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Finding reaction coordinates with machine learning techniques for free energy computations

Gabriel STOLTZ

(CERMICS, Ecole des Ponts & MATHERIALS team, Inria Paris)

With Zineb Belkacemi, Tony Lelièvre and Paraskevi Gkeka

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Outline

- **Reaction coordinates** and free energy computations
- A (short and biased) review of some machine learning approaches for RC
- **Free-energy biasing and iterative learning with autoencoders**¹
 - **Autoencoders** and their training
 - Working with free energy weighted distributions
 - General presentation of the iterative algorithm
 - Illustration/sanity checks on toy examples
- **Applications to systems of interest**
 - Alanine dipeptide
 - HSP90 (by Zineb Belkacemi)

¹soon to be preprinted...

Reaction coordinates and free energy computations

Reaction coordinates (RC) / collective variables (CV)

- Atomic system with positions $q = (q_1, \dots, q_N) \in \mathcal{D} \subset \mathbb{R}^D$, Hamiltonian

$$H(q, p) = V(q) + \sum_{i=1}^N \frac{p_i^2}{m_i}, \text{ canonical measure } Z^{-1} e^{-\beta H(q, p)}$$

- **Reaction coordinate** $\xi : \mathbb{R}^D \rightarrow \mathbb{R}^d$ with $d \ll D$
(ideally such that $\xi(q_t)$ captures the slow part of the dynamics)

- **Free energy** computed on $\Sigma(z) = \{q \in \mathbb{R}^D \mid \xi(q) = z\}$

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

by various methods (TI, FEP, ABF, metadynamics, etc)²

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

A (short and biased) review of some machine learning approaches for RC

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 classifications⁴ possible, e.g. **slow vs. high variance CV**

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

⁴P. 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)

Rewighted 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)

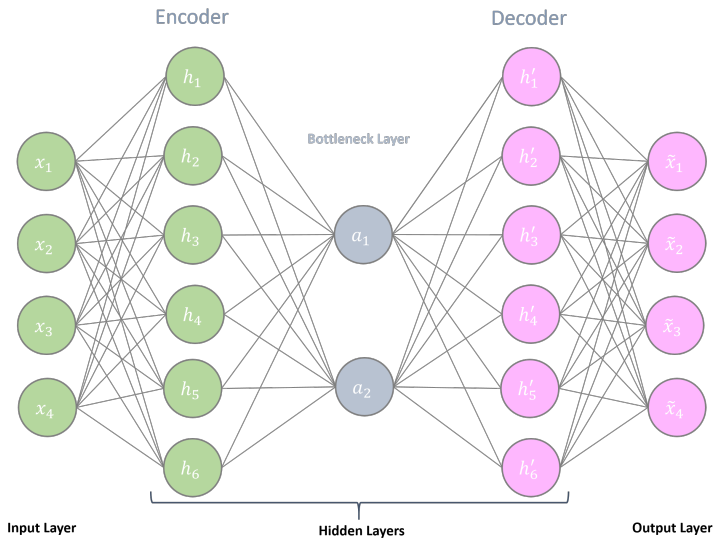
Variational Dynamics Encoders
(VDEs)

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 $d < D$

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

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

Reaction coordinate = 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)

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

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**

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

- Typical choices: canonical measure μ , data points x^i postprocessed from positions q (alignment 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 $\tilde{\mu}$ (**importance sampling**)
- Need for **reweighting** to learn the correct encoding!

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

- **Minimization problem:** theoretical cost function

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

actual cost function

$$\mathcal{L}(\hat{\mu}_{\text{wght}}, \mathbf{p}) = \sum_{i=1}^N \hat{w}_i \|x^i - f_{\mathbf{p}}(x^i)\|^2, \quad \hat{w}_i = \frac{\mu(x^i)/\tilde{\mu}(x^i)}{\sum_{j=1}^N \mu(x^j)/\tilde{\mu}(x^j)}$$

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

How training is actually performed...

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

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

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

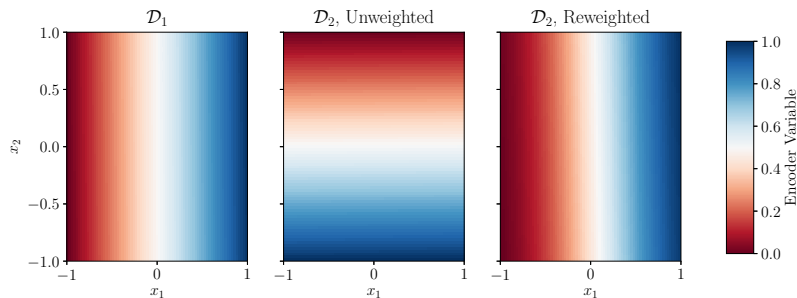
$$\Sigma_1 = \begin{pmatrix} 1 & 0 \\ 0 & 0.01 \end{pmatrix}, \quad \Sigma_2 = \begin{pmatrix} 0.01 & 0 \\ 0 & 1 \end{pmatrix}$$

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 $\hat{w}_i \propto \mu_1/\mu_2$

Proof of concept (2)

Heat maps of f_{enc}

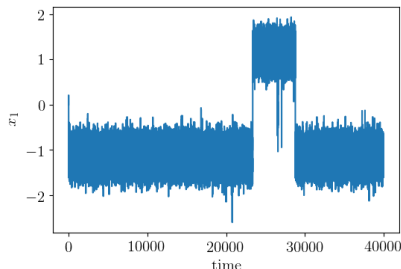
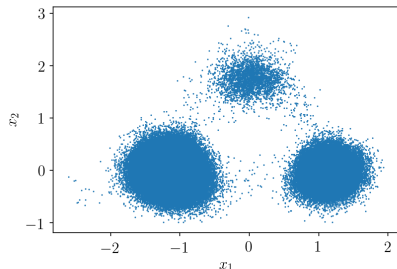


Third encoder very similar to the first: projection on x_1 .
Second encoder projects on a direction close to x_2 .

Proof of concept with free energy biasing (1)

Two dimensional potential (“entropic switch”)⁵

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



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 $\Delta t = 10^{-3} \rightarrow$ **metastability** in the x_1 direction

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

Proof of concept with free energy biasing (2)

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

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

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

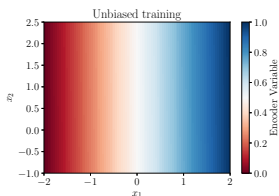
- **Five training scenarios:**

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

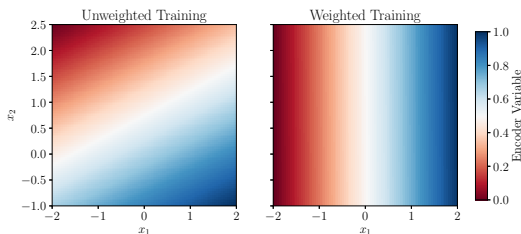
Proof of concept with free energy biasing (3)

Normalize to compare

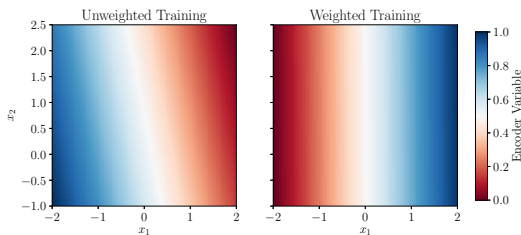
$$\xi_{\text{SAE}}^{\text{norm}}(x) = \frac{\xi_{\text{SAE}}(x) - \xi_{\text{SAE}}^{\text{min}}}{\xi_{\text{SAE}}^{\text{max}} - \xi_{\text{SAE}}^{\text{min}}}$$



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 $\text{traj}_0 \leftarrow S(q_0, N)$

Initialize autoencoder $\text{AE}_0 \leftarrow A_{\text{init}}$

Train AE_0 on traj_0 with weights $(\hat{w}_0, \dots, \hat{w}_N) = (1, \dots, 1)$

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 $i < I_{\text{max}}$ and $s < s_{\text{min}}$

Set $i \leftarrow i + 1$

Sample $\text{traj}_i, F_i \leftarrow S_{\text{AB}}(q_0, N, \xi_{i-1})$

Compute weights $\hat{w}_j \propto e^{-\beta F_i(\xi_{i-1}(x^j))}$

Initialize autoencoder $\text{AE}_i \leftarrow A_{\text{init}}$

Train AE_i on traj_i with sample weights \hat{w}_j

Extract the encoder function $\xi_i : x \mapsto \xi_i(x)$

Set $s \leftarrow \text{regscore}(\xi_{i-1}, \xi_i)$

Set $\xi_{\text{final}} \leftarrow \xi_i$

Threshold s_{min} to be determined

in our case: extended ABF

Convergence metric to be made precise

Production of output:

Sample $\text{traj}_{\text{final}}, F_{\text{final}} \leftarrow S_{\text{AB}}(q_0, N_{\text{final}}, \xi_{\text{final}})$ 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'

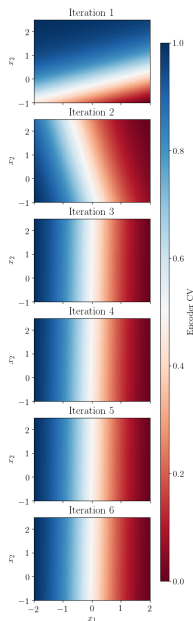
- Two sets of values of RC $(\xi(q^1), \dots, \xi(q^N))$ and $(\xi'(q^1), \dots, \xi'(q^N))$
- Match them with a linear model $M(z) = Wz + b$

- Coefficient of determination $R^2 = 1 - \frac{\sum_{i=1}^N \|\xi'(q^i) - M(\xi(q^i))\|^2}{\sum_{i=1}^N \|\xi'(q^i) - \bar{\xi}'\|^2}$

- Maximization of R^2 w.r.t. W, b provides $\text{regscore}(\xi', \xi)$

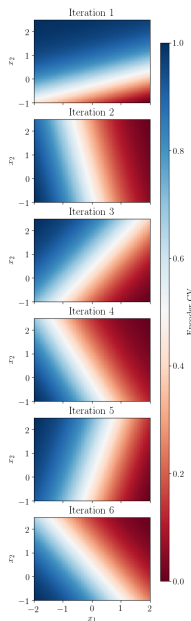
- **Value of s_{\min}** computed using some bootstrap procedure

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:**

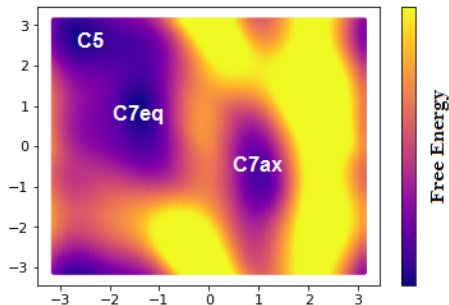
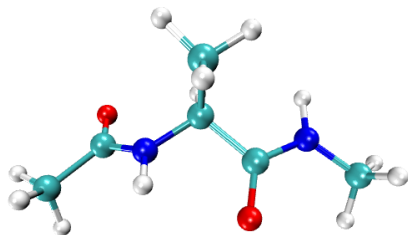
openmm with openmmplumed to link it with plumed
colvar module for eABF and computation of free energies
timestep 1 fs, friction $\gamma = 1 \text{ ps}^{-1}$ in Langevin dynamics

- **Machine learning:**

keras for autoencoder training

input = carbon backbone (realignment to reference structure and centering)

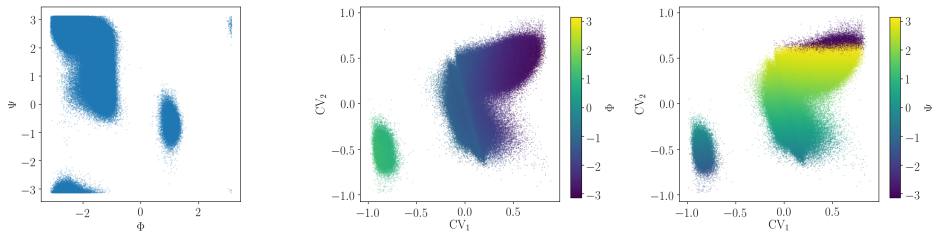
neural network: topology 24-40-2-40-24, tanh activation functions



Ground truth computation

Long trajectory ($1.5 \mu\text{s}$), $N = 10^6$ (frames saved every 1.5 ps)

RC close to dihedral angles Φ, Ψ

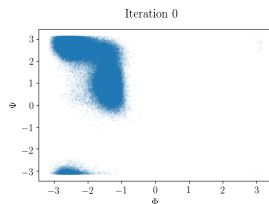


Quantify $s_{\min} = 0.99$ for $N = 10^5$ using a bootstrapping procedure

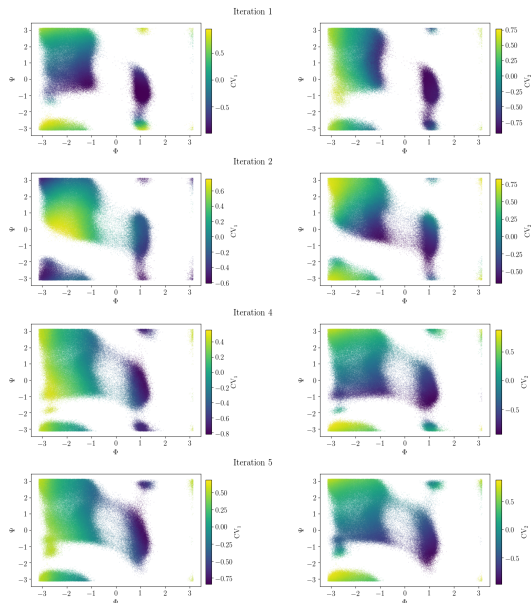
For the iterative algorithm: 10 ns per iteration

(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 – by Zineb Belkacemi