The accelerated weight histogram method, AWH

for PMF calculations in GROMACS

Viveca Lindahl, KTH, Stockholm, Sweden

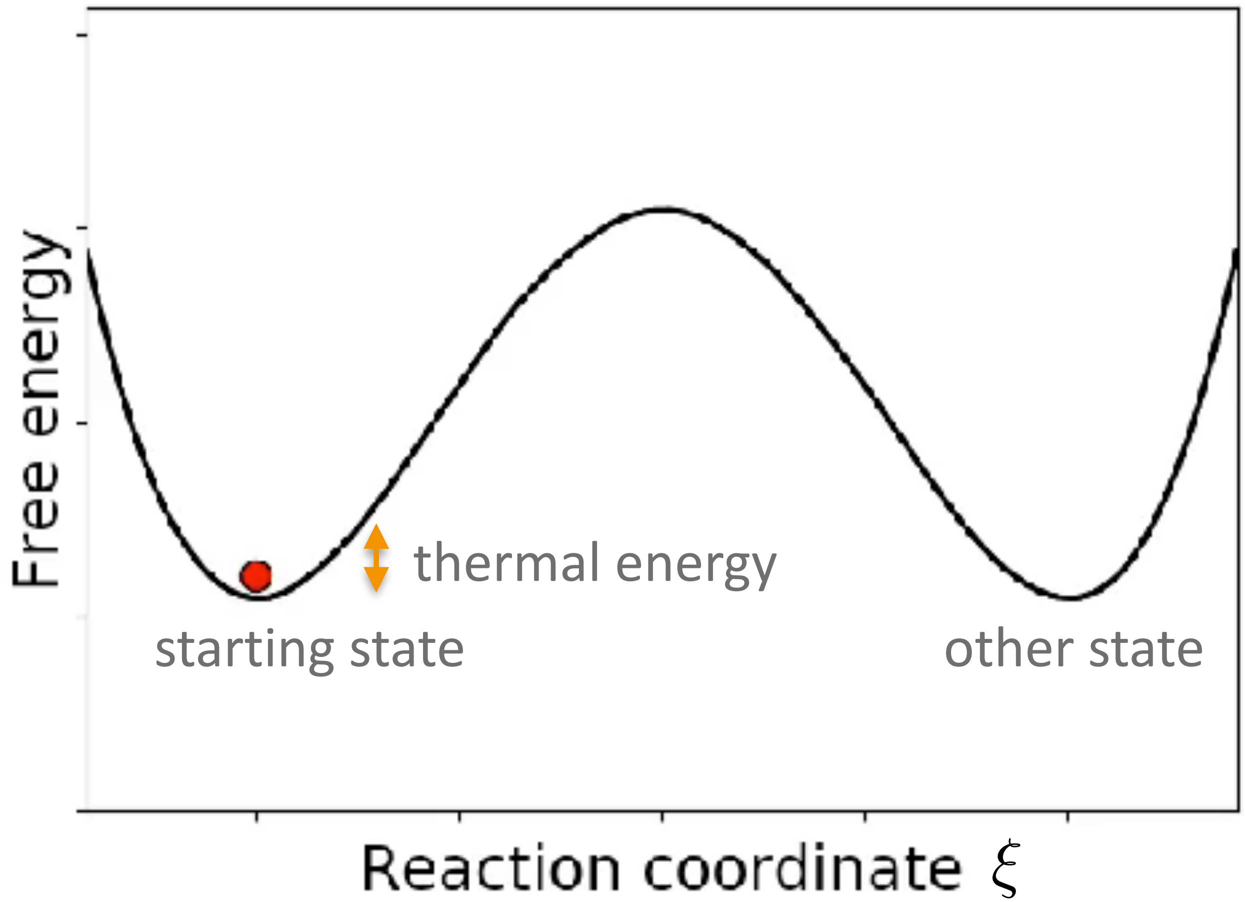
June 18, BioExcel Summer School 2018

Partners

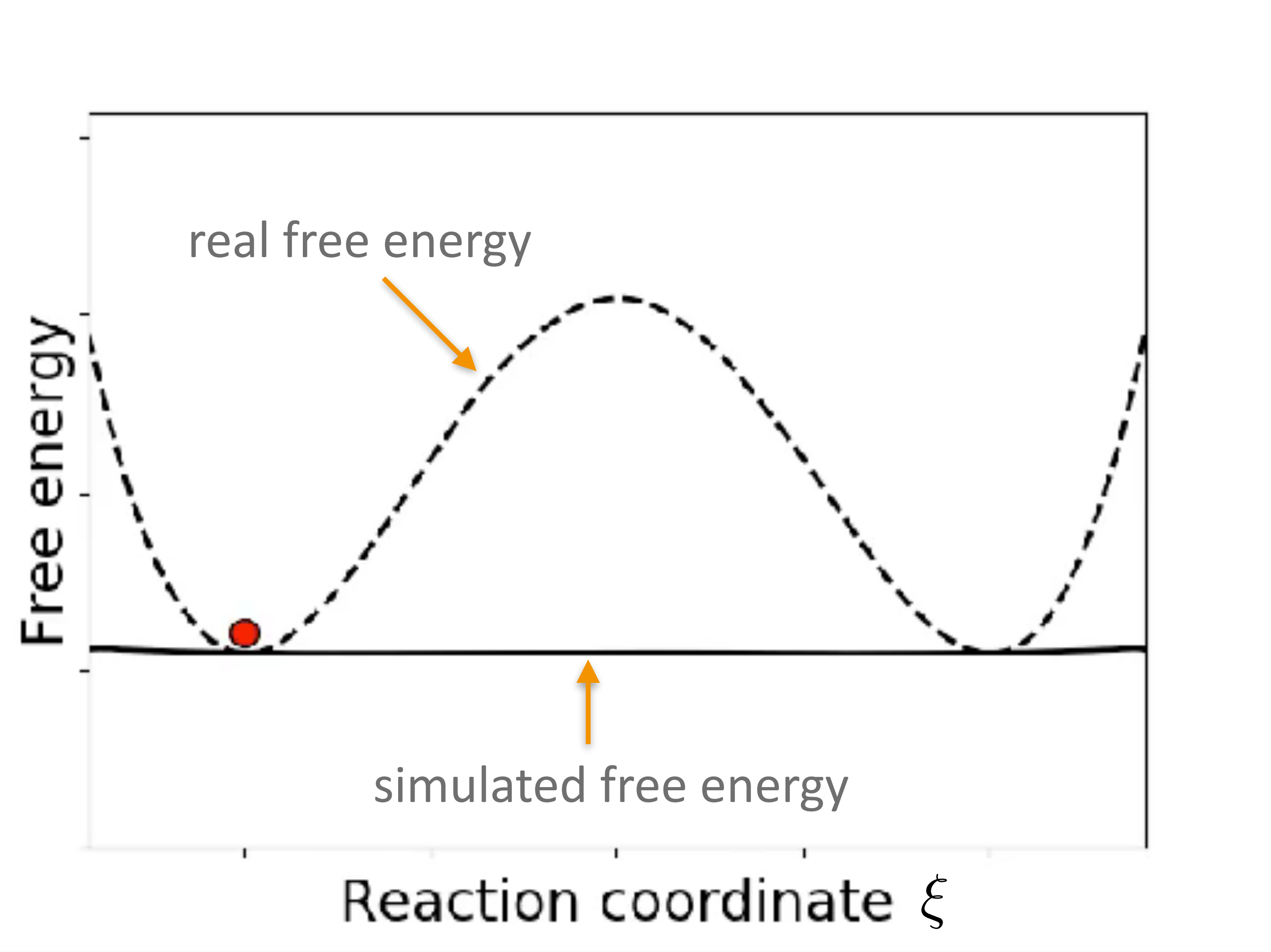
Funding

Horizon 2020 European Union Funding for Research & Innovation

The problem of free energy barriers



How we'd like to sample



Need the free energy to apply the right bias

reaction coord. free energy

$$\rho(\xi) = e^{-\beta F(\xi) + g(\xi)} \Leftrightarrow g(\xi) = \beta F(\xi) + \ln \rho(\xi)$$

target distribution bias function

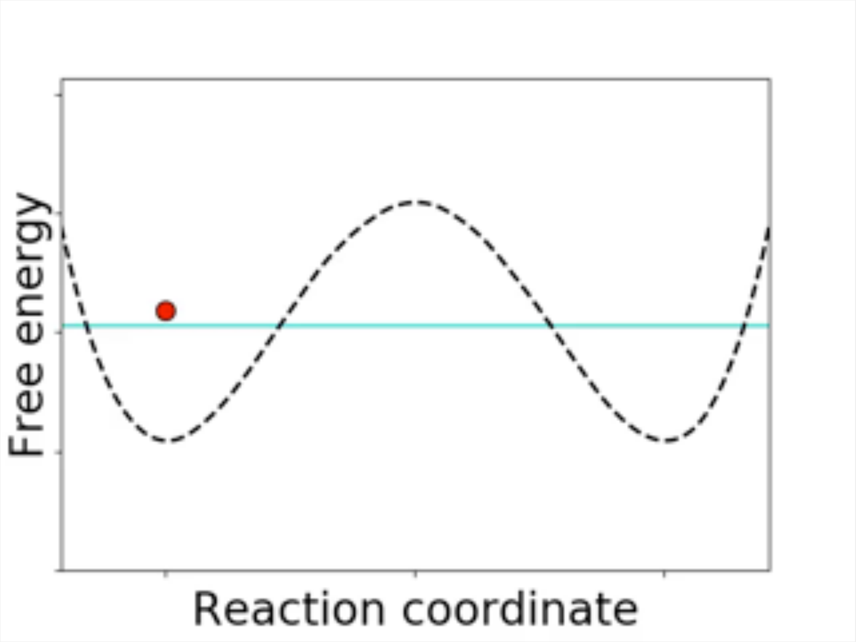
Calculating the free energy requires the bias,
the bias requires the free energy
— proceed adaptively!

AWH— Accelerated Weight Histogram method

Adaptively estimates free energy and applies the bias

Basic algorithm:

1. Estimate free energy
2. Set bias
3. Collect (biased) samples
4. Update free energy estimate

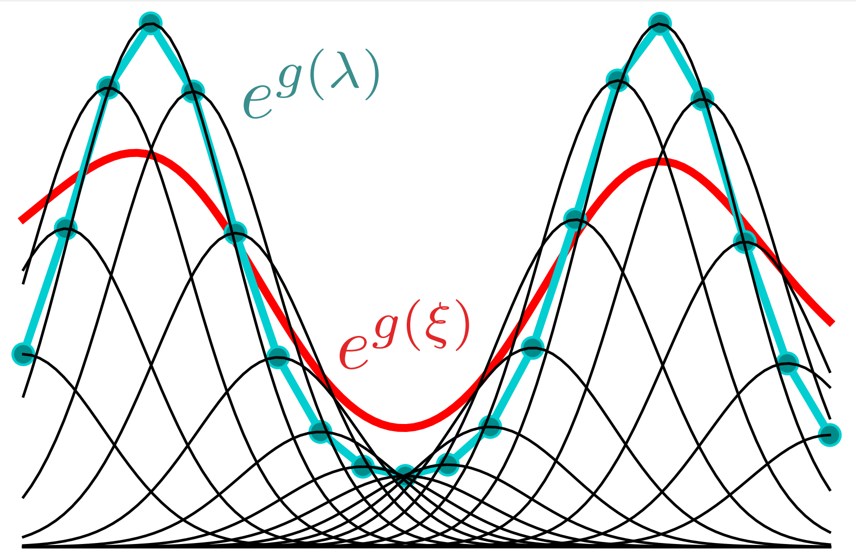


How is the bias represented and applied?

- Discretize ξ space with grid points λ
- Parameterize bias using Gaussian “basis” functions*

$$e^{g(\xi)} = \sum_{\lambda} e^{g(\lambda)} e^{-\frac{1}{2}\left(\frac{\xi-\lambda}{\sigma}\right)^2}$$

- Width σ sets resolution
- Bias force: $\nabla g(\xi(x))$



*abuse of notation: two different (but similar) functions *g*

Physical interpretation of λ

$$e^{g(\xi)} = \sum_{\lambda} e^{g(\lambda)} e^{-\frac{1}{2}\left(\frac{\xi-\lambda}{\sigma}\right)^2}$$

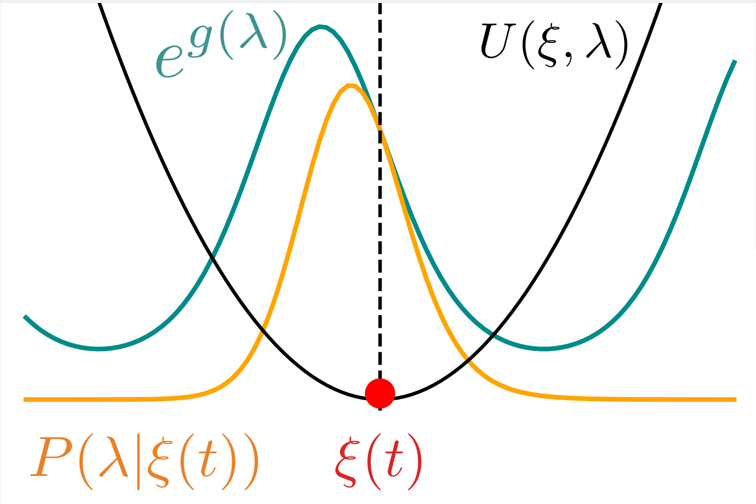
Probabilistically the same as a having a "particle" at λ that experiences an external bias g(λ) and interacts with ξ through a harmonic potential

$$U(\xi,\lambda) = \frac{k}{2}(\xi-\lambda)^2, \qquad k = \frac{\beta}{\sigma^2}$$

force constant

λ stays close to ξ for large force constants:

$$P(\lambda|\xi(t)) \propto e^{g(\lambda)-\frac{1}{2}\beta k(\xi(t)-\lambda)^2}$$



AWH works on λ rather than ξ

The algorithm again, now with more detail

1. Estimate free energy 2. Set bias 3. Collect samples 4. Update free energy

estimate $F_n(\lambda) \approx F(\lambda)$ exact

$$e^{-\beta F(\lambda)} = \int e^{-\beta F(\xi)} e^{-\frac{1}{2}\left(\frac{\xi-\lambda}{\sigma}\right)^2}$$

"convolved free energy"

- The PMF F(ξ) is extracted by an on the fly reweighting procedure

AWH works on λ rather than ξ

The algorithm again, now with more detail

1. Estimate free energy **2. Set bias** 3. Collect samples 4. Update free energy

$$g_n(\lambda) = \beta F_n(\lambda) + \ln \rho(\lambda)$$

bias free energy estimate target

AWH works on λ rather than ξ

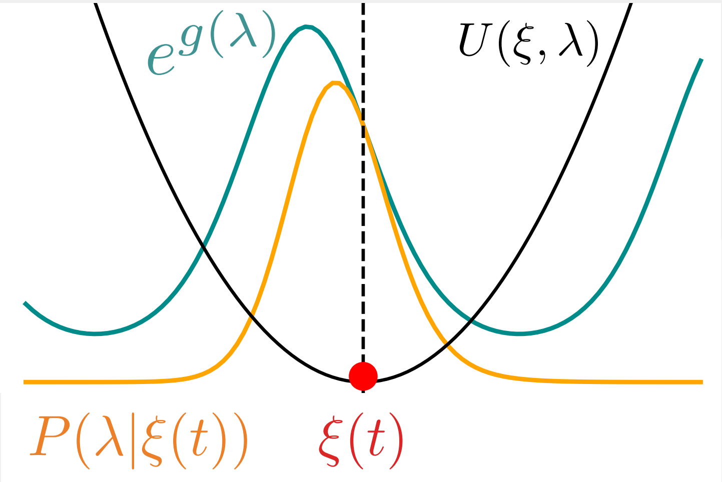
The algorithm again, now with more detail

1. Estimate free energy 2. Set bias **3. Collect samples** 4. Update free energy

sample at time t, bias g_n

$$w_n(\lambda|\xi(t)) = P_n(\lambda|\xi(t))$$
$$= e^{g_n(\lambda) - \frac{1}{2}\beta k(\xi(t)-\lambda)^2}$$

a “biased” Gaussian



AWH works on λ rather than ξ

The algorithm again, now with more detail

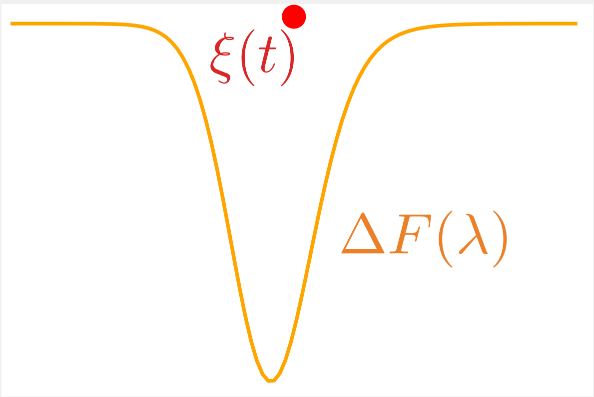
1. Estimate free energy 2. Set bias 3. Collect samples **4. Update free energy**

what was sampled

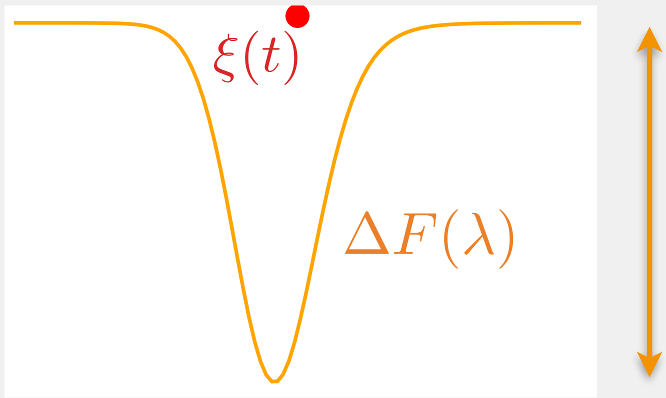
$$\Delta F_n(\lambda) \approx -\frac{\sum_t w_n(\lambda|t)}{N_n \rho(\lambda)}$$

prior number of samples

how we hoped to sample



The free energy update size



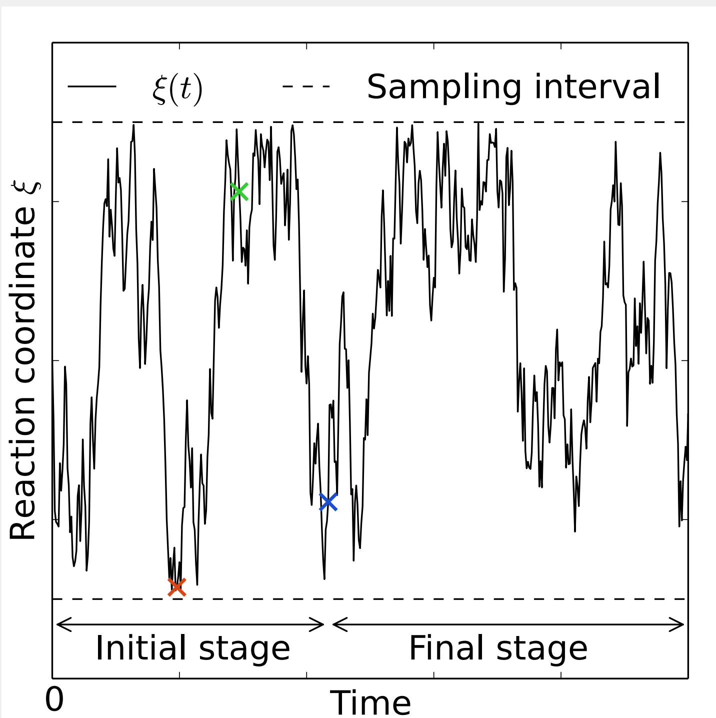
$$|\Delta F_n| \sim \frac{1}{N_n}$$

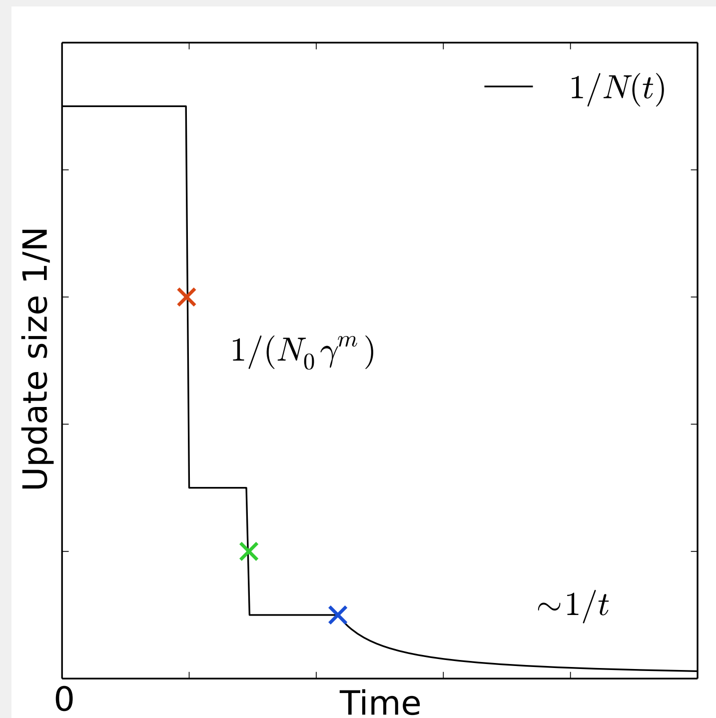
- N ~ total number of prior samples
- reflects the accuracy of the free energy estimate
- should grow at sampling rate

$$N_n \sim t$$

Adding robustness — the initial stage

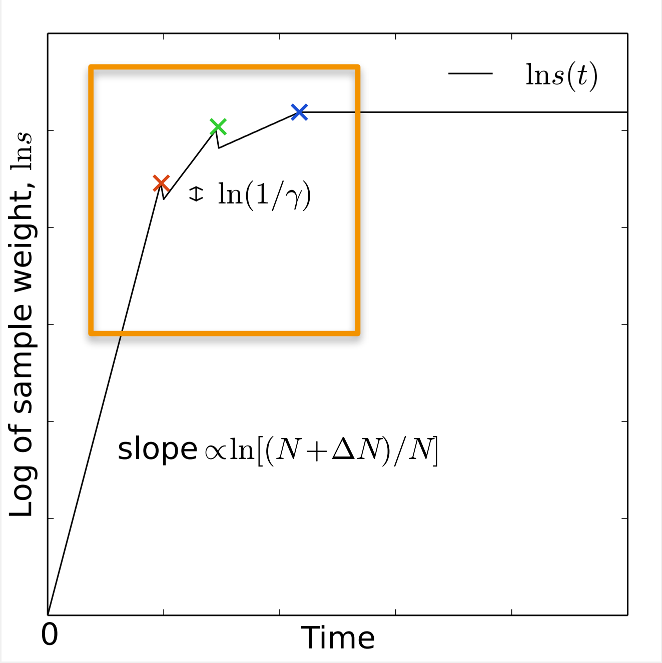
- Letting N grow at “naturally” decreases the update size too rapidly initially
- *The initial stage:* keep the update size large for the first few transitions.
- After each covering of the sampling interval $N_{n+1} = \gamma N_n$

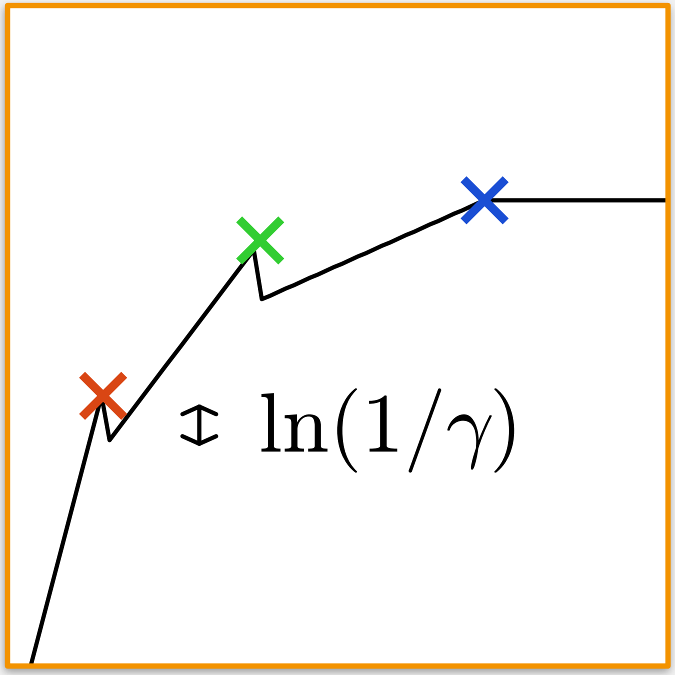




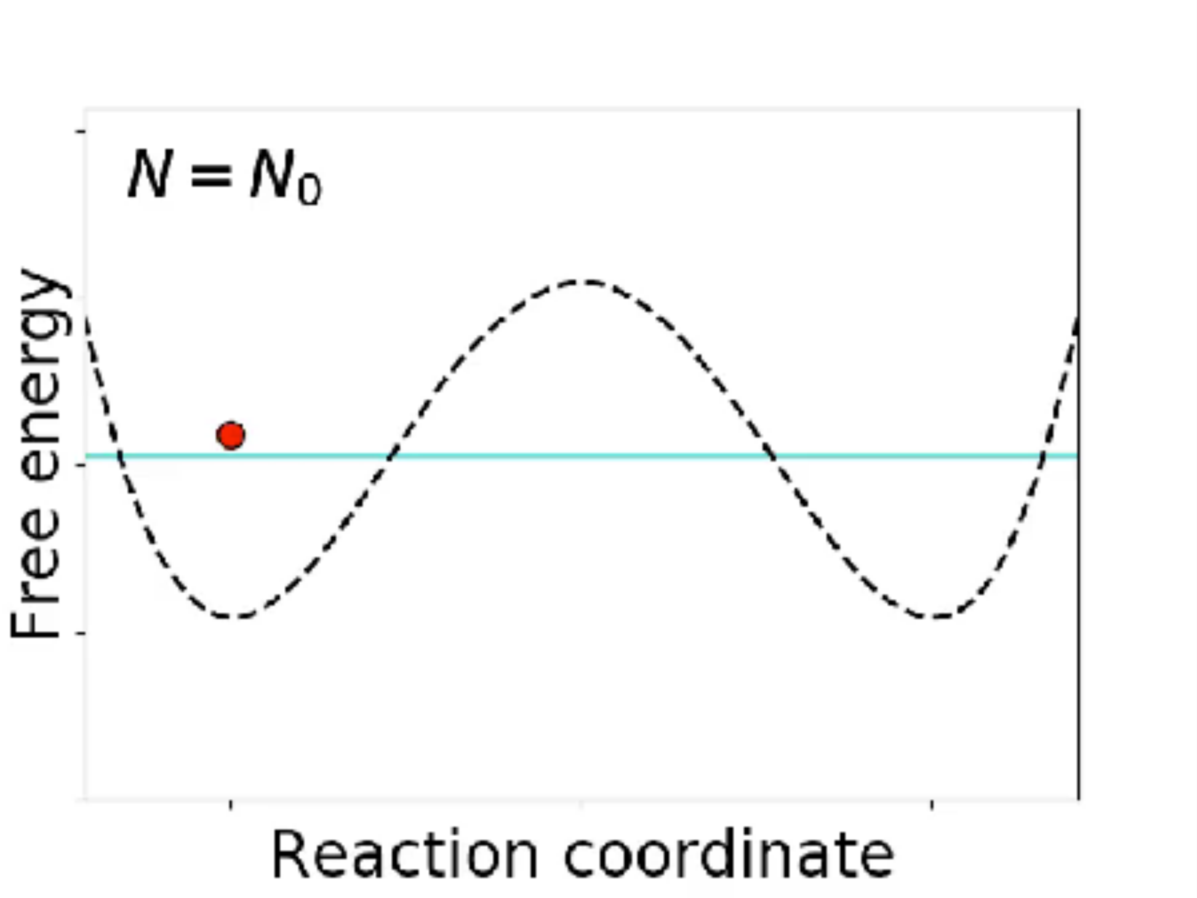
Exiting the initial stage

- Scaling N is corresponds to rescaling the current sample weight
- Scaling up, $N_{n+1} = \gamma N_n$, *decreases* sample weight
- Scaling down, $N_n = \text{const.}$, *increases* sample weight
- Exit initial stage when sample weight is no longer increasing





AWH in action

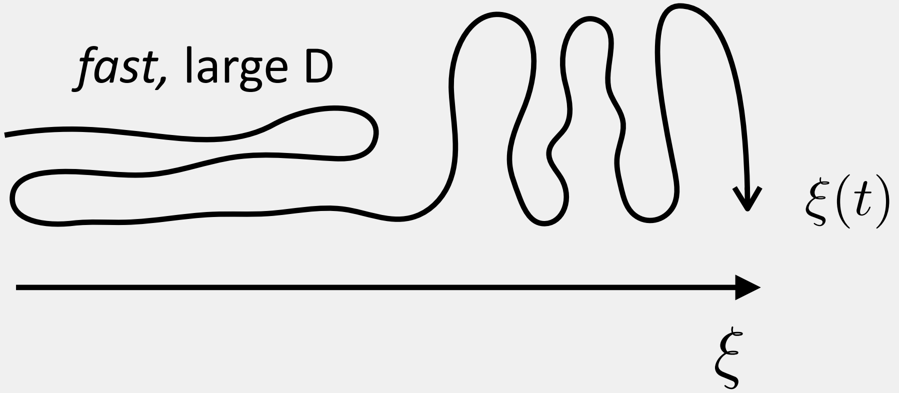


The initial update size $|\Delta F| \sim \frac{1}{N}$

- Sets fluctuation of the free energy and the bias.
- Slow regions get larger fluctuations than fast ones (given N)
- Parameterized in AWH by a *diffusion constant* D

$$\frac{1}{N_0} \sim D$$

- Slow system — small D
- Fast system — large D



Acknowledgements

Berk Hess and Jack Lidmar, KTH