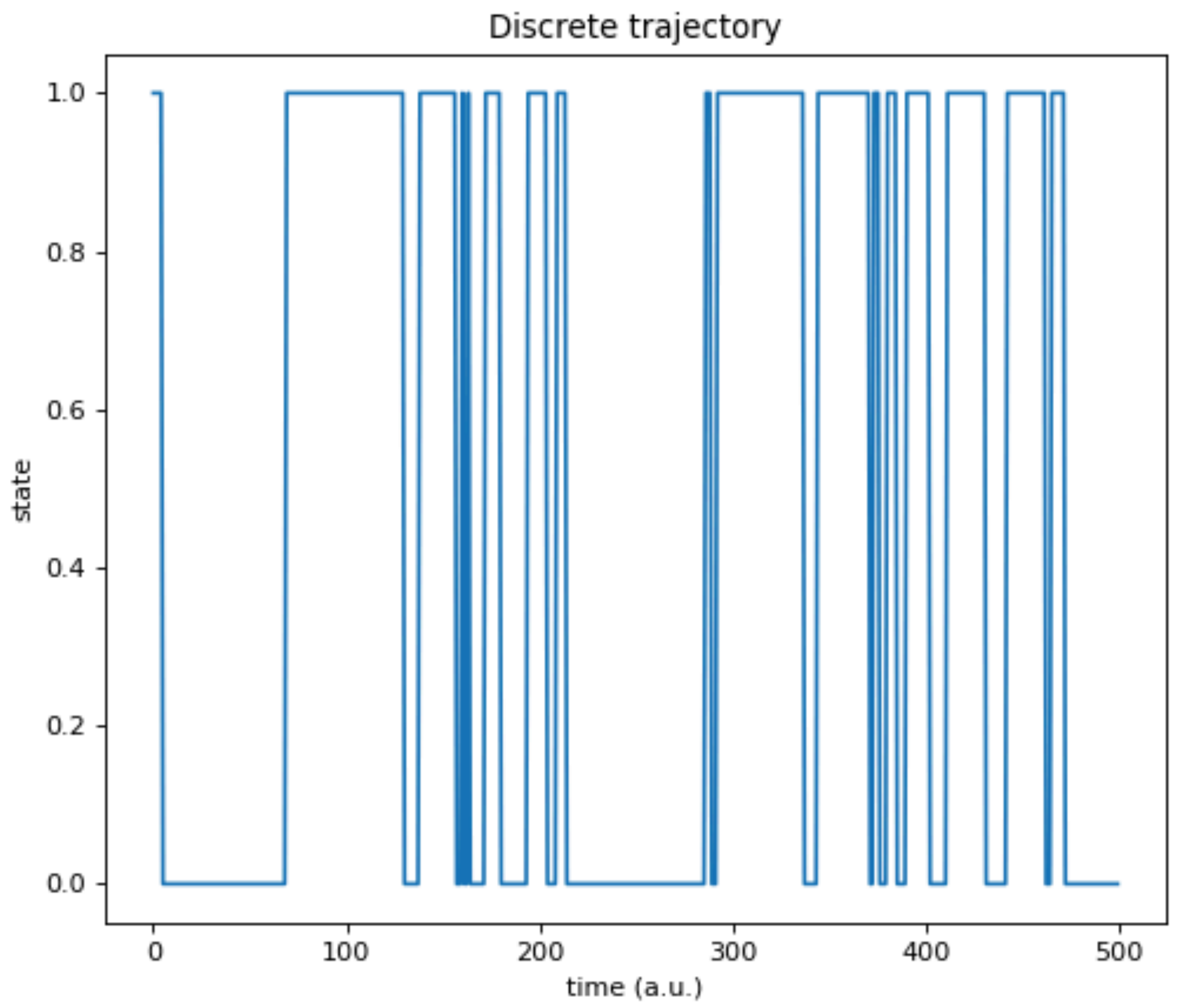
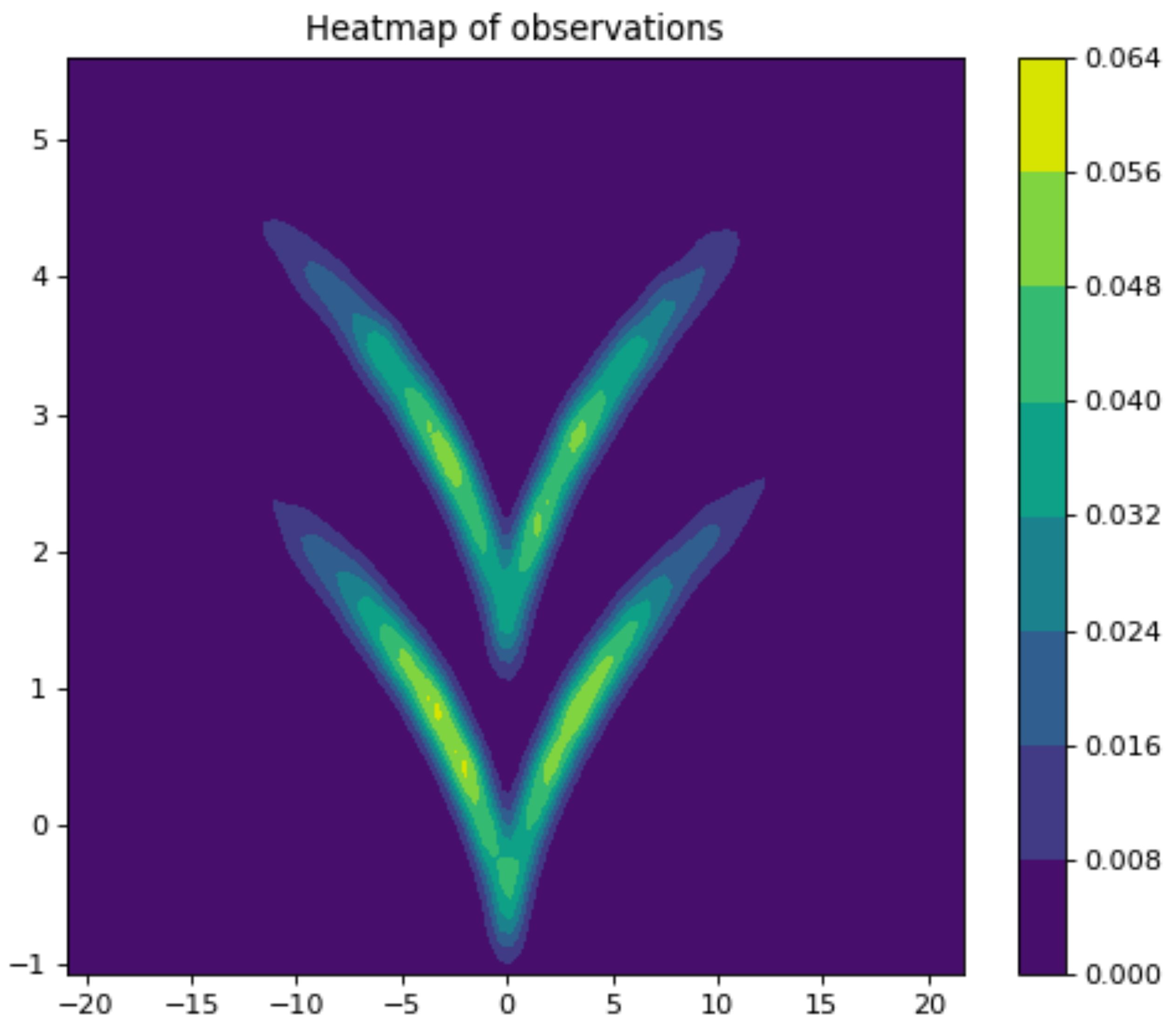
# Markov State Models

Theory, properties, estimation, and validation

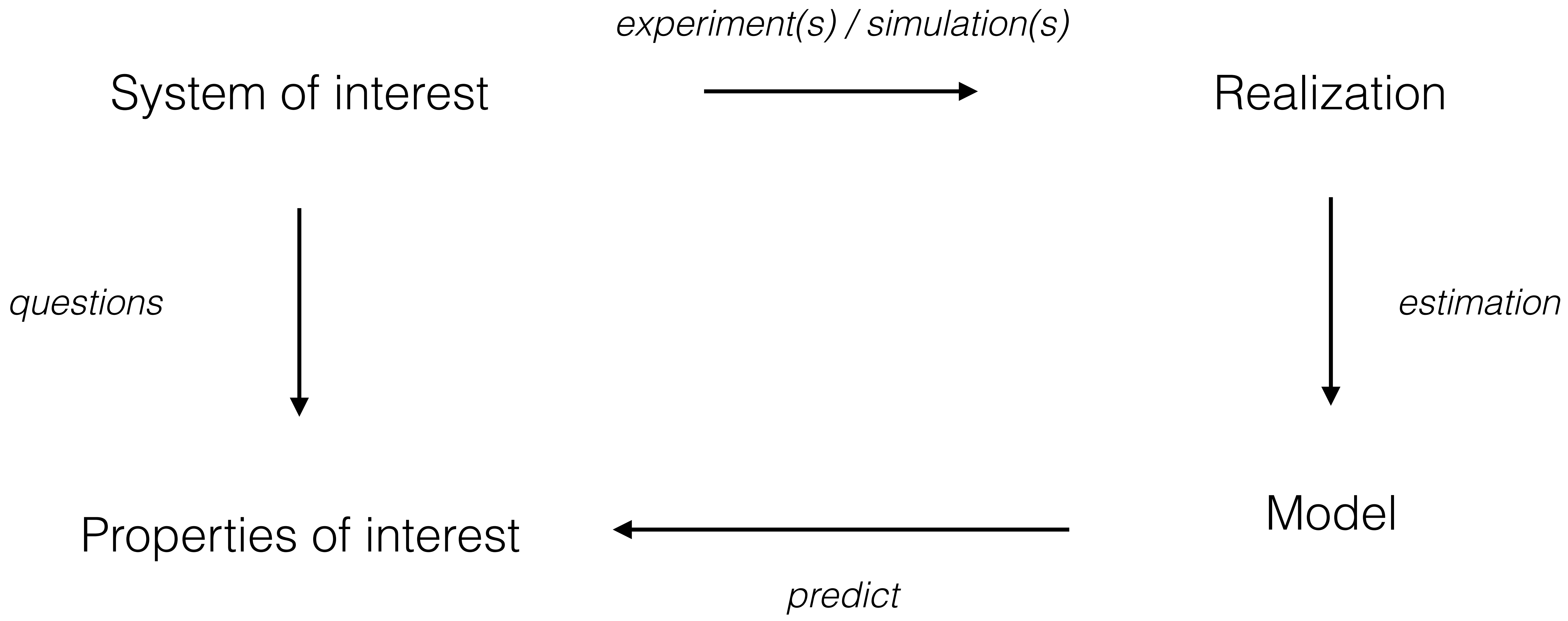




$$P = \begin{pmatrix} 0.95 & 0.05 \\ 0.05 & 0.95 \end{pmatrix}$$

Slides courtesy of J.H. Prinz and S. Olsson

# Motivation



System of interest

*experiment(s) / simulation(s)*

Realization

*questions*

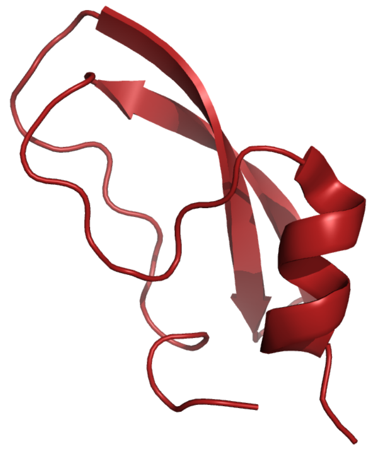
*estimation*

Properties of interest

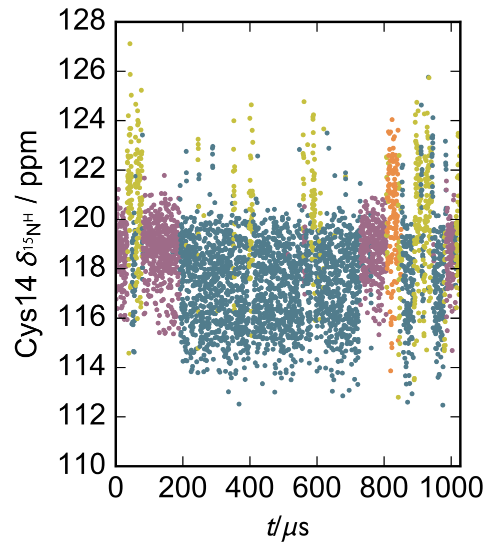
*predict*

Model

# Motivation

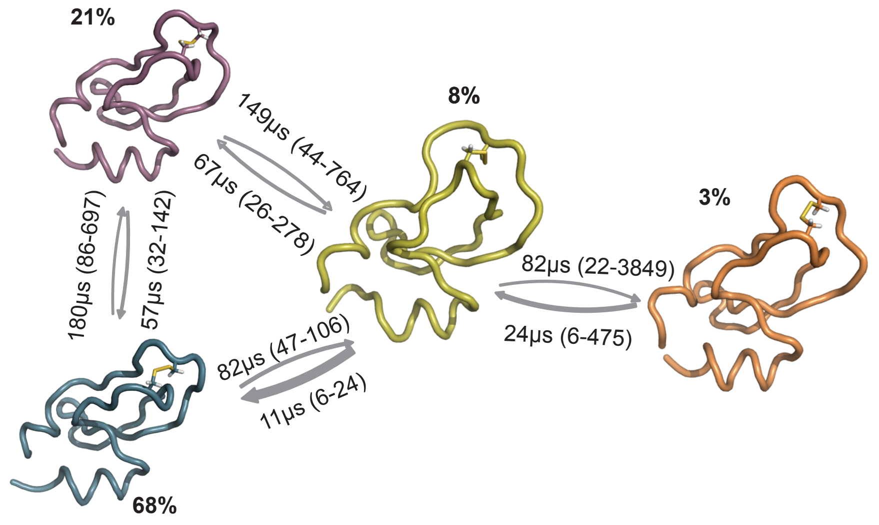


*experiment(s) / simulation(s)*

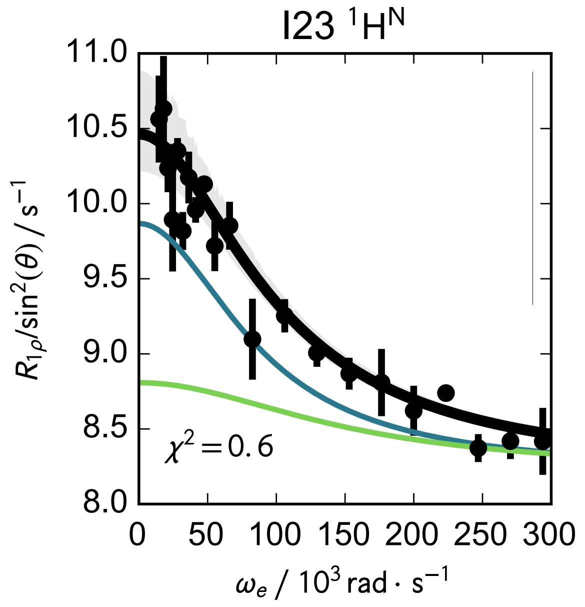


*questions*

*estimation*



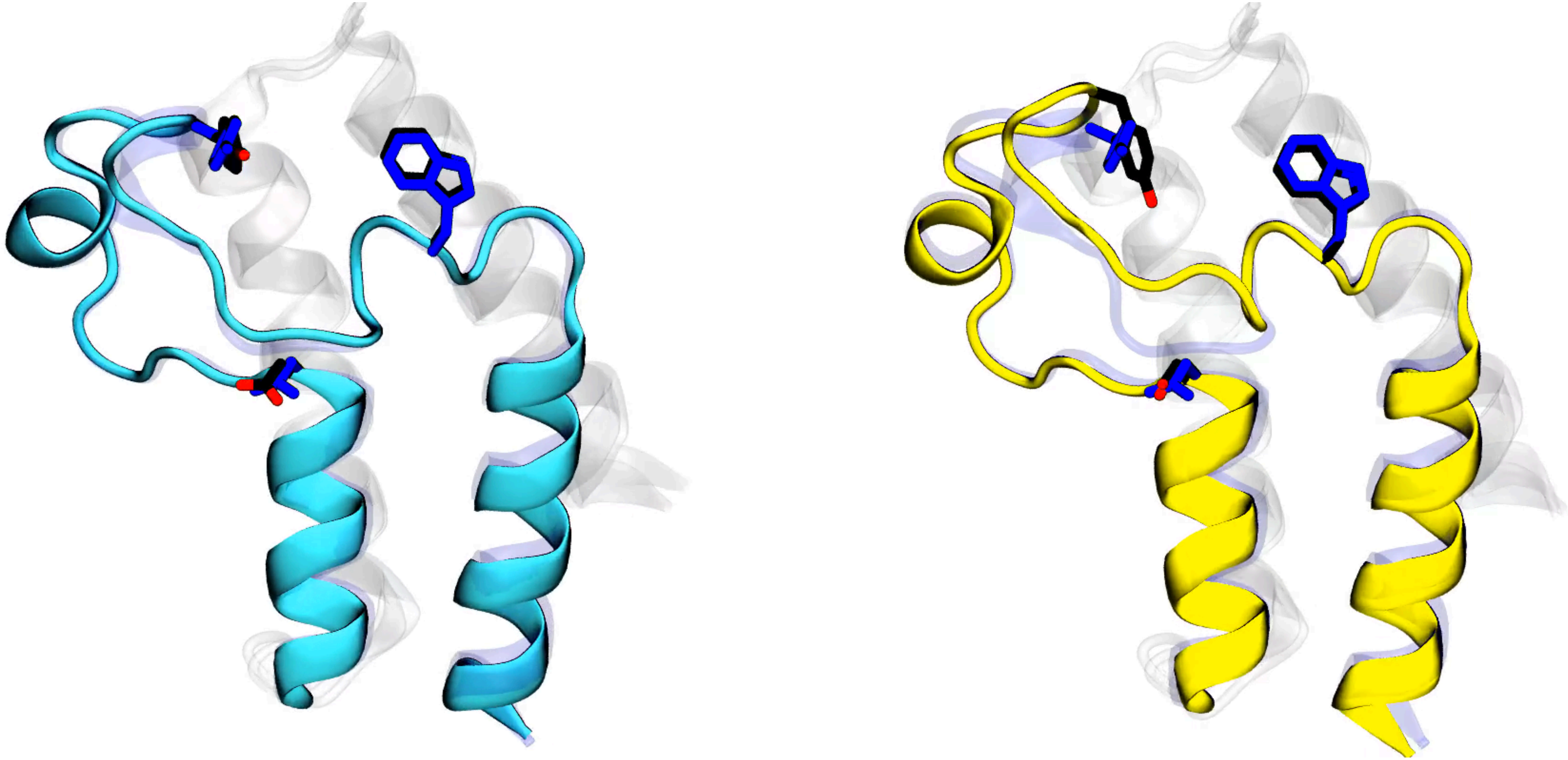
*predict*



*„Find properties of a system of interest*
*using a simple model parametrized from observations“*

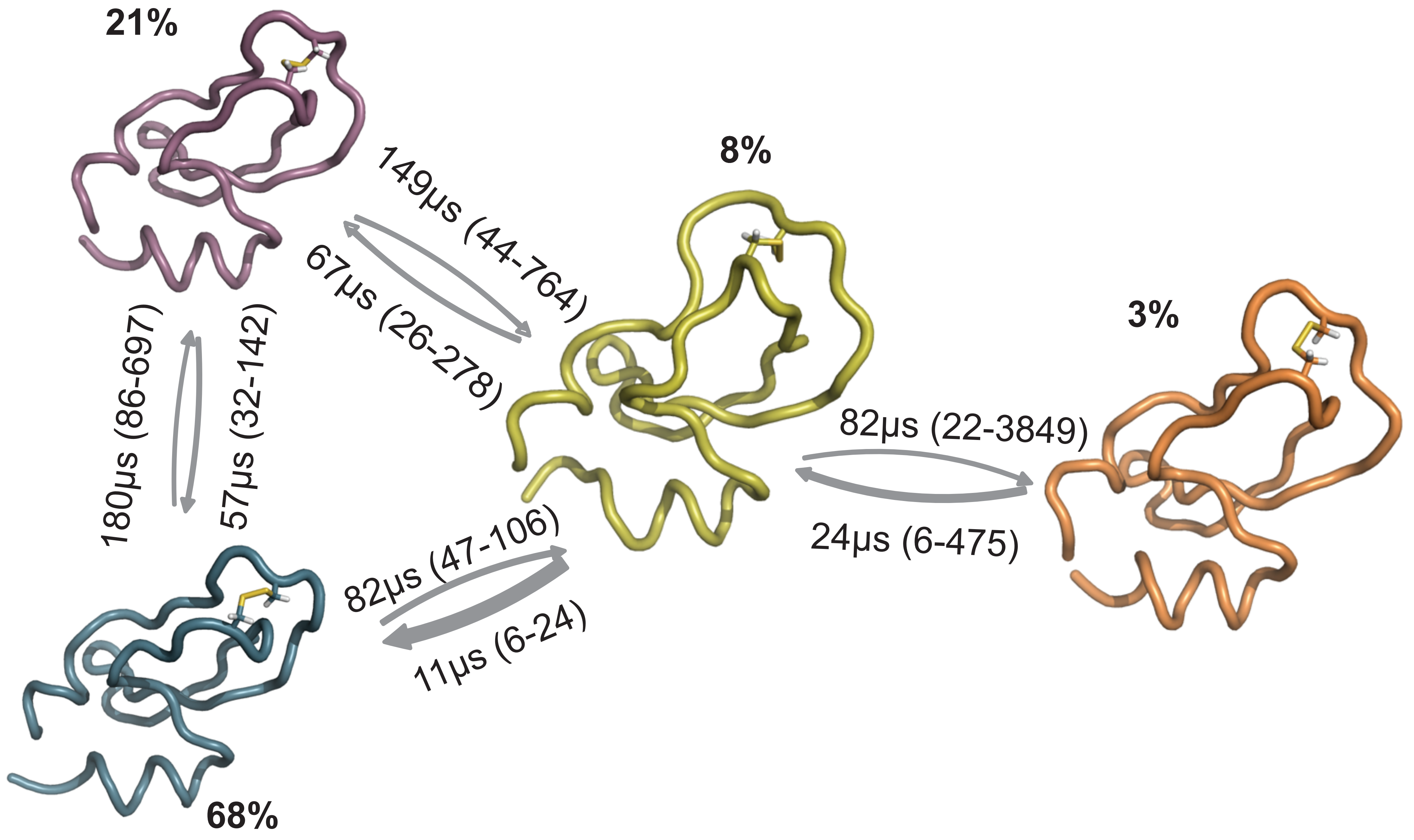
# Example: CECR2

Protein related to Epigenetics



Raich *et al.* **Proceedings of the National Academy of Sciences** 118.4 (2021)

# Markov state models

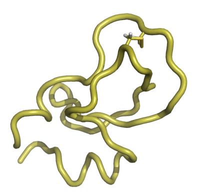
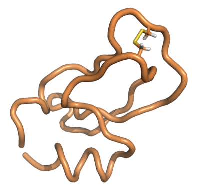
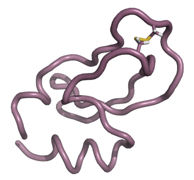
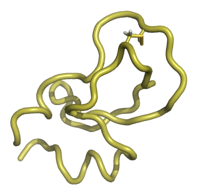
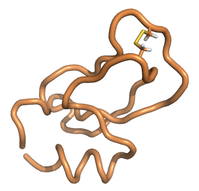
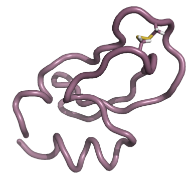
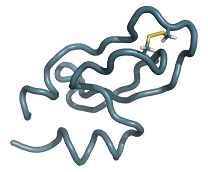


<u>Metastability of states</u> allow us to significantly simplify the dynamics of our system of interest

# Markov state models

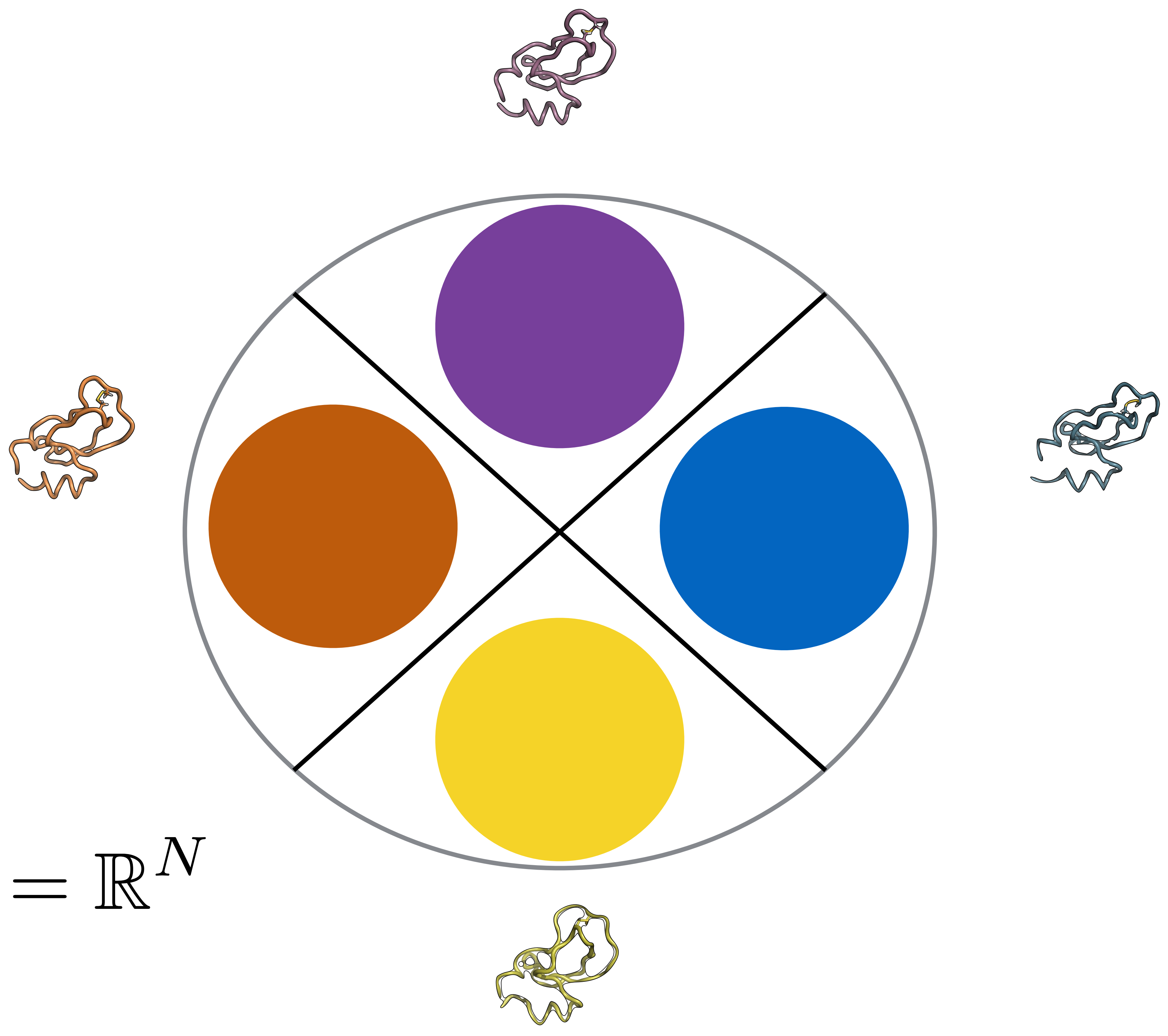
Final state

Initial state

| |  |  |  | |
|---|---|---|---|---|
|  | 96% | 1% | 2% | 1% |
|  | 5% | 95% | 0% | 0% |
|  | 1% | 0% | 97% | 2% |
|  | 1% | 0% | 2% | 97% |

A Markov state model describes the dynamics of a system as conditional transition probabilities

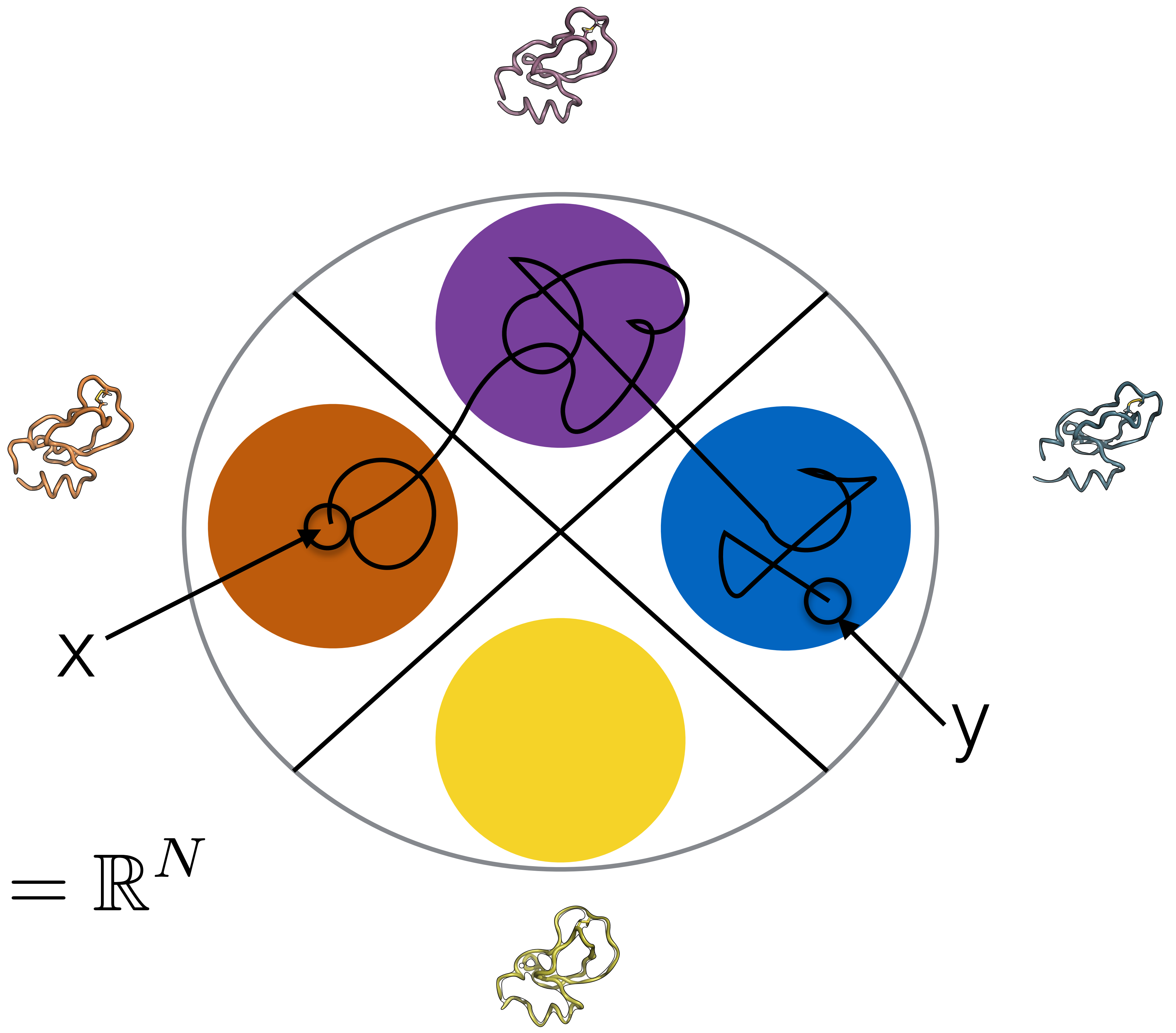
# What is meta-stability?



$$x \in \Omega = \mathbb{R}^N$$

sets of configurations which are long-lived.
Markov state models assume these states, and exchange between them is important.

# What is meta-stability?



$$x \in \Omega = \mathbb{R}^N$$

sets of configurations which are long-lived.
Markov state models assume these states, and exchange between them
is important.

# Molecular simulations

- Molecular simulations are realizations of stochastic process on $\Omega$ and are Markovian w.r.t. this space.

$$p(\mathbf{x}, \mathbf{y}; \tau)\, d\mathbf{y} = \mathbb{P}[\mathbf{x}(t+\tau) \in \mathbf{y} + d\mathbf{y} \mid \mathbf{x}(t) = \mathbf{x}]$$

$$\mathbf{x}, \mathbf{y} \in \Omega,\ \ \tau \in \mathbb{R}_{0+},$$

*Transition probabilities are well defined*

Prinz *et al.* (2011) JCP 134, 174105

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$$\mathbf{x}, \mathbf{y} \in \Omega,\ \tau \in \mathbb{R}_{0+},$$

*Transition probabilities are well defined*

$$\begin{aligned} p(\mathbf{x}, A; \tau) &= \mathbb{P}[\mathbf{x}(t+\tau) \in A | \mathbf{x}(t) = \mathbf{x}] \\ &= \int_{\mathbf{y} \in A} d\mathbf{y}\ p(\mathbf{x}, \mathbf{y}; \tau). \end{aligned}$$

*Also applies for regions*

Prinz *et al.* (2011) JCP 134, 174105

# Molecular simulations (2)

*Ergodicity*

*No two or more segments of the space* $\Omega$ *are dynamically disconnected from each other.*

and

*For an infinitely long simulation we will have visited every state* $\mathbf{x} \in \Omega$ *infinitely many times.*

Prinz *et al.* (2011) JCP 134, 174105

# Molecular simulations (3)

*Reversibility*

Simulations fulfill the detailed-balance condition:

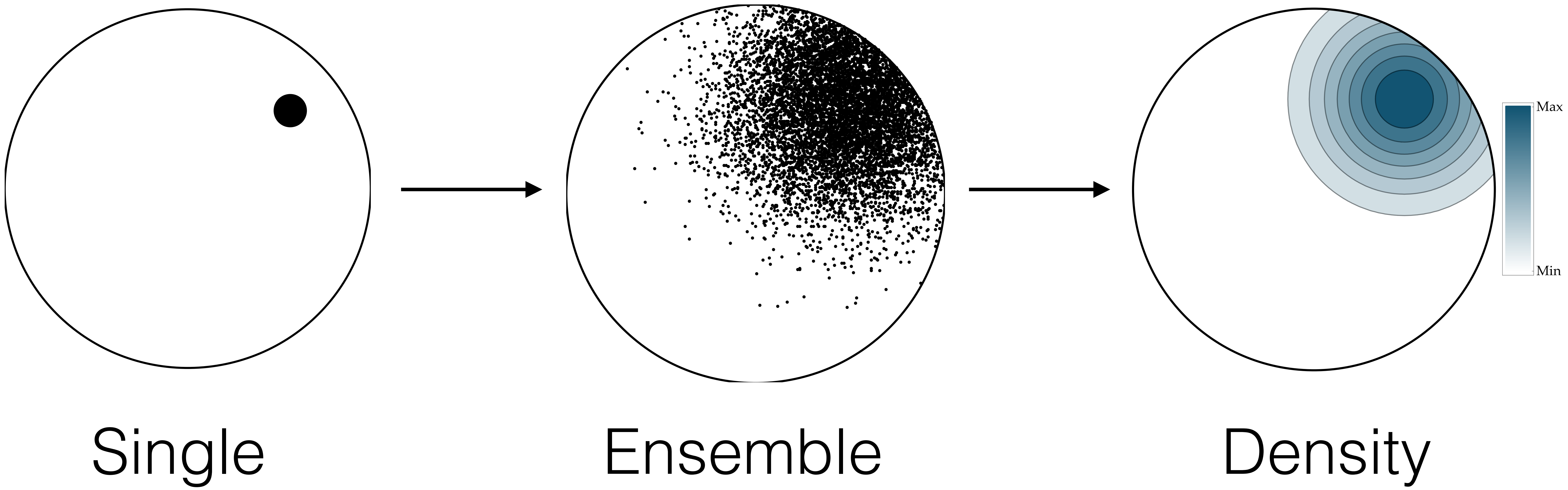
$$\mu(\mathbf{x})\ p(\mathbf{x}, \mathbf{y}; \tau) = \mu(\mathbf{y})\ p(\mathbf{y}, \mathbf{x}; \tau)$$

$$\mu(\mathbf{x}) = Z(\beta)^{-1} \exp\left(-\beta H(\mathbf{x})\right)$$

*At equilibrium the probability of jumping from any x to any y is the same as jumping from y to x.*

Prinz *et al.* (2011) JCP 134, 174105

# An illustration of the transition density



Single

Ensemble

Density

Figure courtesy of JH Prinz

# Assumptions about the full dynamics

## Markovian

$$\mathbb{P}(x_{t+\tau} \in A \mid x_{t_1}, \ldots, x_t = x) = \mathbb{P}(x_{t+\tau} \in A \mid x_t = x)$$

*Factorization of the dynamics into conditional probabilities*

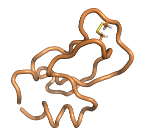
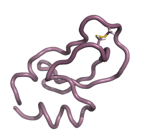
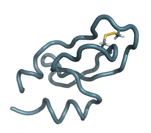
## Chapman-Kolmogorov property

$$p_{\tau_1+\tau_2}(x, A) = \int_\Omega p_{\tau_1}(x, y) p_{\tau_2}(y, A) \, \mathrm{d}y$$

Direct combination of conditional probabilities with different lag-times

Final state

Initial state

| | |  |  |  |
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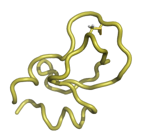
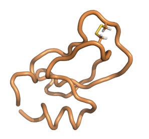
|  | 96% | 1% | 2% | 1% |
|  | 5% | 95% | 0% | 0% |
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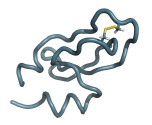
|  | 1% | 0% | 2% | 97% |

# Assumptions about the full dynamics

## Irreducibility

All states of the state space can be reached from any other state in a finite time.
**Ensures unique stationary distribution.**

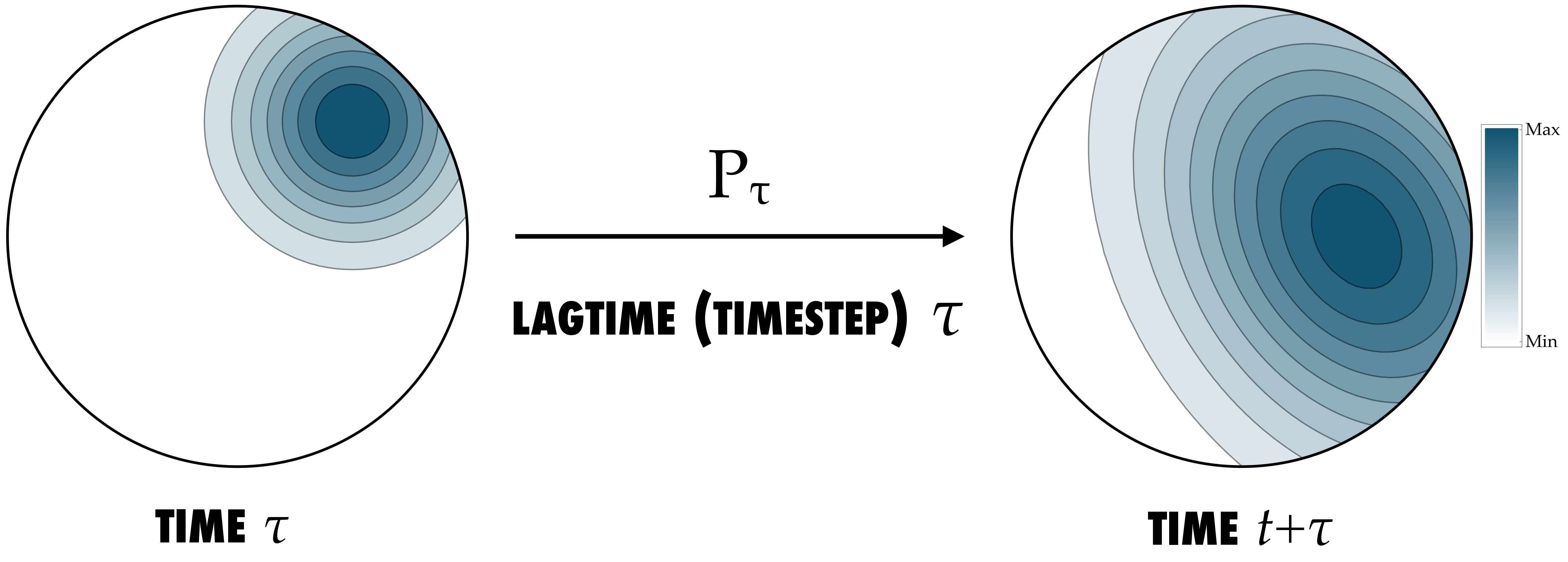
## Ergodicity

No states are disconnected
No cyclic dynamics.
**Ensures time and ensemble average properties are equal.**

## Reversibility

No net-probability flux at equilibrium. => no energy production/absorption => mass conservation.
Not strictly necessary for Markov models

# Ensemble view of dynamics

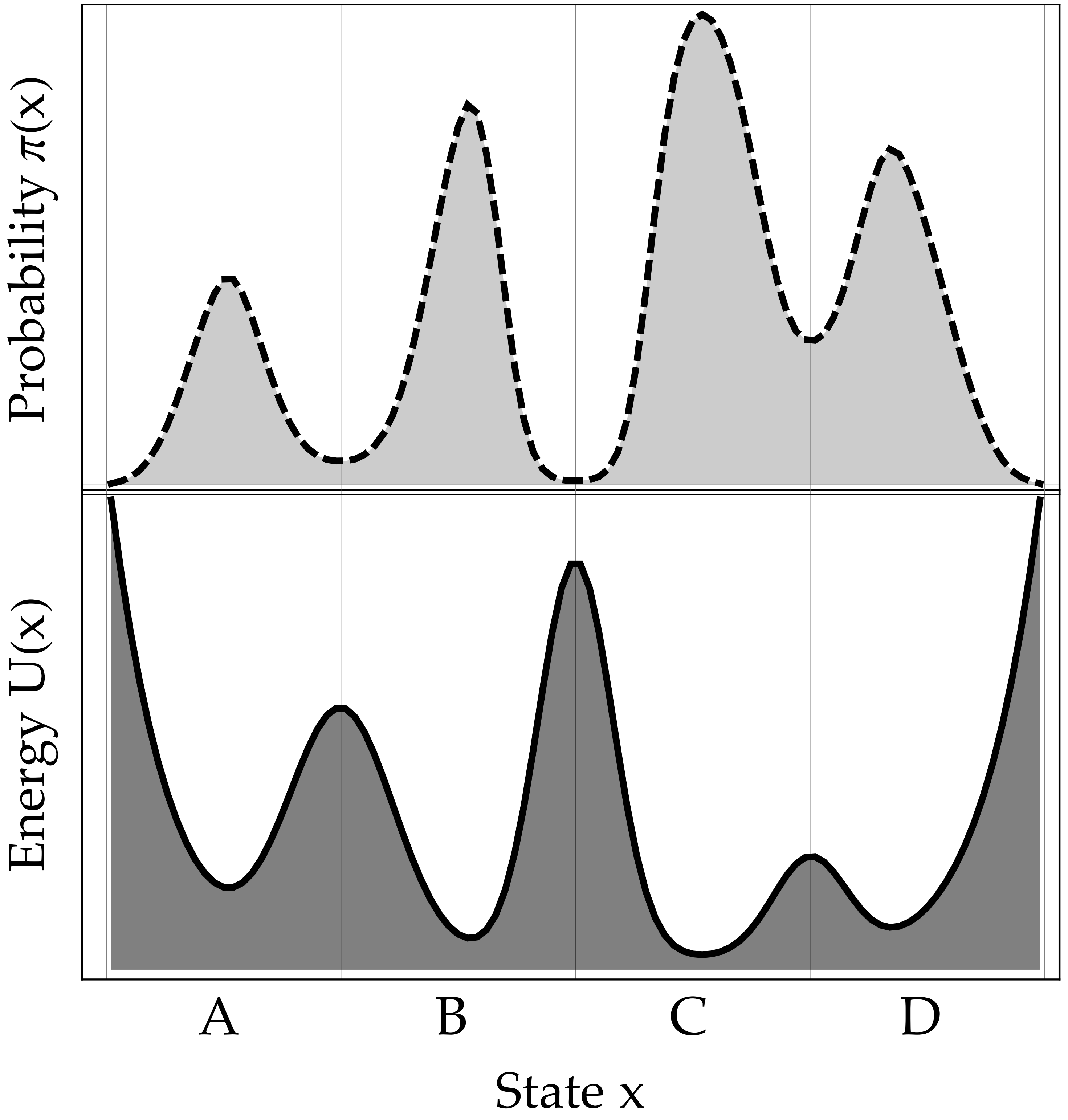


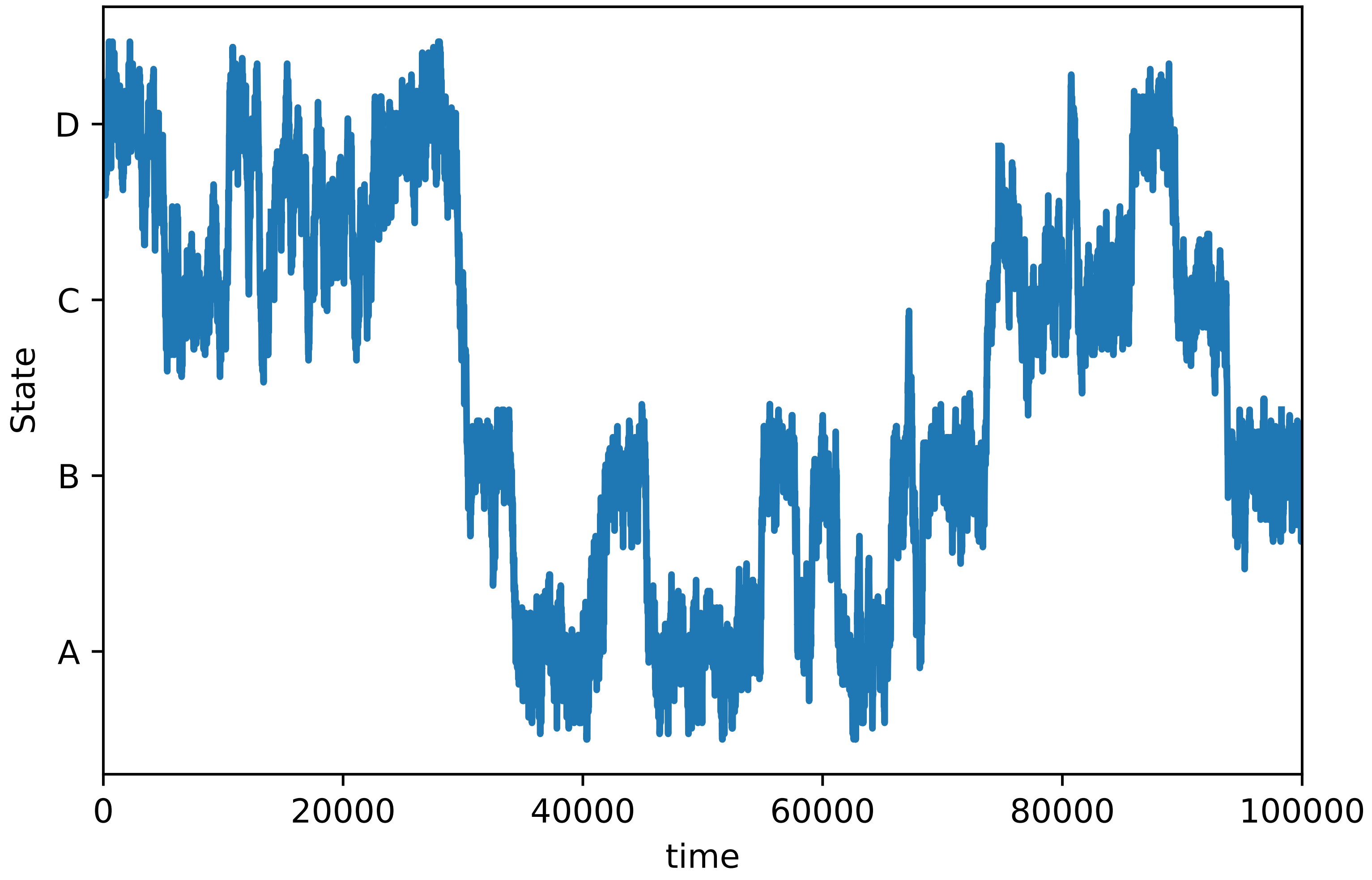
**A propagator is an operator which transports probability densities in time**

$$\mathrm{p}_{t+\tau}(x) = [\mathrm{P}_\tau\, \mathrm{p}_t](x) = \int_\Omega \mathrm{d}y\, \mathrm{p}_\tau(y,x)\mathrm{p}_t(y)$$

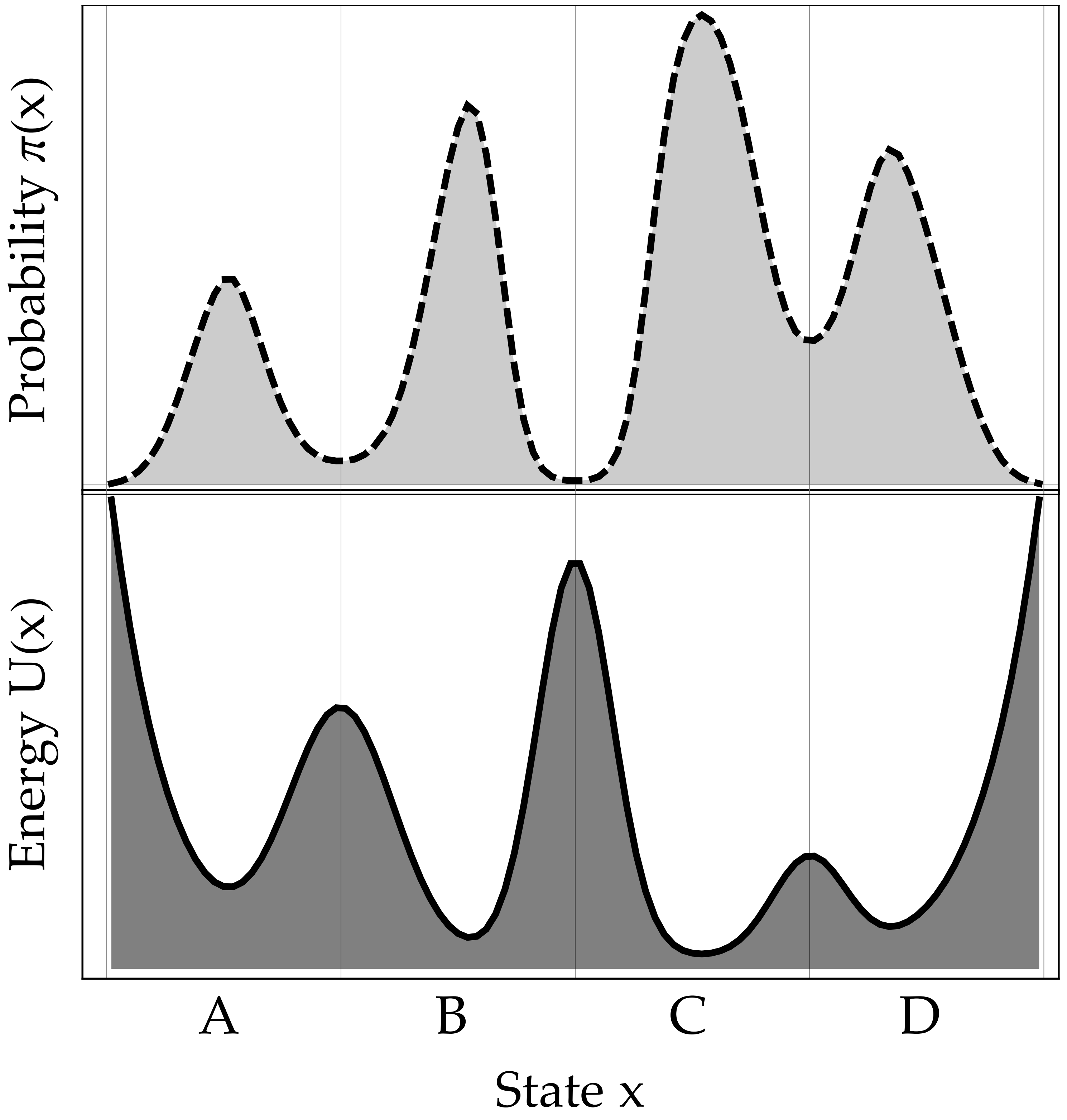
Figure courtesy of JH Prinz

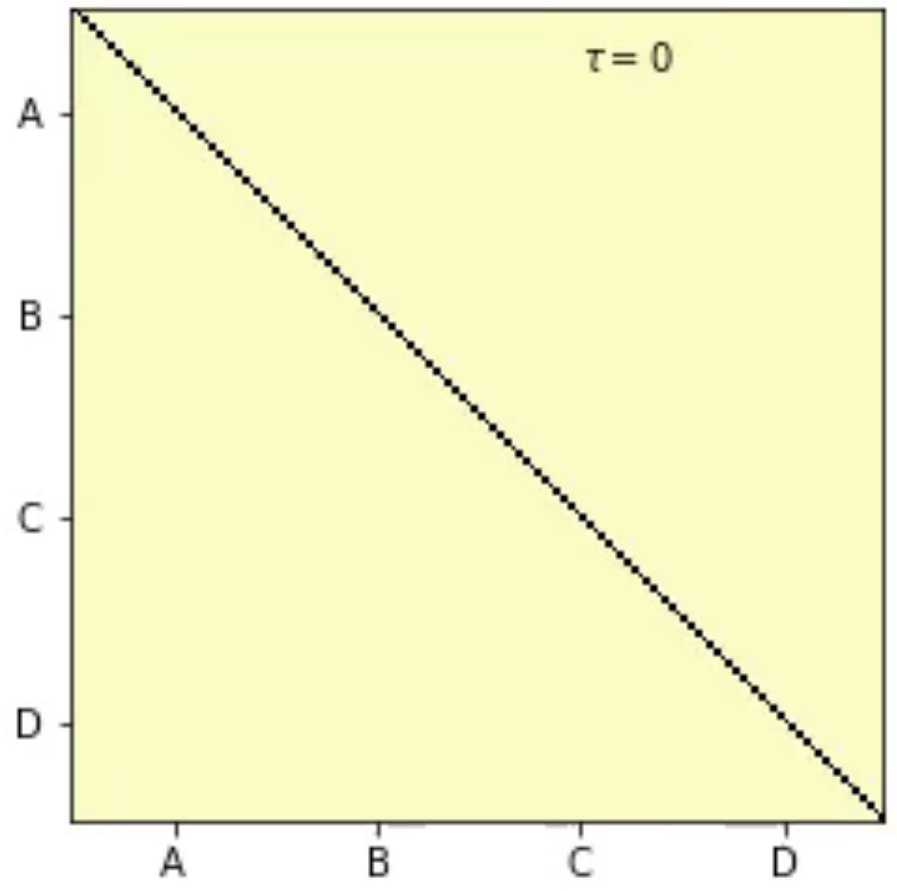
# Example dynamics





# Propagator depends on lag time





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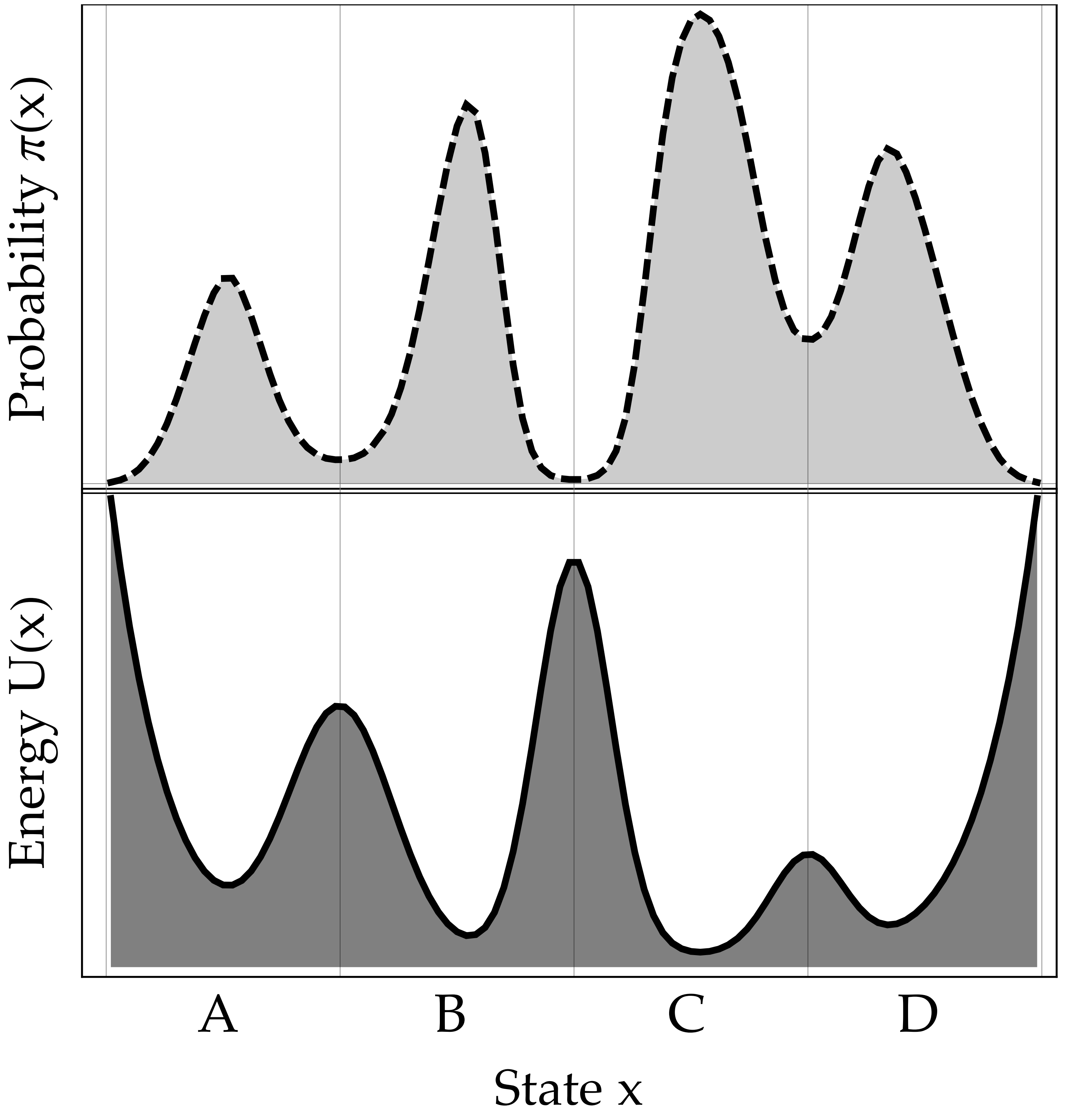

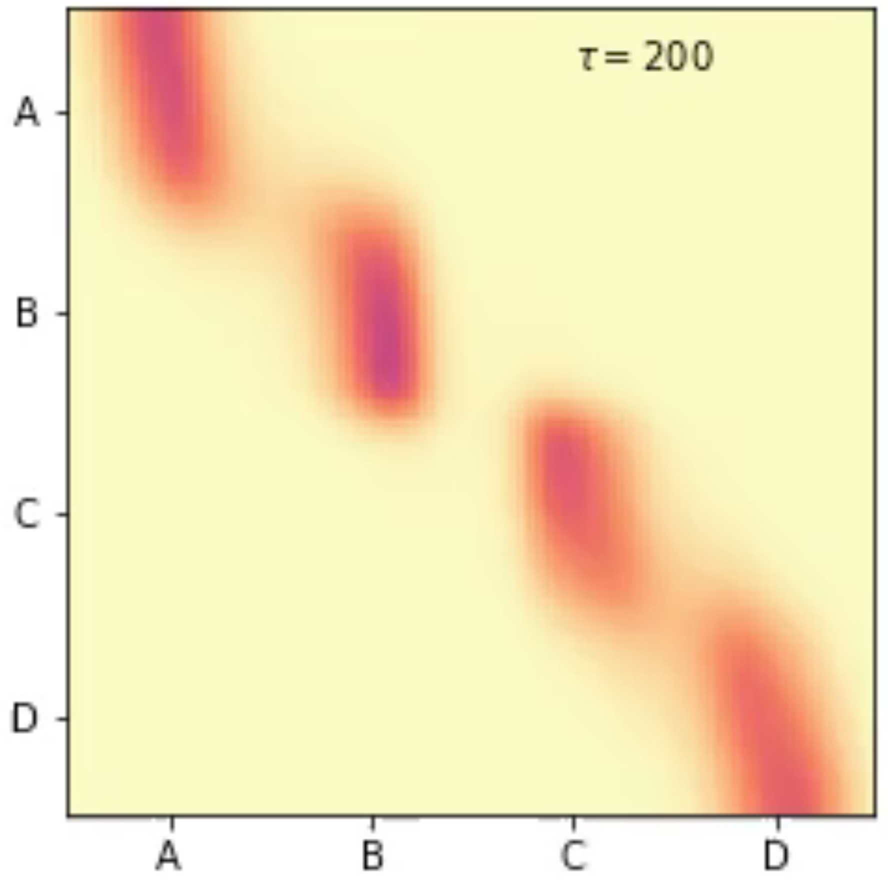

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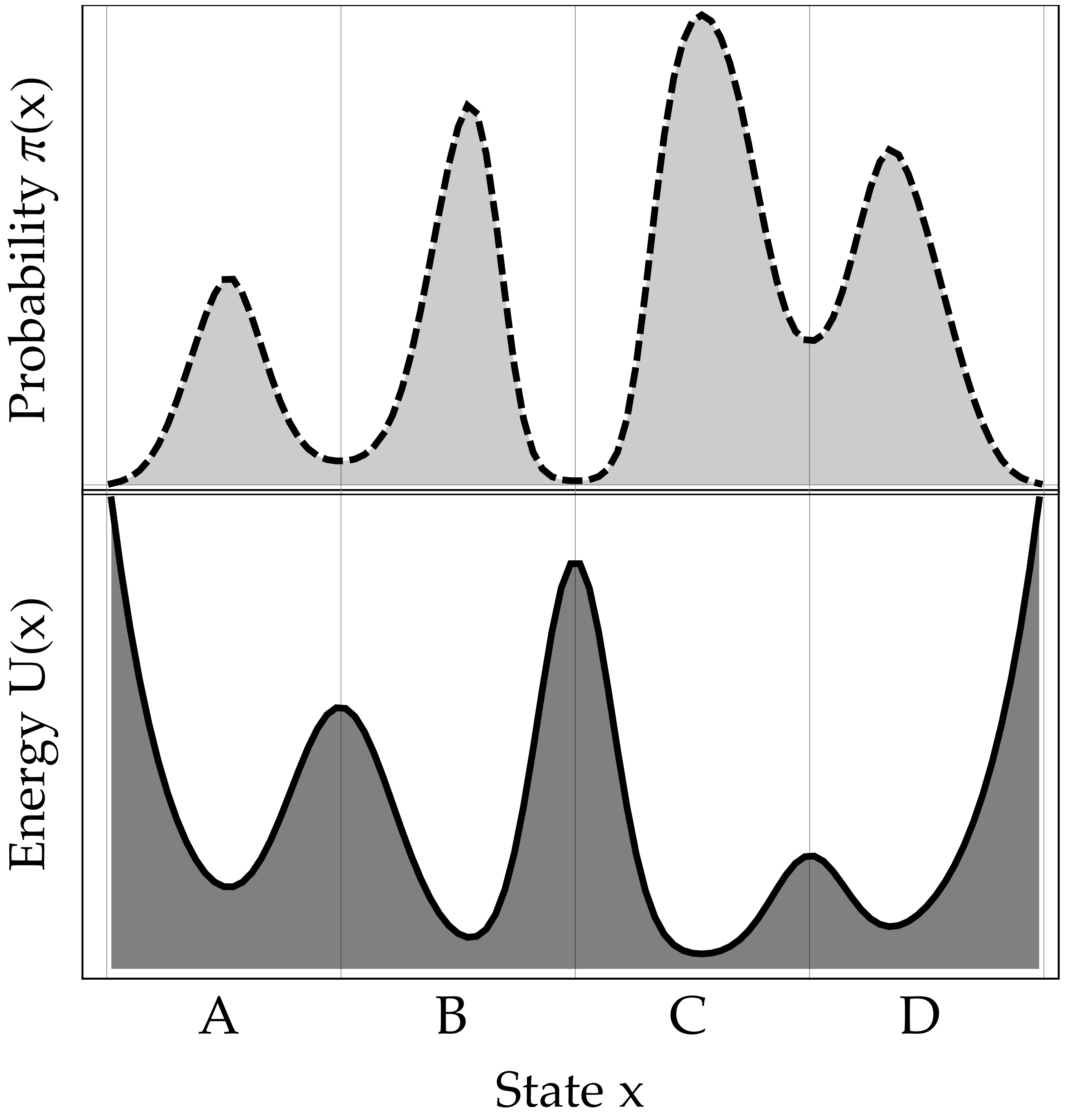
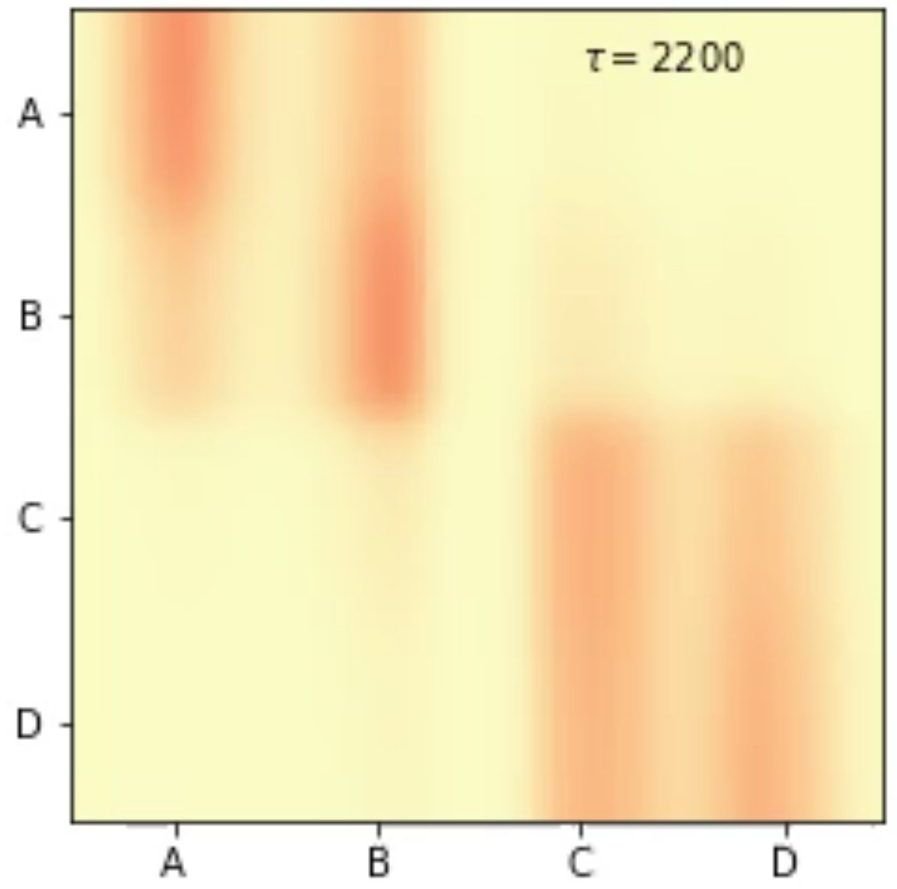




So why is this?

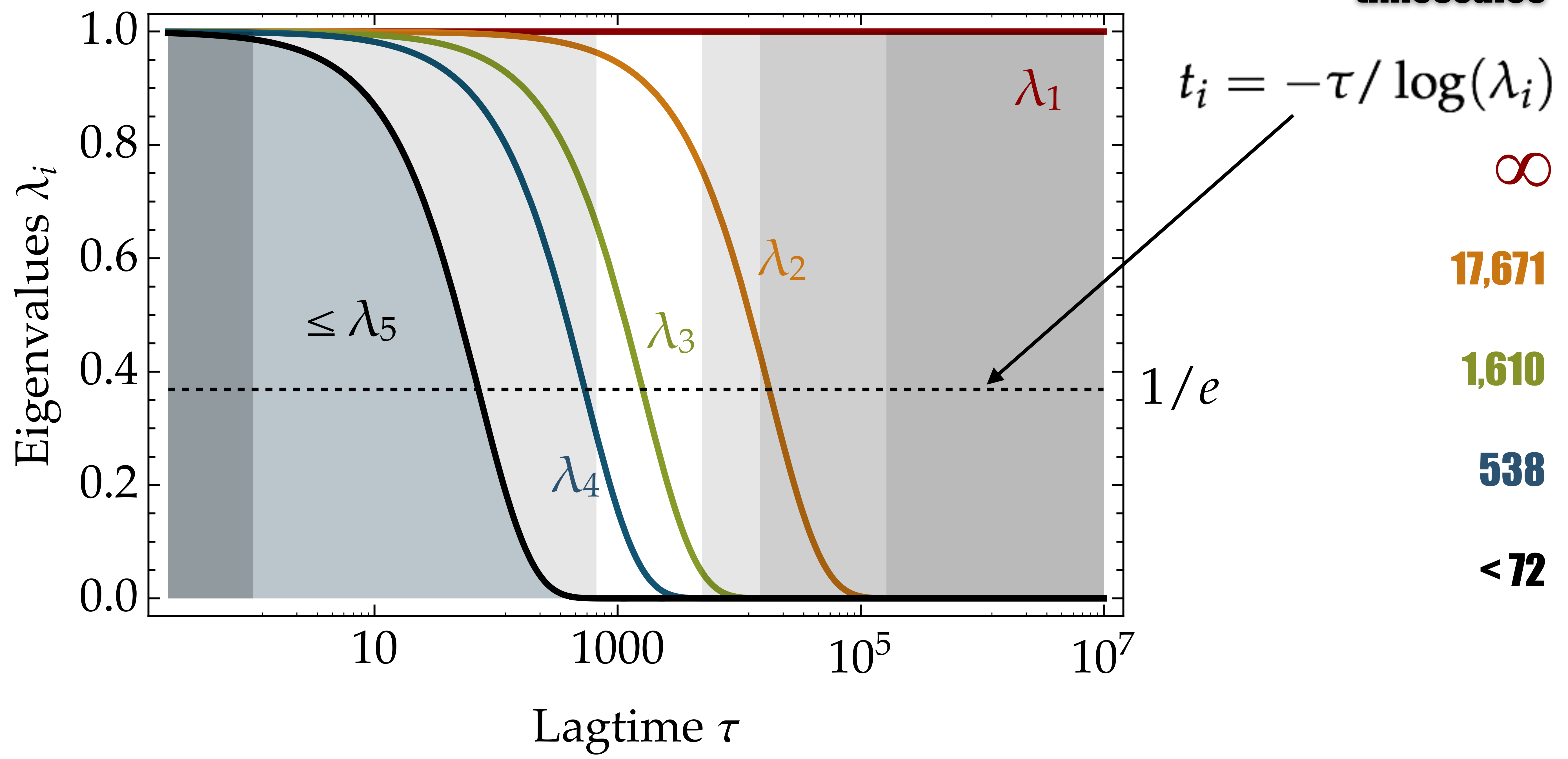
# Implied time-scales

**Eigenvalues of the propagator**

$$P_\tau \phi_i = \lambda_i \phi_i$$

**Chapman-Kolmogorov Implies exponential lag-time dependence**

$$\lambda_i(k \cdot \tau) = \lambda_i^k(\tau)$$



**timescales**

$\infty$

17,671

1,610

538

< 72

Figure courtesy of JH Prinz

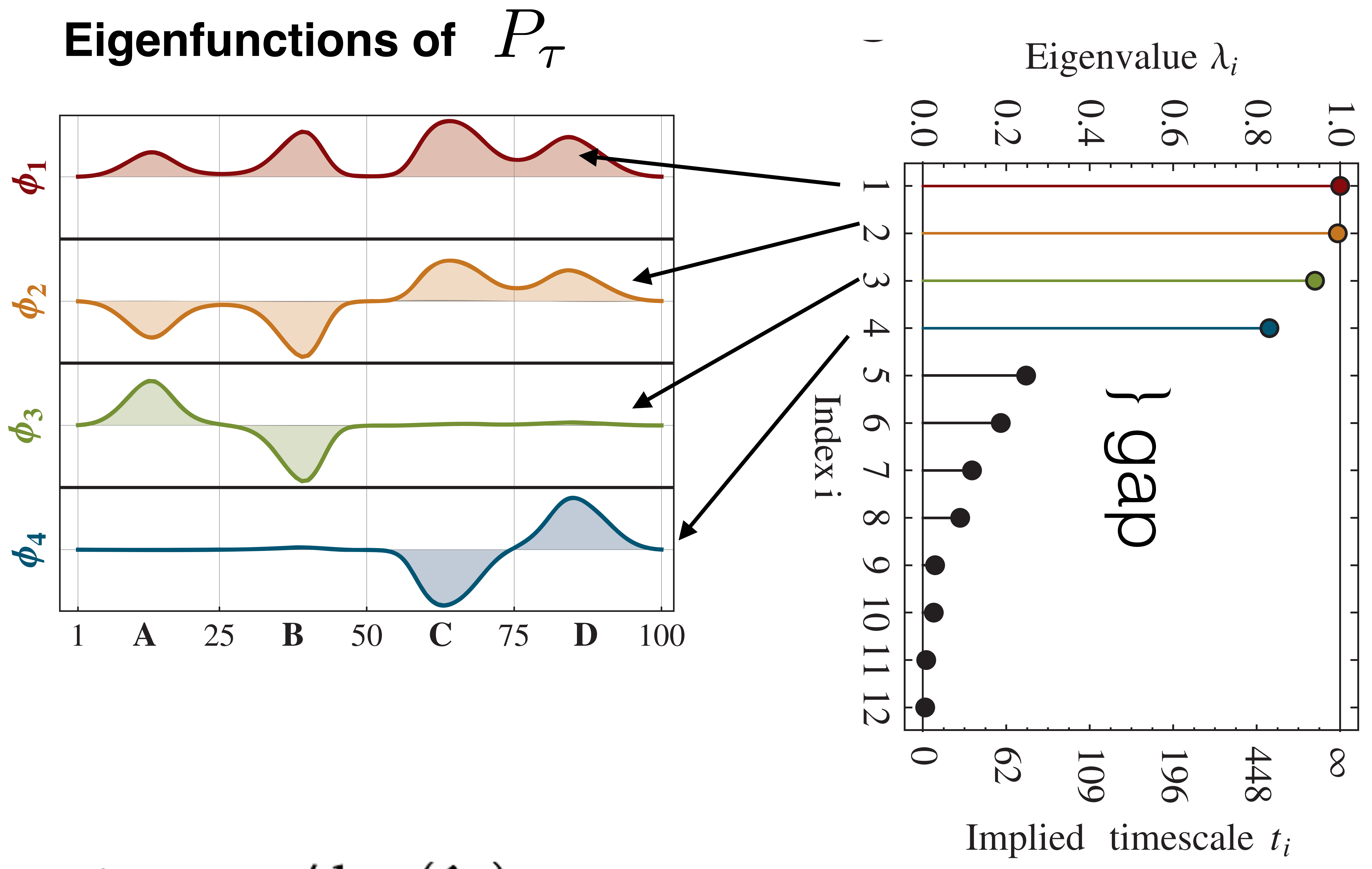
# Meta-stability

- We can approximate the propagator by a finite number of processes with non-zero Eigenvalues

- If we have a gap in the Eigenvalue spectrum, we can choose the lag-time in a manner such that we fulfill this assumption

- When we do this, processes faster than the lag-time ‘have decayed’ or ‘are not resolved’.

# What do you mean by processes?



Eigenfunctions of $P_\tau$

$$t_i = -\tau / \log(\lambda_i)$$

Prinz *et al.* (2011) JCP 134, 174105

# Estimation

# Discretization of $\Omega$

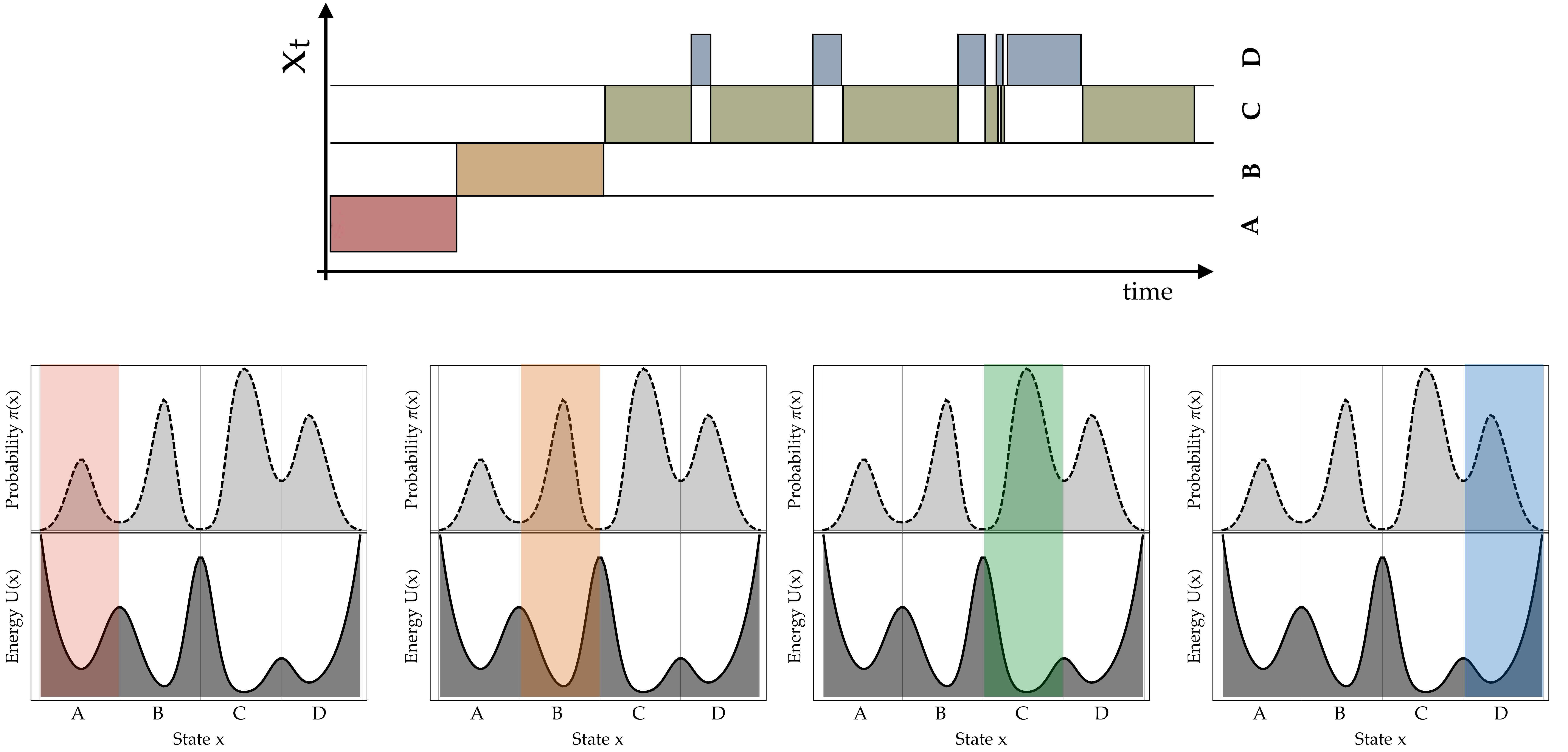
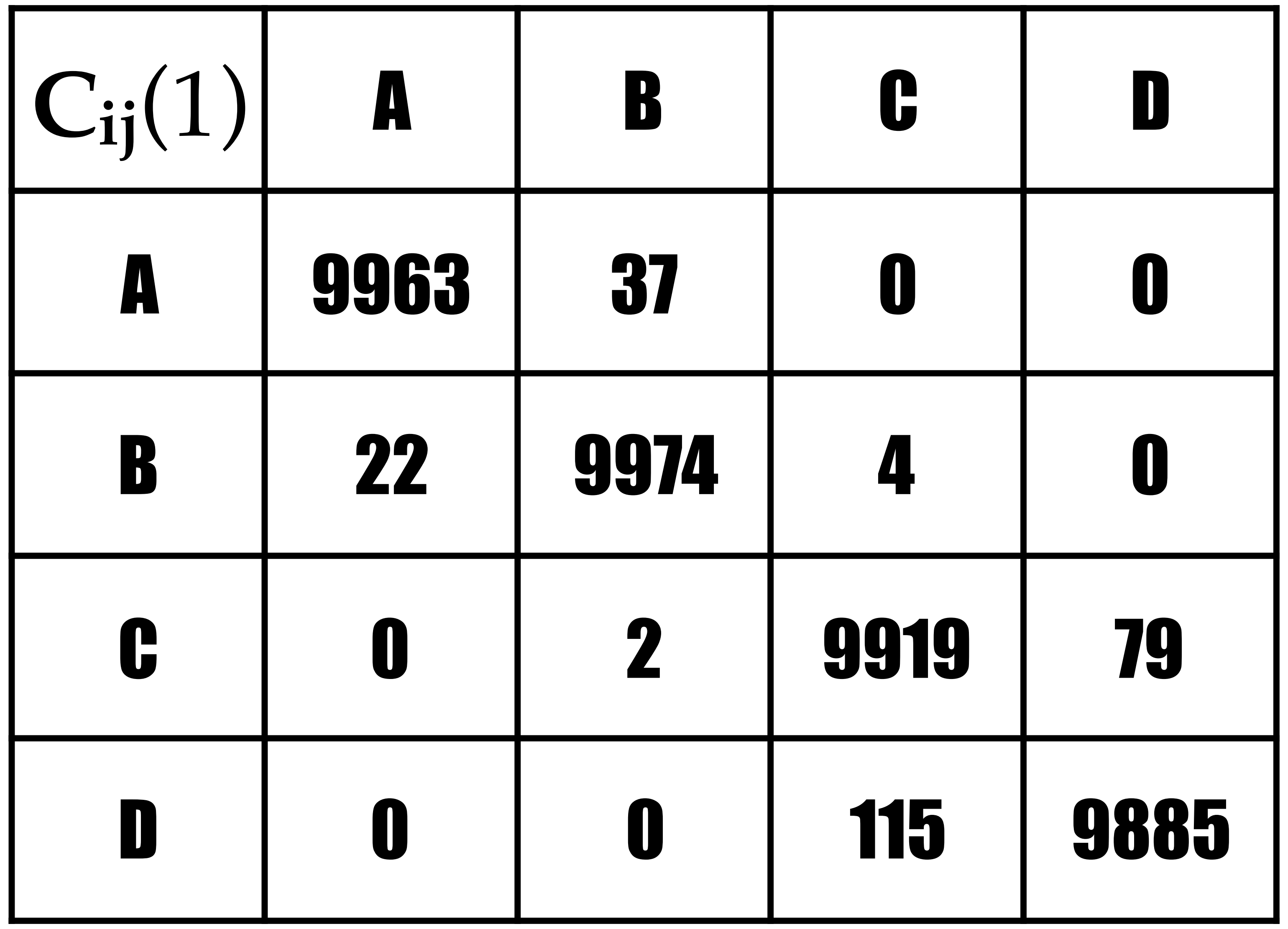


Figure courtesy of JH Prinz

# Count matrix



| $C_{ij}(1)$ | A | B | C | D |
|---|---|---|---|---|
| A | 9963 | 37 | 0 | 0 |
| B | 22 | 9974 | 4 | 0 |
| C | 0 | 2 | 9919 | 79 |
| D | 0 | 0 | 115 | 9885 |

$$C_{ij}(\tau) = \sum_{n=\tau}^{T} \delta(x_{n-\tau} = i, x_n = j)$$

Figure courtesy of JH Prinz

# Maximum likelihood estimator

We can express the probability of the observed data - discrete trajectory - given a transition probability matrix of an MSM

$$\begin{aligned}\mathbb{P}(x_1, \ldots, x_t \mid P) &= \prod_{k=1}^{L} p_{x_{k-1},x_k} \\ &= p_{x_0,x_1} \cdot \ldots \cdot p_{x_L - 1, L} \\ &= \prod_{ij} p_{ij}^{c_{ij}} \\ &= p_{11}^{c_{11}} \cdot \ldots\end{aligned}$$

The aim is then to find the *P* which maximizes this expression - That is, the *Maximum likelihood estimator.*

# Analytical solution for Non-reversible case

- We enforce the constraint that the transition probability matrix is row-stochastic:

$$\sum_j p_{ij} = 1, \quad \forall i$$

- One can show the estimator is simply:

$$\hat{p}_{ij} \ = \frac{\hat{C}_{ij}}{\sum_j \hat{C}_{ij}}$$

Prinz *et al.* (2011) JCP 134, 174105

# Reversible estimator

- Enforces the detailed balance condition.
- No exact analytical solution:
  - Fixed-point iteration algorithm available.
  - Approximate solutions.
- Implemented in deeptime

# Bayesian inference of MSMs

- The less simulation data we have, the more ambiguous the solution of the likelihood problem will be.
- Consequently, if we limit ourselves to the MLE, we are *ignorant* as to how **robust** our inferred MSM is.
- One way to quantify the uncertainty of MSMs is through **Bayesian inference**

# Bayesian inference of MSMs

Likelihood from before

$$\mathbb{P}(x_i, \ldots, x_t \mid P) = p(C \mid P) \propto \prod_{i,j=1}^{n} p_{ij}^{c_{ij}}$$

# Bayesian inference of MSMs

Likelihood from before

$$\mathbb{P}(x_i, \ldots, x_t \mid P) = p(C \mid P) \propto \prod_{i,j=1}^{n} p_{ij}^{c_{ij}}$$

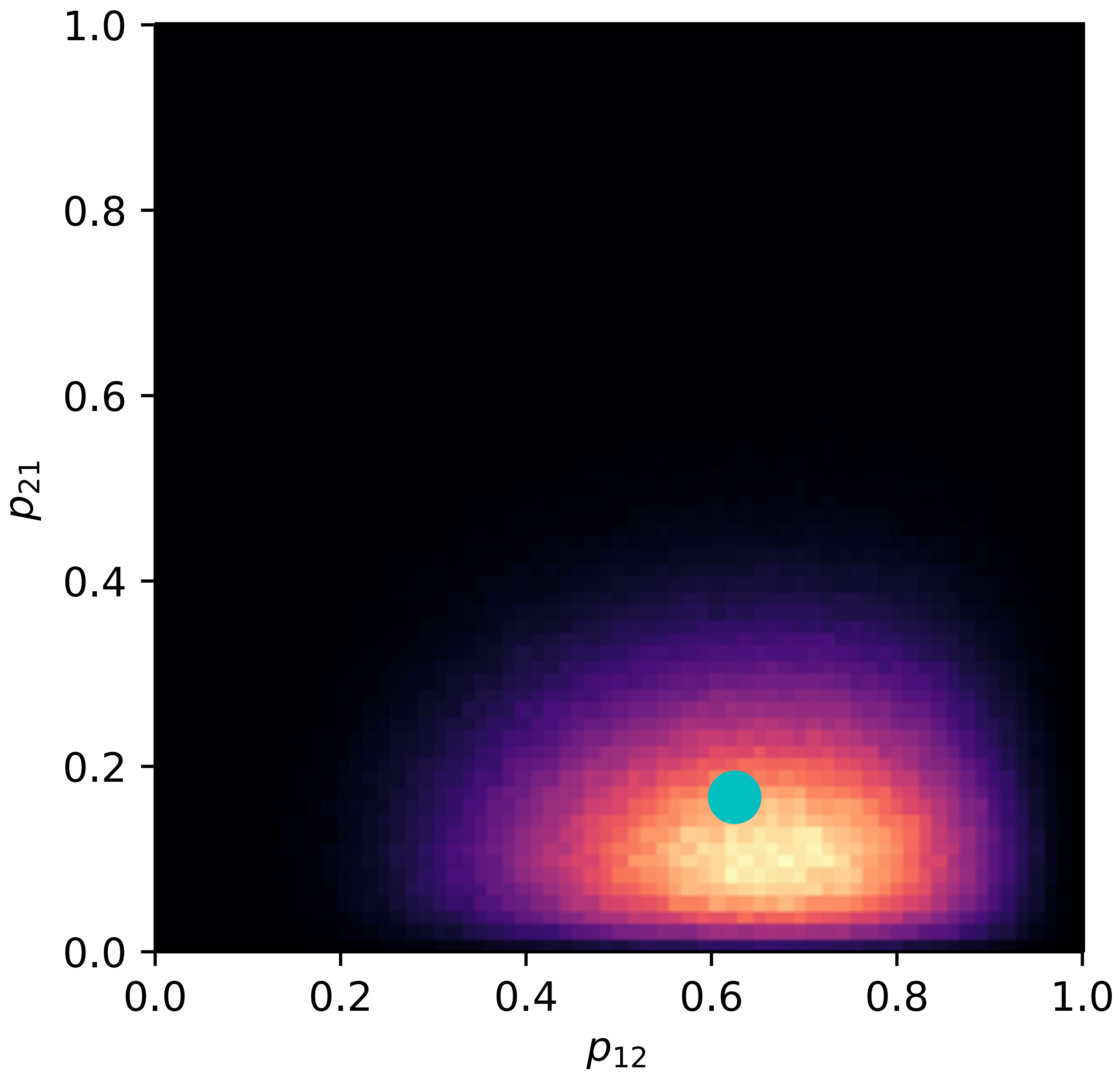
Introduction of prior information

$$p(P \mid C) \propto p(C \mid P) p(P)$$

**The prior can encode useful constraints: row-stochasticity, reversibility, fixed stationary distribution, sparsity etc**

# Bayesian inference of MSMs

Inference is done by MCMC sampling



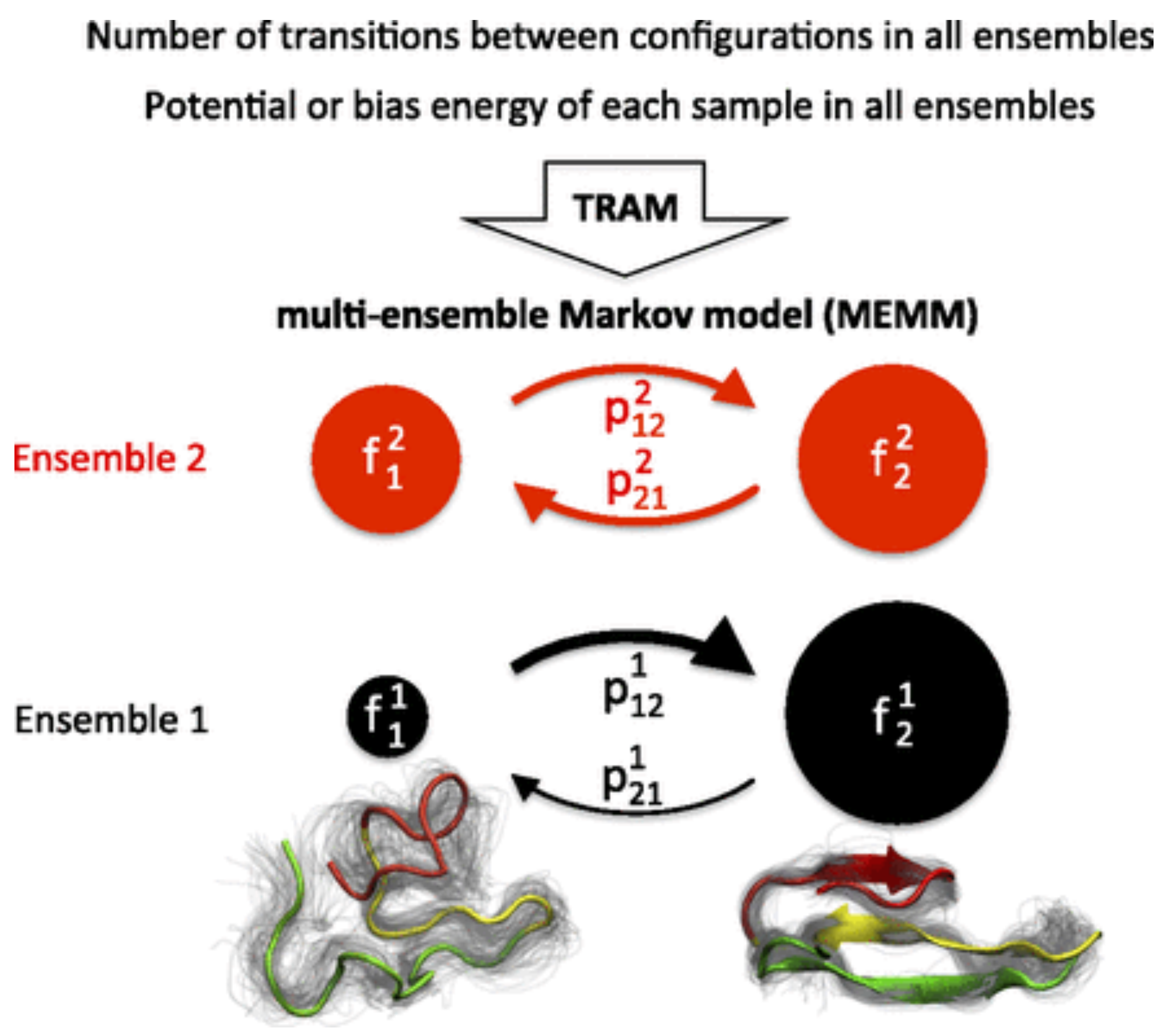
Noé (2008) JCP 128, 244103
Trendelkamp-Schroer & Noé (2013) JCP 138, 164113

# Alternative estimators

# Transition(-based) Reweighting Analysis Method

- Allows taking into account simulation data from multiple thermodynamic ensembles.

- That means, we can **use data from enhanced sampling simulations together with unbiased simulation data to generate models more efficiently.**



Number of transitions between configurations in all ensembles

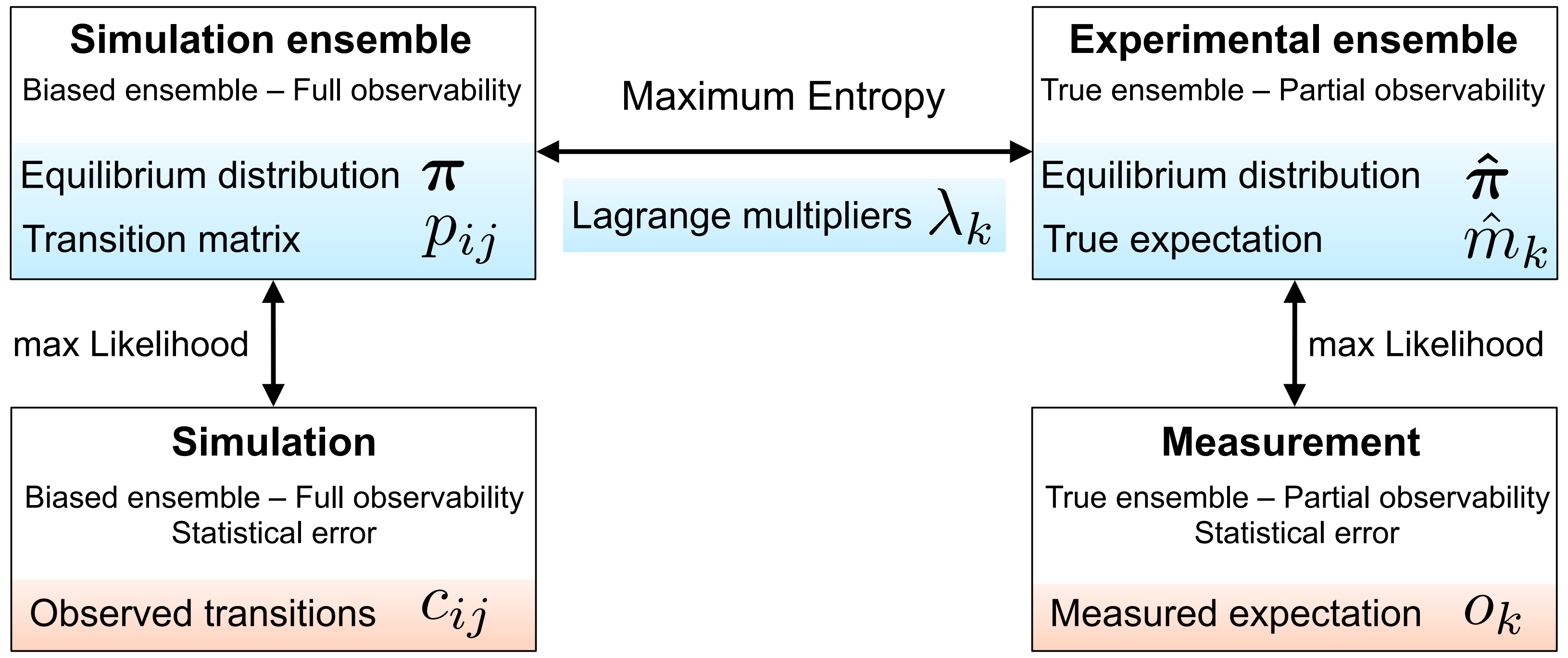
Potential or bias energy of each sample in all ensembles

Wu et al. *PNAS* 2016, 113(23), E3221–E3230

Implemented in PyEMMA

# Augmented Markov models

- Enables integration of external information into the estimation of Markov state models.
- Fx use of experimental constraints from biophysical experiments such as NMR.
- A notebook tutorial distributed with PyEMMA 2.5 and up.


Simulation ensemble
Biased ensemble – Full observability
Equilibrium distribution $\boldsymbol{\pi}$
Transition matrix $p_{ij}$
Maximum Entropy
Lagrange multipliers $\lambda_k$
Experimental ensemble
True ensemble – Partial observability
Equilibrium distribution $\hat{\boldsymbol{\pi}}$
True expectation $\hat{m}_k$
max Likelihood
max Likelihood
Simulation
Biased ensemble – Full observability
Statistical error
Observed transitions $c_{ij}$
Measurement
True ensemble – Partial observability
Statistical error
Measured expectation $o_k$

Olsson et al. *PNAS* 2017, 114(31), pp. 8265-8270. doi: 10.1073/pnas.1704803114

**Implemented in Deeptime**

# Analysis of our estimate

| $P_{ij}(1)$ | A | B | C | D |
|---|---|---|---|---|
| A | 0,9963 | 0,0037 | | |
| B | 0,0022 | 0,9974 | 0,0004 | |
| C | | 0,0002 | 0,9919 | 0,0079 |
| D | | | 0,0115 | 0,9885 |

| projected timescales | original timescales |
|---|---|
| $\infty$ | $\infty$ |
| 2,746 | 17,671 |
| 165 | 1,610 |
| 51 | 538 |

***Time-scales are always under-estimated***

Figure courtesy of JH Prinz

# Increasing the lag-time

**COUNT MATRIX**

| $C_{ij}(100)$ | A | B | C | D |
|---|---|---|---|---|
| A | 9533 | 477 | 40 | 0 |
| B | 1644 | 8014 | 262 | 80 |
| C | 0 | 40 | 9025 | 935 |
| D | 0 | 0 | 1366 | 8634 |

| projected timescales | original timescales |
|---|---|
| $\infty$ | $\infty$ |
| 15,397 | 17,671 |
| 1211 | 1,610 |
| 379 | 538 |

May improve estimates of predicted time-scales

Figure courtesy of JH Prinz

# Projection/discretization error

$$t_i = -\tau / \log(\lambda_i)$$

metastable region

**GOOD PROJECTION**

Figure courtesy of JH Prinz

# Projection/discretization error

metastable region

$$t_i = -\tau / \log(\lambda_i)$$

BAD PROJECTION

Figure courtesy of JH Prinz

# Known problems

- Observations (projections, discretizations) are in many cases <u>not Markovian</u>

- However, we are often interested in understanding the full system not just the observation.

- Since we often have a lot of freedom to choose the projections and discretization, it is important to chose one which is as Markovian as possible.

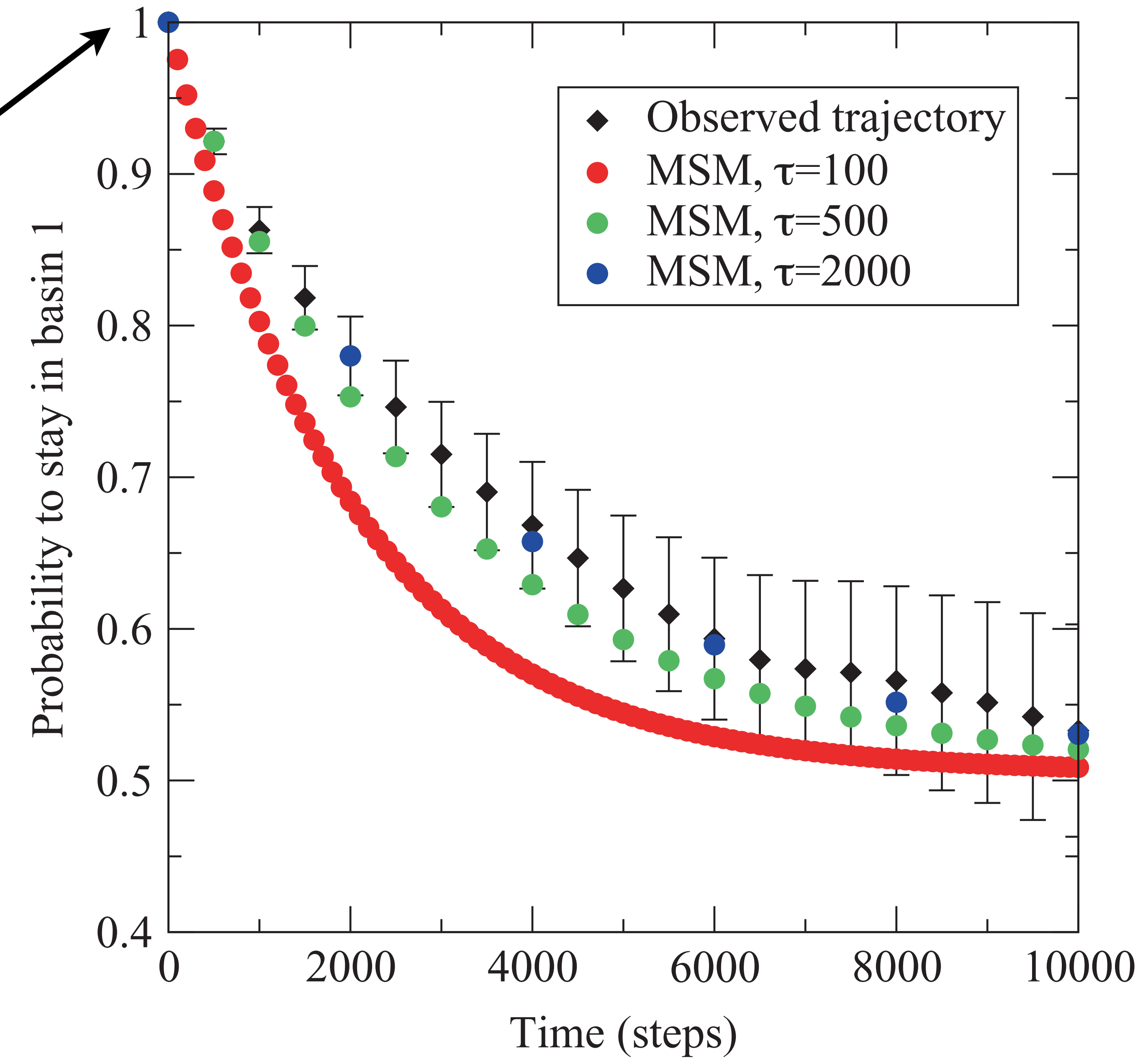
# Validation

# Chapman-Kolmogorov test

Compare the evolution of the data with the model

$$\underbrace{T^k(\tau)}_{\text{Markov model prediction}} \approx \underbrace{T(k\tau)}_{\text{estimation from data}}$$

assume
any initial distribution



# General scheme for Markov state model generation

- Discretize a suitable projection of your data.
- Construct a transition matrix.
- Estimate the number of meta-stable states (time-scale gap)
- Perform Chapman-Kolmogorov test.

# Analysis

Useful predictions from a MSM

# Common properties

- Relaxation time-scales
- Dominant processes
- Stationary distribution (thermodynamics)
- Meta-stable sets (more about this later)
- Correlation functions (spectroscopic observables)
- Mean first passage times
- Path probabilities

# Summary

- Markov state models are derived coarse-grained models of the full original (Markovian) dynamics .
- MSMs may be parameterized (estimated/learned) from simulation data to compute properties of interest.
- MSMs are particularly useful if the projection/ discretization error can be minimized: then the predicted quantities match the original.

Questions?