Machine-learned reaction coordinates for energy-entropy disentanglement

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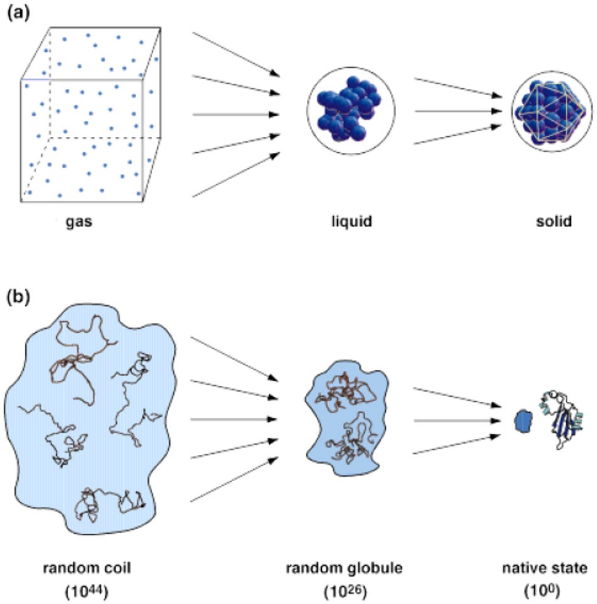
Outline

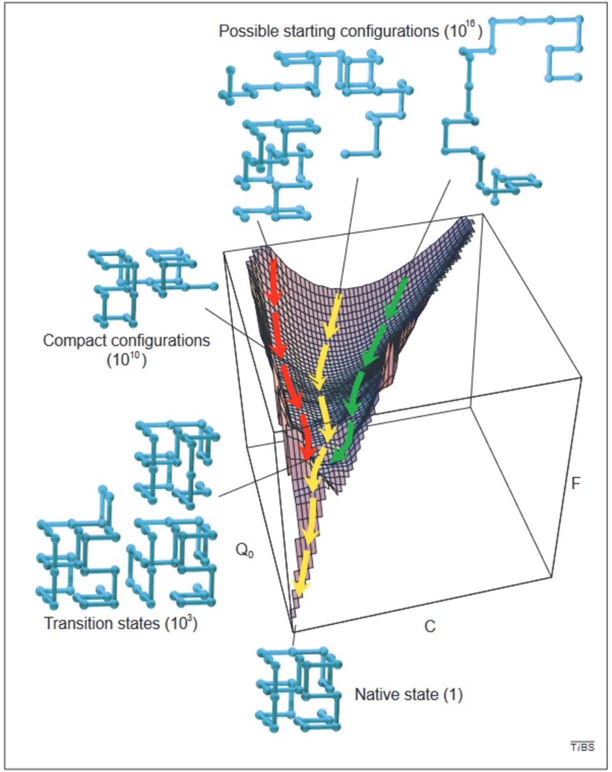
1. Introduction – free energy in physical systems
2. Discovering a relevant latent space – SPIB
3. Energy and entropy in the SPIB latent space
4. Application to simple systems
5. Augmenting the SPIB loss function to learn energetic and entropic pathways
6. Conclusions

Introduction

- All physical processes occurring in a thermostatted ensemble are subject to free-energy barriers, which are a sum of energy and entropy:

$$\Delta A = \Delta U - T\Delta S$$
$$\Delta G = \Delta H - T\Delta S$$
$$= \Delta A + P\Delta V$$





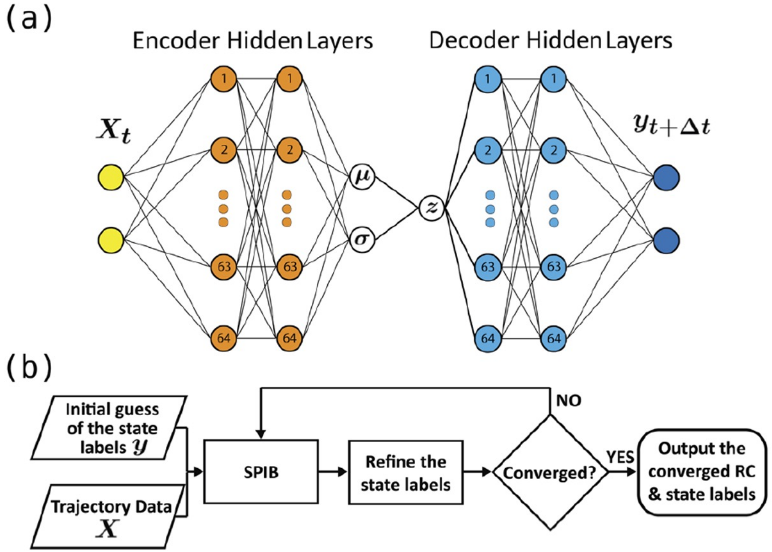
Dinner, Sali, Smith, Dobson, and Karplus, “Understanding protein folding via free-energy surfaces from theory and experiment,” *Trends in Biochemical Sciences*, **25**, 331-339, 2000

Dobson, Sali, and Karplus, “Protein Folding: A Perspective from Theory and Experiment,” *Angew. Chem. Int. Ed.* **37**, 868 - 893, 1998

Introduction

- Generally, there is not a simple, low-dimensional coordinate system describing the entropy- and energy-dominated pathways.
    - Important for determing enhanced sampling method utilized
- Goal of the research described here is to embed the system dynamics in a low-dimensional latent space where energy and entropy pathways are disentangled.
- Our embedding method of choice is to use a modified version of the reweighted autoencoder variational Bayes (RAVE) method called SPIB.

SPIB



$$\mathcal{L}_{\text{SPIB}} = \frac{1}{M \cdot L} \sum_{n=1}^{N} \sum_{l=1}^{L} \left[\underbrace{\log q_\theta \left(\mathbf{y}^{n+s} \middle| \mathbf{z}^{(n,l)} \right)}_{\text{reconstruction error}} - \underbrace{\beta_{\text{SPIB}} \log \frac{p_\theta \left(\mathbf{z}^{(n,l)} \middle| \mathbf{X}^{\mathbf{n}} \right)}{q_\theta \left(\mathbf{z}^{(n,l)} \right)}}_{\text{KL divergence}} \right]$$

$$\mathcal{L}_{\text{SPIB}} \leq \mathcal{L}_{\text{IB}} = \underbrace{I(\mathbf{y}, \mathbf{z})}_{\sim\text{accuracy}} - \beta \underbrace{I(\mathbf{X}, \mathbf{z})}_{\sim\text{compression}}$$

Wang and Tiwary, “State predictive information bottleneck,” *J. Chem. Phys.* **154**, 134111, 2021

Energy and Entropy in the Embedded SPIB Latent Space

- Use the formulation provided by Hartmann et al.[1] to determine the free energy and energy along the discovered RCs:

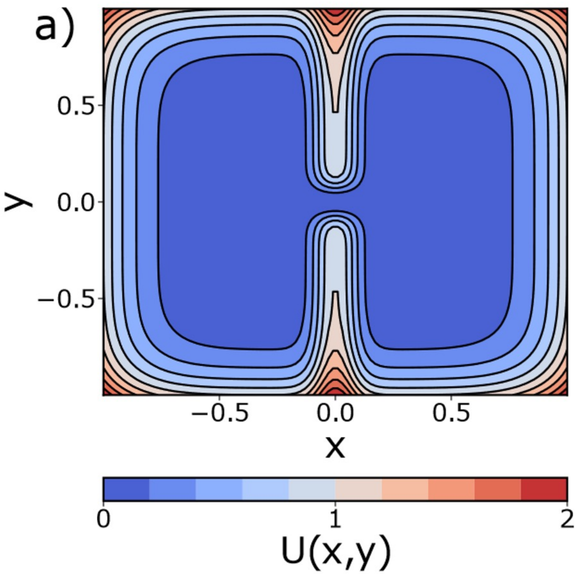
$$G(\mathbf{z}) = -\beta^{-1} \ln \int_{\mathbb{R}^n} \underbrace{d\mathbf{x} \exp(-\beta V(\mathbf{x}))}_{\text{Boltzmann weight of feature } \mathbf{x}} \underbrace{\det\left(\tilde{G}\right)^{\frac{1}{2}}}_{\text{Grammian}} \underbrace{\delta\left(\Phi(\mathbf{x}) - \mathbf{z}\right)}_{\text{Count points on the level set/histogram bin of interest}}$$

$$\begin{aligned} \langle U(z) \rangle_{\Sigma(z)} &:= U(z) \\ &= \frac{1}{N_z} \int U(\mathbf{x}) e^{-U(\mathbf{x})/k_B T} \times \delta(\Phi(\mathbf{x}) - z) \det(\tilde{G})^{1/2} \, d\mathbf{x} \end{aligned}$$

$$\begin{aligned} \Delta G(z) &= \Delta U(z) - T \Delta S(z) \\ &\Rightarrow \Delta S(z) \\ &= \frac{1}{T}(\Delta U(z) - \Delta G(z)) \end{aligned}$$

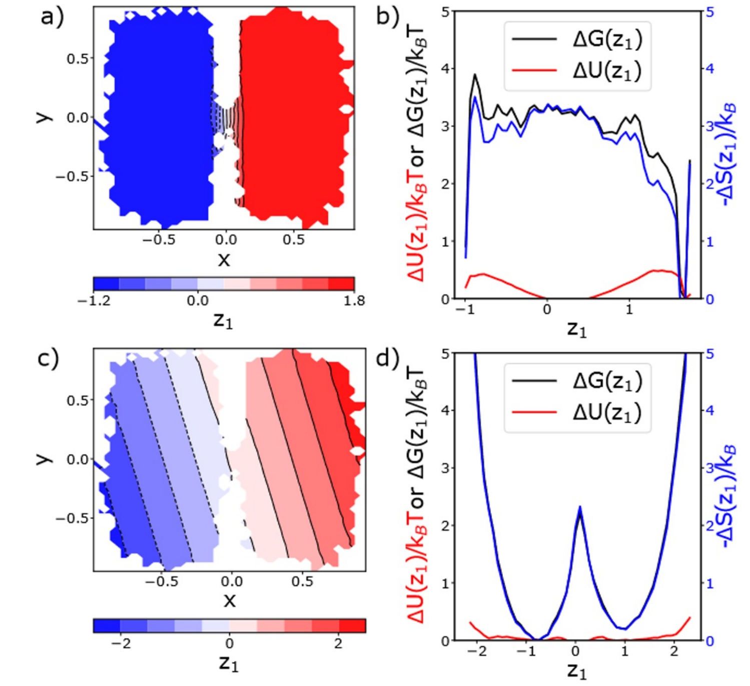
[1]Hartmann, Latorre, and Ciccotti, "On two possible definitions of the free energy for collective variables," *Eur. Phys. J Special Topics*, **200**, 73-89, 2011

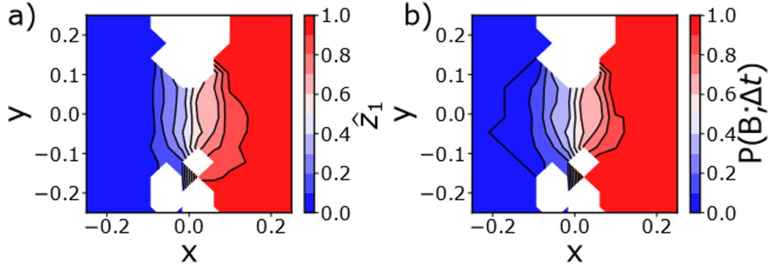
Energy-Entropy for Some Simple Systems



$$U(x,y) = x^6 + y^6 + \exp\left[-y^2/\sigma_y^2\right]\left(1 - \exp\left[x^2/\sigma_x^2\right]\right)$$

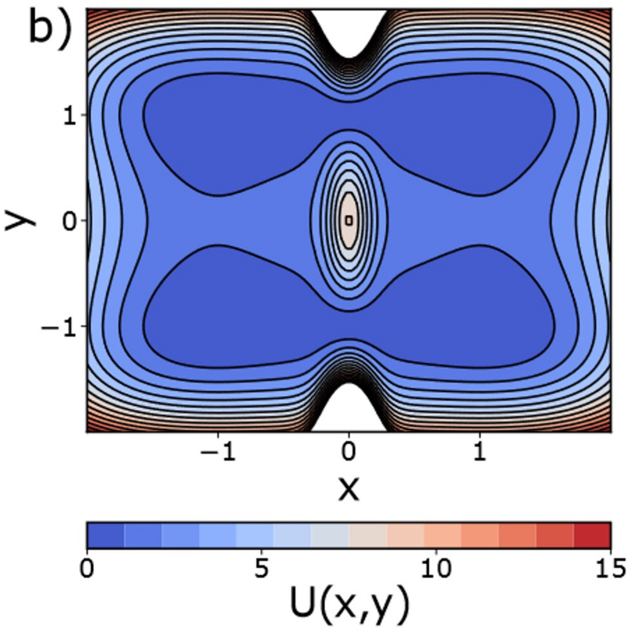
"Elber potential"

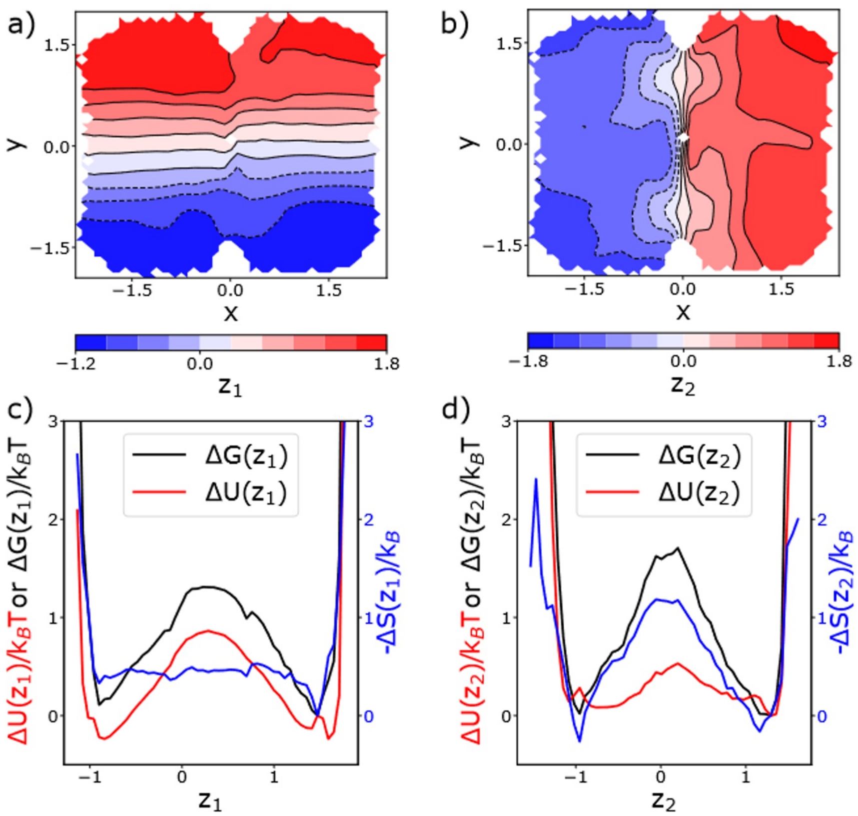




Beyerle, Mehdi, and Tiwary, "Quantifying Energetic and Entropic Pathways in Molecular Systems," *J. Phys. Chem. B*, **126**, 3950-3960, 2022

Energy-Entropy for Some Simple Systems



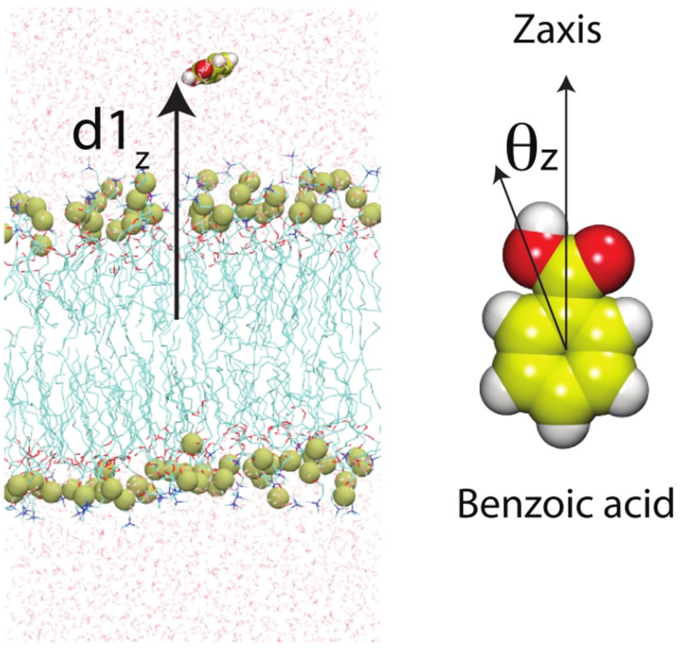


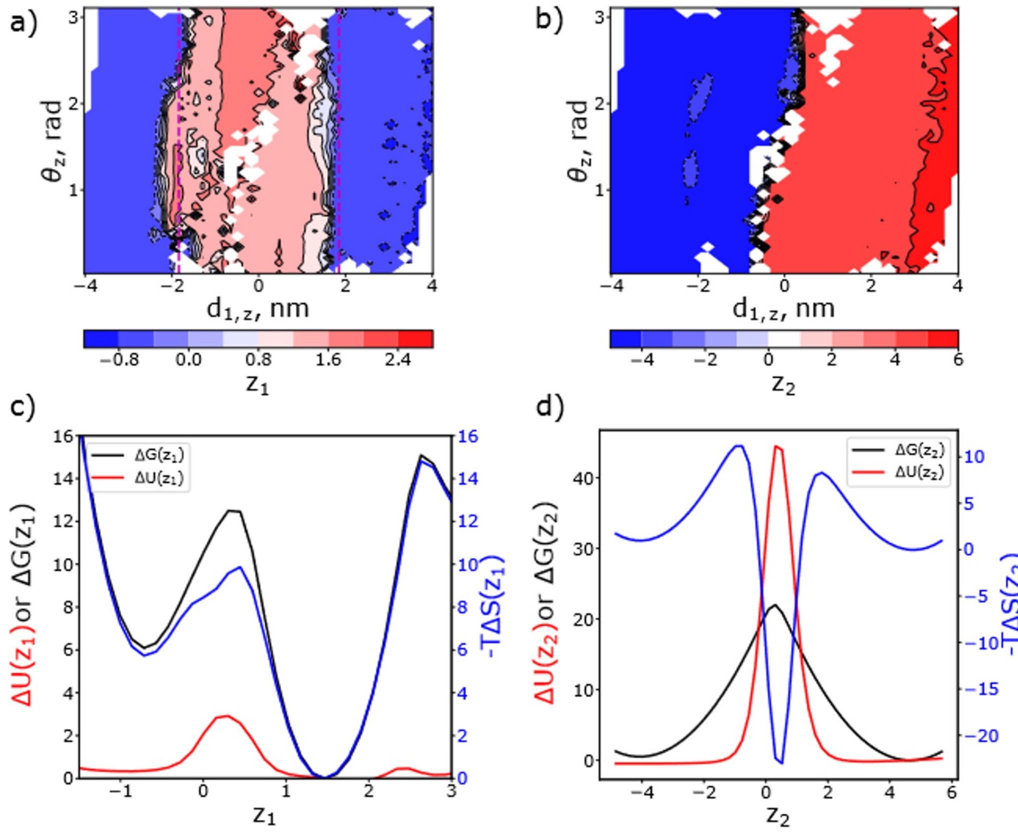
$$U(x, y) = h_x\left(x^2 - 1\right)^2 + (h_y + a((x, \delta))\left(y^2 - 1\right)^2$$

"Temperature switch"

Beyerle, Mehdi, and Tiwary, "Quantifying Energetic and Entropic Pathways in Molecular Systems," *J. Phys. Chem. B*, **126**, 3950-3960, 2022

Energy-Entropy for Some Simple Systems





Beyerle, Mehdi, and Tiwary, "Quantifying Energetic and Entropic Pathways in Molecular Systems," *J. Phys. Chem. B*, **126**, 3950-3960, 2022

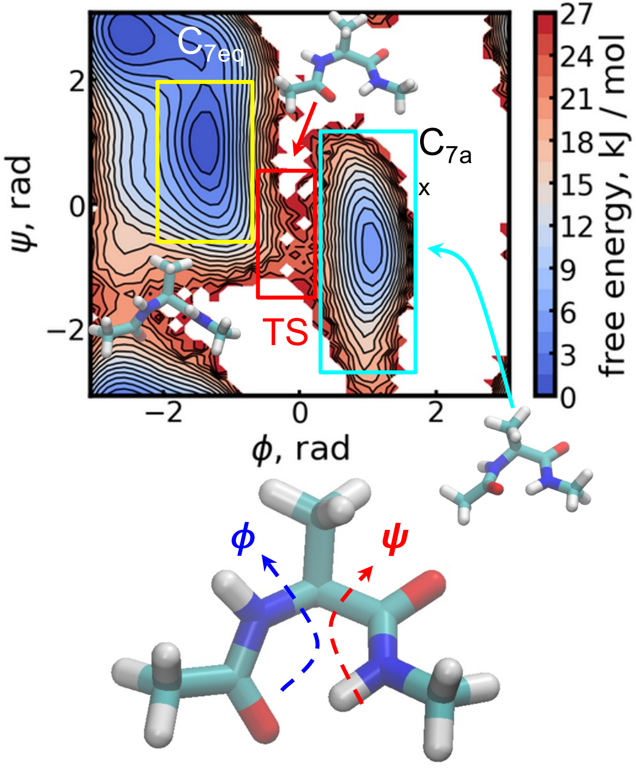
Forcing the Latent Space to Learn Thermodynamics

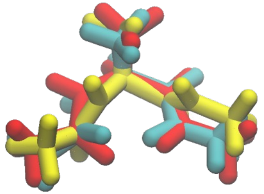
- Add an extra regularization term to the loss function to force the latent space to learn the energy and energy pathways for an arbitrary system.

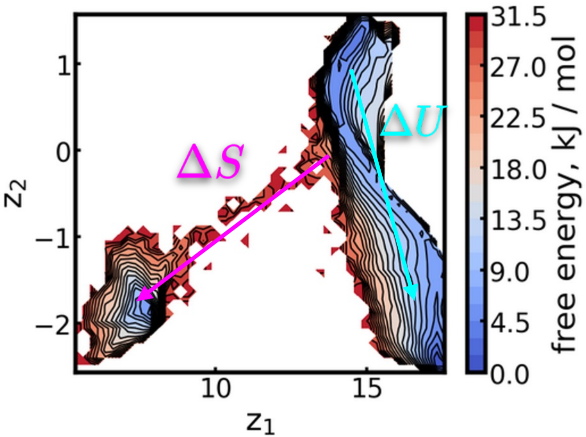
$$\mathcal{L} = \sum_{n=1}^{N} \left[\log(p(\mathbf{y}^{n+s} | \mathbf{z}^{n})) - \beta \log\left(\frac{p(\mathbf{z}^{n} | \mathbf{X}^{n})}{p(\mathbf{z}_{\theta})} \right) \right] + \gamma f(\mathbf{z})$$

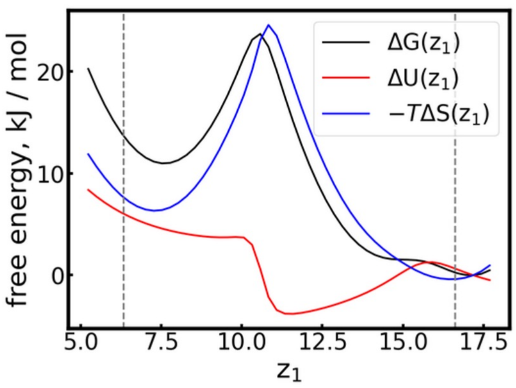
$$f(\mathbf{z}) = \max_{\mathrm{int}(z_1)} \left(-T\Delta S(z_1) \right) + \max_{\mathrm{int}(z_2)} \left(\Delta U(z_2) \right)$$

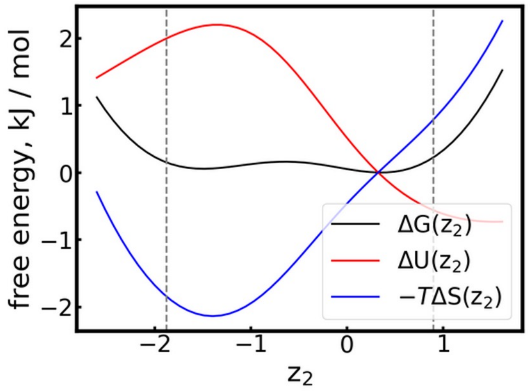
Case Study: Alanine Dipeptide in Vacuum

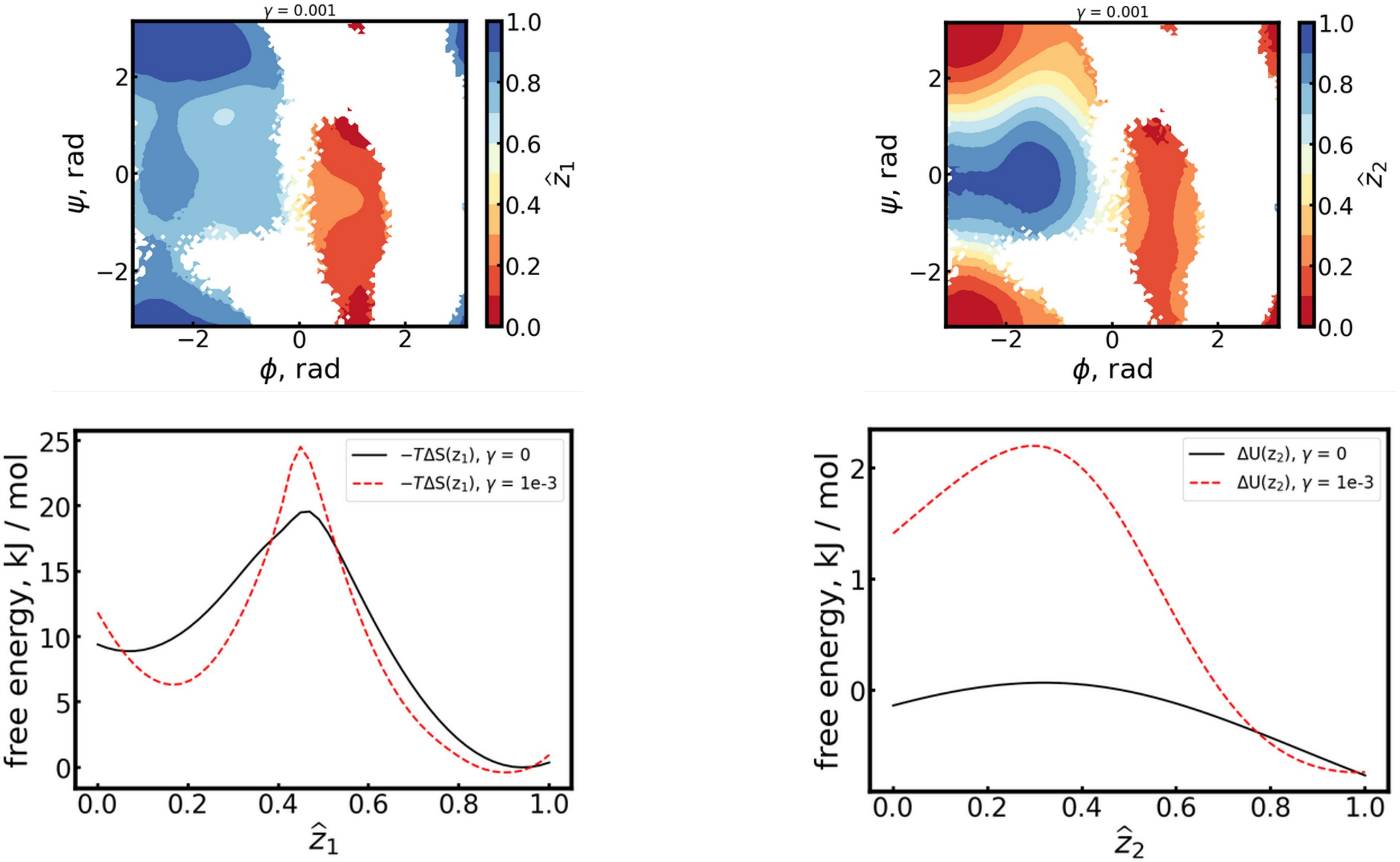












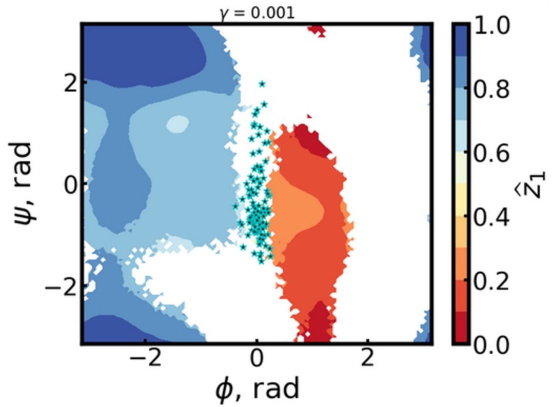
γ = 0.001
ψ, rad
ϕ, rad
$\hat{z}_1$
γ = 0.001
ψ, rad
ϕ, rad
$\hat{z}_2$
free energy, kJ / mol
−TΔS(z1), γ = 0
−TΔS(z1), γ = 1e-3
$\hat{z}_1$
free energy, kJ / mol
ΔU(z2), γ = 0
ΔU(z2), γ = 1e-3
$\hat{z}_2$

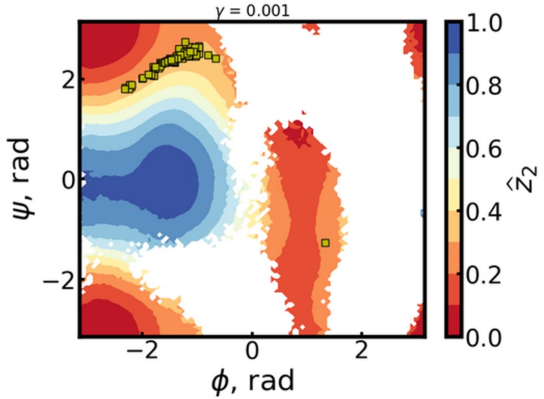
Interpretation

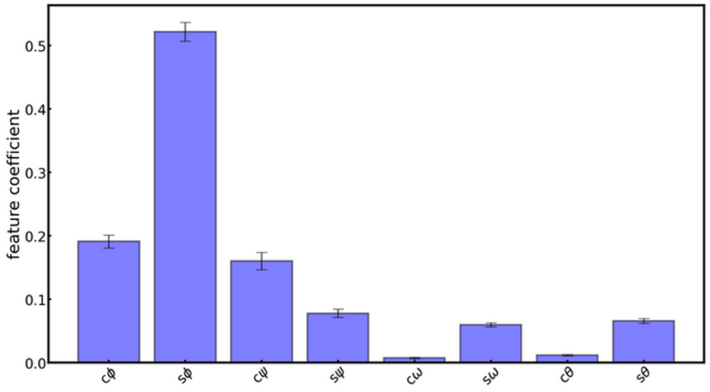
Use an in-house method called TERP[1]:

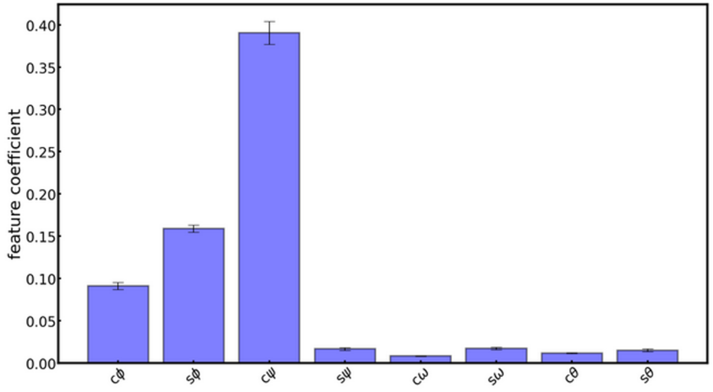
"Unfaithfulness" "Simplicity"

$$\zeta[f, d] = U[f, d] - \theta S[f]$$





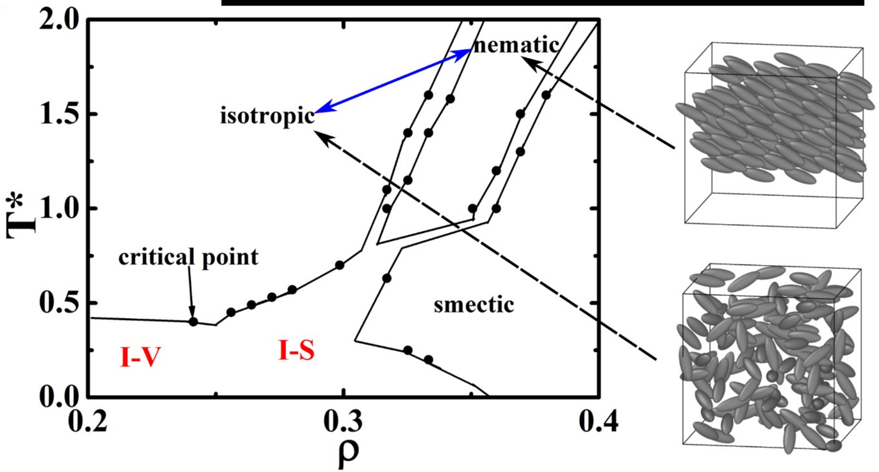




[1]Mehdi and Tiwary, "Thermodynamics of Interpretation," *arXiv,* arXiv:2206.13475v1, 2022

Conclusions and Coming Attractions

- SPIB can discover an effective low-dimensional latent space for crossing energetic and entropic barriers.
- For alanine dipeptide in vacuum, energy and entropy barriers can be enhanced by adding a regularization term to the loss function.
- We look to apply this method to more complicated soft matter systems (hydrophobic ligand binding, liquid crystal models) in the near future.



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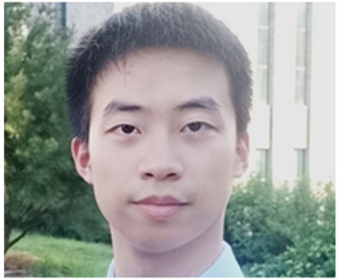
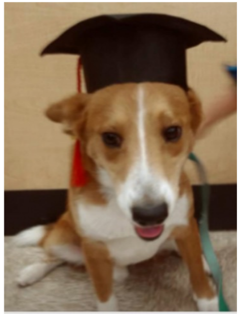


Dedi Wang



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