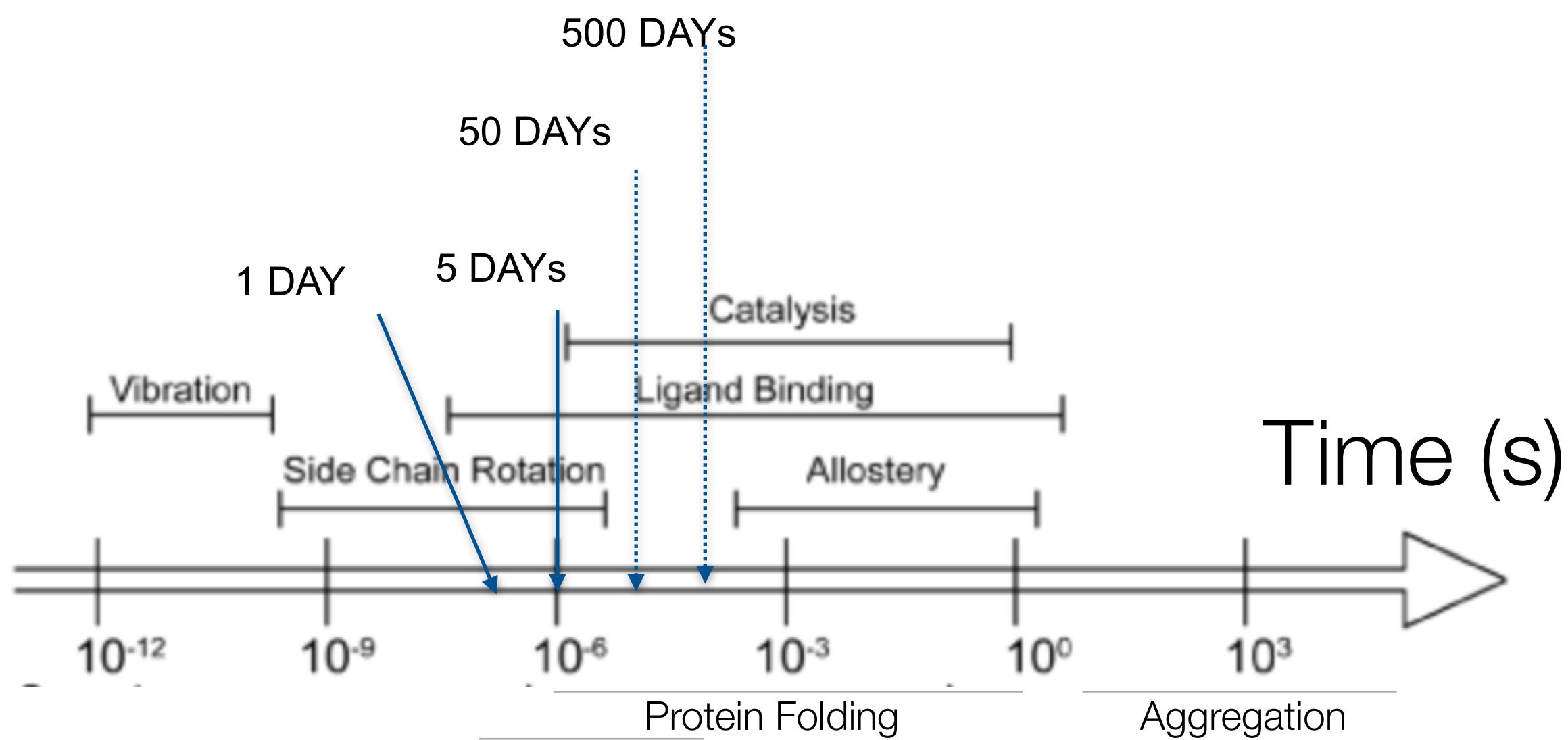


Enhanced Sampling

Structural Bioinformatics

MD simulations: time step, time scales and probabilities



So if we can run our simulation at
~200 ns/day

the probability of observing an event
with a rate of 1 ms with a simulation
of 10 us is ~1% in the case of a two
state kinetics

How many simulations can we run in
parallel?





Free Energy Methods

How can we tweak probabilities to make more likely the observation of important configurations?

Remember that the probability to observe a configuration follow Boltzmann

$$pdf(x) = \rho(x) \propto \exp\left[\frac{-U(x)}{k_B T}\right]$$

And that in MD we approximate $U(x)$ [the potential energy] using the force-field $V(r)$

We could:

- Modify the temperature;
- Modify the force-field;
- Add some additional energy term, possibly chosen with a clear rationale

Then we have a new pdf

$$pdf'(x) \propto \exp\left[\frac{-(U(x) + f(x))}{k_B T'}\right]$$

In the end we want to go back to the original probability, because that is the one we think is correct. So we need to remove the effect of the BIAS (the modification).

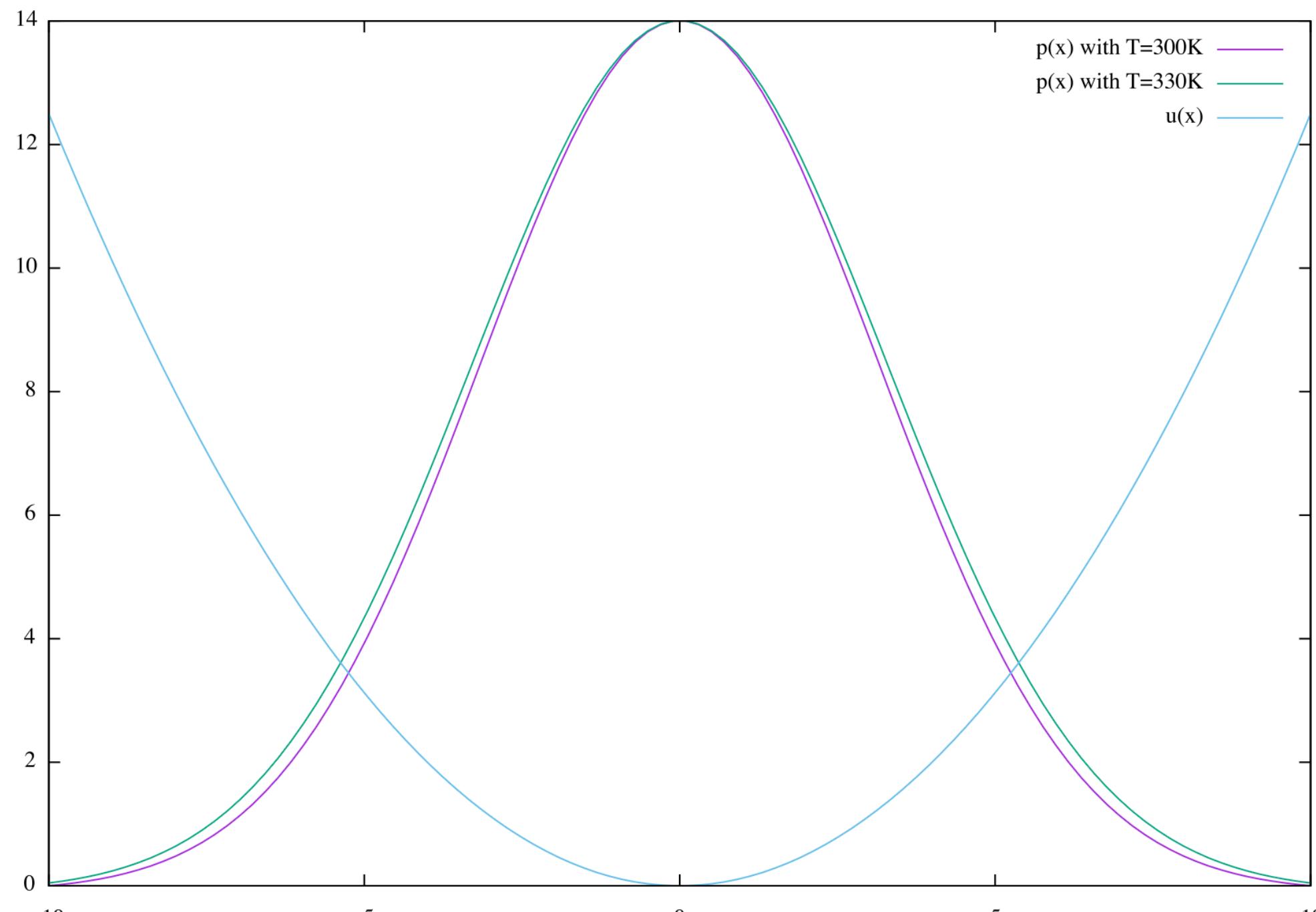




Free Energy Methods: Parallel Tempering

How can we tweak probabilities to make more likely the observation of important configurations?

$$pdf(x) \equiv \rho(x) \propto \exp \left[\frac{-U(x)}{k_B T} \right]$$



The probability density function depends on the **Temperature**, so by changing the temperature we change the probability. In particular we increase the probability of observing high-energy conformations.

By increasing the temperature we are actually looking at different pdf . But for small temperature changes the difference is tiny, so is not that helpfull.

We would like to explore a large temperature range.



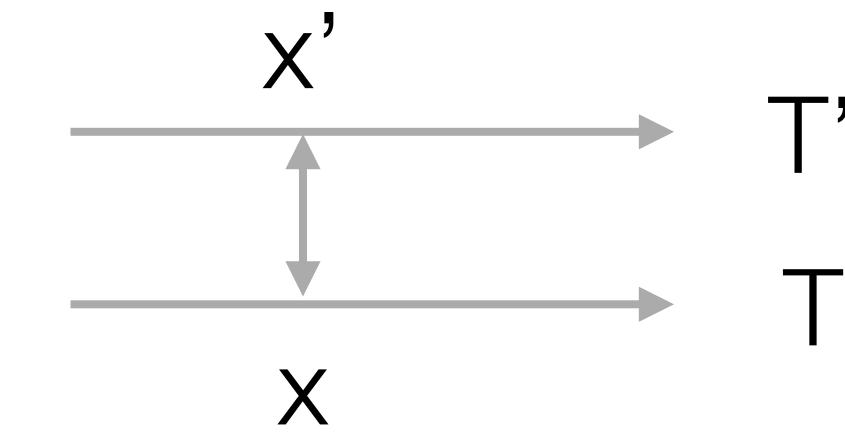
Parallel Tempering

In Parallel Tempering, one runs multiple replica of the same simulation at different temperature, and then allow configurations to be exchanged between the simulations, so a configuration that is found at high temperature can donated to a simulation at the correct temperature.

To make it work we need to write the probability to find two configurations x and x' in the two simulations at their respective temperatures:

$$P(x, T, x', T') \propto \exp\left[\frac{-U(x)}{k_B T}\right] \exp\left[\frac{-U(x')}{k_B T'}\right]$$

$$\frac{P(x', T)P(x, T')}{P(x, T)P(x', T')} = \frac{\exp[-U(x')/k_B T - U(x)/k_B T']}{\exp[-U(x)/k_B T - U(x')/k_B T']} = \exp\left[\left(\frac{U(x') - U(x)}{k_B}\right)\left(\frac{1}{T} - \frac{1}{T'}\right)\right]$$



Then we would like to know what would be the probability of finding x in the simulation at T' and x' in the simulation at T :

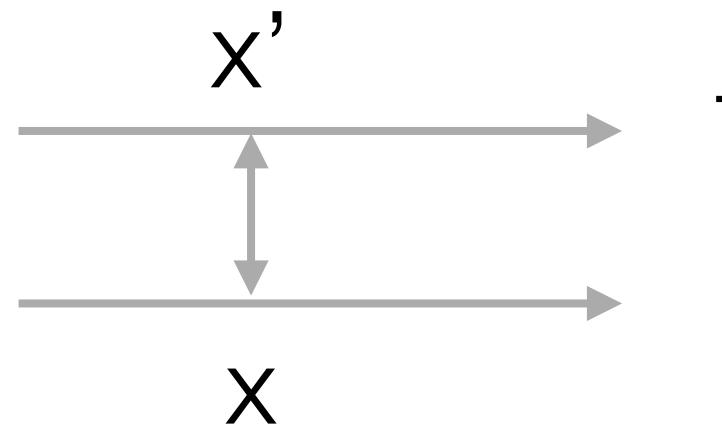
$$P(x', T, x, T') \propto \exp\left[\frac{-U(x')}{k_B T}\right] \exp\left[\frac{-U(x)}{k_B T'}\right]$$

The exchange probability is their ratio:





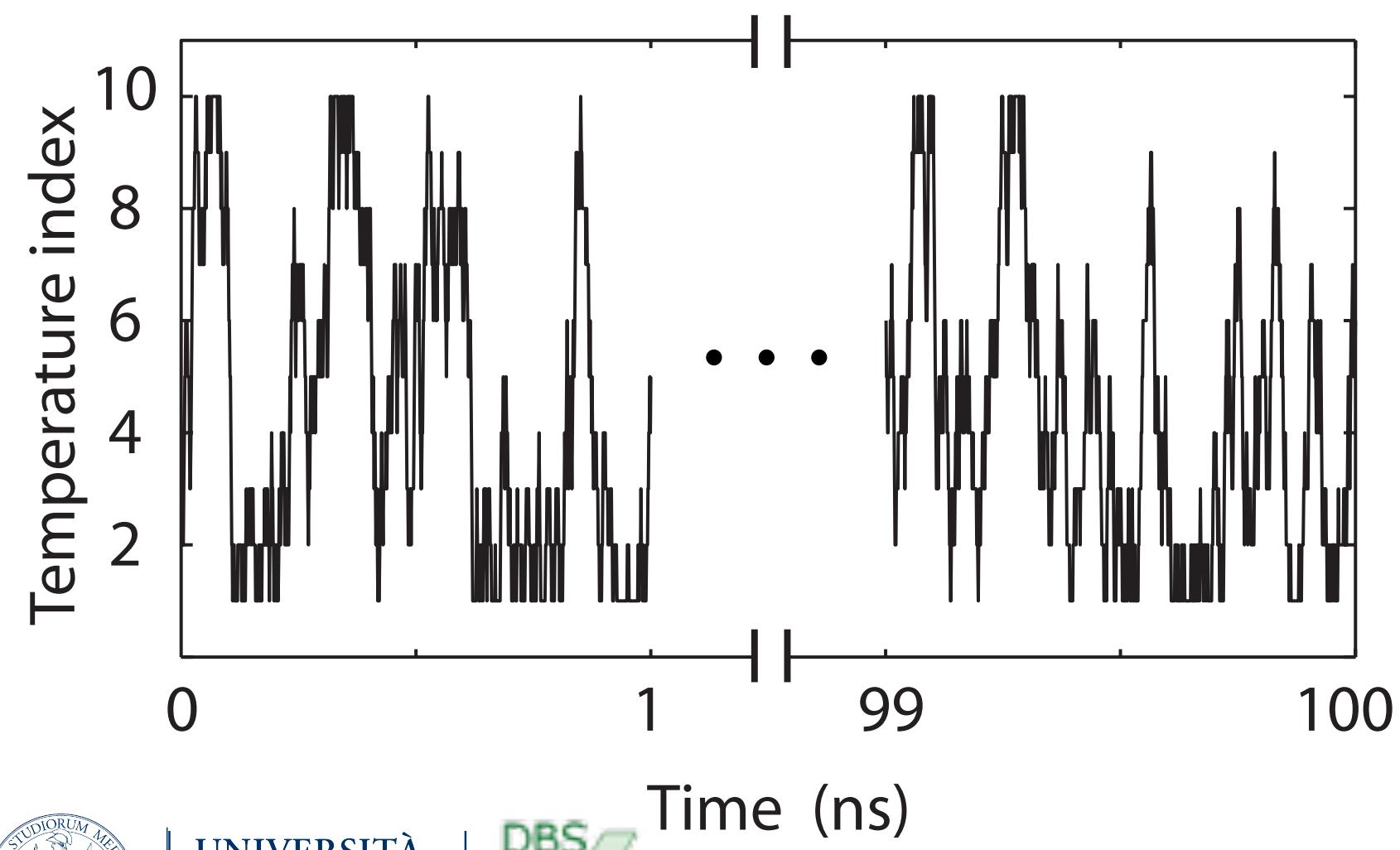
Parallel Tempering



$$P_{acc}(x, x', T, T') = \min(1, \exp \left[\left(\frac{U(x') - U(x)}{k_B} \right) \left(\frac{1}{T} - \frac{1}{T'} \right) \right])$$

Apart from the math what happen in practice is that we have many MD at many temperatures, and with some frequency an exchange is attempted between configurations at different temperature. This is done using a **Metropolis-Monte-Carlo algorithm**, with a probability of acceptance given by:

MMC: A random number $[0,1]$ is generated and compared with $P_{acc}(x,x')$ if it is smaller the exchange ($x \leftrightarrow x'$) is accepted.



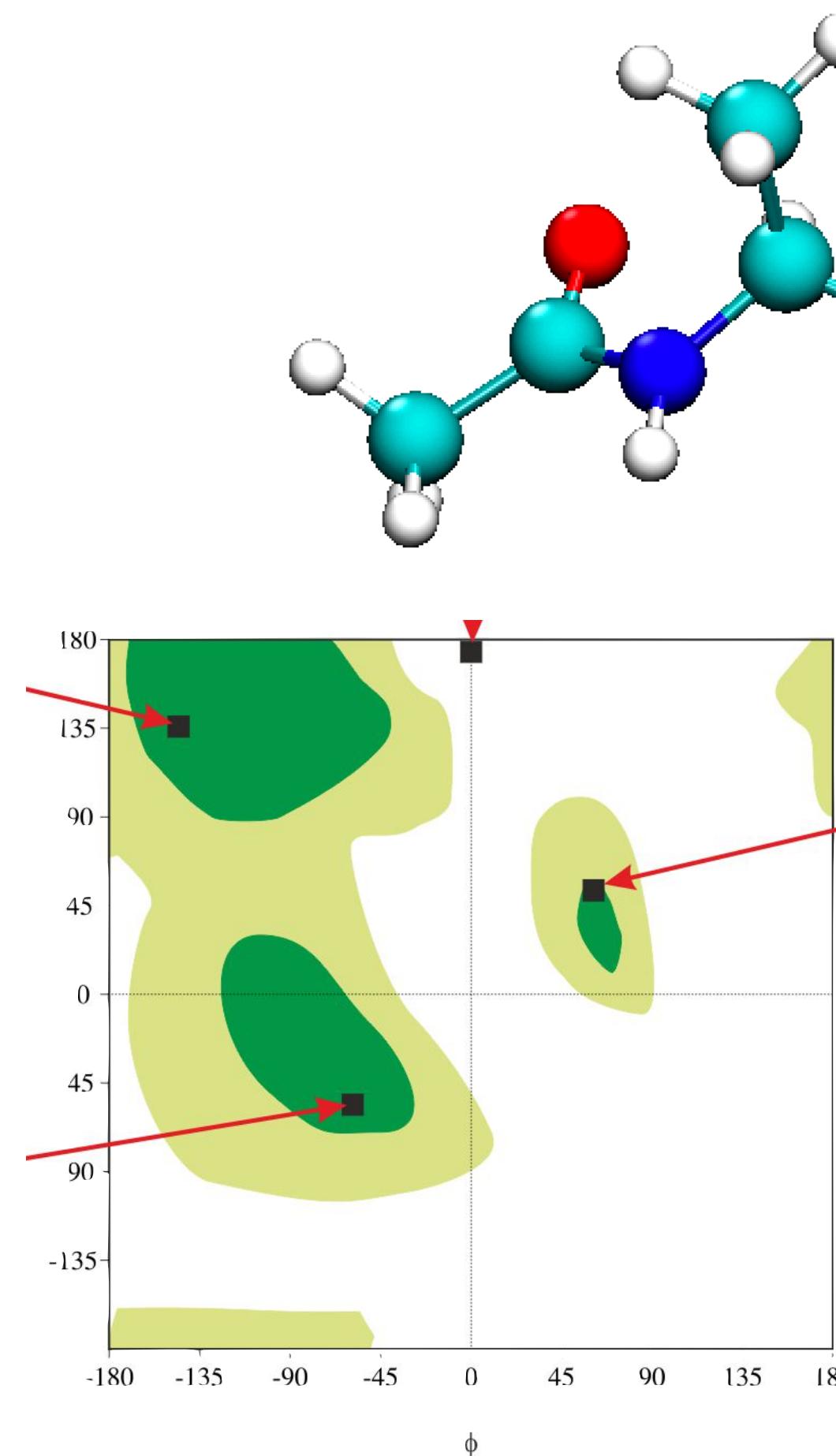
Pros:

- Sampling is enhanced by moving in time and temperature.
- We also learn the temperature dependence of the system.

Cons:

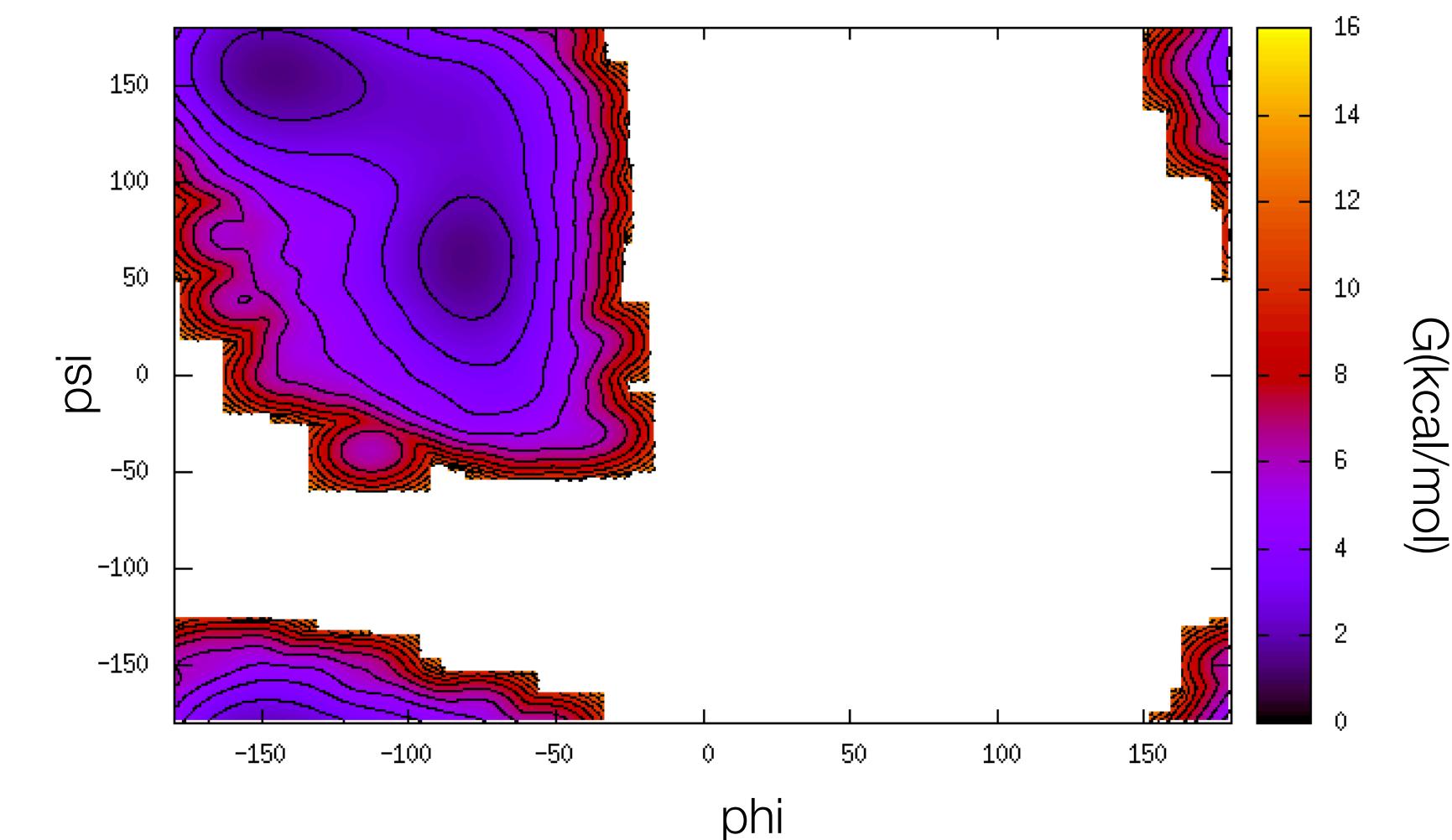
- The probability of exchange decreases a lot with the system size, so for large system one could easily need hundreds of replicas.
- Lack of control of the sampling, not all processes depends in the same way from temperature.

Parallel Tempering



The expectation for this system is to sample three relevant conformations.

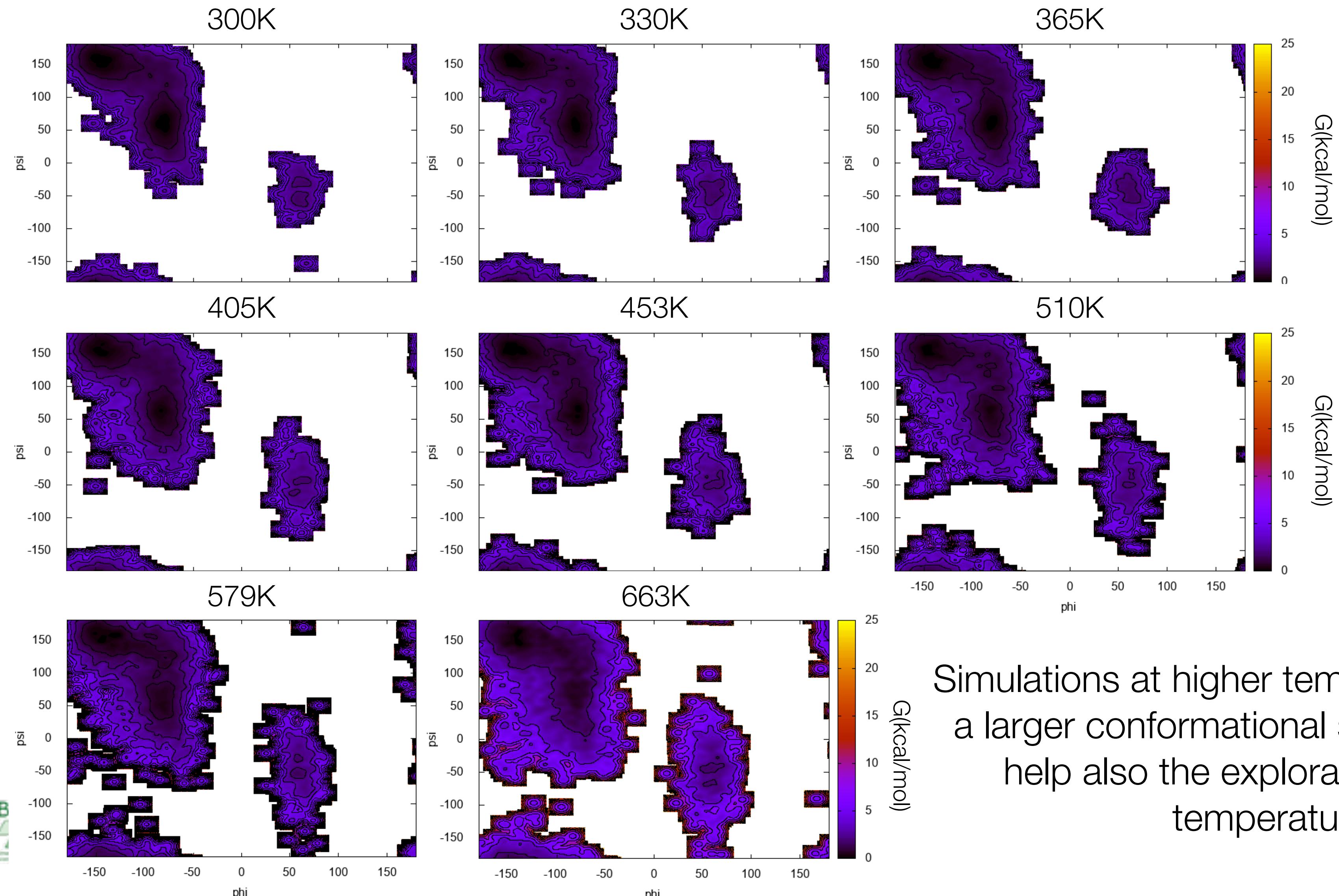
A short MD (80ns) at 300K samples only the left region:



A longer simulation could sample the right region as well, but how longer? Alternatively here we run 8 simulations at 8 different temperature for 10ns each (the same total simulation time)



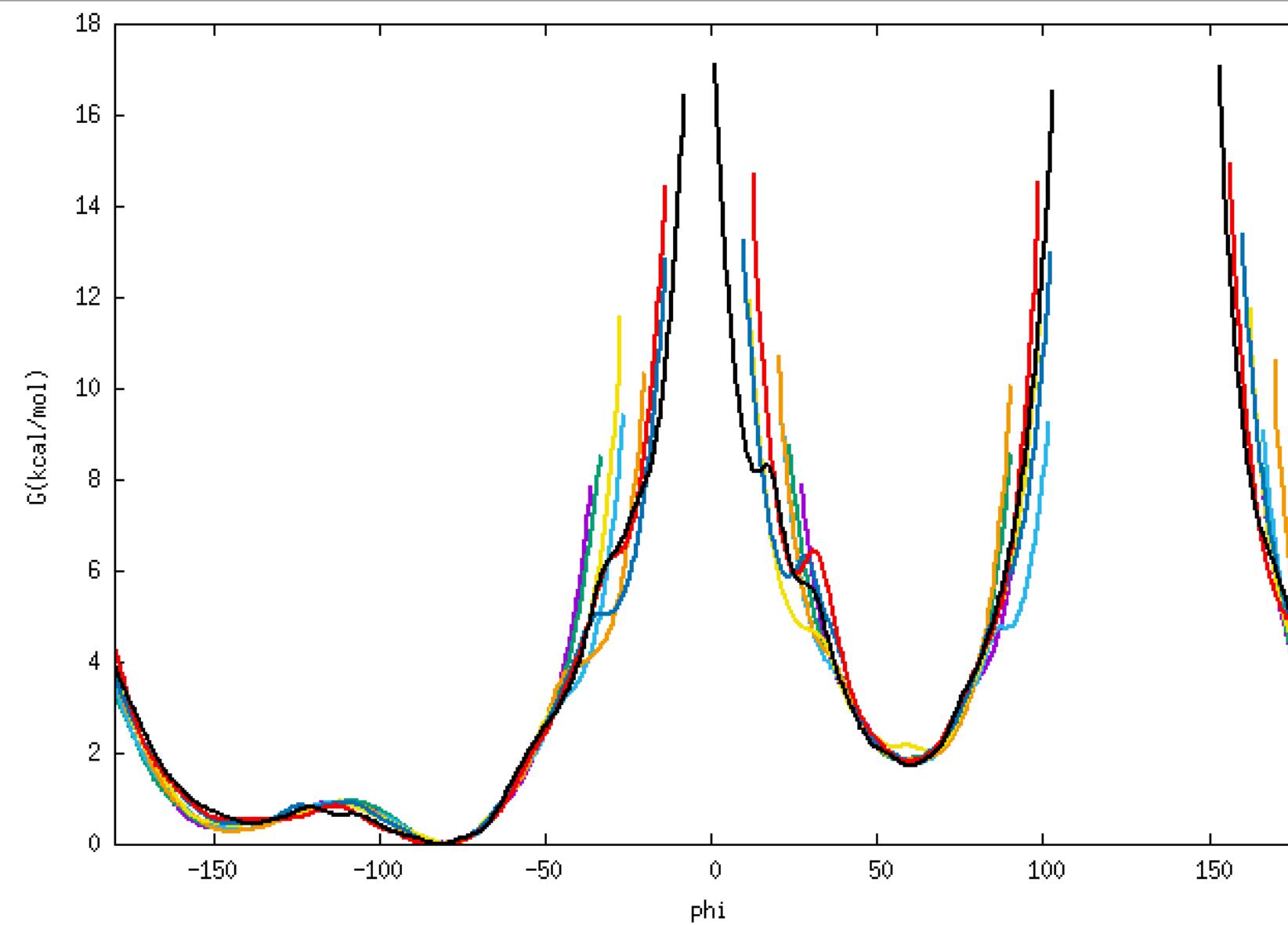
Parallel Tempering



Simulations at higher temperature explore a larger conformational space and thus help also the exploration at lower temperature

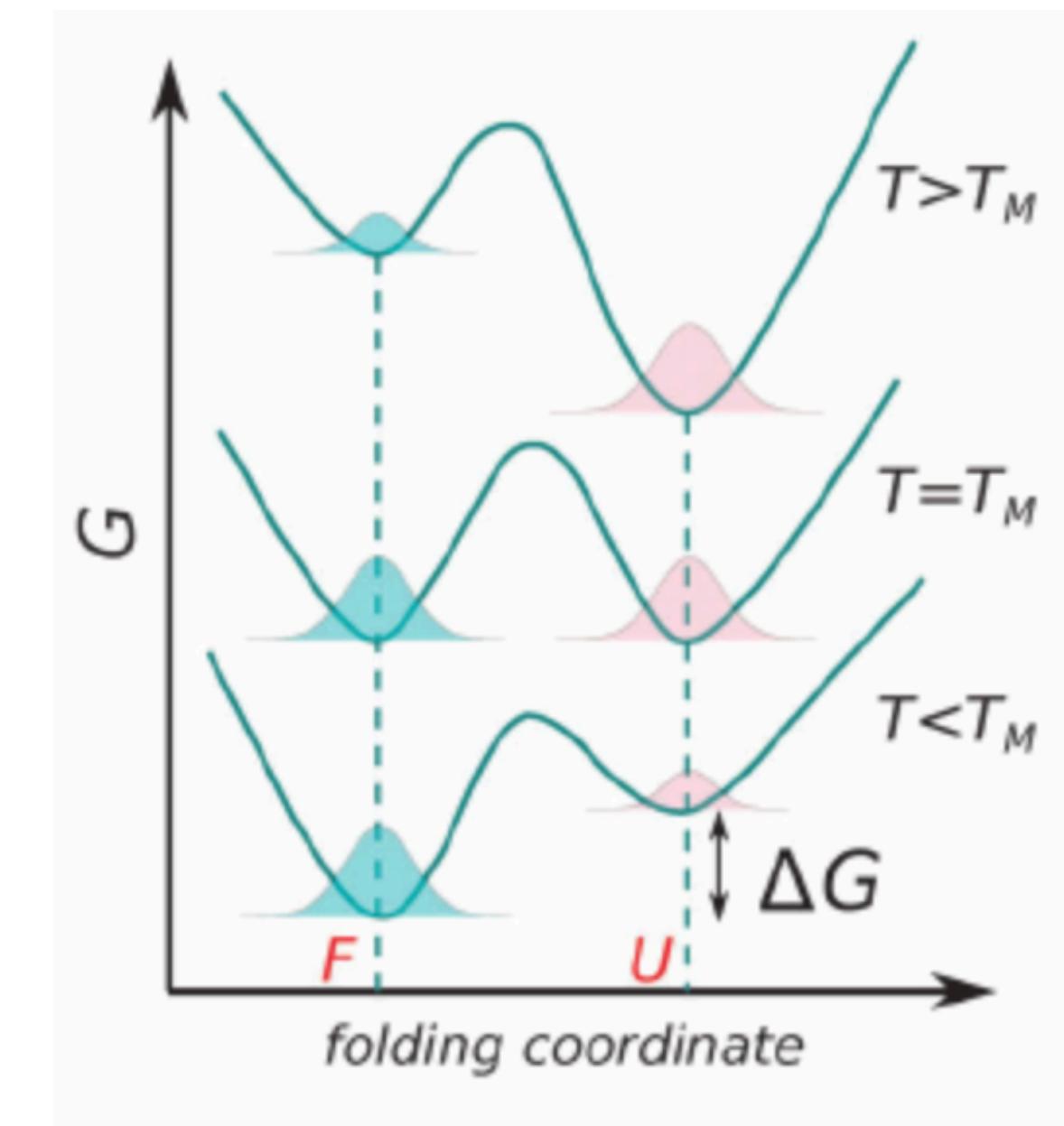


Parallel Tempering

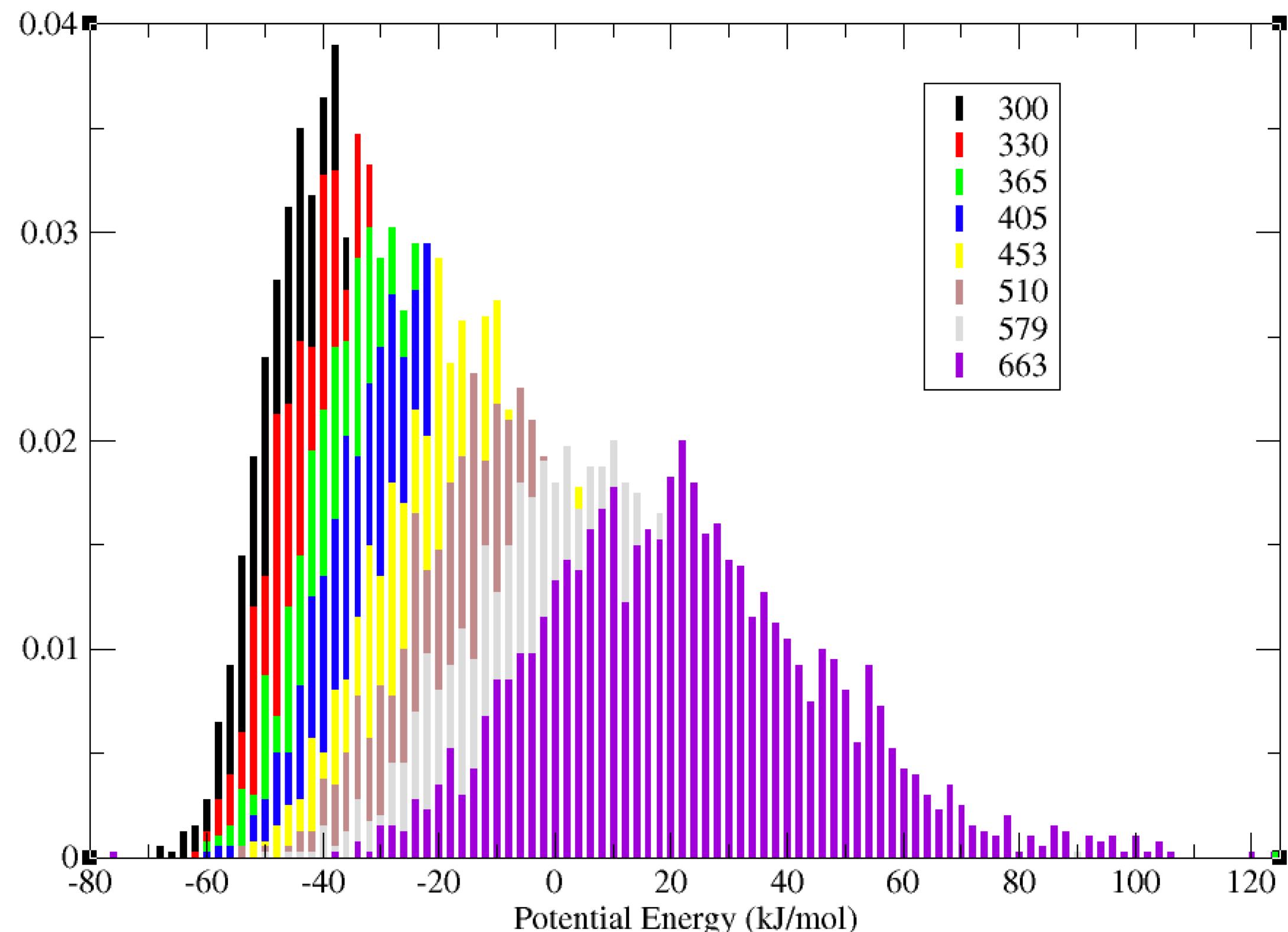


This is an extreme case, usually the free energy will change with the temperature, think at proteins, the higher the temperature the more is gonna be populated the unfolded state. In this case the high temperature will not help too much.

By looking at the free energy projected only on phi it is clear that the free energy in this case does not change with the temperature, so using higher temperature here is particularly efficient. Furthermore from the barrier estimate of $\sim 10\text{kcal/mol}$ we could say that we would have needed a 1us simulation to sample this conformational change! We got the result with 80ns so we have speed up the simulation by a factor >10



Parallel Tempering: How to set the temperatures



In order to have a good probability of exchange

$$P_{acc}(x, x', T, T') = \min(1, \exp \left[\left(\frac{U(x') - U(x)}{k_B} \right) \left(\frac{1}{T} - \frac{1}{T'} \right) \right])$$

The histograms of the potential energy should overlap significantly (~10-30%), here it means that we could have used even less replicas, the overlap is very high, but for real system in water (here we are in vacuum) the temperature difference needed can become of the order ~1 K.





Free Energy Methods: Hamiltonian Replica Exchange

How can we tweak probabilities to make more likely the observation of important configurations?

$$pdf(x) \equiv \rho(x) \propto \exp\left[\frac{-U(x)}{k_B T}\right]$$

The probability density function depends on the **Force Field**, so by changing the force field we change the probability. In particular we can decrease the interaction energy of some specific term.

$$\begin{aligned} V(r) = & \sum_{bonds} k_b(b - b_0)^2 + \sum_{angles} k_\theta(\theta - \theta_0)^2 + \sum_{torsions} k_\phi[\cos(n\phi + \delta) + 1] \\ & + \sum_{\substack{nonbond \\ pairs}} \left[\frac{q_i q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^6} \right] \end{aligned}$$

By decreasing the contribution of dihedral angles for example we speed up the motion of the backbone and side chains.

We could then implement the same approach used for temperature, using multiple replicas with scaled force-field modifications. This generalised method is then called Hamiltonian Replica Exchange.





Biassing and Unbiasing (reweighting)

If I know how I am modifying a system, for example adding some potential energy to specific configurations, the exponential nature of Boltzmann allows to partition the effect of the bias:

$$P'(x) \propto \exp \left[-\frac{U(x) + V_{bias}(x)}{k_B T} \right] = \exp \left[-\frac{U(x)}{k_B T} \right] \exp \left[-\frac{V_{bias}(x)}{k_B T} \right] = P(x) \exp \left[-\frac{V_{bias}(x)}{k_B T} \right]$$

This means that if one samples $P'(x)$ it is then possible, at least in principle, to recover information about $P(x)$:

$$P(x) \propto P(x') \exp \left[+\frac{V_{bias}(x)}{k_B T} \right]$$

So we are unbiasing or reweighting the BIASED simulation to recover the original one.



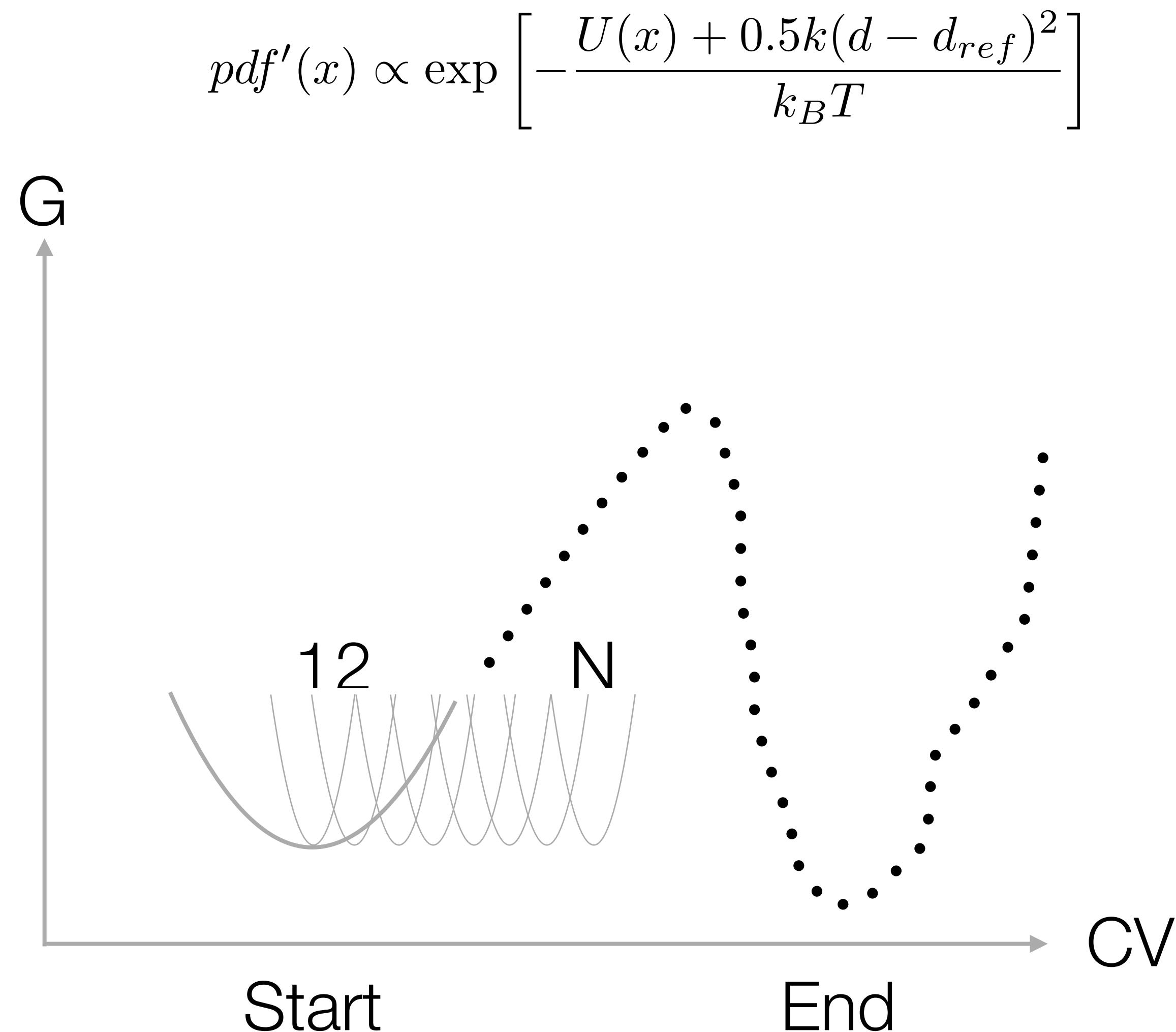


Free Energy Methods: Umbrella Sampling

We can add a new potential energy term to favor or disfavor specific motions. For example we may try to force a ligand to get farther or closer to its binding site.

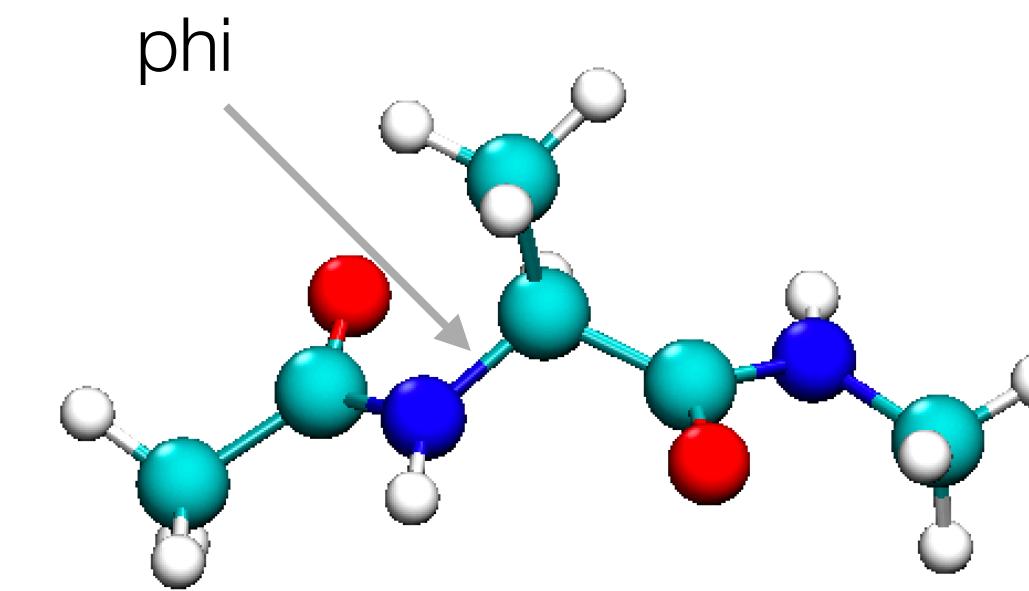
In particular we may try to force the system to explore a set of particular configurations by adding an harmonic potential centered on them:

In the case of Alanine dipeptide we may force the phi value to be close to specific values and then run multiple simulations using different values

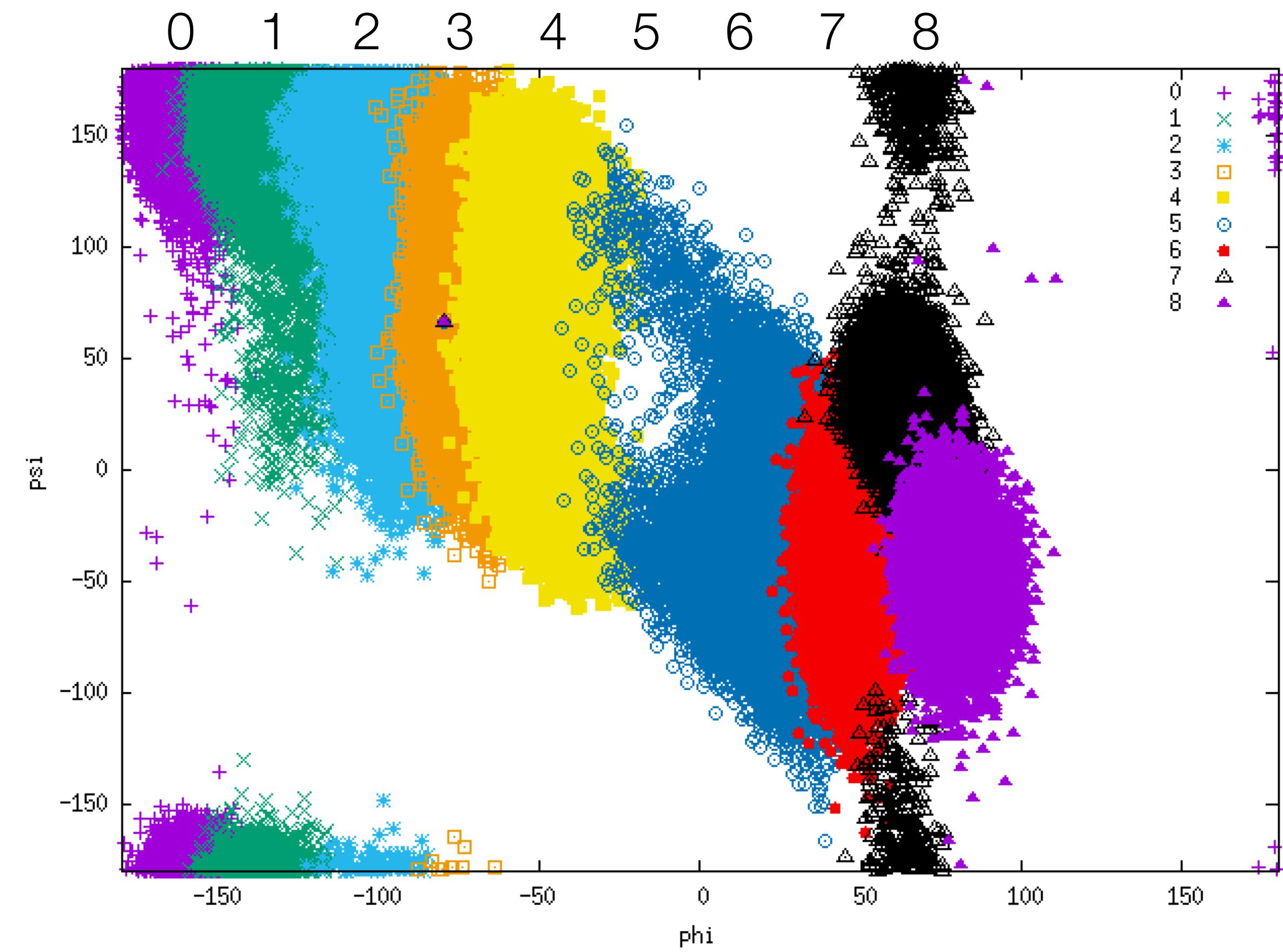


Umbrella Sampling

Many simulations are performed each one centred around a specific value of a conformational parameter

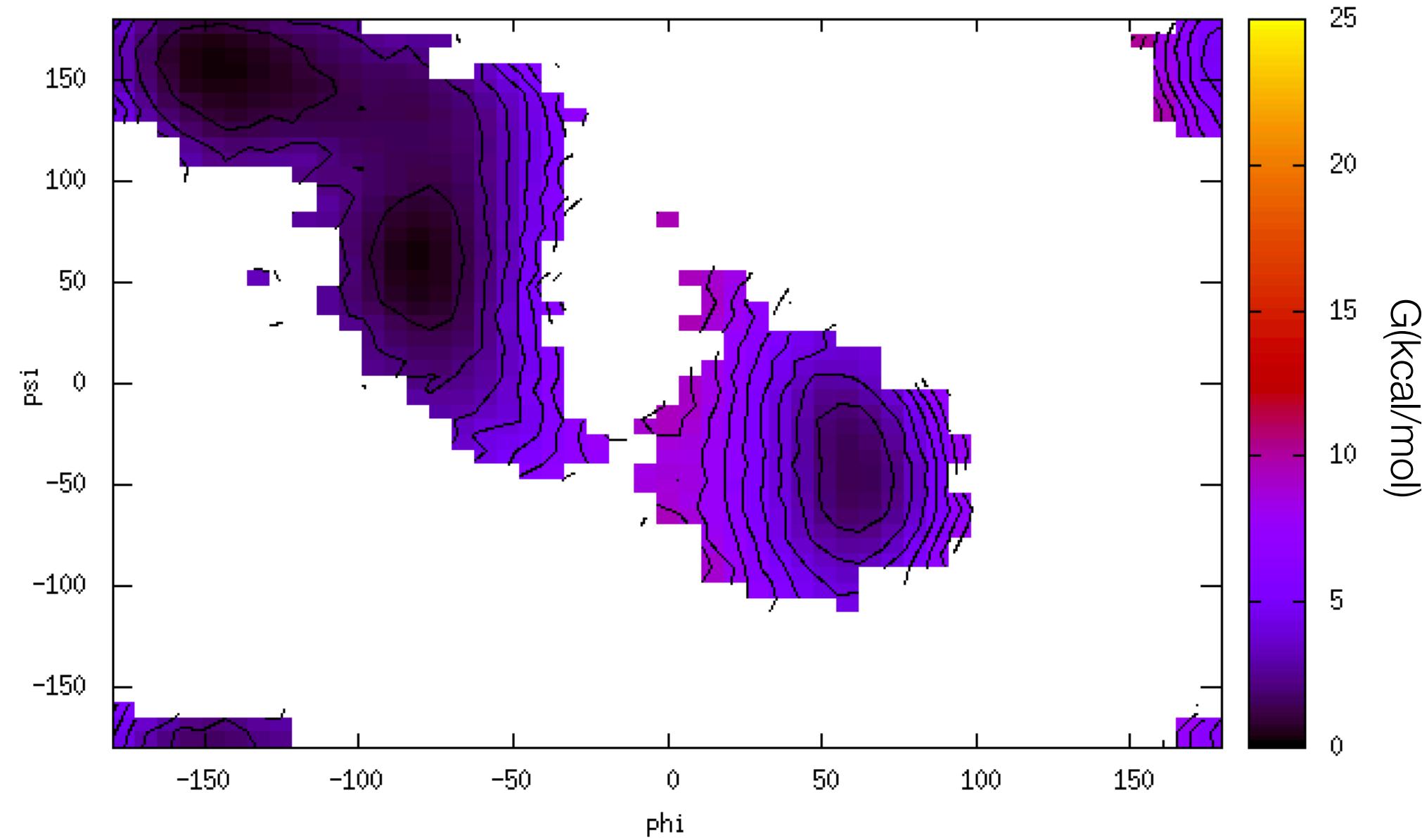
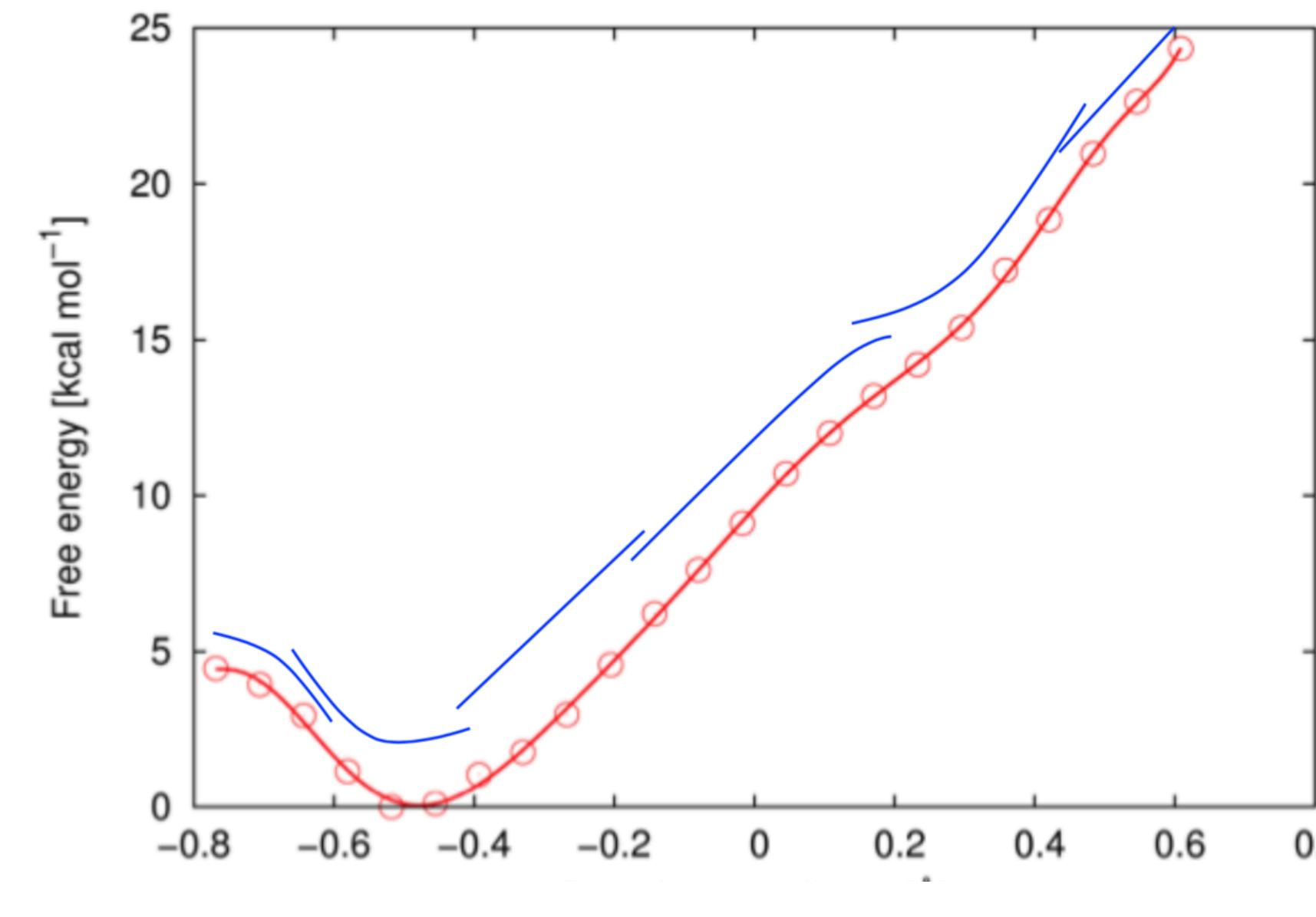


In this way we can force the simulation to sample regions that would not normally sample



Umbrella Sampling

Qualitatively the idea is that each simulation will give a local estimate and that we need to merge them together:





Metadynamics: learning on the fly

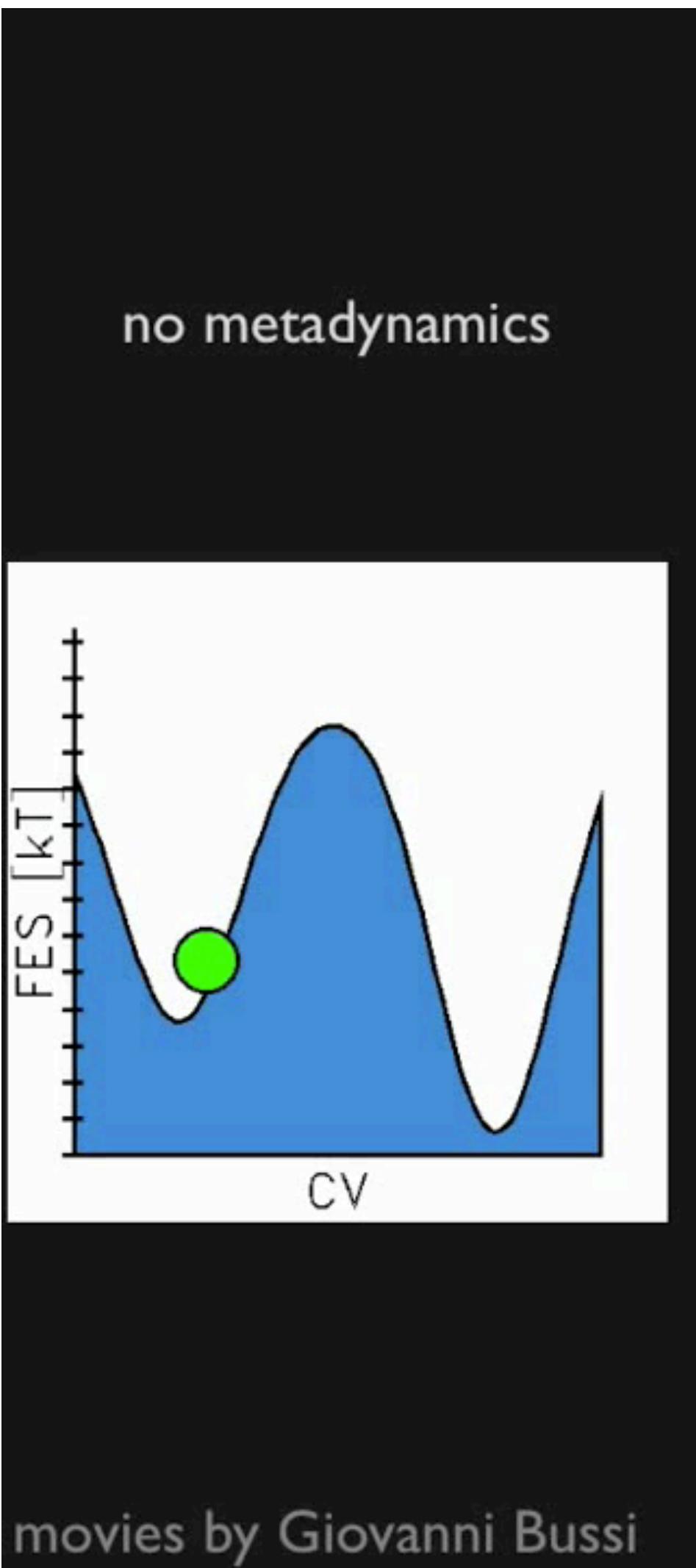
$$pdf'(x, t) \propto \exp \left[\frac{-(U(x) + V(f(x), t))}{k_B T} \right]$$

As a last case we will see how we can build a bias to speed up the simulation that learns by going.

In a standard MD the probability of visiting a conformation is constant

$$\dot{V}(s, t) = 0$$

This means that if two states are separated by a barrier it will be unlikely to cross the barrier (low probability) and visit a different state



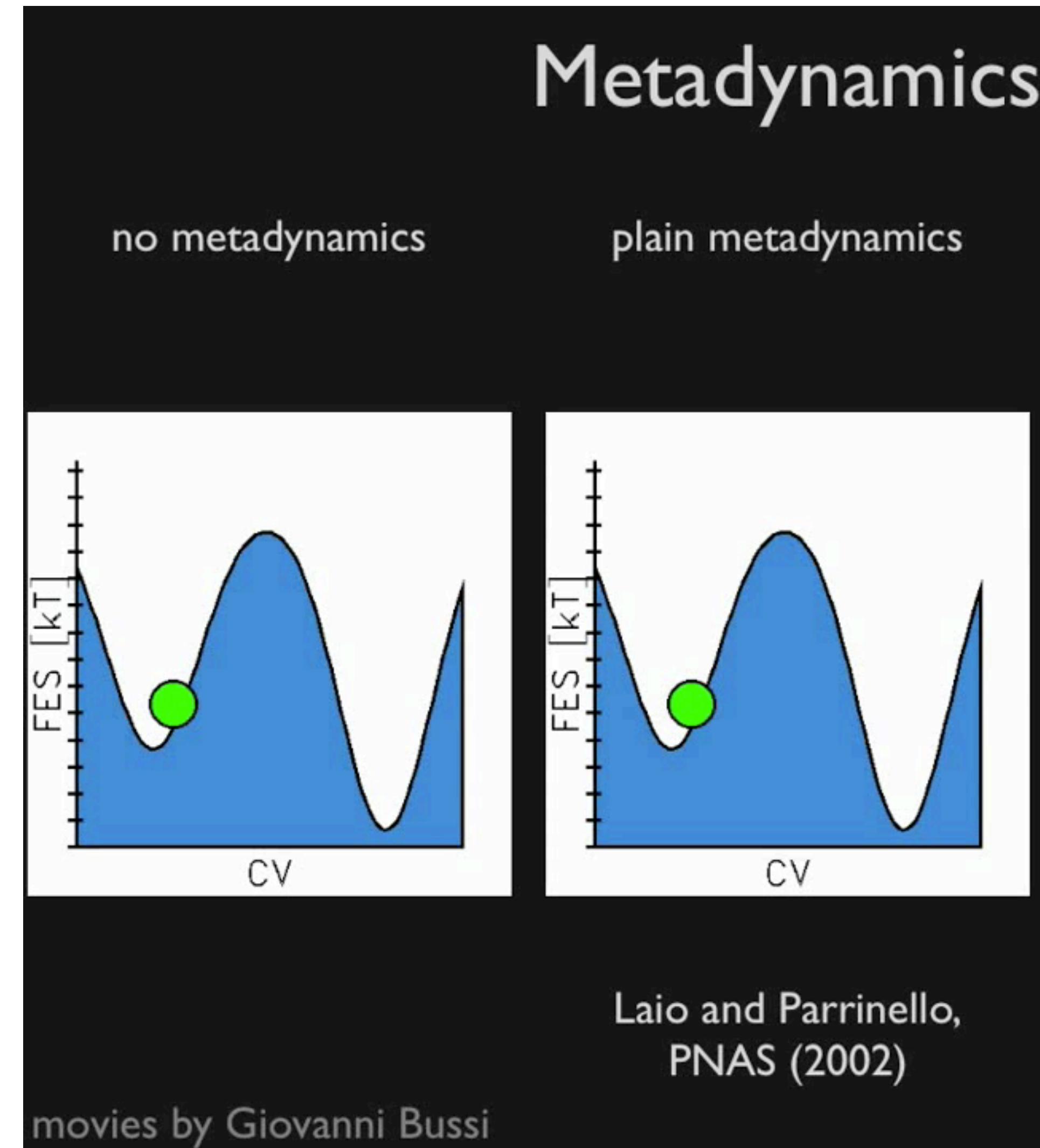


Metadynamics: learning on the fly

We can add a bias proportional to the time spent in a particular region. The problem is this never ends.

$$\dot{V}(s, t) = \omega e^{-(s-s(t))^2/2\sigma_s^2}$$

The original idea of metadynamics was to try to make the probability of visiting any conformation equal. But this result in making likely also very uninteresting configurations.



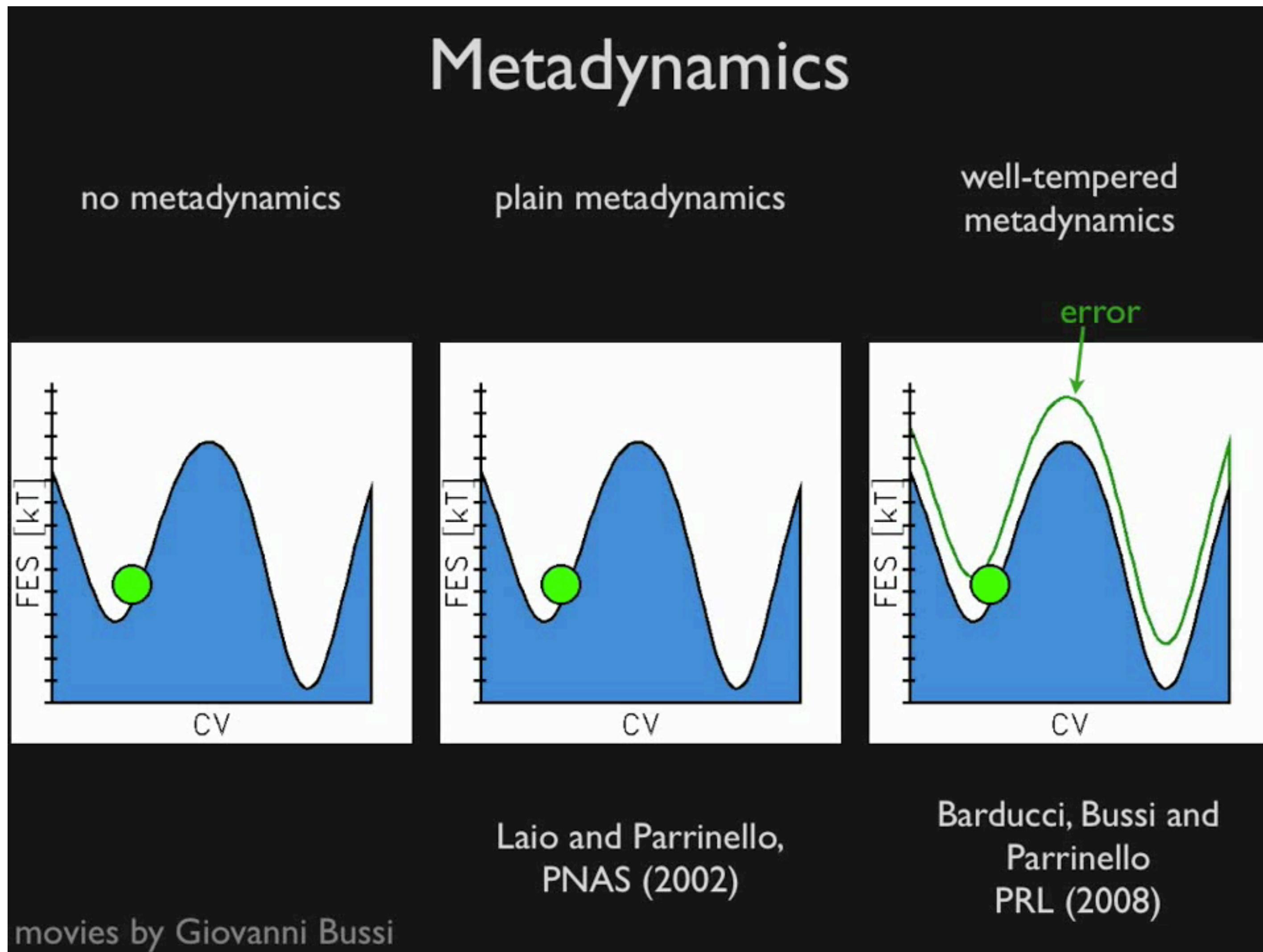


Metadynamics: learning on the fly

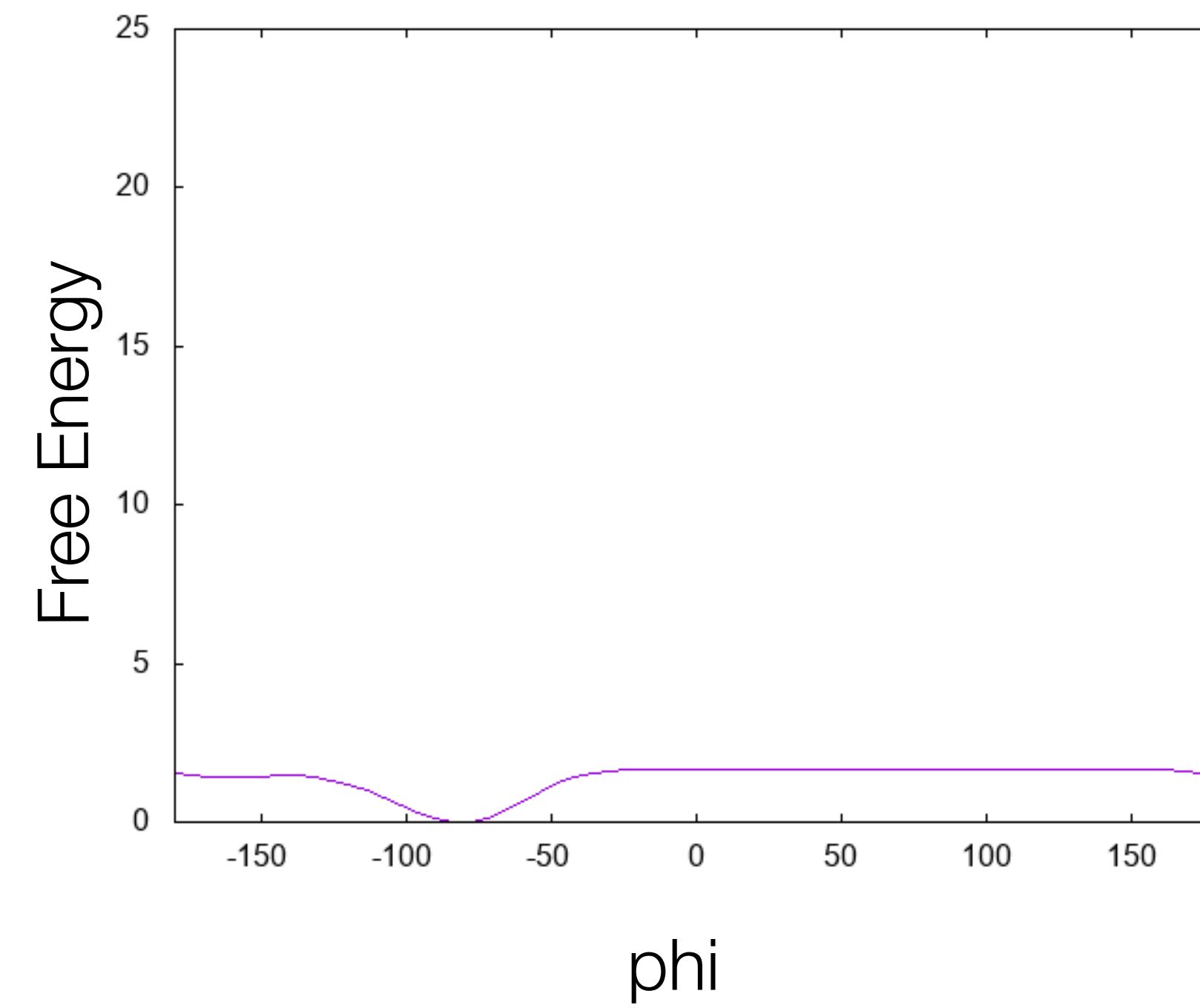
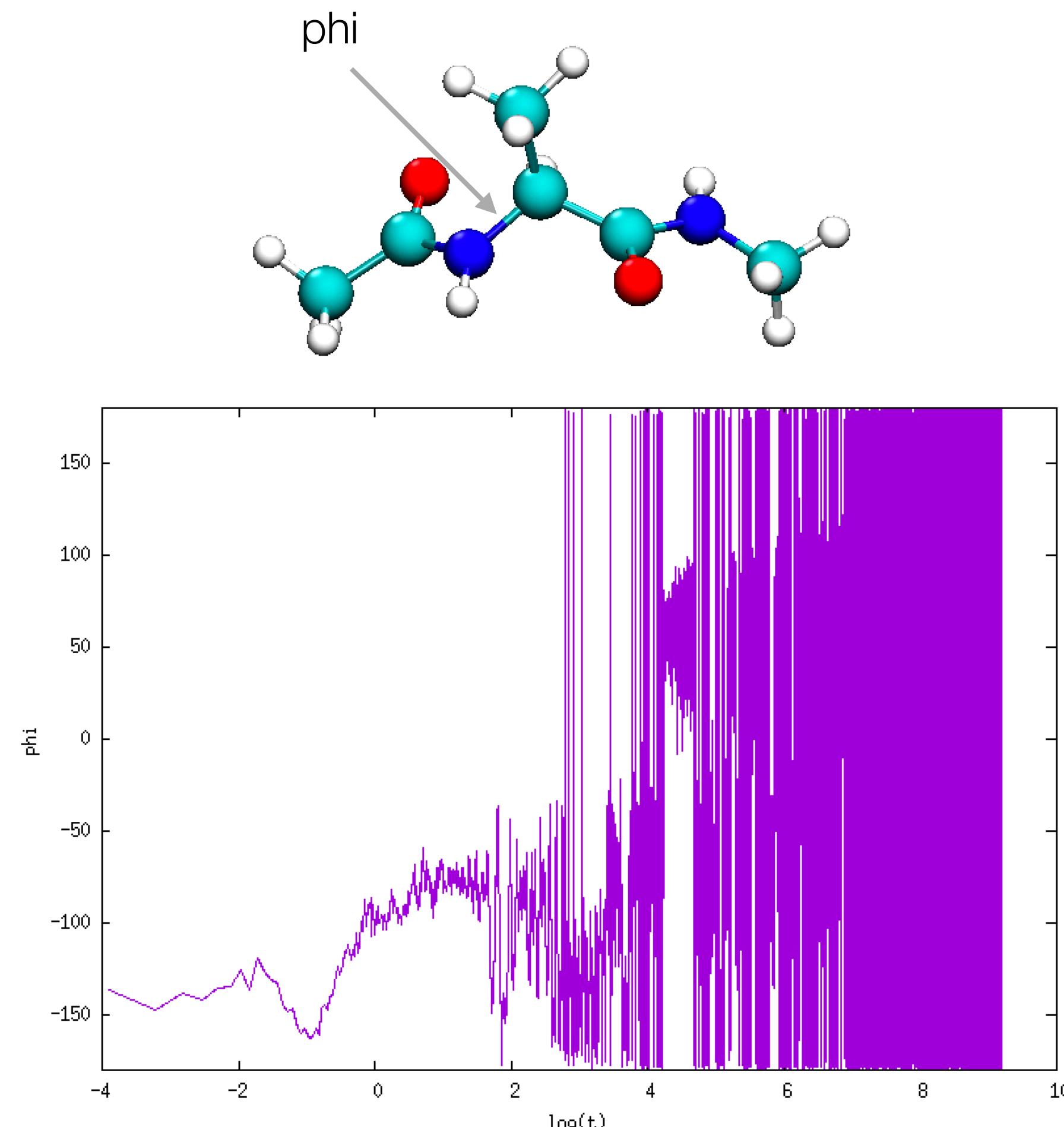
In Well-Tempered Metadynamics the idea is to increase the probability only of conformations up to some energy defined from a parameter ΔT

$$\dot{V}(s, t) = \omega e^{-[V(s, t)/\Delta T]} e^{-(s - s(t))^2 / 2\sigma_s^2}$$

We can add a bias proportional to the time spent in a particular region. But counting every addition as $1/t$

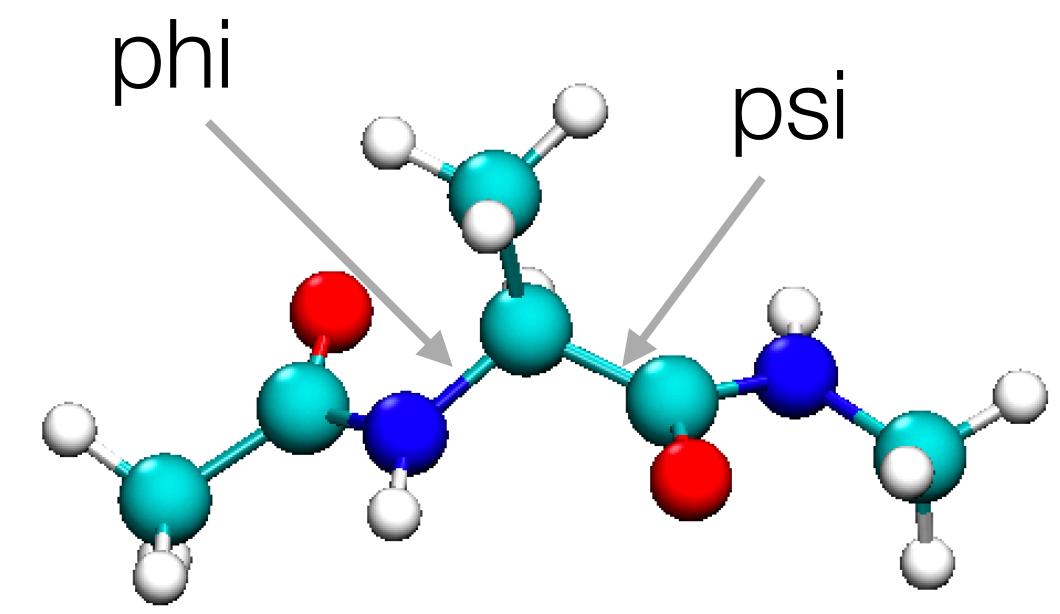


Metadynamics: learning on the fly

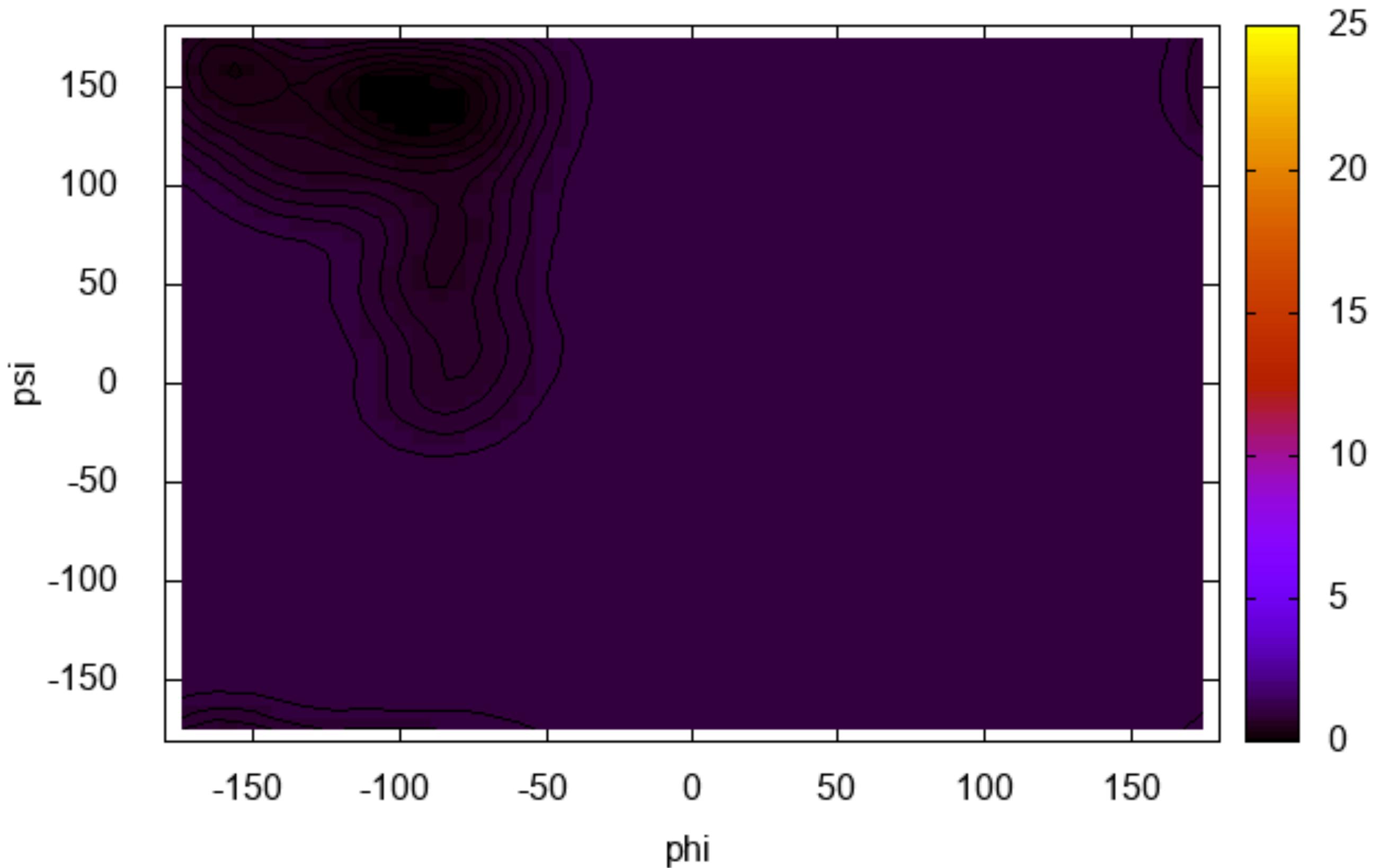


Now this is done with a single 10ns simulation (so 8x faster than PT or US)

Metadynamics: learning on the fly

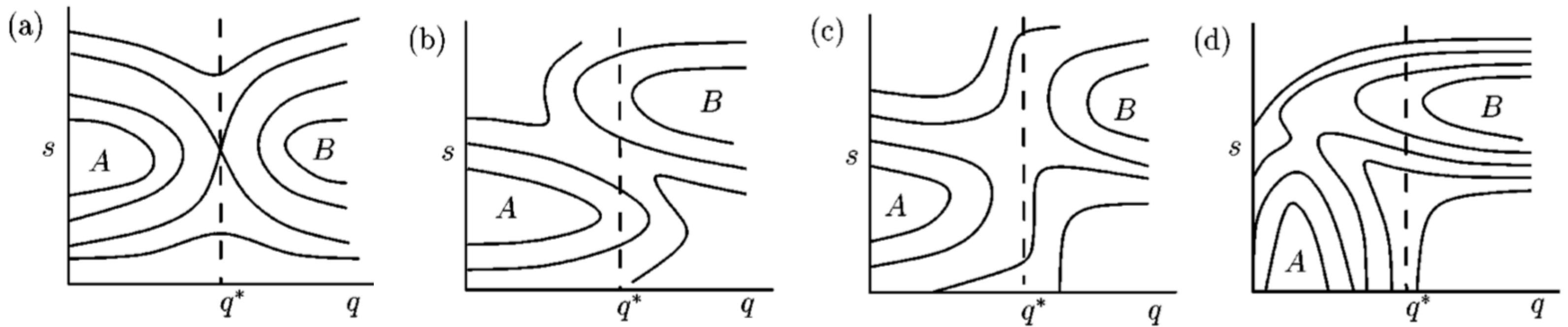


We can now easily run it in
more than 1D (2 or 3, not
much more)



Choosing CV can be tricky

Projections are tricky:



With Umbrella Sampling and Metadynamics the problem is not anymore how to speed up the sampling but how to choose a good collective variable, that is a good function that describes the process you are interested in.



Questions:

- What is the probability of finding a configuration given its potential energy and the environment temperature?
- What is the effect of increasing the temperature on the Boltzmann probability?
- If between two configurations one has lower potential energy, which one is more likely?
- How does Parallel Tempering work?
- What is the effect of adding a bias to Boltzmann?
- How does Umbrella Sampling work?
- How does Metadynamics work?

