Model reduction and *machine learning* for quantifying rare events in stochastic systems

RIT: ML for Rare Events

AMSC689, Section 0802

Maria Cameron

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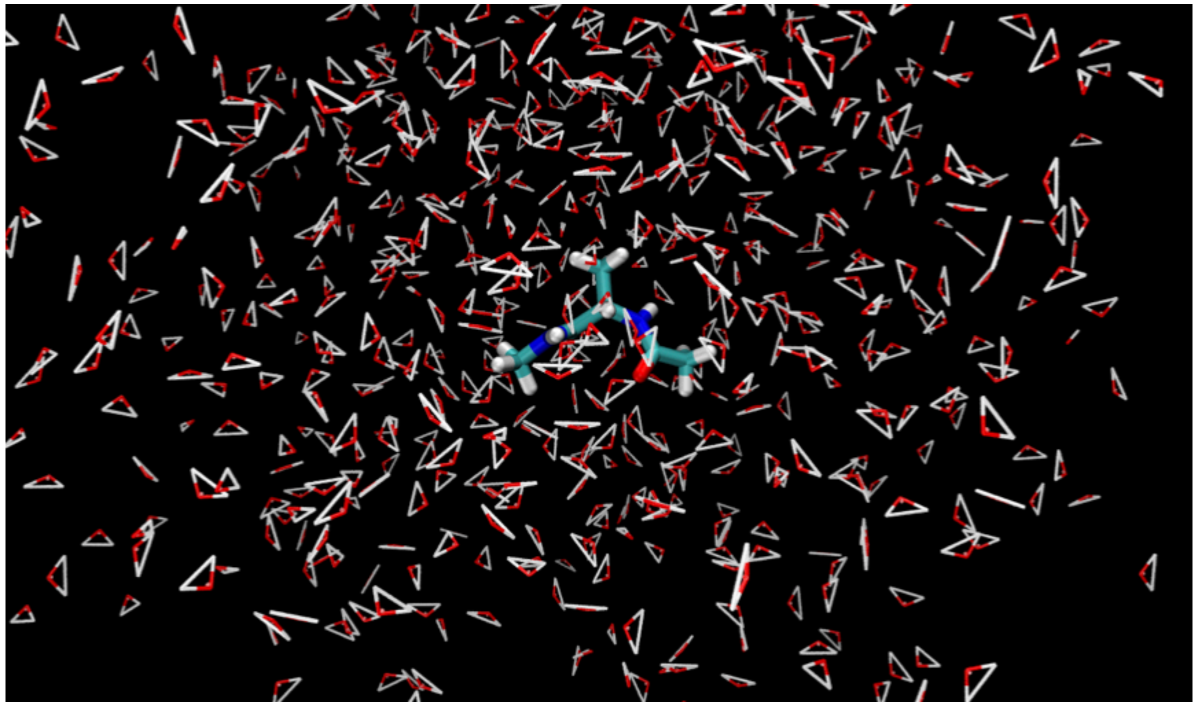
Model reduction

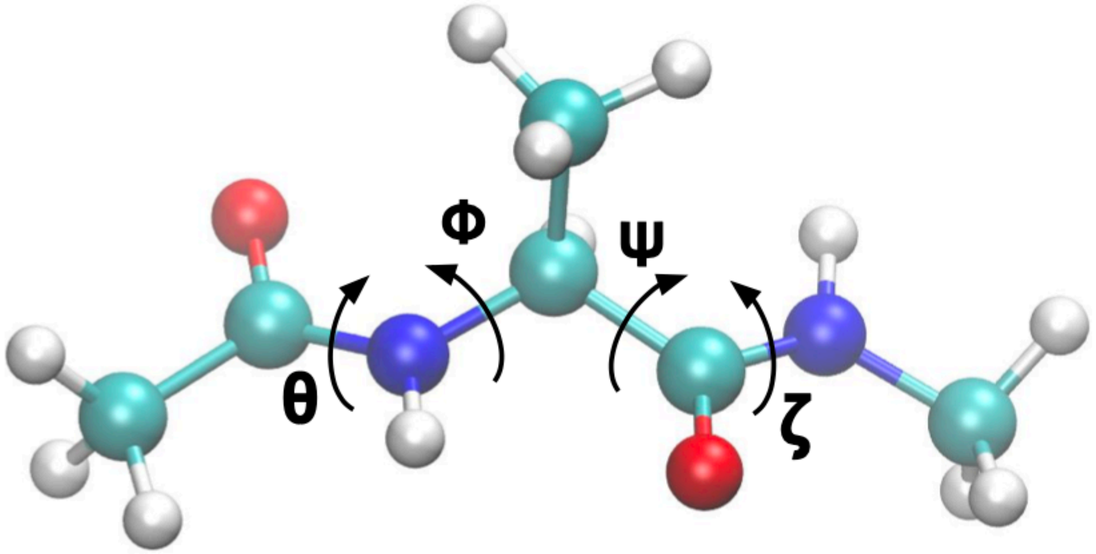
Rare events are those that occur rarely on the timescale of the system

Dynamics of
an alanine-dipeptide molecule
pushed around by water molecules



https://ambermd.org/tutorials/basic/tutorial0/index.php

Conformal changes in molecules



Langevin all-atom dynamics

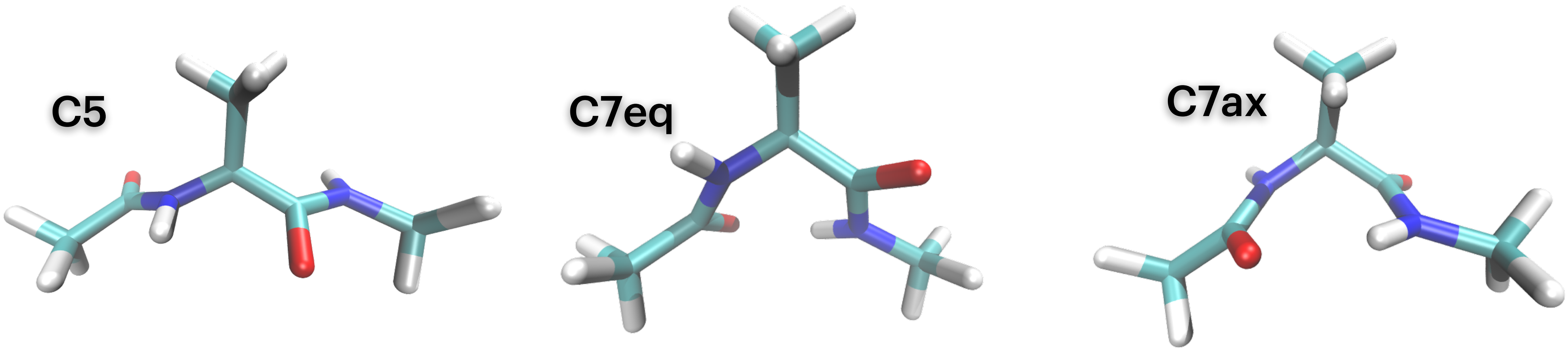
$$dq = \frac{p}{m}dt$$
$$dp = (-\nabla V(q) - \gamma p)dt + \sqrt{2\gamma m \beta^{-1}}dw$$

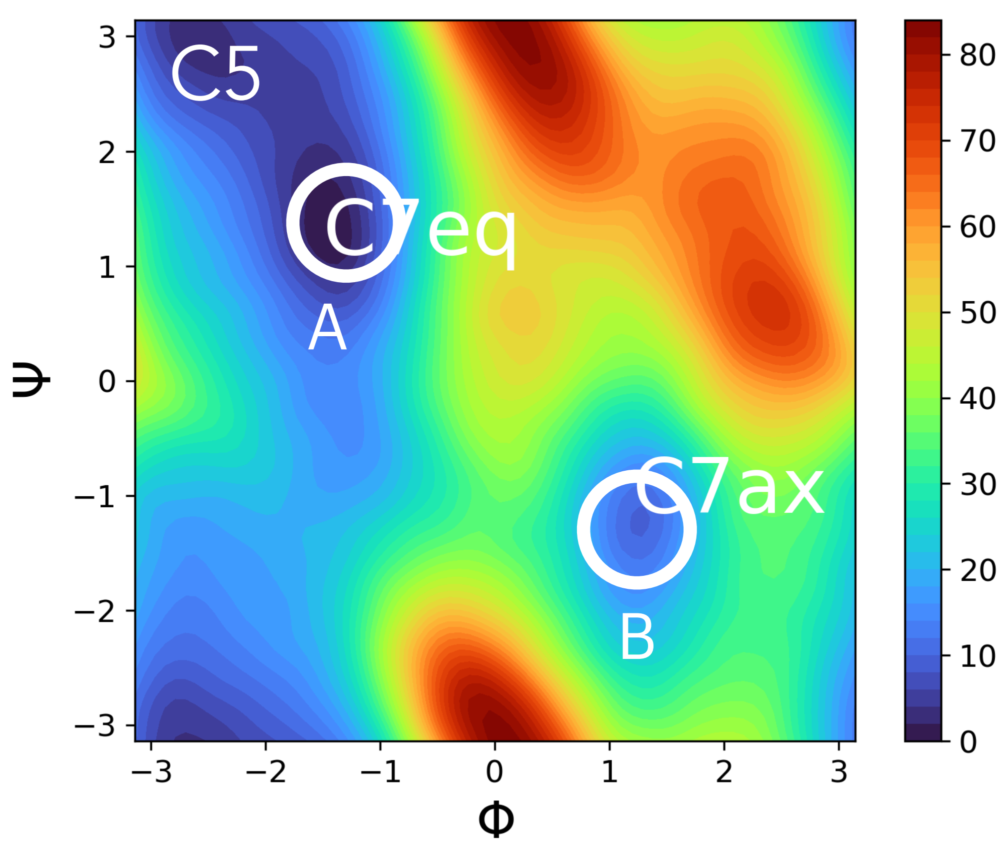
Dynamics in collective variables

$$dX_t = [-M(X_t)\nabla F(X_t) + \beta^{-1}\nabla \cdot M(X_t)]dt$$
$$+ \sqrt{2\beta^{-1}}M(X_t)^{1/2}dw_t$$

Model reduction

Alanine dipeptide. Three metastable states.

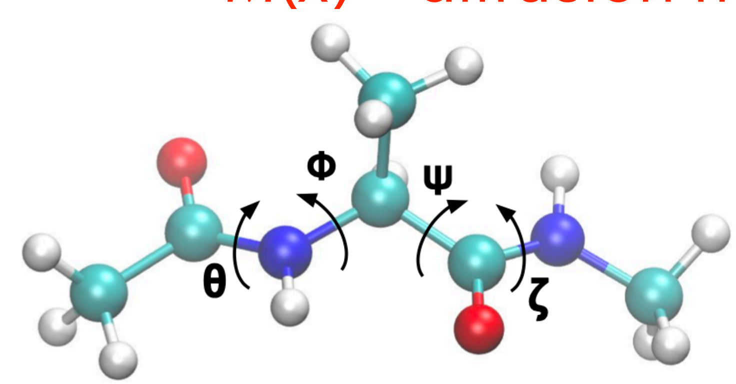




Dynamics in collective variables

$$dX_t = [-M(X_t)\nabla F(X_t) + \beta^{-1}\nabla \cdot M(X_t)]dt$$
$$+ \sqrt{2\beta^{-1}}M(X_t)^{1/2}dw_t$$

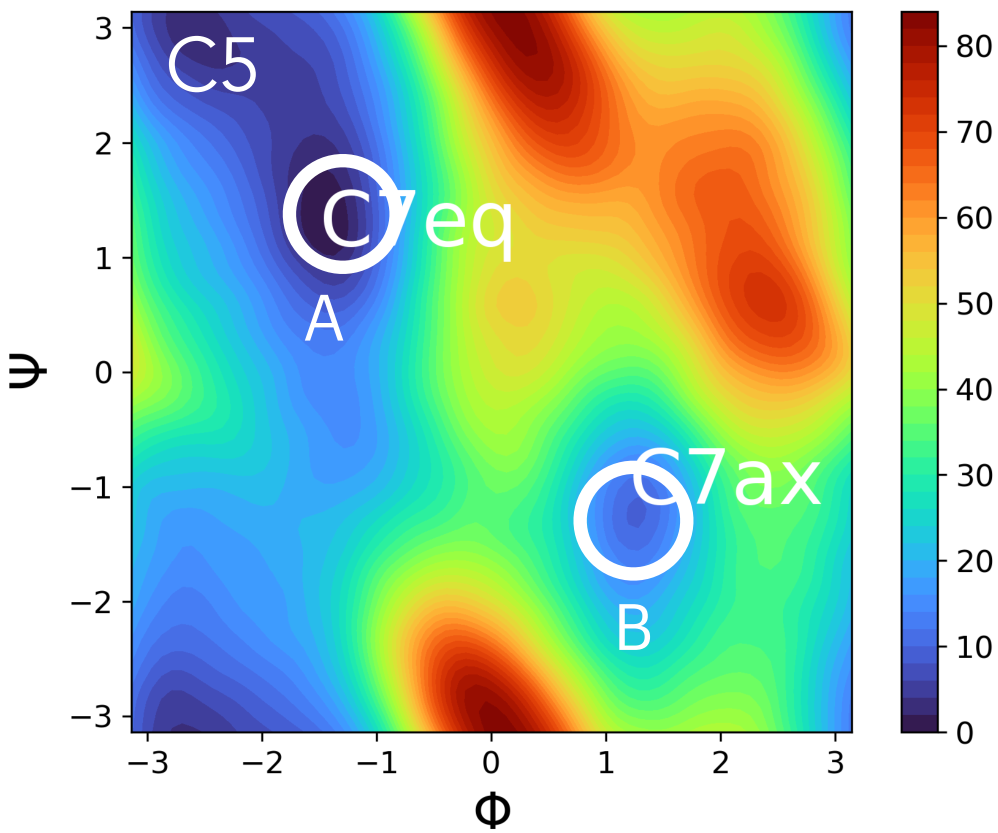
$F(x)$ = free energy
$M(x)$ = diffusion matrix



$x = (\varphi,\psi,\theta,\varsigma)$
or
$x = (\varphi,\psi)$

Model reduction

Alanine dipeptide. Finding the reduced model.



Dynamics in collective variables

$$dX_t = [-M(X_t)\nabla F(X_t) + \beta^{-1}\nabla \cdot M(X_t)]dt$$
$$+ \sqrt{2\beta^{-1}} M(X_t)^{1/2} dw_t$$

Free energy

$$F(x) = -\beta^{-1} \ln \left(\int_{\mathbb{R}^n} Z_V^{-1} e^{-\beta V(y)} \delta(\theta(y) - x) dy \right)$$

Diffusion matrix

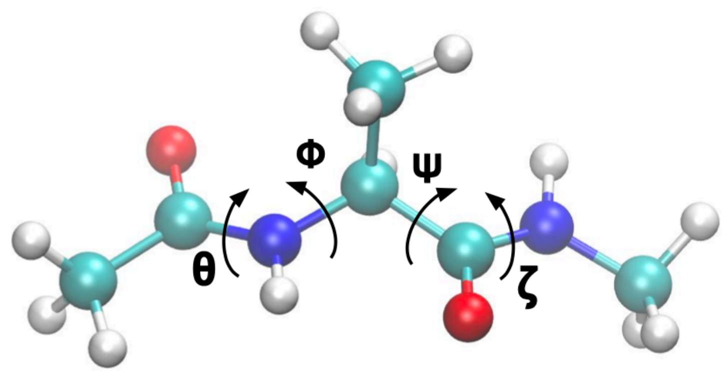
$$M(x) = e^{\beta F(x)} \int_{\mathbb{R}^n} J(y) m J^\top(y) Z_V^{-1} e^{-\beta V(y)} \delta(\theta(y) - x) dy$$

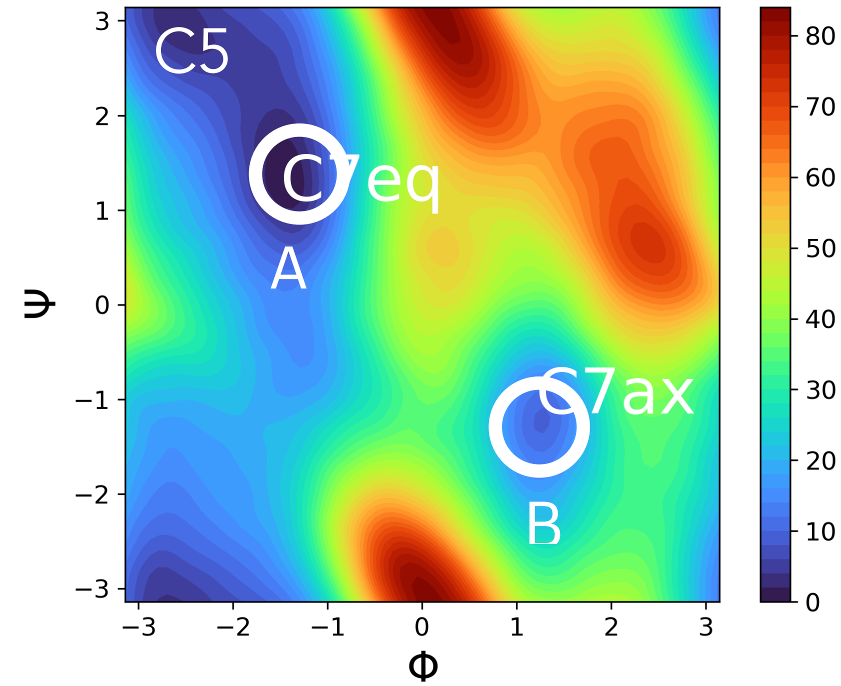
M and ∇F are found using restrained dynamics

$$\nabla F(x) = \frac{\kappa}{n} \sum_{k=1}^{n} (x - \theta(q(t_k)))$$

$$M_{ij}(x) \approx \frac{1}{n} \sum_{k=1}^{n} \sum_{l=1}^{N} m_l^{-1} \frac{\partial \theta_i(q(t_k))}{\partial q_l} \frac{\partial \theta_j(q(t_k))}{\partial q_l}.$$

Transition rate in alanine dipeptide C7eq ↔ C7ax





Settings	Source	Rate
2D, FEM $x = (\varphi,\psi)$	Evans, MC, Tiwary, 2022	6.6e-6 ps^{-1}
2D, tm-mmap+deltanet $x = (\varphi,\psi)$	Evans, MC, Tiwary, 2022	6.3e-6 ps^{-1}
4D, tm-mmap $x = (\varphi,\psi,\theta,\varsigma)$	Evans, MC, Tiwary, 2022	2.0e-6 ps^{-1}
132D, very long unbiased trajectory	Vani, Weare, Dinner, 2022	1.4e-6 ps^{-1}

Questions

- How can we construct a reduced model?
- How can we access a model reduction error?
- How can we choose a good set of collective variables for building a reduced model?
- How can we promote the transition process between metastable states of interest in such a way that allows us to estimate transition rates?

Model reduction

F. Legoll and T. Lelievre, *Effective dynamics using conditional expectations*, 2010

Overdamped Langevin dynamics

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\beta^{-1}}dW_t, \quad X_t \in \mathbb{R}^d$$

$X_0 = x_0$ The initial condition

A single collective variable $\xi(x)$

Ito's formula gives:

$$d\xi(X_t) = \left[-\nabla V \cdot \nabla\xi + \beta^{-1}\Delta\xi\right](X_t)dt + \sqrt{2\beta^{-1}}\|\nabla\xi(X_t)\|dB_t,$$

$$dB_t = \frac{\nabla\xi}{\|\nabla\xi\|} \cdot dW_t$$

Problem: this equation is not closed! It depends explicitly on X_t!

Model reduction

F. Legoll and T. Lelievre, *Effective dynamics using conditional expectations*, 2010

Gyoengy, 1986

$$dz_t = b(t, z_t)dt + \sqrt{2\beta^{-1}}\sigma(t, z_t)dB_t$$

$$b(t, z) = \mathbb{E}\left[(-\nabla V \cdot \nabla\xi + \beta^{-1}\Delta\xi)(X_t) \mid \xi(X_t) = z\right]$$

$$\sigma^2(t, z) = \mathbb{E}\left[\|\nabla\xi\|^2(X_t) \mid \xi(X_t) = z\right]$$

Problem: the drift and the diffusion coefficient are hard to compute because the expectations are taken with respect to the actual pdf of X_t which can take a very long time to approach the invariant pdf is the system is metastable.

Model reduction

Legoll and Lelievre, 2010:
a practical closure

$$dz_t = b(z_t)dt + \sqrt{2\beta^{-1}}\sigma(z_t)dB_t$$

$$b(z) = \mathbb{E}_\mu\left[(-\nabla V \cdot \nabla\xi + \beta^{-1}\Delta\xi)(X) \mid \xi(X) = z\right]$$

$$\sigma^2(z) = \mathbb{E}_\mu\left[\|\nabla\xi\|^2(X) \mid \xi(X) = z\right]$$

$$\mu(x) = Z^{-1}e^{-\beta V(x)}$$

Key result: a bound for the relative entropy in terms of technical characteristics of ξ(x) and $\nabla\xi$(x) and the relative entropies of the pdf for *x* at times 0 and *t* with respect to μ:

pdf for ξ(x)

$$E(t) = \int_{\mathbb{R}} \log\left(\frac{\psi^\xi(t,z)}{\phi(t,z)}\right)\psi^\xi(t,z)dz$$

pdf for z

Legoll and Lelievre, 2010: an illustrative example

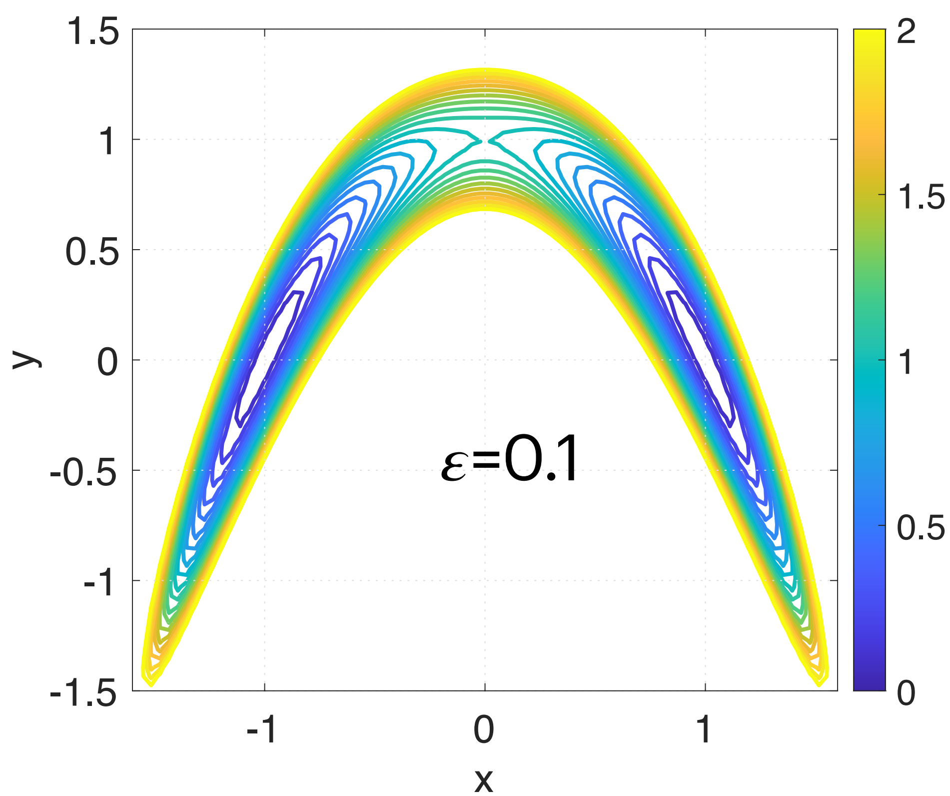
$V_\varepsilon(x,y) = V_0(x,y) + \varepsilon^{-1}\, q(x,y)$

Criterion for a good collective variable: $\nabla q \cdot \nabla \xi = 0$

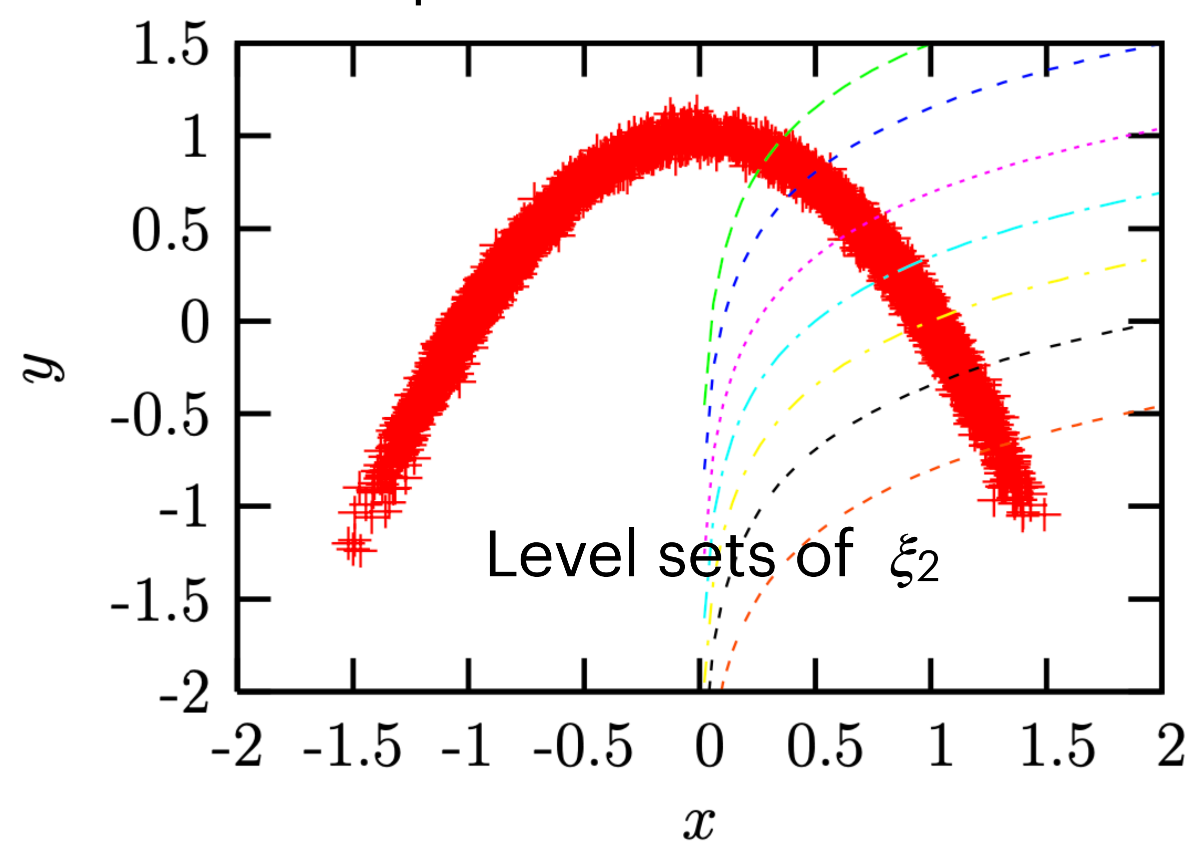
$$V_\epsilon(x,y) = (x^2-1)^2 + \epsilon^{-1}(x^2+y-1)^2$$

$$\xi_1(x,y) = x$$

$$\xi_2(x,y) = xe^{-2y}$$



Samples obtained at ε = 0.01



Reac. Coord.	ξ^{th}	Ref. residence time	Reduced dyn. type	CG residence time
$\xi_2(x,y)$	0.13	32.5 ± 0.5	Legoll and Lelievre	32.7 ± 0.5
$\xi_2(x,y)$	0.13	32.5 ± 0.5	Overdamped Lang. w. FE	6.4 ± 0.3
$\xi_1(x,y)$	0.5	31.6 ± 0.5	Legoll and Lelievre	24.4 ± 0.4

Legoll and Lelievre, 2010: conclusion

- ***Pick collective variables*** so that their level sets are ***normal to the manifold*** on which the stochastic dynamics lives.

- The reduced dynamics proposed and studied by L&L ***is NOT consistent*** with the time-reversible dynamics proposed in Maragliano et al. (2006)

$$dY_t = -\left[M(Y_t)\nabla F(Y_t) + \beta^{-1}\nabla\cdot M(Y_t)\right]dt + \sqrt{2\beta^{-1}}M(Y_t)^{1/2}dw_t$$

- The estimates obtained in L&L are ***limited*** to a ***single collective variable*** and the underlying ***overdamped Langevin dynamics***. L&L do not know if their result is generalizable to Langevin dynamics and a vector of collective variables.

Choosing collective variables

- Physical intuition
- Machine learning: autoencoders.

JCTC Journal of Chemical Theory and Computation

pubs.acs.org/JCTC Article

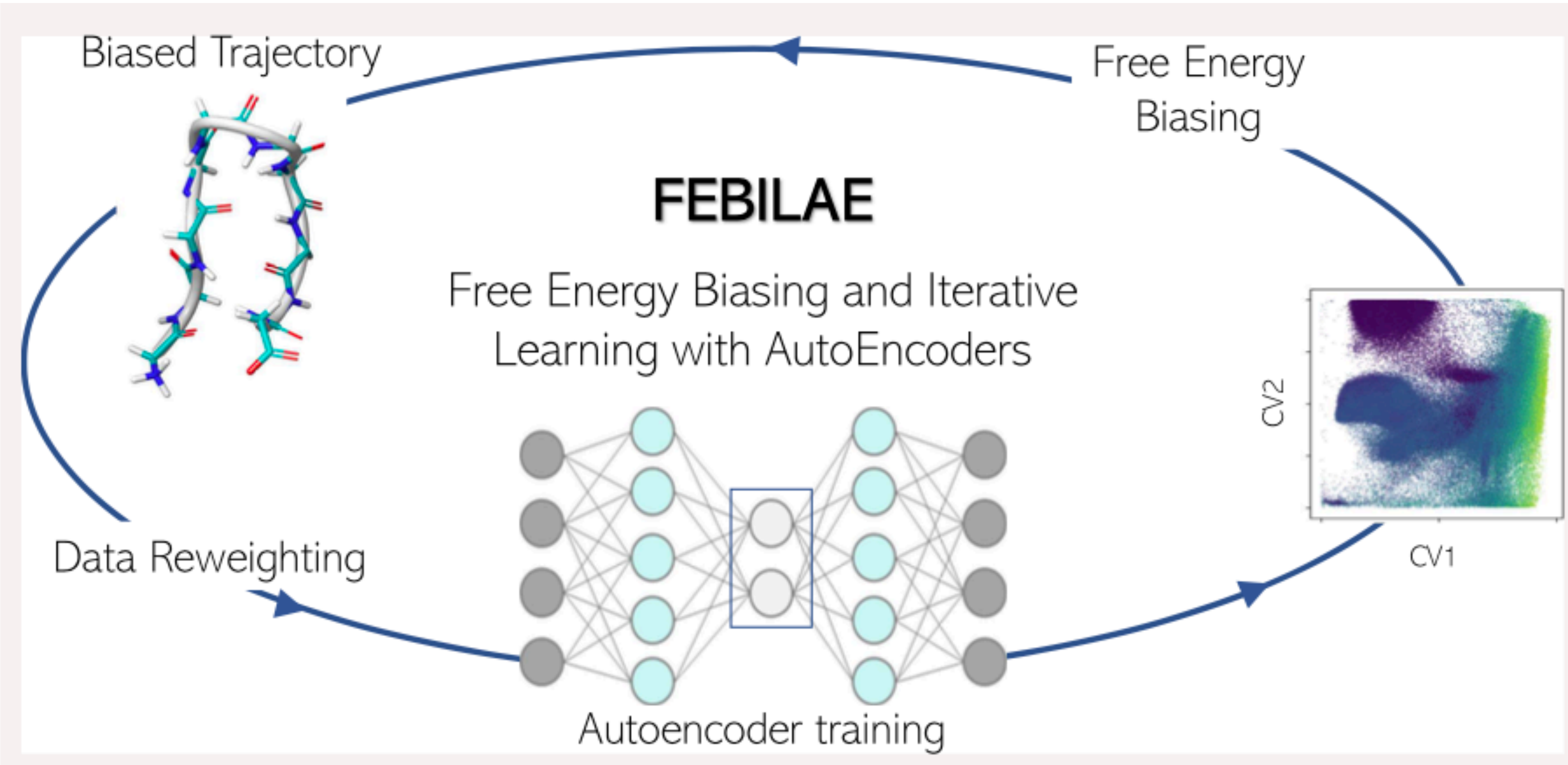
Chasing Collective Variables Using Autoencoders and Biased Trajectories

Zineb Belkacemi,* Paraskevi Gkeka, Tony Lelièvre, and Gabriel Stoltz

Cite This: *J. Chem. Theory Comput.* 2022, 18, 59–78 Read Online

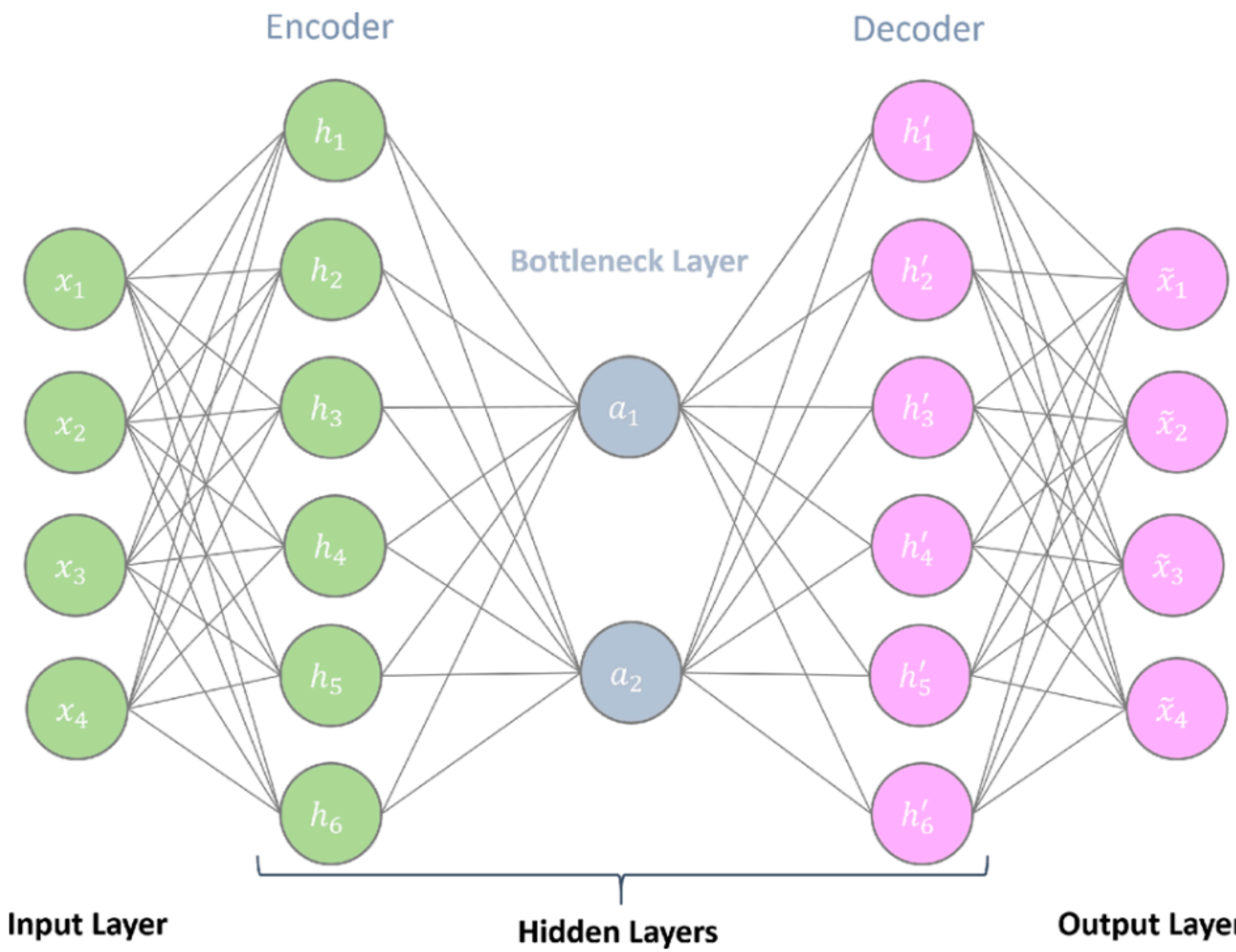
Autoencoders

Belkacemi et al., 2022



Autoencoders

Belkacemi et al., 2022



Autoencoders

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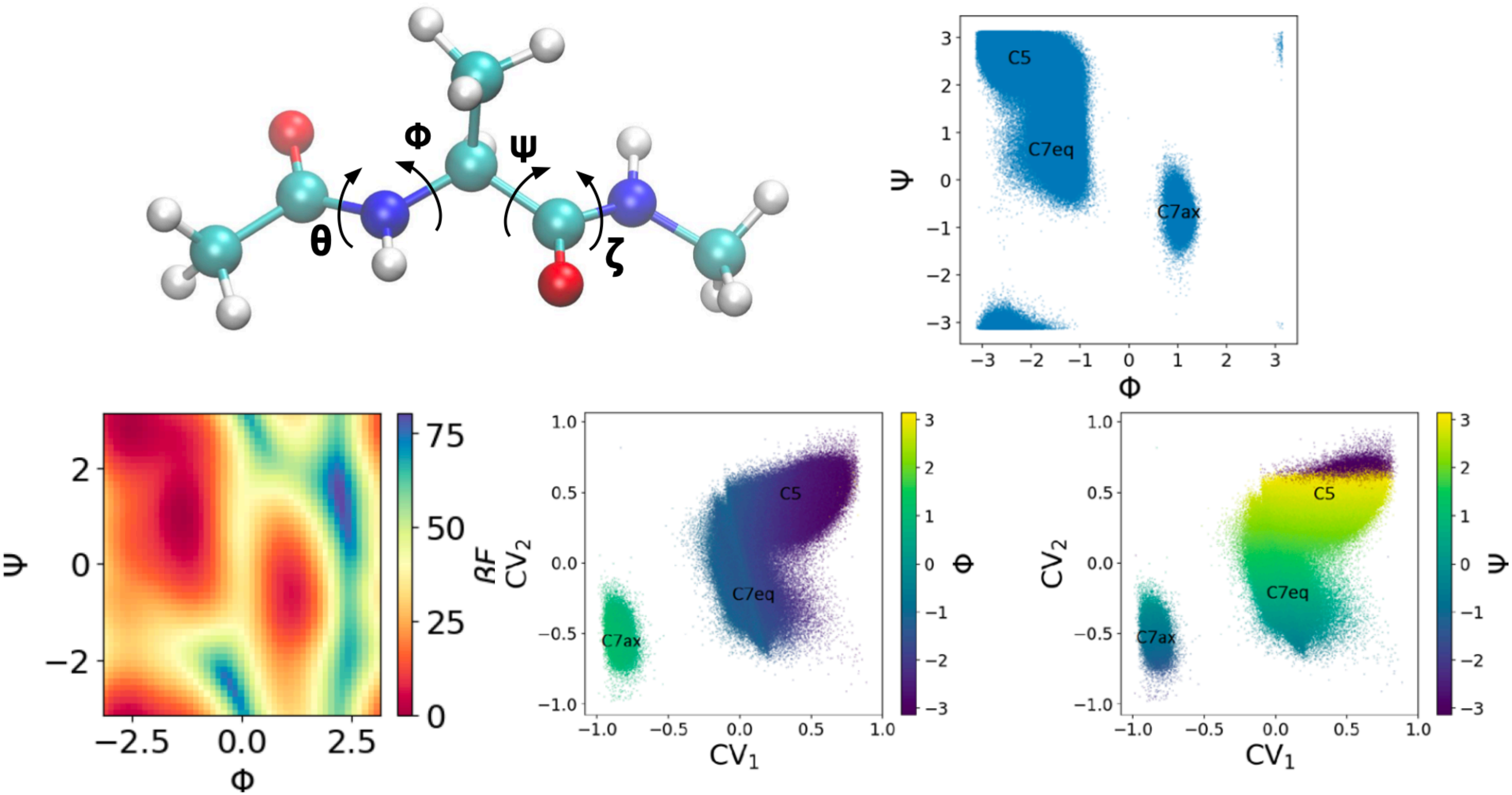

Suggested papers

- L. Maragliano, A. Fischer, E. Vanden-Eijnden, G. Ciccotti, String method in collective variables: minimum energy paths and isocommittor surfaces, 2006
- F. Legal and T. Lelievre, Effective dynamics using conditional expectations, Nonlinearity 2010
- I. Gyoengy, Mimicking the One-dimensional marginal distributions of processes having an Ito differential, 1986
- W. Zhang, C. Hartmann, C. Schuette, Effective dynamics along given reaction coordinate and reaction rate theory, 2016
- C. Hartmann, C. Schuette, W. Zhang, Model reduction algorithms for optimal control and importance sampling, 2016
- F. Nueske, P. Koltai, L. Boninsegna, C. Clementi, Spectral properties of effective dynamics from conditional expectations, 2021

Model reduction

Suggested papers

- W. Chen, A. Ferguson, Molecular enhances sampling with auto encoders: on-the-fly collective variable discovery and accelerated free energy landscape exploration, 2018
- W. Chen, A. Tan, A. Ferguson, Collective variable discovery and enhanced sampling using auto encoders: innovations in network architecture and error function design, 2018
- C. Wehmeyer and F. Noe, time-lagged auto encoders: deep learning of slow collective variables from molecular kinetics, 2018
- Z. Belkacemi, P. Gkeka, T. Lelievre, G. Stoltz, Chasing collective variables using auto encoders and biased trajectories, 2022
- E. Crabtree, J. Bello-Rivas, A. Ferguson, I. Kevrekidis, GANs and closures: micro-macro consistency in multiscale modeling, 2022

Autoencoders