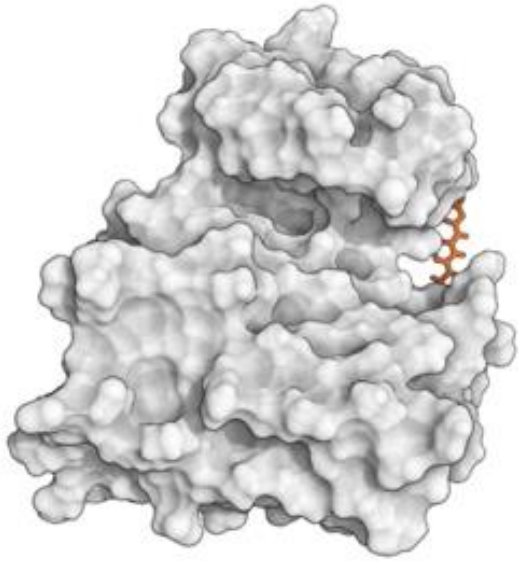
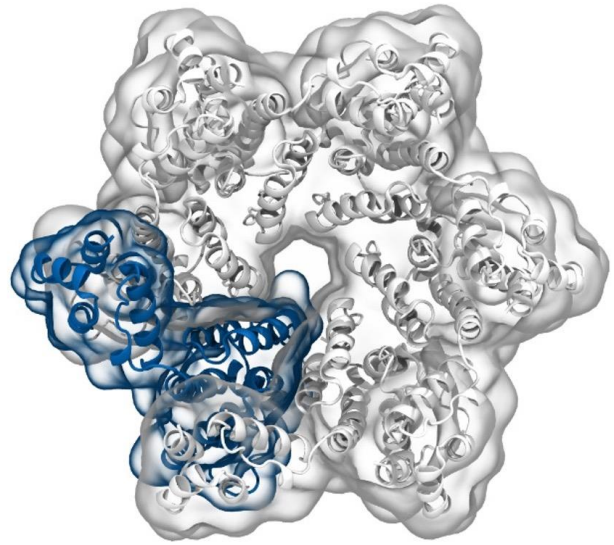
Simulation of Biomolecules



Markov State Modelling



2024 CCP5 Summer School

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Markov State Modelling (MSM)

Can we predict the equilibrium structure of a peptide?

Run 5 μs molecular dynamics simulation

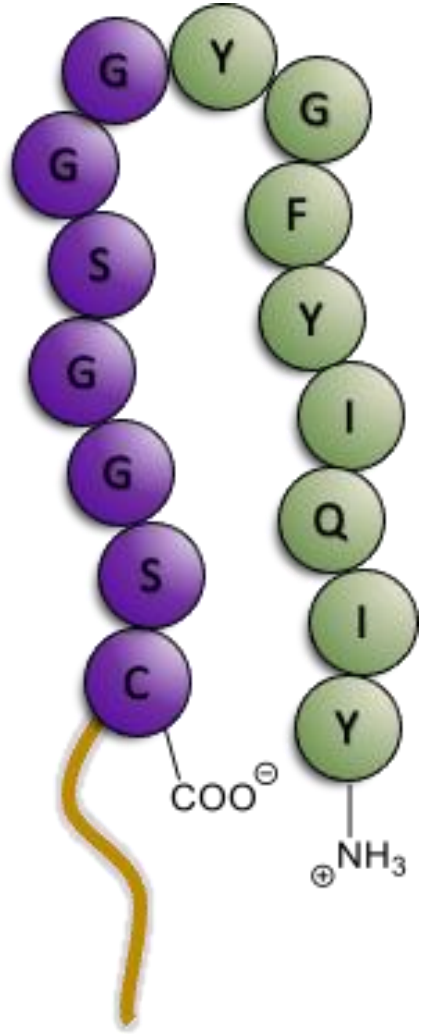
↓

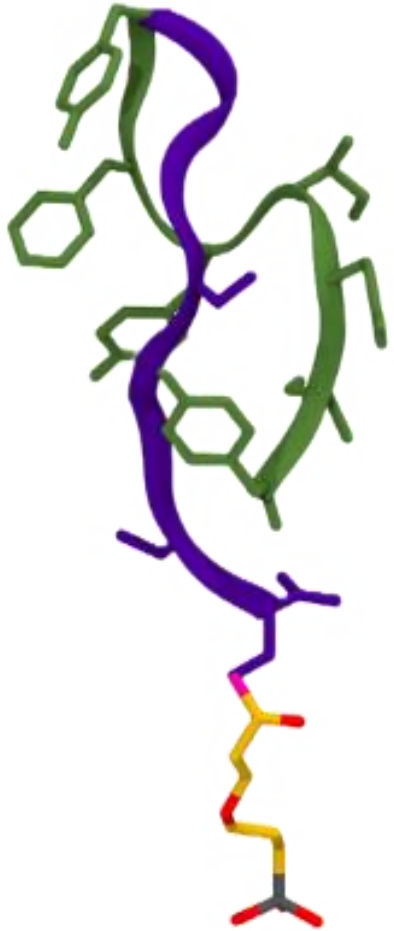
Use a Markov Model to identify dominant conformations in solution

↓

Report most stable structure

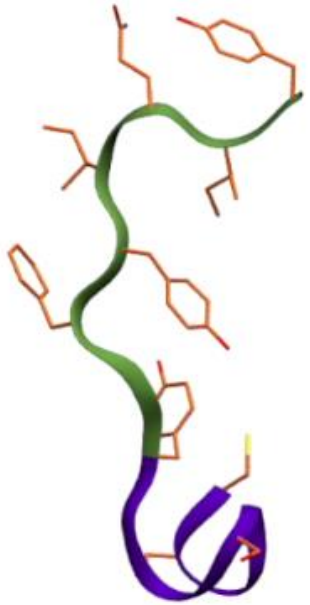
AlphaFold suggestion





MSMs allow for quantitive data from molecular simulations

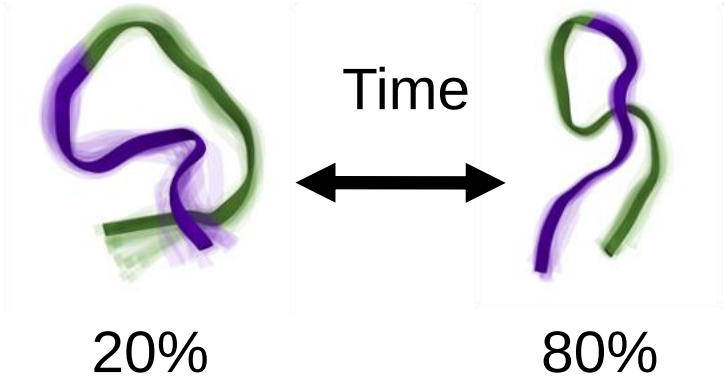
YITIY TAYAG SGGSC



Protein dynamics

Clustering is the first step towards a model providing quantitive equilibrium and kinetic information from the simulation

Simulation movie

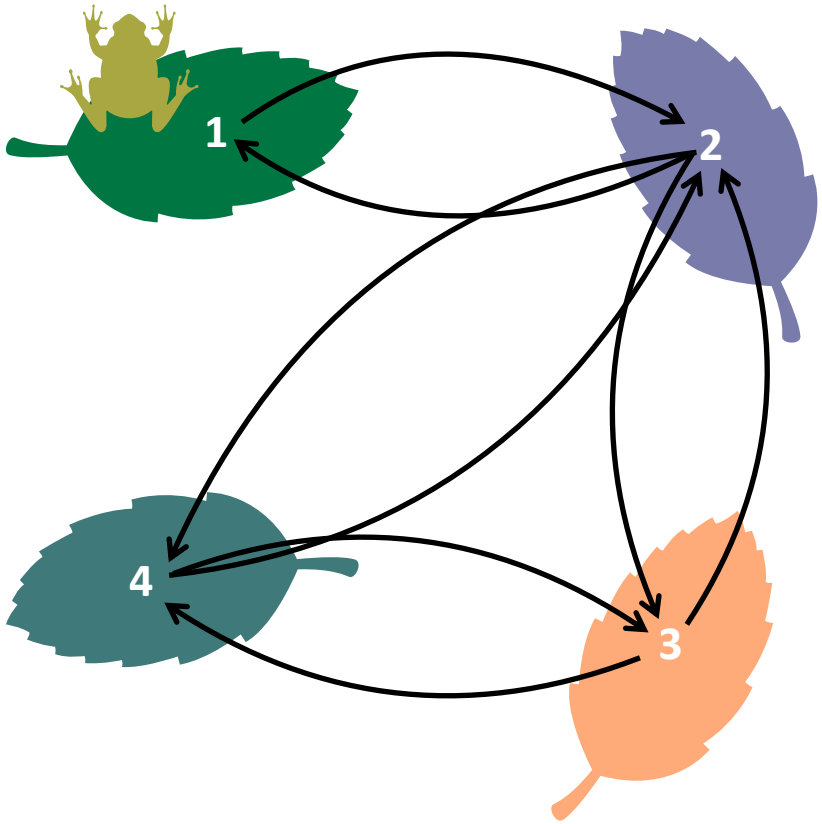


Probabilistic understanding of the trajectory

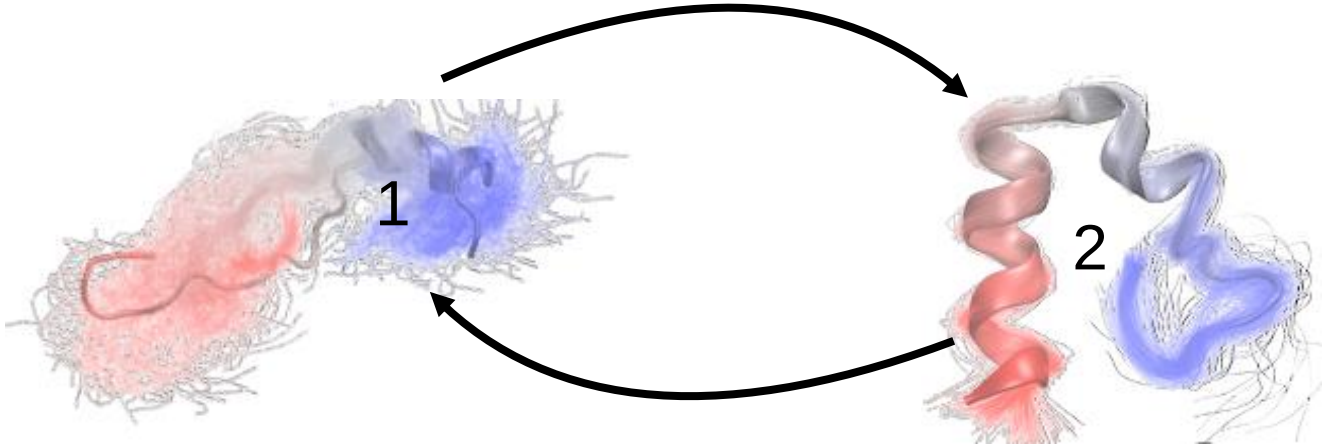
[…] Ryan Zhu, A. Mey […], ***Viruses***, 2023

Frogs jumping and proteins moving

Over the period of a day:

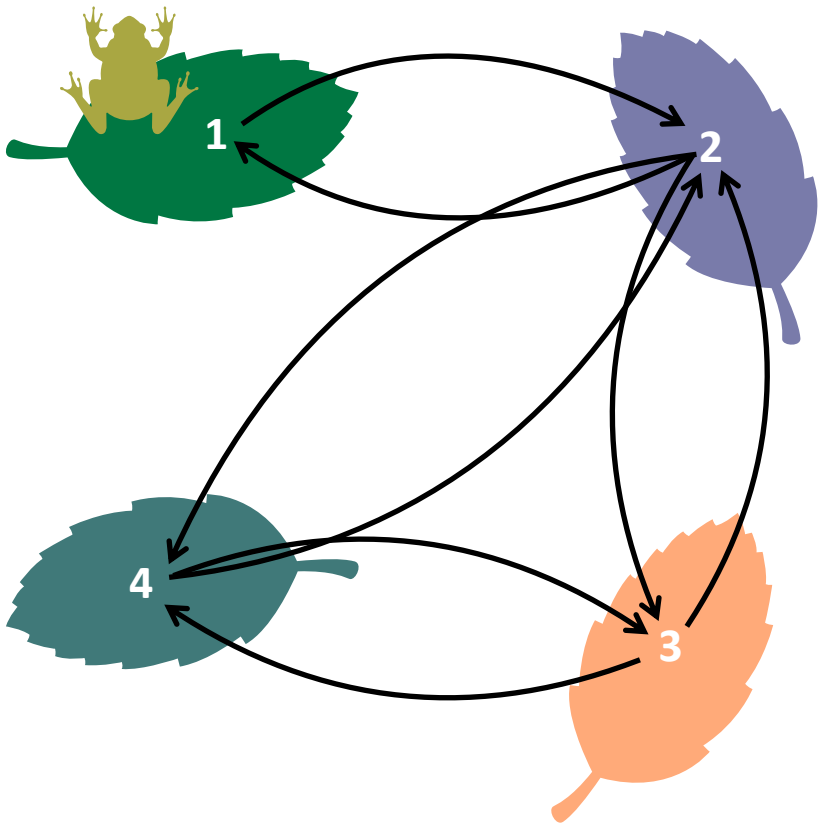


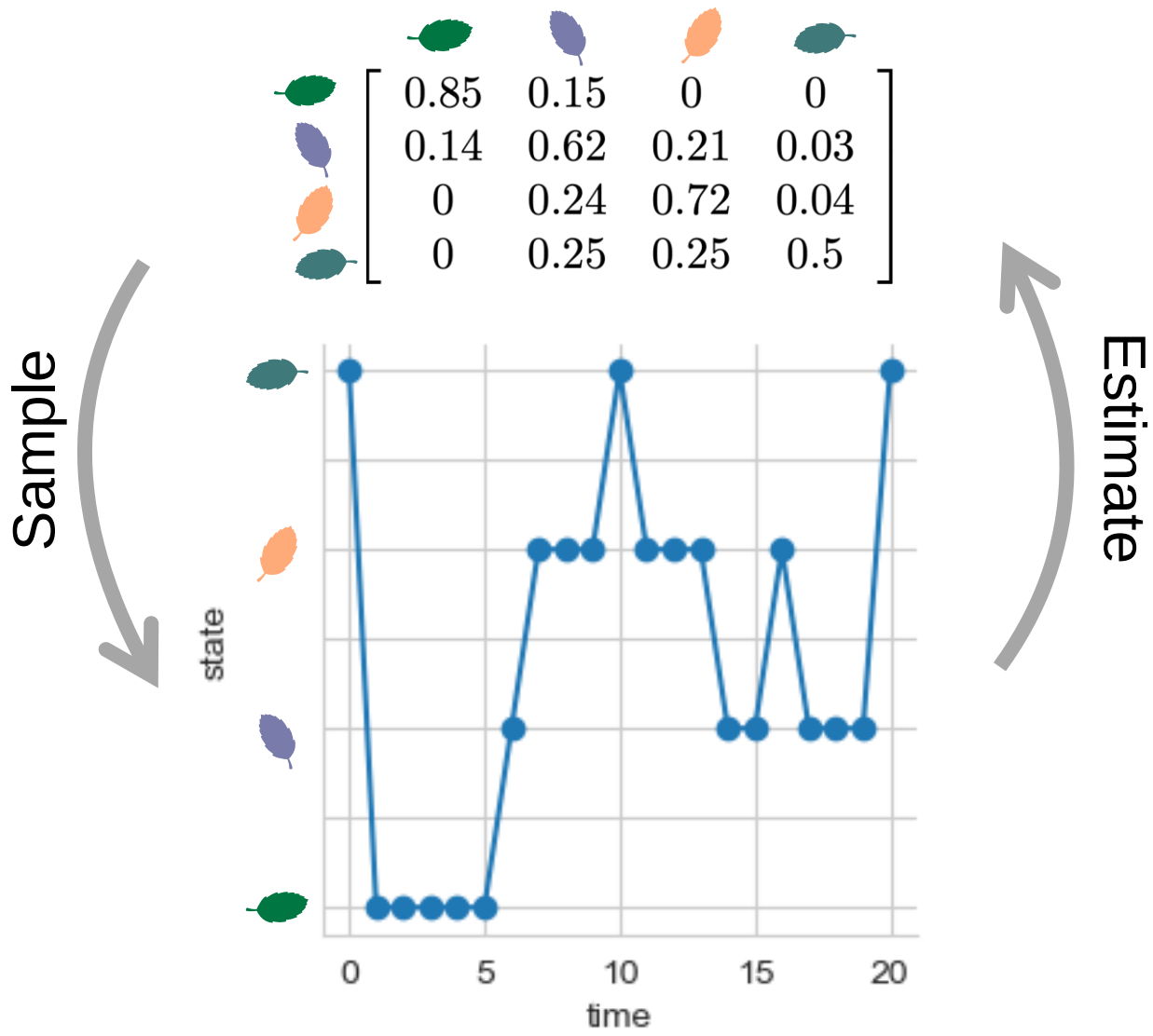
What do a protein and a frog jumping have in common?



What is a Markov chain?

Over the period of a day:





What is a Markov chain?

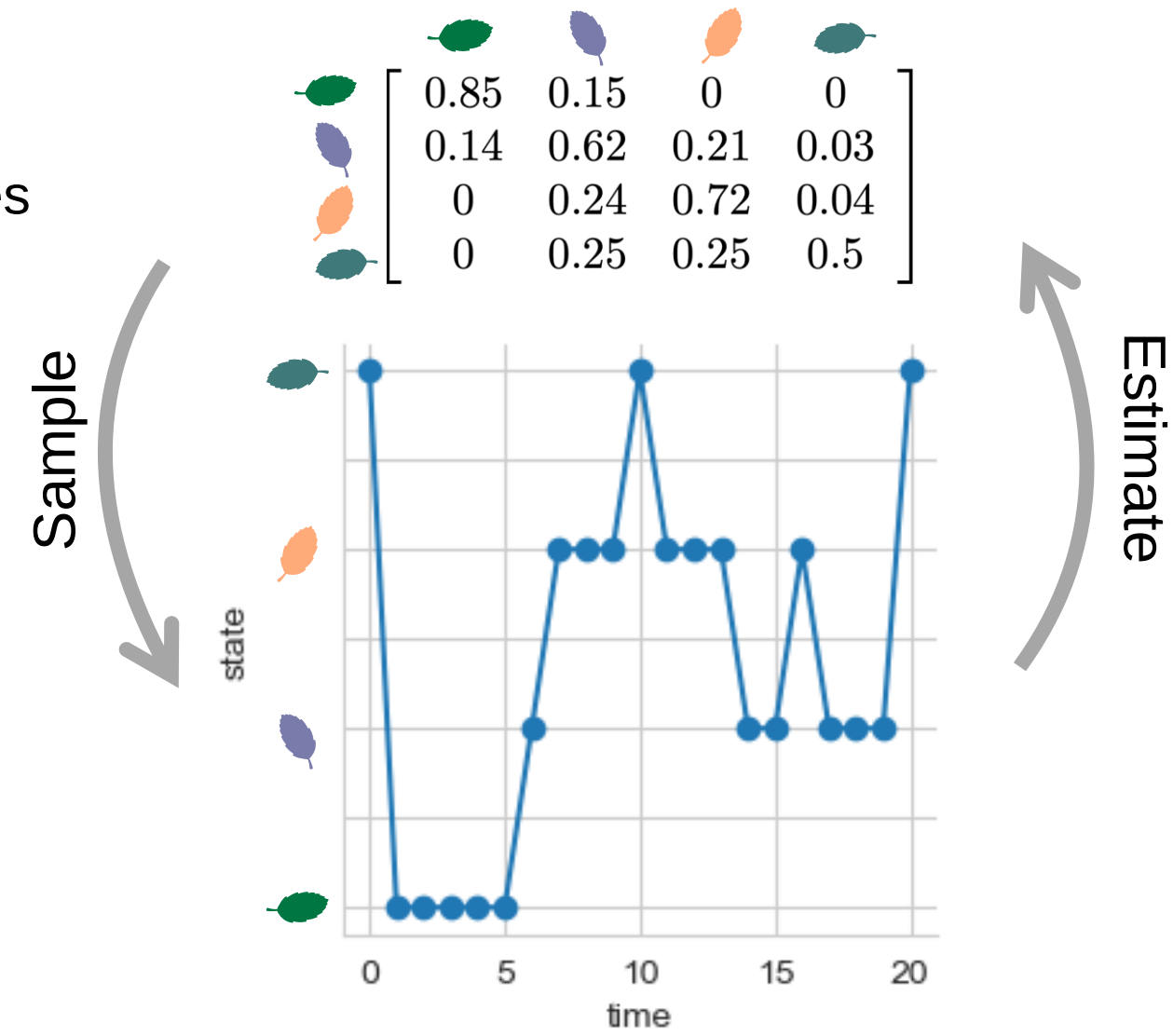
Transition matrices are:
- Stochastic matrices
- Containing conditional jump probabilities

If they are **irreducible** and **ergodic**:
- They have a stationary probability
- Has a stationary probability **π.**
- The stationary probability is the eigenvector of the eigenvalue λ_1

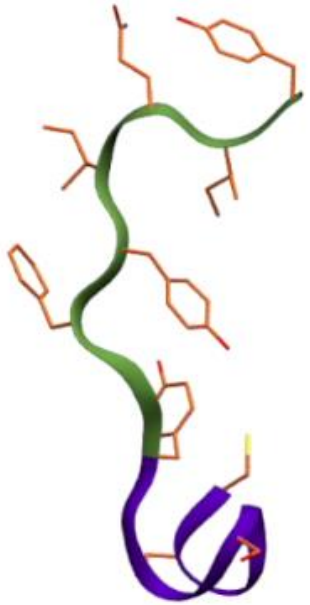
$$\lambda_1 = 1 > \lambda_2 > \lambda_3, \ldots, > \lambda_n$$

If they are reversible

$$\pi_i P_{ij} = \pi_j P_{ji}$$



How to model protein dynamics using a Markov approach?

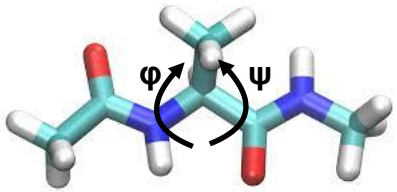


?

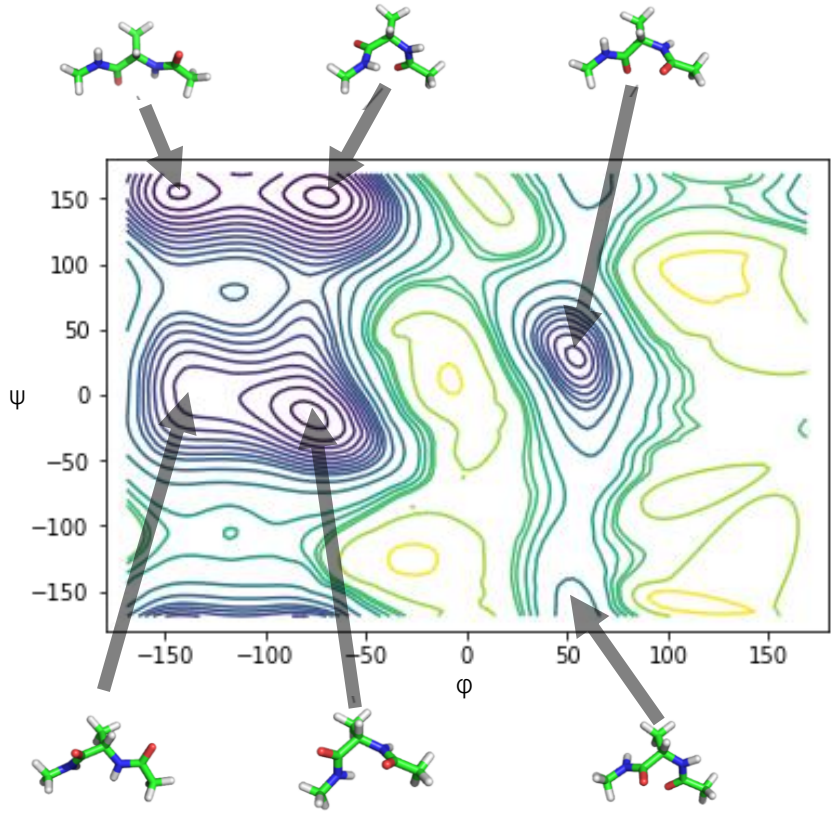
Approximate with a transition matrix from the trajectory:

$$P = \begin{bmatrix} P_{1,1} & P_{1,2} & \dots & P_{1,j} & \dots & P_{1,S} \\ P_{2,1} & P_{2,2} & \dots & P_{2,j} & \dots & P_{2,S} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ P_{i,1} & P_{i,2} & \dots & P_{i,j} & \dots & P_{i,S} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ P_{S,1} & P_{S,2} & \dots & P_{S,j} & \dots & P_{S,S} \end{bmatrix}.$$

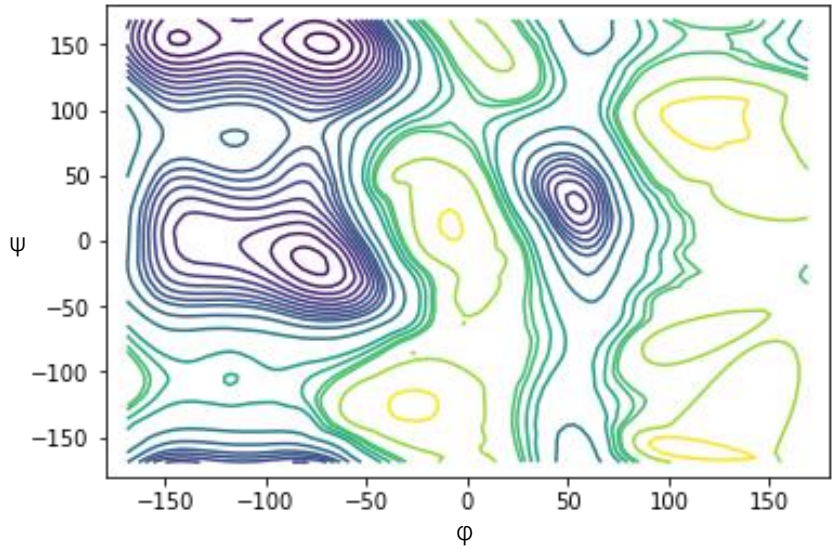
Dimensionality reduction is (often) needed for MSM



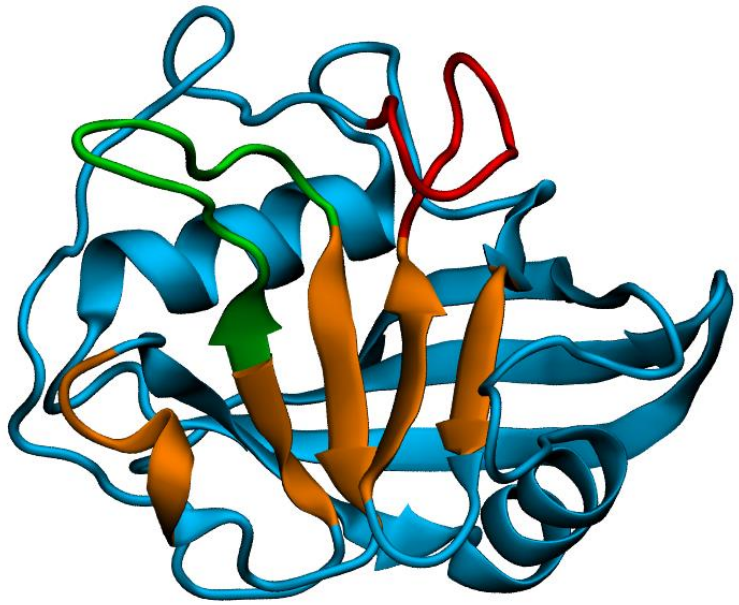
Alanine dipeptide



['PHI 0 ALA 2', 'PSI 0 ALA 2']



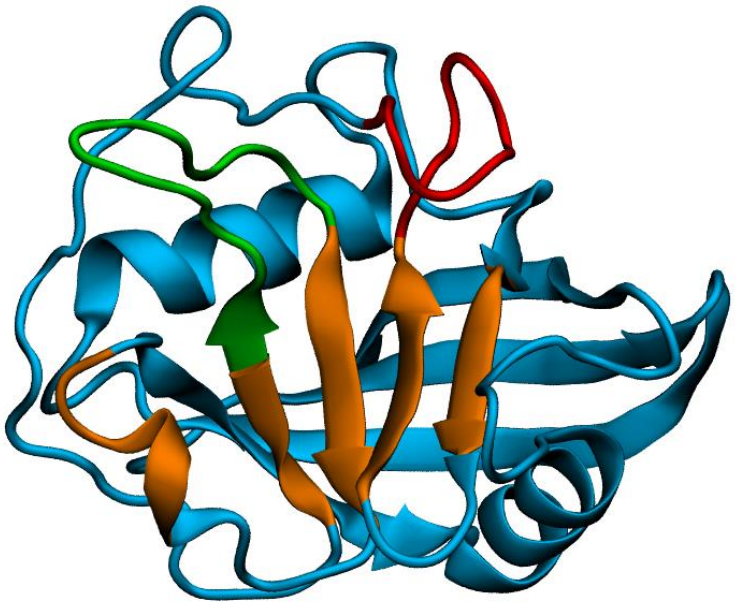
Dimensionality reduction is (often) needed for MSM



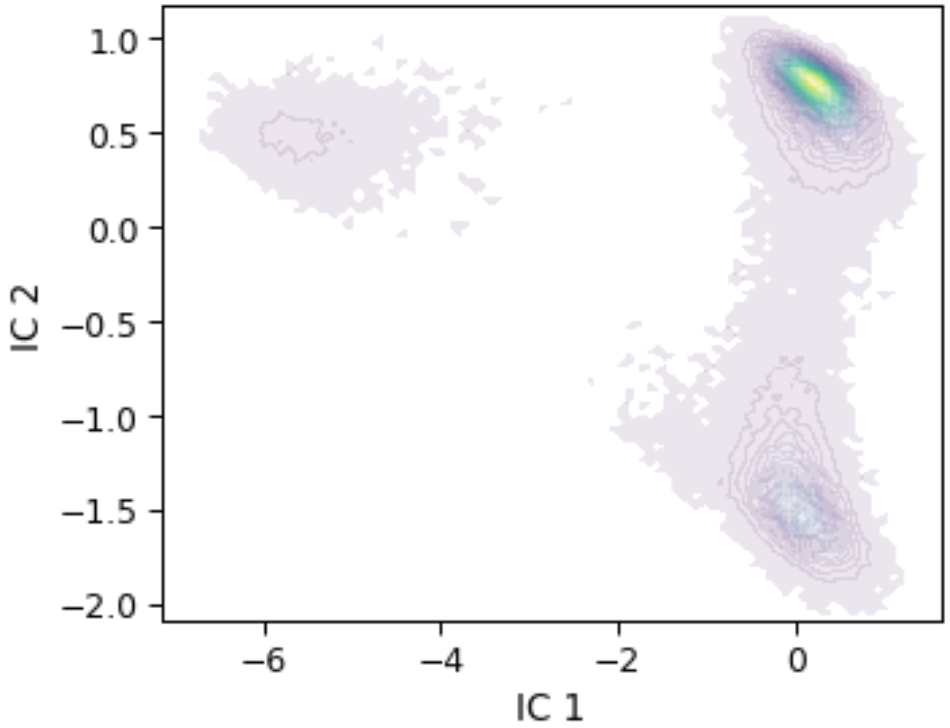
```
['ATOM:ACE 1 CH3 1 x',
 'ATOM:ACE 1 CH3 1 y',
 'ATOM:ACE 1 CH3 1 z',
 'ATOM:ACE 1 C 4 x',
 'ATOM:ACE 1 C 4 y',
 'ATOM:ACE 1 C 4 z',
 'ATOM:ACE 1 O 5 x',
 'ATOM:ACE 1 O 5 y',
 'ATOM:ACE 1 O 5 z',
 'ATOM:ALA 2 N 6 x',
 'ATOM:ALA 2 N 6 y',
 'ATOM:ALA 2 N 6 z',
 'ATOM:ALA 2 CA 8 x',
 'ATOM:ALA 2 CA 8 y',
 'ATOM:ALA 2 CA 8 z',
 'ATOM:ALA 2 CB 10 x',
 'ATOM:ALA 2 CB 10 y',
 'ATOM:ALA 2 CB 10 z',
 'ATOM:ALA 2 C 14 x',
```

```
['PHI 0 ALA 2', 'PSI 0 ALA 2']
```

Dimensionality reduction — TICA, PCA, VAMP



Project features onto low dimensional subspace



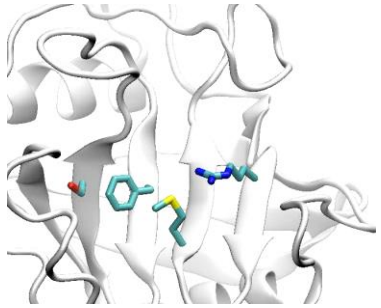
PCA: Linear combination of input features maximising the variance

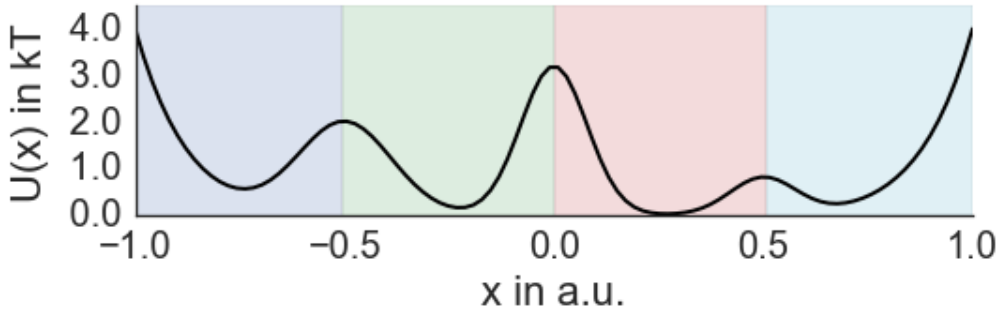
TICA: Linear combination of input features maximising time autocorrelation

VAMP: Variational approach for Markov Process, true for non-equilibrium data

VAMP: W. Chen et al., ***J. Chem. Phys.***, 2019

Building a Markov Model requires several steps





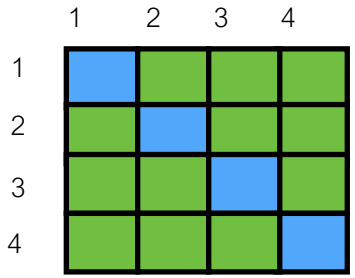
MD data

Featurization (select features)

Dimensionality Reduction (tICA)

Discretization (k-means)

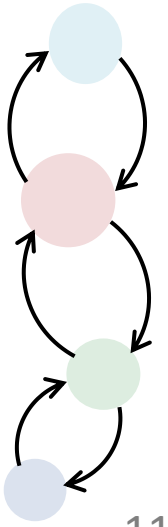
Discrete Trajectories



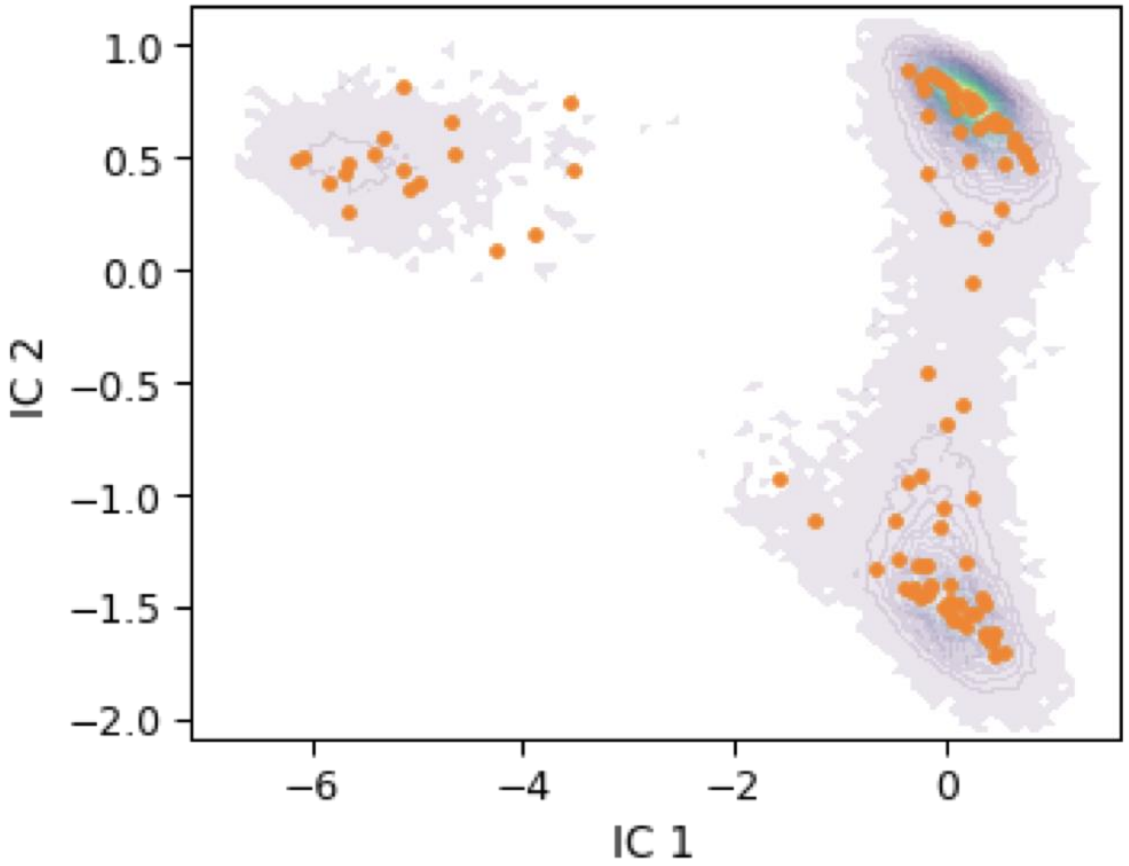
MSM estimation (MLE)

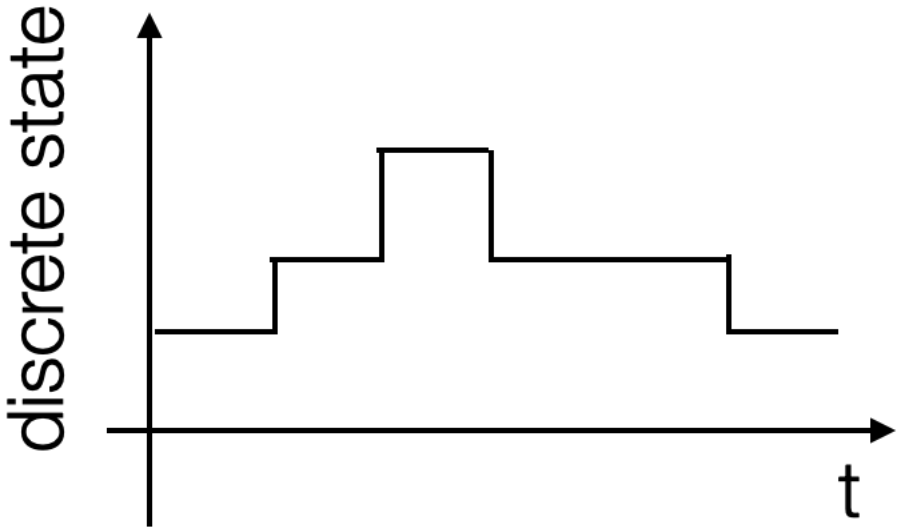
MSM validation (ITS convergence & CK test)

MSM



Clustering on reduced dimensional space





k-means

regular spatial

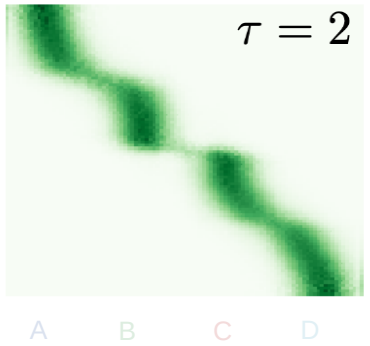
etc.

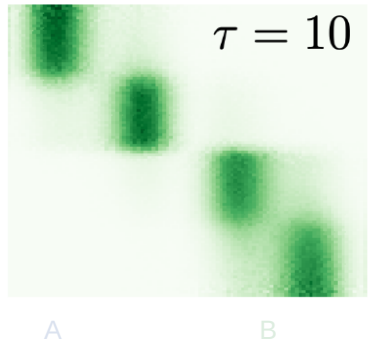
Dimensionality reduction and discretisation require a lot of parameter optimisation. It is necessary to spend a good amount of time on hyper parameter optimisation.

The transition matrix contains all quantative properties

Approximate with a transition matrix from the trajectory:

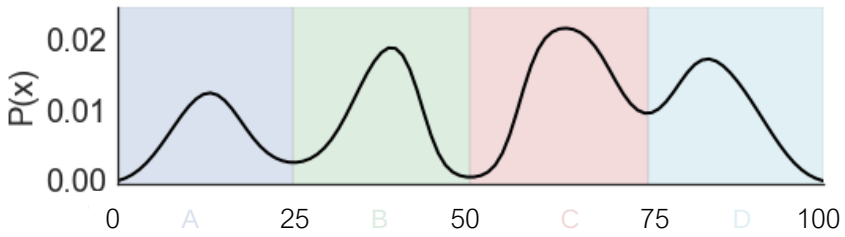
$$P = \begin{bmatrix} P_{1,1} & P_{1,2} & \dots & P_{1,j} & \dots & P_{1,S} \\ P_{2,1} & P_{2,2} & \dots & P_{2,j} & \dots & P_{2,S} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ P_{i,1} & P_{i,2} & \dots & P_{i,j} & \dots & P_{i,S} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ P_{S,1} & P_{S,2} & \dots & P_{S,j} & \dots & P_{S,S} \end{bmatrix}.$$

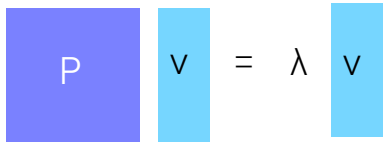




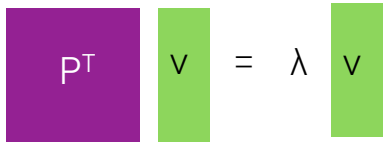
varying the lag time

$$\lambda_1 = 1 > \lambda_2 > \lambda_3, \dots, > \lambda_n$$





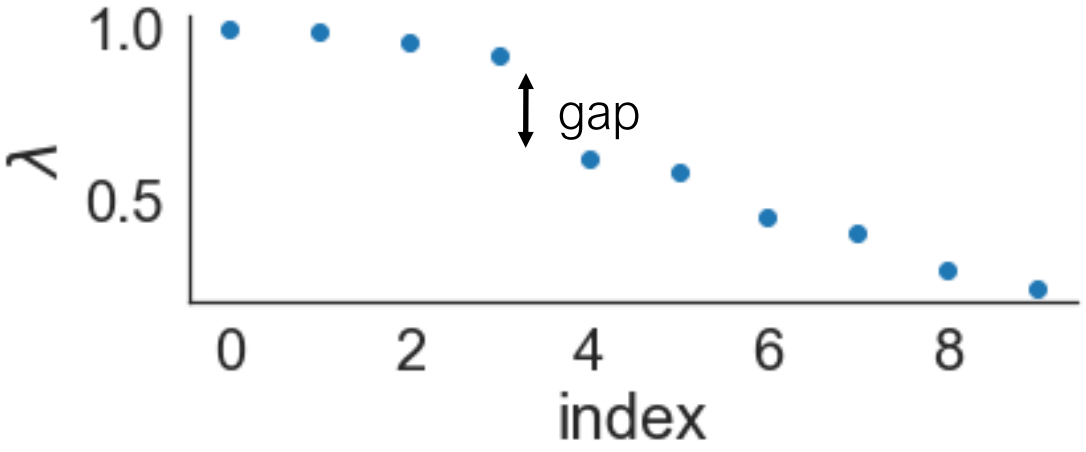
right eigenvector



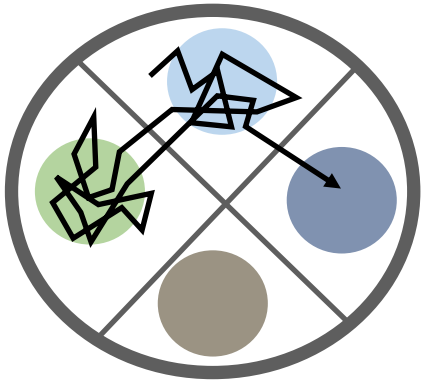
left eigenvector

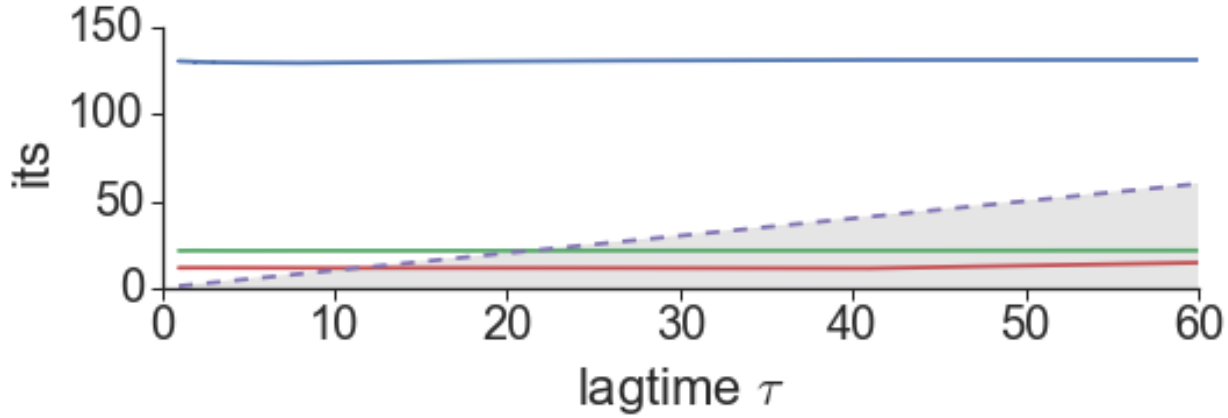
We can find the most likely structure/coordinates!

Eigenvalues tell us about timescales



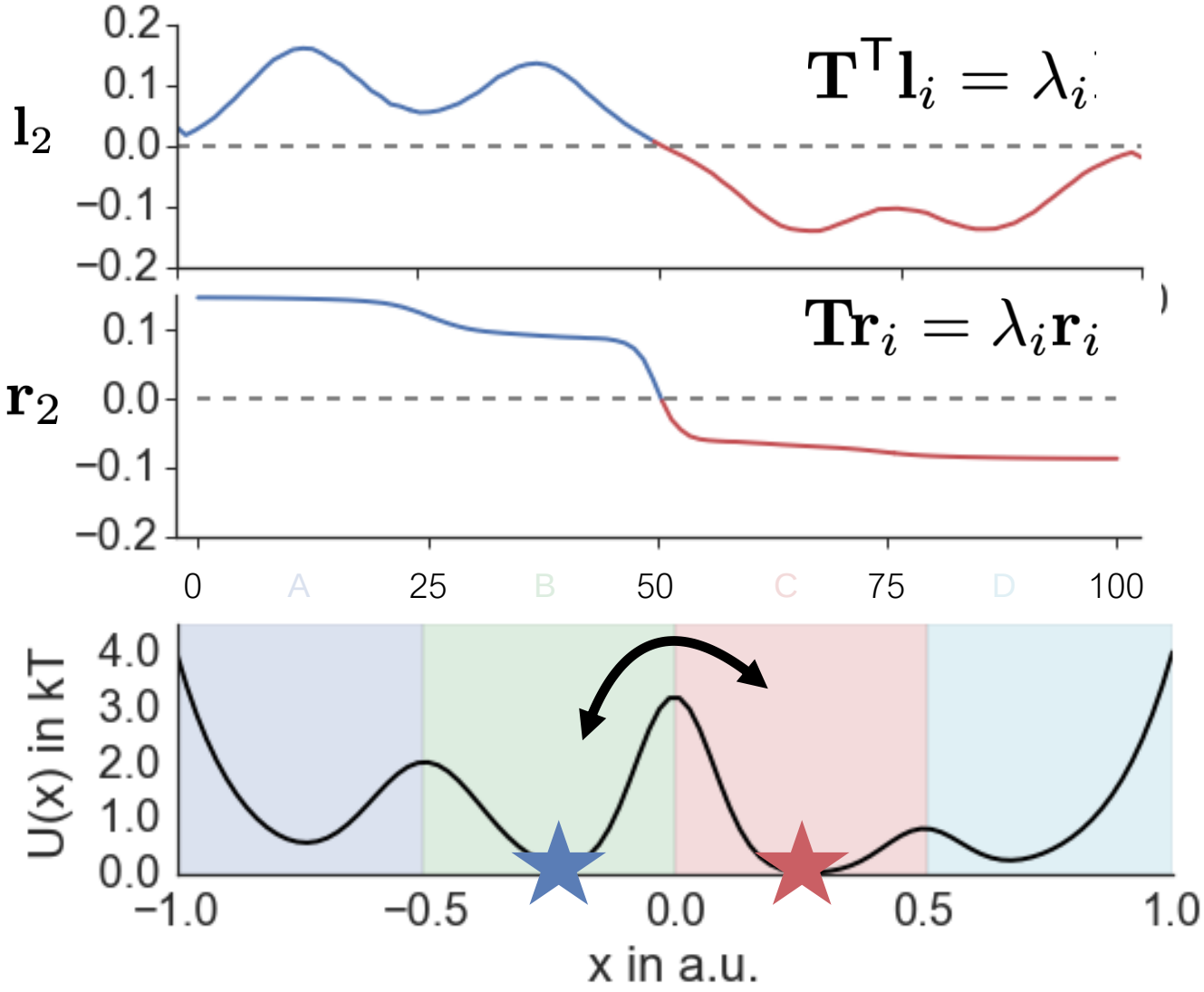
$$\lambda_1 = 1 > \lambda_2 > \lambda_3, \ldots, > \lambda_n$$





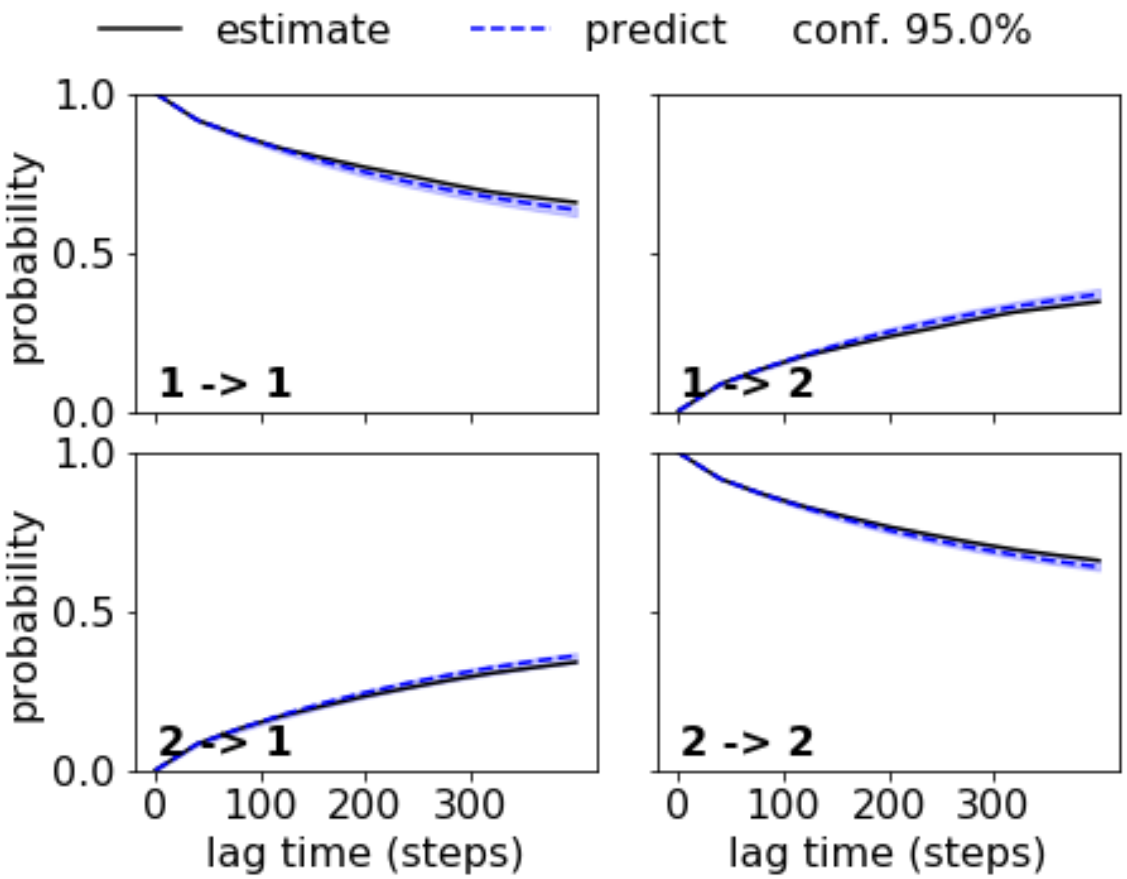
$$t_i = -\frac{\tau}{\ln|\lambda_i|}$$

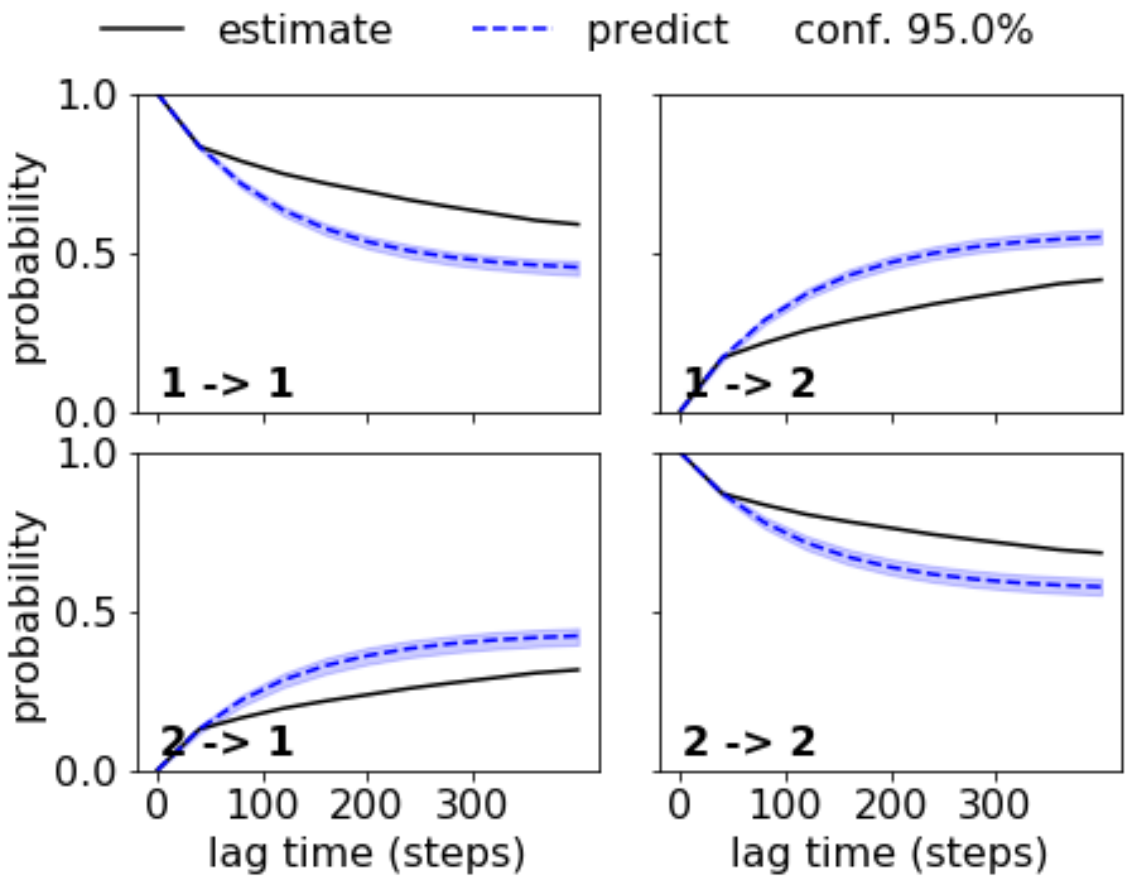
The eigenvectors tell us about the slowest processes



Validation with the Chapman-Kolmogorov (CK) test

$$T(k\tau) = T(\tau)^k$$





Conformational dynamics of a peptide

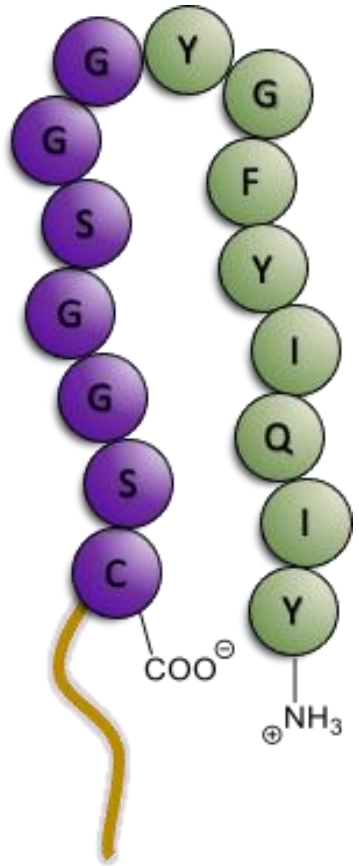
Can we predict the equilibrium structure of a peptide?

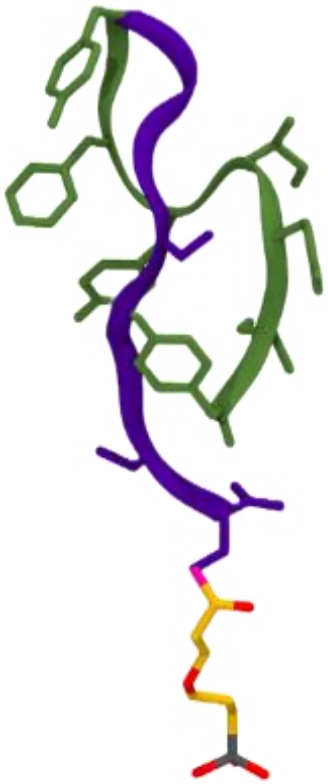
Run 5 μs molecular dynamics simulation

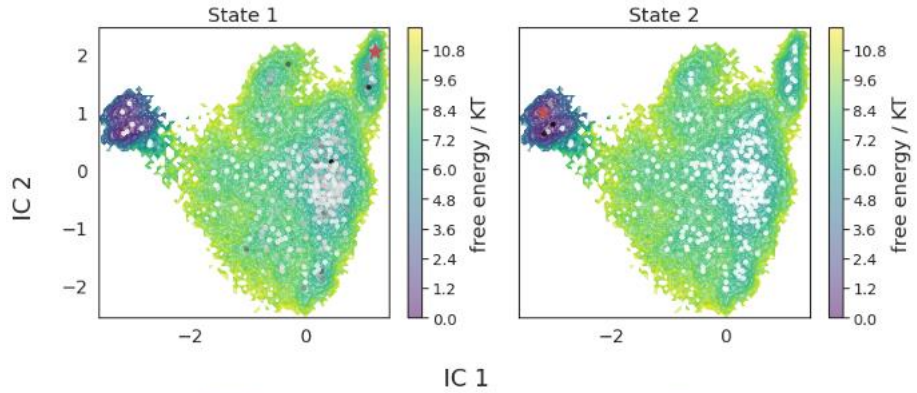
Use a Markov Model to identify dominant conformations in solution

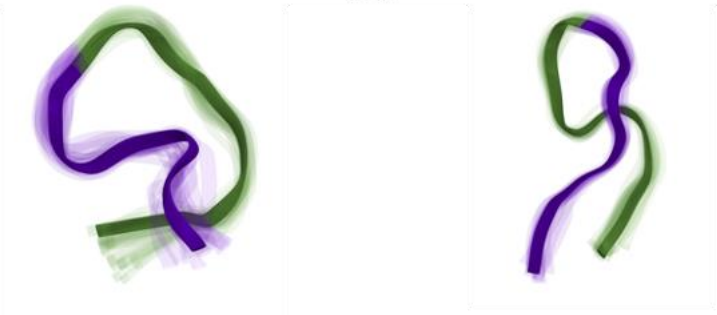
Report most stable structure

AlphaFold suggestion







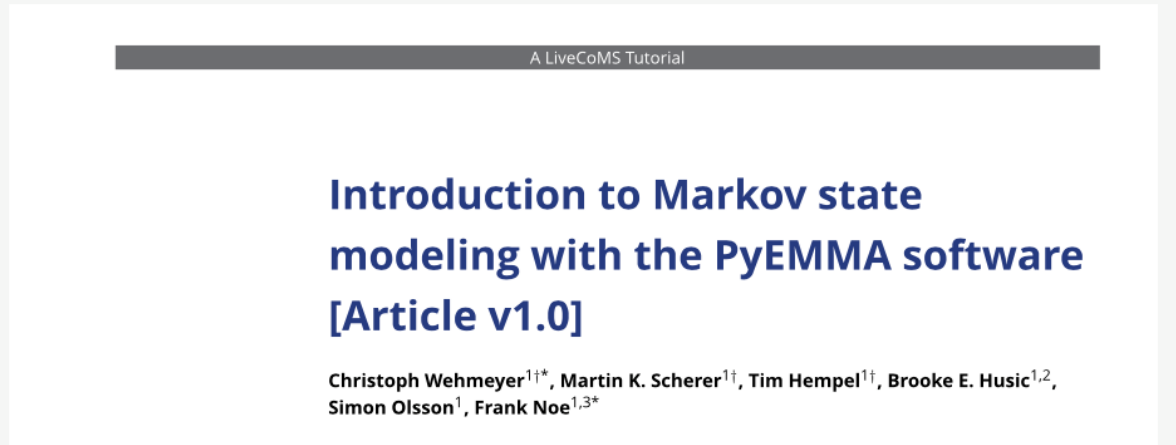


20%

80%

Python tools are available for building MSMs

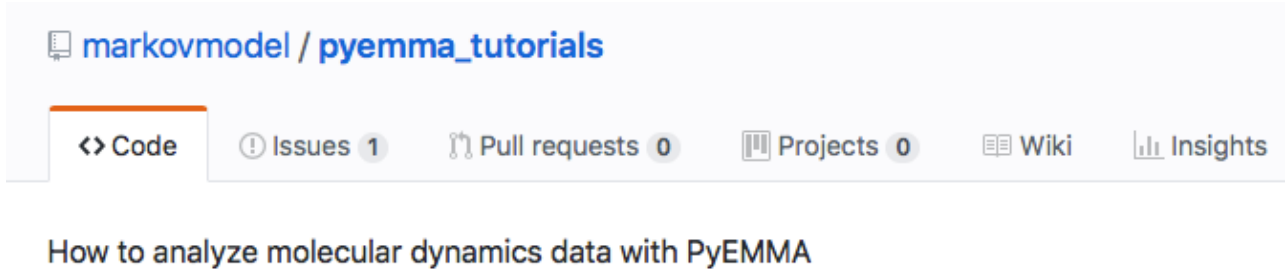
https://www.livecomsjournal.org


A LiveCoMS Tutorial

Introduction to Markov state modeling with the PyEMMA software [Article v1.0]

Christoph Wehmeyer[1†*], Martin K. Scherer[1†], Tim Hempel[1†], Brooke E. Husic[1,2], Simon Olsson[1], Frank Noe[1,3*]

https://github.com/markovmodel/pyemma_tutorials



https://github.com/deeptime-ml/deeptime