Adaptive Biasing Force Simulations with Multiple Replicas

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Introduction

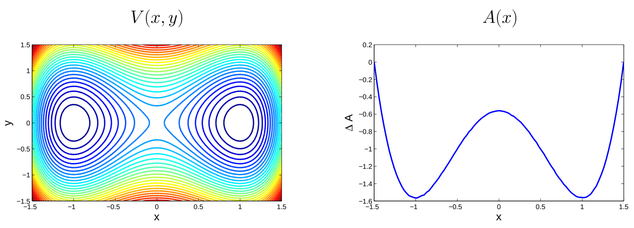
- In computational physics, one common and challenging task is to calculate statistical properties according to the canonical (NVT) ensemble with density $\mu(dq) = Z^{-1}e^{-\beta V(q)}dq$
- This measure can be sampled by the dynamics: $dX_t = -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dW_t$
- Ensemble averages can then be estimated using trajectorial averages $\int_{\mathcal{D}} A(q)\mu(dq) = \lim_{T\to\infty}\frac{1}{T}\sum_{t=0}^{T} A(X_t)$

Free energy calculation

We are interested in calculating free energy associated to some slow degree of freedom or "reaction coordinate" ξ such as a dihedral angle or end-end distance of a protein.

Free energy

$$A(z) = -\beta^{-1}\ln\int_{\mathcal{D}}\mu(q)\delta_{\xi(q)-z}dq$$



In fact the derivative of the free energy, the so-called local mean force, can be expressed as a conditional expectation, which is much easier to estimate. The free energy can then be recovered up to an additive constant by numerical integration.

Local mean force: $A'(z) = \mathbb{E}_\mu\left[f(q)\,|\,\xi(q)=z\right]$ where $f = \frac{\nabla\xi\cdot\nabla V}{|\nabla\xi|^2} - \beta^{-1}\mathrm{div}\left(\frac{\nabla\xi}{|\nabla\xi|^2}\right)$

The above can be approximated by sampling the canonical measure and taking averages in bins along the reaction coordinate. The convergence however can be very slow due to metastabilities in the potential energy surface, most often these large energy barriers are found in along the reaction coordinate ξ.

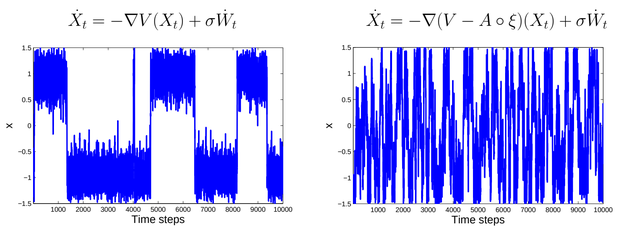
Adaptive Biasing Force method (ABF)

The ABF method is an adaptive importance sampling method. The idea is to approximate the local mean force at $\xi(q) = z$ by averaging over instantaneous forces observed by the system trajectory. This estimated mean force A'_t is then subtracted from the dynamics to reduce and eventually eliminate any force along ξ.

ABF dynamics:

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

Under certain regularity conditions, it is clear that $A'_t \to A'$ as $t\to\infty$. Once the biasing force has converged, we observe free diffusive behaviour in ξ. The graphics show the standard (left) and biased (right) dynamics for the potential $V(x,y)$ above.



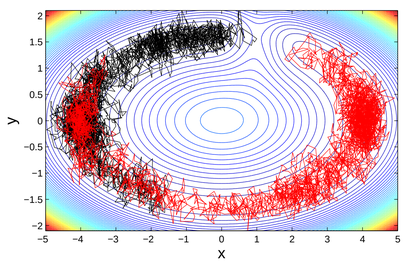
Calculating the bias

In recent literature different approaches have been proposed to calculate the bias A'_t.

- Standard ABF [2]: time average on single trajectory $\quad A'_t(z) \approx \frac{\sum_{s=0}^{t-1} f(X_s)\delta_{\xi(X_s)-z}}{\sum_{s=0}^{t-1}\delta_{\xi(X_s)-z}}$
- Multiple replica ABF [5]: instantaneous average on $R>0$ replicas $\quad A'_t(z) \approx \frac{\sum_{i=0}^{R-1} f(X_t^i)\delta_{\xi(X_t^i)-z}}{\sum_{i=0}^{R-1}\delta_{\xi(X_t^i)-z}}$

Overcoming metastability at the microscopic level

- It has been shown [6] that the convergence of ABF is limited by the log-Sobolev constant of the conditional measure $d\mu_{t,z} = \frac{\psi\, dz}{\psi^\xi(z)}$.
- The log-Sobolev constant can be very small in the presence of metastabilities at fixed $\xi(q) = z$.
- The image on the right demonstrates this: two parallel 'valleys' are separated by a large energy barrier at fixed x.
- Multiple replicas help to overcome this problem: it is likely that each replica will explore a different valley. The separating barrier at fixed ξ therefore no longer slows down convergence [4]!



References

[1] C. Chipot and J. Hénin, Exploring the free-energy landscape of a short peptide using an average force, *J. Chem. Phys.*, **123**, 244906 (2005).

[2] E. Darve and A. Porohille, Calculating free energy using average forces, *J. Chem. Phys.* **115**, 9196-9183 (2001).

[3] J. Hénin and C. Chipot, Overcoming free energy barriers using unconstrained molecular dynamics simulations *J. Chem. Phys.*, **121**, 2904 (2004)

[4] B. Jourdain, T. Lelièvre and K. Minoukadeh, Long-time convergence of an Adaptive Biasing Force method: the bi-channel case, In preparation.

[5] T. Lelièvre, M. Rousset and G. Stoltz, Computation of free energy profiles with parallel adaptive dynamics, *J. Chem. Phys.*, **126**, 134111 (2007).

[6] T. Lelièvre, M. Rousset and G. Stoltz, Long-time convergence of an adaptive biasing force method, *Nonlinearity*, **21**, 115-1181 (2008).

[7] K. Minoukadeh, C. Chipot and T. Lelièvre, Reversible stretching of a short peptide using parallel adaptive biasing force simulations, In preparation.

Numerical results [7]: Deca-alanine peptide

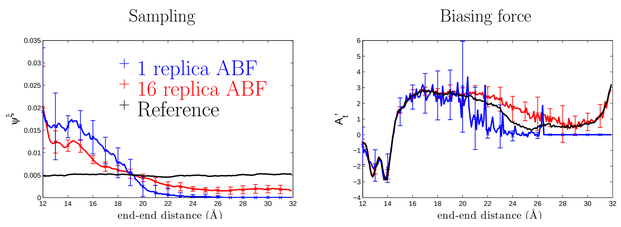
Numerical tests were carried out on the deca-alanine peptide, previously studied in [1].

▷ The parallel molecular dynamics code NAMD was used.

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

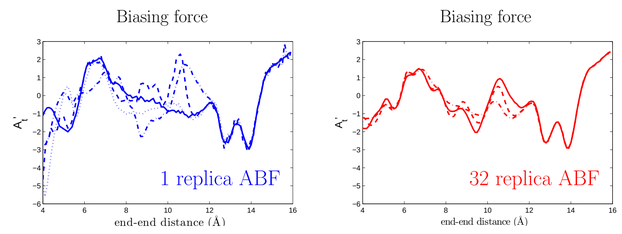
12 – 32 Å (extended states)

- Results after **0.25 ns**.
- **Standard 1-replica ABF:** system rarely explores beyond 22 Å.
- **Multiple replica ABF (16 walkers):** local mean force estimations nearly converged.



4 – 16 Å (compact states)

- Results after **100 ns**.
- **Metastabilities at microscopic level** common in compact states.
- **Standard 1 replica ABF:** each replica trapped in a 'valley'. Very slow convergence.
- **Multiple replica ABF:** proves essential for convergence.



Enhancing sampling through selection

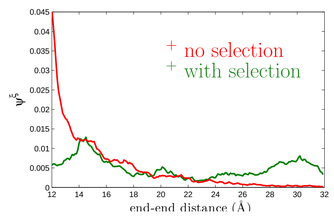
Further improvements have been made to the multiple replica ABF through a selection process [5].

- At time t, bin z in the reaction coordinate is assigned fitness value $S(t,z) = c\frac{\delta_{zz}\psi_t^\xi}{\psi_t^\xi}$.
- Every t_{ex} timesteps, replica i is assigned a weight $w_{t+t_{\mathrm{ex}}}^i \propto \exp\left(\int_t^{t+t_{\mathrm{ex}}} S(s,\xi(X_s^i))ds\right)$.

Selection speeds up convergence, most efficiently in the presence of metastabilities along ξ.

Numerical tests

- Multiple replica ABF simulations run with 16 walkers.
- System constrained between 12 and 32 Å.
- Figure on the right shows sampling distribution after 0.25 ns.
  - Faster exploration of the reaction coordinate space is observed for simulations **with selection**.

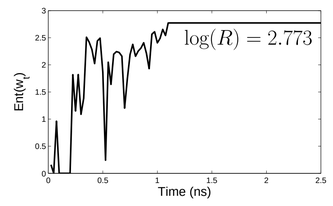


Selection constant and stopping criterion

- To avoid under-selection and degeneration of replica weights, the selection constant c must be chosen to be neither too small nor too large.
- Selection should be carried out at large intervals to avoid costly operations, e.g. relaunch of NAMD with new configuration files.
- The selection mechanism must be turned off once a certain criterion is satisfied to avoid unnecessary computational costs. Intuitively the criterion is chosen to be $\mathrm{Ent}(w_t) \geq 0.95\times\log(R)$, where

$$\mathrm{Ent}(w_t) = -\sum_{i=1}^{R} w_t^i\log(w_t^i).$$

Figure on the right shows the entropy of weights for a 2.5 ns simulation. Selection is stopped after about 1.25 ns once weights are distributed 'sufficiently' uniformly.



Implementation

In practice for multiple replica ABF, each replica runs independently on a separate processor. Exchange of information between replicas is carried out at every t_{ex} time steps.

Local information gathered independently on each processor

- We denote by $n_{\mathrm{local}}^i(t,z)$ the number of times the system trajectory X_t^i has visited bin z since the last exchange.
- We denote by $n_{\mathrm{total}}^i(t,z)$ the total number of times the system trajectory X_t^i has visited bin z.
- Mean force estimates, calculated locally on processor i and denoted by $A'_{t,i}$, will depend solely on its own trajectory X_t^i. At each timestep, the bias is updated as follows:

$$A'_{t,i}(z) = \frac{n_{\mathrm{local}}^i(t,z) - \delta_{\xi(X_t^i)-z}}{n_{\mathrm{local}}^i(t,z)}A'_{t-1,i}(z) + \frac{\delta_{\xi(X_t^i)-z}}{n_{\mathrm{local}}^i(t,z)}f(X_t^i)$$

Global information shared between processors

- The biasing force $\mathcal{A}'_t$, which is finally applied to the dynamics of all replicas, is updated to account for locally gathered information.

$$\mathcal{A}'_t(z) = \left(1 - \frac{N_{\mathrm{local}}(t,z)}{N_{\mathrm{total}}(t,z)}\right)\mathcal{A}'_t(z) + \frac{N_{\mathrm{local}}(t,z)}{N_{\mathrm{total}}(t,z)}A'_{\mathrm{local}}(t,z)$$

where $A'_{\mathrm{local}}(t,z)$ is the weighted average of the locally estimated mean forces $A'_{t,i}$, N_{local} is the number of visits from all replicas to bin z since the last exchange and N_{total} is the total number of visits to bin z since the beginning of the simulation.

Selection

- In practice, to make m_i copies of replica i, its coordinate and velocity files are passed to NAMD as the start-up files for N_i replicas.