TICA-Based Free Energy Matching for Machine-Learned Molecular Dynamics

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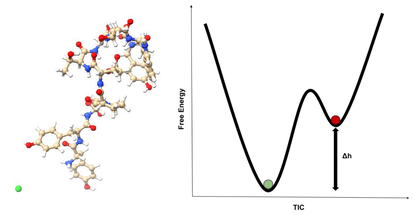
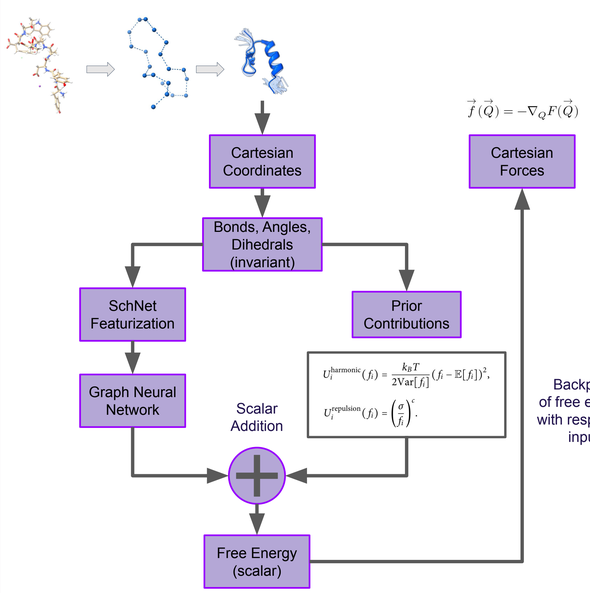
Background & Motivation

1. **Molecular dynamics simulations are computationally expensive due to fine time resolution** (femtosecond timesteps) and the need for extremely long trajectories to observe biologically relevant events. The high dimensionality of molecular systems and stiff intramolecular forces necessitate billions of integration steps to access meaningful timescales.
2. **Coarse-grained force fields speed up MD simulations by reducing degrees of freedom,** but often miss important aspects of global thermodynamics.
3. **Force matching captures potential mean forces by fitting gradients of the free energy surface,** but it does not directly constrain the absolute energy differences between metastable states. This limitation means models may accurately reproduce local dynamics while failing to distinguish the relative stability of different conformational basins.
4. **Matching free energies should better reflect the thermodynamic landscape by directly capturing the relative stability of metastable states through their equilibrium populations.** By incorporating energy-based loss terms that use the Boltzmann relation between free energy and probability density, models can hopefully reproduce both local forces and global thermodynamic structure.



Model Architecture



Loss Function

The model outputs the coarse grain free energy *F(Q)*. We only have the fine grain force, the gradient of the Hamiltonian in the all-atom space, which with a coarse graining function Ξ can be matched with. The loss to match

$$L_{\text{force}}(\theta) = \frac{1}{N}\sum_{i=1}^{N}\left\| \nabla_Q F(\theta, \Xi(\vec{q_i})) - \left(\mathbf{B}(\vec{q})\nabla_q H(\vec{q}) - k_B T \nabla_q \cdot \mathbf{B}(\vec{q})\right)\right\|$$

where **B** is a left inverse of the transposed Jacobian of the coarse graining function.

$$\mathbf{B}(\vec{q}) J_{\Xi}^{\top}(\vec{q}) = I$$

If we can also get an estimate of the free energy (which we will using TICA) we can also match free energy directly using

$$L_{\text{energy}}(\theta) = \frac{1}{N}\sum_{i=1}^{N}\left\| F(\theta, \Xi(\vec{q})) - F_{\text{target}}(\Xi(\vec{q}))\right\|^2$$

Then one can combine them using some hyperparameters

$$L(\theta) = \lambda_{\text{force}} L_{\text{force}}(\theta) + \lambda_{\text{energy}} L_{\text{energy}}(\theta)$$

Energy Matching Theory

Energy Separation

In the canonical ensemble the probability is below, but there's not really a way to get *Z*.

$$\rho(\vec{Q}) = \frac{e^{\frac{F(\vec{Q})}{k_B T}}}{\int e^{\frac{F(\vec{Q})}{k_B T}} d\vec{Q}} = \frac{1}{Z} e^{\frac{F(\vec{Q})}{k_B T}}$$

If we can separate it into independent components.

$$\rho(\vec{Q}) = \rho(Q_1 \ldots Q_k) = \prod_{i=1}^{k} \rho(Q_i)$$

So the free energy can be found up to a constant, which doesn't matter since only the gradient contributes.

$$F(\vec{Q}) = -k_B T \ln\left(Z \prod_{i=1}^{k} \rho(Q_i)\right) = -k_B T \sum_{i=1}^{k} \ln(\rho(Q_i)) - k_B T \ln(Z)$$

Time-lagged Independent Component Analysis

While PCA decomposes into eigenvectors that maximize the variance, TICA decomposes based on maximizing the ratio of time lagged variance to variance. Intuitively the vectors corresponds to the slow degrees of motion. The time lagged covariance matrix is

$$C(\tau)_{ij} = \text{Cov}[X_i(t), X_j(t+\tau)]$$

which is a generalization of the standard covariance matrix

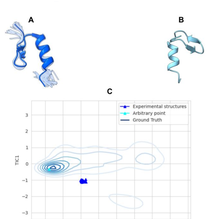
$$C_{0,ij} = C_{ij}(0) = \text{Cov}[X_i, X_j]$$

TICA eigenvectors are defined to be the solutions to the generalized eigenvalue problem

$$C(\tau)\vec{v} = \lambda C_0 \vec{v}$$

If the features of the time lagged covariance matrix are even under time reversal, it should be symmetric too. The solutions to the eigenvalue problem can be shown to be the critical points of the Reighley quotient:

$$\vec{v}_0 = \max_{\vec{w} \neq \vec{0}} \frac{\vec{w}^{\top} C(\tau) \vec{w}}{\vec{w}^{\top} \vec{w}}$$



Uncorrelated Decomposition

The covariance is semi-positive definite symmetric, so it can be eigenvalue decomposed.

$$C_0 = WDW^{\top} \quad L = D^{\frac{1}{2}}W$$

If it's strictly positive definite then the inverse $L^{-1} = W^{\top} D^{-\frac{1}{2}}$ exists .

Defining $A = L^{-\top} C(\tau) L^{-1}$ with eigenvalue decomposition $A = K\Lambda K^{\top}$ then the column vectors $V = L^{-1}K$ can be shown to be a solution to both the generalized eigenvalue problem, and are simultaneously uncorrelated.

Stochastic Benchmarking

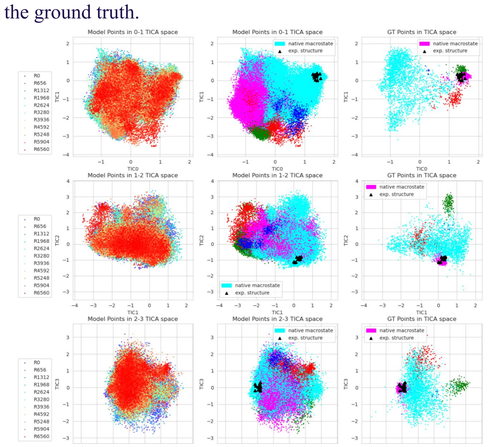
The model doesn't take special relativity into account, so the free energy represented as a Hamiltonian is simply

$$F(\vec{Q}, \vec{P}) = \frac{1}{2}\vec{P}^{\top} M \vec{P} + E(\vec{Q})$$

And we can then sample from the Boltzmann distribution using the Langevin stochastic differential equation.

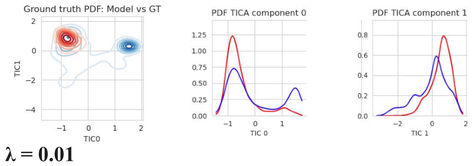
$$d\vec{Q} = M^{-1} P dt$$
$$d\vec{P} = -\nabla_Q F(\vec{Q}) dt - \gamma \vec{P} dt + \sqrt{2\gamma k_B T} M^{1/2} d\vec{W}$$

After sufficiently sampling from the model, we get an approximate probability distribution, that can then be compared to the ground truth.

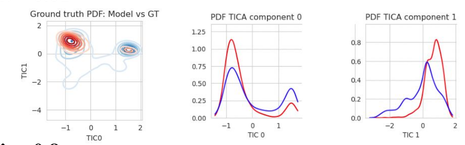


Results

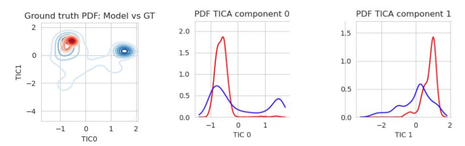
- *No statistically significant gain*, but qualitative trends show promise.
- **λ** = energy weight
- **λ = 0** (Force Matching)



- **λ = 0.01**



- **λ = 0.8**



Future Work

Entropy Matching

While free energy in the Isobaric-Isothermal ensemble is intractable, internal energy of data can be calculated by the average of the fine grained energy (Hamiltonian).

$$U(\vec{Q}, P, T) = \langle H(\vec{q}) \rangle_Q$$

Differentiating the model with respect to temperature gives the entropy

$$S(\vec{Q}, P, T) = \frac{\partial F(\vec{Q}, P, T)}{\partial T}$$

Then the internal energy (and entropy) can be matched.

$$U(\vec{Q}, P, T) = F(\vec{Q}, P, T) + TS(\vec{Q}, P, T)$$

Volume matching

Similarly, the average volume can be found by differentiating with respect to pressure, and can also be matched in the loss.

$$\langle V \rangle_Q = \frac{F(\vec{Q}, P, T)}{\partial P}$$