An adaptive method for free energy computations

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Sampling the canonical measure

Consider a system of N particles with coordinates $q \in \mathbb{R}^{3N}$ interacting through the potential $V : \mathbb{R}^{3N} \to \mathbb{R}$.

In statistical physics we are often interested in sampling the canonical measure

$$\mu(dq) = Z^{-1} e^{-\beta V(q)} dq$$

where $\beta = 1/(k_B T)$.

To sample this measure we use the overdamped Langevin dynamics

$$dX_t = -\nabla V(X_t) dt + \sqrt{2\beta^{-1}} dW_t$$

where $X_t \in \mathbb{R}^d$ is the system trajectory and W_t a standard Brownian motion.

However, sampling is often difficult due to metastabilities

- Assume that the slow variable is $\xi(q) = z$, where $\xi : \mathbb{R}^{3N} \to \mathbb{R}$.
- ξ is called the collective variable or reaction coordinate (RC).
- The image of the canonical measure in ξ has density

$$\psi^{\xi}(z) = \int_{\mathbb{R}^d} \psi(q)\delta_{\xi(q)-z}$$

- The free energy is then defined by $A(z) = -\beta^{-1} \ln \psi^{\xi}(z)$.

How can we efficiently compute the free energy?

Free Energy difference

One more often computes the free energy difference

$$\Delta A = A(z_1) - A(z_0) = \int_{z_0}^{z_1} A'(z)\, dz.$$

It can be shown that $A'(z)$ is the conditional expectation

$$A'(z) = \mathbb{E}\left[F^V(X)|\xi(X) = z\right]$$

where $F^V = \frac{\nabla V \cdot \nabla \xi}{|\nabla \xi|^2} - \beta^{-1}\text{div}\left(\frac{\nabla \xi}{|\nabla \xi|^2}\right)$.

Adaptive Biasing Force methods

The idea of the Adaptive Biasing Force (ABF) method is to bias the standard dynamics:

$$\begin{cases} dX_t = -\nabla(V - A_t \circ \xi)(X_t)dt + \sqrt{2\beta^{-1}}dW_t \\ A_t'(z) = \mathbb{E}\left[F^V(X_t)|\xi(X_t) = z\right] \end{cases}$$

If the process X_t has law $\psi_t dq$ then the marginal law in ξ satisfies

$$\partial_t \psi_t^\xi = \beta^{-1}\partial_{zz}\psi_t^\xi$$

Furthermore, if $A_t' = A'$, then $\psi_\infty = Z^{-1}e^{-\beta(V - A\circ\xi)}$ and the marginal measure in ξ is uniform.

The aim of the ABF method is therefore twofold:

1. to serve as an adaptive importance sampling method.
2. to compute free energy differences efficiently.

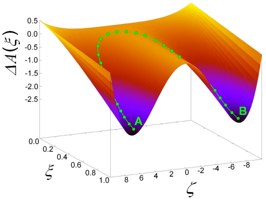
But in practice, how is A'_t computed?

Single-replica ABF

1. Original ABF: trajectorial averaging (Darve *et al.*, 2001)

$$A'_t(z) = \frac{\int_0^t F^V(X_s)\delta_{\xi(X_s)-z}\, ds}{\int_0^t \delta_{\xi(X_s)-z}\, ds}$$

- Single-replica simulations can lead to slow convergence
- We may be overlooking other slow degrees of freedom



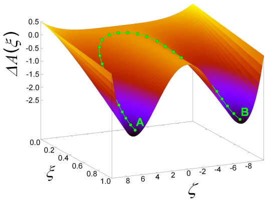
Multiple-replica ABF

Use of multiple replicas can speed up convergence (Lelièvre et al., 2007)

2. MR-ABF: averaging over trajectories and $R > 1$ replicas

$$A'_t(z) = \frac{\displaystyle\sum_{i=0}^{R-1} \int_0^t F^V(X_s^i)\delta_{\xi(X_s^i)-z}\, ds}{\displaystyle\sum_{i=0}^{R-1} \int \delta_{\xi(X_s^i)-z}\, ds}$$

- Replicas are likely to explore different valleys
- Method is easily parallelized...



Selection: improving sampling in ξ

Advantage of MR-ABF: we can further accelerate the diffusion in ξ:

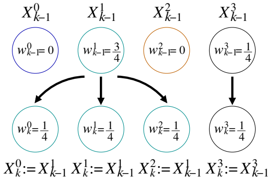
$$\partial_t \psi_t^\xi = \beta^{-1} \partial_{zz} \psi_t^\xi + S(t,z) \psi_t^\xi$$

Choosing $S(t,z) = c \frac{\partial_{zz} \psi_t^\xi(z)}{\psi_t^\xi(z)}$ gives rise to

$$\partial_t \psi_t^\xi = \left(\beta^{-1} + c\right) \partial_{zz} \psi_t^\xi$$

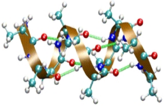
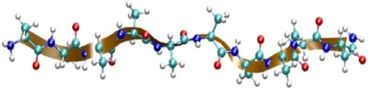
This can be implemented by assigning each replica i with weight

$$w_t^i \propto \exp\left(\int_{t_0}^{t} S(s, \xi(X_s^i)) ds \right)$$



Application: deca-alanine

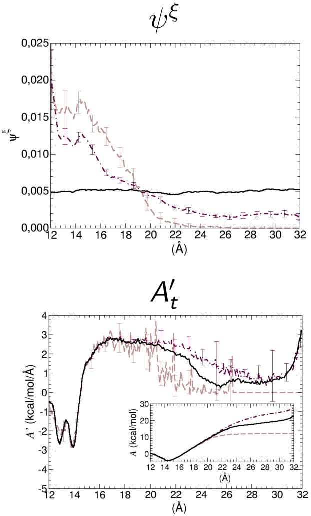
These two methods are compared for the unfolding of the deca-alanine peptide

 $\longrightarrow$ 

The reaction coordinate ξ is chosen as the end-to-end distance of the peptide chain.

- From α-helix to extended states $\xi : 12 - 32$ Å
- Compact states $\xi : 4 - 16$ Å

Extended conformations



ξ : **12 – 32 Å** 

Results from simulations after 0.25 ns:

- Single-replica simulations rarely stretch beyond $\xi = 22$ Å
- Multiple-replica simulations explore the whole RC space and mean force approximations nearly converged

– – – Original ABF (1 replica)

– · –· MR-ABF (16 replicas)

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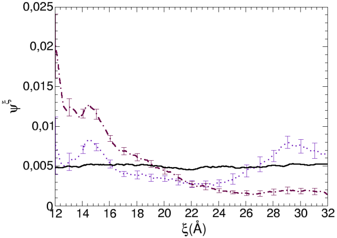
Results in range ξ : 12 – 32 Å



ξ : **12 – 32 Å** 

Results from 16-replica simulations after 0.25 ns

— · — · MR-ABF

· · · · · · MR-ABF with selection

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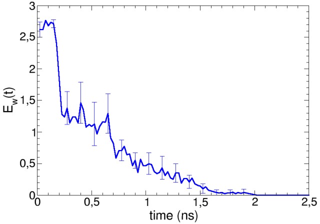
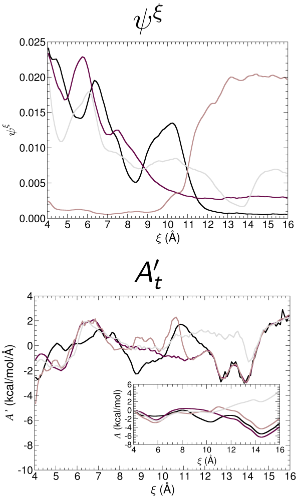


Relative entropy of weights:

$$E_w(t) = \sum_{i=0}^{R-1} w_t^i \log(w_t^i) - \log(1/R)$$

Stop selection when $E_w(t) < \varepsilon \log(R)$



ξ : **4 – 16 Å** 

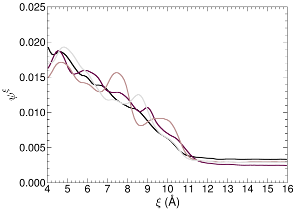
Results from four independent single-replica simulations after 100 ns:

- Mean force estimations are inconsistent
- One simulation shows global minimum at $\xi = 6$ Å

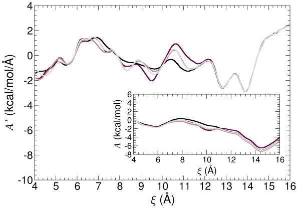
Why? Metastabilities at fixed ξ.

Compact conformations: 32-replica ABF

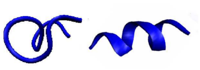
ψ^ξ



A'_t



ξ : **4 – 16 Å**



Results from four independent 32-replica simulations after 100 ns:

- Qualitatively consistent mean force approximations
- The α-helix conformation recovered as the global minimum

Conclusion

Conclusion

Multiple replicas speed up convergence of ABF

- well chosen RC: selection can accelerate diffusion in ξ.
- suboptimal RC: multiple replicas help to explore parallel valleys

Current work

Mathematical proof of the convergence of MR-ABF in the case of multiple valleys.

Reference: K. Minoukadeh, C. Chipot and T. Lelièvre, *Parallel algorithms for free energy calculations: a multiple replicas adaptive biasing force approach.* In preparation