Interpretable embeddings from molecular simulations using Gaussian mixture variational autoencoders

Applied Machine Learning Days – EPFL 2022

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30-03-2022

MAX PLANCK INSTITUTE
FOR POLYMER RESEARCH

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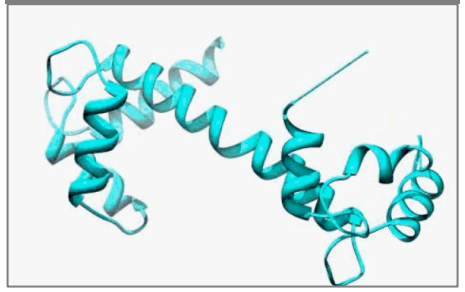
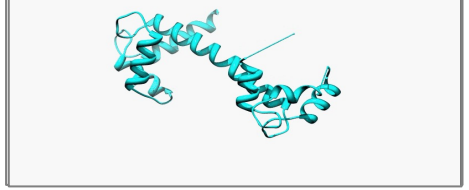
Structure + Dynamics = Function

Structure → Function ← Dynamics





Experiments

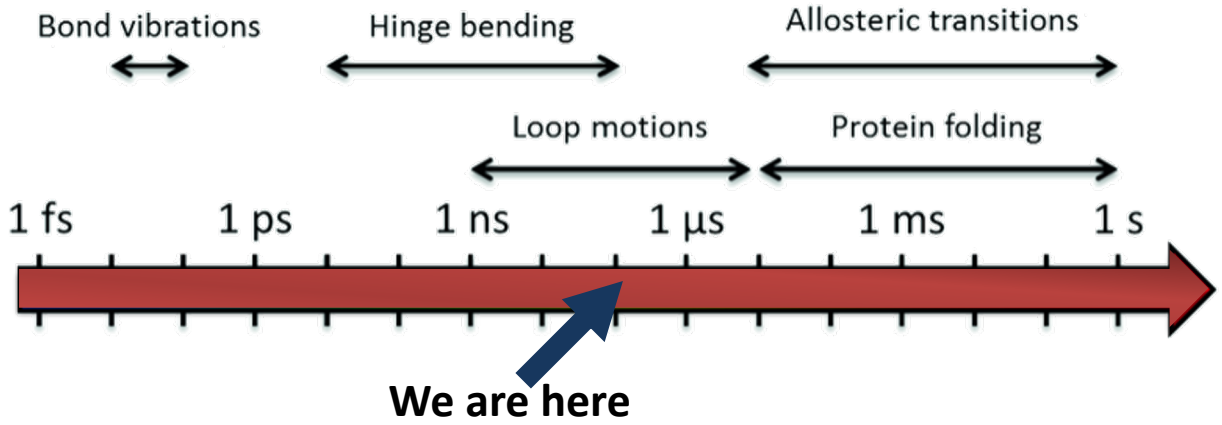
High spatial **or** temporal resolution

- High spatial but low temporal resolution
  Cryo-electron microscopy, X-ray diffraction
- High temporal but low spatial resolution
  Single molecule fluorescence resonance energy transfer

Molecular Dynamics (MD) Simulations

High spatial **and** temporal resolution

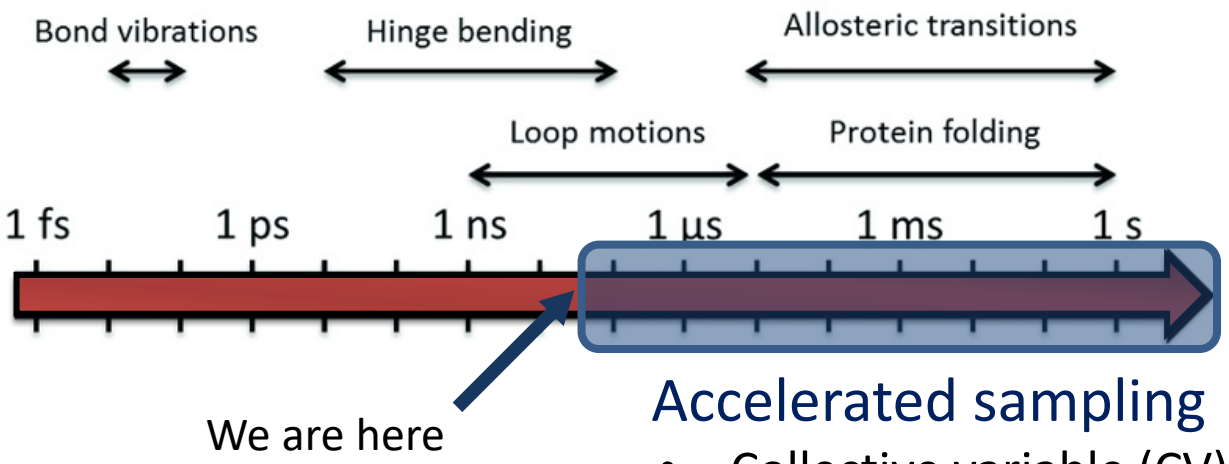
- By iteratively solving **equations of motion**
  Computationally expensive
  Timescale gap problem



Movie credit *Kozlowski et al. "A meta-server fpr prediction of IDPs". BMC Bioinformatics (2012)*
Nobel prize in Chemistry 2013 awarded to Karplus, Levitt and Warshel for development of MD

Figure credit *Adrien et al. "Raman and Infrared Spectra of Acoustical, Functional Modes of Proteins from All-Atom and Coarse-Grained Normal Mode Analysis". Springer (2019)*

Unsupervised ML in molecular simulations



Accelerated sampling

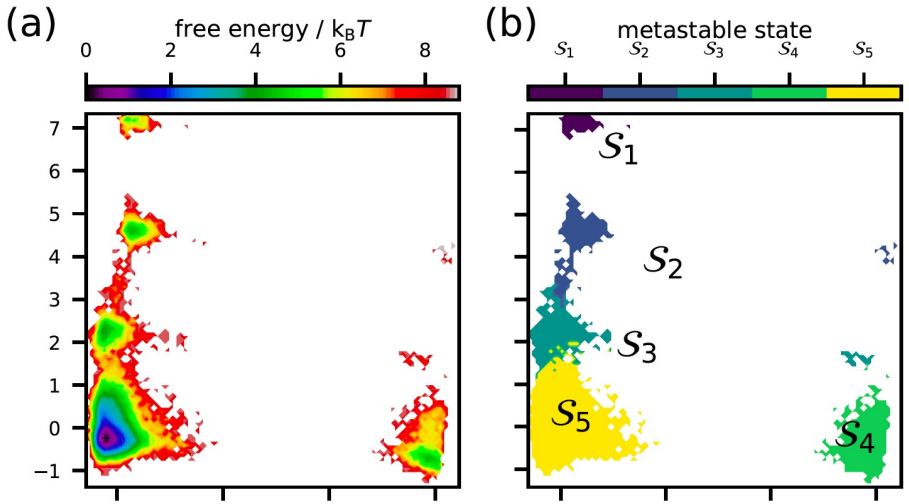
- Collective variable (CV) biasing

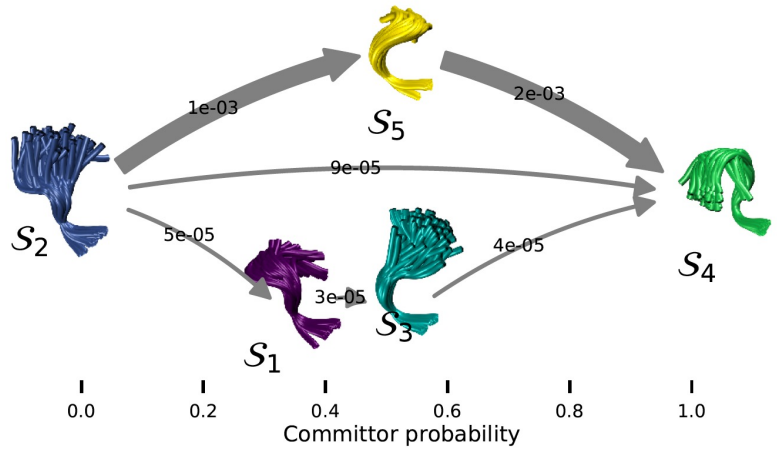
A good CV

- separates metastable states
- characterizes slow motions
- helps build kinetic models

CV examples

internal angles, pairwise distances, coordination numbers etc.





$$P(E) = \frac{1}{Z} \exp\left(-\frac{E}{k_B T}\right)$$

Data-driven route to discover good low-D representations <<<

Andrew Ferguson, "Machine learning-enabled enhanced sampling in biomolecular simulation and data-driven design", IPAM talk (2019)

Wehmeyer et al. "Introduction to Markov state modeling with the PyEMMA software", (2018)

(Vanilla) Autoencoder

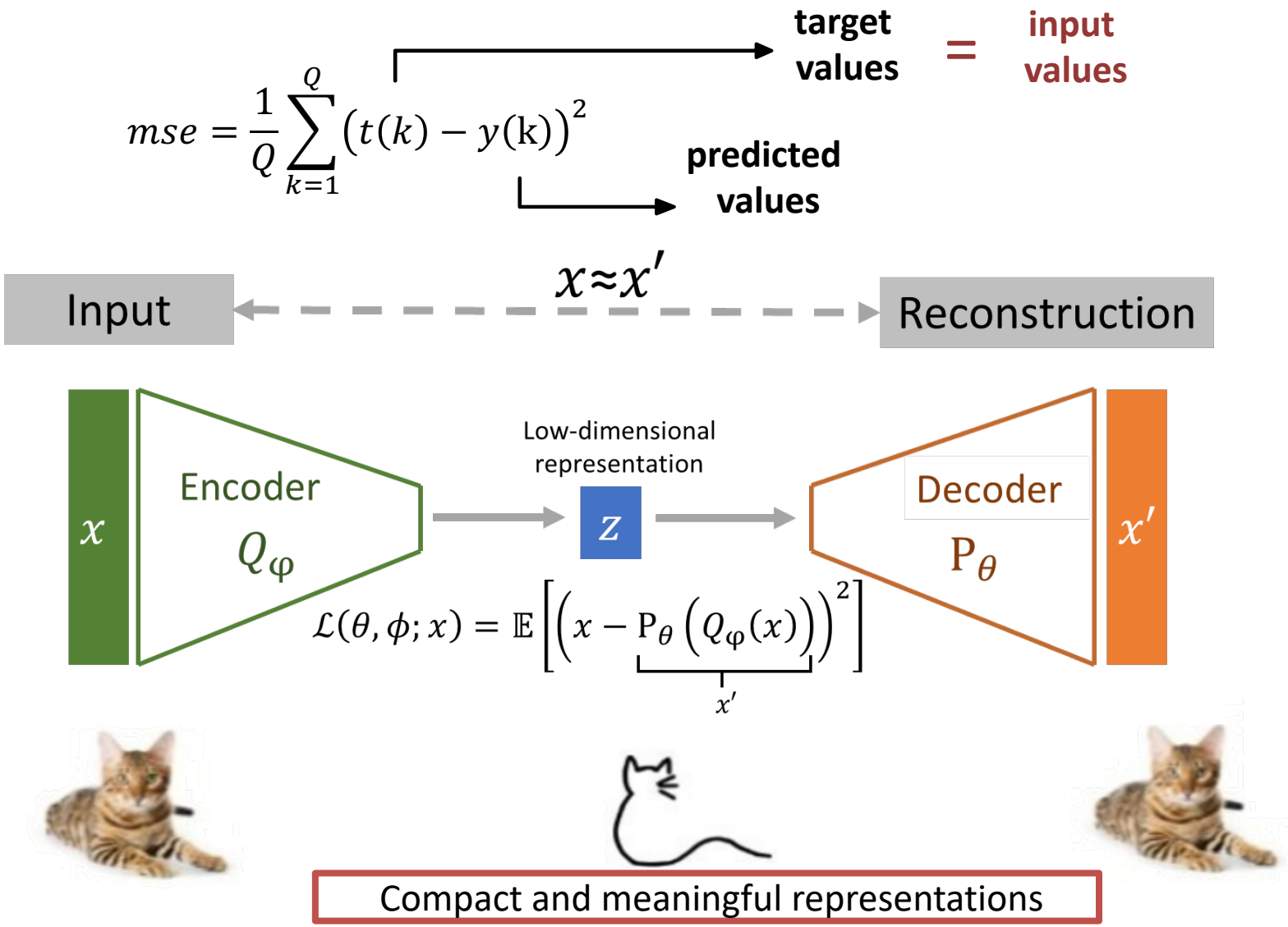
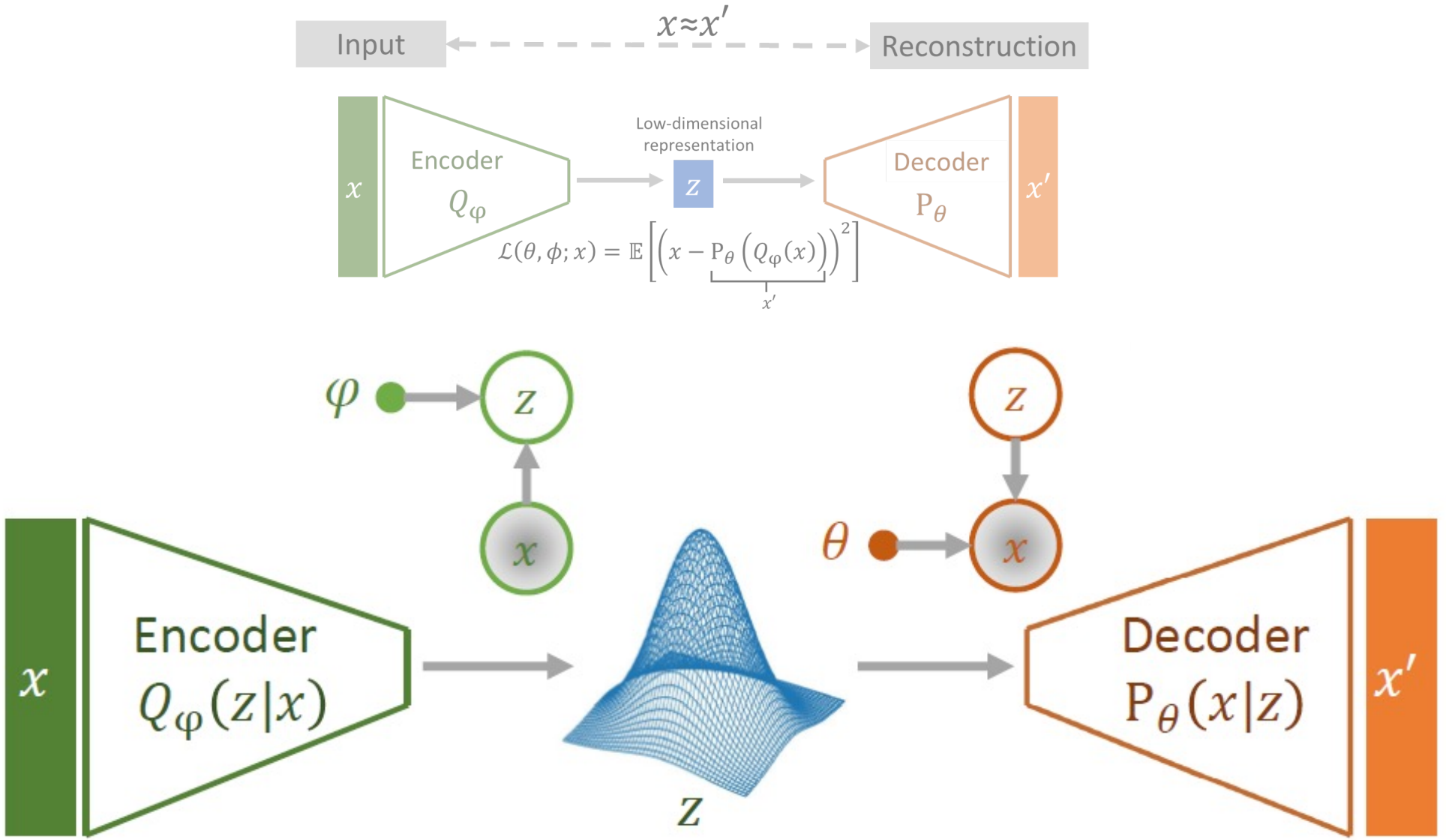


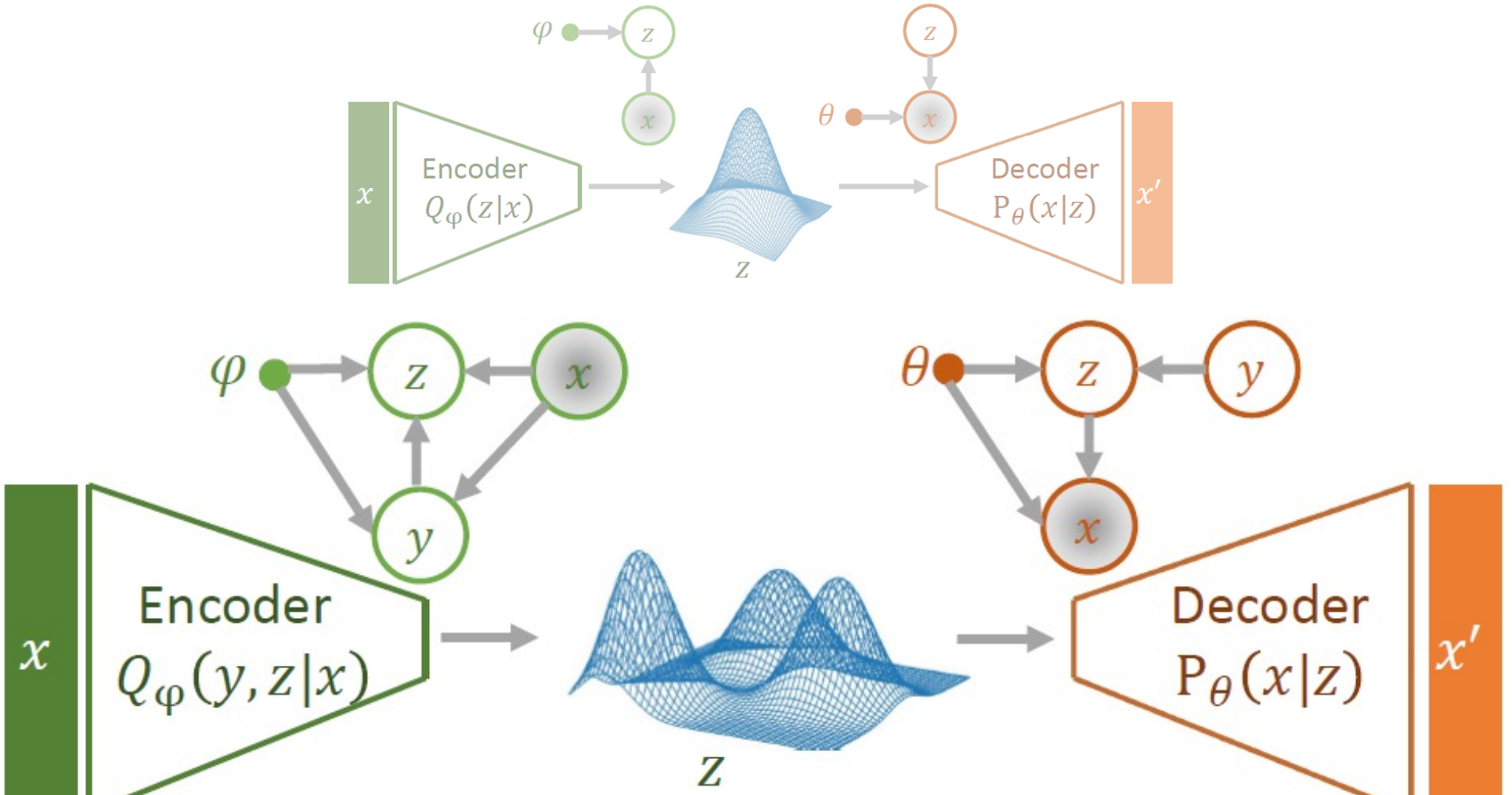
Figure credit *https://sefiks.com/2018/03/21/autoencoder-neural-networks-for-unsupervised-learning*

Variational autoencoder (VAE)



Kingma et al. "Auto-encoding Variational Bayes" arXiv, (2013)

Gaussian mixture variational autoencoder (GMVAE)



$$\mathcal{L}(\theta,\phi;x) = \mathbb{E}_{Q_\phi(y,z|x)}\left[\log P_\theta(x,y,z) - \log Q_\phi(y,z|x)\right]$$

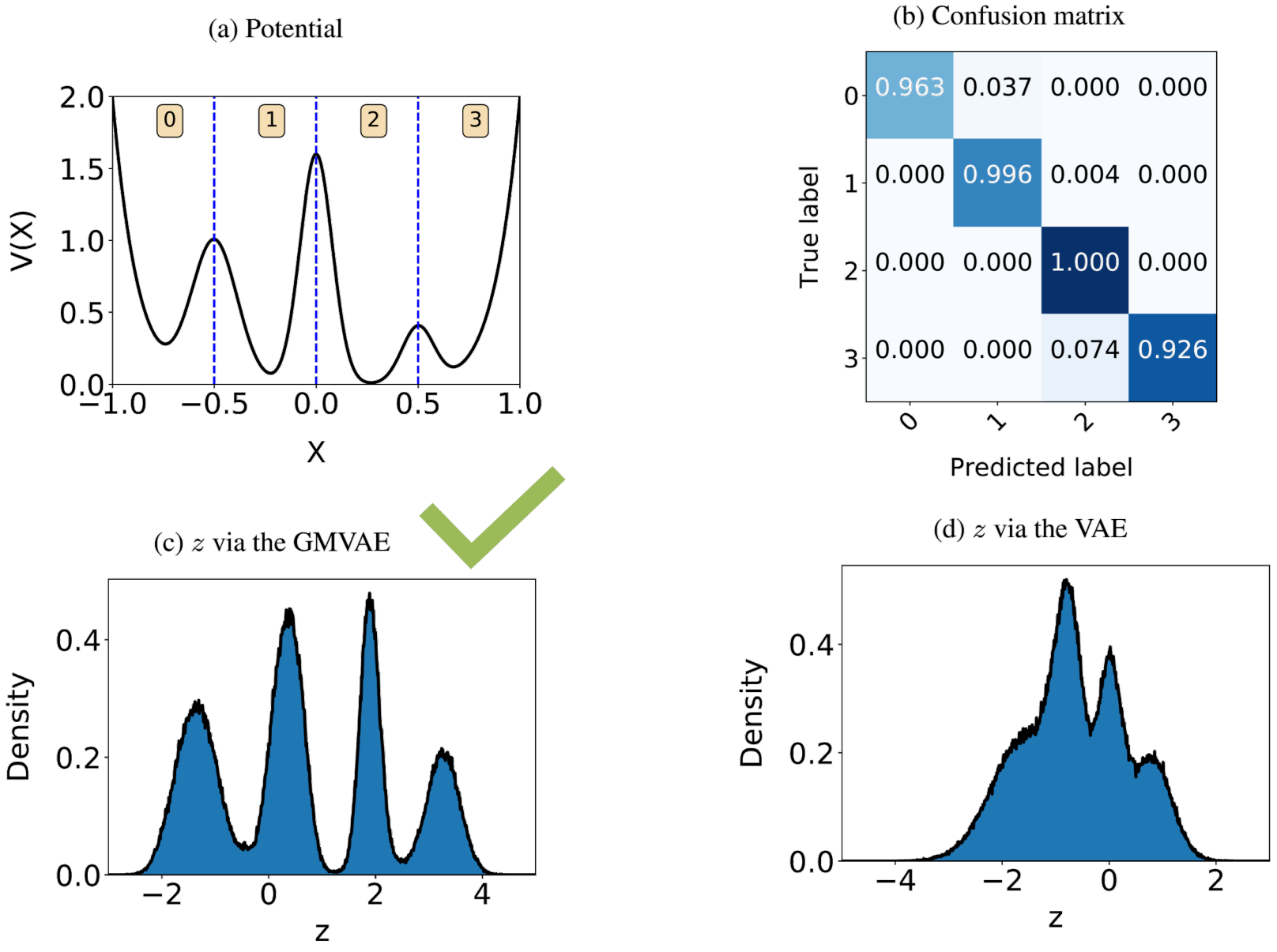
$$\mathcal{L}(\theta,\phi;x) = \mathbb{E}_{Q_\phi(y,z|x)}\left[\log\frac{P(y)}{Q_\phi(y|x)} + \log\frac{P_\theta(z|y)}{Q_\phi(z|x,y)} + \log P_\theta(x|z)\right]$$

Bozkurt et al. "Interpretable embeddings from molecular simulations using Gaussian mixture variational autoencoders." Machine Learning: Science and Technology (2020)
http://ruishu.io/2016/12/25/gmvae/

The GMVAE accurately identifies the clusters.

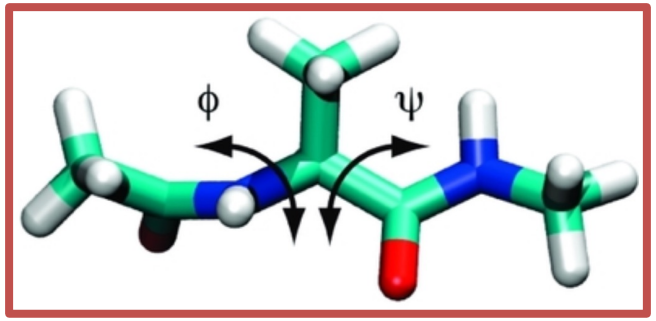
1D 4 well potential

1D ⟶ 1D



Test for conformational dynamics

Alanine dipeptide



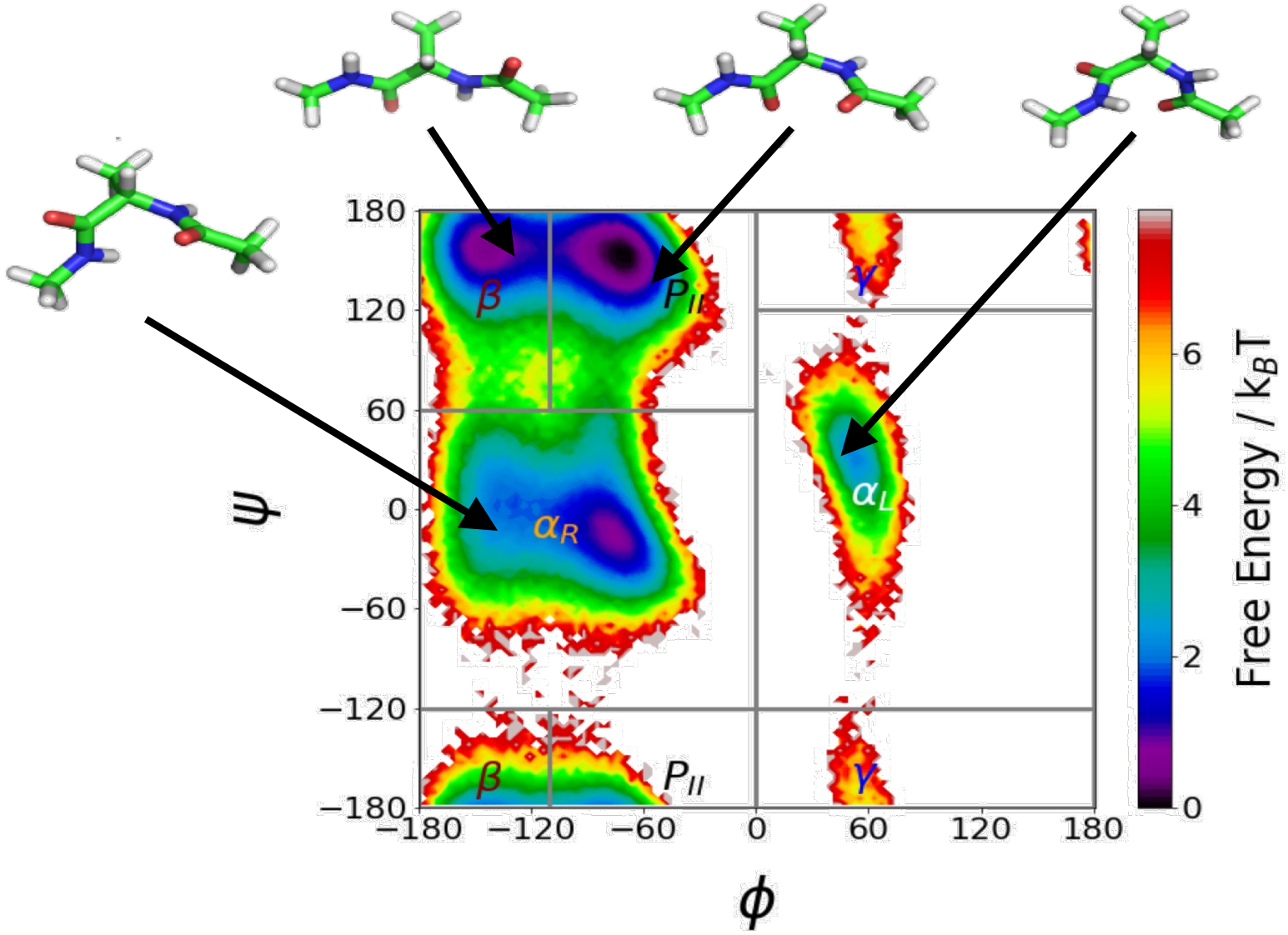
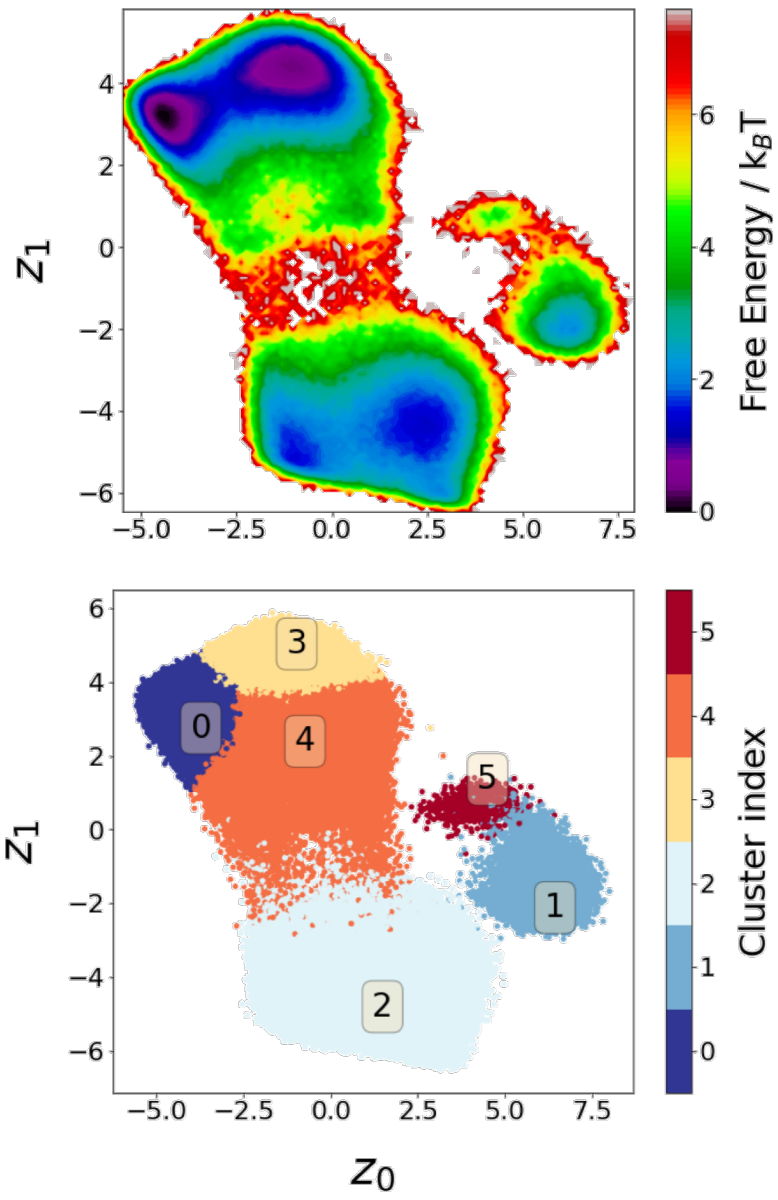


Figure credit *Devaurs et al. " A multi-tree approach to compute transition paths on energy landscapes." Workshops at the 27. AAAI Conference on Artificial Intelligence. 2013 (2017)*

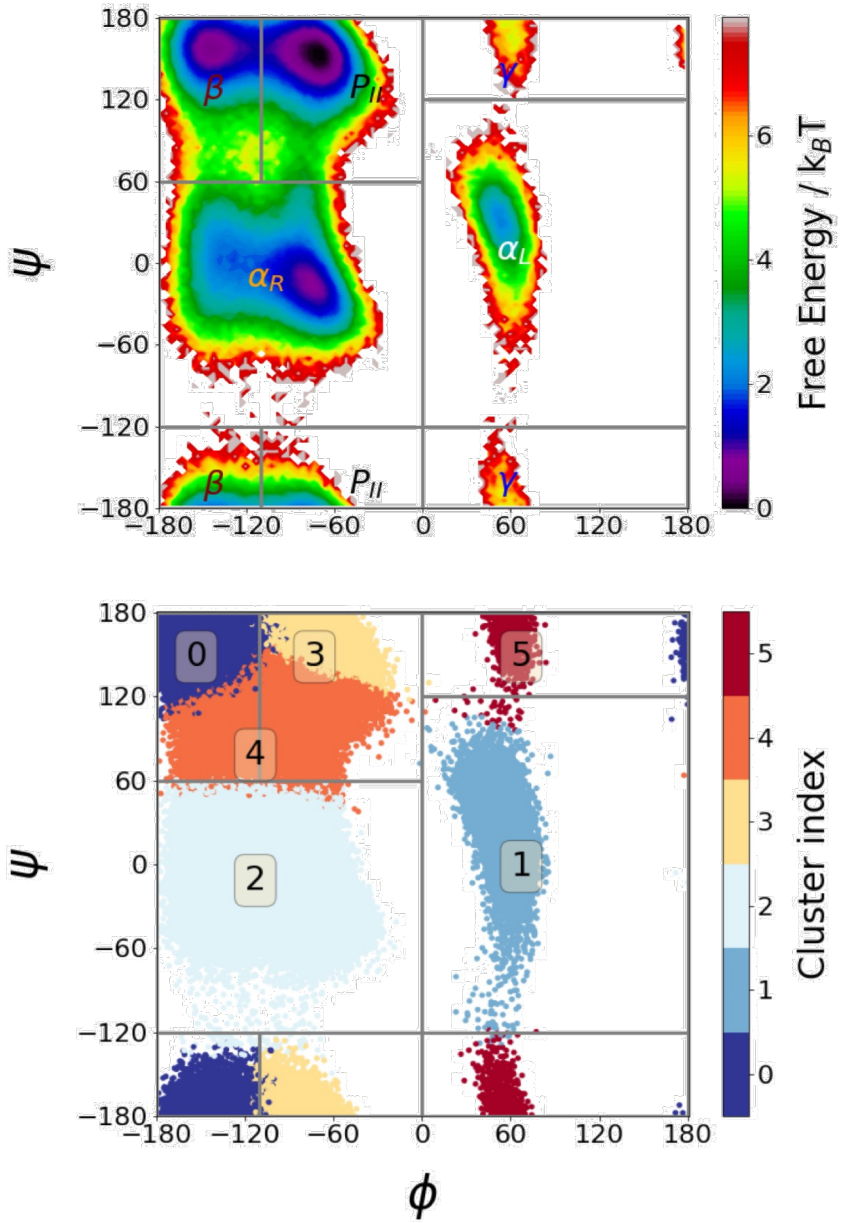
Free energy landscape of alanine dipeptide

25D → 2D

GMVAE landscape

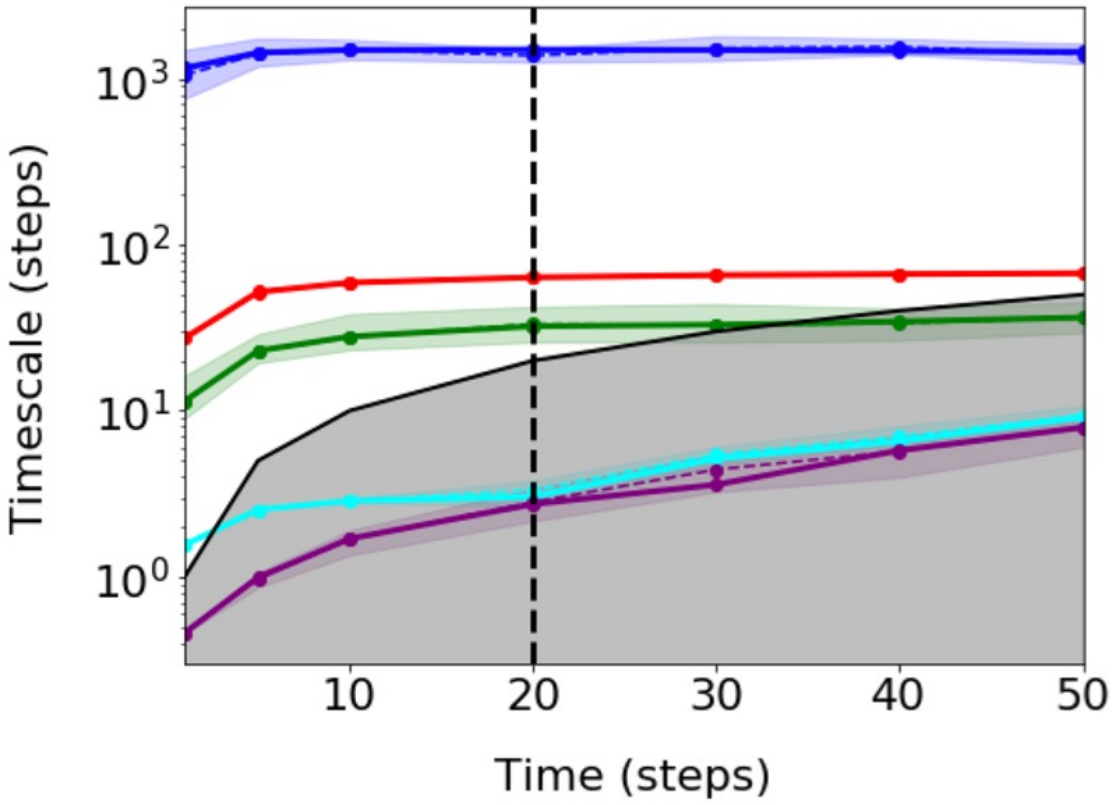


Ramachandran plot

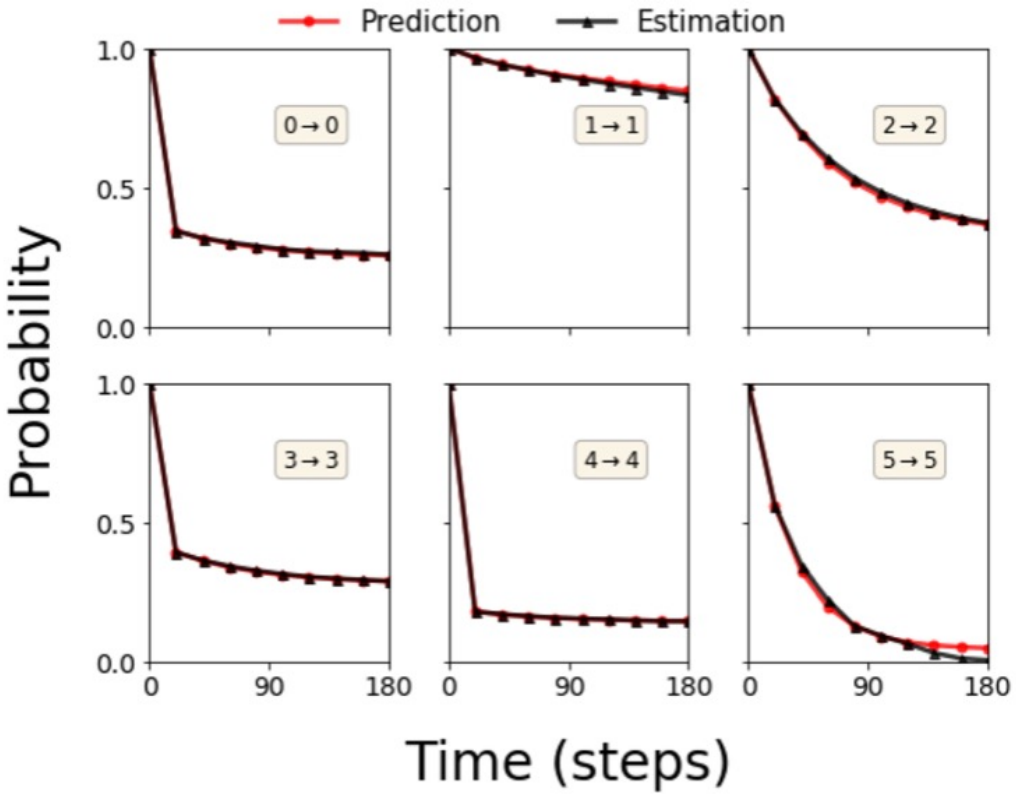


Markovian model

(a) Implied timescales



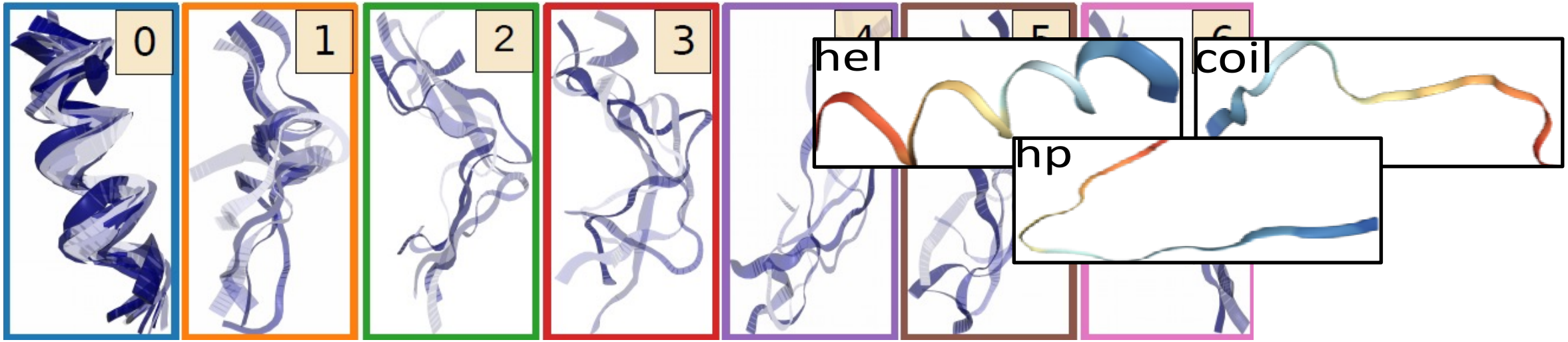
(b) Chapman-Kolmogorov test



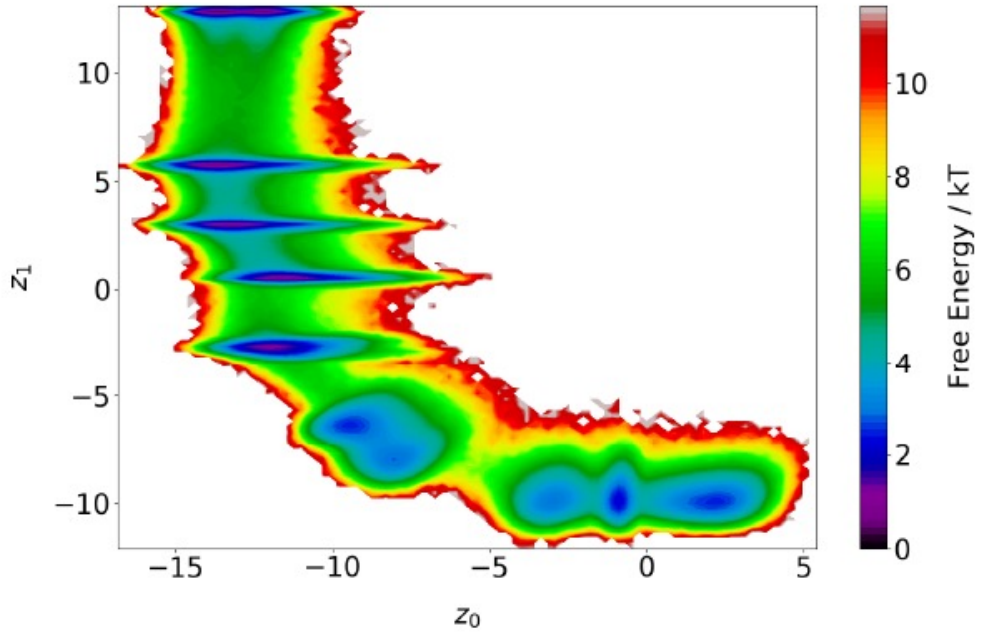
$$t_i(\tau) = -\frac{\tau}{\ln|\lambda_i(\tau)|}$$

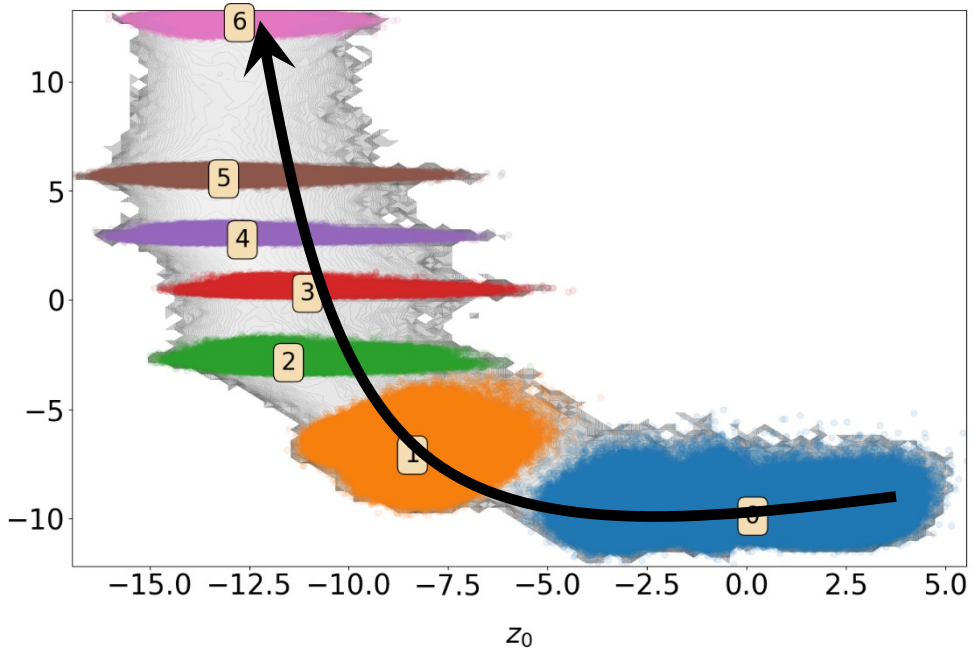
$$p_{ij}(m\tau) = p_{ij}^m(\tau)$$

$AAQAA_3$ peptide

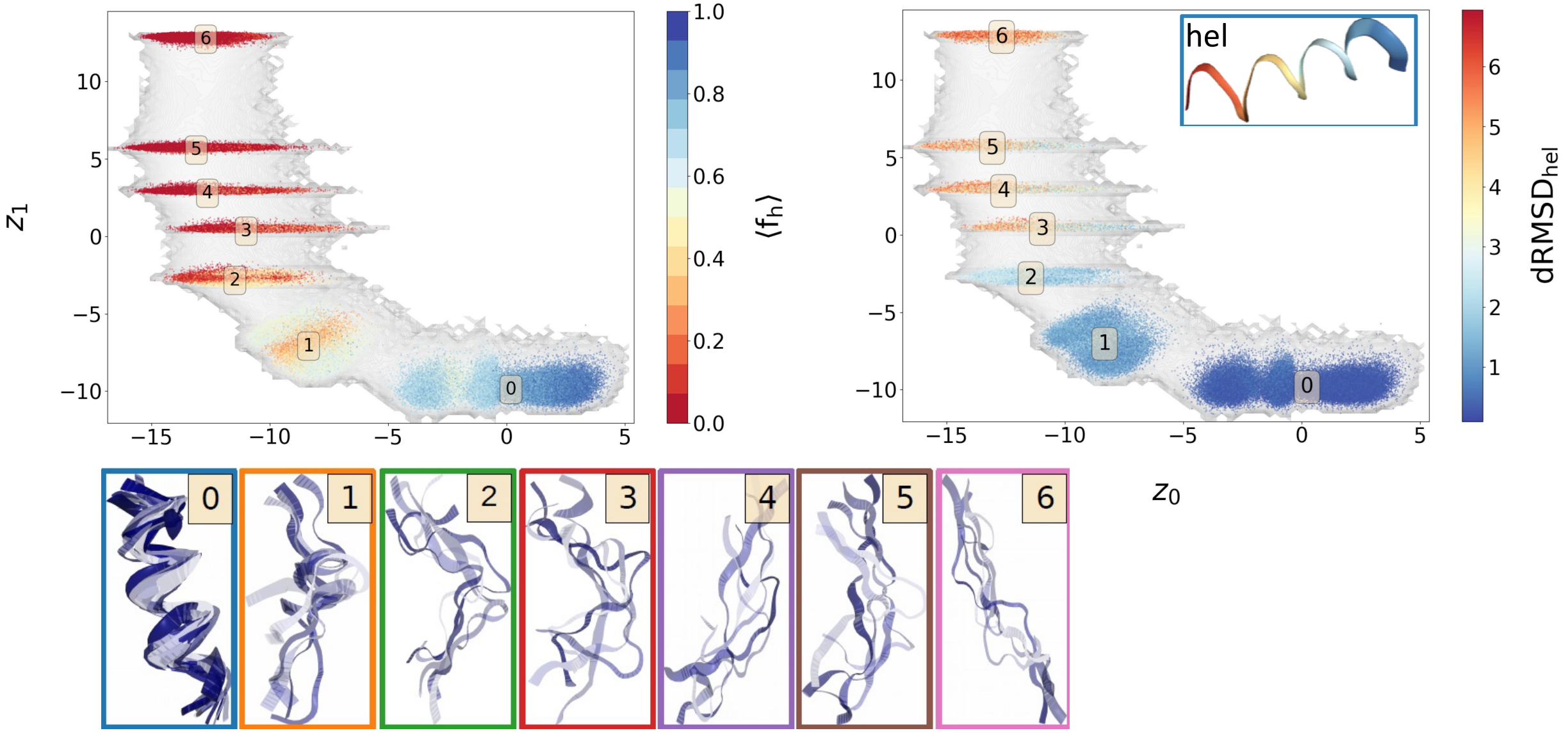


60D ⟶ 2D





Checking the projections in more detail

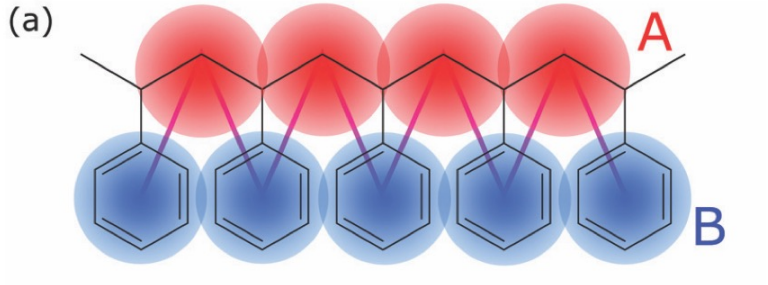


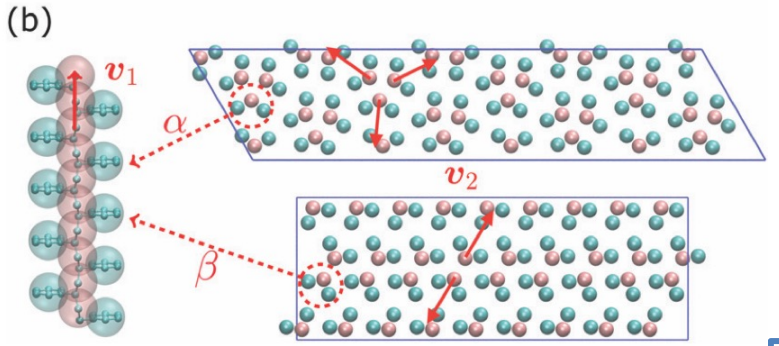
Material science application: polystyrene

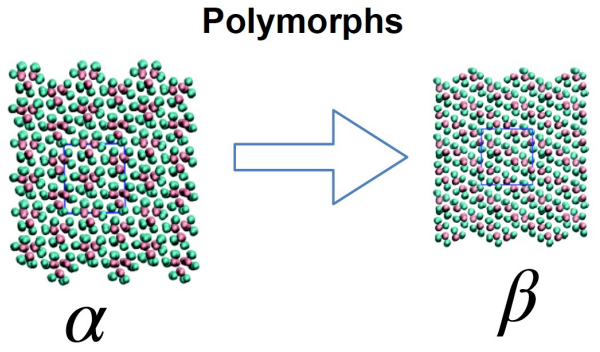
Polymorphs are different crystalline forms of the same substance in which molecules have **different arrangements** and/or different molecular conformations → Display **different properties**

Figure credit: https://letstalkscience.ca/educational-resources/stem-in-context/polystyrene-pros-cons-chemistry

Material science application: Polymorphism in polystyrene

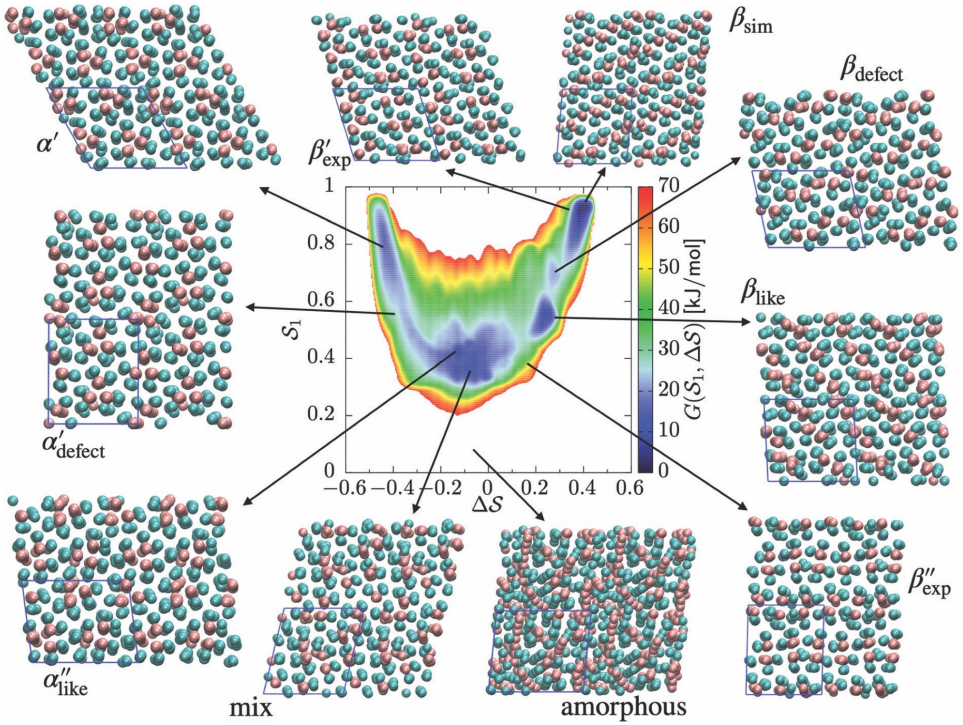






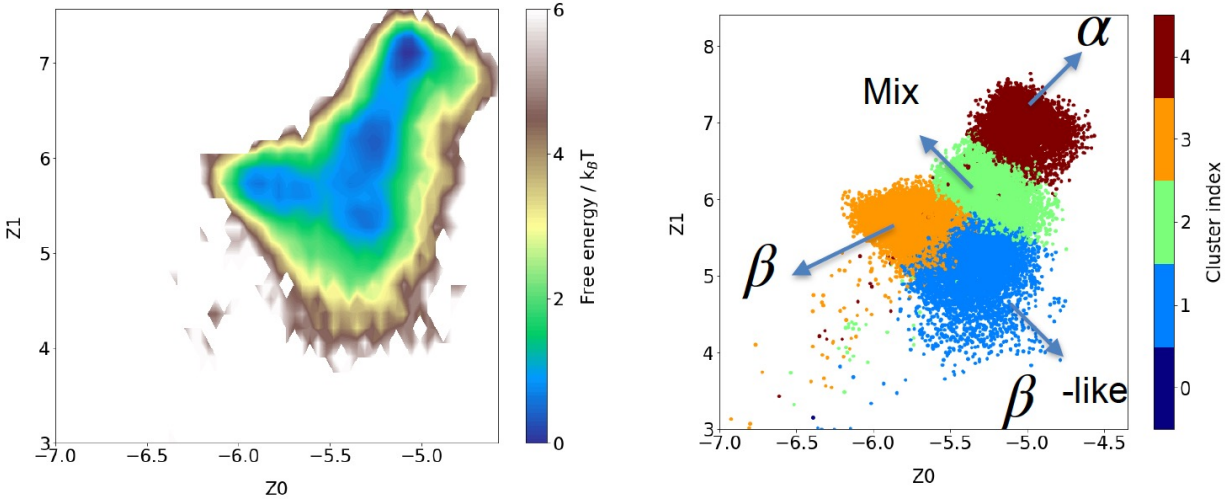
Rugged free energy landscape leads to long timescales of α to β transition.

Conformational landscape of polystyrene



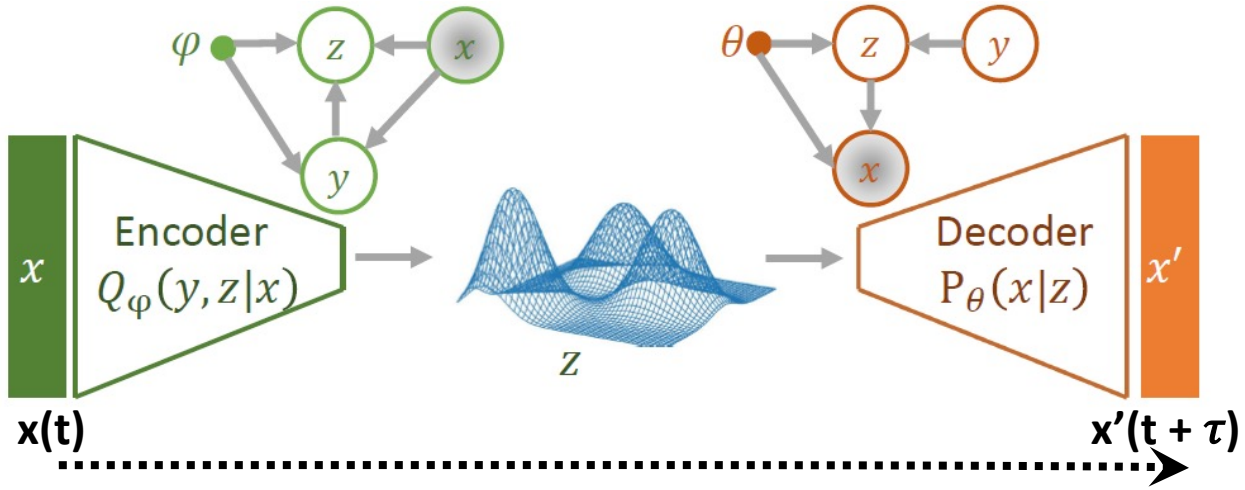
Identifying good CVs that describe the full conformational landscape is challenging.

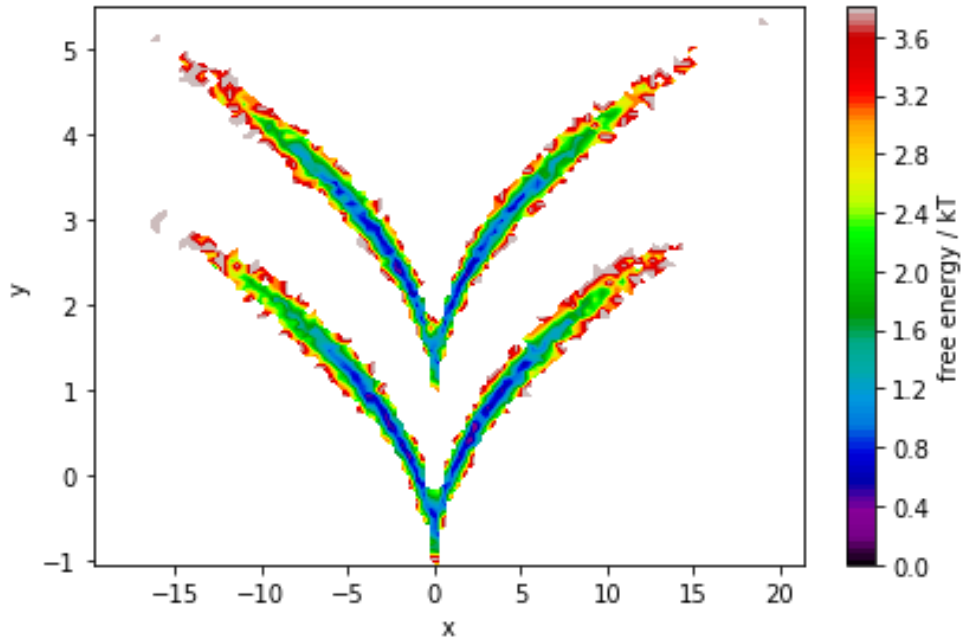
GMVAE results (preliminary)

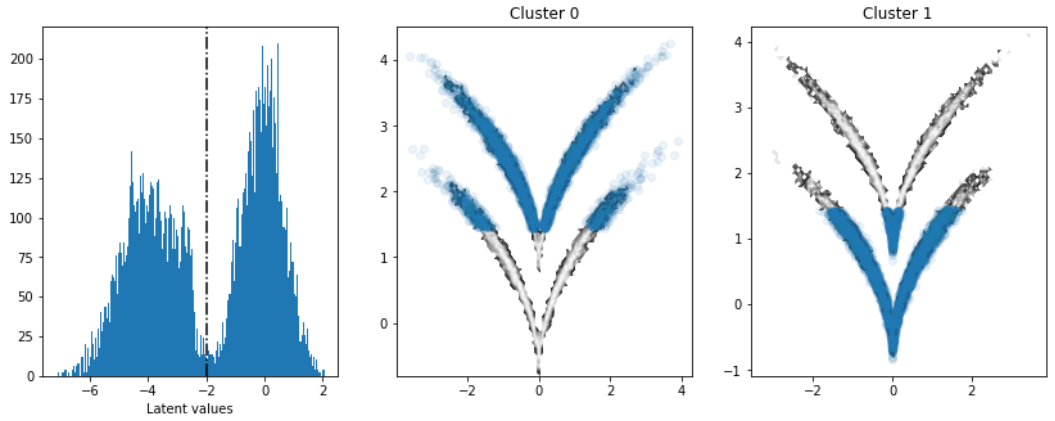


Liu et al. Soft Matter (2020)

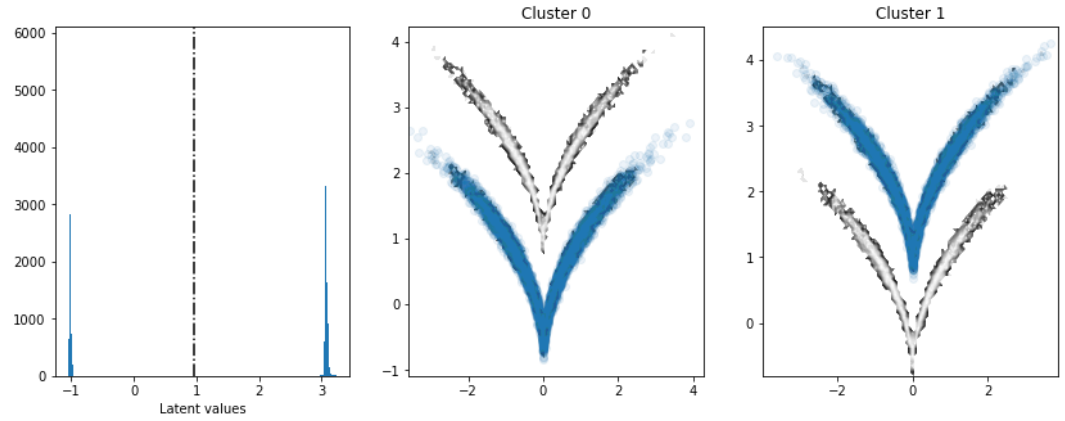
Incorporation of time-information into the GMVAE







no lag



with time-lag

Conclusion

- The GMVAE
  - restricts the latent space representation with a Gaussian mixture model,
    - ✓promoting the separation of metastable states
    - ✓allowing simultaneous dimensionality reduction and clustering.

Bozkurt et al. "Interpretable embeddings from molecular simulations using Gaussian mixture variational autoencoders." Machine Learning: Science and Technology (2020)

github.com/yabozkurt/gmvae

Acknowledgments

Assist. Prof. Tristan Bereau
University of Amsterdam, MPIP

Dr. Joseph F. Rudzinski
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Dr. Atreyee Banerjee
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TÜBİTAK

Thank you for your attention!

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