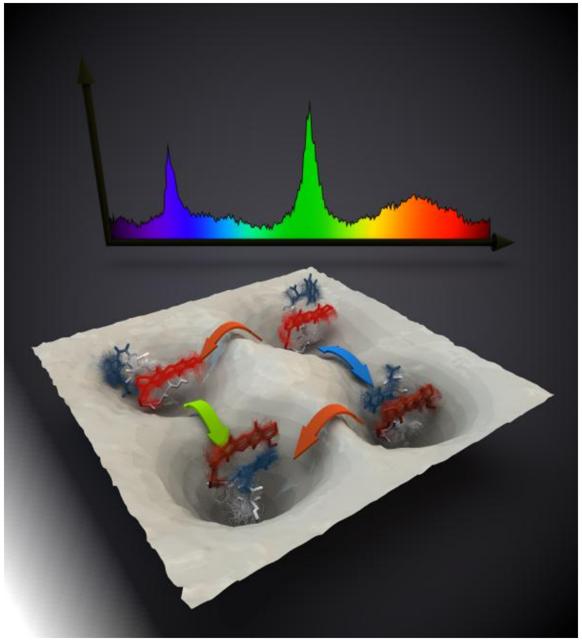
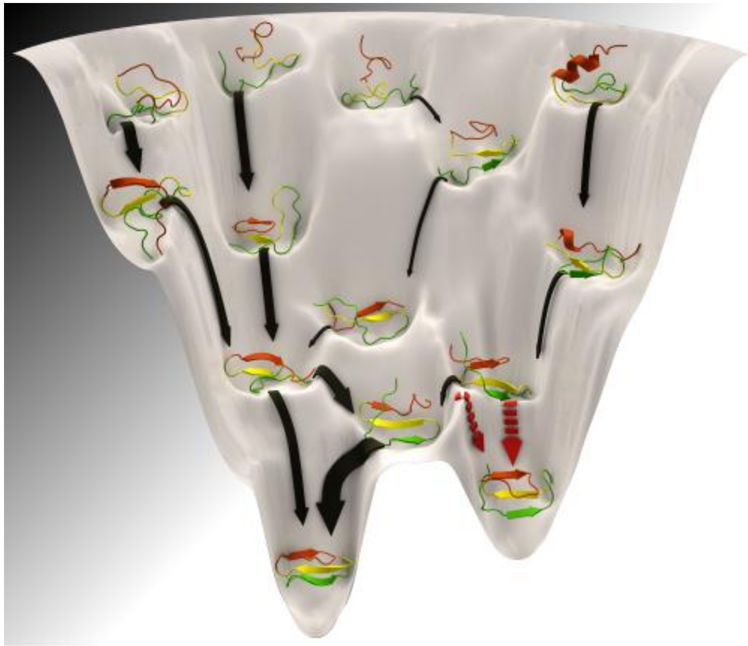
Beyond the second timescale in all-atom MD: shallow and deep kinetic models for biomolecules



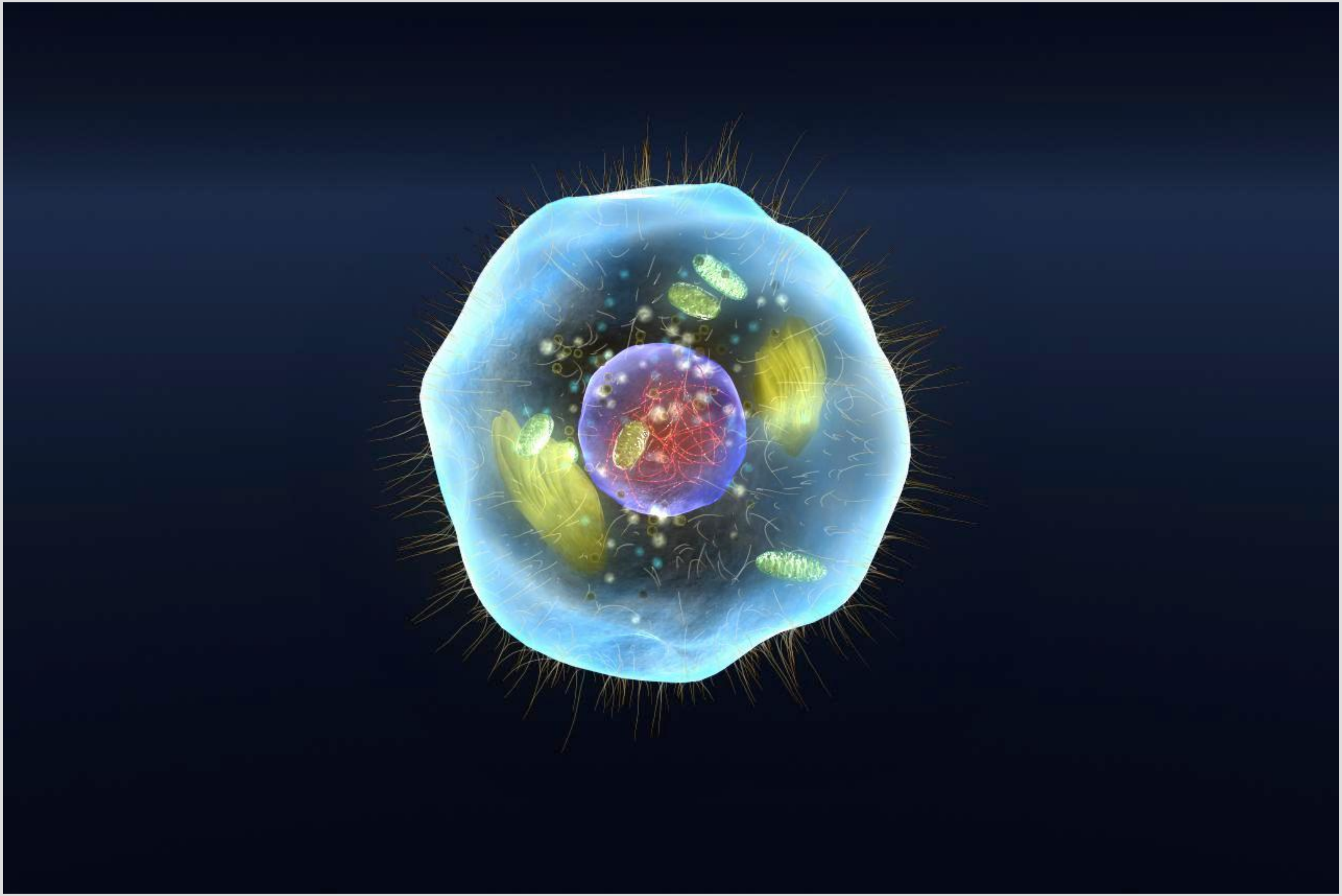


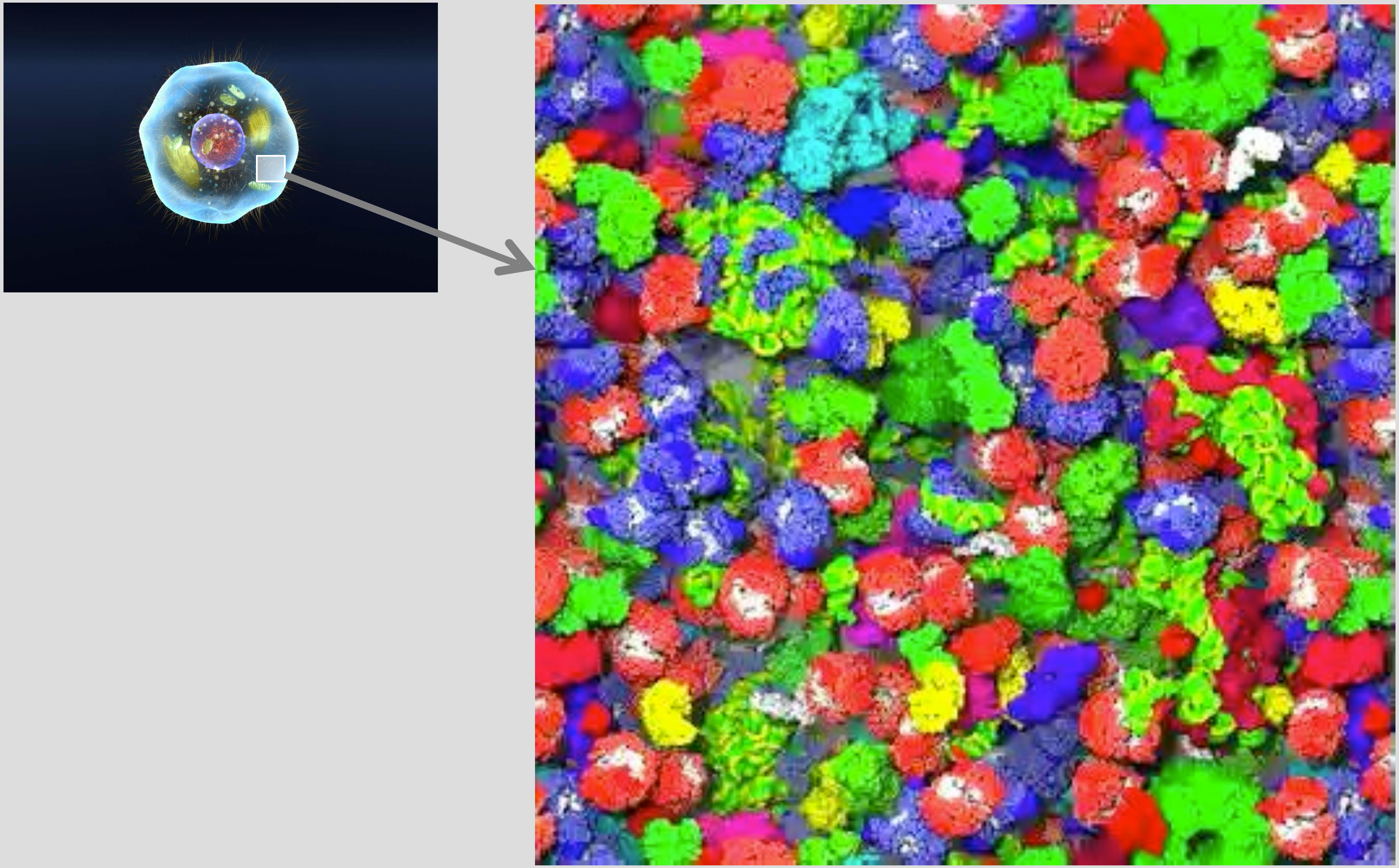
Frank Noé (FU Berlin)
frank.noe@fu-berlin.de

Computational
Molecular Biology

Freie Universität Berlin

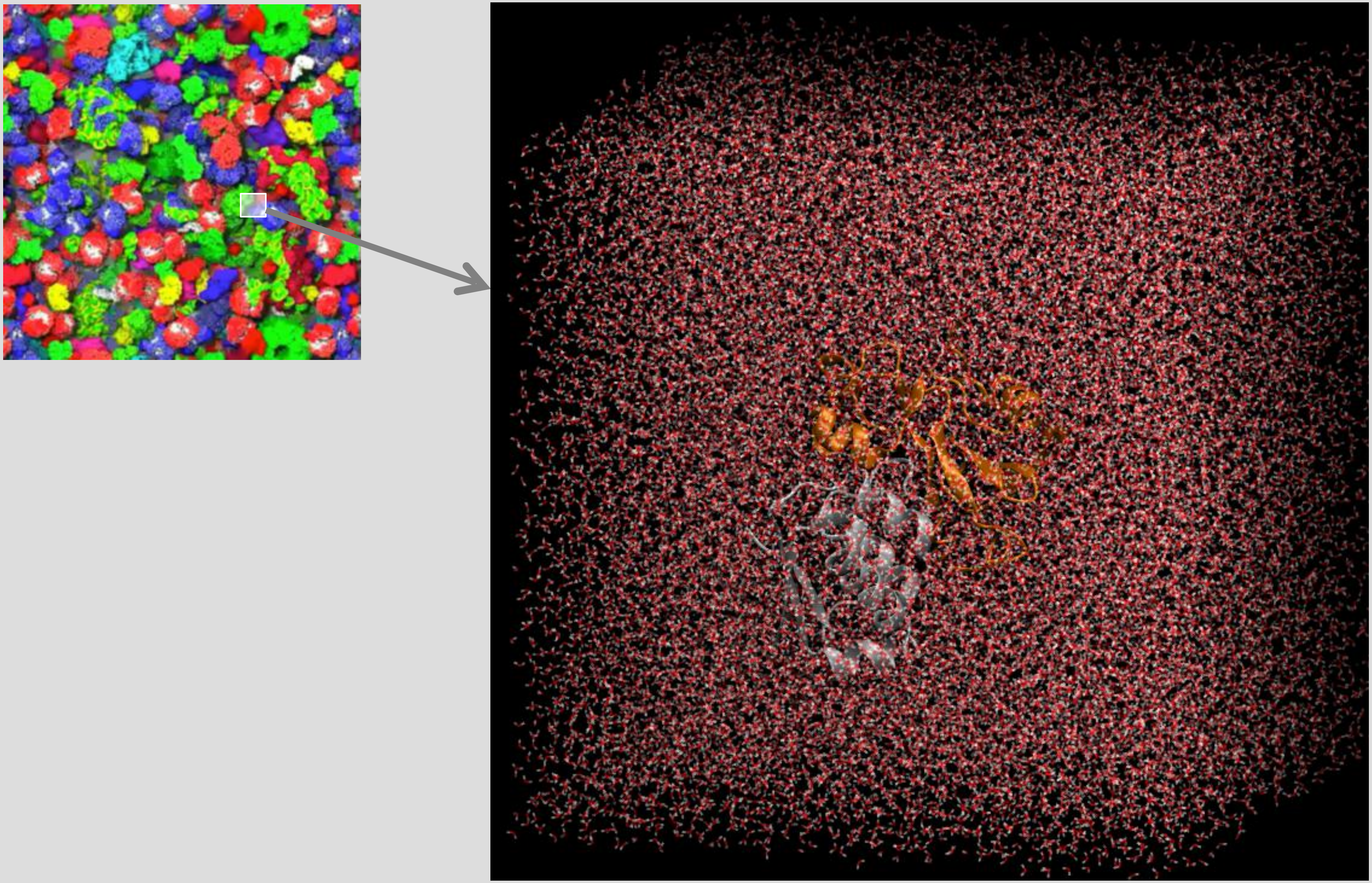
Cell



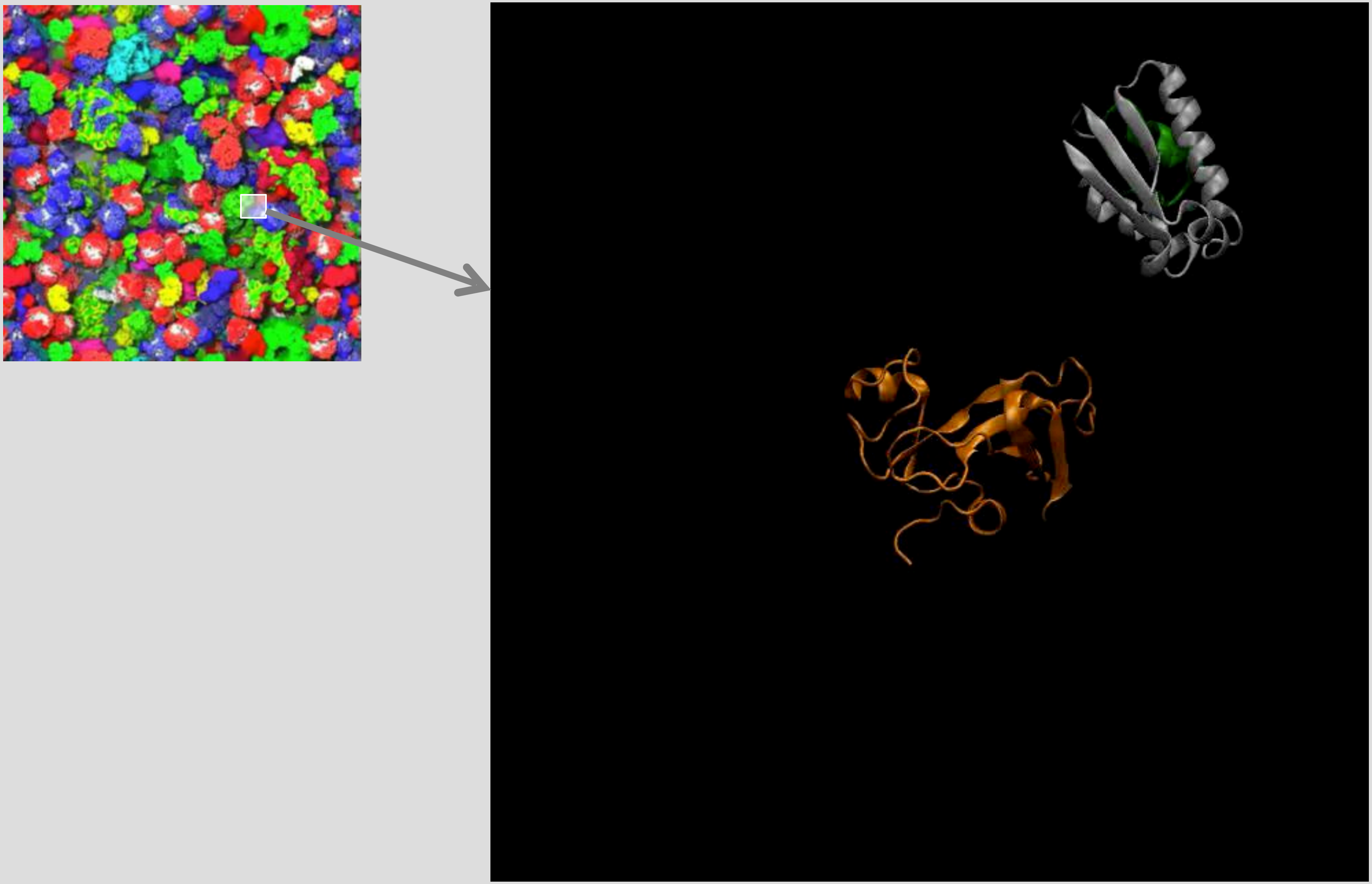


McGufee and Elcock, PloS Comput Biol 2010

Protein-Protein binding



Protein-Protein binding



Plattner, Doerr, De Fabritiis, Noé

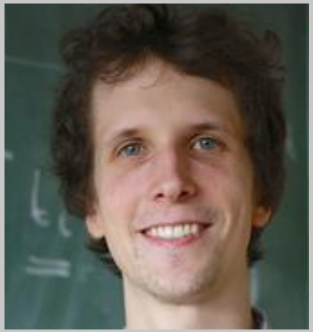
0.1 microseconds

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)



Feliks Nüske

Bettina Keller

Guillermo Pérez Hernandez

Fabian Paul

Variational approach

TICA

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

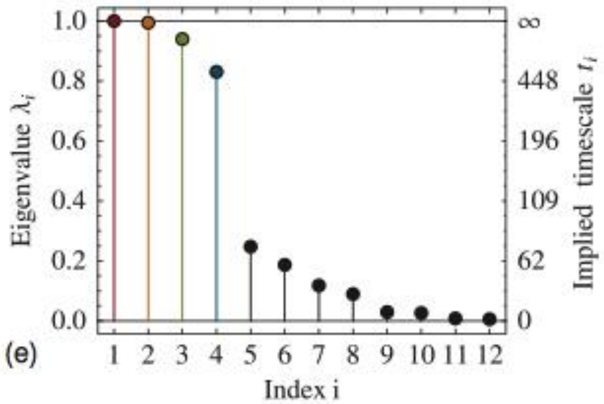
$$\rho_\tau = \mathcal{T}(\tau)\rho_0$$

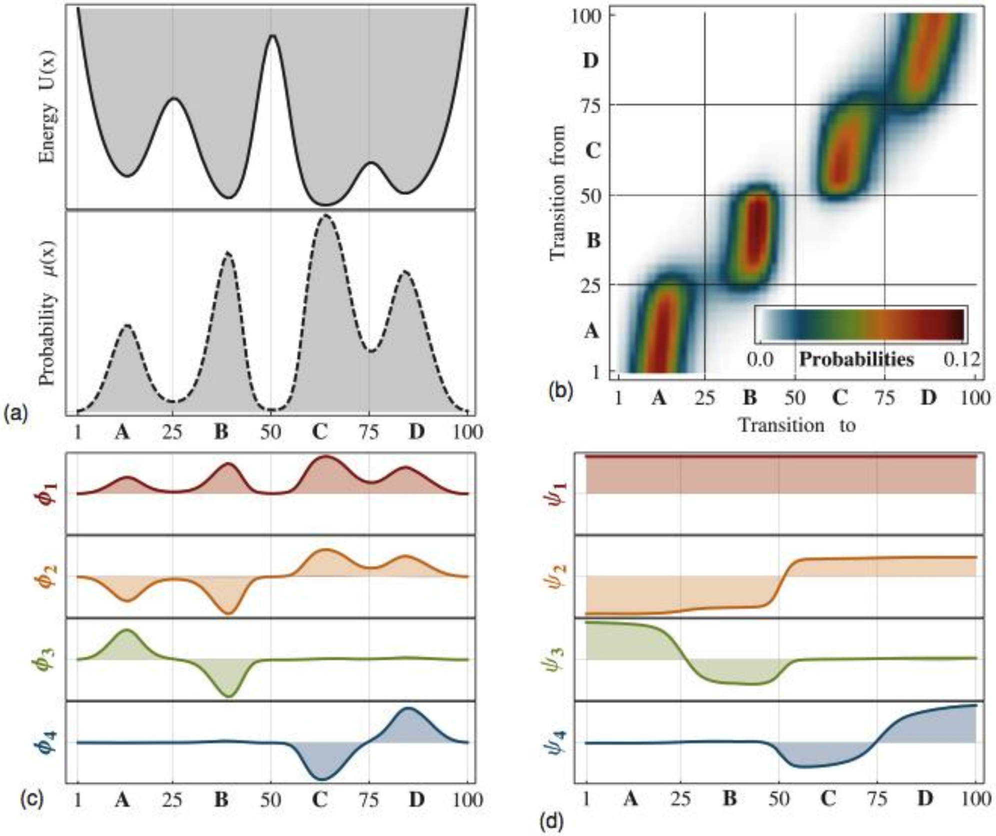
Spectral decomposition

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

Processes:

Eigenvalues / timescales κ_i^{-1}





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

Variational approach for reversible 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*

$$\begin{aligned} \max_{f_1,\ldots,f_m} \sum_{i=1}^{m} \mathbb{E}\left[f_i\left(\mathbf{x}_t\right) f_i\left(\mathbf{x}_{t+\tau}\right)\right] \\ \text{s.t.} \quad \mathbb{E}\left[f_i\left(\mathbf{x}_t\right)^2\right] = 1 \\ \mathbb{E}\left[f_i\left(\mathbf{x}_t\right) f_j\left(\mathbf{x}_{t+\tau}\right)\right] = 0, \ \textit{for } i \neq j \end{aligned} \tag{1}$$

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

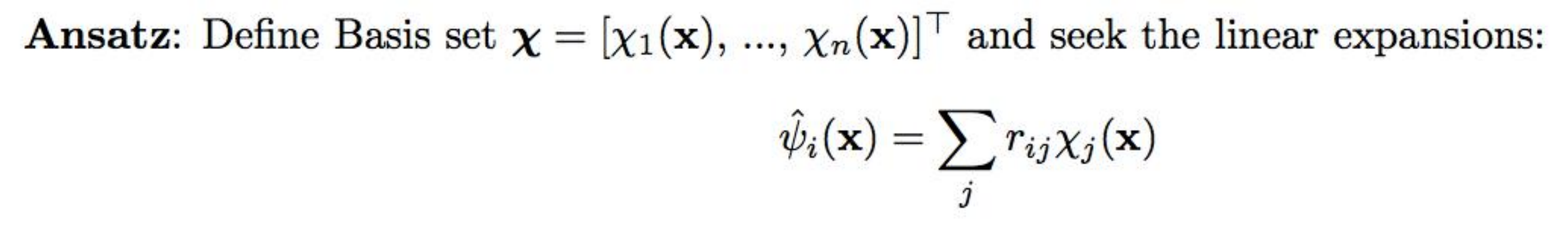
Properties:

- 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 reversible Markov processes

Method of linear variation



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

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

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

Variational approach for reversible Markov processes: Estimator

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

$$\mathbf{\Psi} = \mathbf{XR}$$

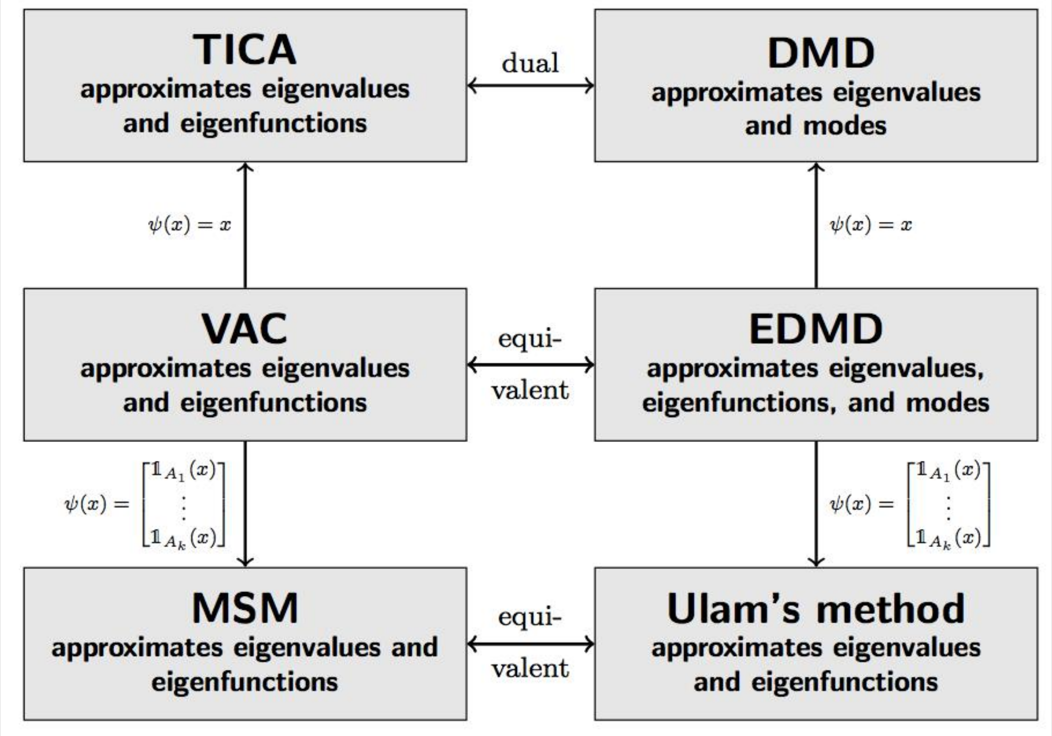
approximate the transfer operator eigenfunctions on the sampled configurations x_t.

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

Comparison between methods

Molgedey and Schuster, **PRL** 72 3634-3637 (1994)
Pérez-Hernández et al, **JCP** 139, 015102 (2013)

Schmidt, Sesterhenn,
Ann. Meet. APS Div. Fluid Mech. (2008)



Noé & Nüske **MMS** 11, 635-655 (2013)

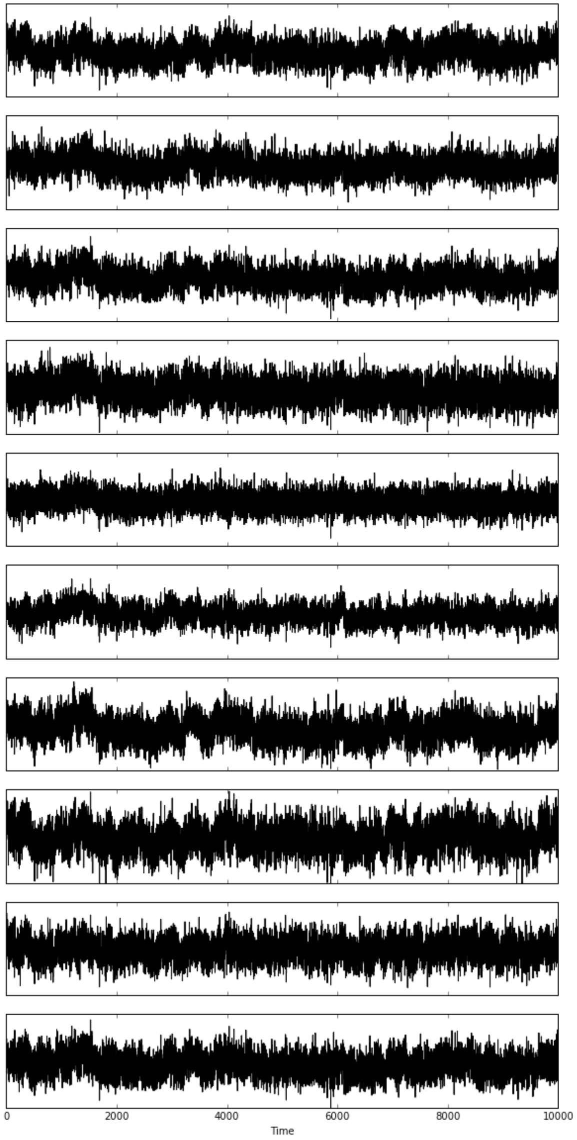
Nüske et al, **JCTC** 10, 1739-1752 (2014)

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

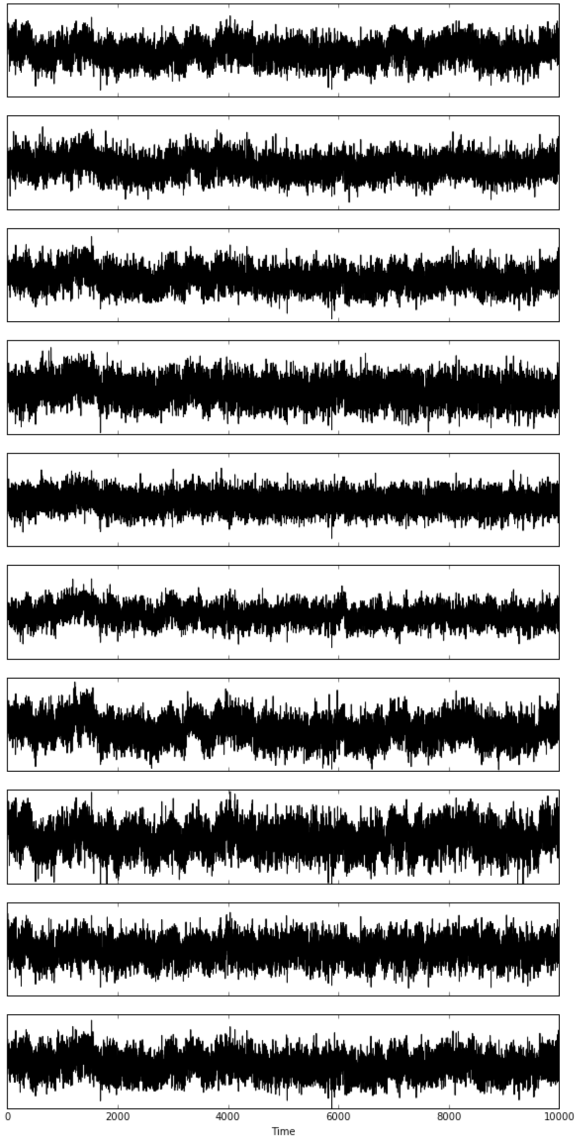
Schütte et al: **J. Comput. Phys.** (1999)
also: Noé, Pande, Hummer, Weber, Swope, …

Overview paper: Klus, Nüske, Koltai, Wu, Krevrekidis, Schütte, Noé
Data-driven model reduction and transfer operator approximation (**arXiv**:1703.10112)

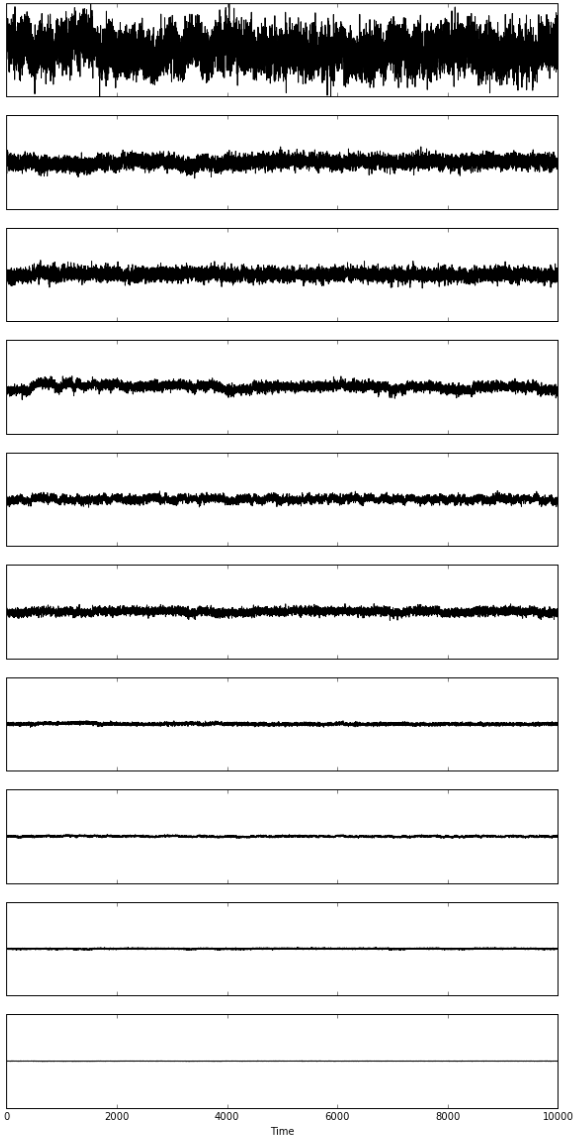
Input

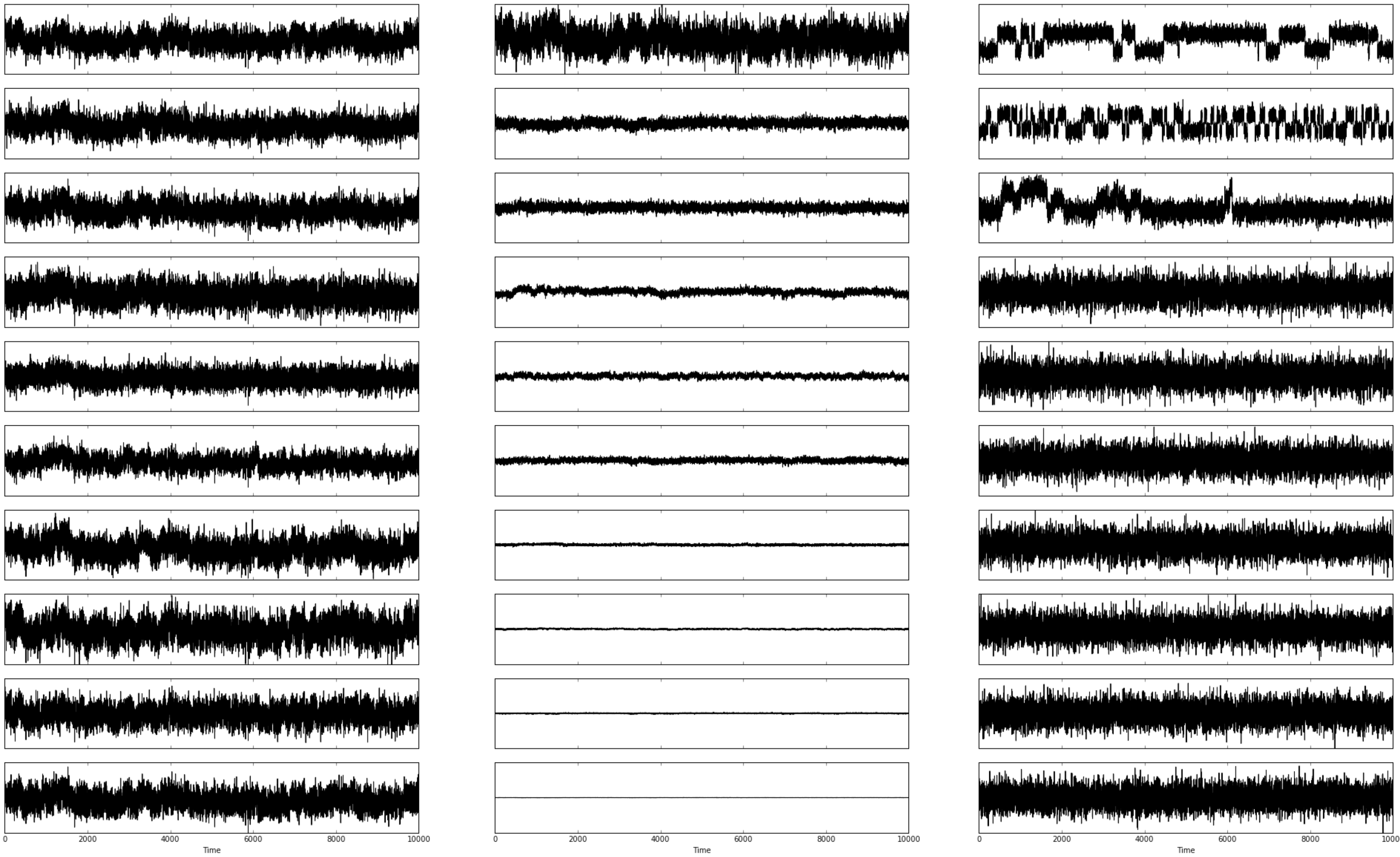


Input


0
2000
4000
6000
8000
10000
Time

PCA

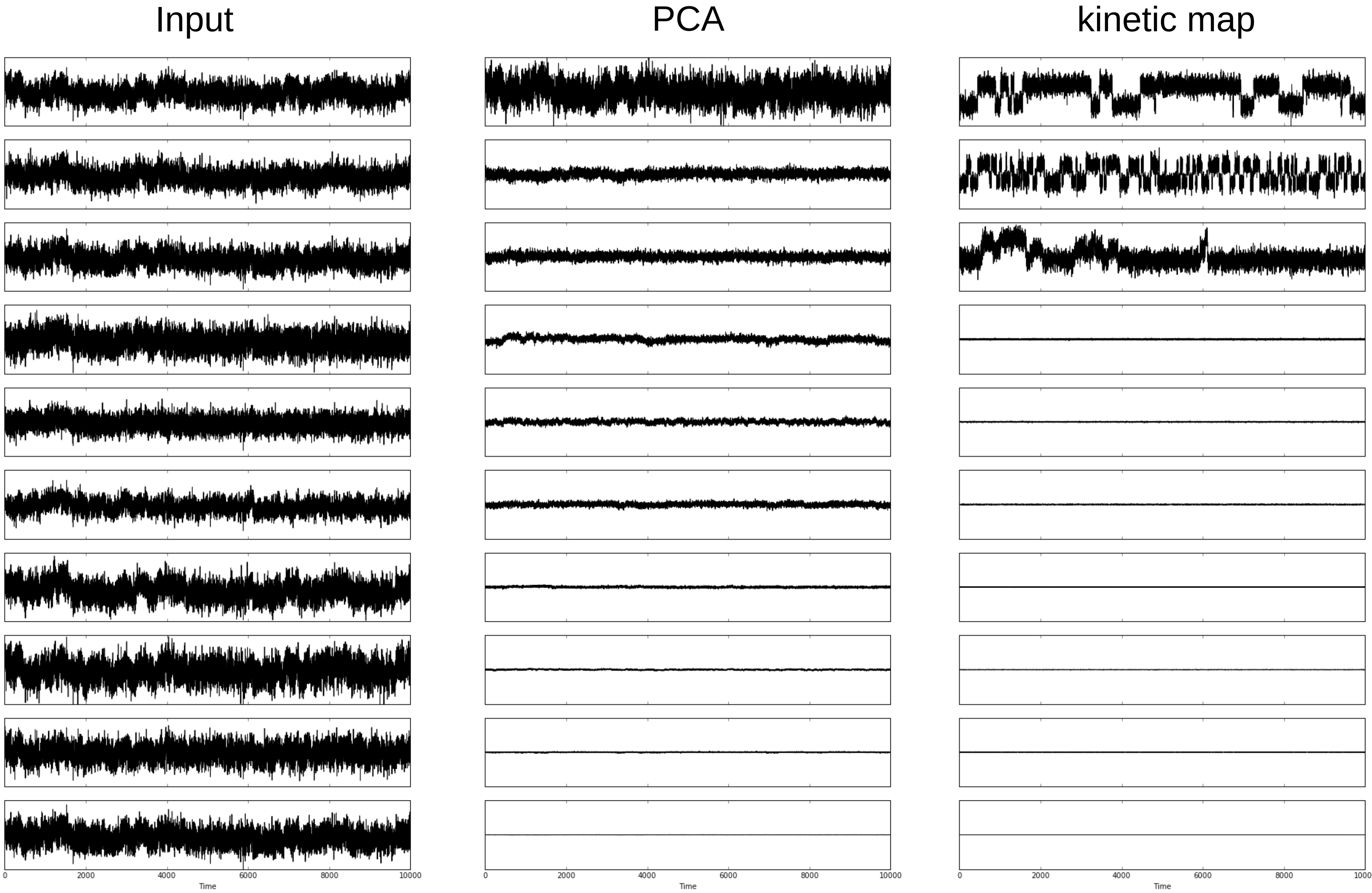

0
2000
4000
6000
8000
10000
Time



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

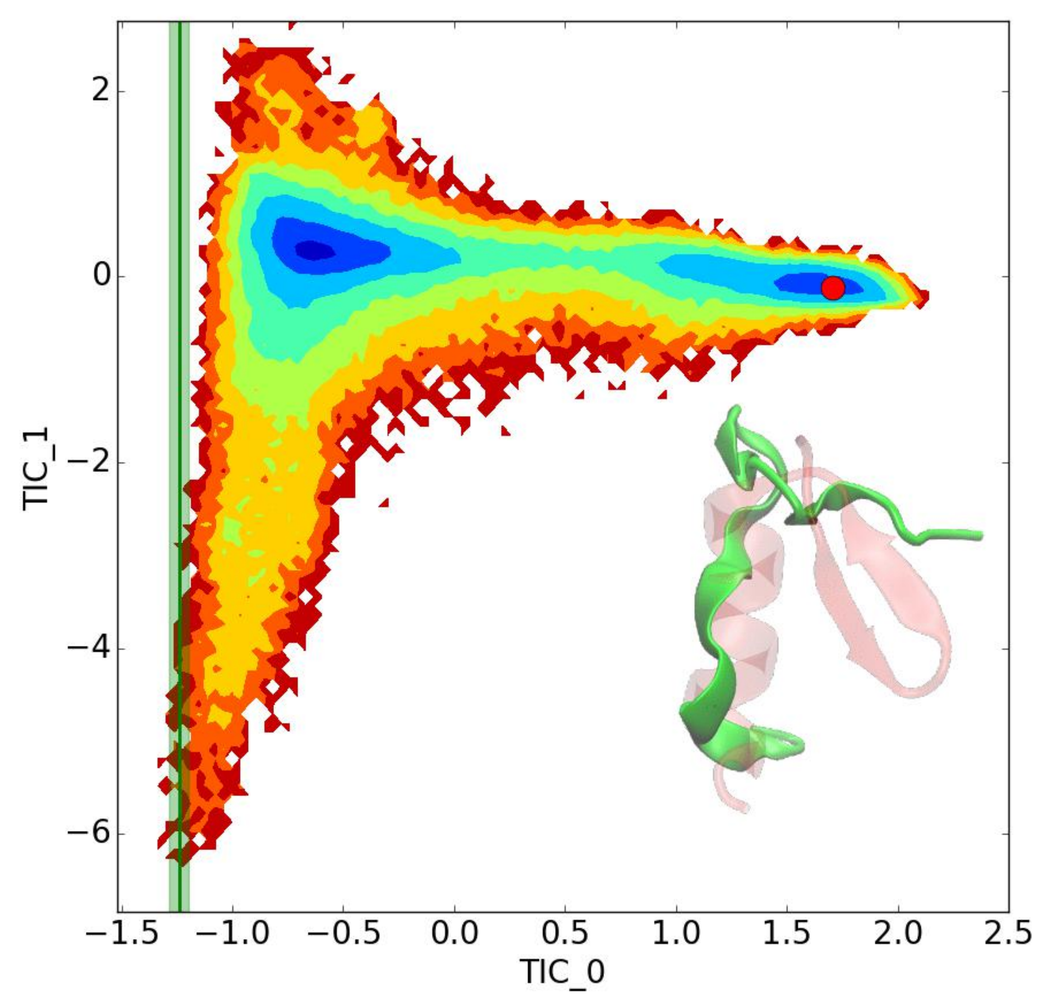


Variational Approach

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

Kinetic map:

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



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

Part II: Generalization

Variational approach for Markov processes (VAMP)

Wu and Noé, **arXiv**:1707.04659 (2017)

Hao Wu

Variational approach for Markov processes (VAMP)

Koopman operator

$$\begin{aligned}\mathcal{K}_\tau f(x) &= \mathbb{E}\left[f(x_{t+\tau})\,|x_t = x\right]\\ &= \int p_\tau(x,y)\,f(y)\,\mathrm{d}y\end{aligned}$$

Wu and Noé, **arXiv**:1707.04659 (2017)

Variational approach for Markov processes (VAMP)

Koopman operator

$$\begin{aligned}\mathcal{K}_\tau f(x) &= \mathbb{E}\left[f(x_{t+\tau})\,|x_t = x\right] \\ &= \int p_\tau(x,y)\, f(y)\, \mathrm{d}y\end{aligned}$$

Singular value decomposition:

$$\mathcal{K}_\tau f = \sum_i \sigma_i \langle \phi_i, f \rangle_{\rho_1} \psi_i$$

Wu and Noé, **arXiv**:1707.04659 (2017)

Variational approach for Markov processes (VAMP)

Koopman operator

$$\begin{aligned}\mathcal{K}_\tau f(x) &= \mathbb{E}\left[f(x_{t+\tau})\,|x_t = x\right] \\ &= \int p_\tau(x,y)\, f(y)\,\mathrm{d}y\end{aligned}$$

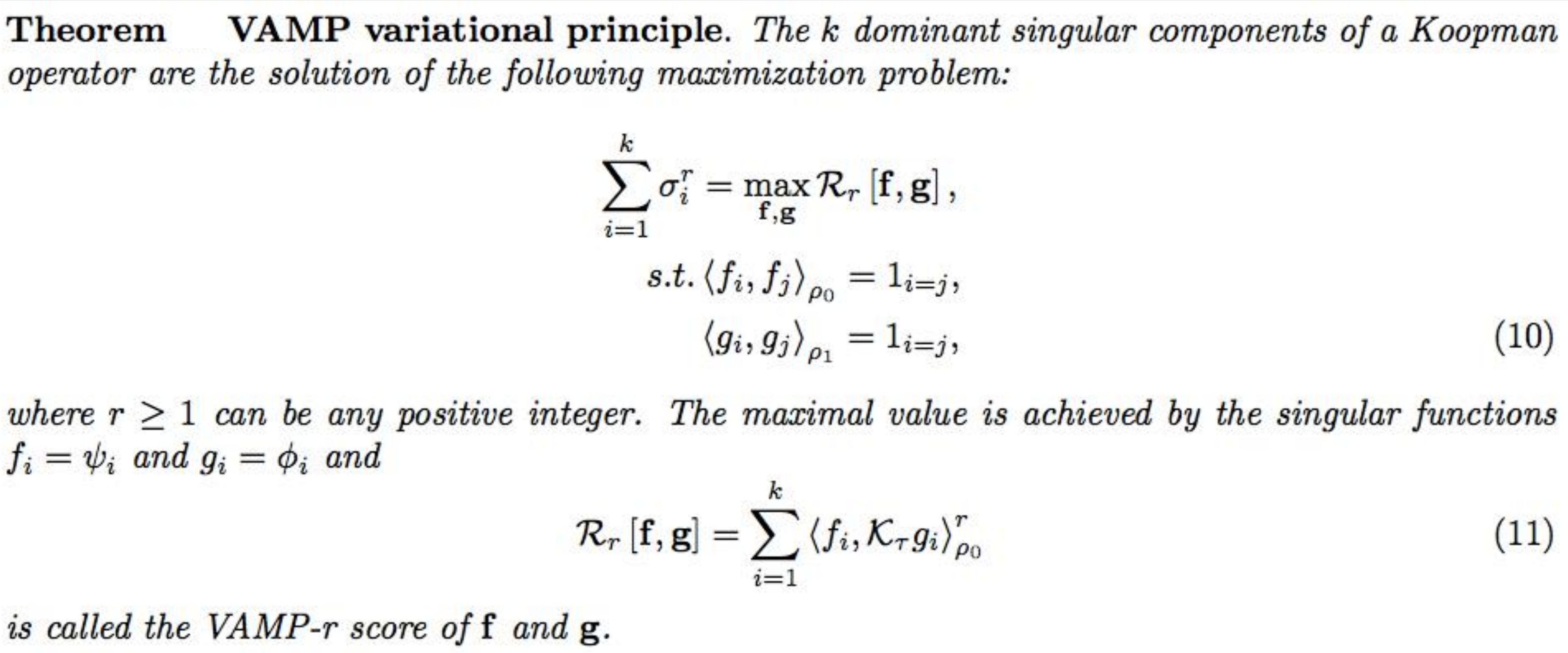
Singular value decomposition:

$$\mathcal{K}_\tau f = \sum_i \sigma_i \left\langle \phi_i, f\right\rangle_{\rho_1} \psi_i$$

- ρ_0, ρ_1 : empirical distribution of x_t, $x_{t+\tau}$
- If data are in equilibrium: stationary distribution $\mu = \rho_0 = \rho_1$
- $\{\phi_i\}$ and $\{\psi_i\}$ are both orthonormal bases with respect to $\langle\cdot,\cdot\rangle_{\rho_1}$ and $\langle\cdot,\cdot\rangle_{\rho_0}$,
- σ_i denotes the ith largest singular value.

Wu and Noé, **arXiv**:1707.04659 (2017)

Variational approach for Markov processes (VAMP)



Theorem **VAMP variational principle.** *The k dominant singular components of a Koopman operator are the solution of the following maximization problem:*

$$\begin{aligned}\sum_{i=1}^{k}\sigma_i^r &= \max_{\mathbf{f},\mathbf{g}} \mathcal{R}_r\left[\mathbf{f},\mathbf{g}\right], \\ s.t. \left\langle f_i, f_j \right\rangle_{\rho_0} &= 1_{i=j}, \\ \left\langle g_i, g_j \right\rangle_{\rho_1} &= 1_{i=j}, \end{aligned} \qquad (10)$$

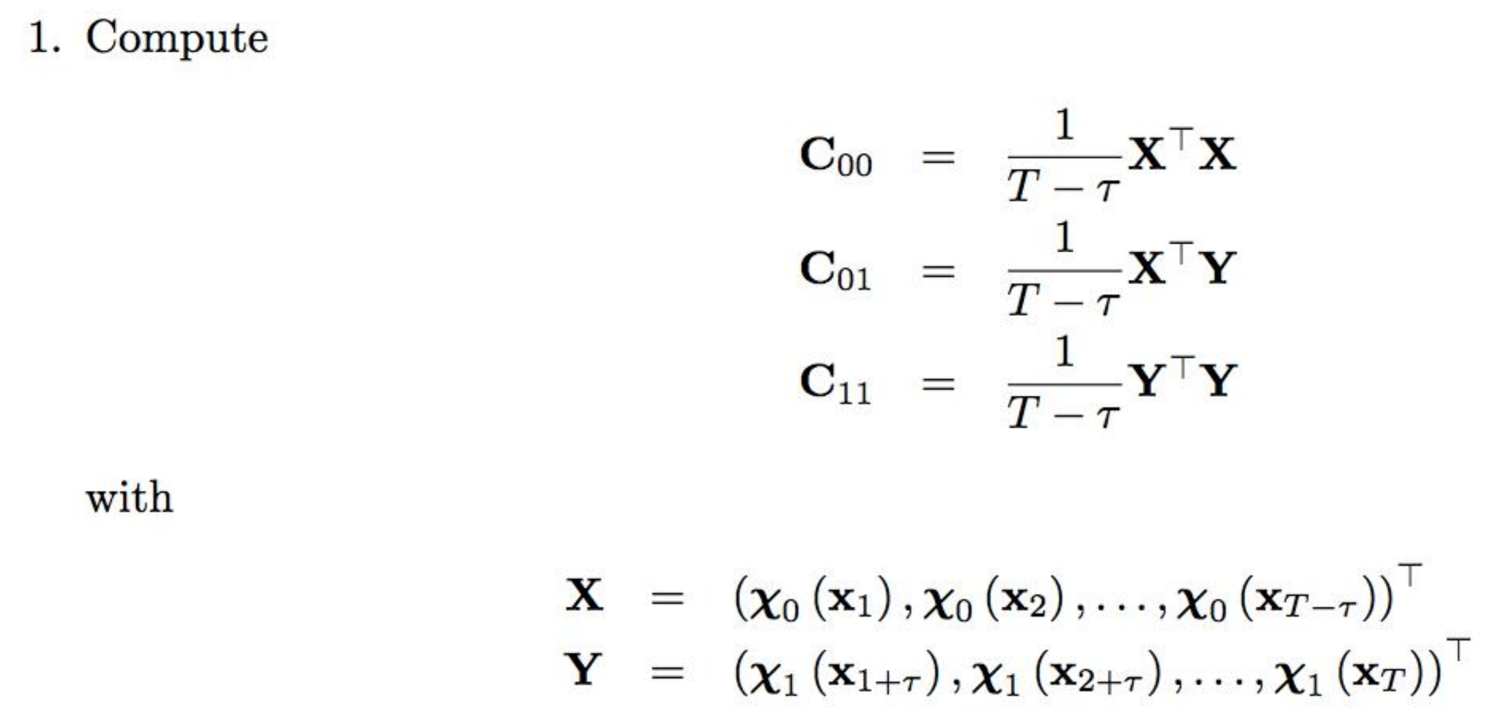
where $r \geq 1$ can be any positive integer. The maximal value is achieved by the singular functions $f_i = \psi_i$ and $g_i = \phi_i$ and

$$\mathcal{R}_r\left[\mathbf{f},\mathbf{g}\right] = \sum_{i=1}^{k} \langle f_i, \mathcal{K}_\tau g_i \rangle_{\rho_0}^r \qquad (11)$$

is called the VAMP-r score of $\mathbf{f}$ *and* $\mathbf{g}$.

Wu and Noé, **arXiv**:1707.04659 (2017)

Implementation: time-lagged canonical covariance analysis (TCCA)



1. Compute

$$
\begin{aligned}
\mathbf{C}_{00} &= \frac{1}{T-\tau}\mathbf{X}^\top\mathbf{X} \\
\mathbf{C}_{01} &= \frac{1}{T-\tau}\mathbf{X}^\top\mathbf{Y} \\
\mathbf{C}_{11} &= \frac{1}{T-\tau}\mathbf{Y}^\top\mathbf{Y}
\end{aligned}
$$

with

$$
\begin{aligned}
\mathbf{X} &= \left(\boldsymbol{\chi}_0\left(\mathbf{x}_1\right), \boldsymbol{\chi}_0\left(\mathbf{x}_2\right), \ldots, \boldsymbol{\chi}_0\left(\mathbf{x}_{T-\tau}\right)\right)^\top \\
\mathbf{Y} &= \left(\boldsymbol{\chi}_1\left(\mathbf{x}_{1+\tau}\right), \boldsymbol{\chi}_1\left(\mathbf{x}_{2+\tau}\right), \ldots, \boldsymbol{\chi}_1\left(\mathbf{x}_T\right)\right)^\top
\end{aligned}
$$

Wu and Noé, **arXiv**:1707.04659 (2017)

Implementation: time-lagged canonical covariance analysis (TCCA)

1. Compute

$$\begin{aligned}\mathbf{C}_{00} &= \frac{1}{T-\tau}\mathbf{X}^\top\mathbf{X}\\ \mathbf{C}_{01} &= \frac{1}{T-\tau}\mathbf{X}^\top\mathbf{Y}\\ \mathbf{C}_{11} &= \frac{1}{T-\tau}\mathbf{Y}^\top\mathbf{Y}\end{aligned}$$

   with

$$\begin{aligned}\mathbf{X} &= \left(\boldsymbol{\chi}_0\left(\mathbf{x}_1\right), \boldsymbol{\chi}_0\left(\mathbf{x}_2\right), \ldots, \boldsymbol{\chi}_0\left(\mathbf{x}_{T-\tau}\right)\right)^\top\\ \mathbf{Y} &= \left(\boldsymbol{\chi}_1\left(\mathbf{x}_{1+\tau}\right), \boldsymbol{\chi}_1\left(\mathbf{x}_{2+\tau}\right), \ldots, \boldsymbol{\chi}_1\left(\mathbf{x}_{T}\right)\right)^\top\end{aligned}$$

2. Perform the truncated SVD

$$\mathbf{C}_{00}^{-\frac{1}{2}}\mathbf{C}_{01}\mathbf{C}_{11}^{-\frac{1}{2}} \approx \mathbf{U}_k\hat{\mathbf{\Sigma}}_k\mathbf{V}_k^\top$$

3. Output $\hat{\mathbf{\Sigma}}_k$, $\boldsymbol{\psi} = \mathbf{U}_k^\top\mathbf{C}_{00}^{-\frac{1}{2}}\boldsymbol{\chi}_0$ and $\boldsymbol{\phi} = \mathbf{V}_k^\top\mathbf{C}_{11}^{-\frac{1}{2}}\boldsymbol{\chi}_1$

Wu and Noé, **arXiv**:1707.04659 (2017)

Implementation: time-lagged canonical covariance analysis (TCCA)

1. Compute

$$\begin{aligned}\mathbf{C}_{00} &= \frac{1}{T-\tau}\mathbf{X}^\top\mathbf{X}\\ \mathbf{C}_{01} &= \frac{1}{T-\tau}\mathbf{X}^\top\mathbf{Y}\\ \mathbf{C}_{11} &= \frac{1}{T-\tau}\mathbf{Y}^\top\mathbf{Y}\end{aligned}$$

   with

$$\begin{aligned}\mathbf{X} &= \left(\boldsymbol{\chi}_0\left(\mathbf{x}_1\right), \boldsymbol{\chi}_0\left(\mathbf{x}_2\right), \ldots, \boldsymbol{\chi}_0\left(\mathbf{x}_{T-\tau}\right)\right)^\top\\ \mathbf{Y} &= \left(\boldsymbol{\chi}_1\left(\mathbf{x}_{1+\tau}\right), \boldsymbol{\chi}_1\left(\mathbf{x}_{2+\tau}\right), \ldots, \boldsymbol{\chi}_1\left(\mathbf{x}_{T}\right)\right)^\top\end{aligned}$$

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3. Output $\hat{\mathbf{\Sigma}}_k$, $\boldsymbol{\psi} = \mathbf{U}_k^\top\mathbf{C}_{00}^{-\frac{1}{2}}\boldsymbol{\chi}_0$ and $\boldsymbol{\phi} = \mathbf{V}_k^\top\mathbf{C}_{11}^{-\frac{1}{2}}\boldsymbol{\chi}_1$

For the choice $\boldsymbol{\chi}_0 = \boldsymbol{\chi}_1$, TCCA is consistent with EDMD:

$$\mathbf{K}_\tau^\top = \mathbf{C}_{01}^\top\mathbf{C}_{00}^{-1}$$

Wu and Noé, **arXiv**:1707.04659 (2017)

Part III

VAMPnets: deep learning of molecular kinetics

Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012

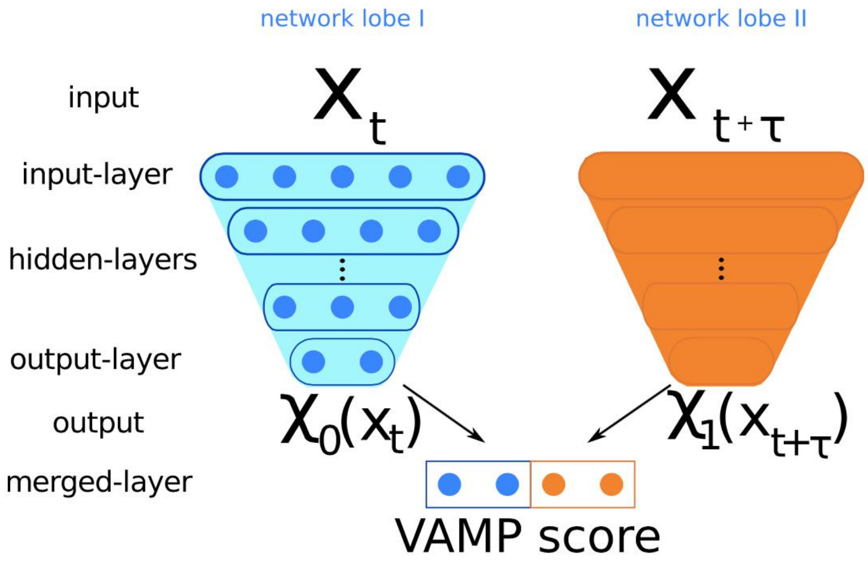
Andreas Mardt

Luca Pasquali

Neural networks

Hao Wu

Theory



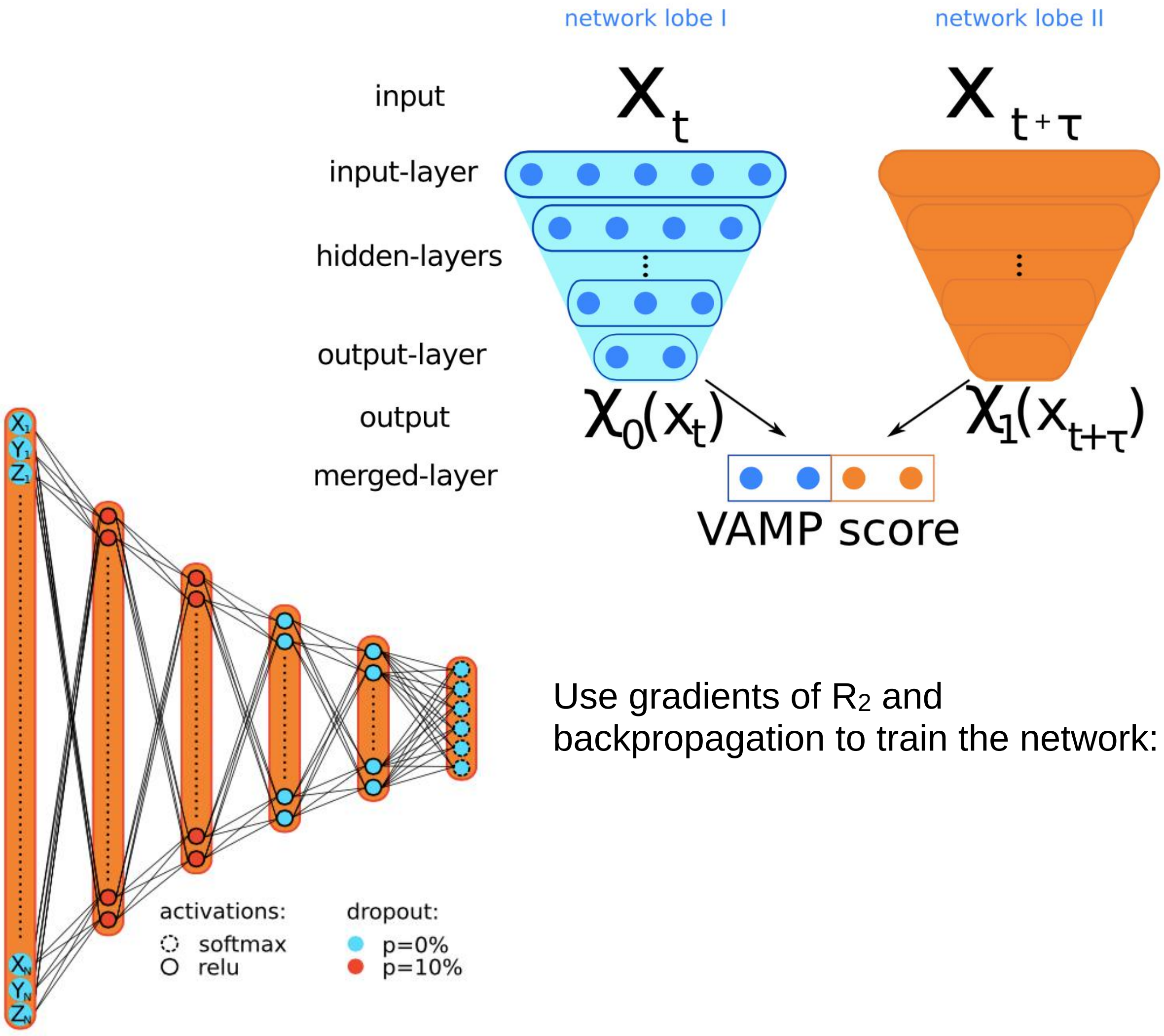
VAMP variational principle (subspace version)

For any two sets of linearly independent functions $\boldsymbol{\chi}_0(\mathbf{x}) = (\chi_{01}(\mathbf{x}), ..., \chi_{0n}(\mathbf{x}))$ *and* $\boldsymbol{\chi}_1(\mathbf{x}) = (\chi_{11}(\mathbf{x}), ..., \chi_{1n}(\mathbf{x}))$, *let us call*

$$\hat{R}_2[\boldsymbol{\chi}_0, \boldsymbol{\chi}_1] = \left\| \mathbf{C}_{00}^{-\frac{1}{2}} \mathbf{C}_{01} \mathbf{C}_{11}^{-\frac{1}{2}} \right\|_F^2$$

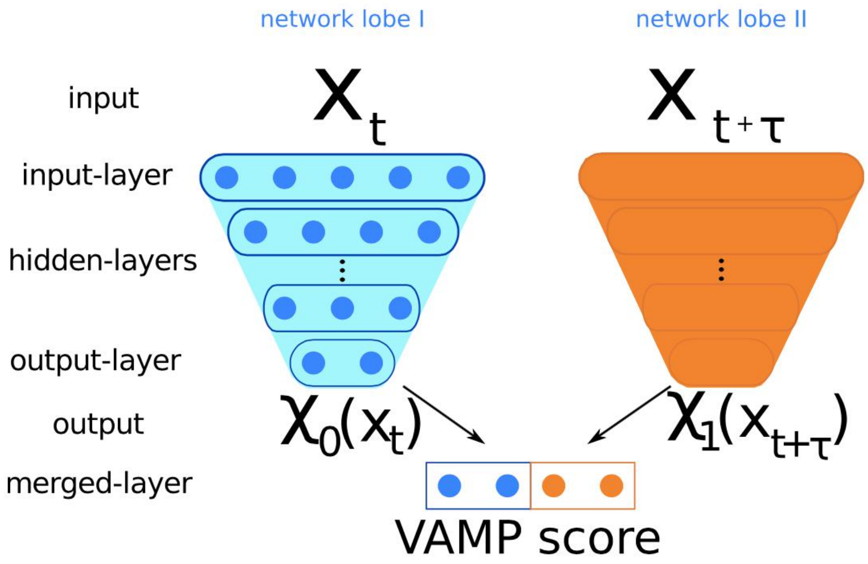
their VAMP-2 score, where $\mathbf{C}_{00}$, $\mathbf{C}_{01}$, $\mathbf{C}_{11}$ *are the feature correlation matrices as defined earlier and* $\|\cdot\|_F$ *indicates the Frobenius norm. The maximum value of the VAMP-2 score is achieved when the top* n *left and right Koopman singular functions belong to* $\mathrm{span}(\boldsymbol{\chi}_0)$ *and* $\mathrm{span}(\boldsymbol{\chi}_1)$, *respectively.*

Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012



Use gradients of R_2 and backpropagation to train the network:

Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012



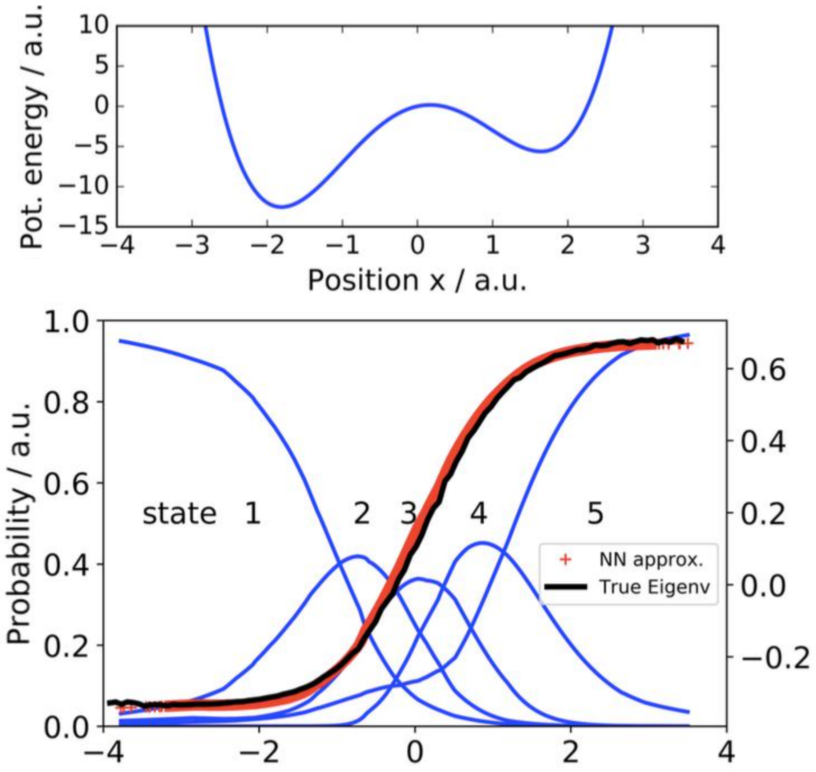
Resulting Koopman model: $\mathbf{K} = \mathbf{C}_{00}^{-1}\mathbf{C}_{01}.$

Relaxation timescales: $t_i(\tau) = -\frac{\tau}{\ln|\lambda_i(\tau)|},$

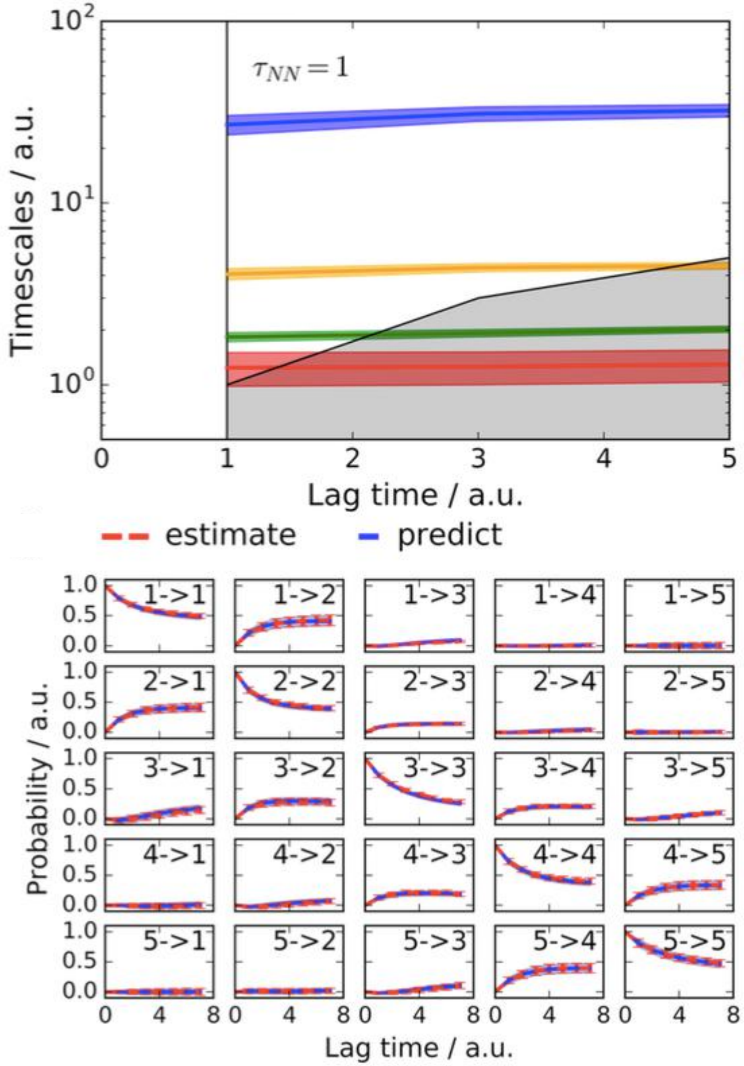
Validate (Chapman-Kolmogorov test): $\mathbf{K}(n\tau) = \mathbf{K}^n(\tau),$

Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012

Asymmetric double well

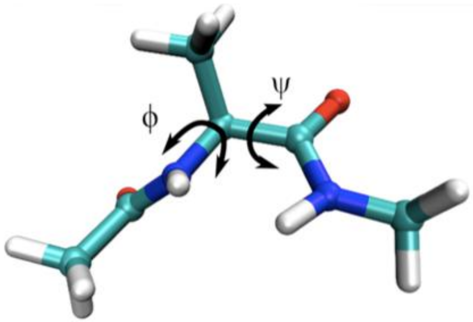


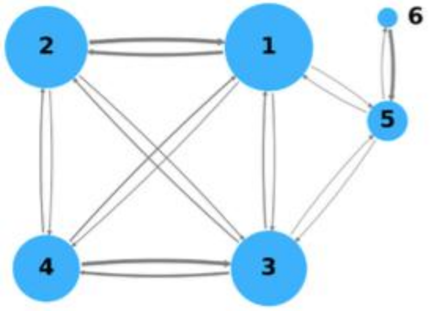
Validation



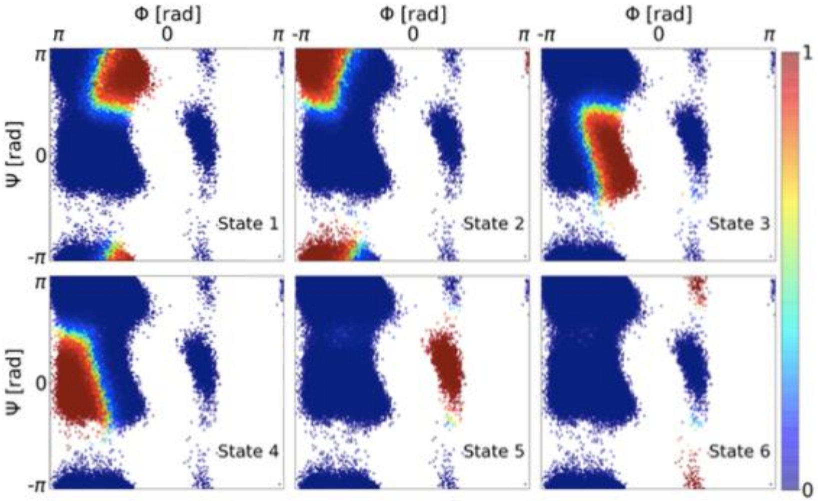
Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012

Alanine dipeptide

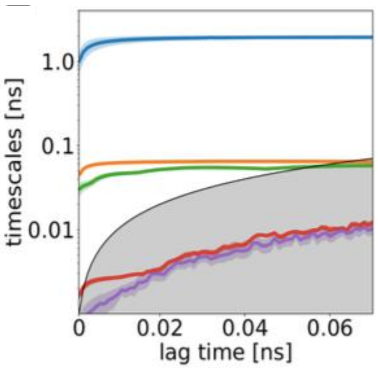


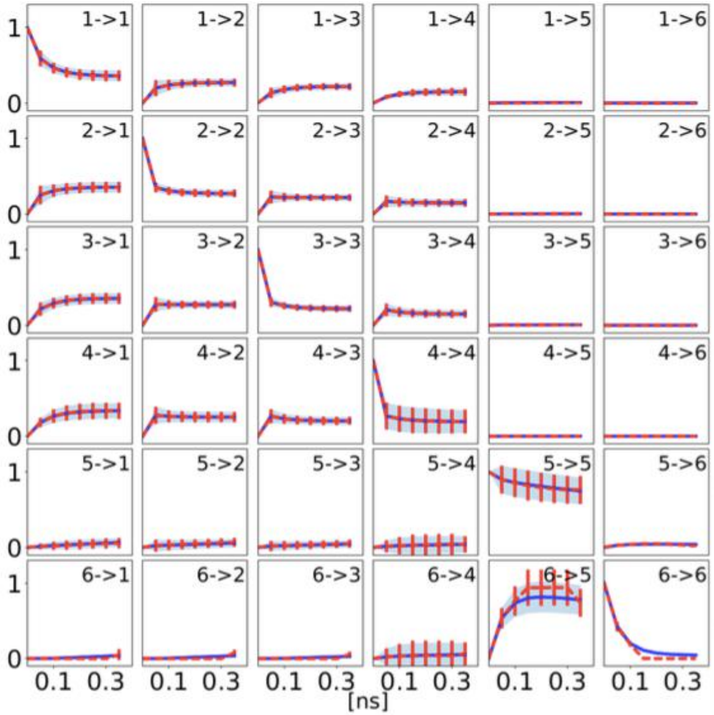


Max. transition probability: 41%
Min. transition probability: 0.5%

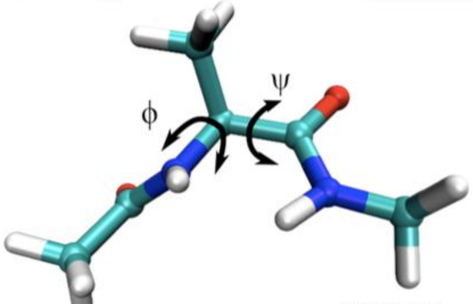


Validation

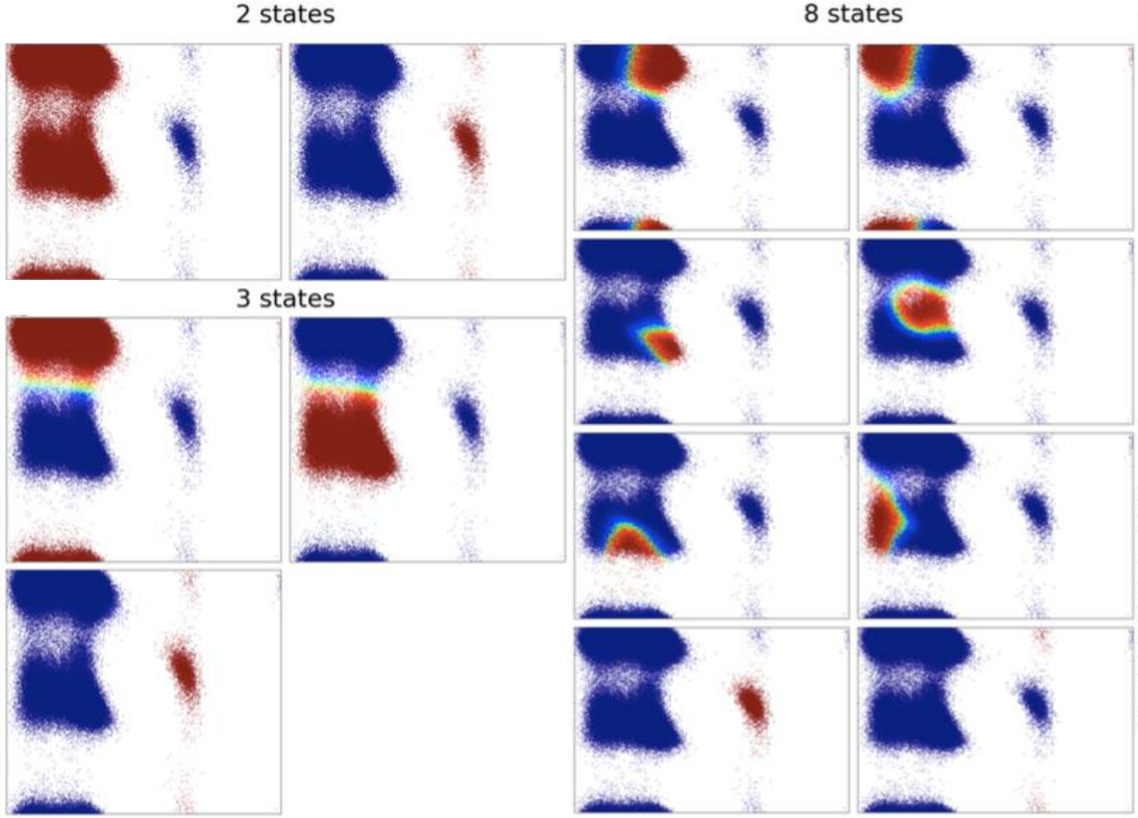


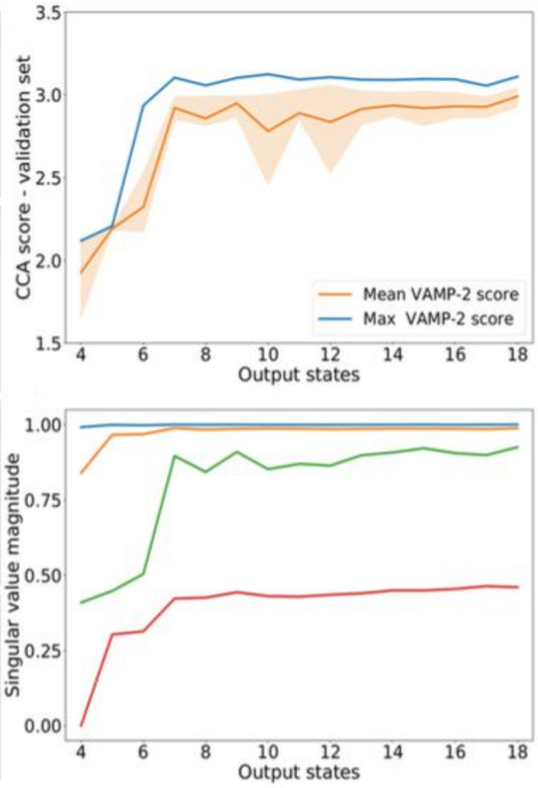


Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012



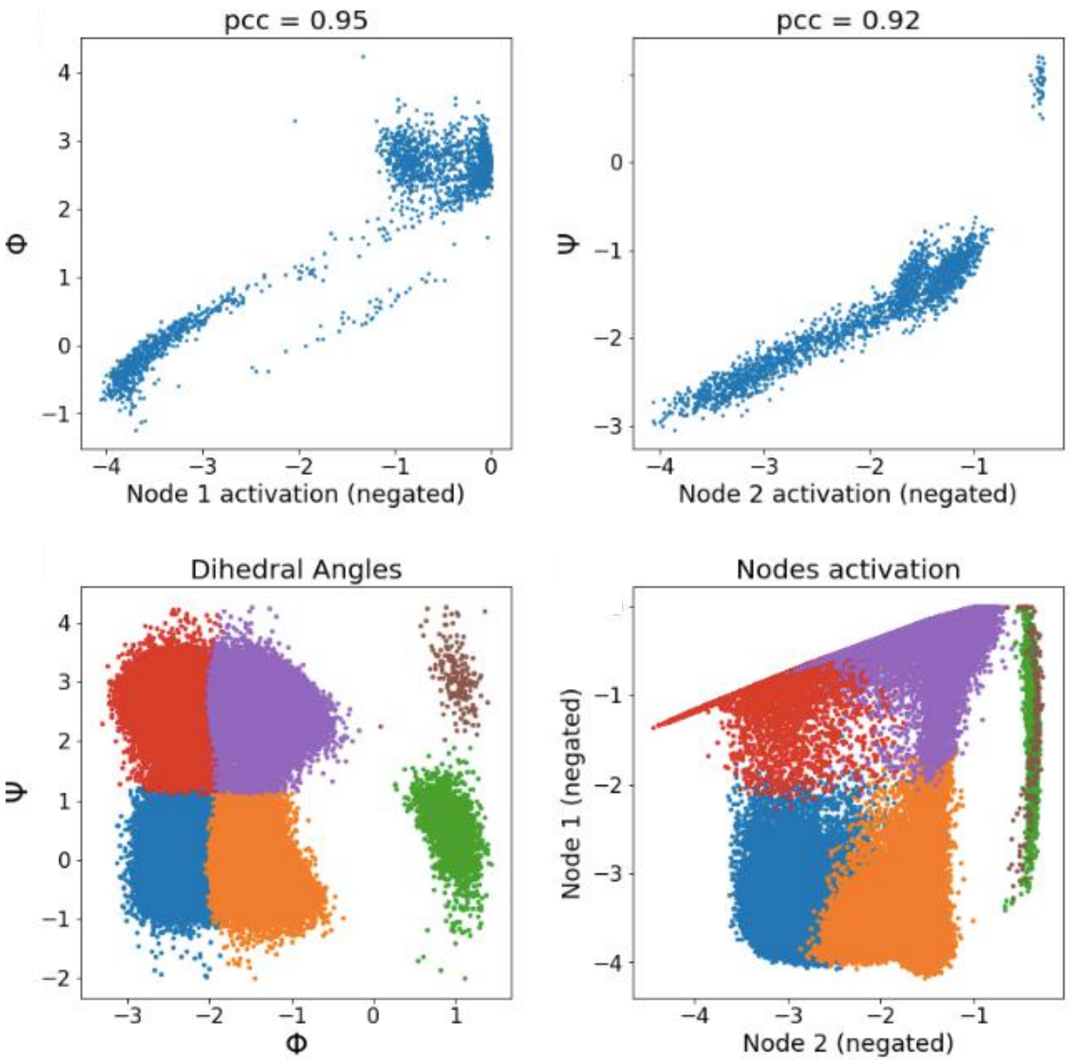
Results as a function of the number of states





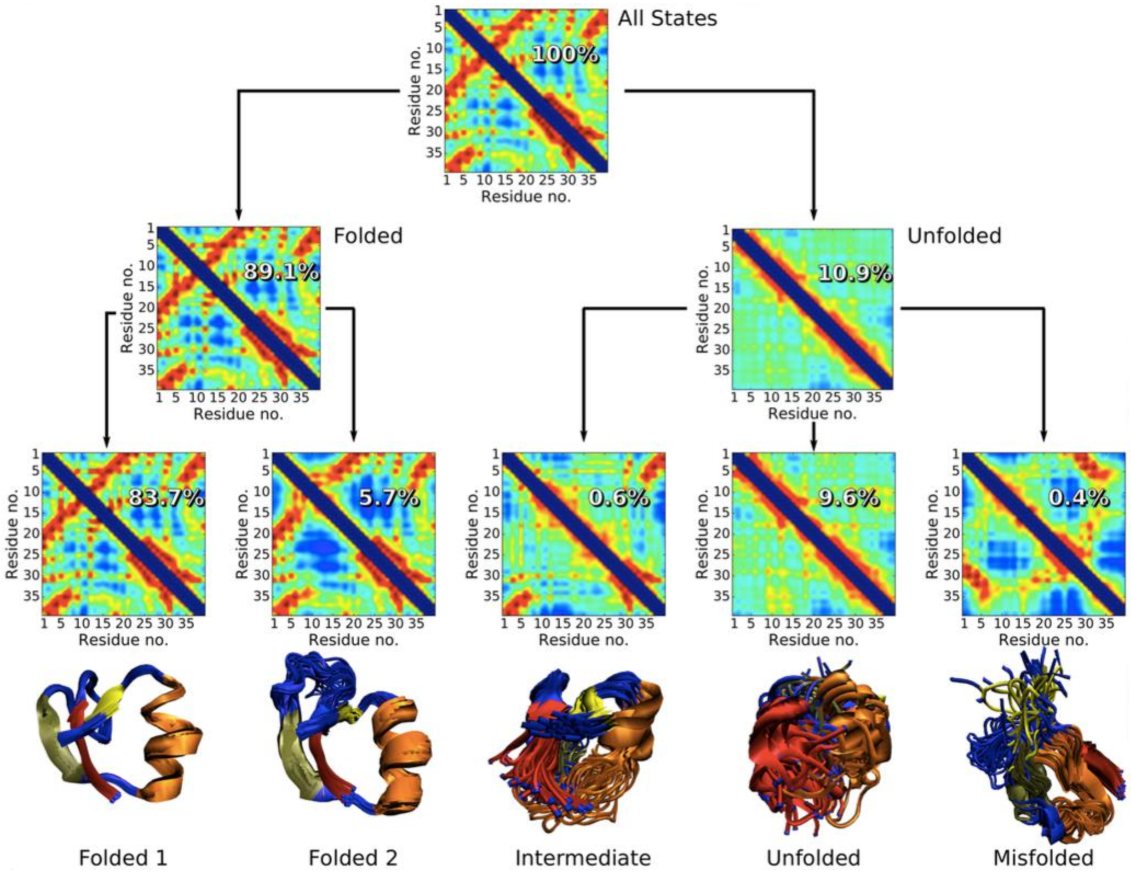
Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012

A network with a bottleneck of 2 neurons learns the phi/psi dihedral angles

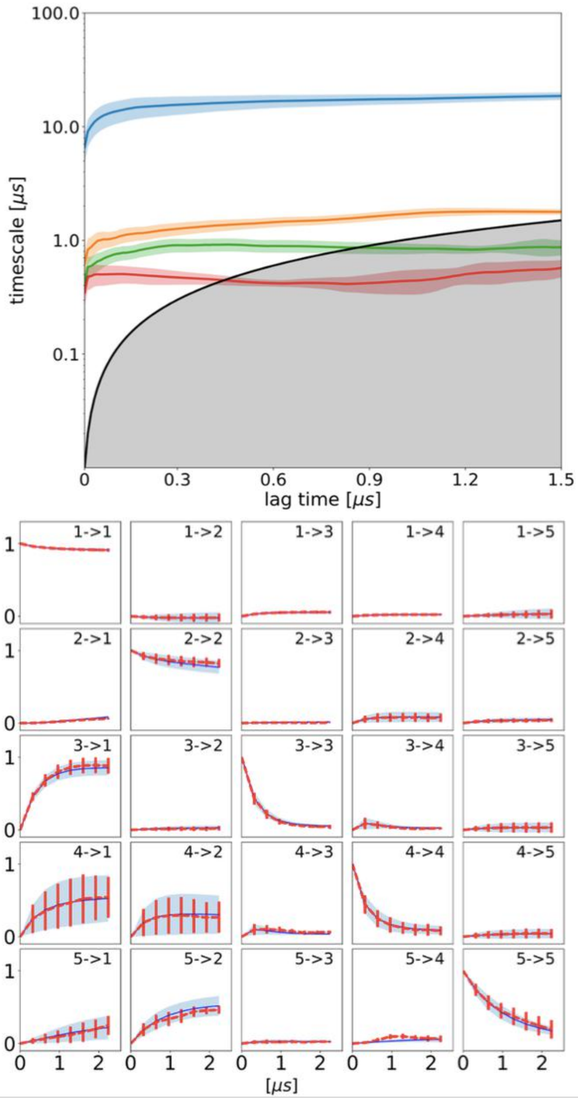


Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012

NTL9 Protein folding



Validation



Mardt, Pasquali, Wu, Noé **arXiv**:1710.06012

Reminder

Application to protein-protein association

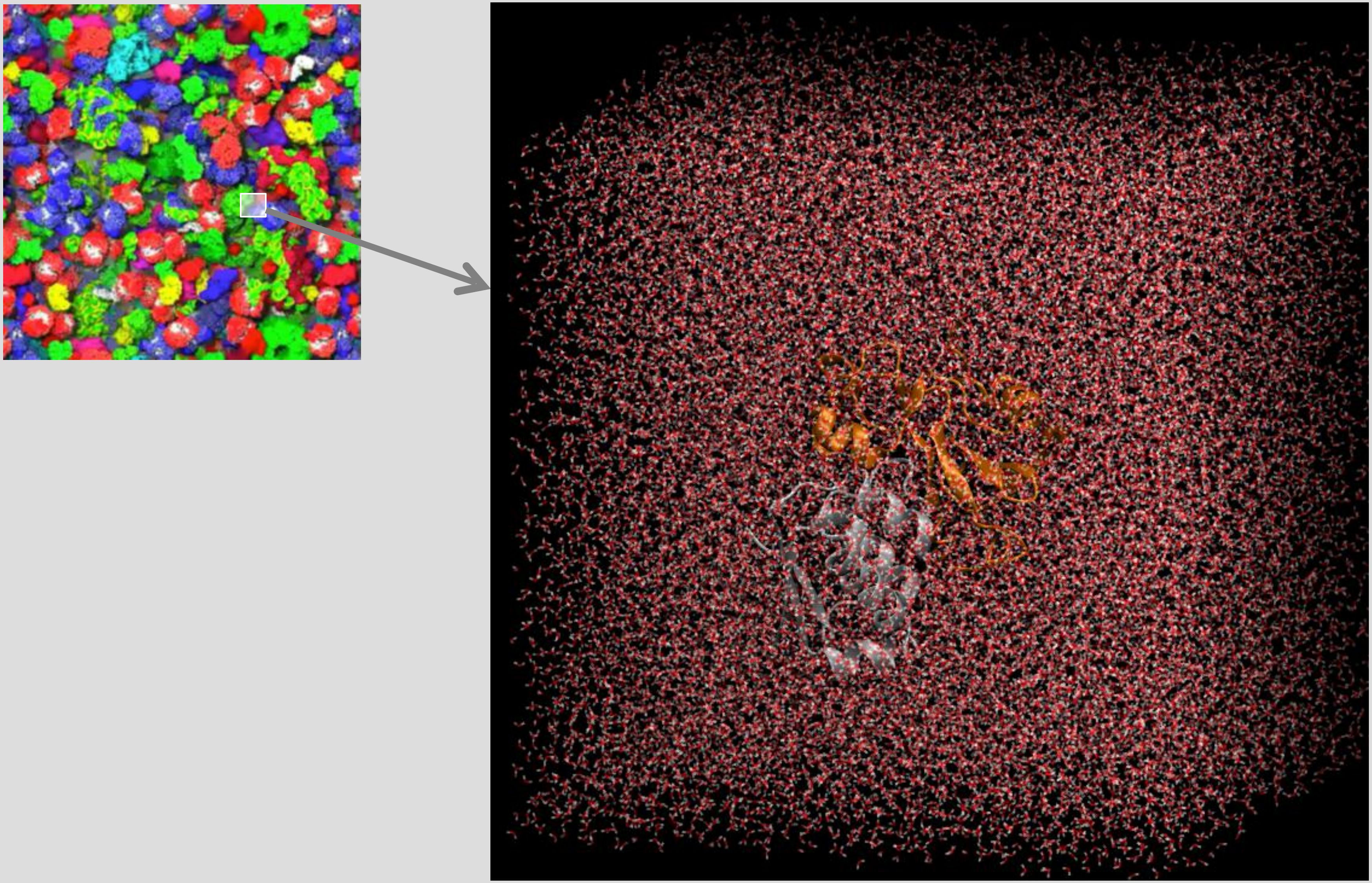
Plattner, Doerr, De Fabritiis, Noé **Nature Chemistry** 9, 1005-11 (2017)

Nuria Plattner

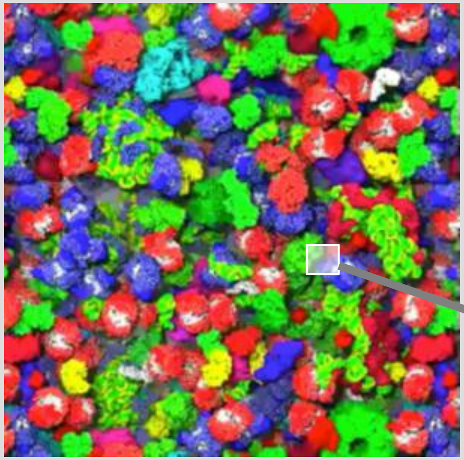
Stefan Doerr

Gianni De Fabritiis

Protein-Protein binding



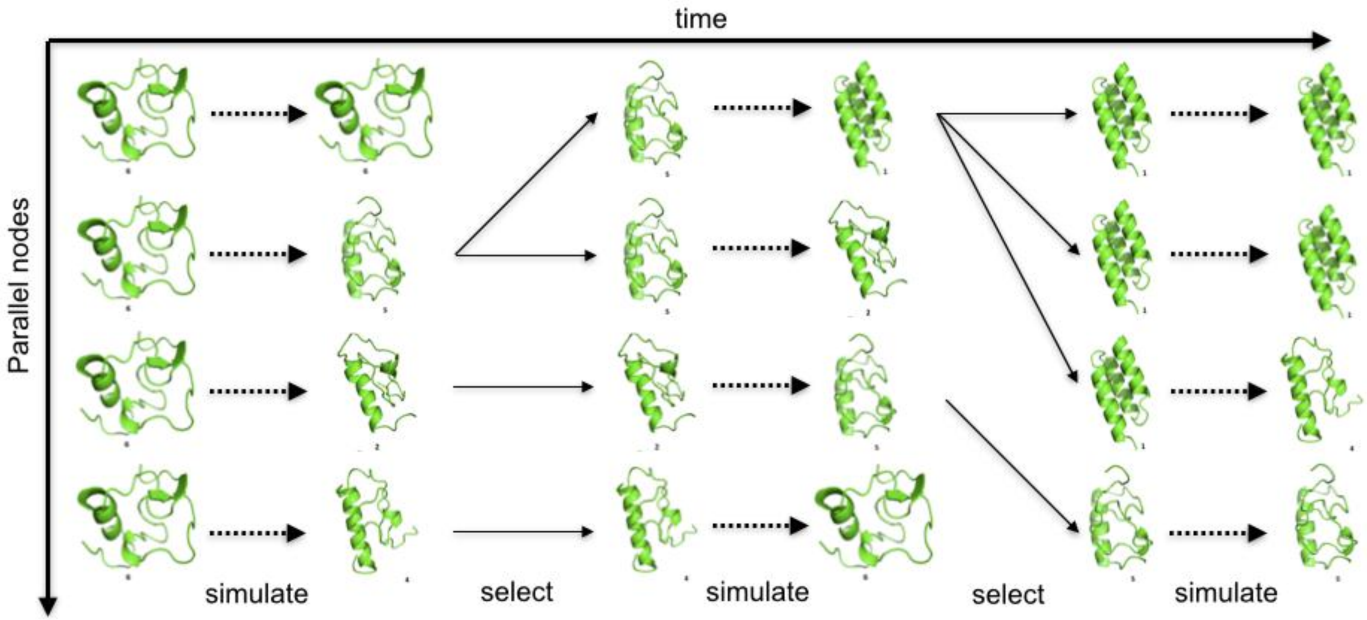
Protein-Protein binding

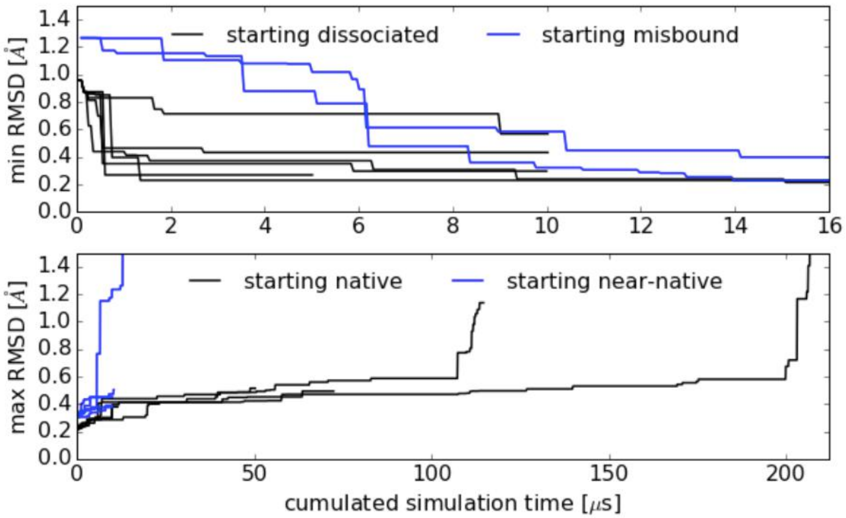


Plattner, Doerr, De Fabritiis, Noé
Nature Chemistry (2017)

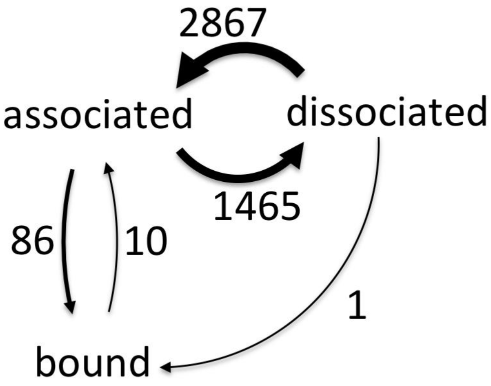
0.1 microseconds

1) Adaptive molecular dynamics

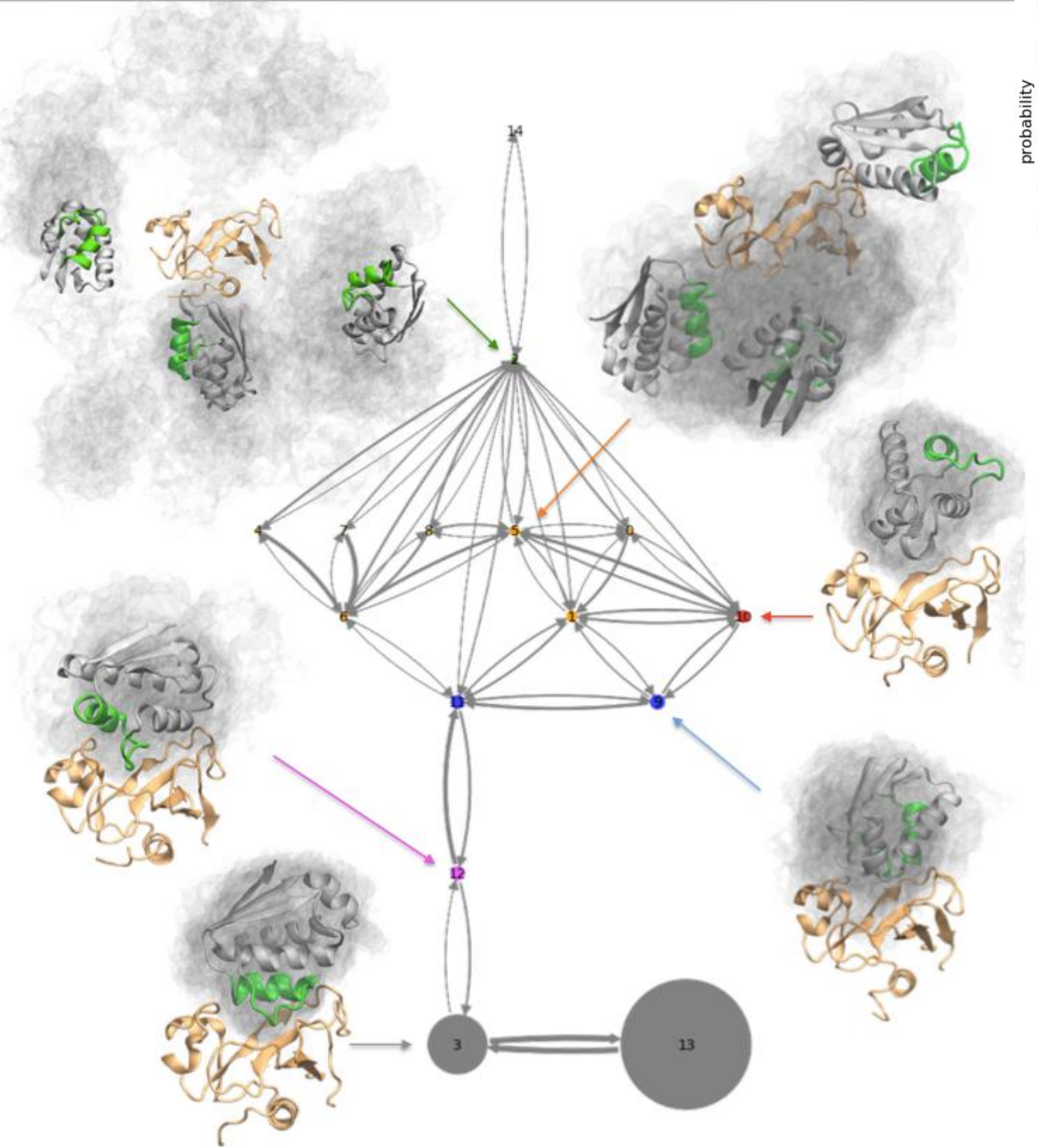


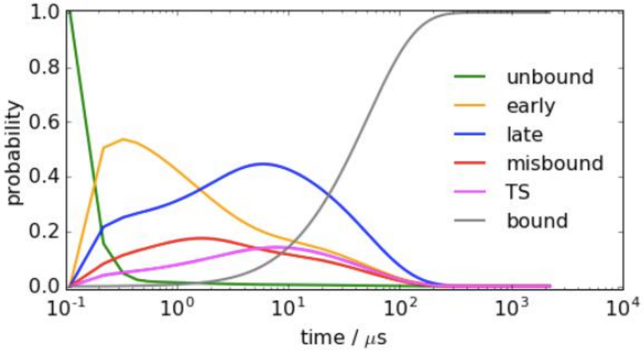


2 ms simulation time total



Plattner, Doerr, De Fabritiis, Noé
Nature Chemistry (2017)





Plattner, Doerr, De Fabritiis, Noé
Nature Chemistry (2017)

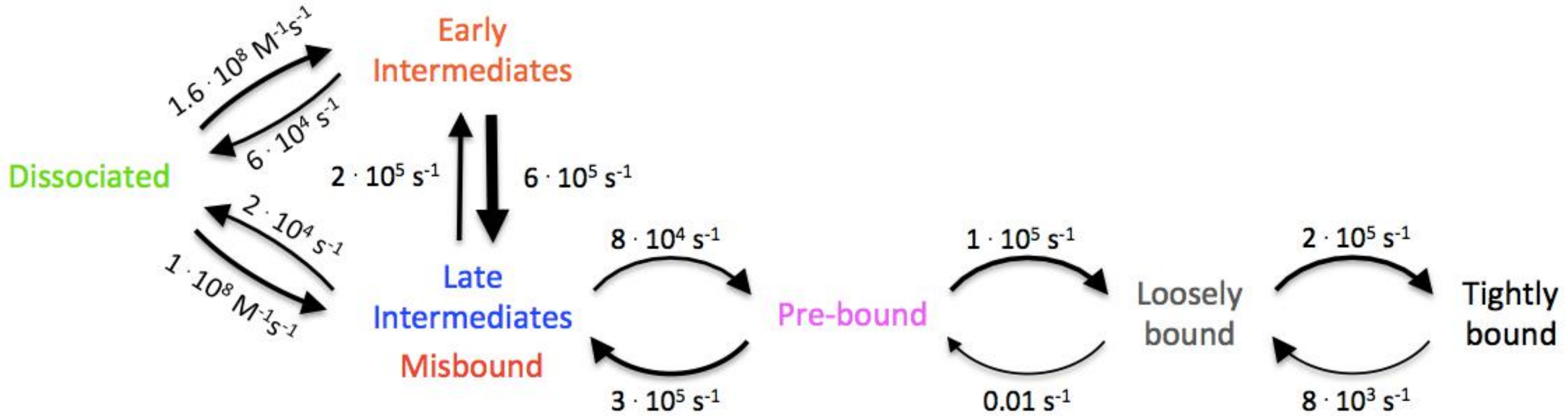
Protein-Protein binding

Plattner, Doerr, De Fabritiis, Noé

Nature Chemistry (2017)

0.1 milliseconds

Coarse-grained model

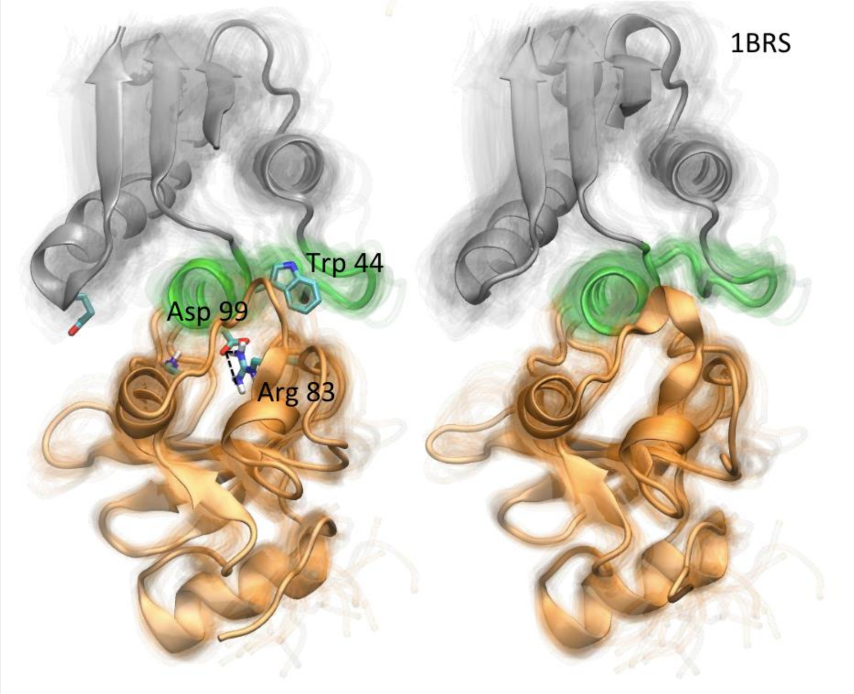


Plattner, Doerr, De Fabritiis, Noé
Nature Chemistry (2017)

Validation of the model

- crystal structure 1BRS predicted by the most stable HMM state (95% population)

  average heavy-atom RMSD 2.1 A



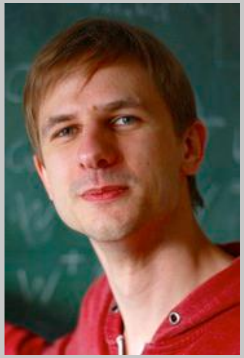
	Model	95% confidence interval	Experiment
• **Binding free energy**	**14.8** kcal / mol	(12.3 … 19.3)	**16.8** kcal/mol
• **Association rate**	**0.74 10^8** $s^{-1}M^{-1}$	(0.72 … 0.75)	**$1 \cdot 10^8$** $s^{-1}M^{-1}$

Plattner, Doerr, De Fabritiis, Noé
Nature Chemistry (2017)

Part IV

Precise kinetics beyond the seconds timescale: Multi-ensemble Markov models

Wu, Paul, Wehmeyer, Noé **PNAS** 113, E3221-E3230 (2016)
Paul et al., **Nature Communications** 8, 1095 (2017)



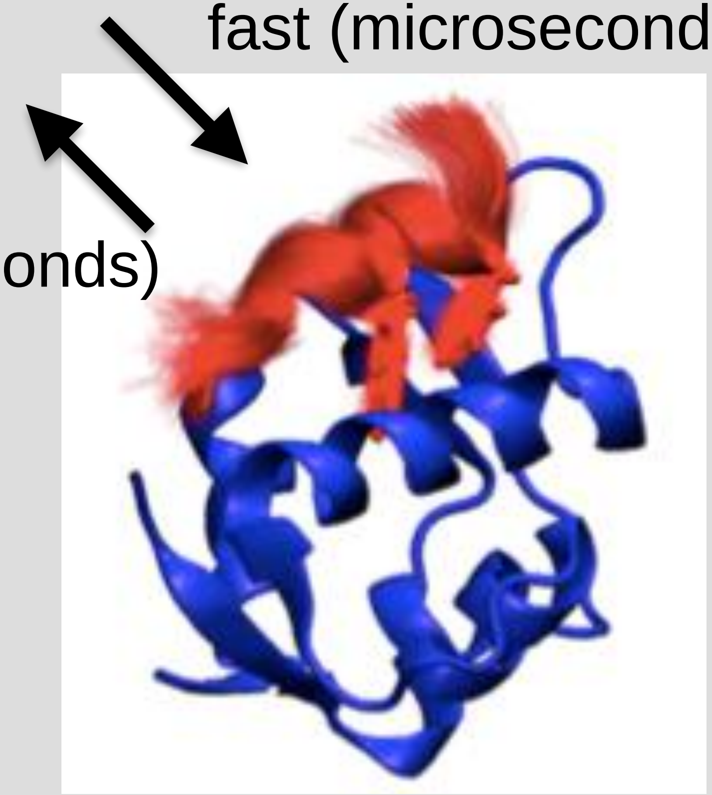
Hao Wu
Theory

Christoph Wehmeyer
Software and Methods

Fabian Paul
Theory and Methods

Esam Abualrous
Experiments

Example: binding and folding of PMI to MDM2

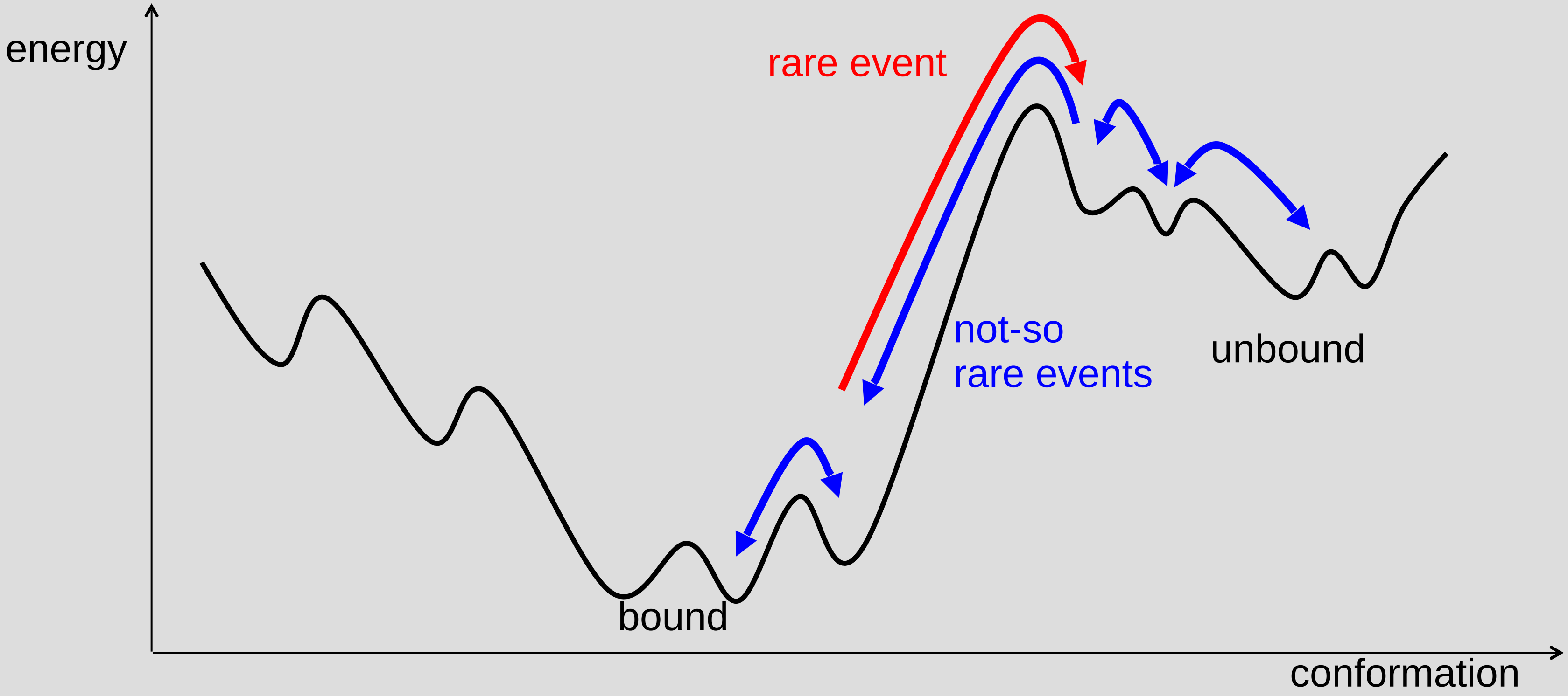


fast (microseconds)

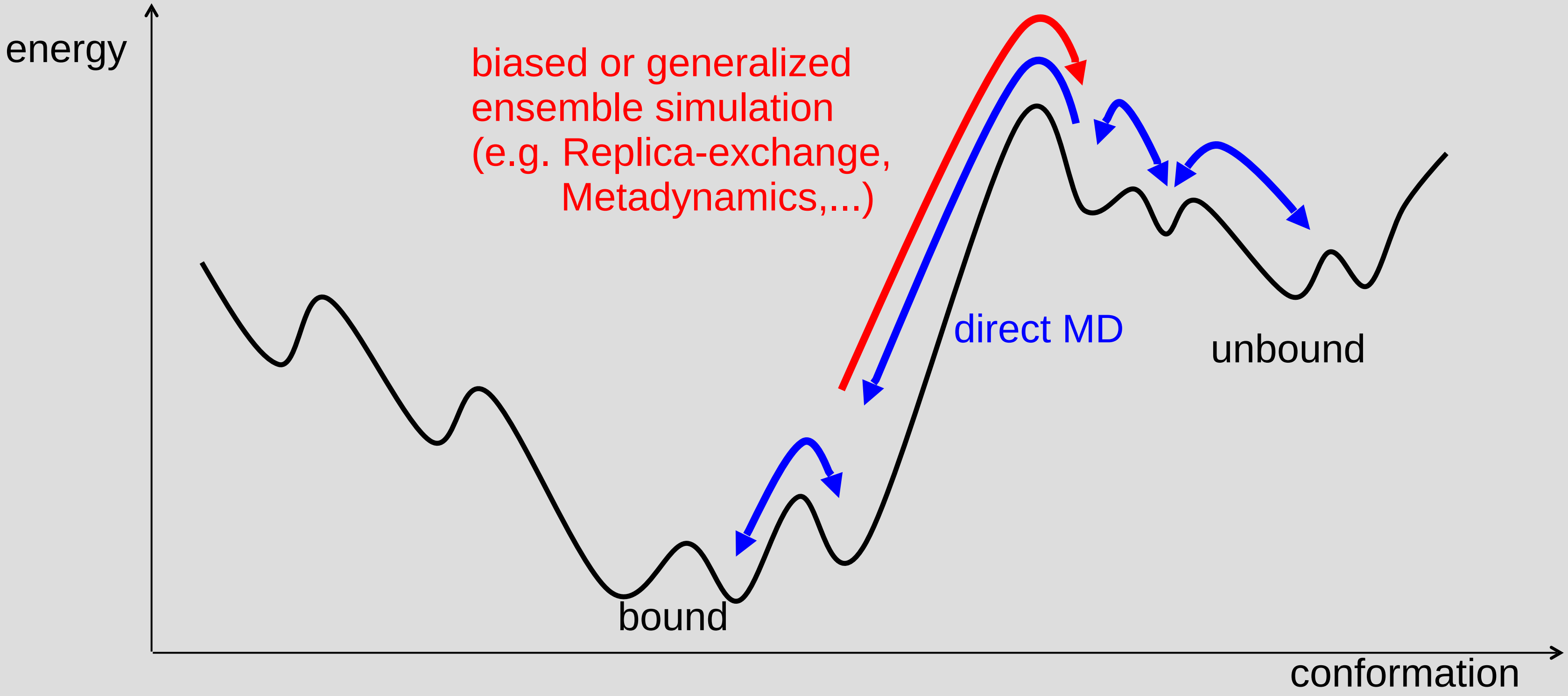
slow (10-100 milliseconds)

nanomolar binder

Bad situation: single high barriers (e.g. salt bridge)



Bad situation: single high barriers (e.g. salt bridge)



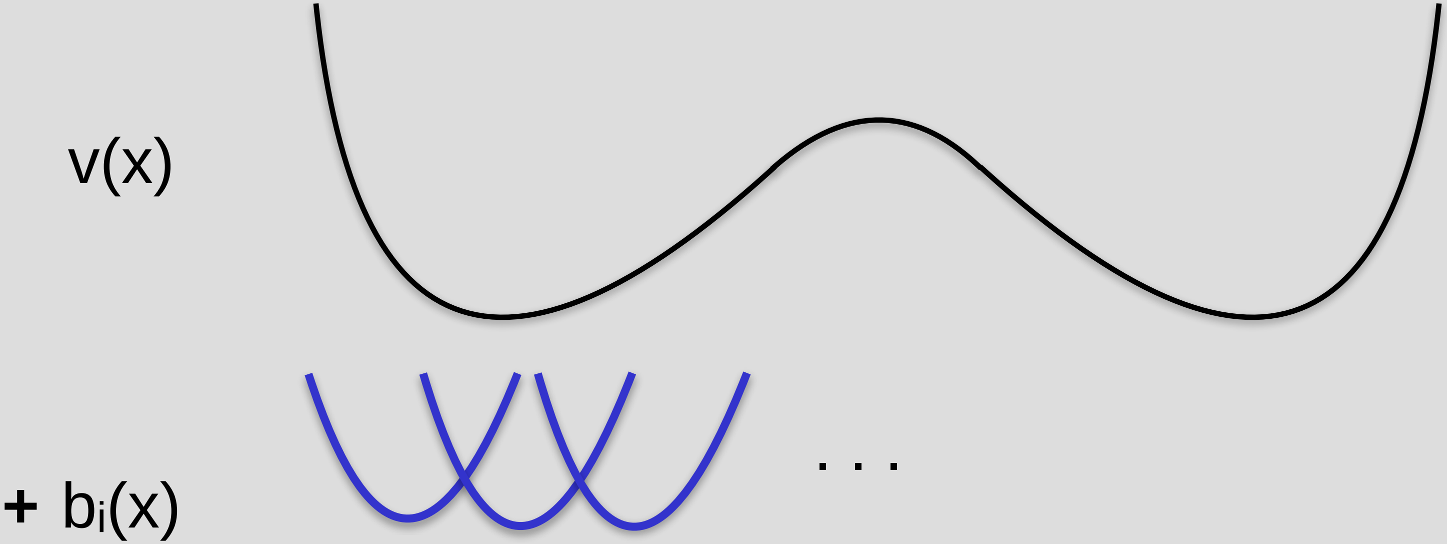
direct molecular dynamics

biased or generalized
ensemble simulation

joint optimal estimate?

Wu, Mey, Rosta, Noé, **JCP** 141, 214106 (2014)

Example for an enhanced sampling method: Umbrella sampling



Equilibrium distribution: $\mu(x) = \mathrm{e}^{f - u(x)}$

Biased equilibrium distribution: $\mu^k(x) = \mathrm{e}^{f^k - b^k(x)} \mu(x)$

Multiensemble Markov model (MEMM)

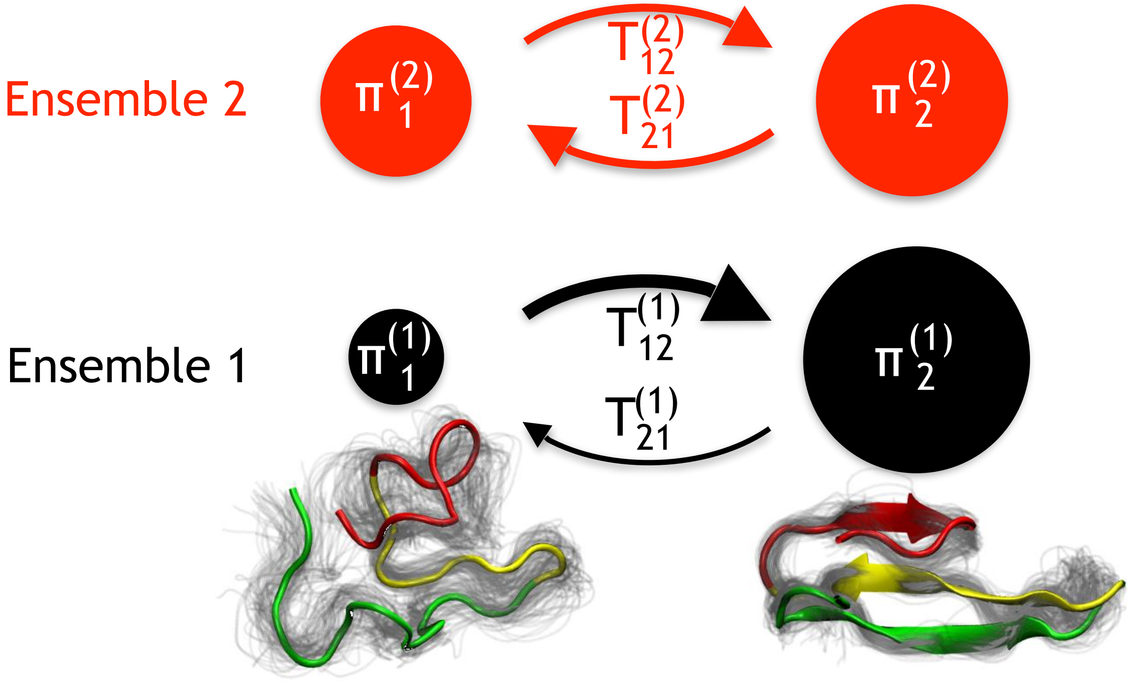
$$\begin{pmatrix} T_{11}^{(1)} & \cdots & T_{1n}^{(1)} \\ \vdots & \ddots & \vdots \\ T_{n1}^{(1)} & \cdots & T_{11}^{(1)} \end{pmatrix}$$

$$\begin{pmatrix} T_{11}^{(2)} & \cdots & T_{1n}^{(2)} \\ \vdots & \ddots & \vdots \\ T_{n1}^{(2)} & \cdots & T_{11}^{(2)} \end{pmatrix}$$

$$\ddots$$

Thermodynamic state / Ensemble

Configuration state



Wu, Paul, Wehmeyer and Noé **PNAS** 113, E3221-E3230 (2016)

TRAM

Transition-based
Reweighting
Analysis
Method

optimally combines reweighting information and transition information to joint estimate of stationary and kinetic quantities

old versions (suboptimal, but asymptotically correct)

Wu and Noé **ArXiv**:1212.6711 (2012) / **SIAM MMS** 12, 25-54 (2014)
Mey, Wu and Noé **Phys. Rev. X** 4, 041018 (2014)

state-discrete version (statistically optimal)

Wu, Mey, Rosta and Noé **J. Chem. Phys.** 141, 214106 (2014)

state-continuous version (statistically optimal)

Wu, Paul, Wehmeyer and Noé **PNAS** 113, E3221-E3230 (2016)

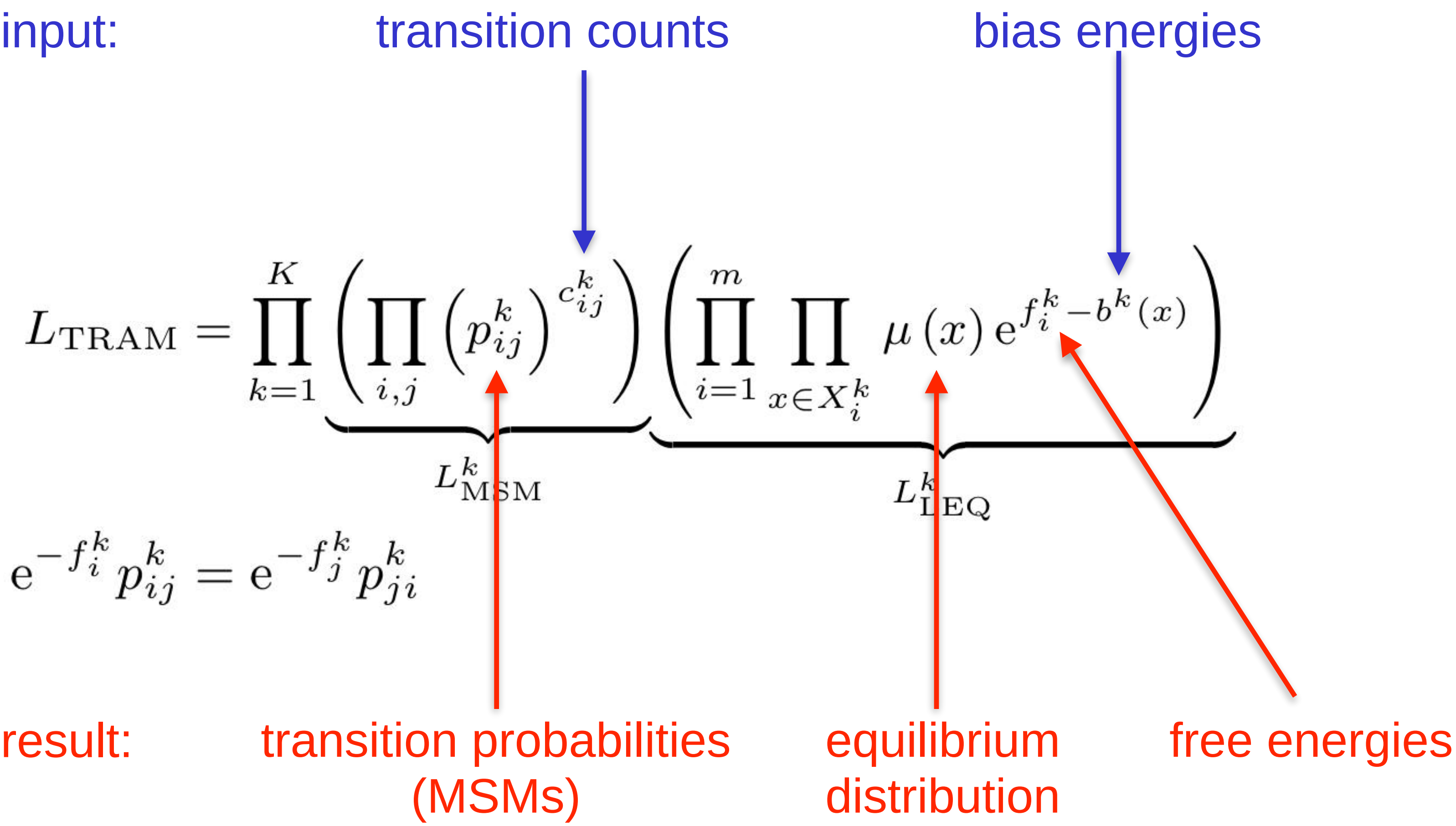
Binless TRAM

$$L_{\mathrm{TRAM}} = \prod_{k=1}^{K} \underbrace{\left(\prod_{i,j} \left(p_{ij}^{k} \right)^{c_{ij}^{k}} \right)}_{L_{\mathrm{MSM}}^{k}} \underbrace{\left(\prod_{i=1}^{m} \prod_{x \in X_i^k} \mu\left(x\right) \mathrm{e}^{f_i^k - b^k\left(x\right)} \right)}_{L_{\mathrm{LEQ}}^{k}}$$

$$\mathrm{e}^{-f_i^k} p_{ij}^{k} = \mathrm{e}^{-f_j^k} p_{ji}^{k}$$

Wu, Paul, Wehmeyer and Noé **PNAS** 113, E3221-E3230 (2016)

Binless TRAM



input: transition counts bias energies

$$L_{\mathrm{TRAM}} = \prod_{k=1}^{K} \underbrace{\left(\prod_{i,j} \left(p_{ij}^{k}\right)^{c_{ij}^{k}}\right)}_{L_{\mathrm{MSM}}^{k}} \underbrace{\left(\prod_{i=1}^{m} \prod_{x \in X_i^k} \mu(x)\, \mathrm{e}^{f_i^k - b^k(x)}\right)}_{L_{\mathrm{LEQ}}^{k}}$$

$$\mathrm{e}^{-f_i^k} p_{ij}^{k} = \mathrm{e}^{-f_j^k} p_{ji}^{k}$$

result: transition probabilities (MSMs) equilibrium distribution free energies

Wu, Paul, Wehmeyer and Noé **PNAS** 113, E3221-E3230 (2016)

Iterative solution

$$v_i^{k,\mathrm{new}} := v_i^k \sum_j \frac{c_{ij}^k + c_{ji}^k}{\exp\left[f_j^k - f_i^k\right] v_j^k + v_i^k}$$

$$f_i^{k,\mathrm{new}} := -\ln \sum_{x \in X_i} \frac{\exp\left[-b^k(x)\right]}{\sum_l R_i^l \exp\left[f_i^l - b^l(x)\right]}$$

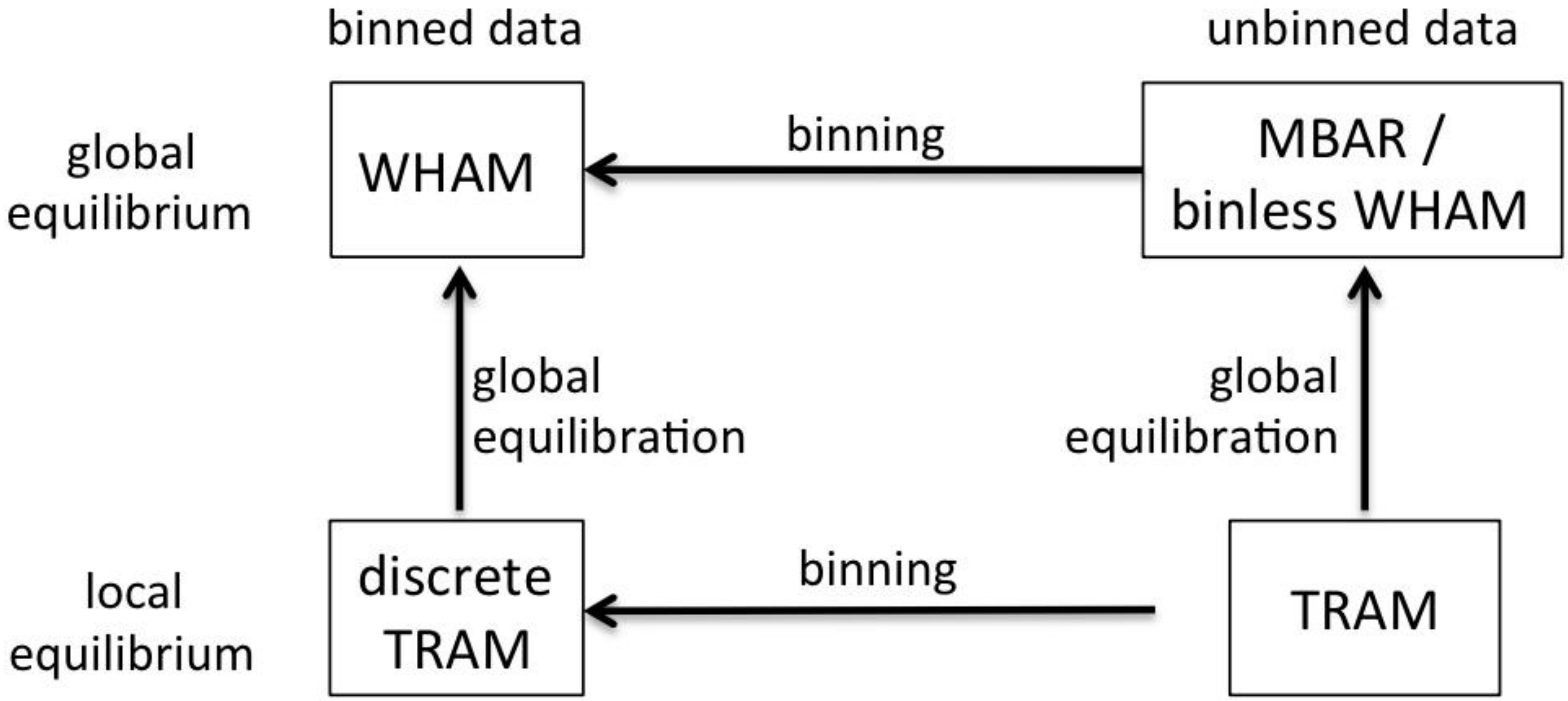
$$R_i^k = \sum_j \frac{\left(c_{ij}^k + c_{ji}^k\right) v_j^k}{v_j^k + \exp\left[f_i^k - f_j^k\right] v_i^k} + N_i^k - \sum_j c_{ji}^k$$

Wu, Paul, Wehmeyer and Noé **PNAS** 113, E3221-E3230 (2016)

Statistically optimal estimators

Ferrenberg & Swendsen, **PRL 63**, 1195 (1989).
Kumar et al, **JCC 13**, 1011 (1992)

Bartels, **CPL** (2000)
Kong et al, **J Roy Stat Soc** (2003)
Shirts & Chodera, **JCP** (2008)



binned data

unbinned data

global equilibrium

WHAM

binning

MBAR / binless WHAM

global equilibration

global equilibration

local equilibrium

discrete TRAM

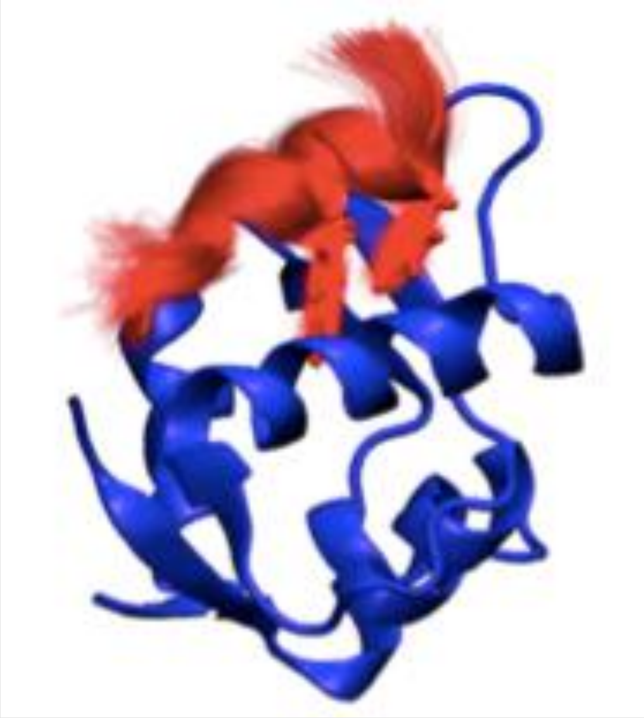
binning

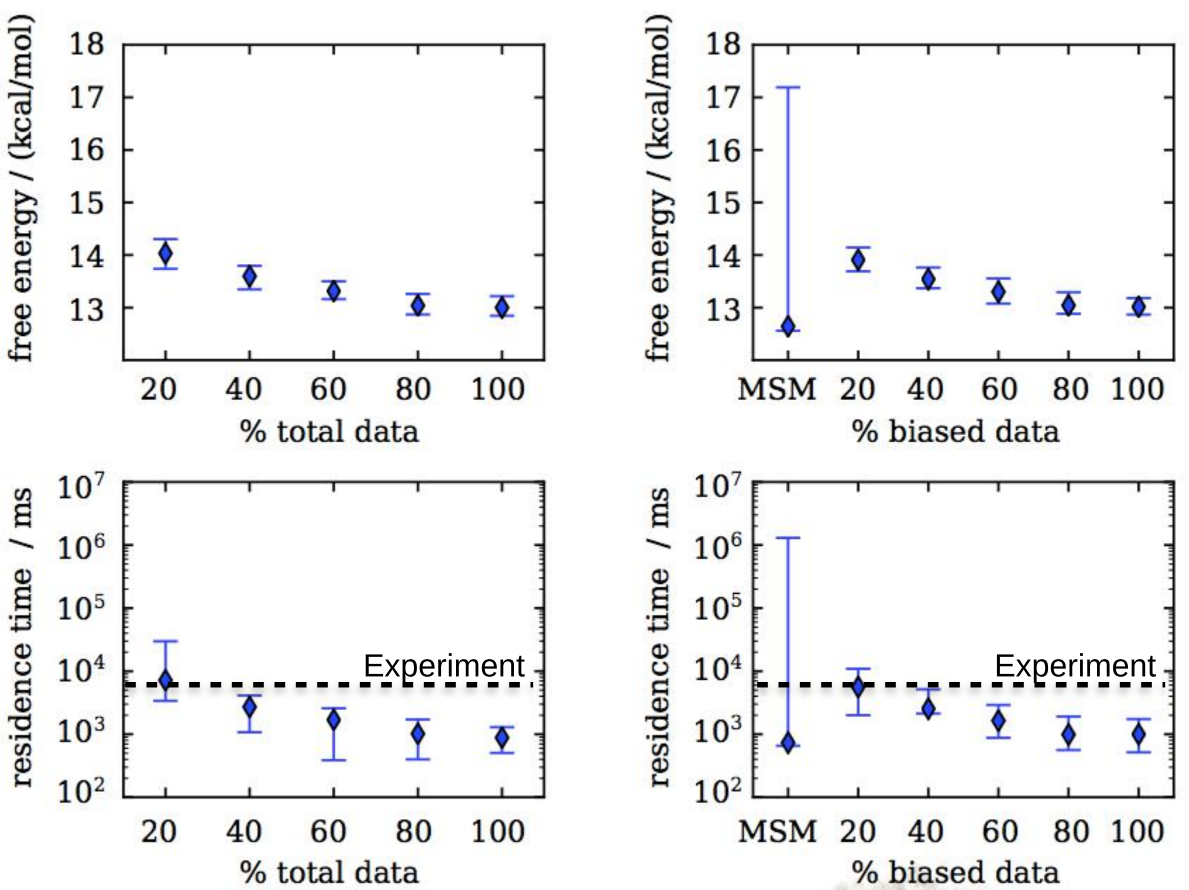
TRAM

Wu, Mey, Rosta & Noé, **JCP** 141, 214106 (2014)

Wu, Paul, Wehmeyer & Noé,
PNAS 113, E3221-E3230 (2016)

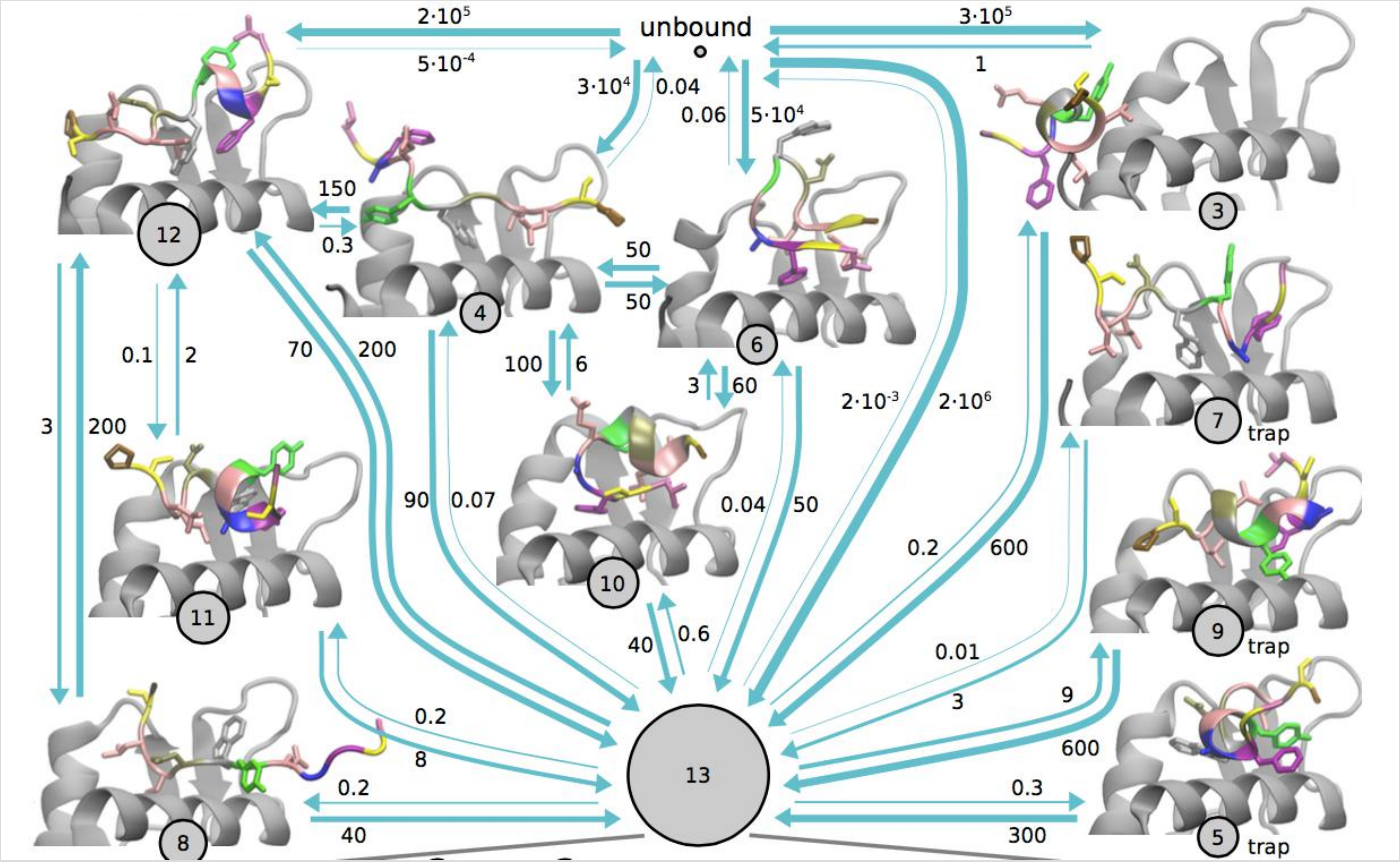
PMI-MDM2: rates and affinities





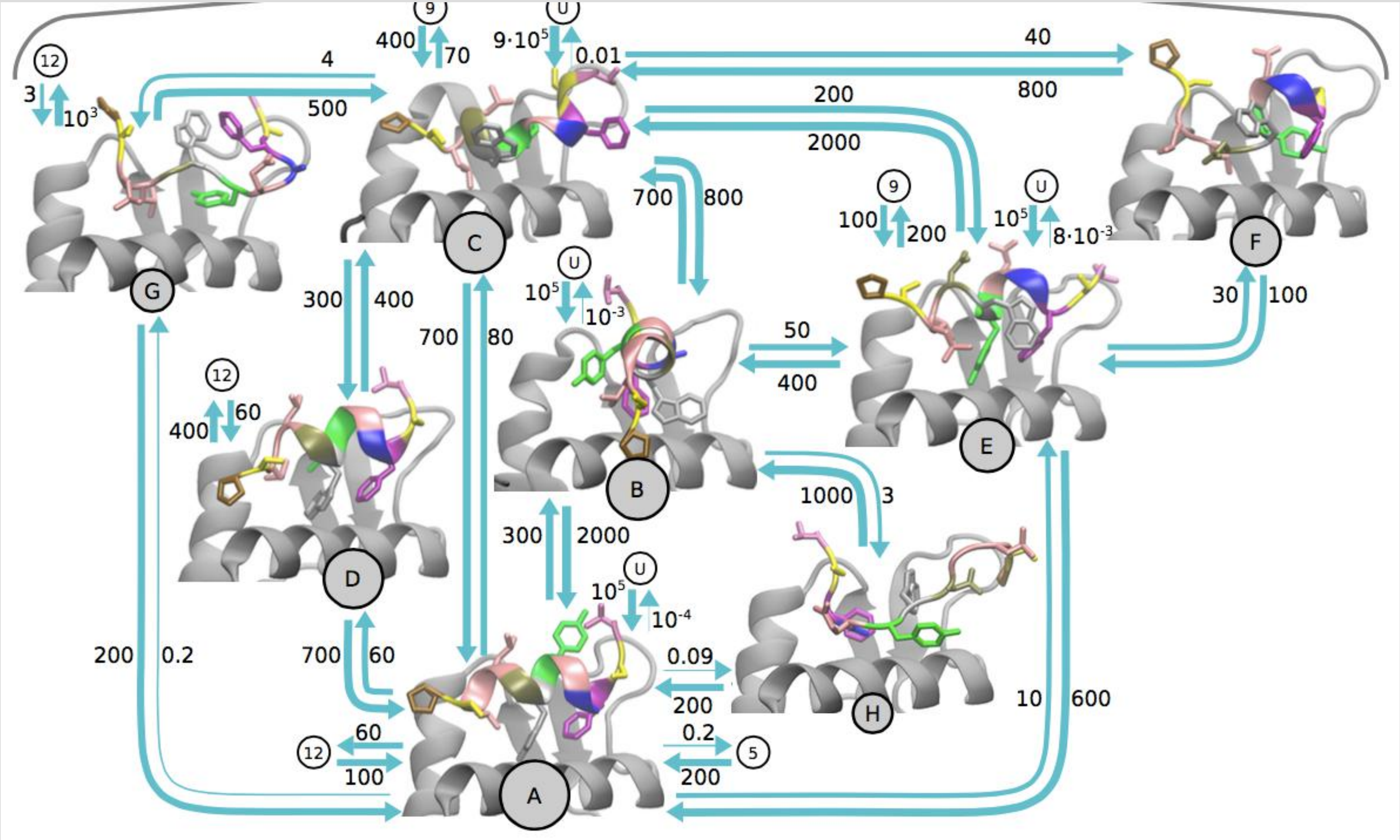
Paul et al., **Nature Communications** 8, 1095 (2017)

PMI-MDM2: mechanism 1



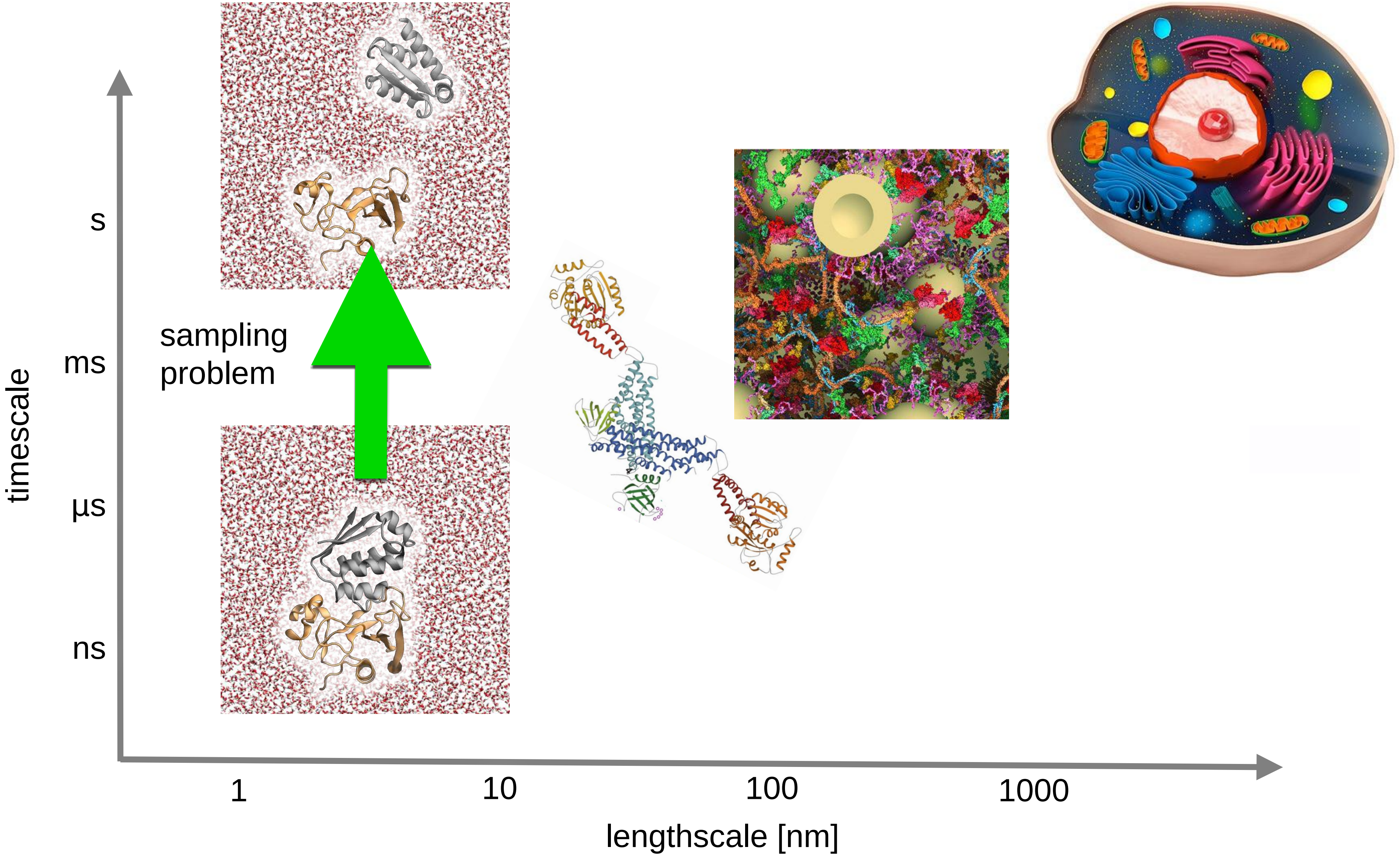
Paul et al., **Nature Communications** 8, 1095 (2017)

PMI-MDM2: mechanism 2

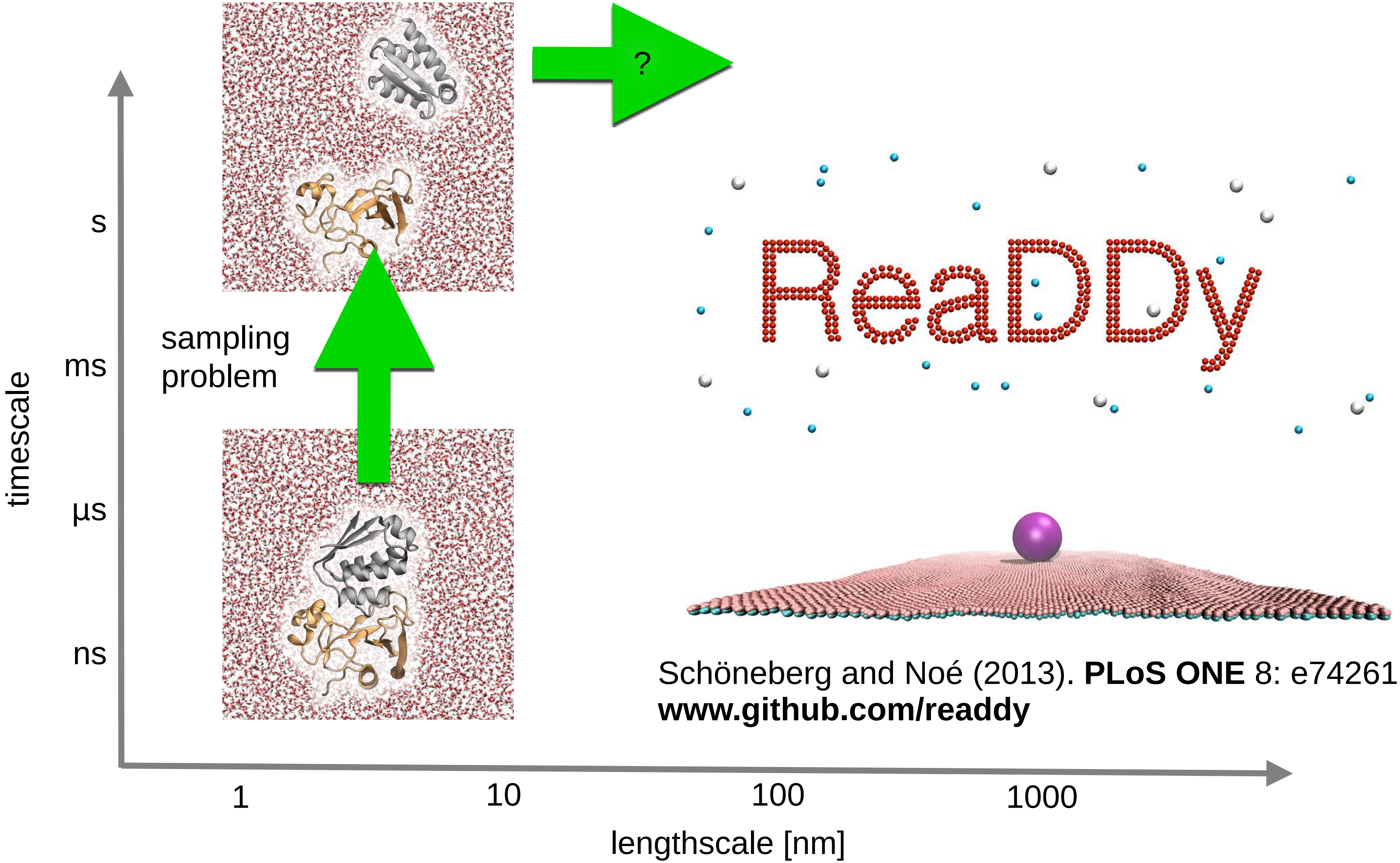


Paul et al., **Nature Communications** 8, 1095 (2017)

Length- and timescales in biology



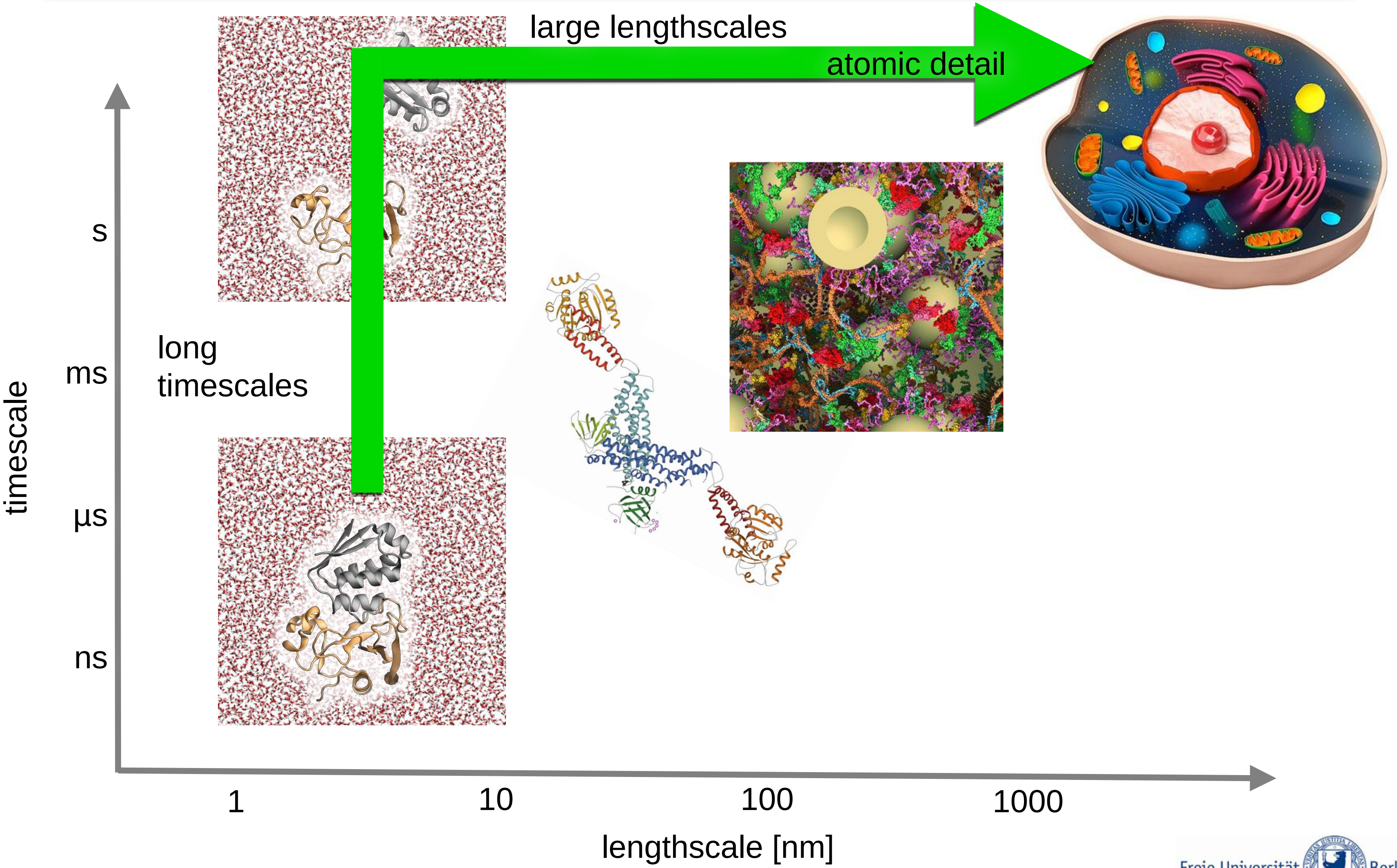
Length- and timescales in biology



Schöneberg and Noé (2013). **PLoS ONE** 8: e74261
www.github.com/readdy

Length- and timescales in biology

How can we **scale** long-timescale simulation with atomistic detail **to large** protein complexes and cellular signaling cascades.



large lengthscales

atomic detail

long
timescales

timescale

s

ms

µs

ns

1

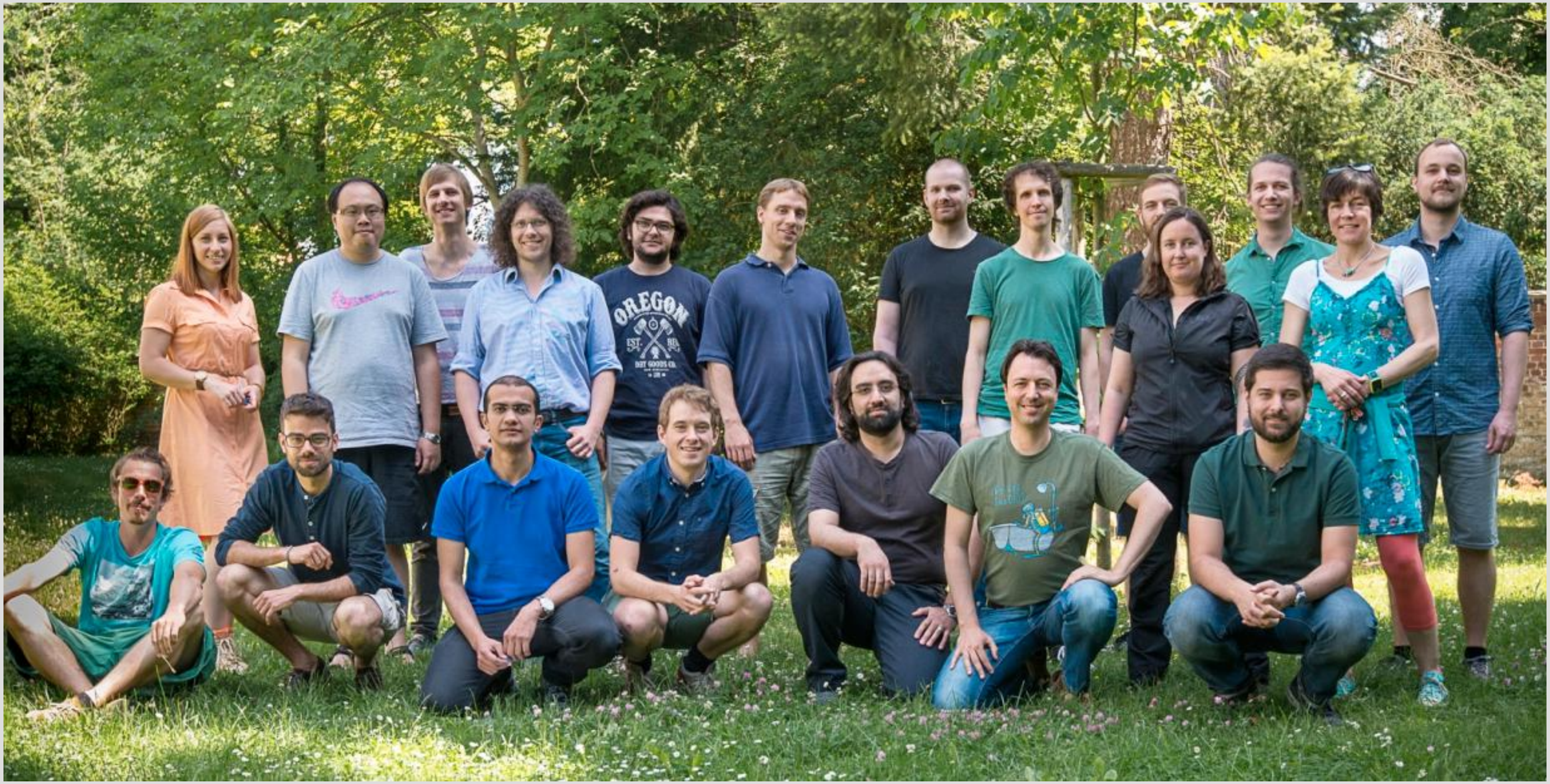
10

100

1000

lengthscale [nm]

Acknowledgements



Collaborations

- Cecilia Clementi (Rice University)
- Christof Schütte (FU Berlin)
- Eric Vanden-Eijnden (Courant NY)
- Thomas Weikl (MPI Potsdam)
- Edina Rosta (King’s College London)
- Bettina Keller (FU Berlin)
- Vijay Pande (Stanford)
- Volker Haucke (FMP Berlin)
- Stephan Sigrist (FU Berlin)
- Oliver Daumke (MDC)
- John Chodera (MSKCC NY)
- Gianni de Fabritiis (Barcelona)

Funding

erc
European Research Council
Established by the European Commission

DFG
SFB 958
SFB 740

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