Targeted, Learned, and Multimap FEP

1 Targeted, learned and multimap FEP

The Jarzynski formula can be expressed as

$$\Delta f_{12} = f_2 - f_1 = -\log \frac{\int_{\Gamma_2} e^{-u_2(\boldsymbol{y})}\, d\boldsymbol{y}}{\int_{\Gamma_1} e^{-u_1(\boldsymbol{x})}\, d\boldsymbol{x}}, \tag{1}$$

where u_1 is the *reference potential* and u_2 is the *target potential*. Recognize that their difference is the work described above.

targeted FEP via invertible maps Perform a change of variable $\boldsymbol{y} = \mathcal{M}(\boldsymbol{x})$ where $\mathcal{M} : \Gamma_1 \to \Gamma_2$ is an invertible map from the reference Boltzmann distribution to the target Boltzmann distribution. Then by multiplying and dividing the integrand by $e^{-u_1(\boldsymbol{x})}$ one obtains

$$\Delta f_{12} = -\log \left\langle e^{-w[\mathcal{M}](\boldsymbol{x})} \right\rangle_1, \tag{2}$$

where the generalized work $w[\mathcal{M}](\boldsymbol{x})$ is

$$w[M](\boldsymbol{x}) = u_2(M(\boldsymbol{x})) - \log |J_M(\boldsymbol{x})| - u_1(\boldsymbol{x}) \ . \tag{3}$$

This is the difference, given configurations sampled from the reference, between the target energy (on mapped configurations) and reference energy minus their change in volume (the Jacobian J).

Computing Δf_{12} thus comes down to running a simulation using the reference potential $u_1(\boldsymbol{x})$, computing the generalized work $w[\mathcal{M}](\boldsymbol{x})$ for each sampled $\boldsymbol{x}$, and taking the average. The convergence of this average is what matters (see chat). This takes advantage of the fact that the change of variable removes the need to comput[e the target partition function directly].

learning the invertible map The next step is defining a loss function, so that each map can be learned. So a Boltzmann distribution associated with the effective potential is defined

$$p_2'[\mathcal{M}](\boldsymbol{x}) = e^{f_2 - u_2'[\mathcal{M}](\boldsymbol{x})}, \tag{4}$$

where we try to find $\mathcal{M}$ such that $p_2'[\mathcal{M}](\boldsymbol{x})$ is as close to $p_1(\boldsymbol{x})$ as possible. Given N samples drawn from $p_1(\boldsymbol{x})$, the negative log-likelihood of the data (up to a constant $1/N$) is

$$\mathcal{L} = -\frac{1}{N} \log \prod_{i=1}^{N} p_2'[\mathcal{M}](\boldsymbol{x}_i), \tag{5}$$

$$\mathcal{L} = \frac{1}{N} \sum_{i=1}^{N} (u_2(\mathcal{M}(\boldsymbol{x}_i)) - \log |J_{\mathcal{M}}(\boldsymbol{x}_i)| - f_2). \tag{6}$$

In the limit of $N \to \infty$, this is equivalent to minimizing the KL divergence between $p_1(\boldsymbol{x})$ and $p_2'(\boldsymbol{x})$.

Obstacle of learned FEP The main theoretical obstacle is that these data come from multiple distributions because the map changes at each optimization step.

2 reference potentials

(cite the multimap paper) Operationally, standard FEP is performed with an additional step in which the maps are gradually improved by exploiting the information within forces.

Experimentally, the HiPen dataset of small molecules is used. The free energy between switching from a general small molecule forcefield to a DFTB3 description of the potential in vacuum is used. Multimap TFEP was more efficient than standard FEP and previous nonequilibrium approaches. This is a fundamental step toward obtaining binding free energies using QM/MM potentials. Furthermore, although the number of torsional states accessible to a ligand might be limited in a water or protein environment, the problem of conformational flexibility (small molecule drugs or protein side chains) is pervasive in binding free energy calculations, often hampering the sampling convergence.

References

[1] Andrea Rizzi, Paolo Carloni, and Michele Parrinello. Free energies at QM accuracy from force fields via multimap targeted estimation. *Proceedings of the National Academy of Sciences*, 120(46):e2304308120, 2023.