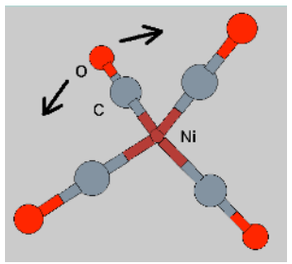
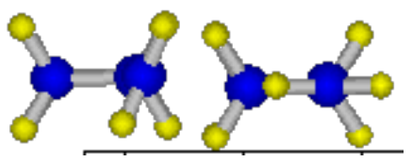
Advanced Molecular Dynamics

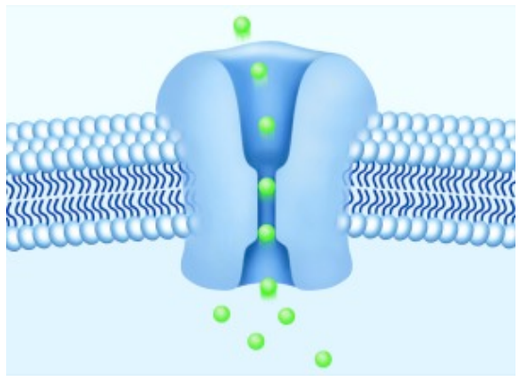
Sampling

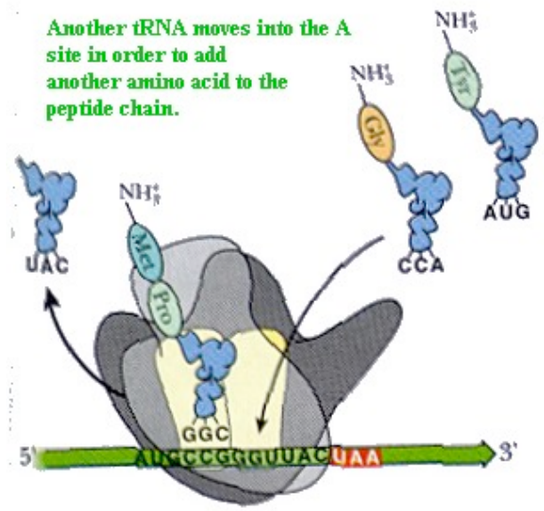
May 12, 2021

Time scales

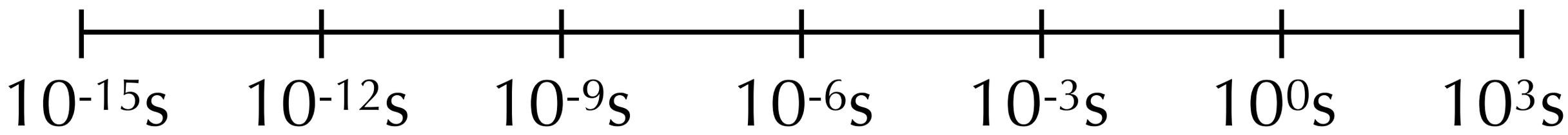








Biological Experiments



where we are

where we need to be

where we want to be

for polymers similar picture

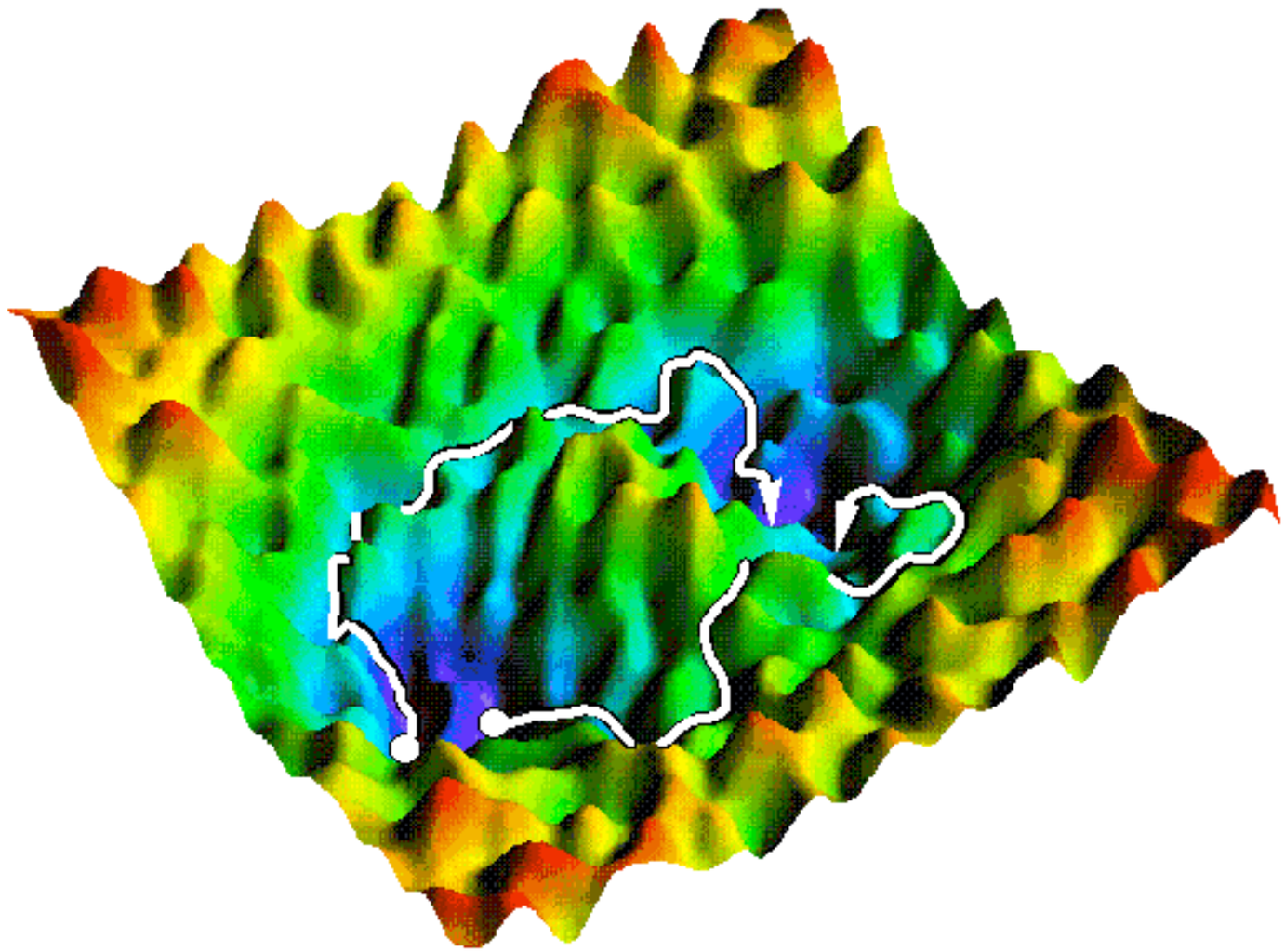
Last lecture

- Efficient algorithms + code:
  - Win 1 order of magnitude in real time
  - Win 1 order of magnitude in total compute time
- Parallel simulations:
  - Win 1-3 orders of magnitude in real time

- More efficient sampling methods:
  - Win 1-3 orders of magnitude in real time
  - Win 1-3 orders of magn. in compute time

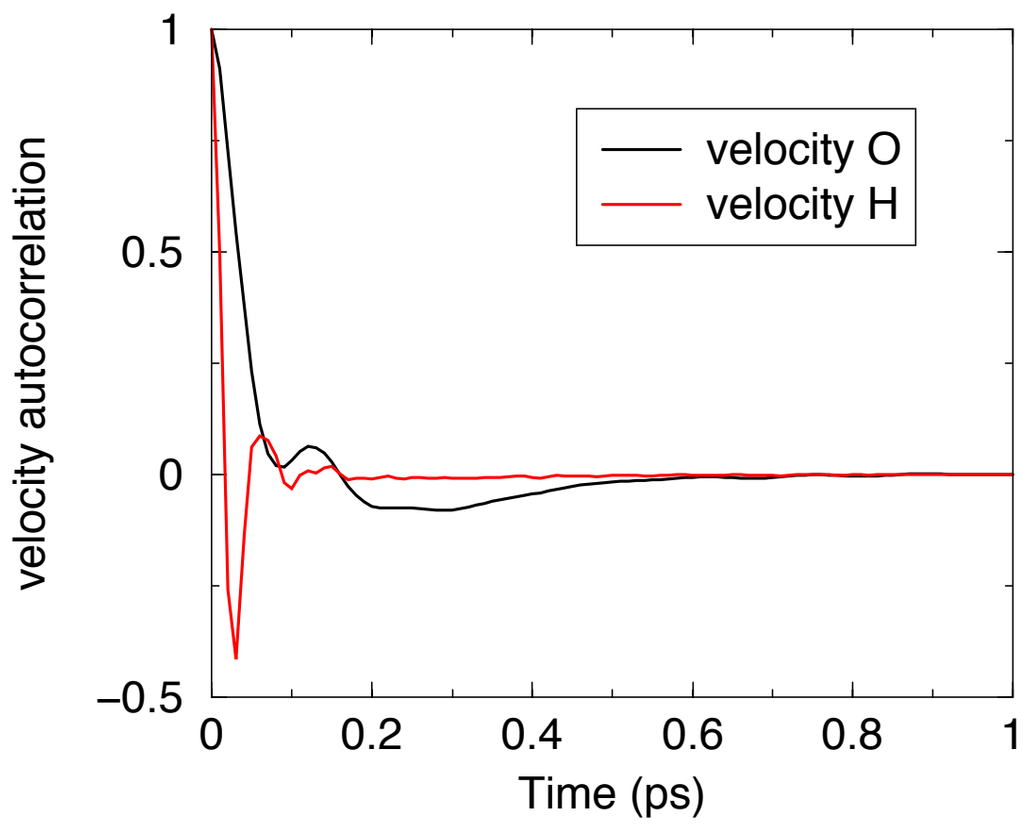
What kind of energy landscape?

- Sampling problems very problem dependent
- Different systems can have very different energy landscapes



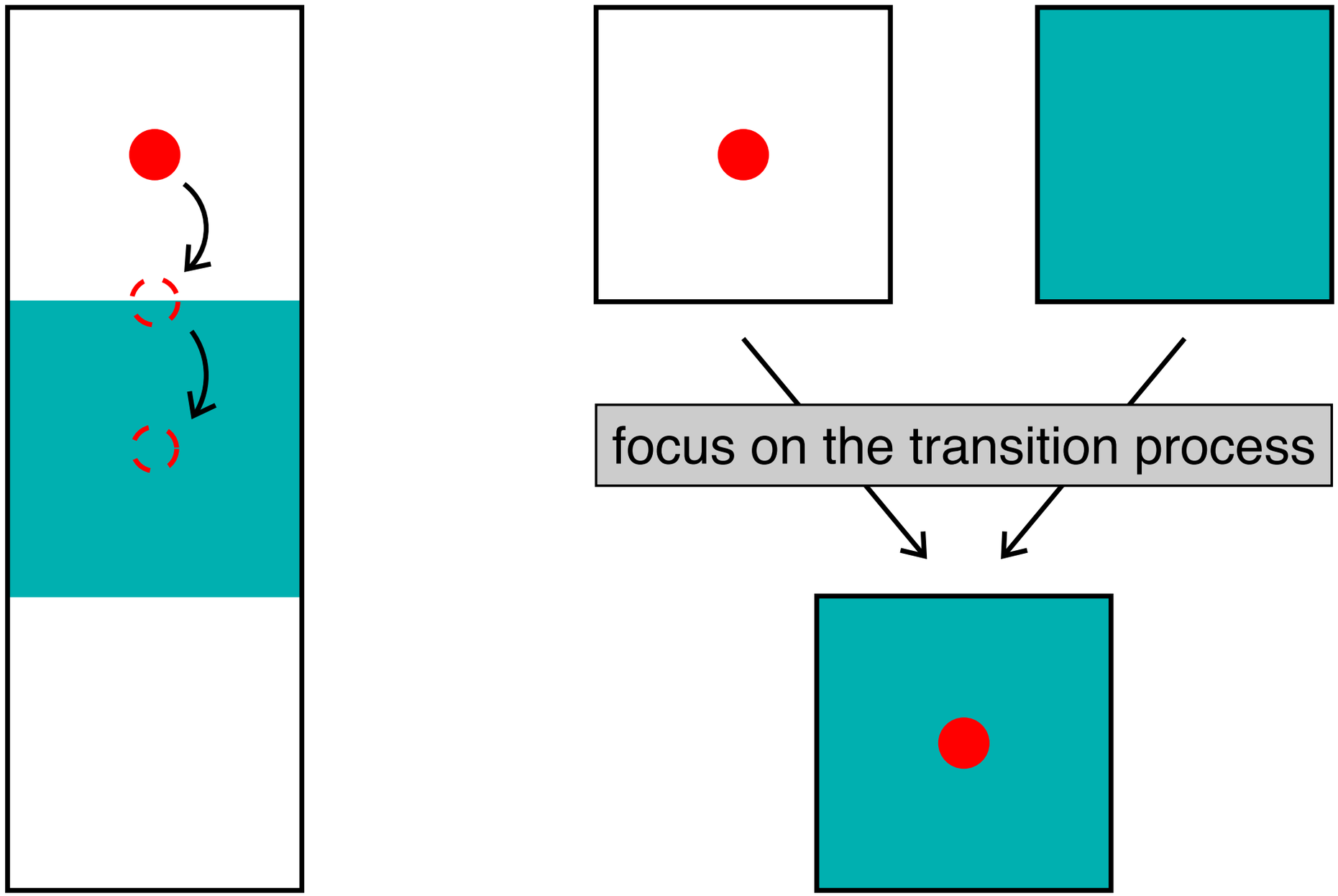
Two very different categories

- Actual dynamics:
  - e.g. flow problems
- Sampling conformations/states:
  - e.g. protein dynamics, polymer structure
    - overdamped
      - inertia: 1ps



Unphysical pathways

for example: calculate solvation free energy



Enhancing sampling

- Three basic ways of enhancing sampling:
  - Fix the system along a reaction coordinate & measure the force or overlap between neighboring points
  - Modify the Hamiltonian (dynamically) to modify the sampled distribution
  - Launch many trajectories from different initial (**x**,**v**), e.g. milestoning, swarms
- All ways allow for more efficient and steered sampling, but knowledge of the system and sampling methods is required

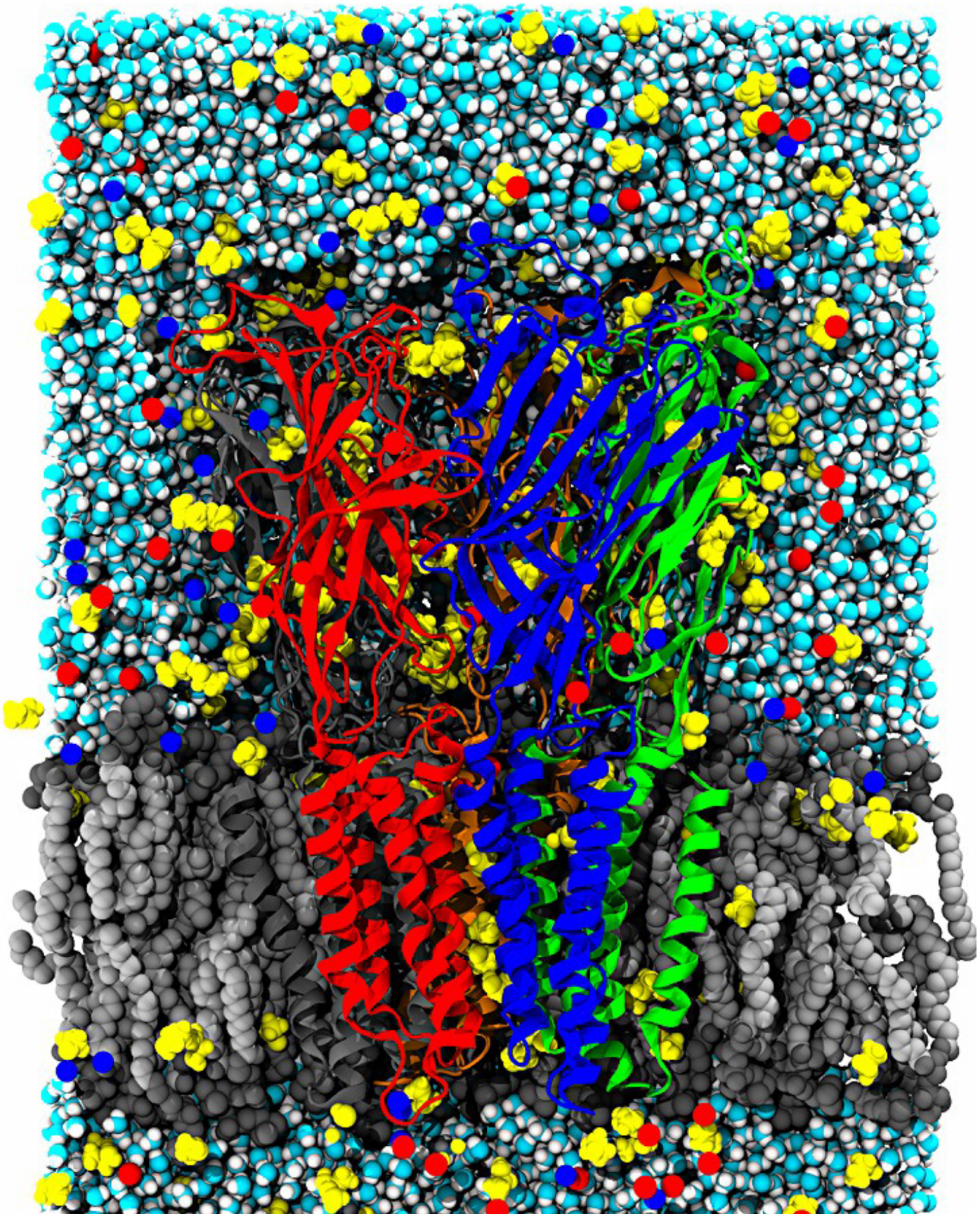
Sampling physical pathways

Question?

- What scientific questions do you want to answer?
- This might seem an obvious question
- But often I get the question:
  "How do I simulate this system?"
- This approach usually leads to nothing

Example: membrane protein

- Many questions
- Many time scales
- Many ways set up simulations



Umbrella sampling

- High barriers in U can make sampling difficult

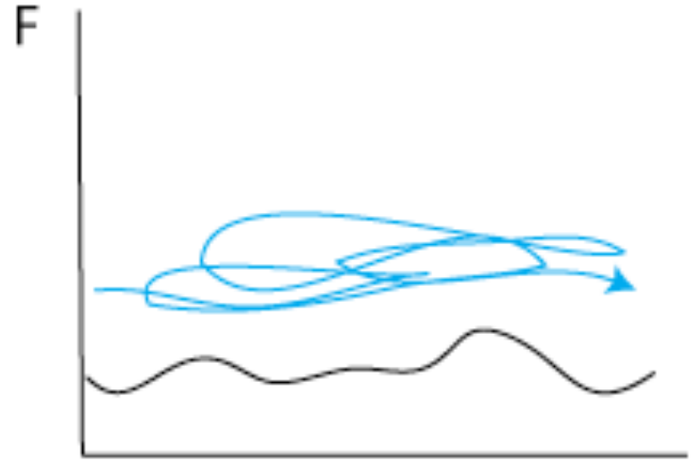
$$\rho(\mathbf{r}) \propto e^{-\beta U(\mathrm{r})}$$

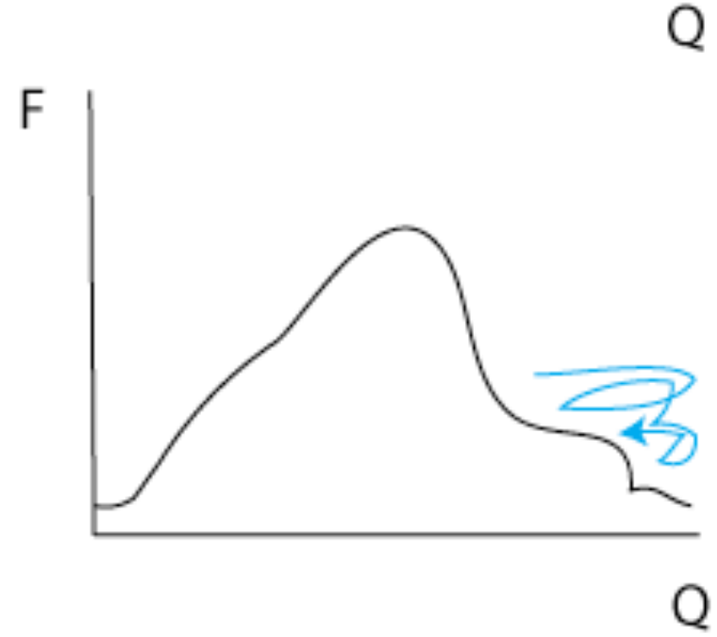
- But we can modify the potential as we like

$$\rho'(\mathbf{r}) \propto e^{-\beta[U(\mathrm{r})+W(\mathrm{r})]}$$

- And correct for it

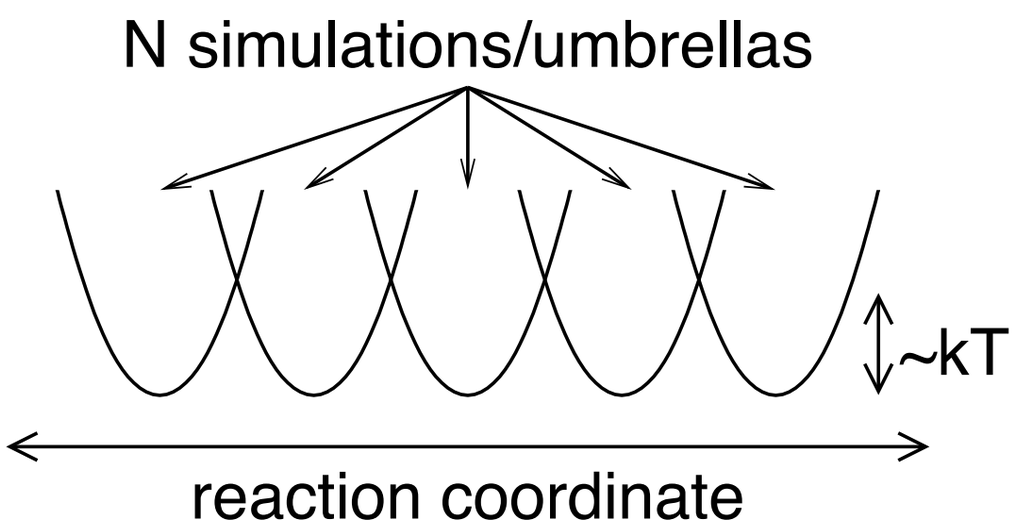
$$\rho(\mathbf{r}) \propto \rho'(\mathbf{r}) e^{\beta W(\mathrm{r})}$$

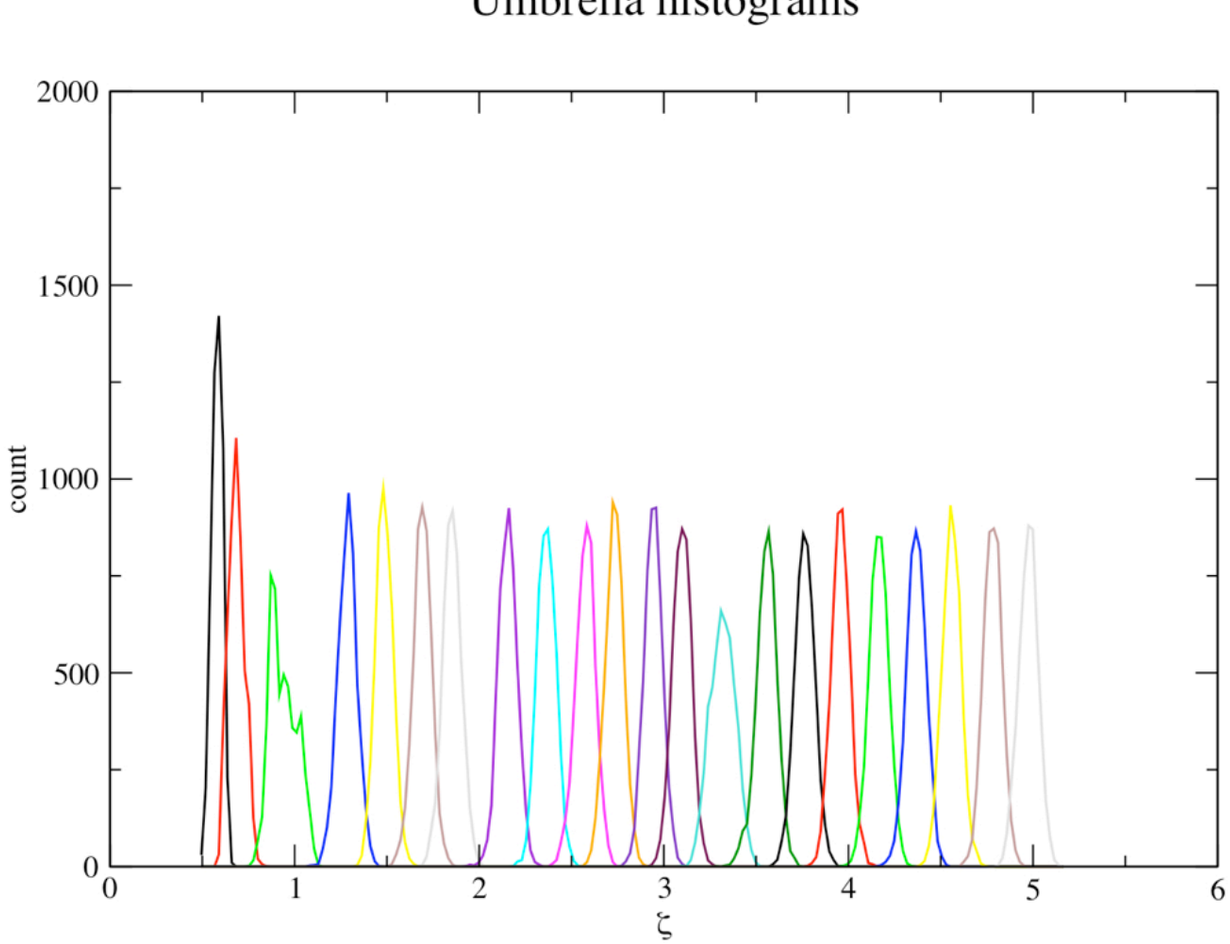




Many umbrellas

- You can do many simulations with different umbrellas
- Need to combine the different histograms using the weighted histogram analysis method (WHAM)





Advantages of umbrella sampling

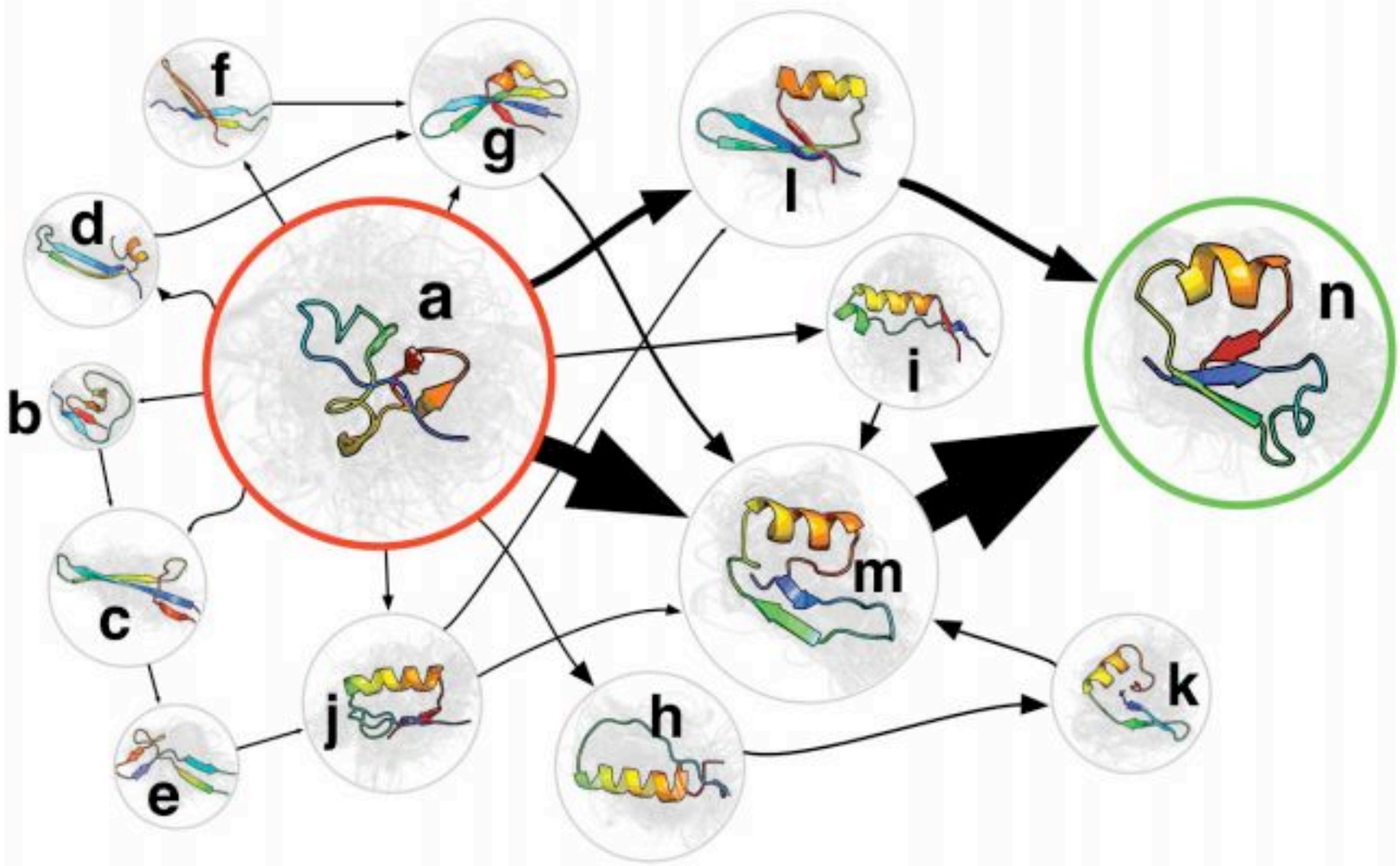
- Covering a range of interest using umbrellas
  - You can overcome any energy barrier
  - Sampling is accelerated:
    - free diffusion: $t = \frac{(\Delta r)^2}{D}$
    - n umbrellas: $t = n\frac{(\Delta r/n)^2}{D} = \frac{1}{n}\frac{(\Delta r)^2}{D}$

How many umbrella's?

- As many as possible
- But relaxation time in perpendicular directions should not be longer than in the biased direction
  - As many bins as gives approximately equal relaxation times

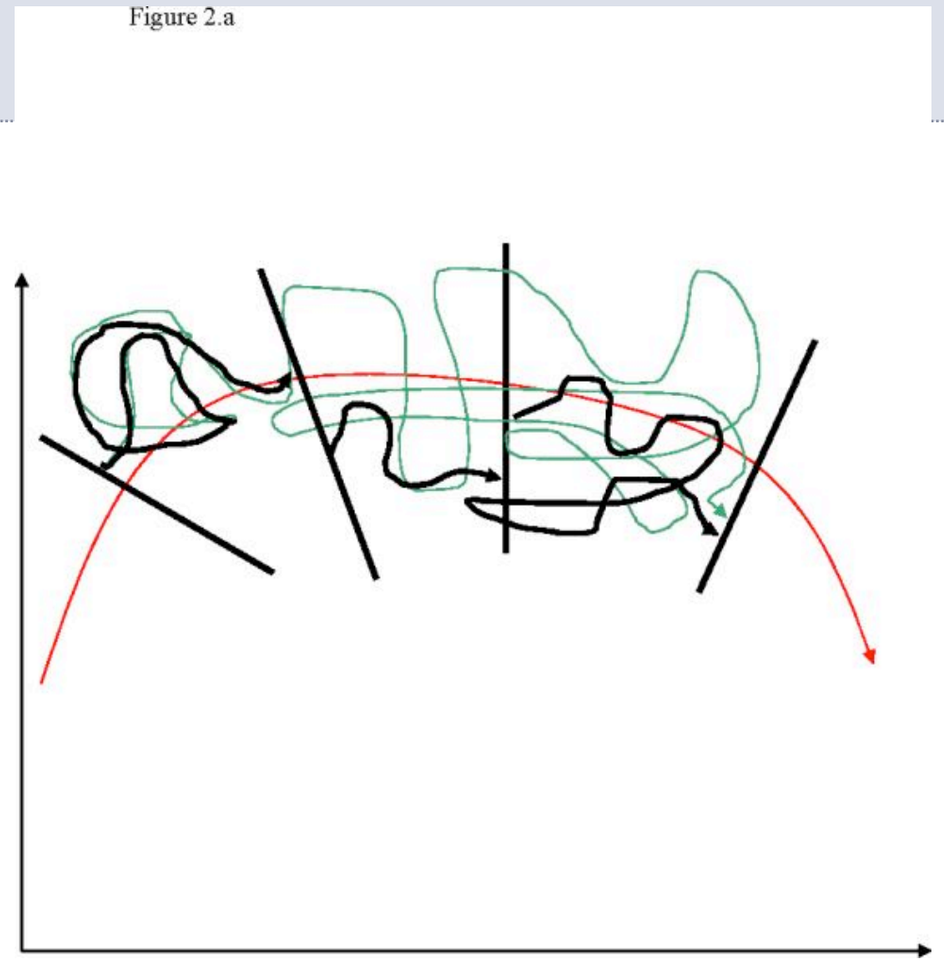
Markov state modeling

- MSM useful with many states & low barriers
- Efficient: don't revisit already visited states
- Can be massively parallel (1000's of sims)

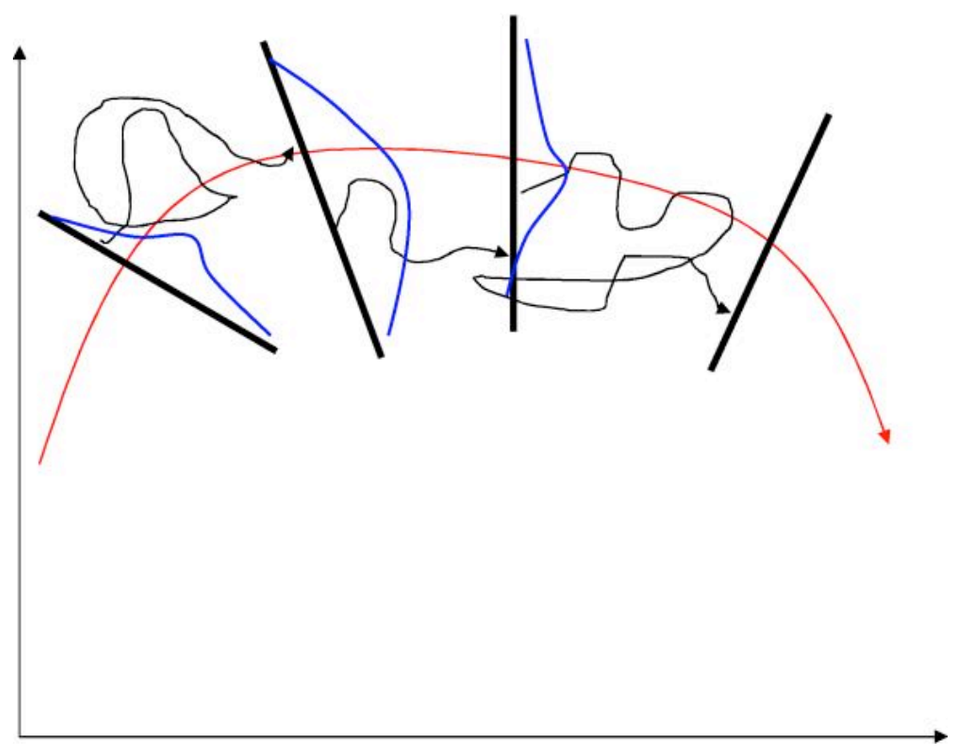


Milestoning

- We place milestones: hyperplanes along a reaction coordinate
- We "shoot" trajectories from one milestone and see where they end up

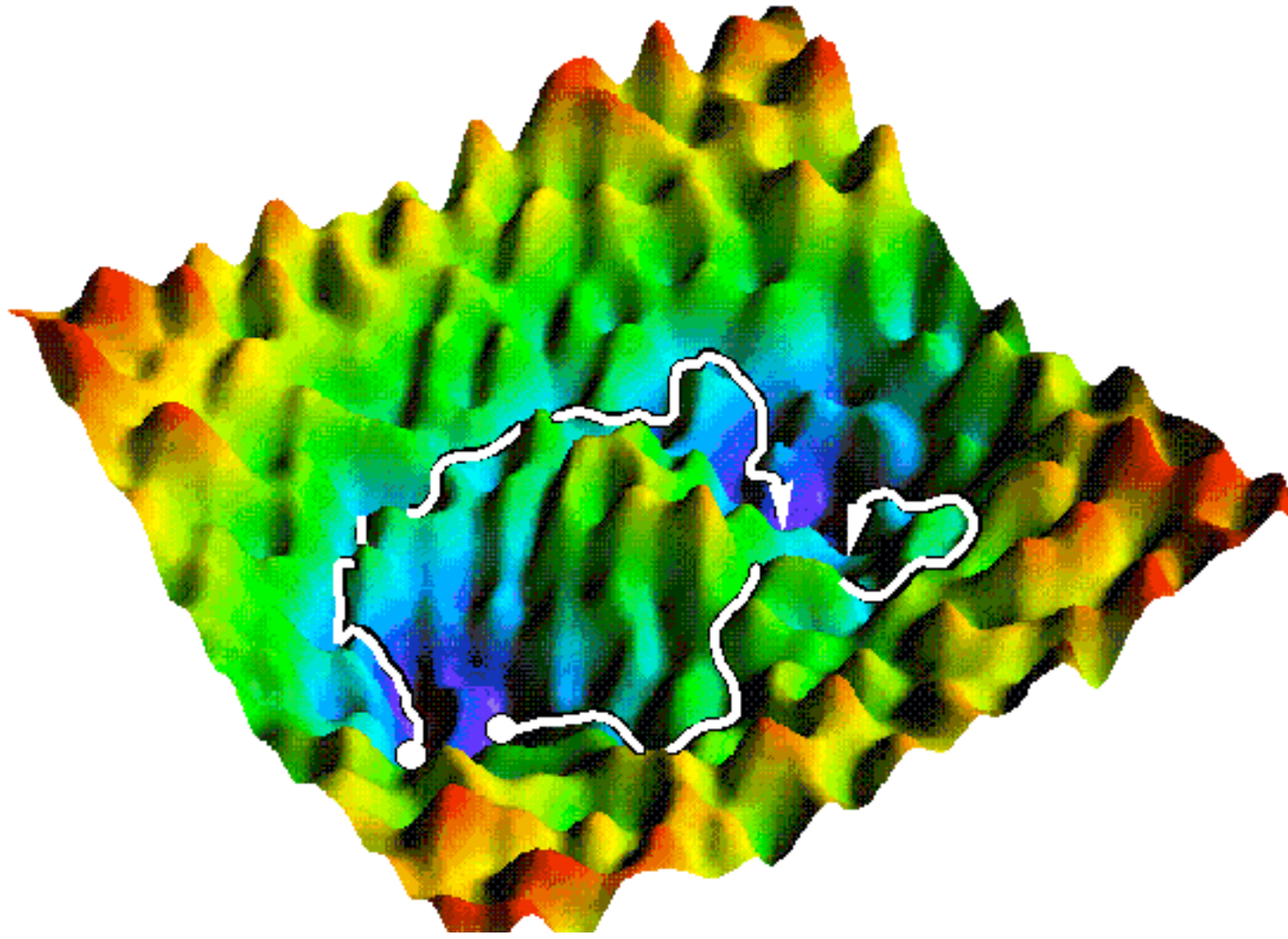


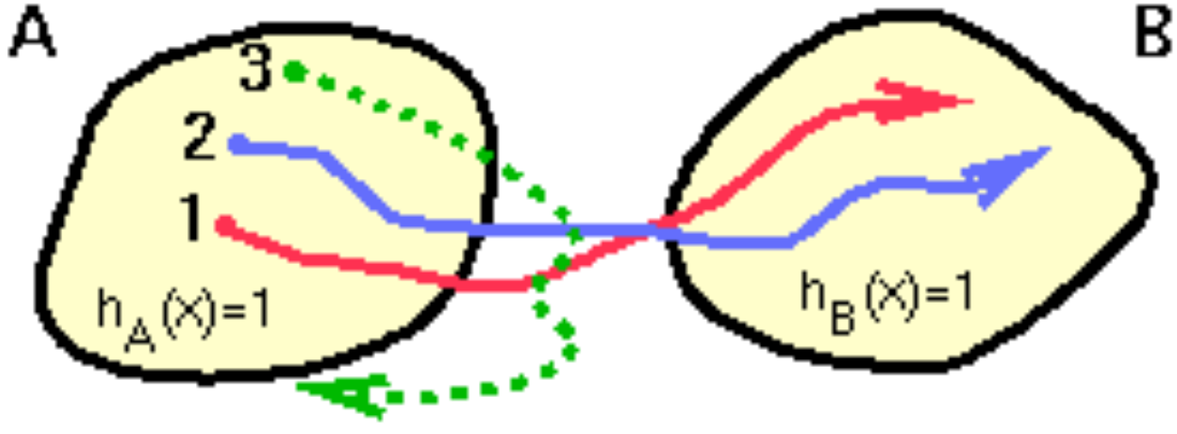
- These trajectories can be glued together to give real pathways
- Milestoning is still in development (a lot of theoretical work)



Path Sampling

- Transition path sampling:
  - Come up with an initial MD path
  - Change path slightly
    - Slightly change the velocity of a particle at a random time along the path
  - Accept/reject based on acceptance criterion:
- Monte Carlo on *paths*



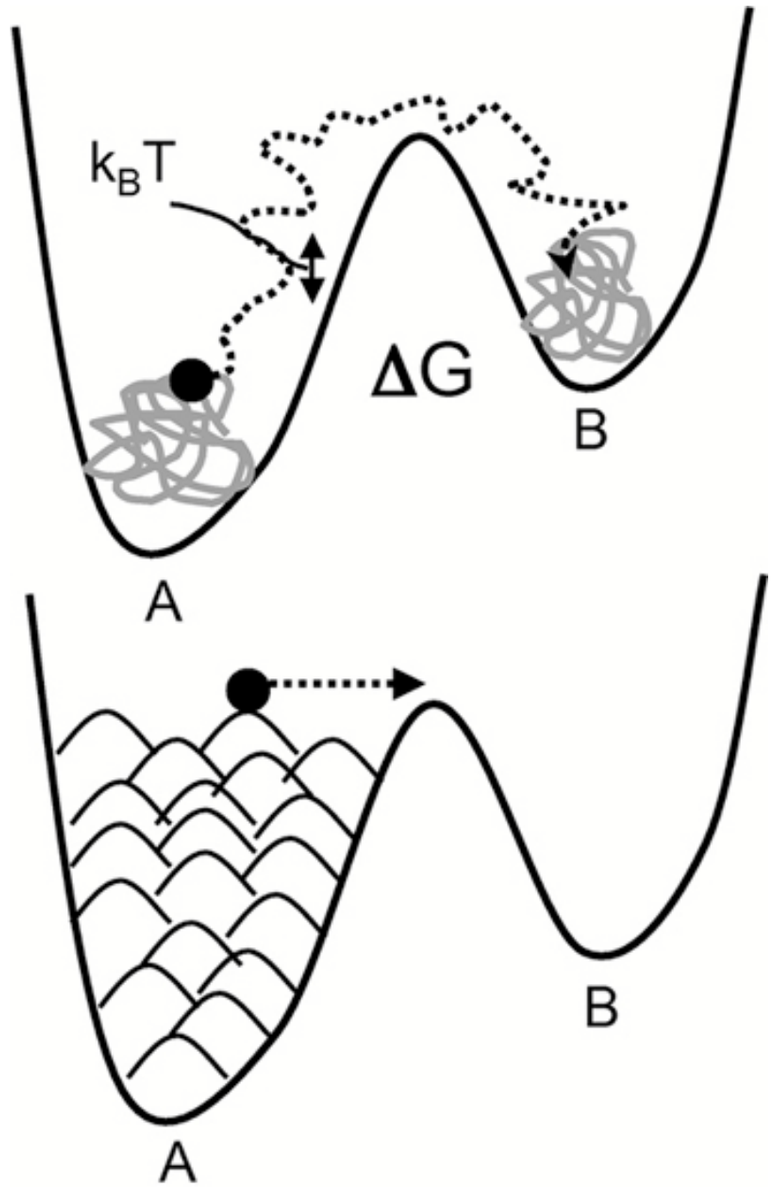


Milestoning

- Method which also gives kinetic information for crossing steep, high barriers

Metadynamics

- Invented a long time ago as local elevation or flooding
- Locally add Gaussians to the potential as you are sampling
- Overcomes barriers
- History dependent, but that will average away
- Sum of Gaussians is your free energy



Biasing methods

- Simple metadynamics does not converge
  - Well-tempered metaD locally decreases the update size: Boltzmann distribution at elevated T
- Many enhanced sampling method share features
  - Metadynamics
  - Adaptive biasing force
  - Accelerated weight histogram method
  - ...

Reaction coordinate / pathway issues

- Umbrella sampling fixes system along RC
- Other methods allow sampling along RC
  - Will the method reveal a bad choice of RC?
  - Does the method allow multiple pathways?
- Usually a starting state is required
  - Does the method require and end state?
  - How reliable is the end state?
- Tips:
  - Try multiple RCs / paths
  - Start from the end state and try to go back