

Hands-on tutorial on data assimilation using Markov state model and Hidden Markov models

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What can we learn?

- We learn basics of a method to **integrate MD simulation data and experimental** data using Markov state model (MSM) and Hidden Markov state model (HMM)
- Starting from an introduction to our Julia package (MDToolbox.jl), we will learn basics of MSM and HMM using simple examples. Then, we will combine MSM and HMM for incorporating experimental data.

Schedule

- 13:00 Installation. Julia and MDToolbox.jl basics
 - Introduction to our in-house Julia package MDToolbox.jl
- 14:00 Markov state model (MSM) basics
 - What is MSM?, and how to construct it
- 14:40 Hidden Markov model (HMM) basics
 - What is HMM? and what can we do with it
- 15:20-16:00 Data assimilation with MSM & HMM

00 Installation. Julia and MDToolbox.jl basics

- Let's follow the descriptions of README at
https://github.com/matsunagalab/hmm_tutorials
1. Install Jupyter Lab
 2. Install Julia and packages
 1. Install Julia
 2. Install required packages including MDToolbox.jl (or update)
 3. Run IJulia
 3. Download tutorial materials

MDToolbox.jl

Julia package for the statistical analysis of MD trajectories

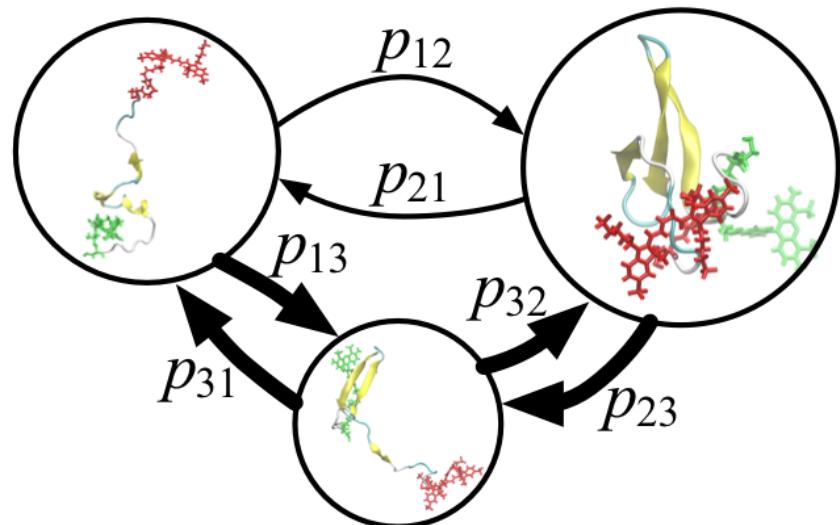
<https://github.com/matsunagalab/MDToolbox.jl>

- I/O for trajectory, coordinate, and topology files
- Atom selections
- Least-squares fitting of structures, and some geometry calculations
- Potential mean force (PMF) or free energy profile from scattered data
- Statistical estimates (WHAM and MBAR methods) from biased data
- Dimensional reductions (Principal Component Analysis, and others)
- **Markov state models and Hidden Markov models**

01 Markov state model basics

What is MSM? MSM is a statistical model to describe conformational dynamics of molecules

Structures are clustered
into **discrete states**



Dynamics are represented by
transition probabilities between states

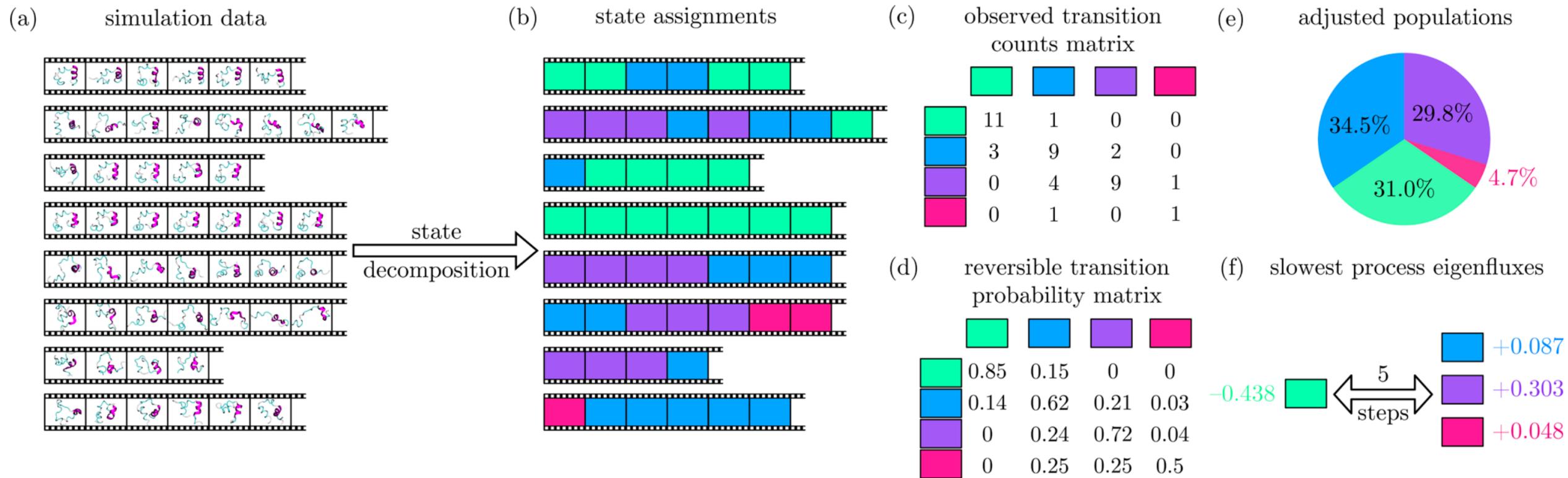
$$T_{\text{simulation}}(\tau) = \begin{bmatrix} p_{11} & p_{12} & p_{13} \\ p_{21} & p_{22} & p_{23} \\ p_{31} & p_{32} & p_{33} \end{bmatrix}$$

Time is coarse-grained in τ

$$P(n\tau) = [T_{\text{simulation}}(\tau)]^n P(0)$$

- 😊 Dynamics is represented by parameters $T(\tau)$
- 😊 Long time dynamics from multiple short simulations
- 😔 Force-field dependence (Incorrect dynamics)

Construction of MSMs



B. E. Husic, V. S. Pande, Markov State Models: From an Art to a Science. *J. Am. Chem. Soc.* **140**, 2386–2396 (2018).

Typical computations for constructing MSMs

Load MD trajectory

MDToolbox functions

`mdload()`

Feature extraction (distance-map, contact-map)
and Dimensional reduction (PCA, tICA)

`compute_distancemap()`

`pca()`

`tica()`

Clustering (k-centers, k-means) for defining states

`clusterbykcenter()`

Count transitions and estimates transition probabilities

`msmcountmatrix()`

`msmtransitionmatrix()`

Validation through implied timescales or others

`msmimpliedtime()`

Estimation of transition probabilities from counting matrix: Maximum likelihood

$$L_{\text{MD}}(\mathbf{T}(\tau)) = p(\mathbf{C}|\mathbf{T}(\tau)) = \prod_{i=1}^M \prod_{j=1}^M T_{ij}^{C_{ij}}(\tau).$$

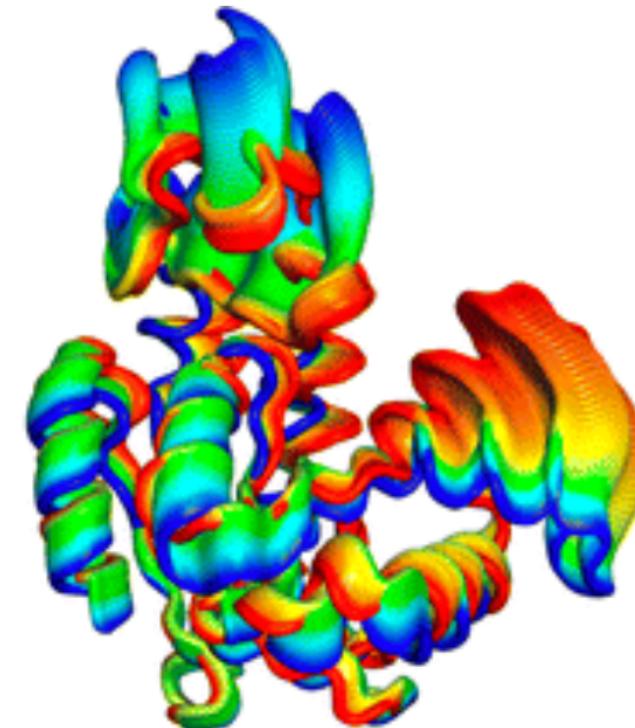
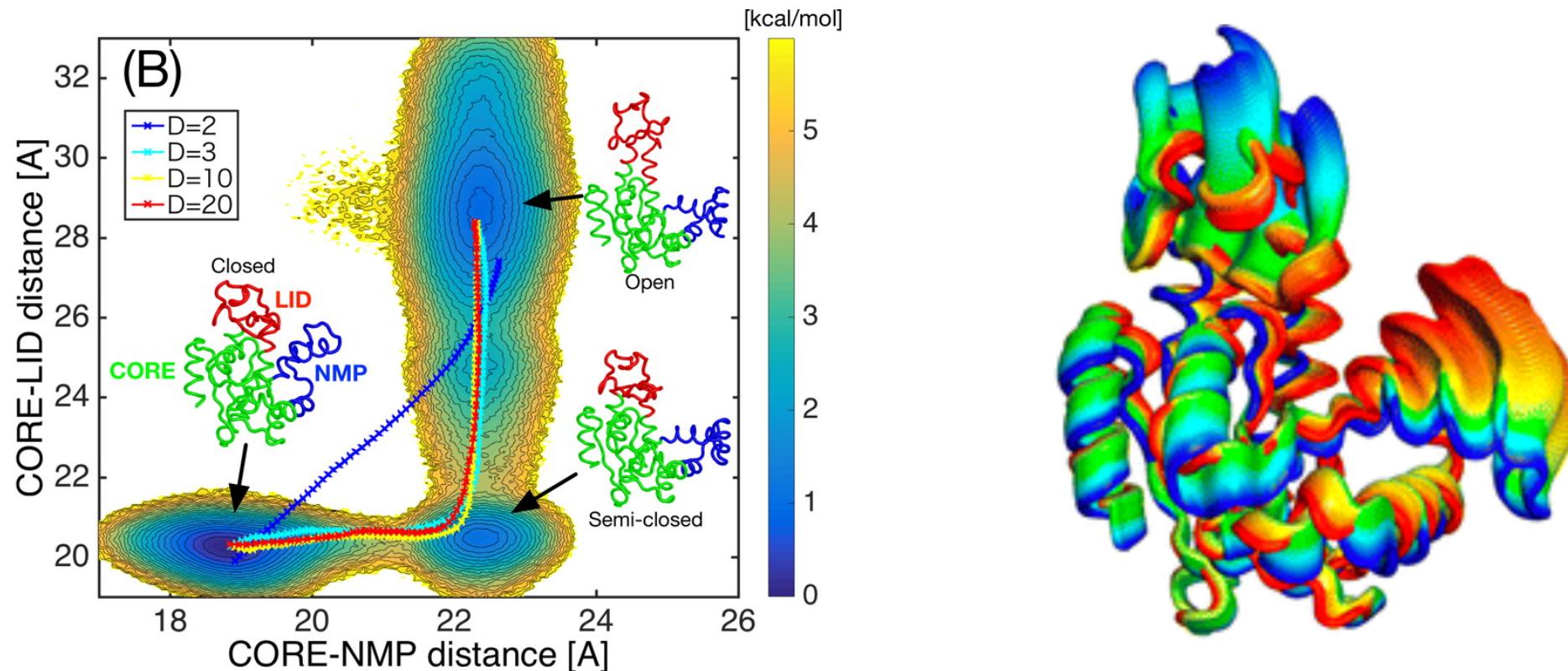
Maximize this function over $T(\tau)$

K. A. Beauchamp, G. R. Bowman, T. J. Lane, L. Maibaum, I. S. Haque, V. S. Pande, MSMBuilder2: Modeling Conformational Dynamics on the Picosecond to Millisecond Scale. *J. Chem. Theory Comput.* **7**, 3412–3419 (2011).

Y. Matsunaga, Y. Sugita, Use of single-molecule time-series data for refining conformational dynamics in molecular simulations. *Curr. Opin. Struct. Biol.* **61**, 153–159 (2020).

MD data in the tutorial

Coarse-grained (DoME-model) model of Adenylate kinase, simulated by GENESIS

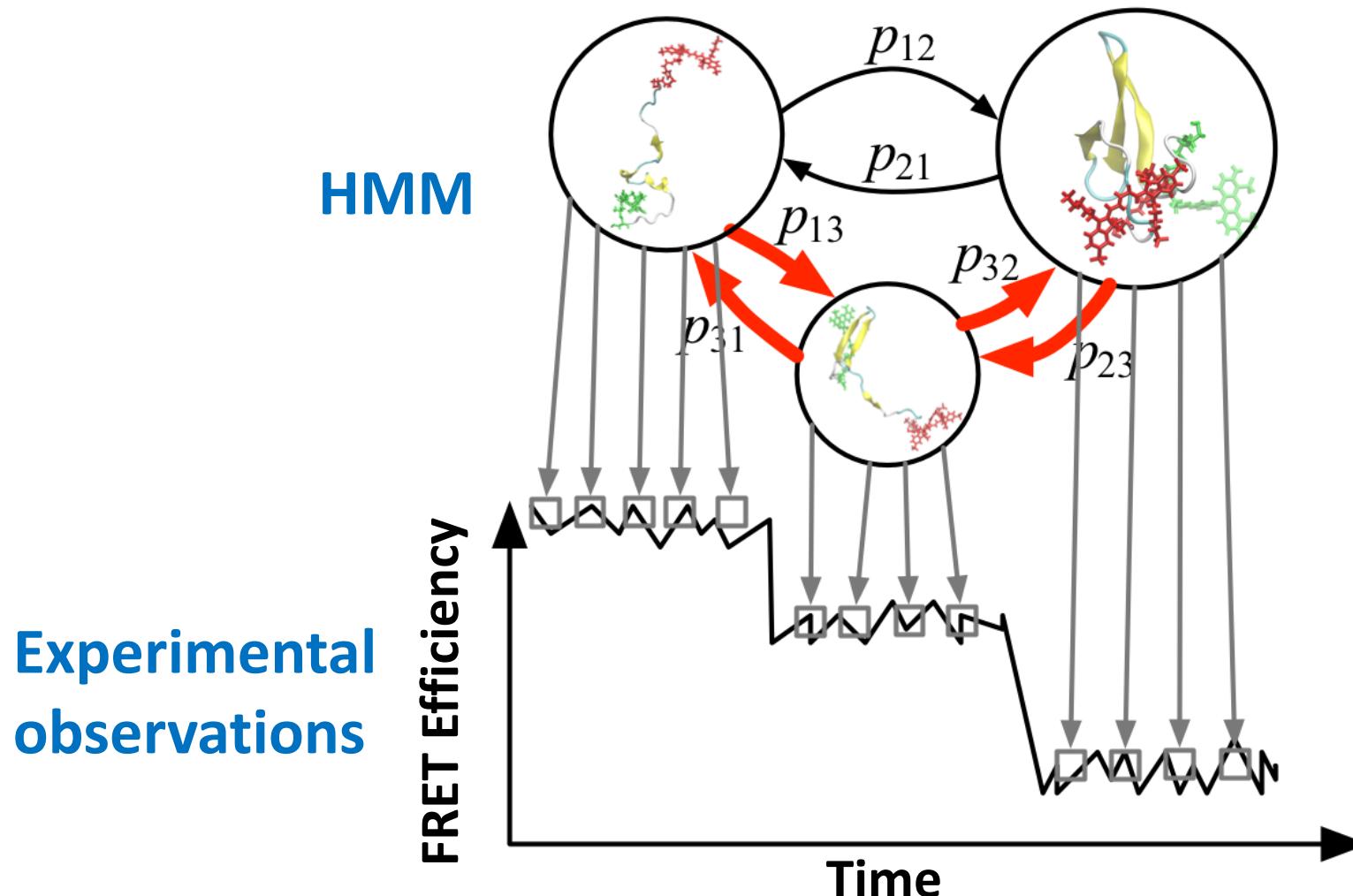


C. Kobayashi, Y. Matsunaga, R. Koike, M. Ota, Y. Sugita, Domain Motion Enhanced (DoME) Model for Efficient Conformational Sampling of Multidomain Proteins. *J. Phys. Chem. B.* **119**, 14584–14593 (2015).

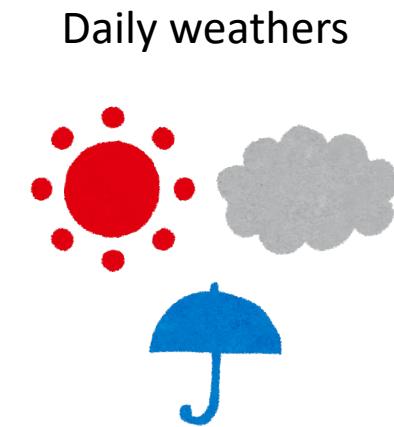
Y. Matsunaga, Y. Komuro, C. Kobayashi, J. Jung, T. Mori, Y. Sugita, Dimensionality of Collective Variables for Describing Conformational Changes of a Multi-Domain Protein. *J. Phys. Chem. Lett.* **7**, 1446–1451 (2016).

02 Hidden Markov model basics

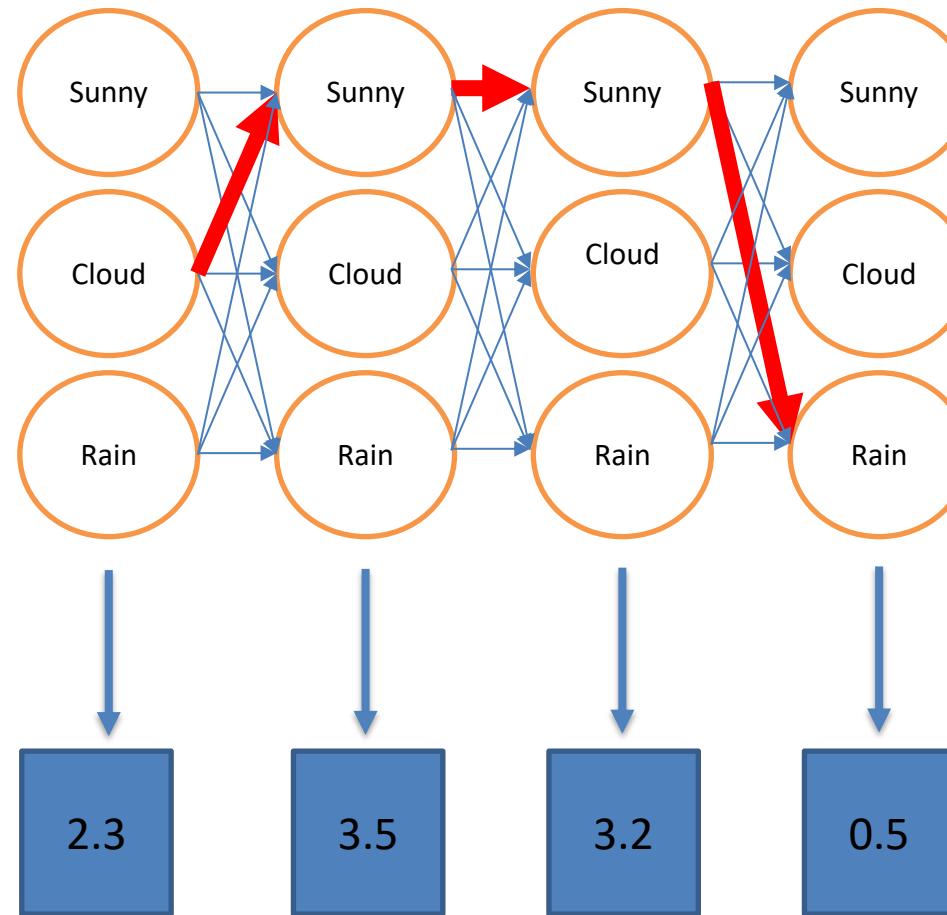
What is HMM? MSM is a latent MSM behind experimental observations



Toy model used in the tutorial



Daily Ice-cream sales



Hidden Markov
Model

Can we estimate daily weathers
Or transition probabilities
from daily ice-creams sales
Time-series data?

Experimental
observations

Toy model used in the tutorial (cont'd)

Transition probabilities of daisy weathers

Weather	value
Rain	x = 1
Cloudy	x = 2
Sunny	x = 3

	Rain (tomorrow)	Cloudy(tomorrow)	Sunny (tomorrow)
Rain (today)	0.200004	0.257922	0.542074
Cloudy (today)	0.242095	0.300014	0.457891
Sunny (today)	0.157926	0.142121	0.699953

Probabilities to observe specific daily sales values given weathers

$$Y = X + \epsilon$$

sales weather Gaussian noise

$$\epsilon = Y - X$$

$$P(y|X = x) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{(y - x)^2}{2}\right)$$

sales weather

Estimation of latent states and transition probabilities from counting matrix: Maximum likelihood

$$\begin{aligned} L_{\text{HMM}}(\mathbf{T}(\tau)) &= p(y_{1:N} | \mathbf{T}(\tau)) \\ &= \sum_{s_1=1}^M \cdots \sum_{s_N=1}^M p(s_1) p(y_1 | s_1) \prod_{t=2}^N T_{s_{t-1}s_t}(\tau) p(y_t | s_t). \end{aligned}$$

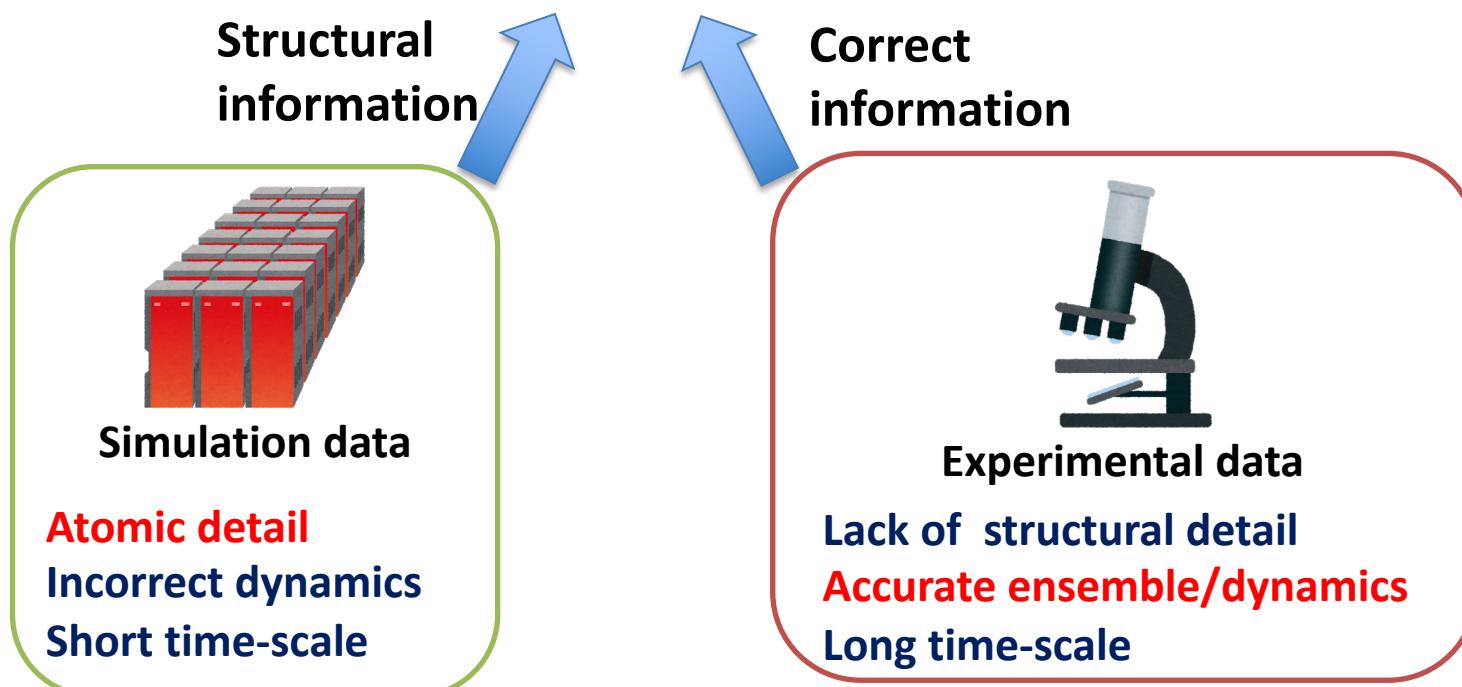
Maximize this function over states or $T(\tau)$

Y. Matsunaga, Y. Sugita, Use of single-molecule time-series data for refining conformational dynamics in molecular simulations. *Curr. Opin. Struct. Biol.* **61**, 153–159 (2020).

03 Data assimilation with MSM and HMM

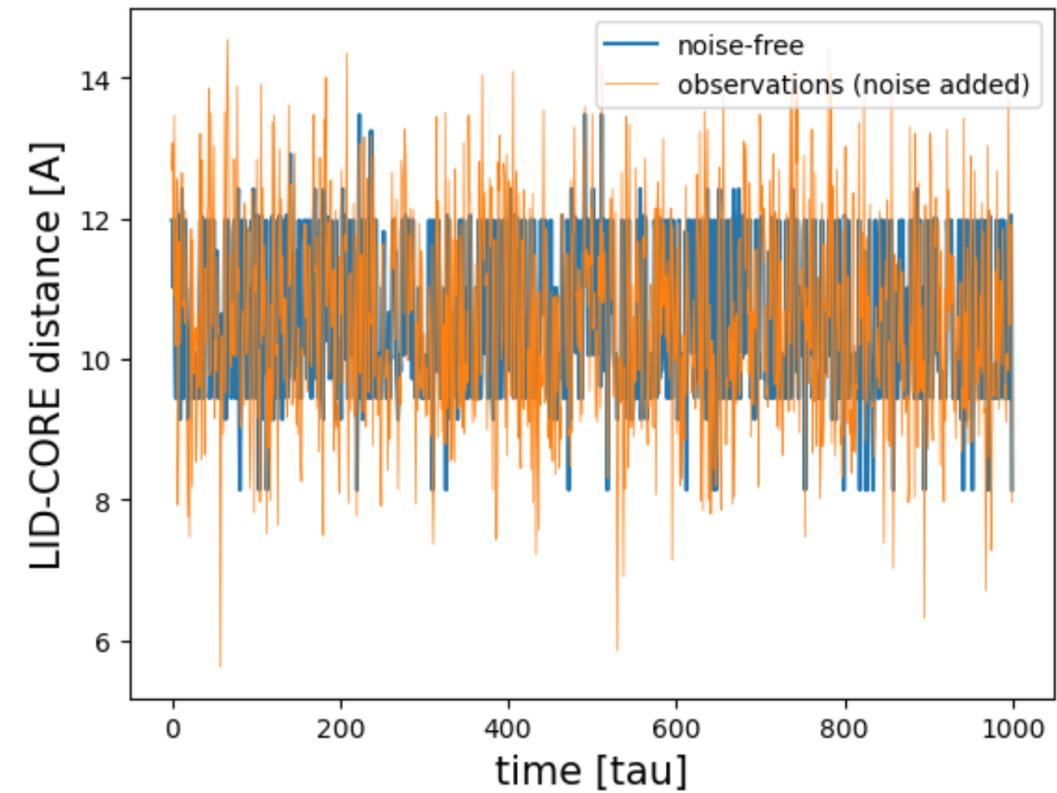
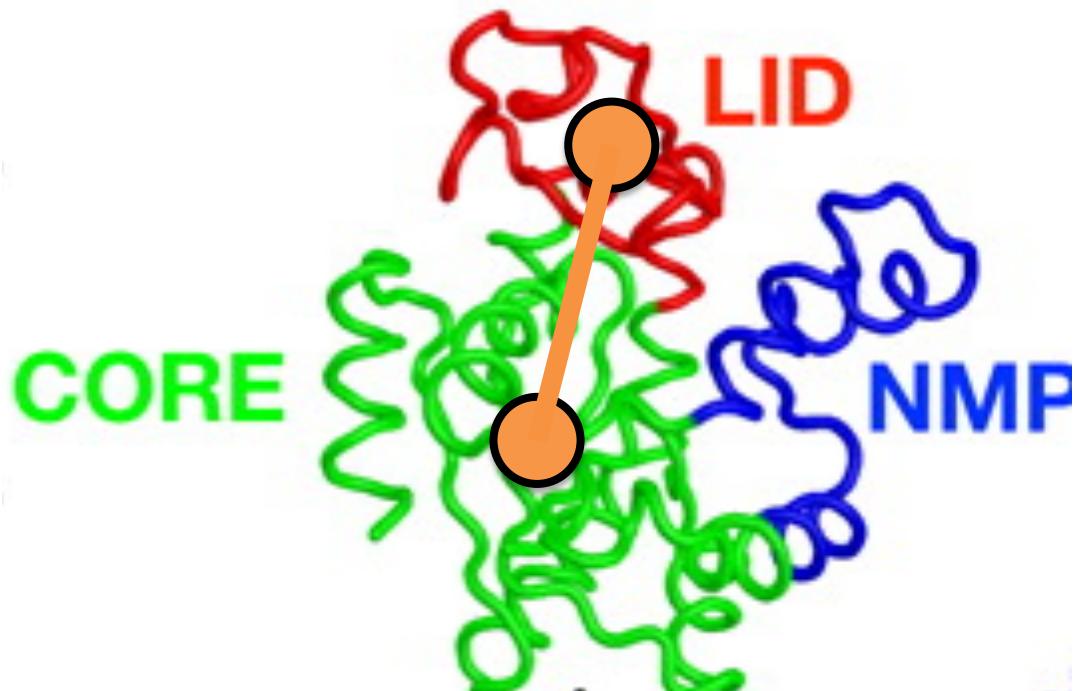
What is the purpose of integrating MD data and HMM data?

- Correct MD data ensemble or dynamics matching with experimental data
- Interpret experimental data in terms of structural details



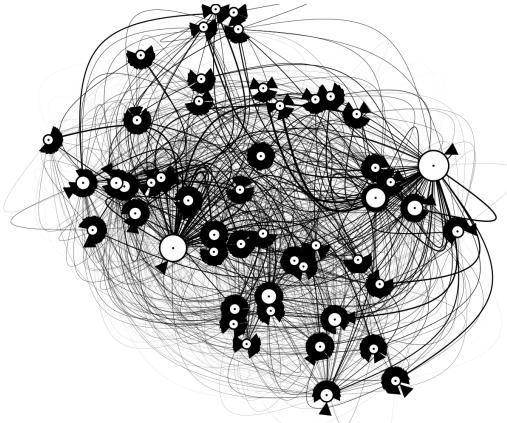
"Experimental data" in the tutorial

Using the original MSM, we generate LID-CORE distance time-series as "experimental data" mimicking single-molecule FRET



“Experimental data” in the tutorial (cont’d)

Transition probabilities of MSM’s states



Probabilities to observe specific daily sales values given weathers

$$Y = X + \epsilon$$

observation LID-CORE Gaussian noise
distance

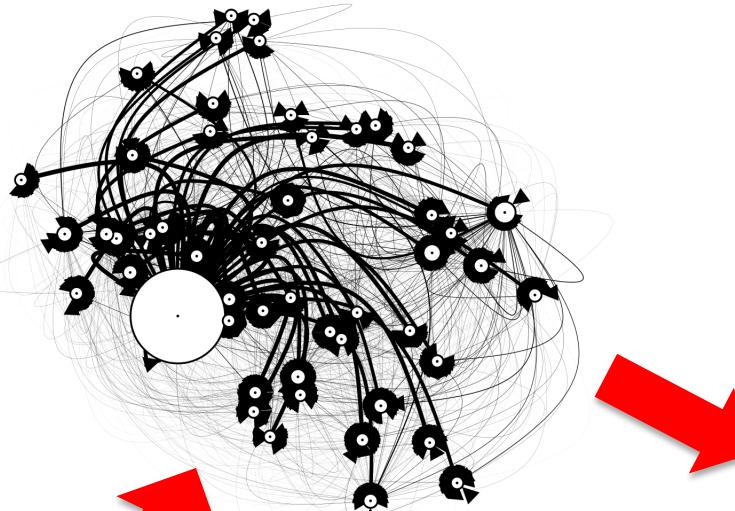
$$\epsilon = Y - X$$

$$P(y|X = x) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{(y - x)^2}{2}\right)$$

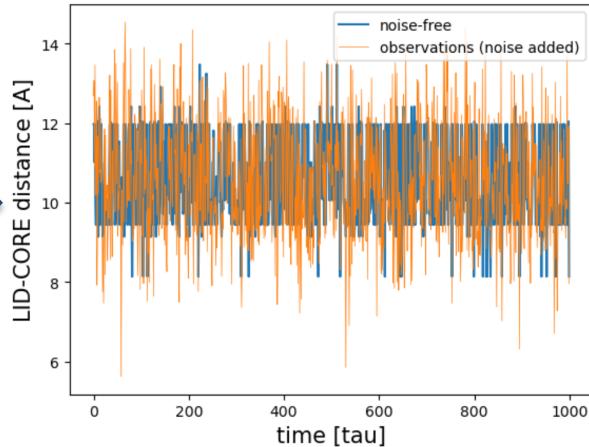
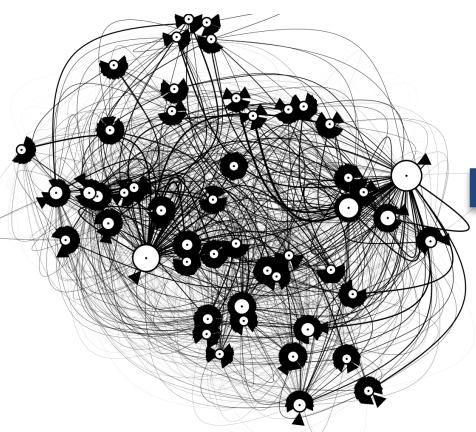
observation LID-CORE
distance

Problem setting in the tutorial

“Distorted” MSM



“experimental data” generated by the original MSM



Data assimilation
or integration

Can we correct the “distorted” MSM and restore the original MSM?

