A Mathematical Analysis of Autoencoders in the Context of Importance Sampling

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Outline

- **A (short/biased) review of machine learning approaches for CV**
- **Constructing CVs with autoencoders**[1]
  - Preliminaries: definitions, training, etc.
  - An interpretation in terms of conditional expectations
  - Constructing transition paths
- **Applications** (alanine dipeptide, chignolin, HSP90)
  - Free energy biasing and iterative learning[2]
  - A semi-supervised approach for complex systems[3]

[1] Lelièvre/Pigeon/Stoltz/Zhang, *J. Phys. Chem. B* (2024)
[2] Belkacemi/Gkeka/Lelièvre/Stoltz, *J. Chem. Theory Comput.* **18** (2022)
[3] Belkacemi/Bianciotto/Minoux/Lelièvre/Stoltz/Gkeka, *J. Chem. Phys.* (2023)

ML approaches for finding CV

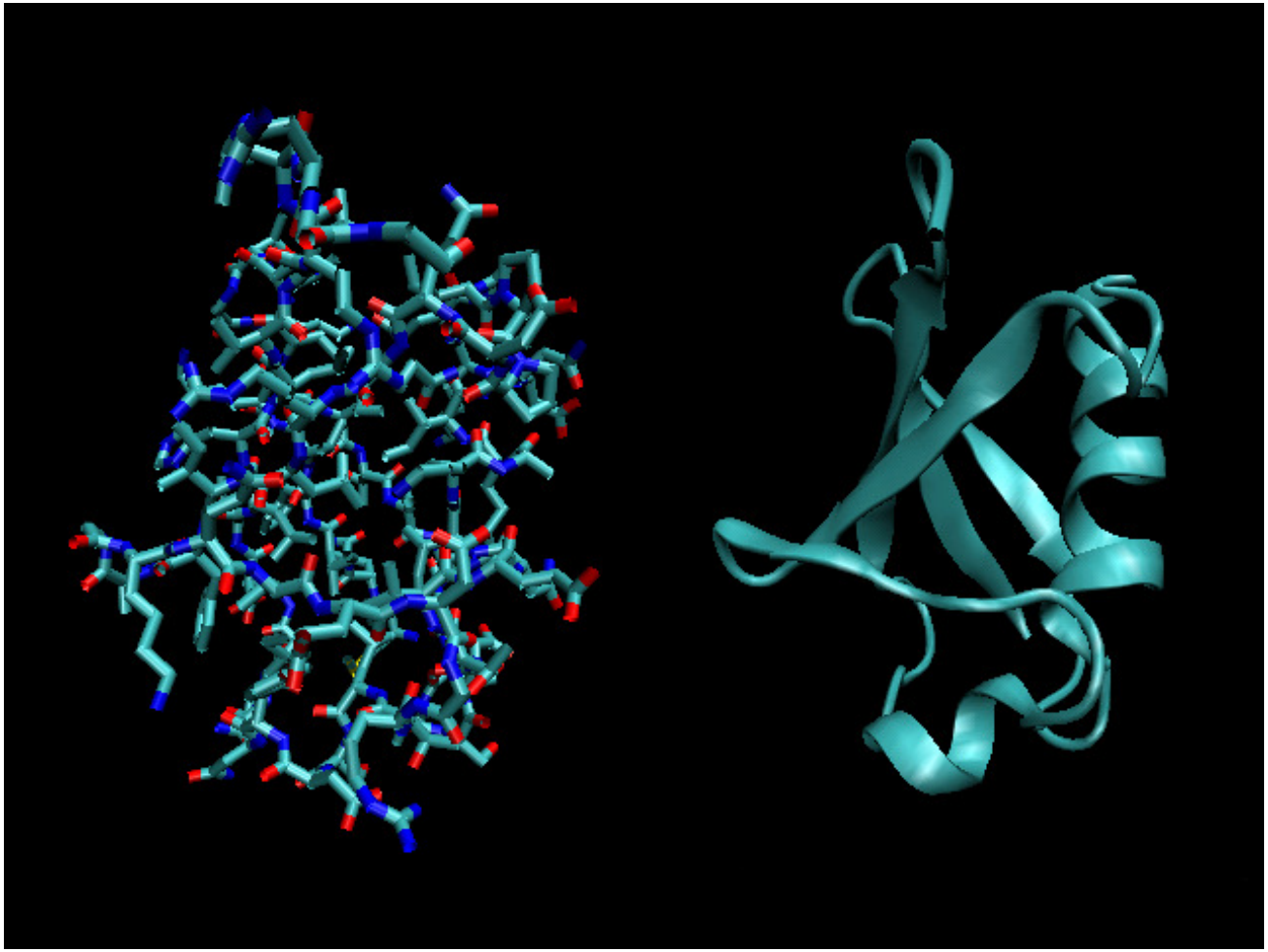
(A biased perspective on some) References

- **ML reviews in MD** (biased for dimensionality reduction, not force fields/generative)
  - A. Gliemlo, B. Husic, A. Rodriguez, C. Clementi, F. Noé, A. Laio, *Chem. Rev.* **121**(16), 9722-9758 (2021)
  - P. Gkeka *et al.*, *J. Chem. Theory Comput.* **16**(8), 4757-4775 (2020)
  - F. Noé, A. Tkatchenko, K.-R. Müller, C. Clementi, *Annu. Rev. Phys. Chem.* **71**, 361-390 (2020)
  - A.L. Ferguson, *J. Phys.: Condens. Matter* **30**, 04300 (2018)
  - M. Chen, *Eur. Phys. J. B* **94**, 211 (2021)

- **More general ML references**
  - P. Mehta, M. Bukov, C.-H. Wang, A.G.R.Day, C. Richardson, C.K. Fisher, D.J. Schwab, A high-bias, low-variance introduction to Machine Learning for physicists, *Physics Reports* **810**, 1-124 (2019)
  - I. Goodfellow, Y. Bengio, A. Courville *Deep Learning* (MIT Press, 2016) `http://www.deeplearningbook.org`
  - K.P. Murphy, *Probabilistic Machine Learning: An Introduction* (MIT Press, 2022)

Statistical physics (1)

What is the structure of the protein? What are its typical conformations, and what are the transition pathways from one conformation to another?



Statistical physics (2)

- Microstate of a classical system of N particles:

$$(q,p) = (q_1, \dots, q_N,\ p_1, \dots, p_N) \in \mathcal{E} = (a\mathbb{T})^{3N} \times \mathbb{R}^{3N}$$

Positions q (configuration), momenta p (to be thought of as $M\dot{q}$)

- Hamiltonian $H(q,p) = V(q) + \sum_{i=1}^{N} \frac{p_i^2}{2m_i}$ (physics is in V)

Macrostate: Boltzmann–Gibbs probability measure (NVT)

$$\mu(dq\,dp) = Z_{\mathrm{NVT}}^{-1}\, \mathrm{e}^{-\beta H(q,p)}\, dq\, dp, \qquad \beta = \frac{1}{k_{\mathrm{B}}T}$$

- Typical evolution equations: Langevin dynamics (friction $\gamma > 0$)

$$\begin{cases} dq_t = M^{-1} p_t\, dt \\ dp_t = -\nabla V(q_t)\, dt - \gamma M^{-1} p_t\, dt + \sqrt{2\gamma\beta^{-1}}\, dW_t \end{cases}$$

Reaction coodinates (RC) / collective variables (CV)

- Reaction coordinate $\xi : (a\mathbb{T})^D \to \mathbb{R}^d$ with $d \ll D$
- Ideally: $\xi(q_t)$ captures the slow part of the dynamics
- **Free energy** computed on $\Sigma(z) = \{q \in (a\mathbb{T})^D \,|\, \xi(q) = z\}$ (foliation)

$$F(z) = -\frac{1}{\beta} \ln \left(\int_{\Sigma(z)} \mathrm{e}^{-\beta V(q)} \, \delta_{\xi(q)-z}(dq) \right)$$

- Various methods: TI, FEP, ABF, metadynamics, etc[4]

[4] Lelièvre/Rousset/Stoltz, *Free Energy Computations: A Mathematical Perspective* (Imperial College Press, 2010)

Some representative approaches for finding CV (1)

- Chemical/physical intuition (distances, angles, RMSDs, coordination numbers, etc)

- **Short list of data-oriented approaches** (depending on the data at hand...)
  - [supervised learning] separate metastable states
  - [unsupervised/static] distinguish linear models (PCA) and nonlinear ones (e.g. based on autoencoders such as MESA[5])
  - [unsupervised/dynamics] operator based approaches (VAC, EDMD, diffusion maps, MSM; incl. tICA and VAMPNets)

(Huge literature! I am not quoting precise references here because the list would be too long)

- Other classifications[6,7] possible, e.g. **slow vs. high variance CV**

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[5] W. Chen and A.L. Ferguson, *J. Comput. Chem.* 2018; W. Chen, A.R. Tan, and A.L. Ferguson, *J. Chem. Phys.* 2018

[6] P. Gkeka et al., *J. Chem. Theory Comput.* (2020)

[7] A. Gliemlo *et al.*, *Annu. Rev. Phys. Chem.* (2021)

Some representative approaches for finding CV (2)

Methods for Choosing Collective variables

High-variance CVs

Principal Components Analysis (PCA)

Locally Linear Embedding (LLE)

Independent Component Analysis (ICA)

Laplacian and Hessian eigenmaps

Local tangent space alignment

Kernel PCA

Nonlinear PCA

Isomap

Diffusion maps

Multidimensional scaling

Semidefinite embedding/ Maximum variance unfolding

Available tools for CV identification

Diffusion-Map-directed MD (DM-d-MD)

Intrinsic Map Dynamics (iMapD)

Smooth and nonlinear datadriven CVs (SandCV)

Molecular Enhanced Sampling with Autoencoders (MESA)

Reweighted Autoencoded Variations Bayes for Enhanced Sampling (RAVE)

REinforcement Learning based on Adaptive samPling (REAP)

Slow CVs

Variational Approach to Conformational dynamics (VAC)

(extended) Dynamical Mode Decomposition ((E)DMD)

Kernel TICA

Markov State Models (MSM)

Time-lagged autoencoders (TAEs)

Time-lagged Independent Component Analysis (TICA)

Deep Canonical Correlation Analysis (DCCA)

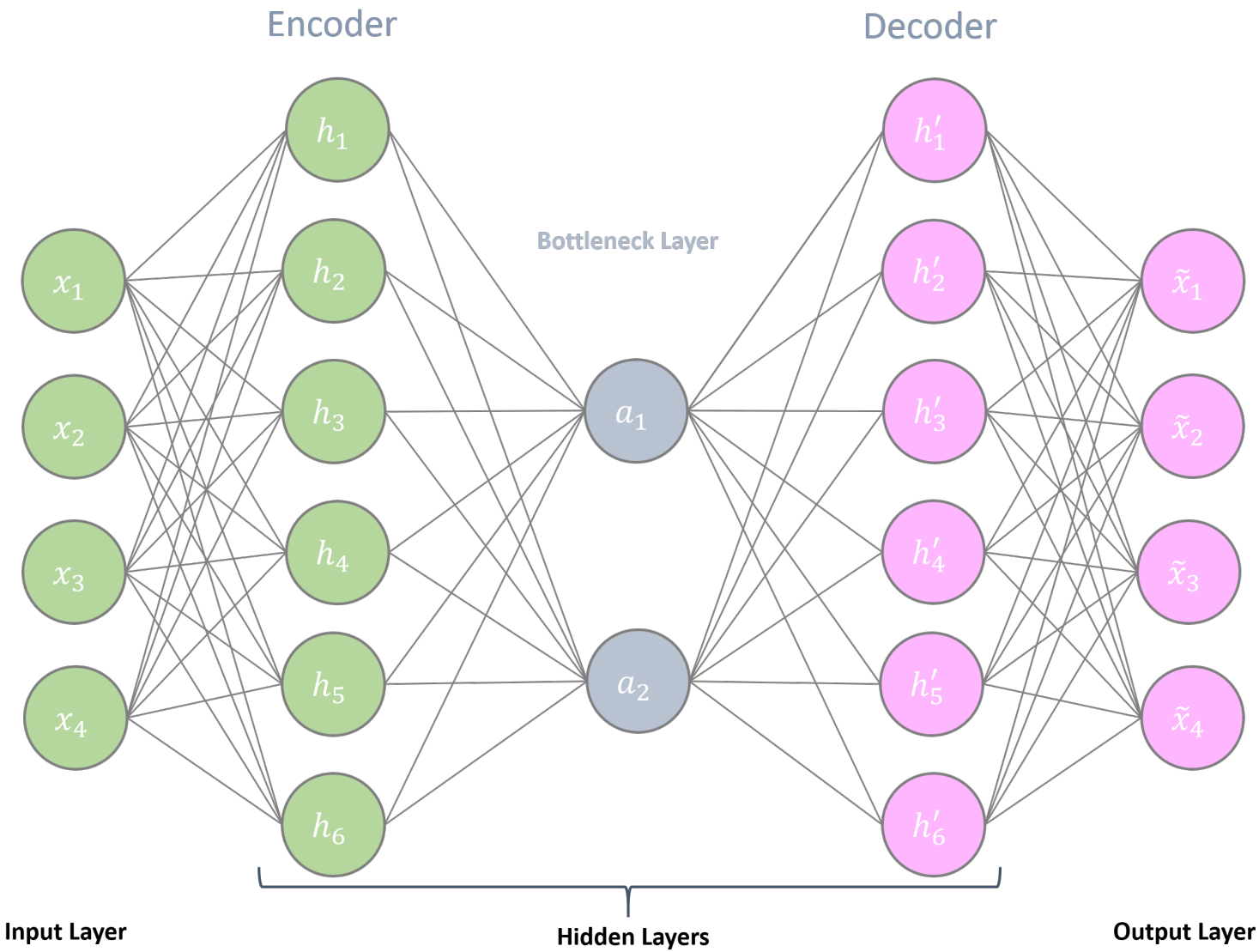
Variational Dynamics Encoders (VDEs)

Variational Approach for Markov Processes nets (VAMPnets)

State-free Reversible VAMPnets (SRV)

Constructing CVs with autoencoders

Bottleneck autoencoders (1)



Bottleneck autoencoders (2)

- Data space $\mathcal{X} \subseteq \mathbb{R}^D$, bottleneck space $\mathcal{A} \subseteq \mathbb{R}^d$ with $d < D$

$$f(x) = f_{\text{dec}}\Big(f_{\text{enc}}(x)\Big)$$

where $f_{\text{enc}} : \mathcal{X} \to \mathcal{A}$ and $f_{\text{dec}} : \mathcal{A} \to \mathcal{X}$

Collective variable = encoder part

$$\xi = f_{\text{enc}}$$

- Fully connected neural network, symmetrical structure, $2L$ layers

- Parameters $\mathbf{p} = \{p_k\}_{k=1,\dots,K}$ (bias vectors b_ℓ and weights matrices W_ℓ)

$$f_{\mathbf{p}}(x) = g_{2L}\left[b_{2L} + W_{2L} \dots g_1(b_1 + W_1 x)\right],$$

with activation functions g_ℓ

(examples: $\tanh(x)$, ReLU $\max(0, x)$, sigmoid $\sigma(x) = 1/(1 + \mathrm{e}^{-x})$, etc)

Training autoencoders

- Theoretically: minimization problem in $\mathcal{P} \subset \mathbb{R}^K$

$$\mathbf{p}_\mu \in \operatorname*{argmin}_{\mathbf{p}\in\mathcal{P}} \mathcal{L}(\mu, \mathbf{p}),$$

with cost function

$$\mathcal{L}(\mu, \mathbf{p}) = \mathbb{E}_\mu(\|X - f_{\mathbf{p}}(X)\|^2) = \int_{\mathcal{X}} \|x - f_{\mathbf{p}}(x)\|^2 \, \mu(dx)$$

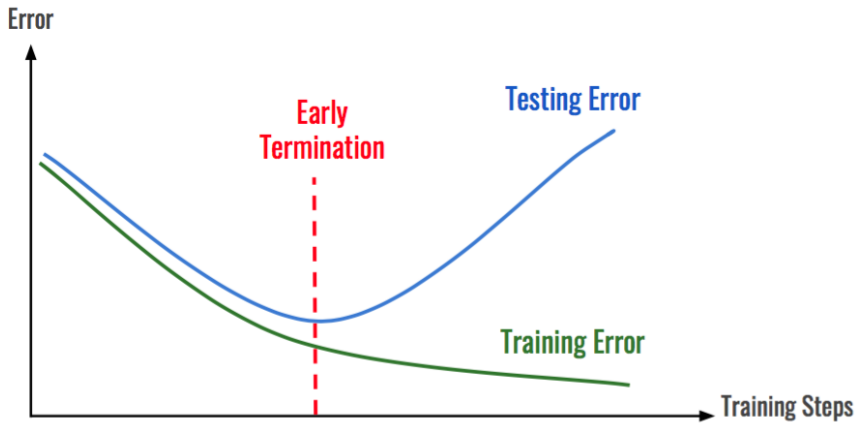
- In practice, access only to a sample: **minimization of empirical cost**

$$\mathcal{L}(\hat{\mu}, \mathbf{p}) = \frac{1}{N}\sum_{i=1}^{N} \|x^i - f_{\mathbf{p}}(x^i)\|^2, \qquad \hat{\mu} = \frac{1}{N}\sum_{i=1}^{N} \delta_{x^i}$$

- **Typical choices:** canonical measure μ, data points x^i postprocessed from positions q (alignement to reference structure, centering, reduction to backbone carbon atoms, etc)

Some elements on training neural networks

- Many local minima...
- **Actual procedure:**
  - "Early stopping": stop when validation loss no longer improves[8]



  - Choice of optimization method[9], here Adam
  - No added regularization here (e.g. ℓ^1/ℓ^2, dropout, etc)

[8] See Section 7.8 in [Goodfellow/Bengio/Courville]
[9] See Chapter 8 in [Goodfellow/Bengio/Courville]

Some properties of autoencoders

Three viewpoints on the loss function (1/2)

Idealized setting: $f_{\text{enc}} : \mathcal{X} \to \mathcal{Z}$ and $f_{\text{dec}} : \mathcal{Z} \to \mathcal{X}$ measurable

$$\mathcal{F} = \{f = f_{\text{dec}} \circ f_{\text{enc}},\ f_{\text{enc}} \in \mathcal{F}_{\text{enc}},\ f_{\text{dec}} \in \mathcal{F}_{\text{dec}}\}$$

Usual loss: $\inf_{f \in \mathcal{F}} \mathbb{E}\left[\|X - f(X)\|^2\right]$

Principal manifold formulation: fix decoder, minimize over encoders

$$\begin{aligned}\inf_{f \in \mathcal{F}} \mathbb{E}\left[\|X - f(X)\|^2\right] &= \inf_{f_{\text{dec}} \in \mathcal{F}_{\text{dec}}} \left\{ \inf_{f_{\text{enc}} \in \mathcal{F}_{\text{enc}}} \mathbb{E}\left[\|X - f_{\text{dec}} \circ f_{\text{enc}}(X)\|^2\right] \right\} \\ &= \inf_{f_{\text{dec}} \in \mathcal{F}_{\text{dec}}} \mathbb{E}\left[\left\|X - f_{\text{dec}} \circ h^\star_{f_{\text{dec}}}(X)\right\|^2\right]\end{aligned}$$

with ideal encoder $h^\star_{f_{\text{dec}}}(x) \in \operatorname{argmin}_{z \in \mathcal{Z}} \|x - f_{\text{dec}}(z)\|$

Hastie/Stützle (1986), Tibshirani (1992)
Venturoli/Vanden–Eijnden (2009)
Gerber/Whitaker, *J. Mach. Learn. Res.* (2013); Gerber, *arXiv preprint* **2104.05000**

Three viewpoints on the loss function (2/2)

Formulation with conditional expectation: fix encoder, minimize over decoders

$$\begin{aligned}\inf_{f\in\mathcal{F}} \mathbb{E}\left[\|X - f(X)\|^2\right] &= \inf_{f_{\text{enc}}\in\mathcal{F}_{\text{enc}}} \left\{ \inf_{f_{\text{dec}}\in\mathcal{F}_{\text{dec}}} \mathbb{E}\left[\|X - f_{\text{dec}}\circ f_{\text{enc}}(X)\|^2\right]\right\} \\ &= \inf_{f_{\text{enc}}\in\mathcal{F}_{\text{enc}}} \mathbb{E}\left[\left\|X - g^\star_{f_{\text{enc}}}\circ f_{\text{enc}}(X)\right\|^2\right]\end{aligned}$$

with ideal decoder $g^\star_{f_{\text{enc}}}(z) = \mathbb{E}[\, X \,|\, f_{\text{enc}}(X) = z]$

Alternative interpretations of the reconstruction error

$$\begin{aligned}\mathbb{E}\left[\left\|X - g^\star_{f_{\text{enc}}}\circ f_{\text{enc}}(X)\right\|^2\right] &= \text{Var}(X) - \text{Var}\left[\mathbb{E}(X|f_{\text{enc}}(X))\right] \\ &= \mathbb{E}\left[\text{Var}(X|f_{\text{enc}}(X))\right]\end{aligned}$$

First equality by developing square, second by conditioning on $f_{\text{enc}}(X)$

Numerical illustration

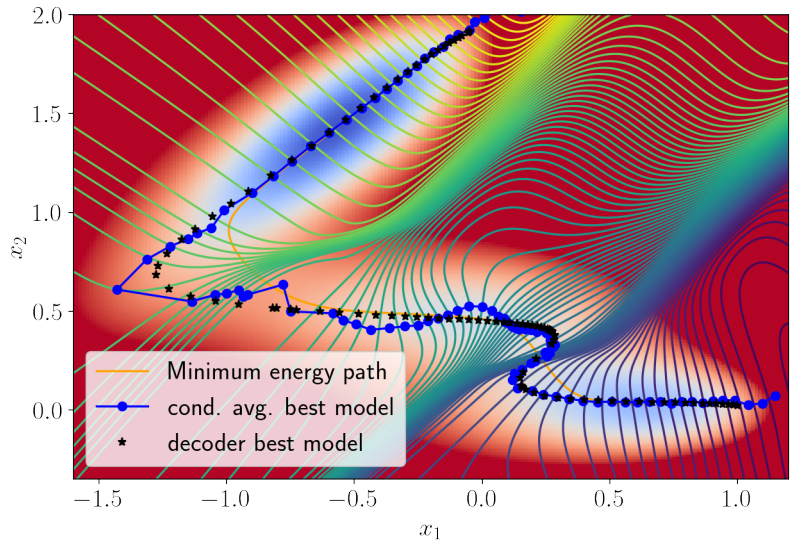
Practical implication: minimizing reconstruction loss amounts to...

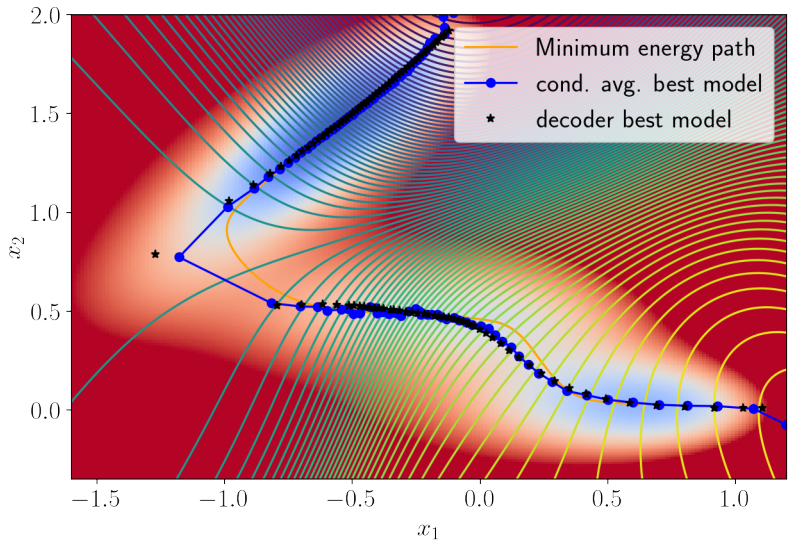
- minimizing intraclass dispersion

  (small spread of data points for f_{enc} given around the mean)

- maximizing interclass dispersion

  (the mean values associated with f_{enc} given should be as spread out as possible)





Left: topology (2, 5, 5, 1, 5, 5, 2). Right: topology (2, 5, 5, 1, 20, 20, 2)

Additional properties

- Necessary condition for critical points of the loss functional on f_{enc}

$$\left[x - g^\star_{f_{\mathrm{enc}}}(f_{\mathrm{enc}}(x))\right]^\top \partial_{z_j} g^\star_{f_{\mathrm{enc}}}(f_{\mathrm{enc}}(x)) = 0, \qquad 1 \leqslant j \leqslant d,\ x \in \mathrm{Supp}(\mu)$$

Low temperature limit: $\{g^\star_{f_{\mathrm{enc}}}(z)\}_{z\in[z_A,z_B]}$ minimum energy path[10]

- **Formulation with conditional expectations for other models:**
  - clustering
  - PCA (= autoencoders with identity activation functions)

- **Various extensions:**
  - change reference measure to better take transition states into account
  - multiple transition paths: single encoder and several decoders
  - possibly add some regularization terms

[10] Venturoli/Vanden–Eijnden (2009)

Free energy biasing and iterative learning

Extended systems

- Computing $\nabla\xi$ already difficult, higher order derivatives is worse
- **Extended system** strategy : $V_{\mathrm{ext}}(q,\lambda) = V(q) + \frac{\kappa}{2}\big(\xi(q)-\lambda\big)^2$
- Free energy for the (simple) collective variable $\xi_{\mathrm{ext}}(q,\lambda) = \lambda$

$$
\begin{aligned}
F_\kappa(z) &= -\frac{1}{\beta}\ln\int_{\mathcal{D}} \mathrm{e}^{-\beta V_{\mathrm{ext}}(q,z)}\,dq + C \\
&= -\frac{1}{\beta}\ln\int\left(\int_{\Sigma(\zeta)} \mathrm{e}^{-\beta V(q)}\delta_{\xi(q)-\zeta}(dq)\right)\mathrm{e}^{-\beta\kappa(\zeta-z)^2/2}\,d\zeta + C \\
&= -\frac{1}{\beta}\ln\int \mathrm{e}^{-\beta F(\zeta)}\chi_\kappa(z-\zeta)\,d\zeta + \widetilde{C}, \qquad \chi_\kappa(s) = \left(\frac{\beta\kappa}{2\pi}\right)^{d/2}\mathrm{e}^{-\beta\kappa s^2/2} \\
&\xrightarrow[\kappa\to+\infty]{} F(z)
\end{aligned}
$$

Calls for taking κ large

Extended ABF

Extended overdamped Langevin dynamics (κ limits Δt...)

$$\begin{cases} dq_t = \Big[-\nabla V(q_t) + \kappa(\xi(q_t) - \lambda_t)\nabla\xi(q_t) \Big] dt + \sqrt{2\beta^{-1}} dW_t^q \\ d\lambda_t = -\kappa[\lambda_t - \xi(q_t)]\, dt + \sqrt{2\beta^{-1}}\, dW_t^\lambda \end{cases}$$

Bias by the free energy: add $F'_\kappa(\lambda)$ = steady state conditional average of $\kappa(\lambda - \xi(q))$

Extended ABF overdamped Langevin dynamics

$$\begin{cases} dq_t = \Big[-\nabla V(q_t) + \kappa(\xi(q_t) - \lambda_t)\nabla\xi(q_t) \Big] dt + \sqrt{2\beta^{-1}} dW_t^q \\ d\lambda_t = \kappa[\xi(q_t) - \mathbb{E}(\xi(q_t) \,|\, \lambda_t)]\, dt + \sqrt{2\beta^{-1}}\, dW_t^\lambda \end{cases}$$

In practice, $\mathbb{E}(\xi(q_t) \,|\, \lambda_t)$ is estimated by $\dfrac{\int_0^t \delta_\varepsilon(\lambda_s - \Lambda)\xi(q_s)\, ds}{\max\left(\eta, \int_0^t \delta_\varepsilon(\lambda_s - \Lambda)\, ds\right)}$

Iterative training on modified target measures

- Interesting systems are metastable (no spontaneous exploration of phase space)
Sample according to a biased distribution $\widetilde{\mu}$ (importance sampling)

- Need for reweighting[11] $w(q) = \mu(q)/\widetilde{\mu}(q)$

$$\mathcal{L}(\widehat{\mu}_{\text{wght}}, \mathbf{p}) = \sum_{i=1}^{N} \widehat{w}_i \|q^i - f_{\mathbf{p}}(q^i)\|^2, \qquad \widehat{w}_i = \frac{\mu(q^i)/\widetilde{\mu}(q^i)}{\sum_{j=1}^{N} \mu(q^j)/\widetilde{\mu}(q^j)}$$

- **Free-energy biasing:** $\mu(q,\lambda) \propto \mathrm{e}^{-\beta V_{\text{ext}}(q,\lambda)}$ and $\widetilde{\mu}(q,\lambda) \propto \mu(q,\lambda)\mathrm{e}^{\beta F_\kappa(\lambda)}$

- Iteration between free energy biasing for ξ fixed and retraining of $\xi = f_{\text{enc}}$

- Convergence: (linear) regression to assess whether $\xi_k \approx \Phi(\xi_{k-1})$

[11] As done in RAVE for instance, see Ribeiro/Bravo/Wang/Tiwary (2018), Wang/Ribeiro/Tiwary (2019)

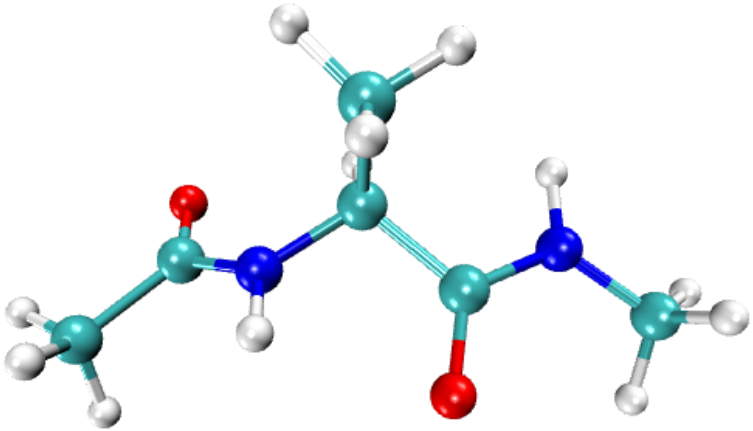
Alanine dipeptide

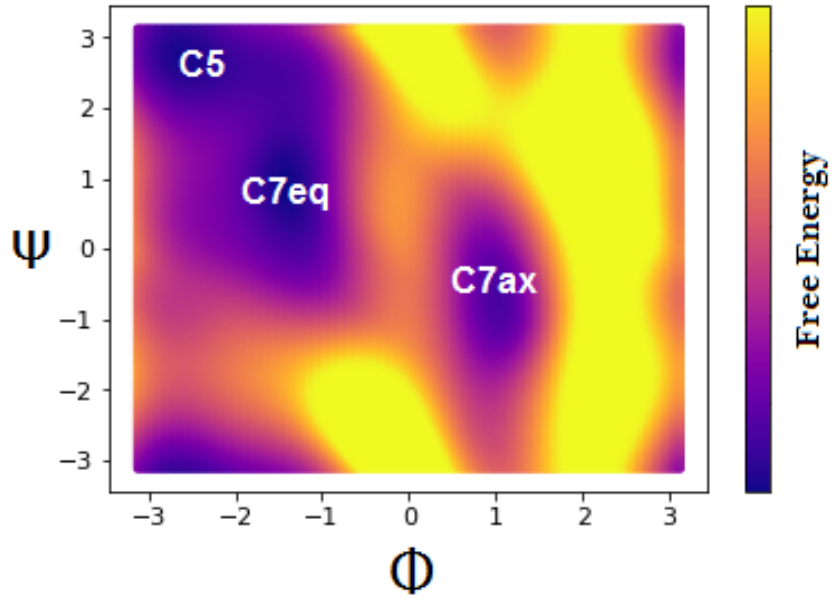
- **Molecular dynamics:**

`openmm` with `openmm-plumed` to link it with `plumed`
`colvar` module for eABF and computation of free energies[12]
timestep 1 fs, friction $\gamma = 1$ ps^{-1} in Langevin dynamics

- **Machine learning:**

`keras` for autoencoder training
input = carbon backbone (realignement to reference structure and centering)
neural network: topology 24-40-2-40-24, tanh activation functions



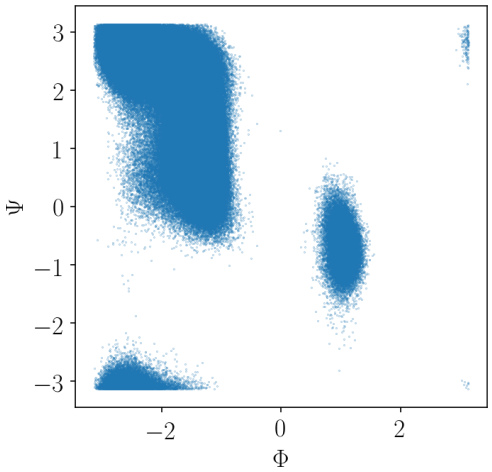


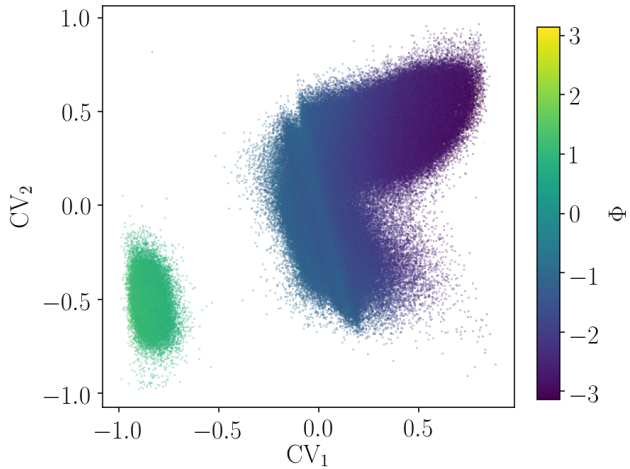
[12] See also Chen/Liu/Feng/Fu/Cai/Shao/Chipot, *J. Chem. Inf. Model.* (2022)

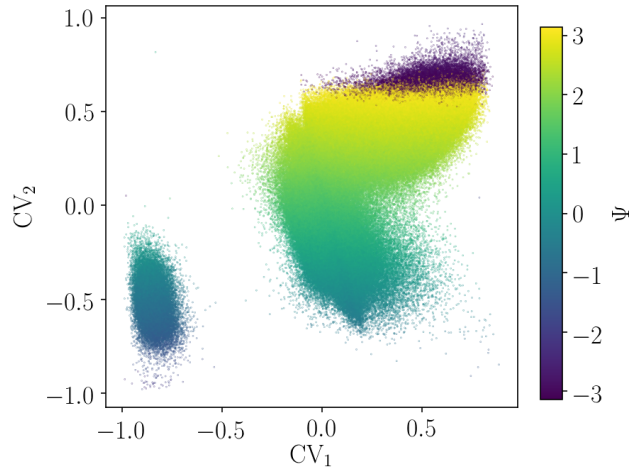
Ground truth computation

Long trajectory (1.5 μs), $N = 10^6$ (frames saved every 1.5 ps)

CV close to dihedral angles Φ, Ψ





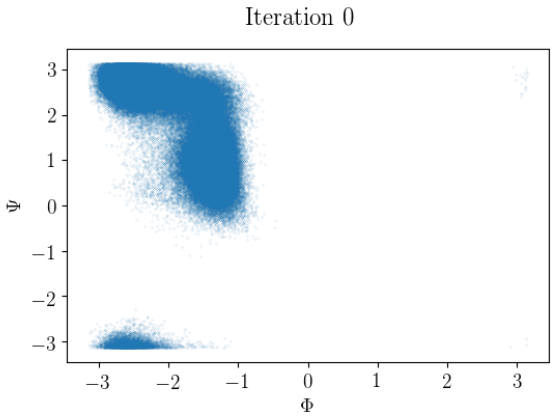


Quantify $s_{\min} = 0.99$ for $N = 10^5$ using a bootstraping procedure

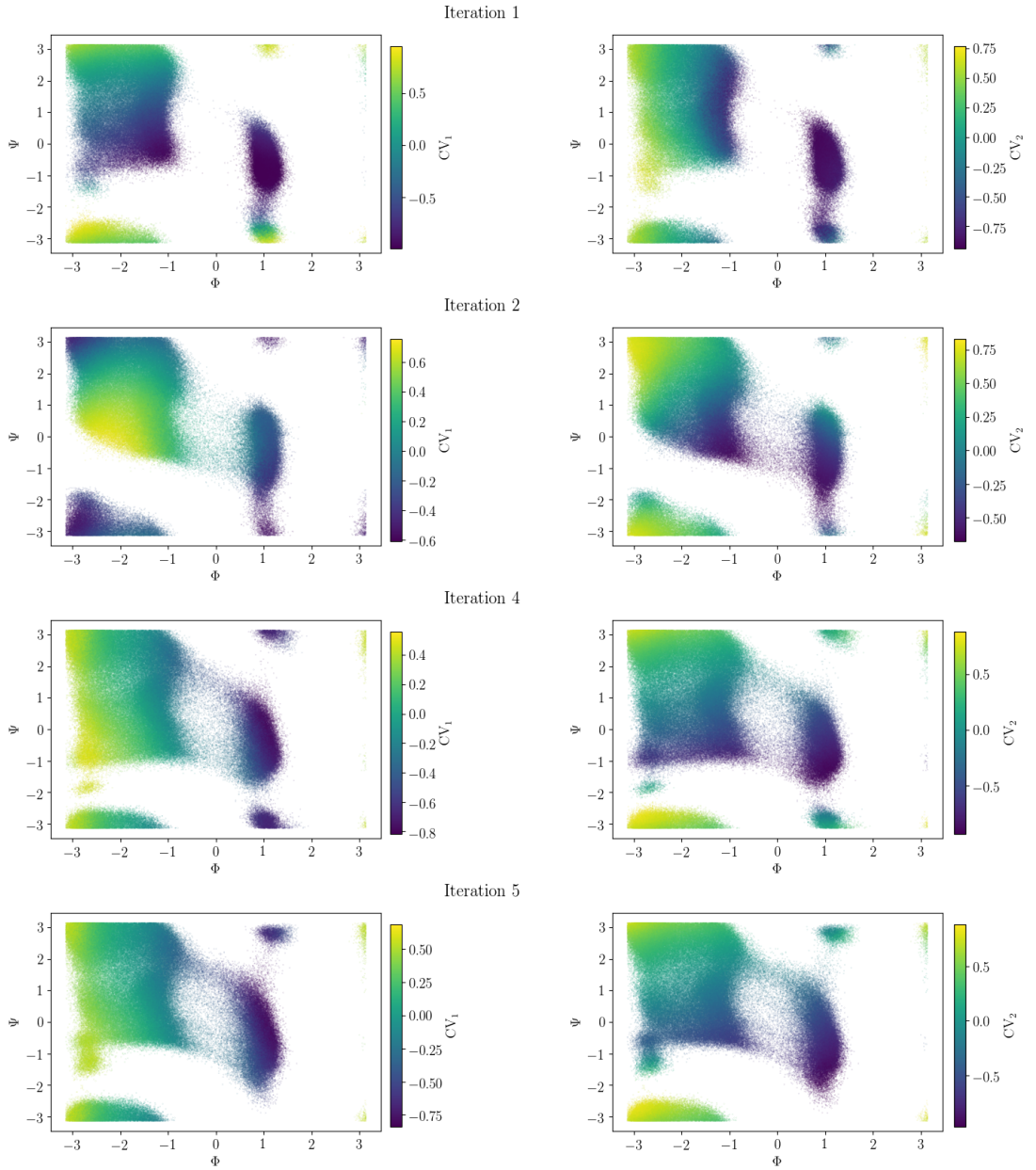
For the iterative algorithm: 10 ns per iteration

(compromise between times not too short to allow for convergence of the free energy, and not too large in order to alleviate the computation cost)

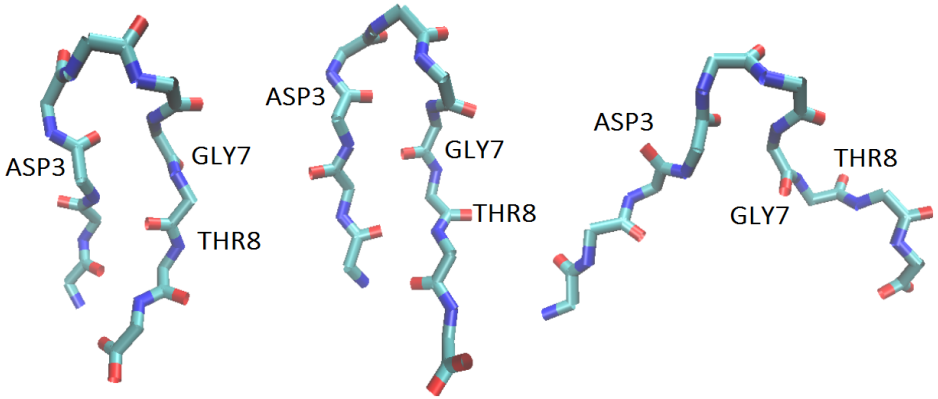
Results for the iterative algorithm



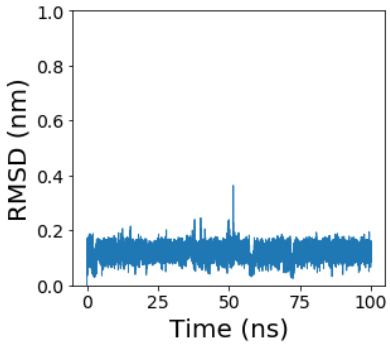
iter.	regscore	(Φ, Ψ)
0	–	0.922
1	0.872	0.892
2	0.868	0.853
3	0.922	0.973
4	0.999	0.972
5	0.999	0.970
6	0.999	0.971
7	0.999	0.967
8	0.998	0.966
9	0.999	0.968

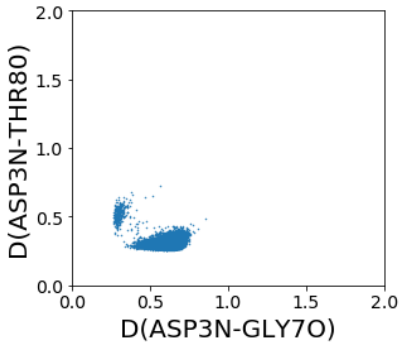


Chignolin (Folded/misfolded/unfolded states)

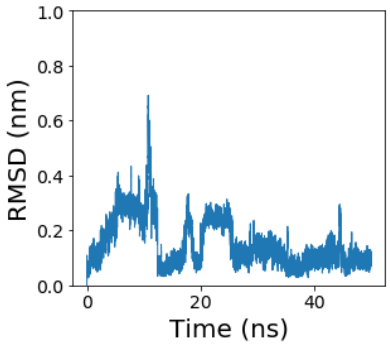


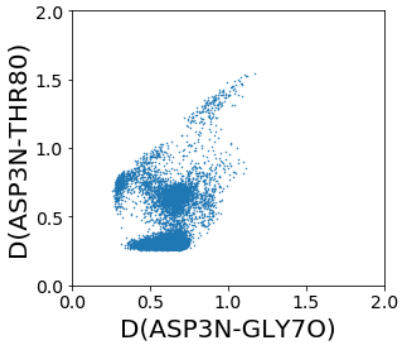
Iteration 0



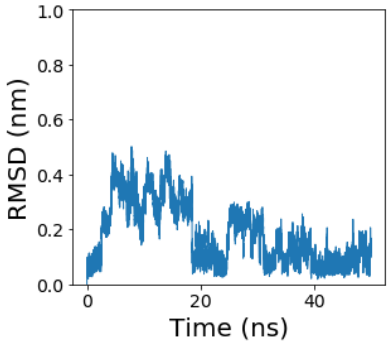


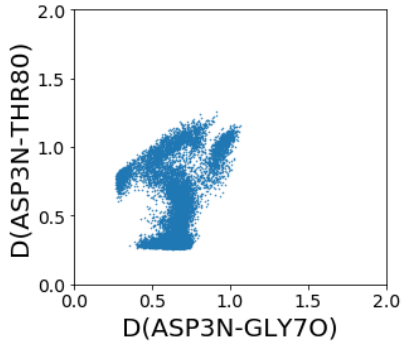
Iteration 1



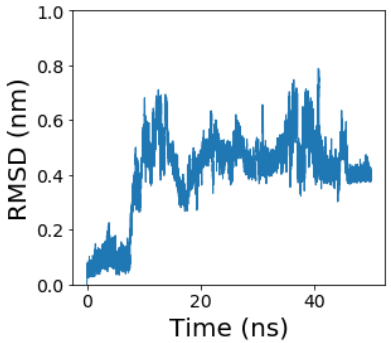


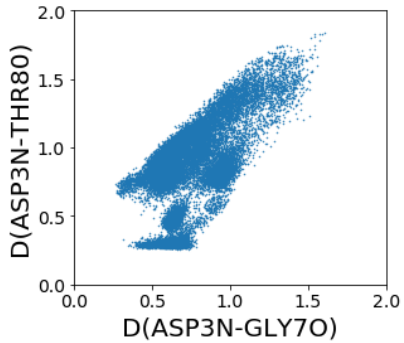
Iteration 3



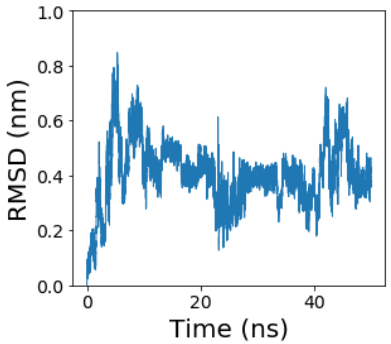


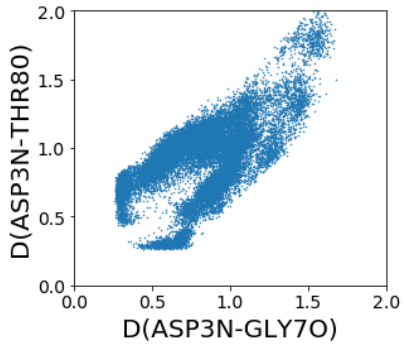
Iteration 5





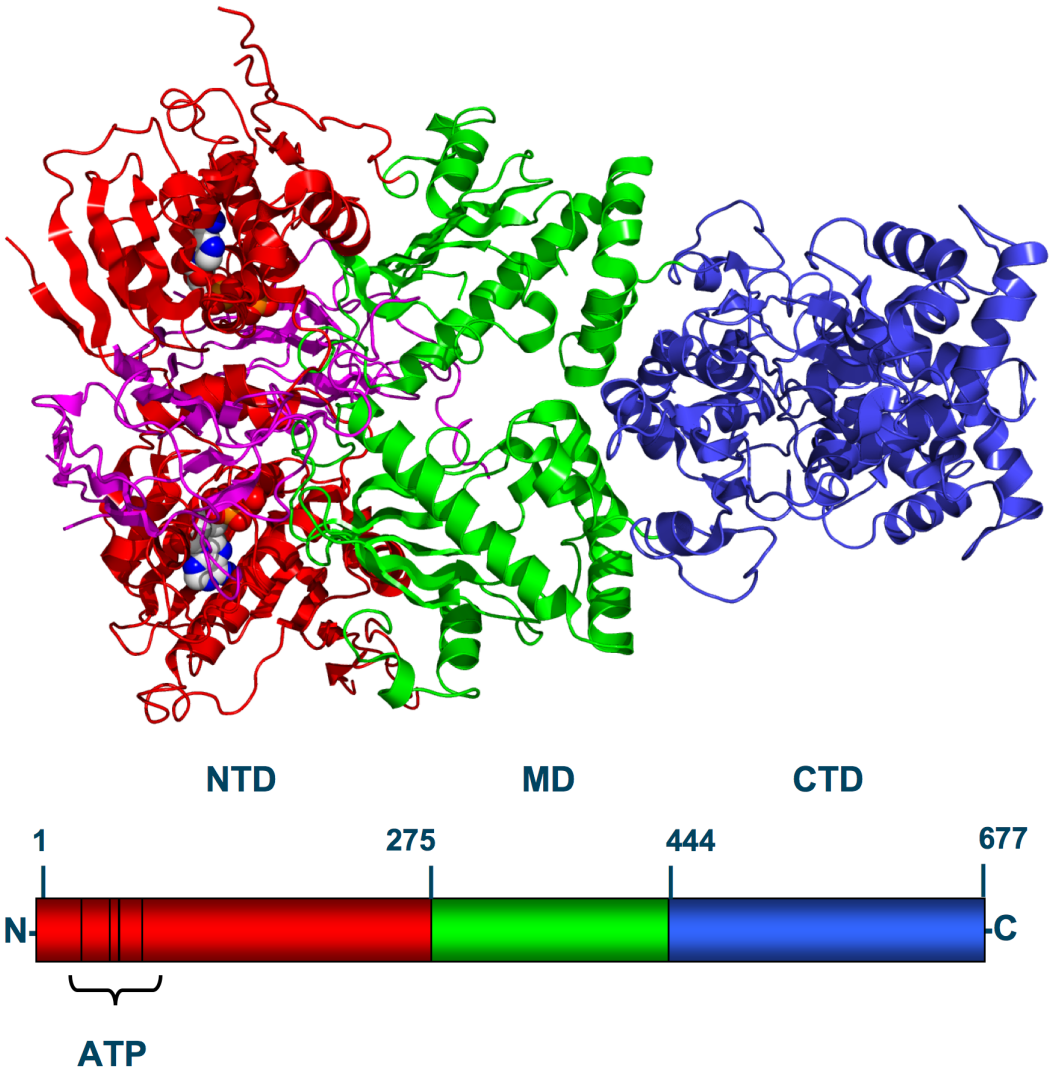
Iteration 6





A semi-supervised approach for complex systems

Case study: HSP90

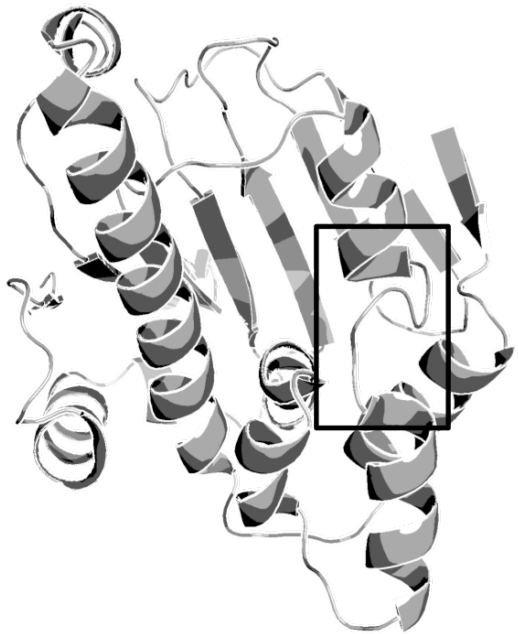


(picture from https://en.wikipedia.org/wiki/File:Hsp90_schematic_2cg9.png)

Chaperone protein assisting other proteins to fold properly and stabilizing them against stress, including proteins required for tumor growth

$\longrightarrow$ look for inhibitors (e.g. targeting binding region of ATP; focus only on the N-terminal domain)

Semi-supervised approach



State 1
pdb 3T10

State 4
pdb 6EYB

State 2
pdb 3T0H

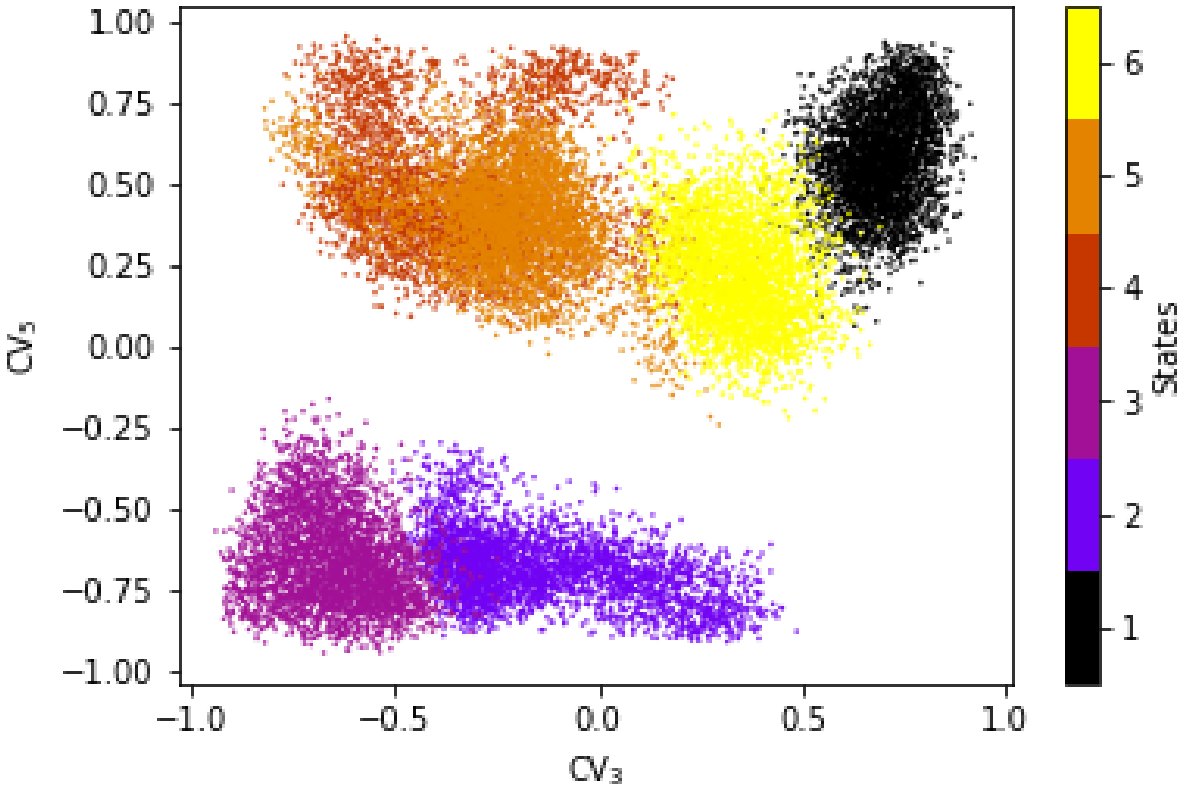
State 5
pdb 2YK9

State 3
pdb 4AWQ

State 6
pdb 3B28

Local sampling from 6 known conformations taken from the protein databank ; 10 $\times$ 20 ns trajectories each (in fact, States 4 and 5 can be merged)

Selecting the most relevant 2D collective variable



Autoencoder

- input $=$ 207 C carbons
- 621-100-k-100-621
- bottleneck $2 \leqslant k \leqslant 10$

Best heuristic:

- $k = 5$
- further reduce with coordinate projection

Free energy biasing with the resulting CV allows to observe transitions between states

On-going work on making these choices more automatic