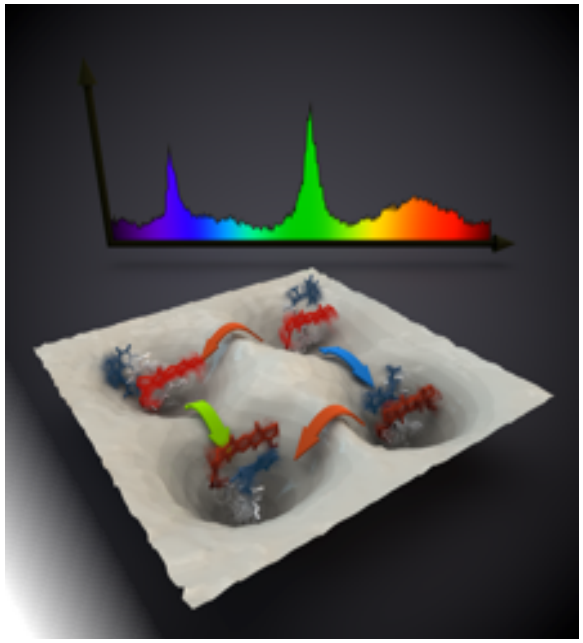
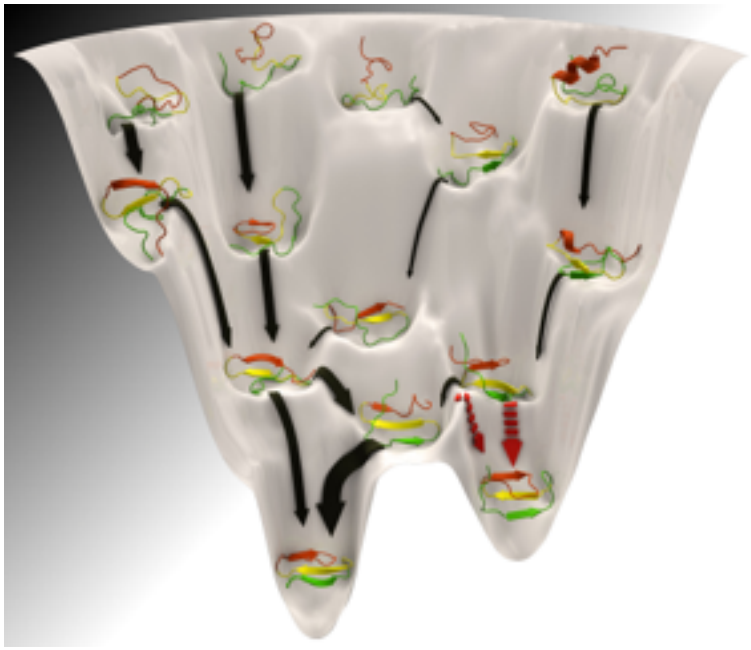
Finding slow modes and accessing very long timescales in molecular dynamics





Frank Noé (FU Berlin)
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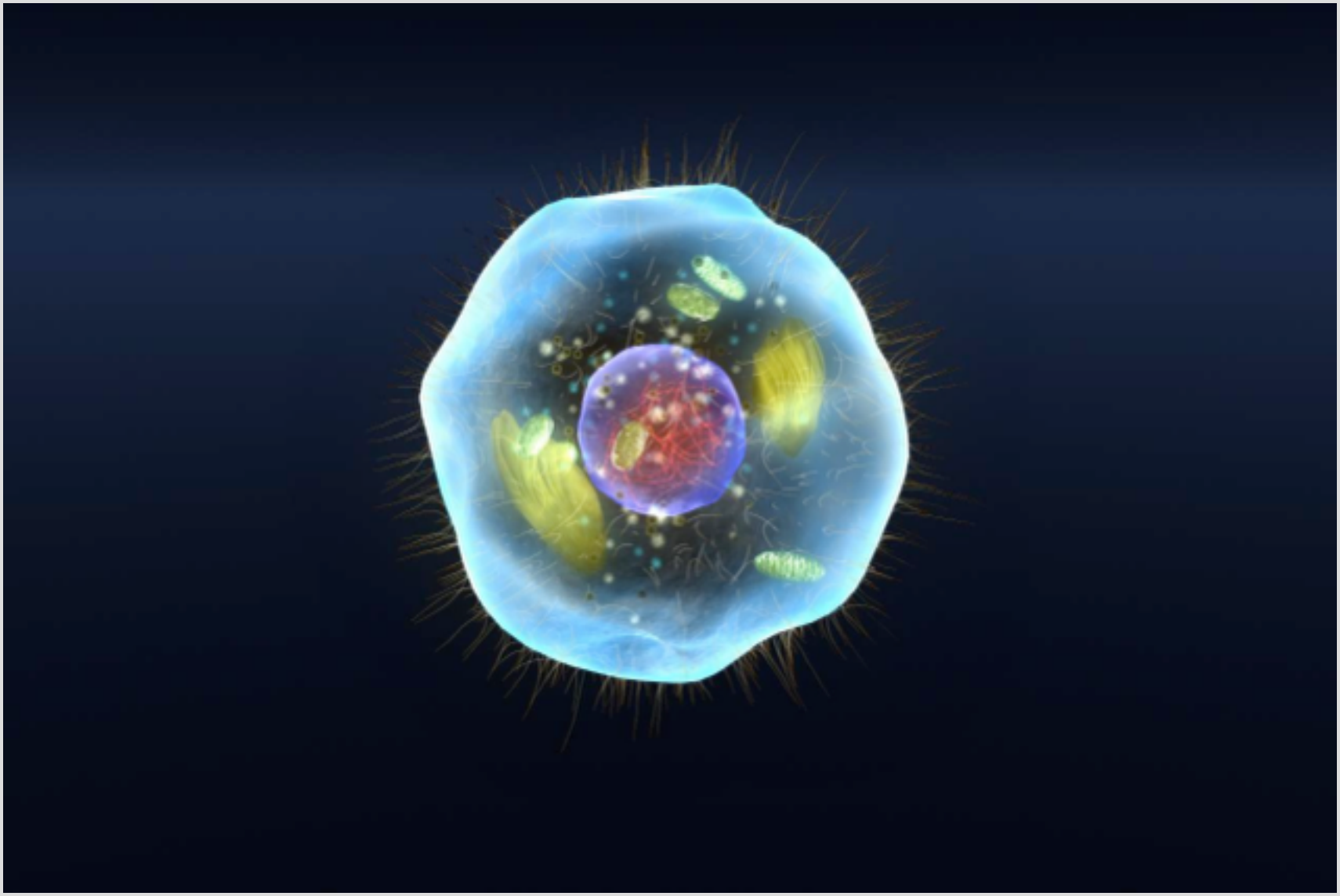
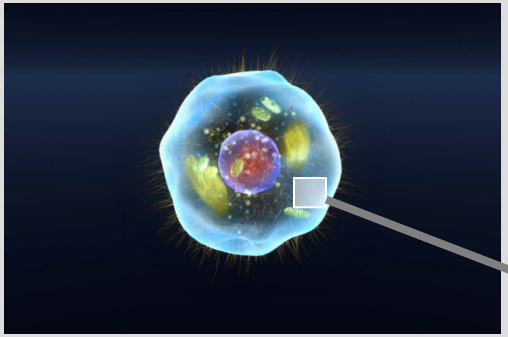
Computational Molecular Biology

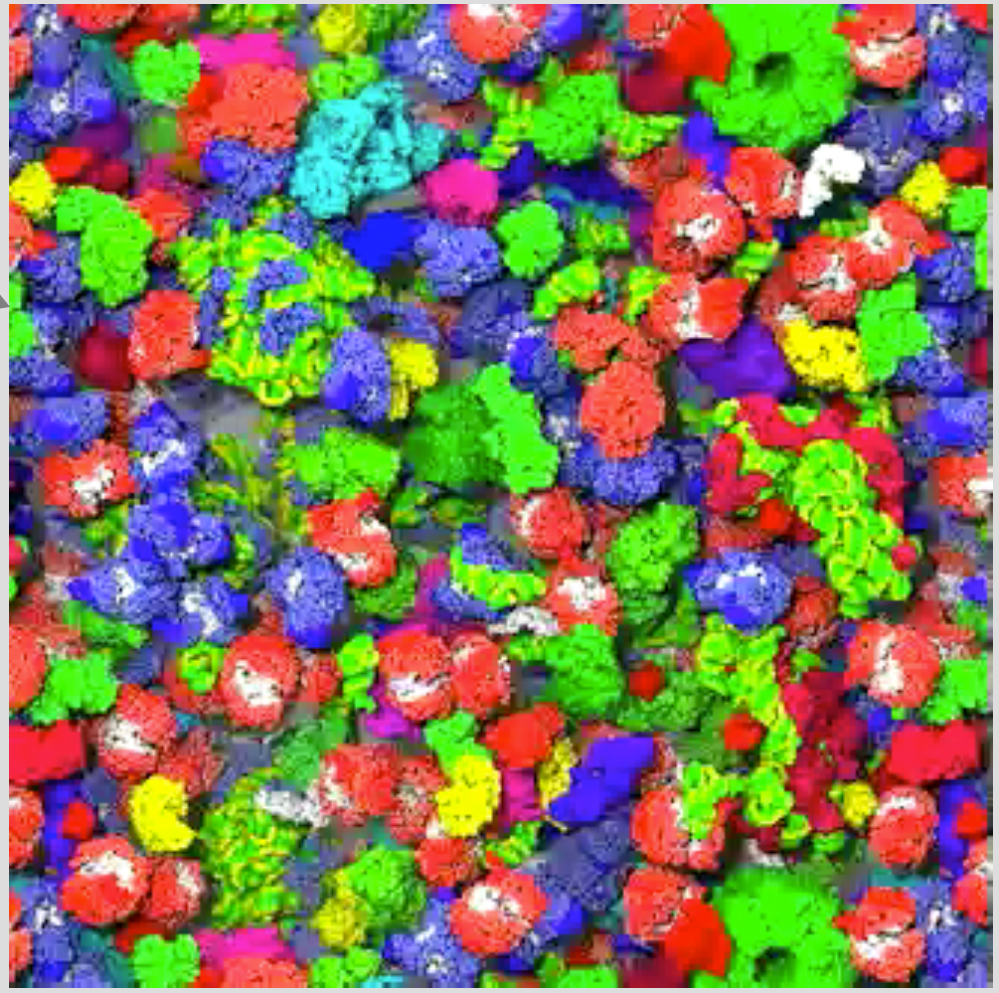
Freie Universität Berlin

Cell



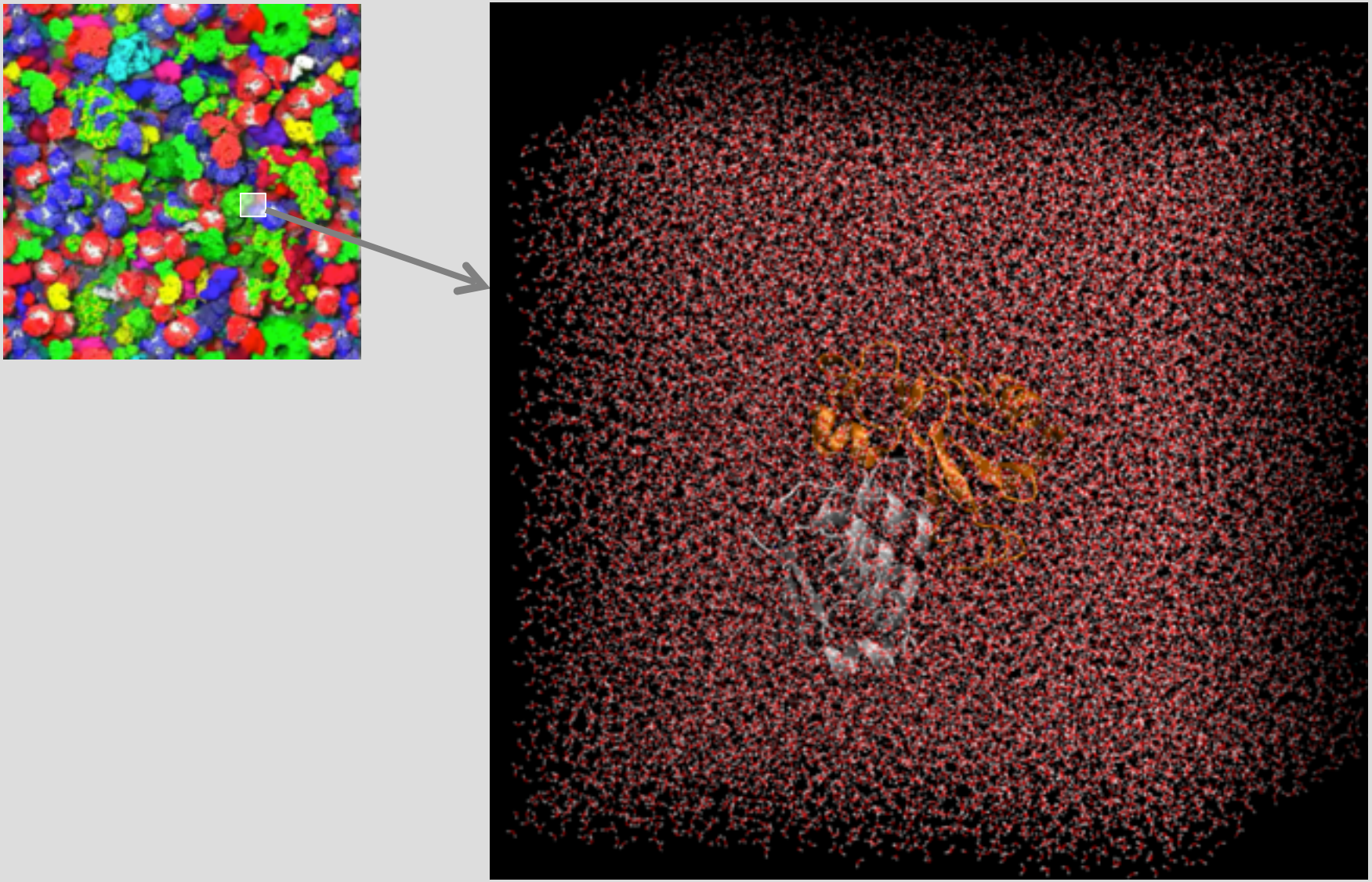
Proteins



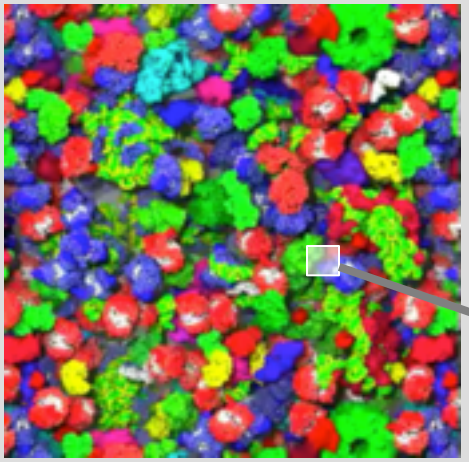


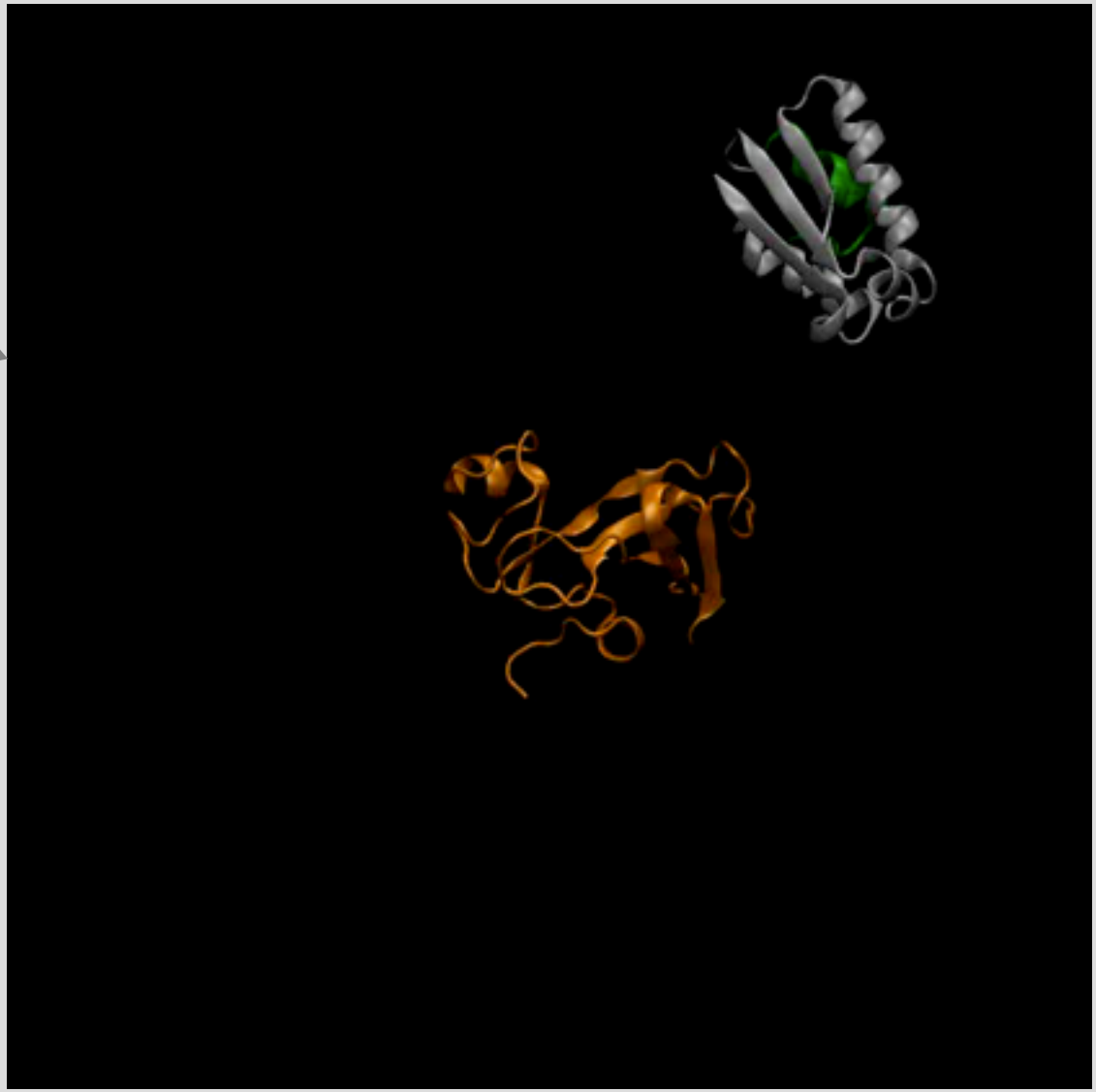
McGufee and Elcock, PloS Comput Biol 2010

Protein-Protein binding



Protein-Protein binding





Plattner, Doerr, De Fabritiis, Noé

0.1 microseconds

Part I

Direct approximation of slow modes / processes

Noé and Nüske, **Mult. Modeling Simul.** 11, 635-655 (2013) / also: **arXiv** (2012)

Nüske, Keller, Pérez-Hernandez, Mey, Noé, **JCTC** 10, 1739-1752 (2014)

Dynamical operators

Propagator

$$\rho_{t+\tau} = \mathcal{P}_\tau \rho_t = \int p_\tau(y \mid x)\, \rho_t(x)\, \mathrm{d}x$$

Transfer operator / Perron-Frobenius operator

= propagator for densities $u(x) = \frac{\rho(x)}{\pi(x)}$ with stationary density $\pi(x)$.

$$u_{t+\tau} = \mathcal{T}_\tau u_t = \int \frac{\pi(x)}{\pi(y)} p_\tau(y \mid x)\, \rho_t(x)\, \mathrm{d}x$$

Koopman operator

Adjoint to $\mathcal{P}$, adjoint to $\mathcal{T}$ with respect to π

$$f_{t+\tau} = \mathcal{K}_\tau f_t = \int p_\tau(y \mid x)\, f_t(y)\, \mathrm{d}y = \mathbb{E}[f_{t+\tau}(x)]$$

with detailed balance: $\pi(x)p_\tau(y \mid x) = \pi(y)p_\tau(x \mid y)$ we have $\mathcal{K}_\tau \equiv \mathcal{T}_\tau$

See: Mesic **Nonlinear Dyn.** 41, 309 (2005).

Slow processes

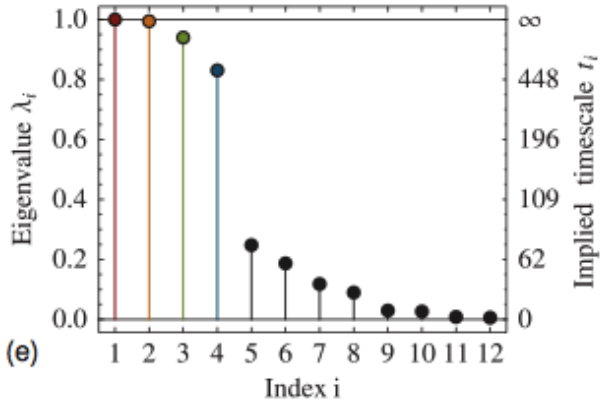
Backward propagator

$$\rho_\tau = \mathcal{T}(\tau)\rho_0$$

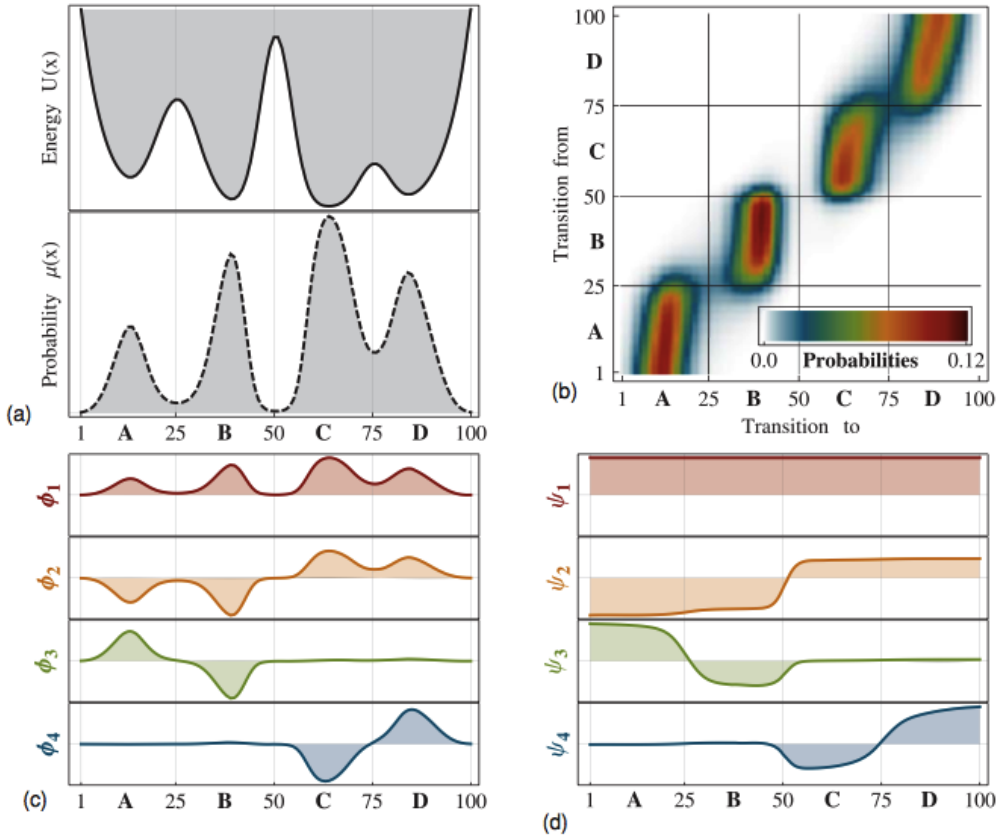
Spectral decomposition

$$\rho_\tau = \sum_{i=1}^{\infty} \mathrm{e}^{-\tau\kappa_i} \langle \psi_i \mid \rho_0 \rangle \psi_i$$

Eigenvalues / timescales κ_i^{-1}



Processes:



Schütte et al: **J. Comput. Phys.** (1999), Prinz et al.: **J. Chem. Phys.** 134, p174105 (2011)

Collective variables: Slow modes versus reaction coordinates

Identify the slowest processes

$$\rho_\tau = \sum_{i=1}^{\infty} \mathrm{e}^{-\tau\kappa_i} \langle \psi_i \mid \rho_0 \rangle \psi_i$$

Approximate Markov operator **eigenfunctions**

Identify the “best” / “slowest” coordinate connecting A and B

$$\begin{aligned} \tau_A, \tau_B & \quad \text{time to hit } A,\ B \text{ next} \\ q_{AB}(\mathbf{x}) & = \mathrm{Prob}(\tau_B < \tau_A) \end{aligned}$$

Approximate **committor**

Eigenfunctions and committor are closely related when considering reactions between metastable states

Schütte, Noé, Lu, Sarich, Vanden-Eijnden JCP 134, 204105

Molecular order parameters

Candidates x_1…x_n

- Cartesian coordinates
- Distances between heavy atoms or Ca's
- cos/sin of dihedrals
- Gaussian densities around sampled configurations (e.g. in RMSD space)
- Field variables or coordination numbers
- Your favorite order parameter
- All of them

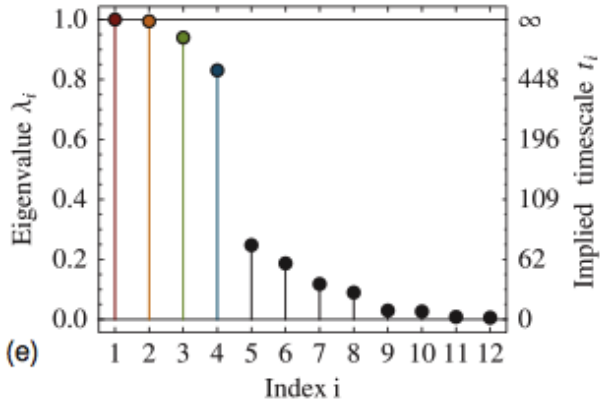
Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Slow processes

Backward propagator

$$\rho_\tau = \mathcal{T}(\tau)\rho_0$$

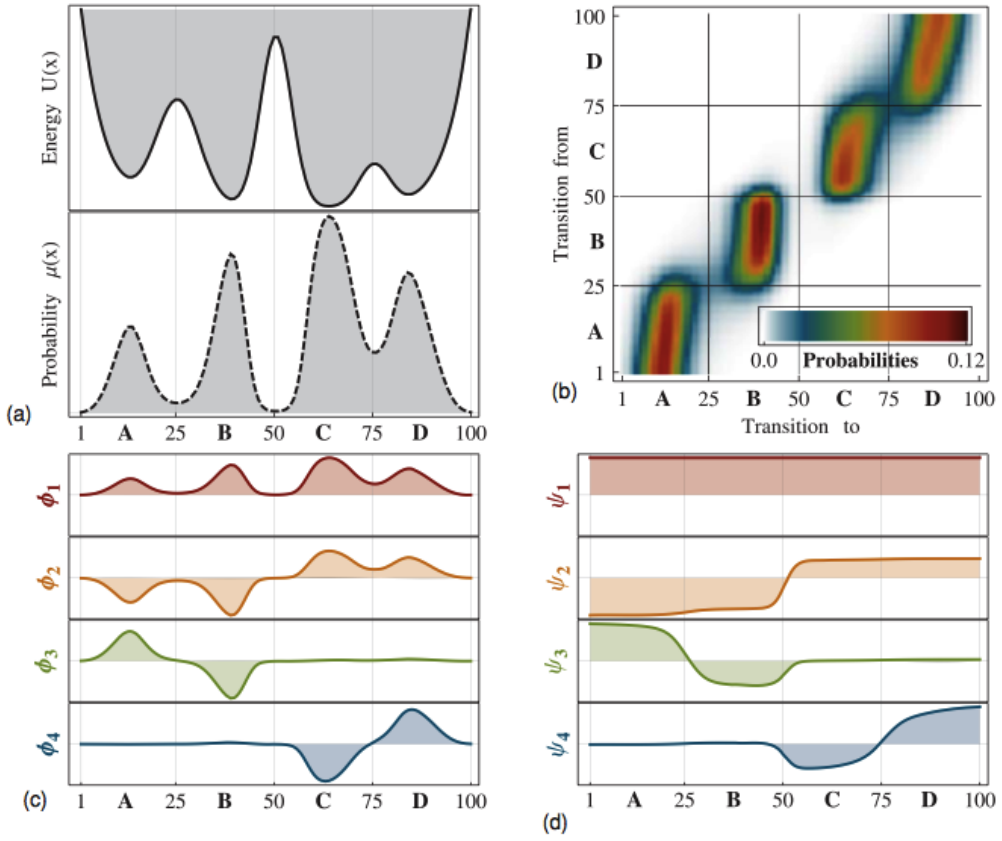
Eigenvalues / timescales κ_i^{-1}



Spectral decomposition

$$\rho_\tau = \sum_{i=1}^{\infty} \mathrm{e}^{-\tau\kappa_i} \langle \psi_i \mid \rho_0 \rangle \psi_i$$

Processes:



Variational approach for Markov processes

Data-based version of: Fan, **PNAS** 35, 652-655 (1949)

The first m eigenfunctions $\psi_1, \ldots, \psi_m$ are the solution to the problem

$$\max_{f_1,\ldots,f_m} \sum_{i=1}^{m} \mathbb{E}\left[f_i\left(\mathbf{x}_t\right) f_i\left(\mathbf{x}_{t+\tau}\right)\right] \tag{1}$$

$$\text{s.t.} \quad \mathbb{E}\left[f_i\left(\mathbf{x}_t\right)^2\right] = 1$$

$$\mathbb{E}\left[f_i\left(\mathbf{x}_t\right) f_j\left(\mathbf{x}_{t+\tau}\right)\right] = 0, \ \textit{for } i \neq j$$

and the maximum value is the sum of $\lambda_1, \ldots, \lambda_m$

Properties:

- ψ_i and ψ_j are uncorrelated for $i \neq j$.
- ψ_i are the directions of slow kinetics with maximal autocorrelations $\mathbb{E}_\mu\left[\psi_i\left(\mathbf{x}_t\right) \psi_i\left(\mathbf{x}_{t+\tau}\right)\right] = \lambda_i\left(\tau\right)$.
- Population changes along ψ_i coordinates decay with $\lambda_i\left(\tau\right) = \mathrm{e}^{-\frac{\tau}{t_i}}$.
- For every other set of functions, the eigenvalues will be underestimated $\hat{\lambda}_i\left(\tau\right) \leq \lambda_i\left(\tau\right)$.

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Variational approach for Markov processes: Linear variation

Ansatz: Define Basis set $\boldsymbol{\chi} = [\chi_1(\mathbf{x}), ..., \chi_n(\mathbf{x})]^\top$ and seek the linear expansions:

$$\hat{\psi}_i(\mathbf{x}) = \sum_j r_{ij}\chi_j(\mathbf{x})$$

Algorithm:

1. Estimate $\mathbf{C}^0$ and $\mathbf{C}^\tau$ with:

$$c^0_{ij} = \mathbb{E}_t[\chi_i(\mathbf{x}_t)\chi_j(\mathbf{x}_t)]$$
$$c^\tau_{ij} = \mathbb{E}_t[\chi_i(\mathbf{x}_t)\chi_j(\mathbf{x}_{t+\tau})]$$

2. Solve

$$\mathbf{C}^\tau \mathbf{r}_i = \mathbf{C}^0 \hat{\lambda}_i \mathbf{r}_i$$

3. Expand

$$\hat{\psi}_i(\mathbf{x}) = \sum_j r_{ij}\chi_j(\mathbf{x})$$

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Variational approach for Markov processes: Empirical estimation

1. Define

$$\mathbf{X}_0 = \begin{bmatrix} \chi_1(\mathbf{x}_0) & \cdots & \chi_n(\mathbf{x}_0) \\ \vdots & & \vdots \\ \chi_1(\mathbf{x}_{T-\tau}) & \cdots & \chi_n(\mathbf{x}_{T-\tau}) \end{bmatrix} \qquad \mathbf{X}_\tau = \begin{bmatrix} \chi_1(\mathbf{x}_\tau) & \cdots & \chi_n(\mathbf{x}_\tau) \\ \vdots & & \vdots \\ \chi_1(\mathbf{x}_T) & \cdots & \chi_n(\mathbf{x}_T) \end{bmatrix}$$

2. Empirical covariance matrices: $\mathbf{C}^0$ and $\mathbf{C}^\tau$ with:

$$\mathbf{C}^0 = \mathbf{X}_0^\top \mathbf{X}_0$$
$$\mathbf{C}^\tau = \mathbf{X}_0^\top \mathbf{X}_\tau$$

3. Solve

$$\mathbf{C}^\tau \mathbf{r}_i = \mathbf{C}^0 \hat{\lambda}_i \mathbf{r}_i$$

4. The projections

$$\mathbf{\Psi} = \mathbf{X}\mathbf{R}$$

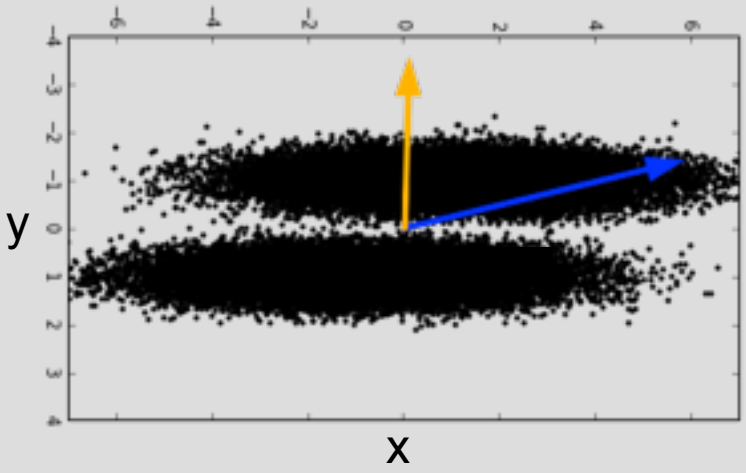
approximate the transfer operator eigenfunctions on the sampled configurations x_t.

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Linear combination of basis functions

ψ_i are the directions of slow kinetics with maximal autocorrelations

$$\mathbb{E}_\mu \left[\psi_i \left(\mathbf{x}_t \right) \psi_i \left(\mathbf{x}_{t+\tau} \right) \right] = \lambda_i \left(\tau \right) = \mathrm{e}^{-\frac{\tau}{t_i}}.$$



Optimal for variational principle of conformation dynamics (maximum autocorrelation)

maximum variance

Simple Ansatz:

$$\psi_2(x, y) = ax + by$$

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Comparison with other algorithms

Extended dynamic mode decomposition (EDMD)
Williams, Kevrikidis, Rowley **J. Nonlinear Sci.** 6, 1-40 (2015) / also: **arXiv** (2014)

Time-lagged independent component analysis TICA / Blind source separation
Molgedey and Schuster, **Phys Rev Lett** 72 3634-3637 (1994)

Dynamic mode decomposition (DMD)
Schmidt, Sesterhenn, **Ann. Meet. APS Div. Fluid Mech.** (2008)
Tu, Rowley, Luchtenburg, Brunton, Kutz, **J. Comput. Dyn.** (2014)

Markov state models (MSM)
Schütte, Fischer, Huisinga, Deuflhard: **J. Comput. Phys.** (1999)
see also papers by: Noé, Pande, Hummer, Weber, Swope, …

Extended dynamic mode decomposition

Relationship to Extended dynamic mode decomposition:

Williams, Kevrikidis, Rowley
J. Nonlinear Sci. 6, 1-40 (2015)

The VAMP eigenvalue problem can be written

$$\mathbf{K}\mathbf{r}_i = \mathbf{r}_i \lambda_i$$

with Koopman matrix

$$\begin{aligned}\mathbf{K} &= (\mathbf{C}^0)^{-1}\mathbf{C}^\tau \\ &= (\mathbf{X}_0^\top \mathbf{X}_0)^{-1}\mathbf{X}_0^\top \mathbf{X}_\tau = \mathbf{X}_0^+ \mathbf{X}_\tau^\top\end{aligned}$$

That is the optimal solution of the regression problem

$$\mathbf{Y} = \mathbf{X}\mathbf{K}$$

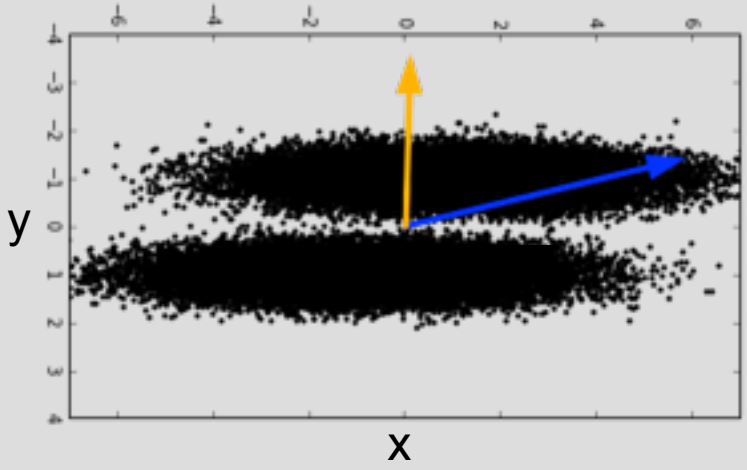
Remarks:

- The VAMP algorithm is equivalent to EDMD.
- VAMP/EDMD are also applicable to nonreversible and nonstationary dynamics.
- VAMP/EDMD results are variationally optimal and we have an eigenvalue bound in the reversible case.
- EDMD and DMD are usually implemented using singular value decomposition of the data matrix instead of computing a covariance matrix.

Special case: Time-lagged independent component analysis (TICA)

Also known as: Blind source separation, Molgedey-Schuster transform

Original paper: Molgedey and Schuster, **PRL** 1994

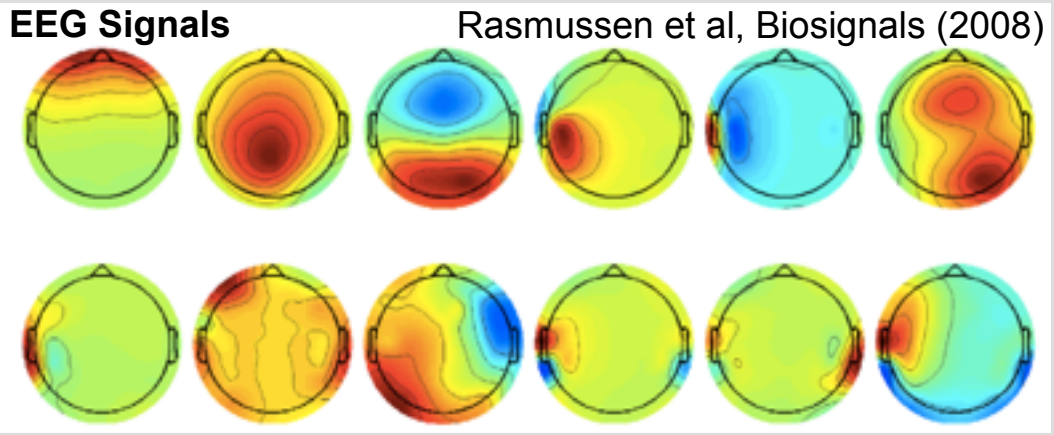


$$\psi_2(x, y) = ax + by$$

TICA is the variationally optimal approximation to the Markov operator eigenfunctions when using **linear combinations of mean-free molecular coordinates**
Perez-Hernandez et al, **JCP**, 139, 1502 (2013)

Applications of TICA

EEG Signals Rasmussen et al, Biosignals (2008)



Molecular Dynamics

Perez-Hernandez et al, **JCP**, 139, 1502 (2013)
Identification of slow molecular order parameters for Markov model construction

Naritomi and Fuchigami, **JCP** (2011)
Slow dynamics in protein fluctuations …

Schwantes and Pande, **JCTC** (2013)
Improvements in Markov state modeling …

Special case: Markov state model

Choice of basis set: Characteristic functions on sets S_1, ..., S_n that partition phase space

$$\chi_i(\mathbf{x}_t) = \begin{cases} 1 & \mathbf{x}_t \in S_i \\ 0 & \text{else.} \end{cases}$$

where $\mathbf{q}$ are the position coordinates of the system.

Covariance matrices:

$$\begin{aligned} \mathbf{C}^0 &= \mathbf{X}_0^\top \mathbf{X}_0 = \mathrm{diag}(\sum_k N_{1k}(\tau), \ldots, \sum_k N_{nk}(\tau)) \\ \mathbf{C}^\tau &= \mathbf{X}_0^\top \mathbf{X}_\tau = [N_{ij}(\tau)]_{i,j=1,\ldots,n} \end{aligned}$$

where $N_{ij}(\tau)$ are the number of transitions from state i to j at lag time τ.

GEV problem:

$$\begin{aligned} \mathbf{C}^\tau \mathbf{R} &= \mathbf{C}^0 \mathbf{R} \hat{\mathbf{\Lambda}} \\ \mathbf{P}\mathbf{R} &= \mathbf{R} \hat{\mathbf{\Lambda}} \end{aligned}$$

with

$$\mathbf{P} = [p_{ij}(\tau)] \qquad p_{ij}(\tau) = \frac{N_{ij}(\tau)}{\sum_k N_{ik}(\tau)}$$

Related: Dynamic mode decomposition (DMD)

DMD: Schmidt, Sesterhenn, **Ann. Meet. APS Div. Fluid Mech.** (2008)
exact DMD: Tu, Rowley, Luchtenburg, Brunton, Kutz, **J. Comput. Dyn.** (2014)

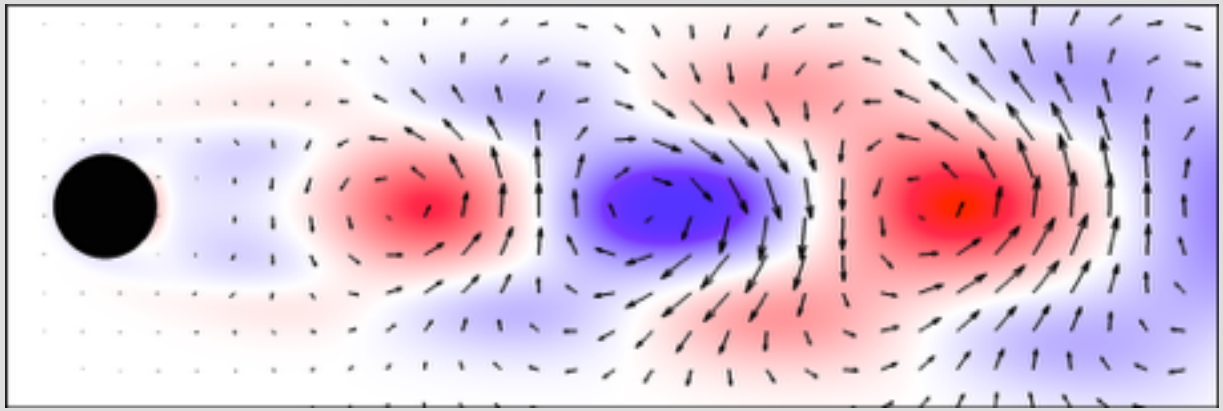
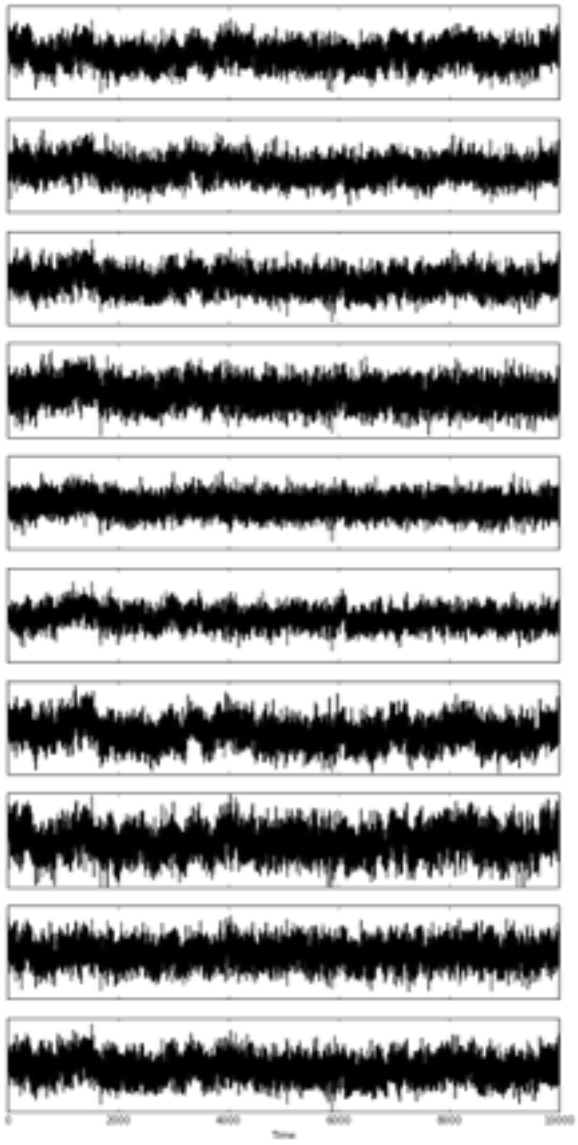


Image from: Chen, Tu, Rowley, J. Nonlinear Sci 22: 887-916 (2012)

DMD: computes left eigenvectors of K ==> dynamic modes
TICA/VAMP compute right eigenvectors of K ==> direct approximation of eigenfunctions

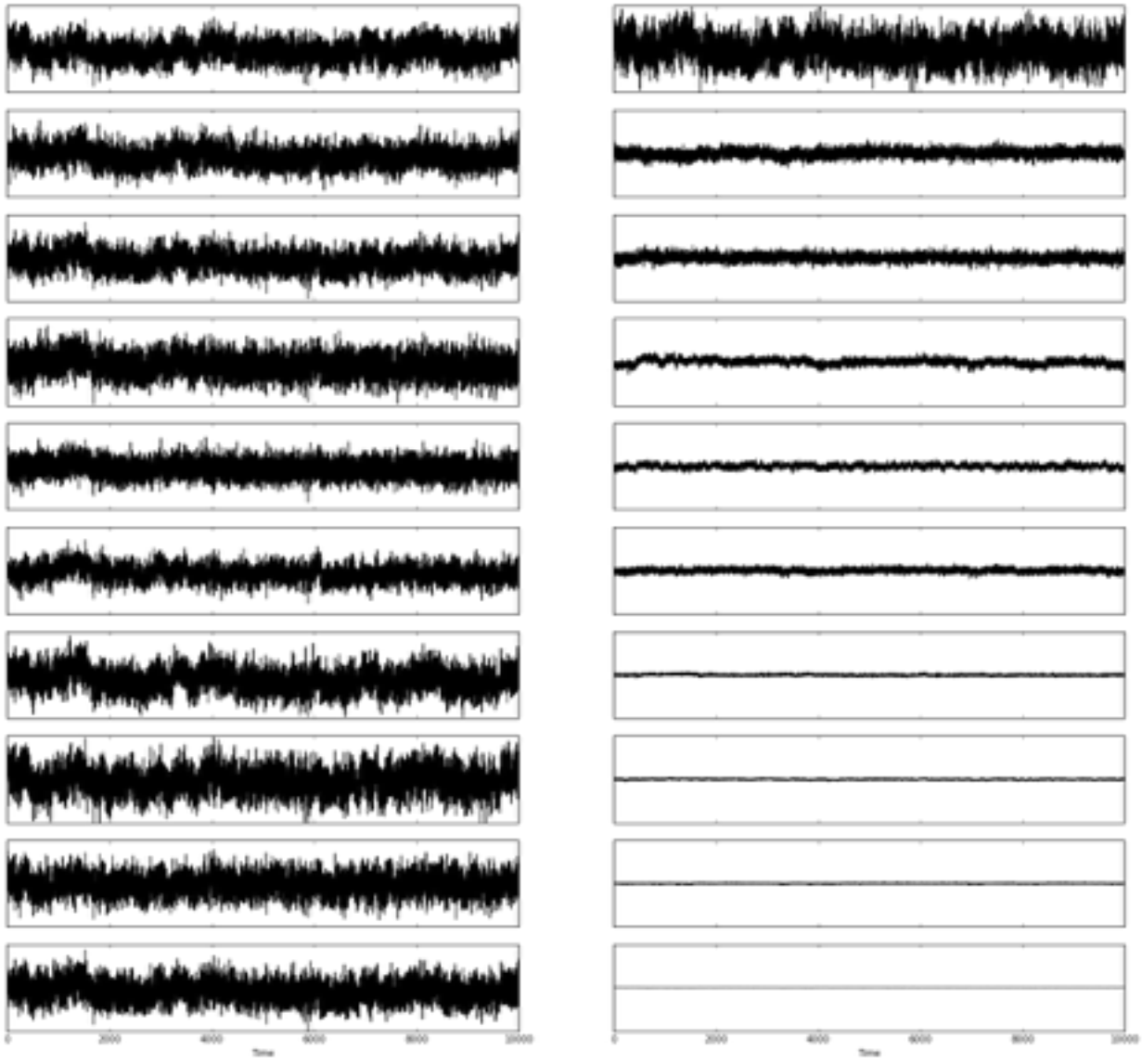
Examples

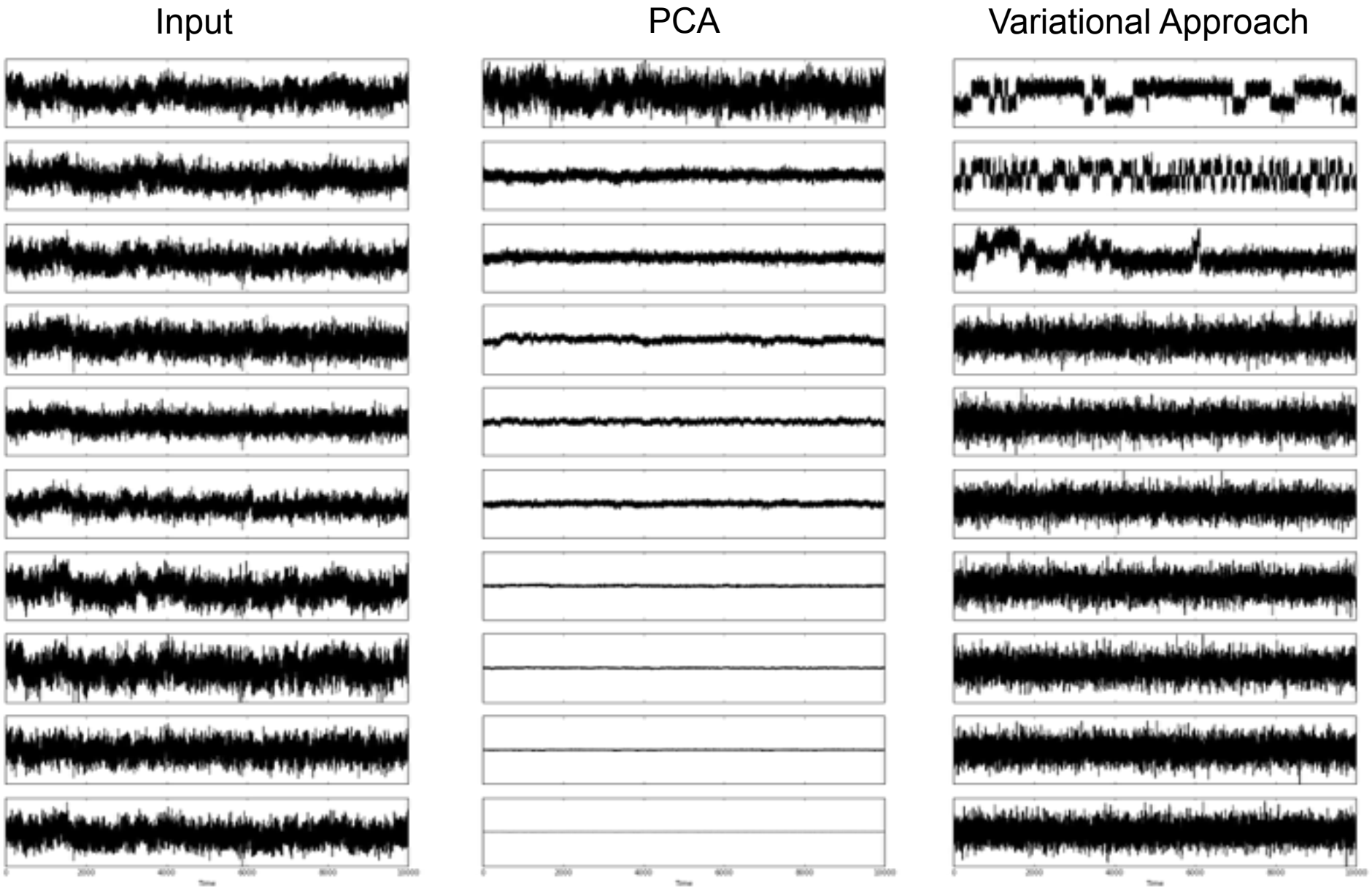
Input



Input

PCA

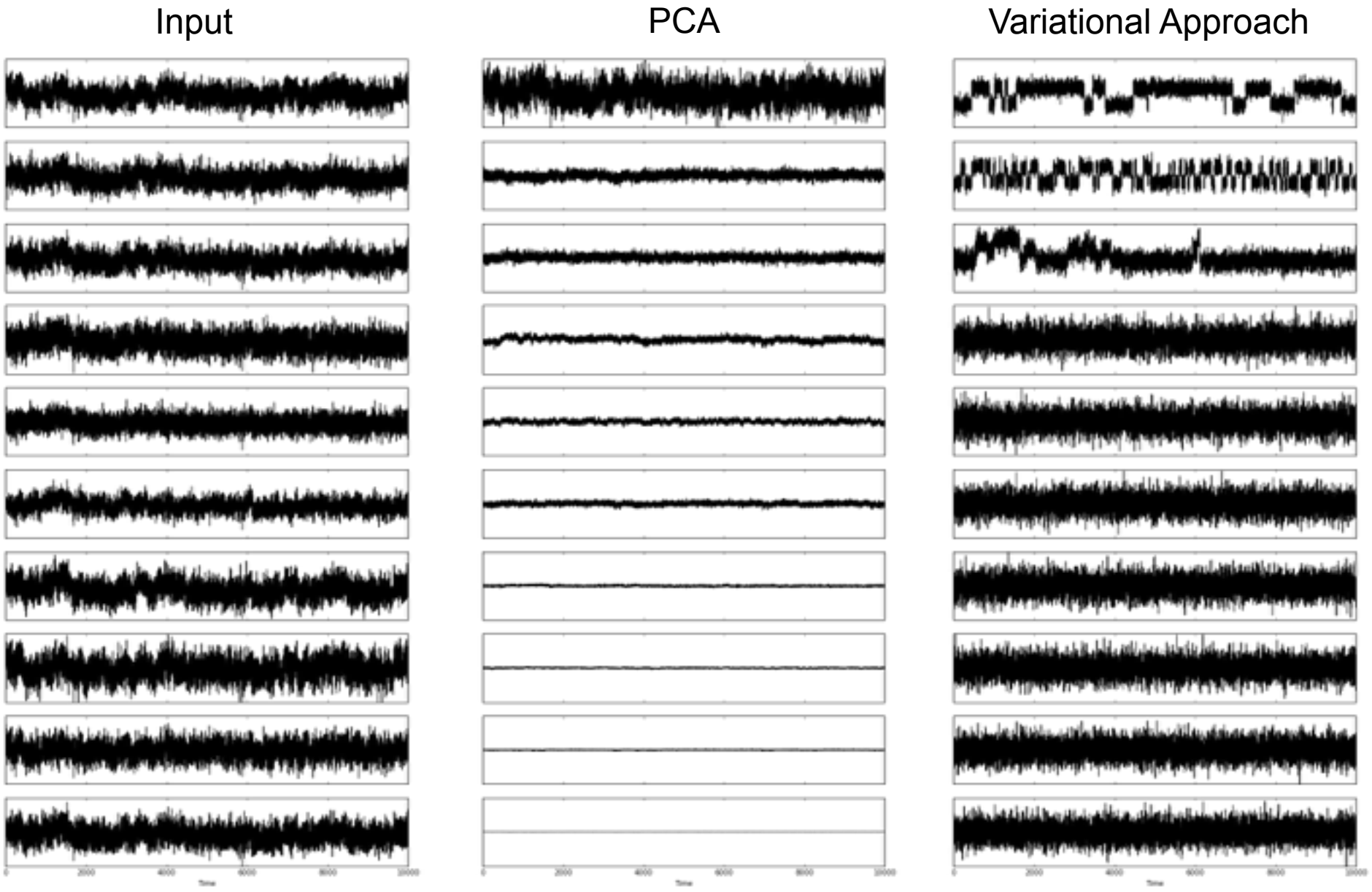




Variational Approach

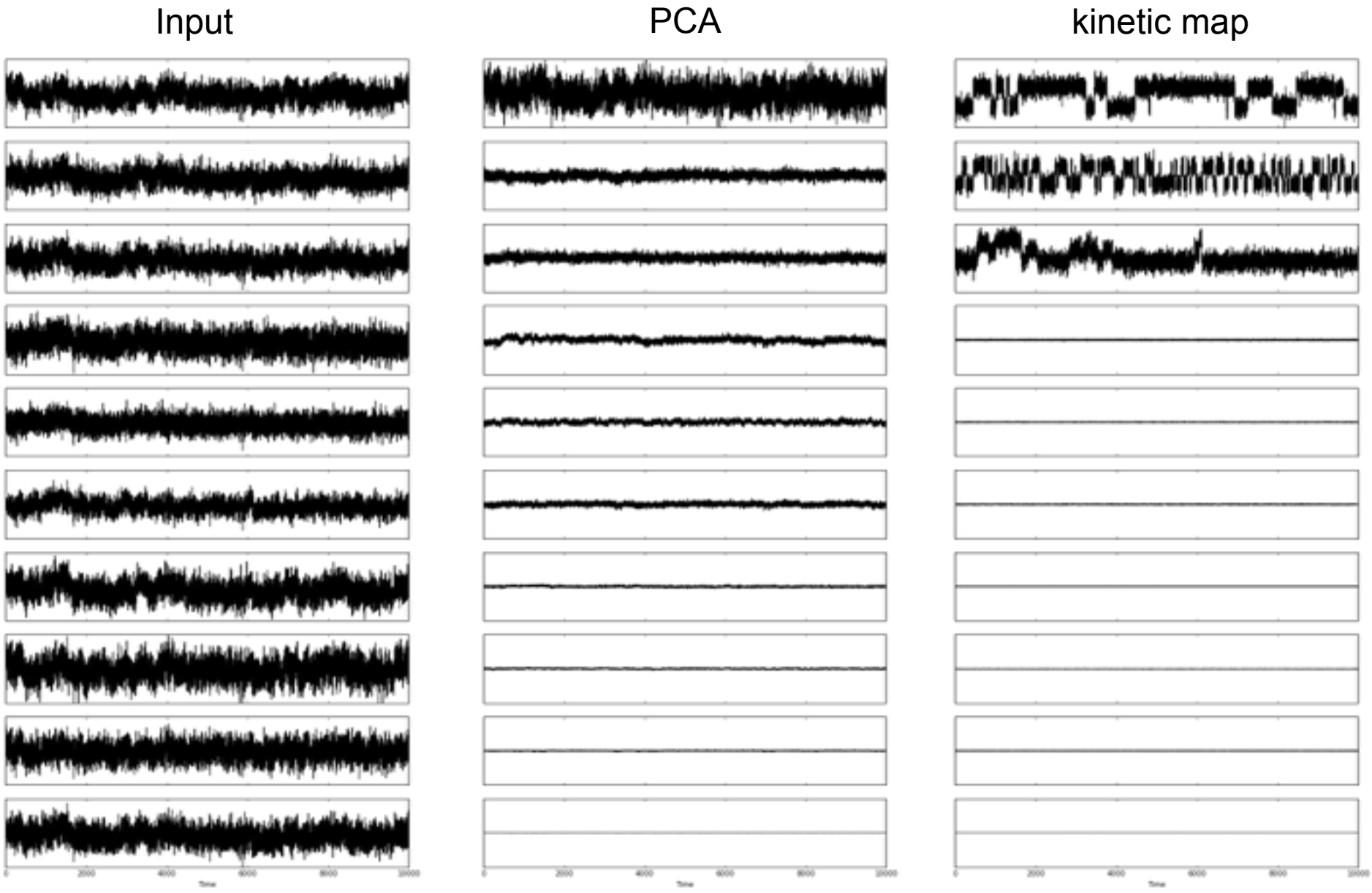
Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Perez-Hernandez et al, **JCP**, 139, 1502 (2013)
Identification of slow molecular order parameters for Markov model construction



Variational Approach

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)



Variational Approach

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)

Kinetic map:

Noé and Clementi, **JCTC** 11, 5002-5011 (2015)

Expansion in molecular order parameters

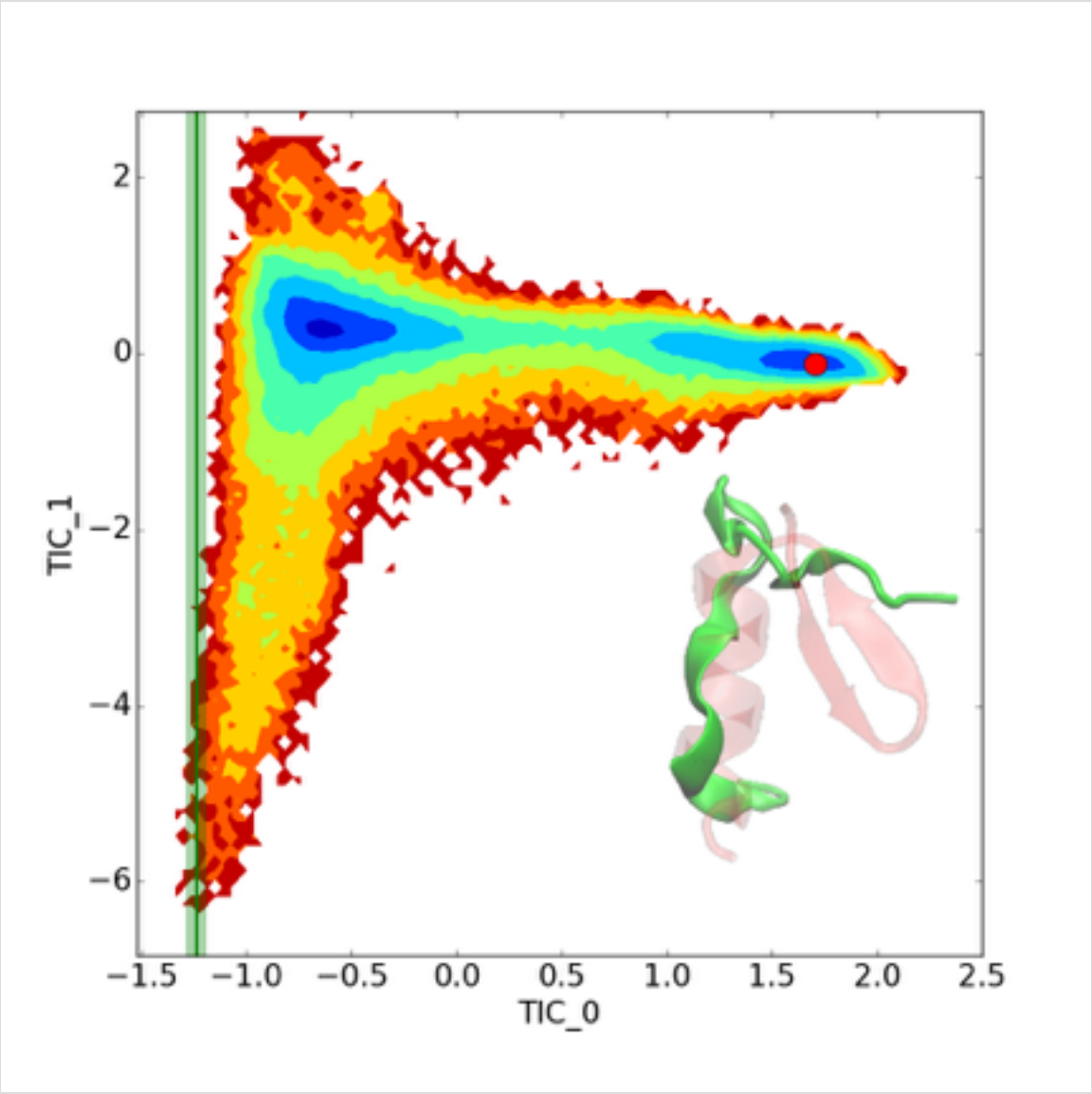
Candidates x_1…x_n

- Cartesian coordinates
- Distances between heavy atoms or Ca's
- cos/sin of dihedrals
- Gaussian densities around sampled configurations (e.g. in RMSD space)
- Field variables or coordination numbers
- Your favorite order parameter
- All of them

Simple Ansatz:

$$\psi_i(\mathbf{x}) = b_{i,1}x_1 + \ldots + b_{i,n}x_n$$

Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)



1FME peptide - Simulation data from DESRES, Lindorff-Larsen et al, Science 2011

Doing this in PyEMMA…


```
from pyemma import coordinates, plots

# define input
feat = coordinates.featurizer("protein.pdb")
feat.add_residue_mindist()
data = coordinates.source("protein.xtc", feat)

# TICA
tica = coordinates.tica(data, lag=100, dim=2)
Y = tica.get_output()[0]

# visualize
plots.plot_free_energy(Y[:, 0], Y[:, 1])
```

Estimation

Estimation problems

1) Nonreversible estimate

$$\hat{\mathbf{C}}(0) = \frac{1}{N}\mathbf{X}^\top\mathbf{X}$$
$$\hat{\mathbf{C}}(\tau) = \frac{1}{N}\mathbf{X}^\top\mathbf{Y}$$

2) Standard reversible estimate

$$\hat{\mathbf{C}}_{\mathrm{sym}}(0) \approx \frac{1}{2N}\left(\mathbf{X}^\top\mathbf{X} + \mathbf{Y}^\top\mathbf{Y}\right)$$
$$\hat{\mathbf{C}}_{\mathrm{sym}}(\tau) \approx \frac{1}{2N}\left(\mathbf{X}^\top\mathbf{Y} + \mathbf{Y}^\top\mathbf{X}\right)$$

This leads to a strong bias for out-of equilibrium data!

Equilibrium estimation from out-of equilibrium data

1. Extend data

$$\mathbf{X}^{\ddagger} = [\mathbf{X}\,\mathbf{1}]$$

2. Compute (nonreversible) Koopman matrix $\mathbf{K}$ from data

3. Compute reweighting vector $\mathbf{u}$ using the eigenvalue problem

$$\hat{\mathbf{u}} = \hat{\mathbf{u}}\mathbf{K}$$

and normalization $\mathbf{u} = \frac{1}{\hat{u}_{n+1}}\hat{\mathbf{u}}$

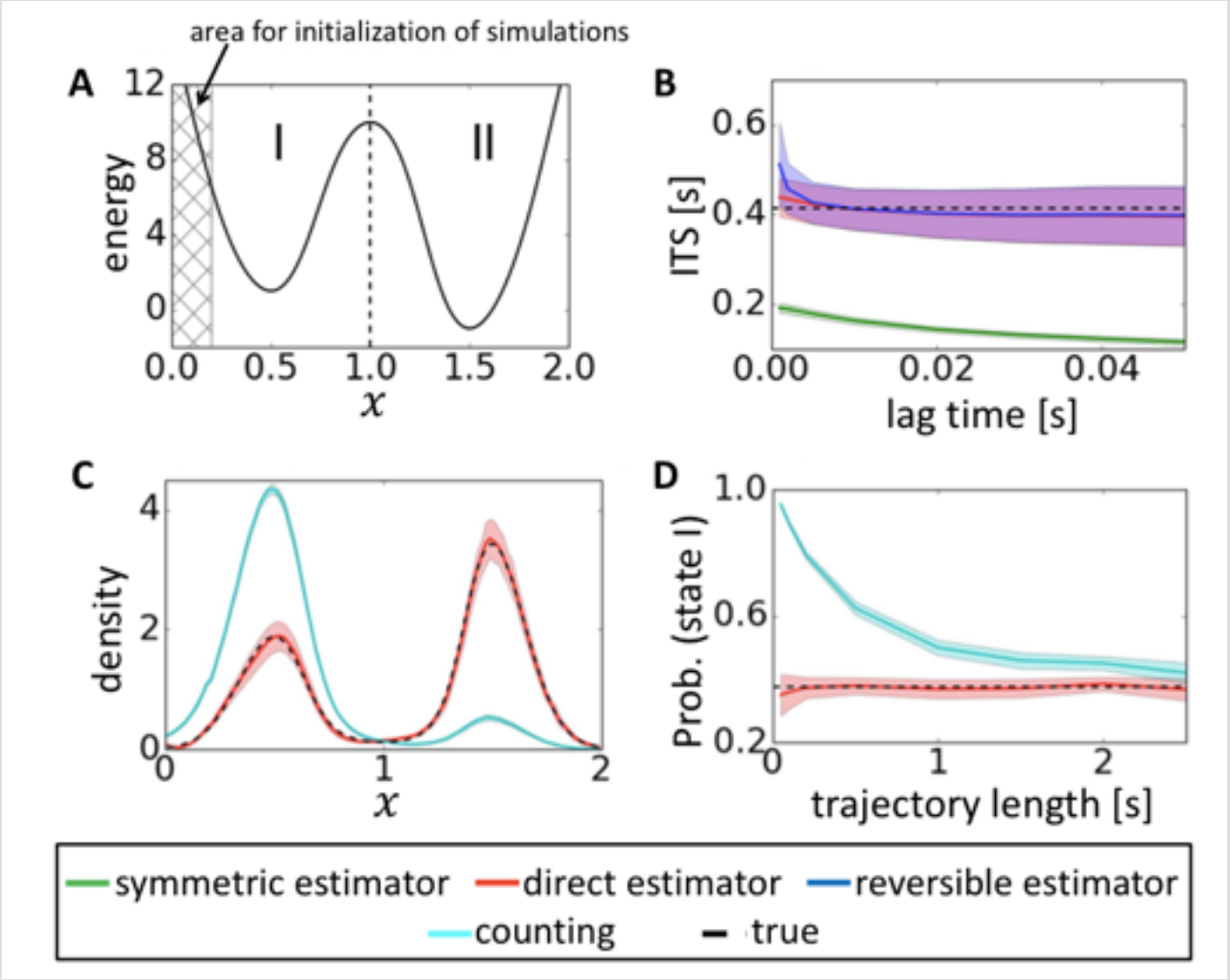
4. Equilibrium expectations:

$$\mathbb{E}_{\pi}[f(\mathbf{x}_t)] = \frac{1}{N}\sum_{t=1}^{T-\tau} \mathbf{u}\,\boldsymbol{\chi}(\mathbf{x}_t)\,f(\mathbf{x}_t)$$

$$\mathbb{E}_{\pi}[\chi_i(\mathbf{x}_t)\chi_j(\mathbf{x}_{t+k\tau})] = \frac{1}{N}\sum_{t=1}^{T-\tau} \mathbf{u}\,\boldsymbol{\chi}(\mathbf{x}_t)\,\boldsymbol{\chi}(\mathbf{x}_t)\boldsymbol{\chi}^{\top}(\mathbf{x}_t)\mathbf{K}^k$$

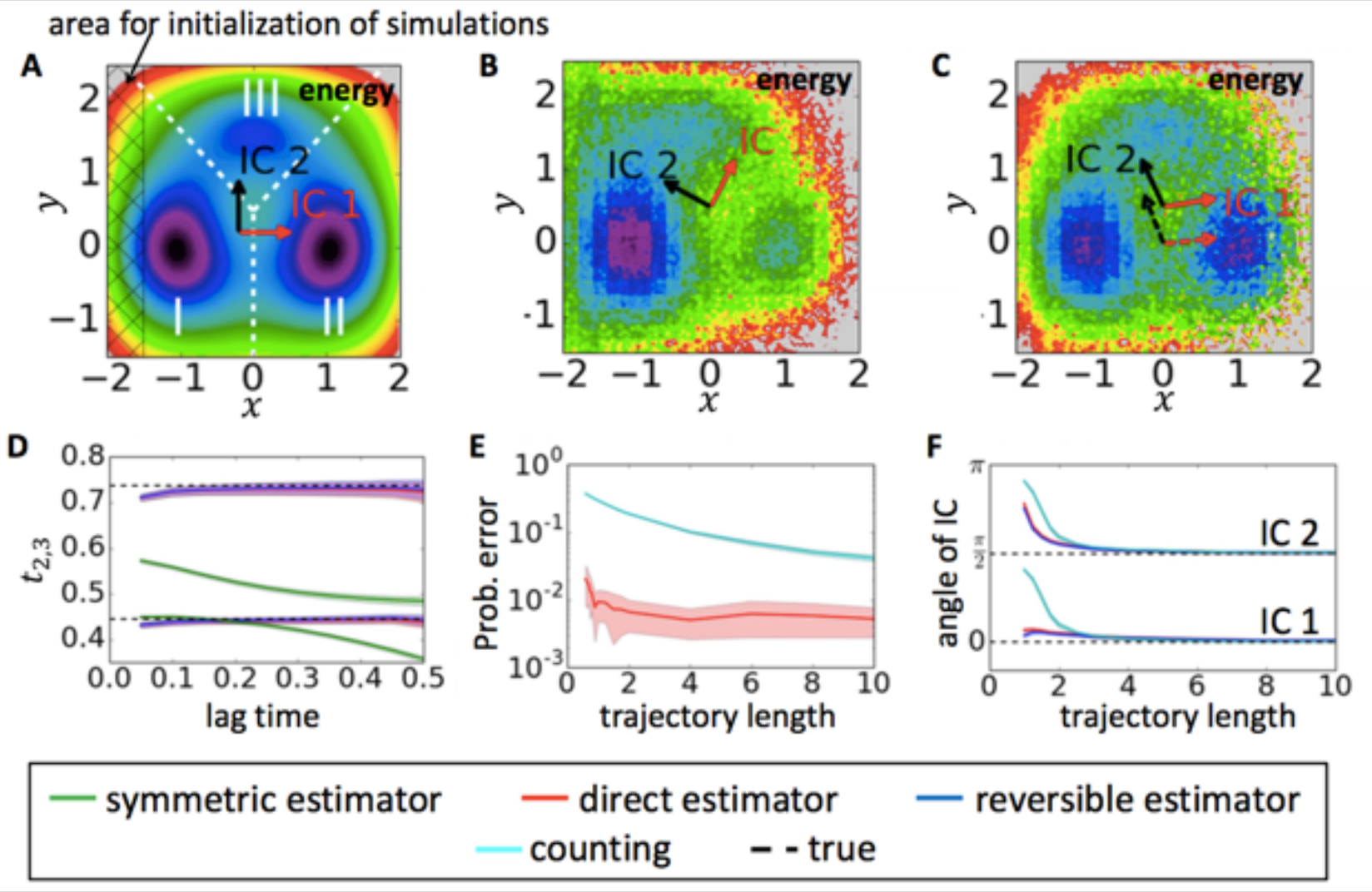
Wu et al, **arXiv** 1610.06773 (2016)

Equilibrium estimation from out-of equilibrium data



Wu et al, **arXiv** 1610.06773 (2016)

Equilibrium estimation from out-of equilibrium data



Wu et al, **arXiv** 1610.06773 (2016)

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Vijay Pande (Stanford)
Volker Haucke (FMP Berlin)
Stephan Sigrist (FU Berlin)
Oliver Daumke (MDC)
John Chodera (MSKCC NY)
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