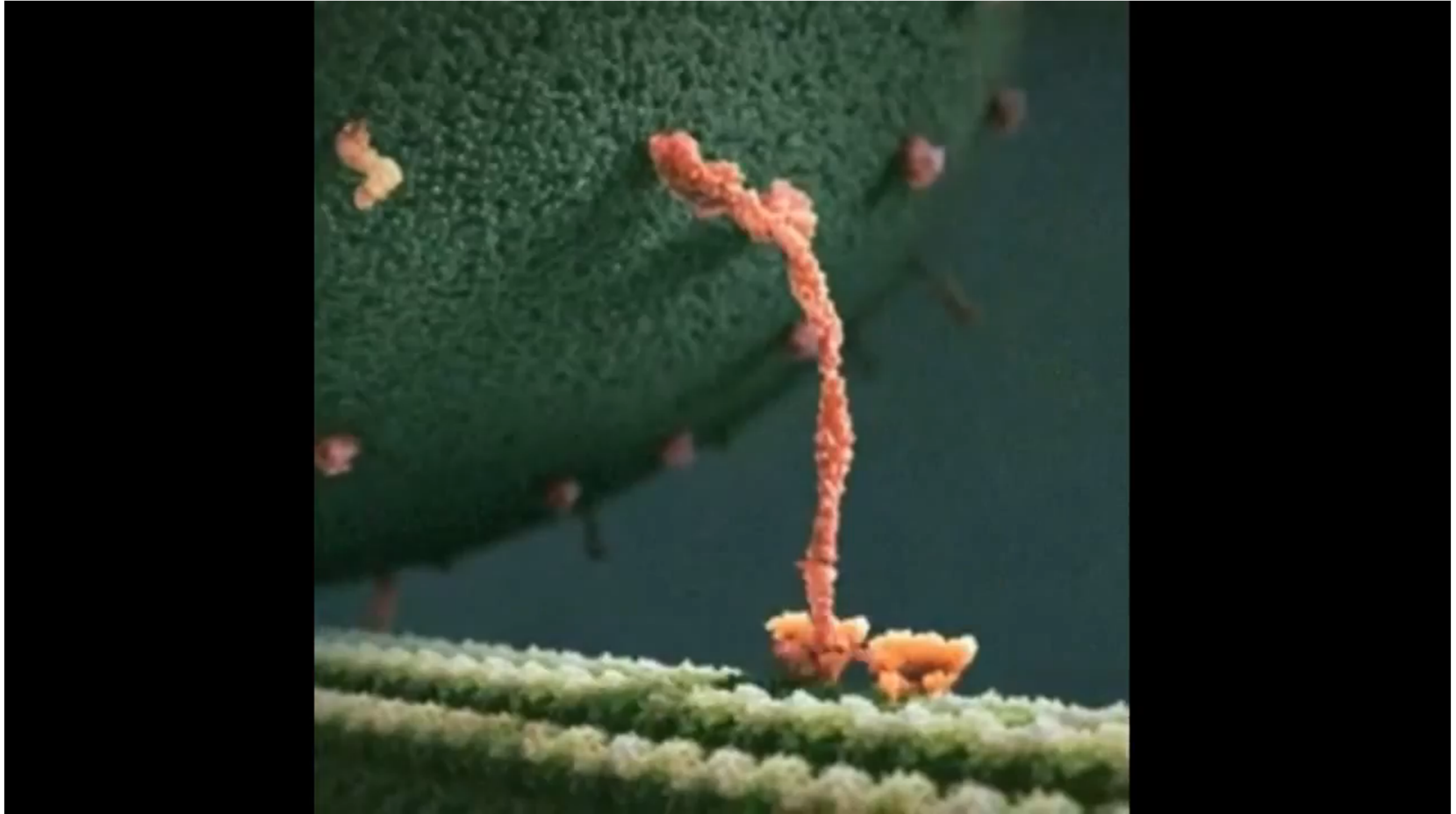
- 48 hour movie
- MCF10A cells in EGF treatment
- Phase contrast only.
- Automated segmentation shown
- Experiment performed by Prof. Laura Heiser's lab



“cyto” = cell



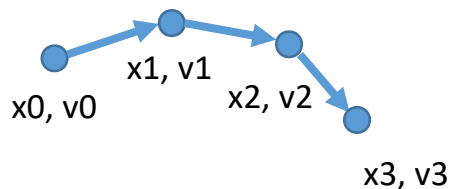
The cell 'runs' using protein 'machines':
Kinesin on microtubule (artistic, not realistic)



Timescale: ~ 0.01 s per step

Molecular Dynamics

Newton: $f = m \cdot a$



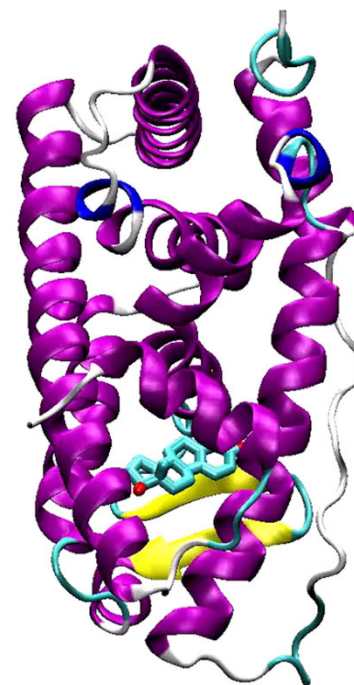
Trajectory Algorithm

$$x_{\text{new}} = x_{\text{old}} + v_{\text{old}} \cdot \Delta t$$

$$v_{\text{new}} = v_{\text{old}} + (f_{\text{old}}/m) \cdot \Delta t$$

Key application – Drug design
on/off rates

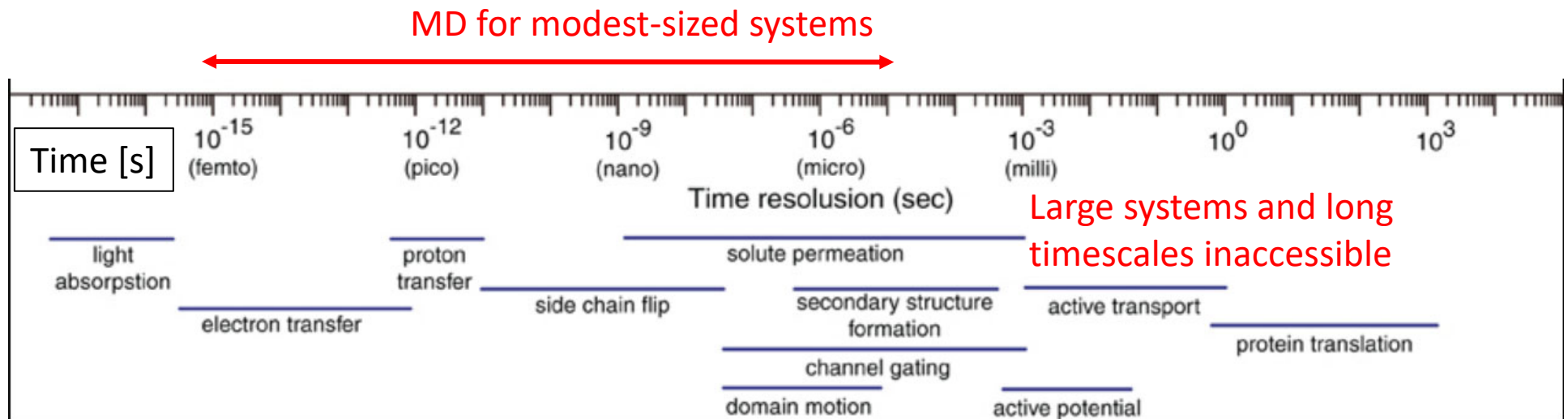
Key limitations: Computers are too slow!



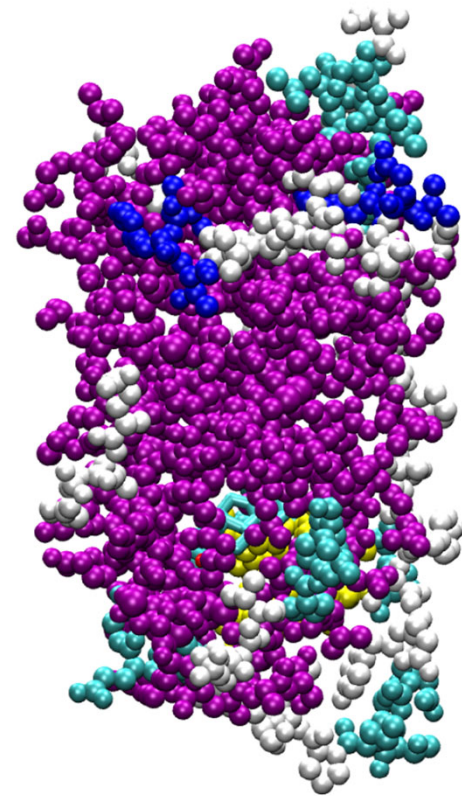
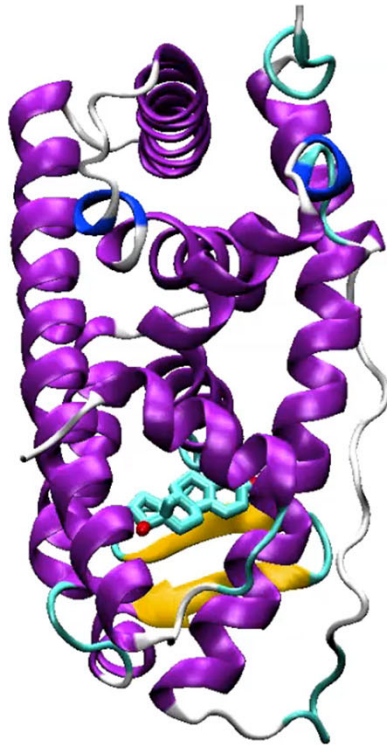
Estrogen Receptor LBD with estradiol

The problem with too-short movies

- Data is not reliable if timescales are inadequate



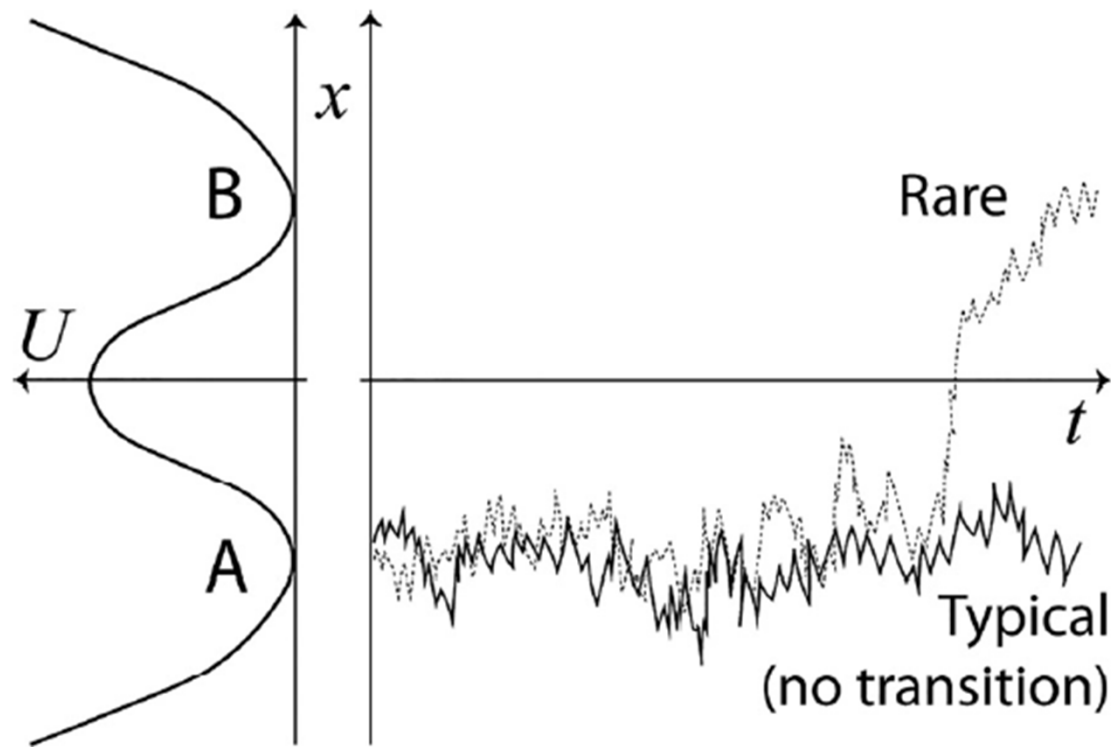
MD Simulation (100 ns)



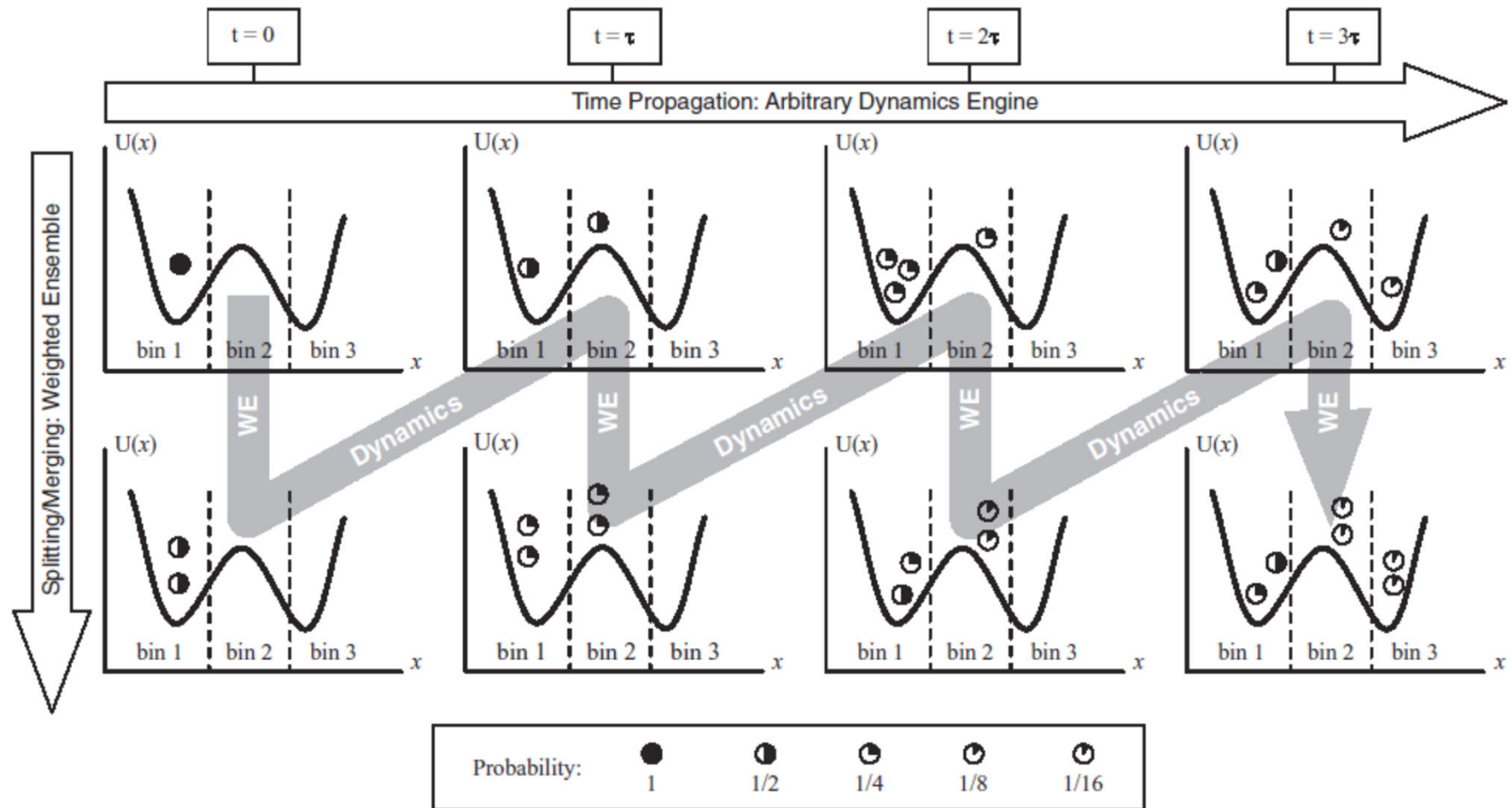
Showing all atoms

Estrogen receptor alpha (ligand-binding domain) with estrogen

Energy landscape: Downhill easier than uphill! Transitions over barriers are rare

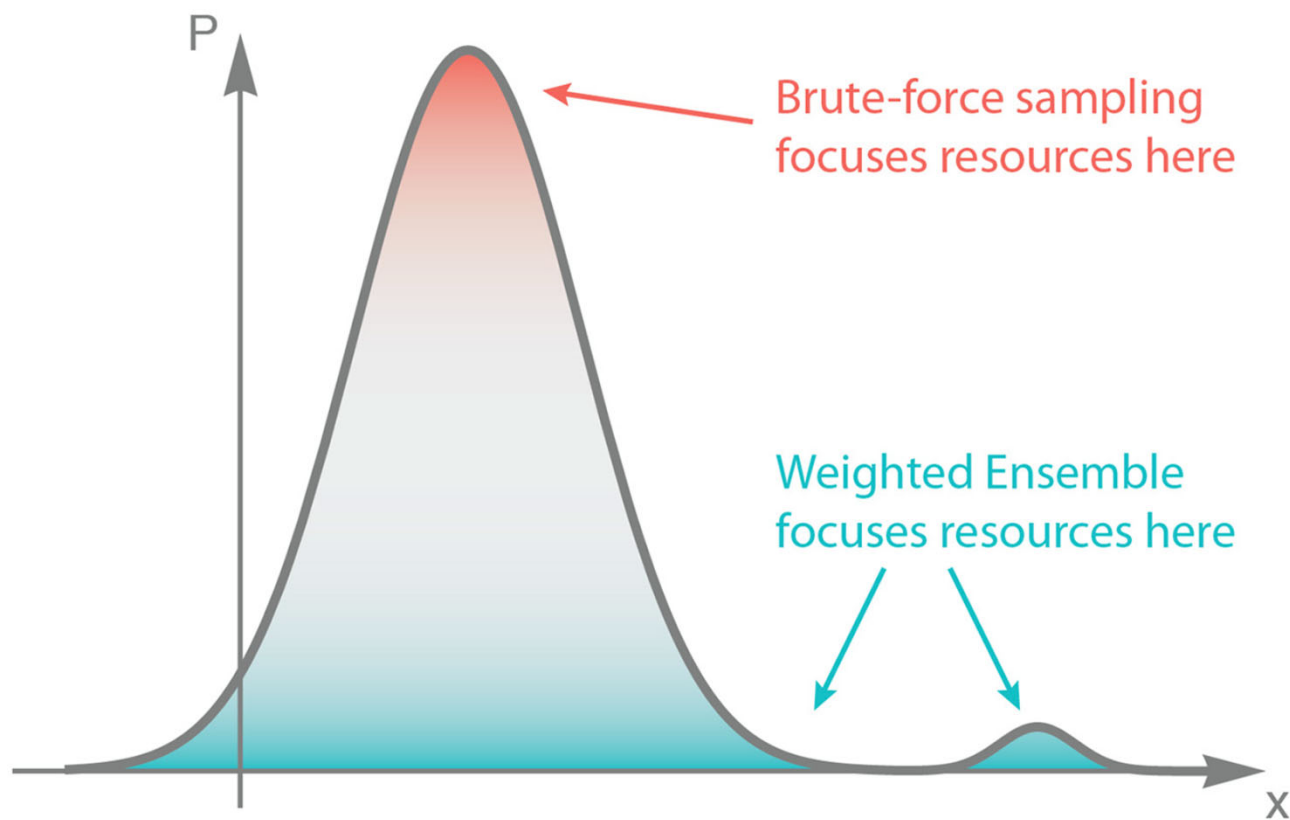


Weighted Ensemble (WE) – “statistical ratchet”



[Original Weighted Ensemble: Huber & Kim, *Biophys J.* 1996;
Figure from Donovan et al., *J Chem Phys* 2013]

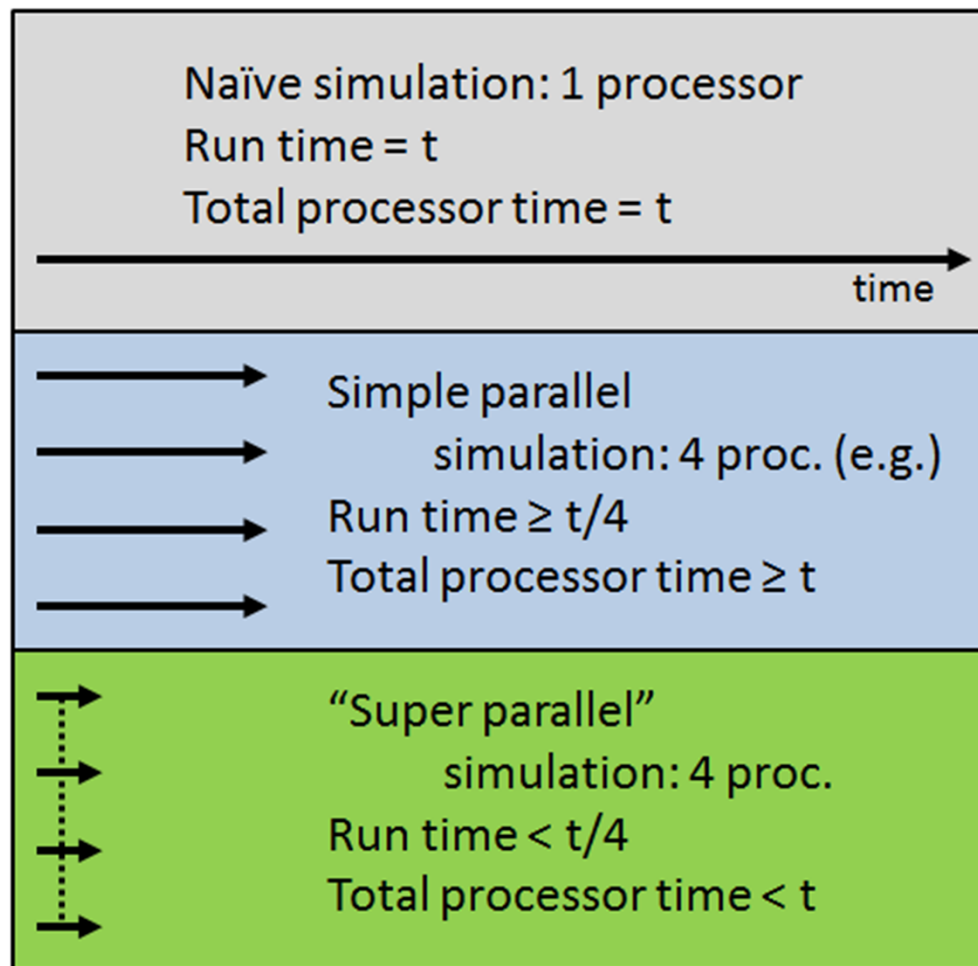
Weighted ensemble can sample “rare events” with high precision – and no bias



[Donovan, Tapia, Sullivan, Faeder, Murphy, Dittrich, Zuckerman, PLoS Comp Bio, 2016]

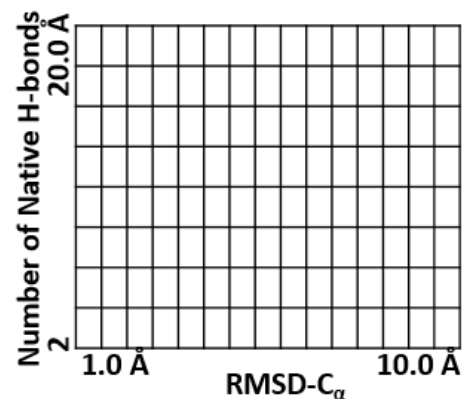
Super-Parallelism

a.k.a. Super-linear performance

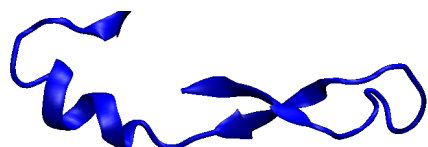


Schematic of time for estimating observables to targeted precision

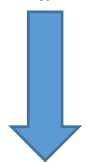
Protein Folding by Weighted Ensemble



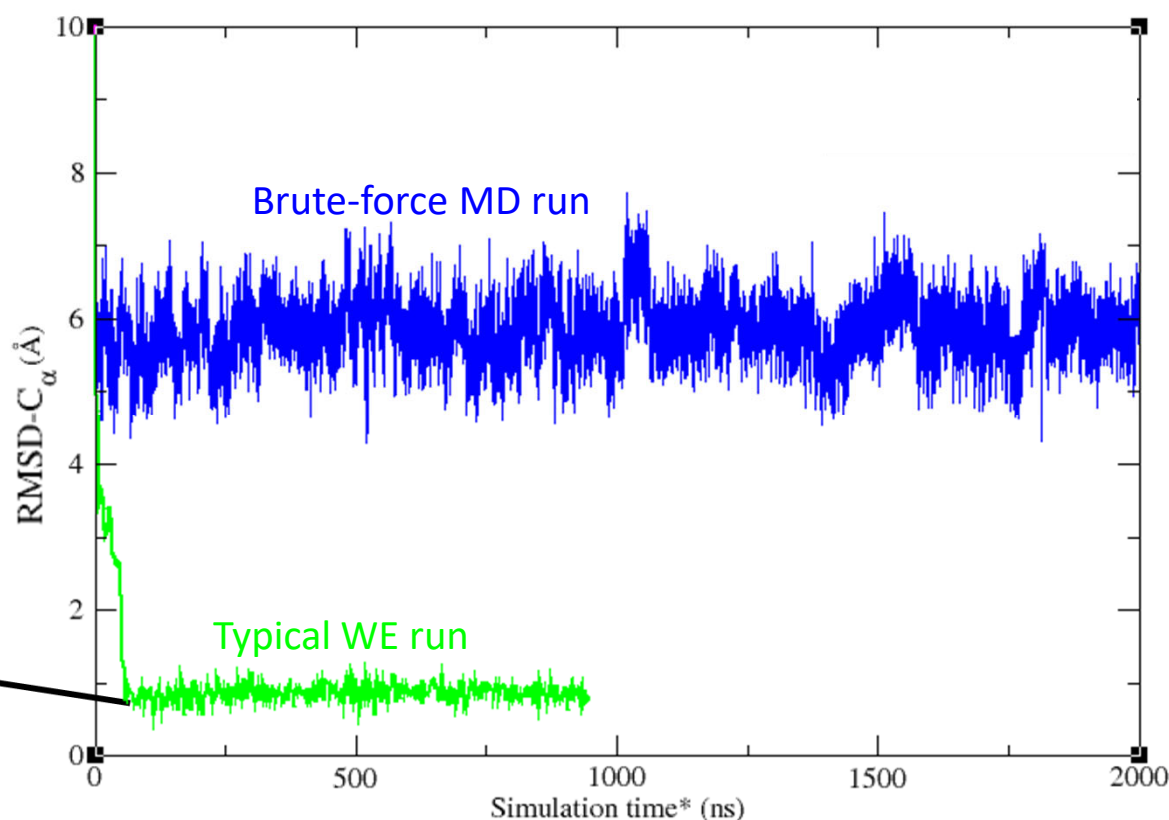
NTL9 (39 residues)
Implicit solvent



Starting structure
(RMSD- C_α ~ 10.0 Å)



Folded structure
(RMSD- C_α ~ 1.0 Å)



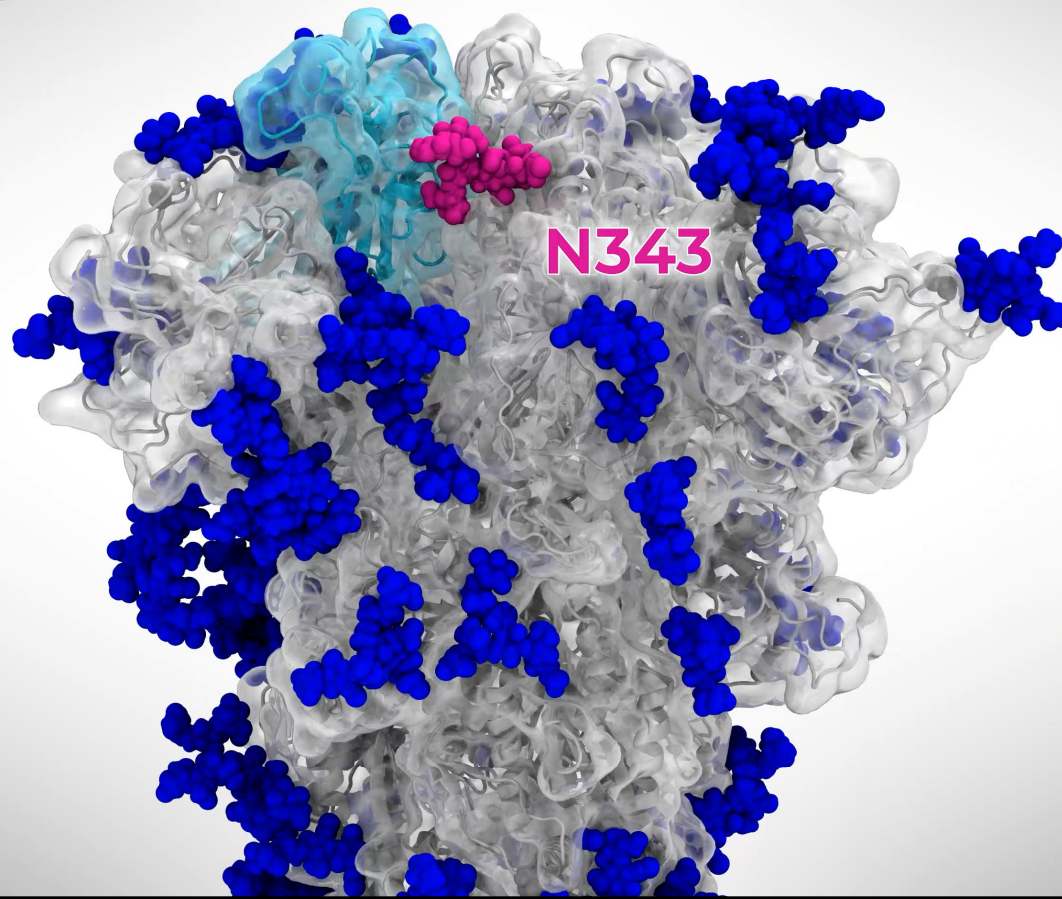
*WE aggregate time

[Adhikari et al., *Journal of the American Chemical Society*, 2019]

A glycan gate at N343 controls opening of the spike

Closed Spike
Side view

RBD “down”



T. SZTAIN, S.-H. AHN et al.
AMARO LAB (UCSD)
CHONG LAB (PITT)

[Amaro, Chong & co, *Nature Chemistry*, 2021; **Delta variant**:

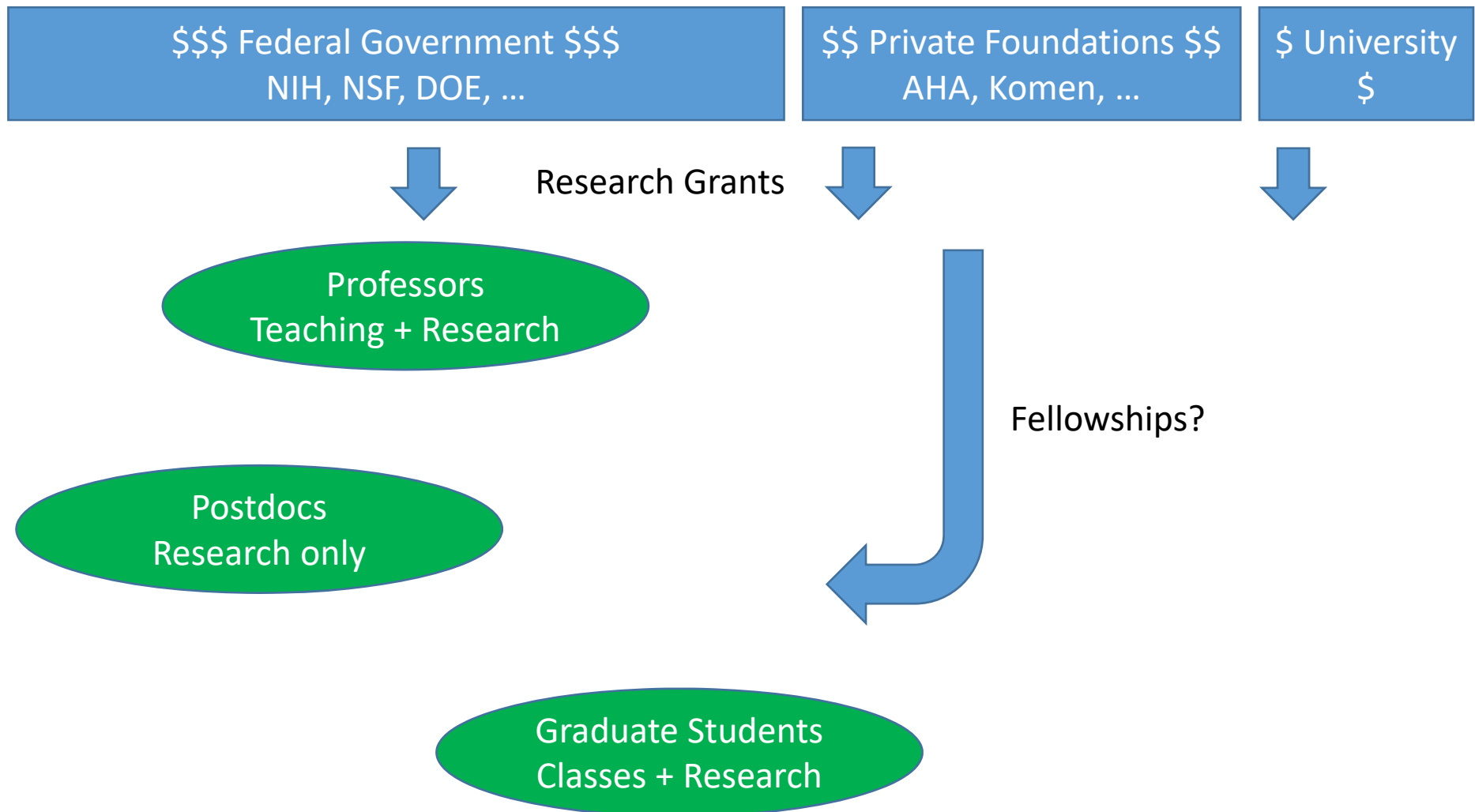
<https://www.nytimes.com/interactive/2021/12/01/science/coronavirus-aerosol-simulation.html>]

How to become a Scientist

- Figure out what you like
 - Classes: Seek best teachers
 - Research: Seek best mentors – ask other group members
- Do research in college
 - Paid programs available
 - Get to know multiple professors
 - [Full disclosure: I didn't major in science]
- Apply to graduate school
 - Seek the best mentor!
 - Best = ? Most accomplished, best connected, healthiest group environment, best research topic
 - Do something you love to do well
 - Get to know multiple professors
- How to 'do good' as a scientist
 - Be a great teacher
 - Be a great mentor (even working for industry)
 - Solve an important problem (even working for industry)

NOTE: You can leave academia at any time to work in industry, and make more money!

How Academic Science Works: Follow the money!



What does a professor do all day?

- Overall: a lot of independence aside from required teaching
- Classroom teaching – varies significantly by institution
- Research
 - **Think up questions and solutions – have an idea and see it through – plan years ahead**
 - Direct research (mostly) – actually do it (a little)
 - Supervise postdocs and graduate students: meet once a day or once a week
- Write grant applications for funding
- Attend local meetings to decide policies and directions for department and/or university
- Peer-review articles, grant applications
- Present at conferences ... travel!
- The proportions of these activities depend on the institution, department and individual!

What does a graduate student do all day?

- First year or two: Mostly required classes (choose a program you like!)
- Later years: Transition to more **research** ... and eventually more research independence
 - Generate and analyze data
 - Write and publish papers
 - Make presentations, some under pressure ... confidence grows over time ... sometimes travel
- Attend seminars
- Train junior group members, help others
- Decide whether to do a postdoc or go to industry
- 5-6 years total for a Ph.D.

Masters degree (MS) vs doctorate (PhD)

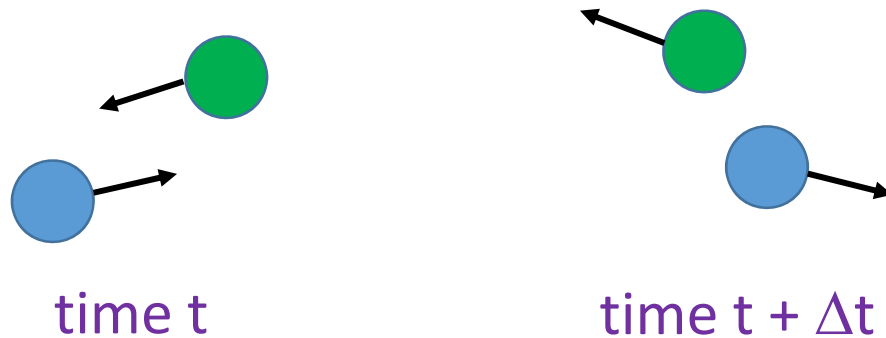
- MS
 - Usually the student pays
 - Research not very in depth
 - Middle of the 'food chain'
 - 1-2 years
- PhD
 - The student gets paid, typically from day 1
 - In-depth research; add to knowledge
 - Top of the food chain ... access to leadership positions in academia and industry and government
 - 5-6 years, typically

What does a postdoc do all day?

- Research!
 - Generate and analyze data
 - Write articles
 - Make presentations ... some travel
- Mentor others in group
- Little teaching unless sought out
- Plan for next step of career
- 2-5 years

end

Molecular dynamics (MD)



- Calculate (classical approximations to) forces f among all atoms every time step ...

$$x(t+\Delta t) = x(t) + v(t)\Delta t$$

$$v(t+\Delta t) = v(t) + (f/m)\Delta t$$

- Time between frames is about $\Delta t = 1$ fs = 10^{-15} sec
- Biology: 100 μ s and beyond
 $\sim 10^{11}$ frames!



Empirical Potential Energy Function

