Finding reaction coordinates with machine learning techniques for free energy computations

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Outline

- **Molecular systems and basics of statistical physics**
  - Reaction coordinates and free energy
  - A (short/biased) review of machine learning approaches for RC

- **Free-energy biasing and iterative learning with autoencoders**[1]
  - Autoencoders and their training
  - General presentation of the iterative algorithm
  - Illustration/sanity checks on toy examples

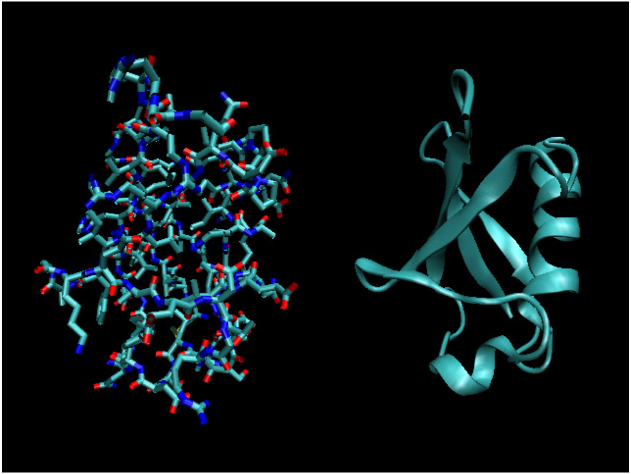
- **Applications to systems of interest** (alanine dipeptive, HSP90)

[1] Z. Belkacemi, P. Gkeka, T. Lelièvre, G. Stoltz, arXiv preprint **2104.11061**

Molecular description of systems

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:

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

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 $\xi : \mathbb{R}^D \to \mathbb{R}^d$ 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[2]

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

Some representative approaches for finding RC/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] distinguish linear models (PCA) and nonlinear ones (e.g. based on autoencoders such as MESA[3])
  - [dynamics] operator based approaches (VAC, EDMD, diffusion maps, MSM; incl. tICA and VAMPNets)

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

- Other classifications[4] possible, e.g. **slow vs. high variance CV**

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

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

Some representative approaches for finding RC/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

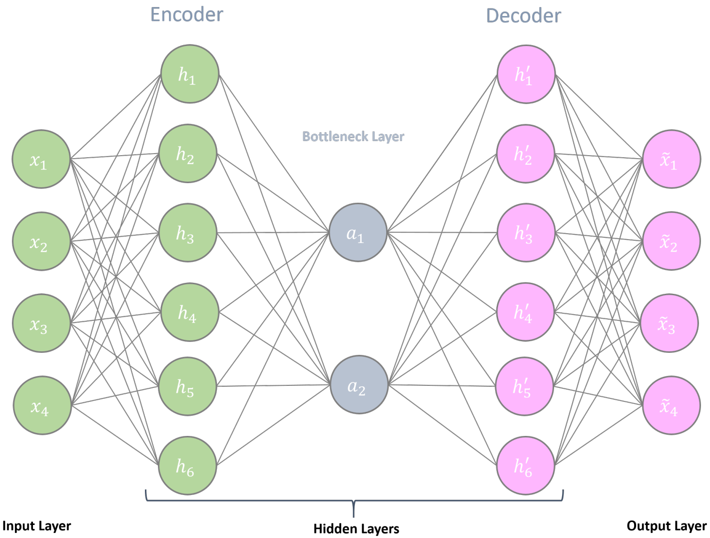
- Diffusion-Map-directed MD (DM-d-MD)
- Intrinsic Map Dynamics (iMapD)
- Smooth and nonlinear datadriven CVs (SandCV)
- Molecular Enhanced Sampling with Autoencoders (MESA)
- Reweighted Autoencoded Variations Bayes for Enhanced Sampling (RAVE)
- REinforcement Learning based on Adaptive samPling (REAP)

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)

Free-energy biasing and iterative learning with autoencoders

Autoencoders (1)



Autoencoders (2)

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

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

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

Reaction coordinate = encoder part

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

- 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: $\tanh(x)$, $\max(0,x)$, etc)

Training autoencoders

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

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

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)

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 to learn the correct encoding!

$$w(x) = \frac{\mu(x)}{\widetilde{\mu}(x)}$$

- **Minimization problem:** theoretical cost function

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

actual cost function

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

- Only requires the knowledge of μ and $\widetilde{\mu}$ up to a multiplicative constant.

How training is actually performed...

- **Gradient descent with minibatching:** randomly reshuffle data points,

$$\mathbf{p}_r = \mathbf{p}_{r-1} - \eta \nabla_{\mathbf{p}} \mathcal{L}_r(\mathbf{p}_{r-1}), \qquad \mathcal{L}_r(p) = \frac{1}{m} \sum_{i=rm+1}^{(r+1)m} \|x^i - f_{\mathbf{p}}(x^i)\|^2$$

One epoch $= \lceil N/m \rceil$ gradient steps (in order to visit all the data)

- **Actual procedure:**
  - Use `keras` module in `python`
  - Computation of gradient performed with backpropagation
  - Optimization in fact performed with Adam algorithm

    (weights summing to 1 to use default optimization parameters)
  - "Early stopping" (stop when validation loss no longer improves)

- Many local minima...

Proof of concept (1)

• **Gaussian distributions** $\mu_i = \mathcal{N}(0, \Sigma_i)$ with

$$\Sigma_1 = \begin{pmatrix} 1 & 0 \\ 0 & 0.01 \end{pmatrix}, \qquad \Sigma_2 = \begin{pmatrix} 0.01 & 0 \\ 0 & 1 \end{pmatrix}$$

Datasets $\mathcal{D}_i$ of $N = 10^6$ i.i.d. points

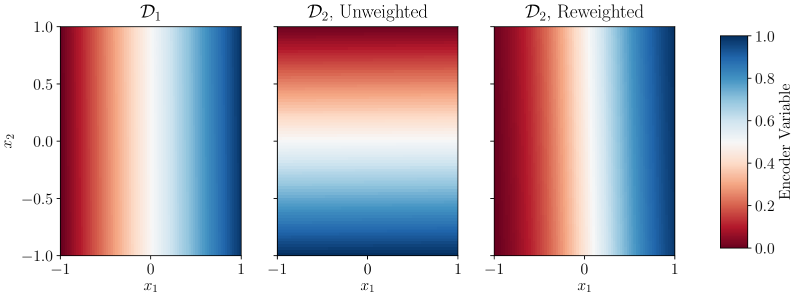
• Autoencoders with 2 layers of resp. 1 and 2 nodes, linear activation functions ($\simeq$ PCA)

• **Training on:**

- $\mathcal{D}_1$
- $\mathcal{D}_2$
- $\mathcal{D}_2$ with reweighting $\widehat{w}_i \propto \mu_1/\mu_2$

Proof of concept (2)

Heat maps of $f_{\rm enc}$

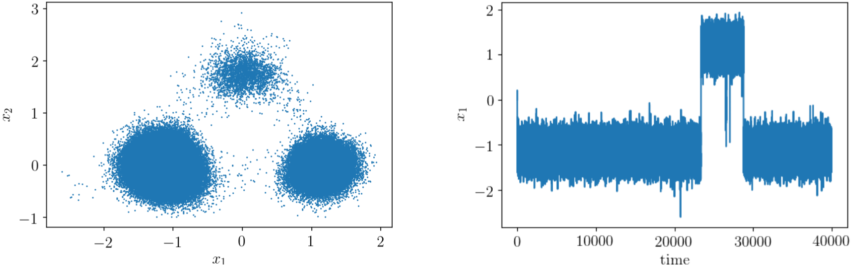


Third encoder very similar to the first: projection on x_1.
Second encoder projects on a direction close to x_2.

Proof of concept with free energy biasing (1)

Two dimensional potential ("entropic switch")[5]

$$V(x_1,x_2) = 3\mathrm{e}^{-x_1^2}\left(\mathrm{e}^{-(x_2-1/3)^2} - \mathrm{e}^{-(x_2-5/3)^2}\right) - 5\mathrm{e}^{-x_2^2}\left(\mathrm{e}^{-(x_1-1)^2} + \mathrm{e}^{-(x_1+1)^2}\right) + 0.2x_1^4 + 0.2(x_2-1/3)^4$$



Trajectory from $q^{j+1} = q^j - \nabla V(q^j)\Delta t + \sqrt{2\beta^{-1}\Delta t}G^j$ for $\beta = 4$ and $\Delta t = 10^{-3}$ $\longrightarrow$ metastability in the x_1 direction

[5] S. Park, M.K. Sener, D. Lu, and K. Schulten (2003)

Proof of concept with free energy biasing (2)

• **Free energy biasing:** distributions $Z_i^{-1} \exp\left(-\beta\left[V(q) - F_i(\xi_i(q))\right]\right)$

$$F_1(x_1) = -\frac{1}{\beta} \ln\left(\int_{\mathbb{R}} \mathrm{e}^{-\beta V(x_1,x_2)} dx_2\right), \qquad F_2(x_2) = -\beta^{-1} \ln\left(\int_{\mathbb{R}} \dots dx_1\right)$$

Three datasets: unbiased trajectory, trajectories biased using F_1 and F_2

(free energy biased trajectories are shorter but same number of data points $N = 10^6$)

• Autoencoders: 2-1-2 topology, activation functions $\tanh$ (so that RC is in $[-1,1]$) then identity

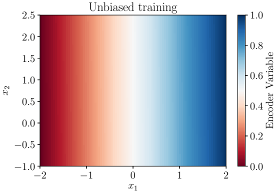
• **Five training scenarios:**

- training on long unbiased trajectory (reference RC)
- ξ_1-biased trajectory, with or without reweighting
- ξ_2-biased trajectory, with or without reweighting

Proof of concept with free energy biasing (3)

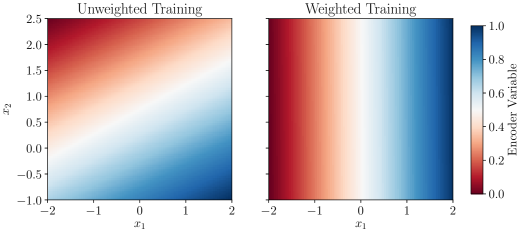
Normalize to compare

$$\xi_{\mathsf{AE}}^{\mathsf{norm}}(x) = \frac{\xi_{\mathsf{AE}}(x) - \xi_{\mathsf{AE}}^{\min}}{\xi_{\mathsf{AE}}^{\max} - \xi_{\mathsf{AE}}^{\min}}$$

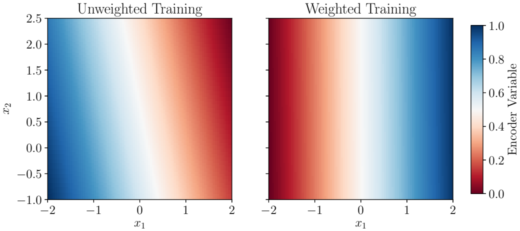


Reference RC

(distinguishes well the 3 wells)



x_1-biased trajectory



x_2-biased trajectory

Full iterative algorithm (Free Energy Biasing and Iterative Learning with AutoEncoders)

Input: Initial condition q_0, autoencoder topology and initialization parameters A_{init}, number of samples N, simulation procedure S and adaptive biasing procedure S_{AB}, maximum number of iterations I_{max}, minimum convergence score s_{min}

Initialization
Sample traj$_0 \leftarrow S(q_0, N)$
Initialize autoencoder AE$_0 \leftarrow A_{\text{init}}$
Train AE$_0$ on traj$_0$ with weights $(\widehat{w}_0, \dots, \widehat{w}_N) = (1, \dots 1)$
Extract the encoder function $\xi_0 : x \mapsto \xi_0(x)$

Iterative update of the reaction coordinate
Set $i \leftarrow 0$, $s \leftarrow 0$
While $i < I_{\max}$ and $s < s_{\min}$ — Treshold $s_{\min}$ to be determined
  Set $i \leftarrow i + 1$
  Sample traj$_i$, $F_i \leftarrow S_{\text{AB}}(q_0, N, \xi_{i-1})$ — in our case: extended ABF
  Compute weights $\widehat{w}_j \propto \mathrm{e}^{-\beta F_i(\xi_{i-1}(x^j))}$
  Initialize autoencoder AE$_i \leftarrow A_{\text{init}}$
  Train AE$_i$ on traj$_i$ with sample weights $\widehat{w}_j$
  Extract the encoder function $\xi_i : x \mapsto \xi_i(x)$
  Set $s \leftarrow$ regscore(ξ_{i-1}, ξ_i) — Convergence metric to be made precise
Set $\xi_{\text{final}} \leftarrow \xi_i$

Production of output:
Sample traj$_{\text{final}}$, $F_{\text{final}} \leftarrow S_{\text{AB}}(q_0, N_{\text{final}} \xi_{\text{final}})$ with N_{final} large enough to ensure PMF convergence

Discussion on the convergence criterion

- Check convergence of CV?

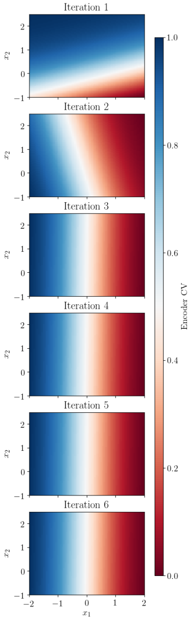
Quantify $\xi_i \approx \Phi(\xi_{i-1})$ for some monotonic function Φ

- Approach: approximate Φ by a linear model $\rightarrow$ linear regression

- **Regression score** between ξ and ξ'
  - Two sets of values of RC $(\xi(q^1), \ldots, \xi(q^N))$ and $(\xi'(q^1), \ldots, \xi'(q^N))$
  - Match them with a linear model $M(z) = Wz + b$
  - Coefficient of determination $R^2 = 1 - \dfrac{\displaystyle\sum_{i=1}^N \left\| \xi'(q^i) - M(\xi(q^i)) \right\|^2}{\displaystyle\sum_{i=1}^N \left\| \xi'(q^i) - \bar{\xi'} \right\|^2}$
  - Maximization of R^2 w.r.t. W, b provides regscore(ξ', ξ)

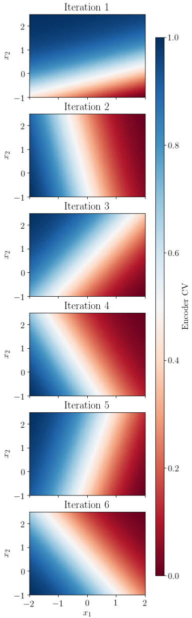
- **Value of** $s_{\min}$ computed using some bootstrap procedure

The iterative algorithm on the toy 2D example



Left: with reweighting
Convergence to RC $\simeq x_1$

Right: without reweighting
No convergence
(cycles between two RCs)



Applications to systems of interest

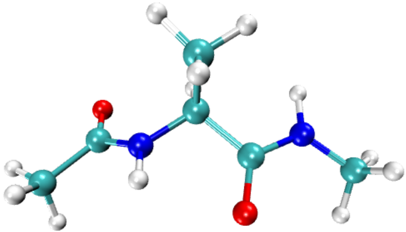
Alanine dipeptide

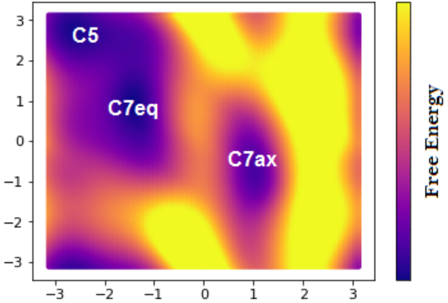
- **Molecular dynamics:**

`openmm` with `openmm-plumed` to link it with `plumed`
`colvar` module for eABF and computation of free energies
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

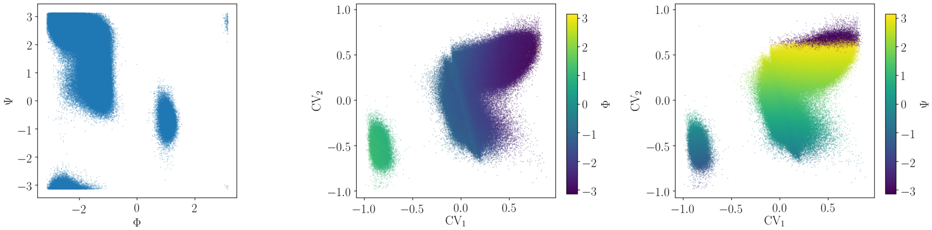




Ground truth computation

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

RC close to dihedral angles Φ, Ψ

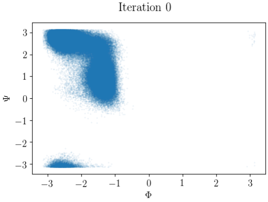


Quantify $s_{\min} = 0.99$ for $N = 10^5$ using a bootstraping procedure

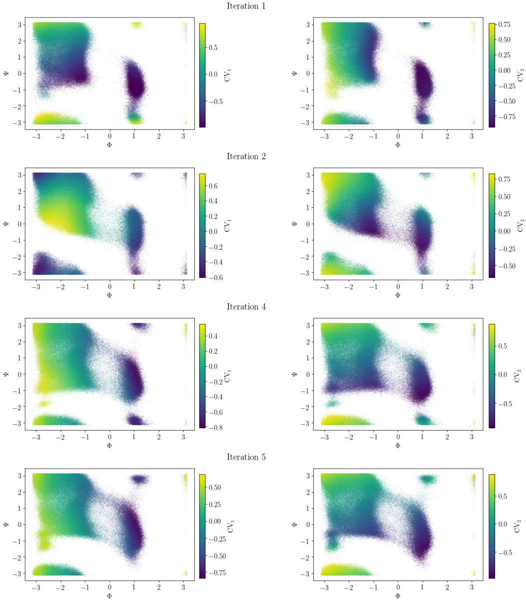
For the iterative algorithm: 10 ns per iteration

(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)

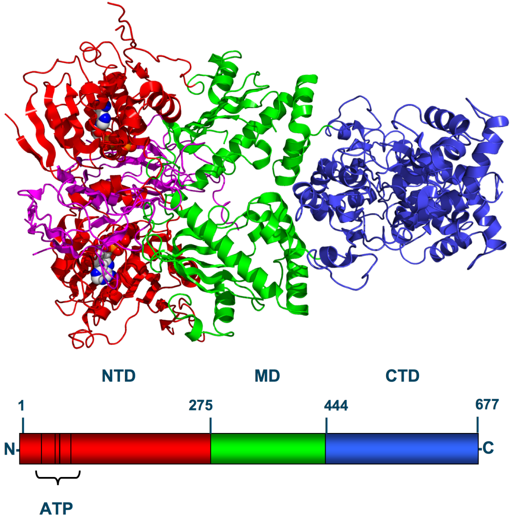
Results for the iterative algorithm



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



HSP90 (work in progress...)

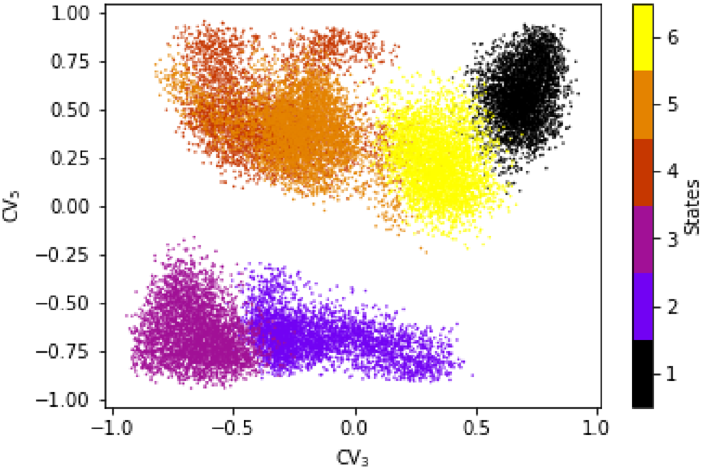


(picture from https://en.wikipedia.org/wiki/File:Hsp90_schematic_2cg9.png)

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-terminus domain)

HSP90 (work in progress...)



6 conformational states, data from 10 $\times$ 20 ns trajectories, input features = 621 C carbons, AE topology 621-100-5-100-621