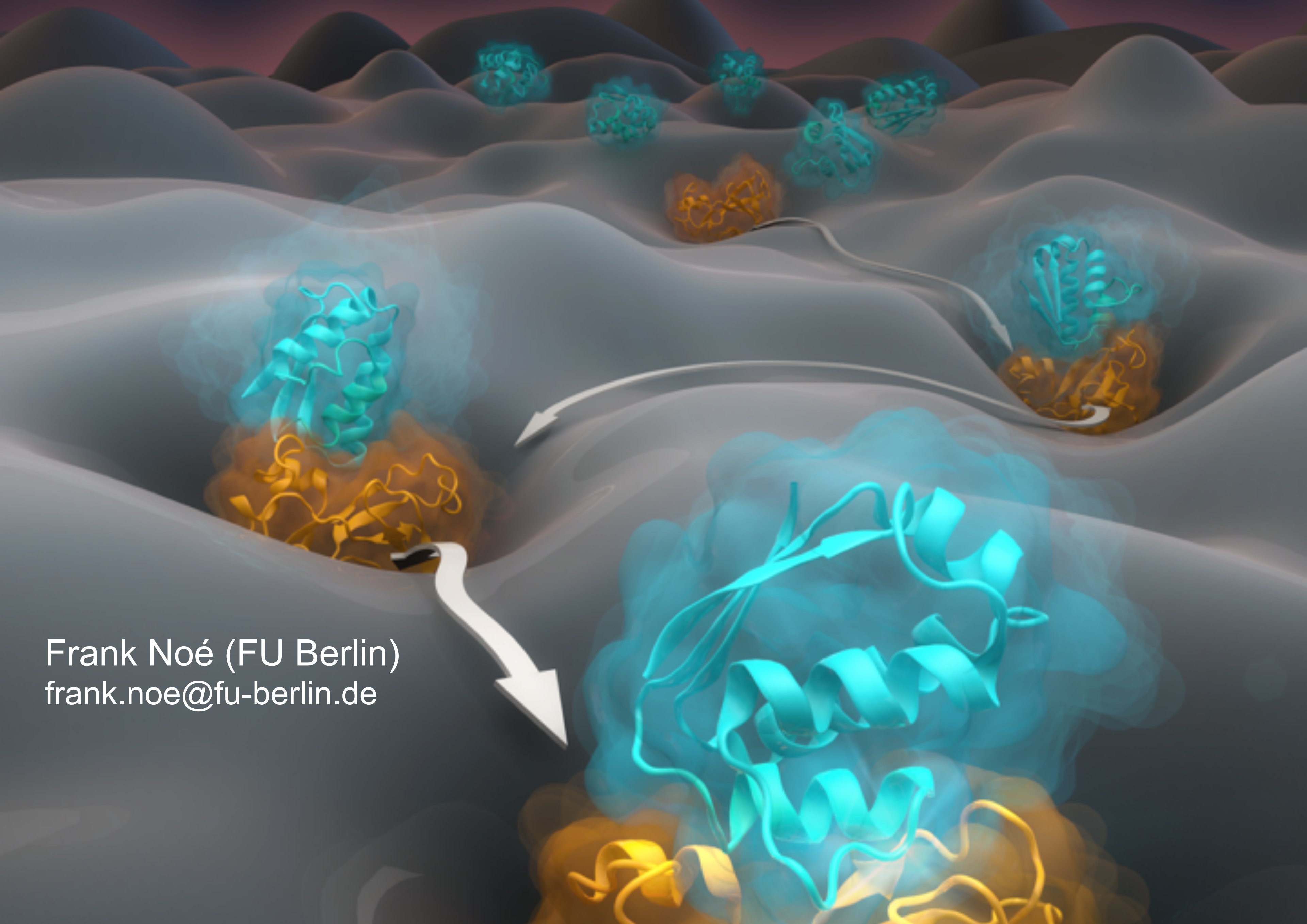
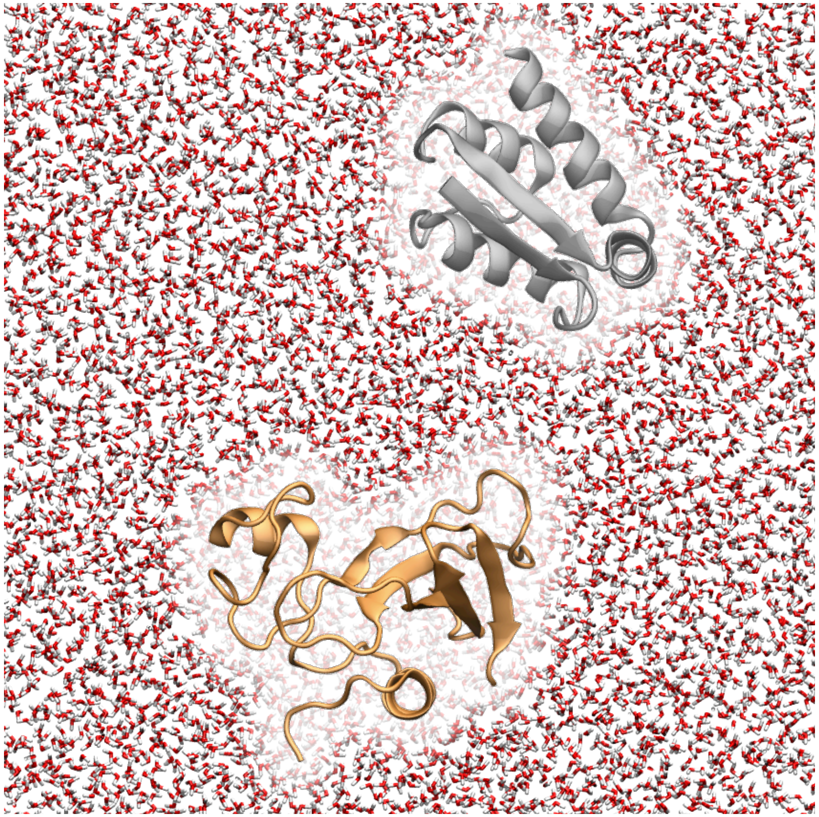
All-atom molecular dynamics beyond the seconds timescale



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

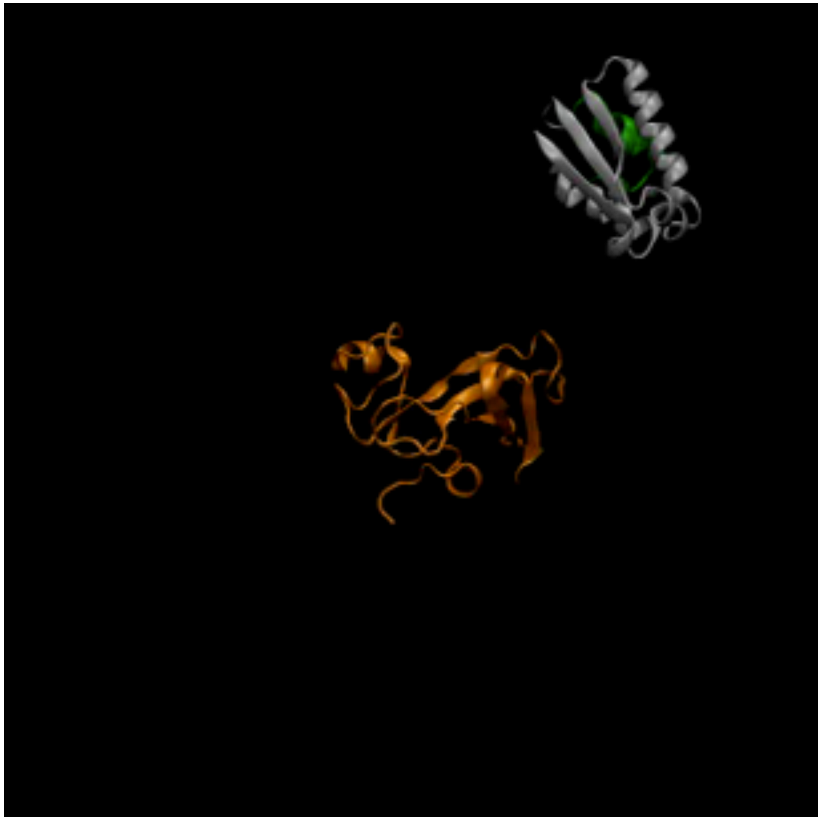
Simulating biological timescales at atomic resolution

Microsecond
MD Trajectories



Simulating biological timescales at atomic resolution

Microsecond
MD Trajectories



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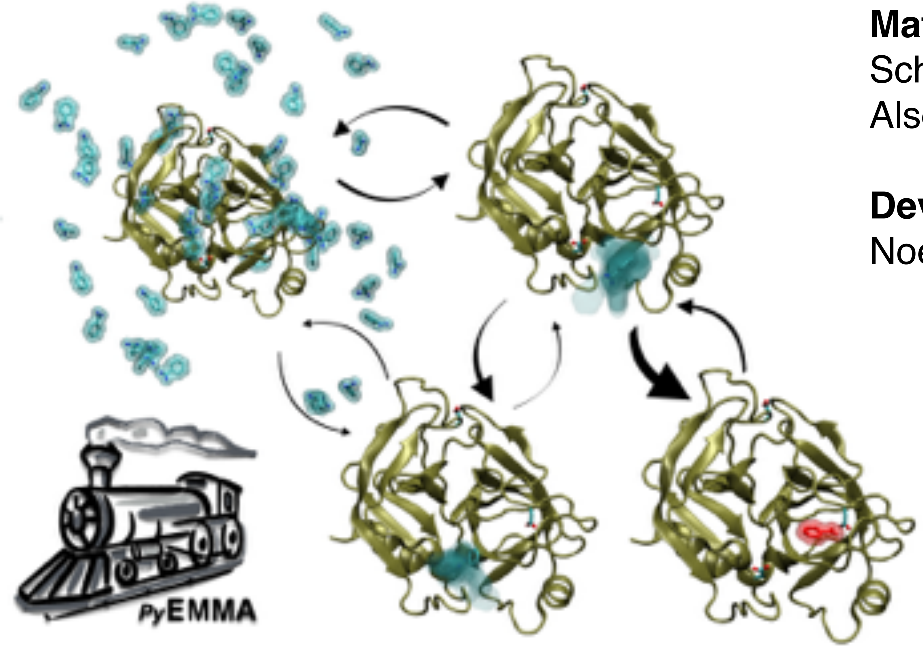
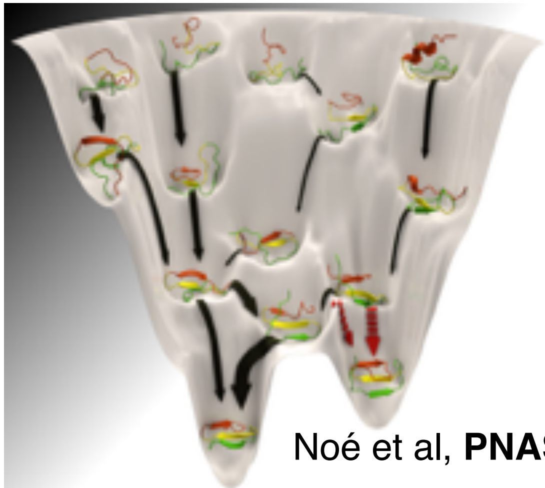


Mathematical theory:
Schütte et al, **J Comp Phys** 1999,
Also: Weber, Deuflhard, Friesecke, Dellnitz …

Developments for high-throuput molecular dynamics:
Noé, Pande, Swope, Hummer (mid 2000’s)

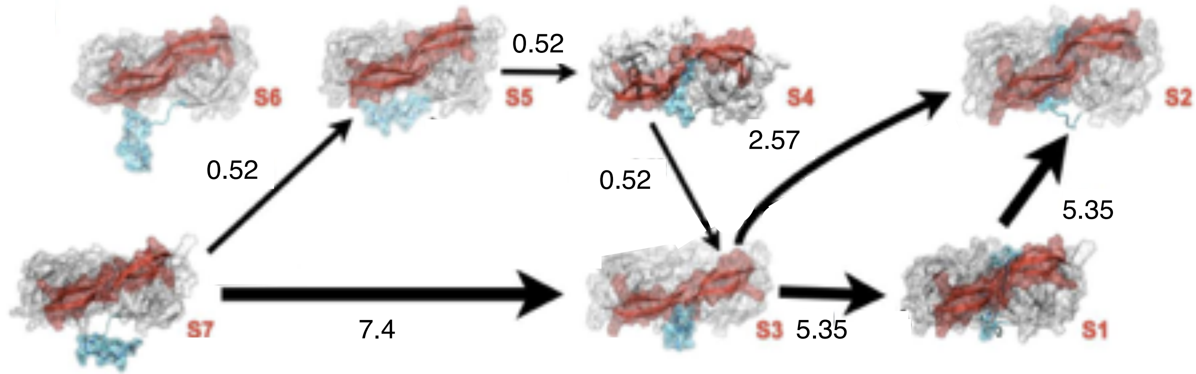
Examples for Markov modeling

Ensemble of protein folding pathways



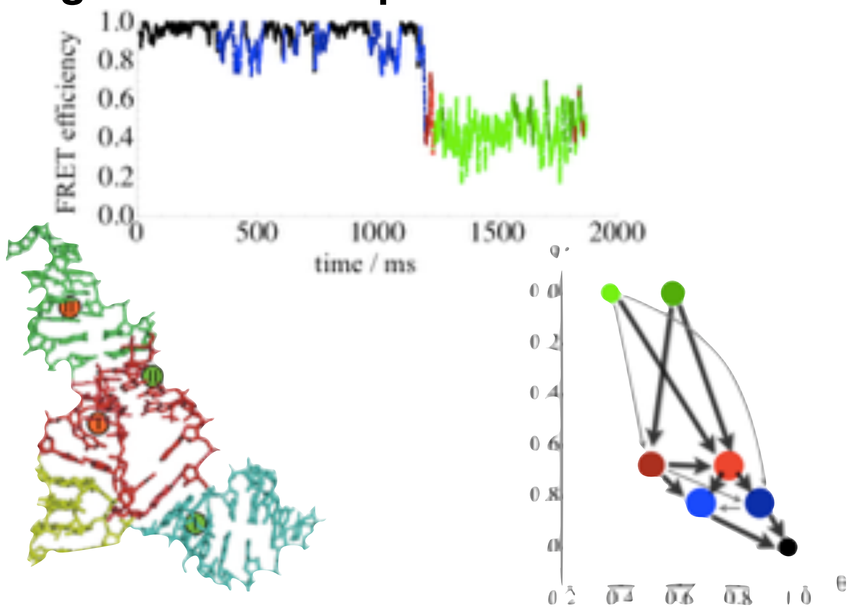
Noé et al, **PNAS** (2009)

Substrate binding to HIV protease



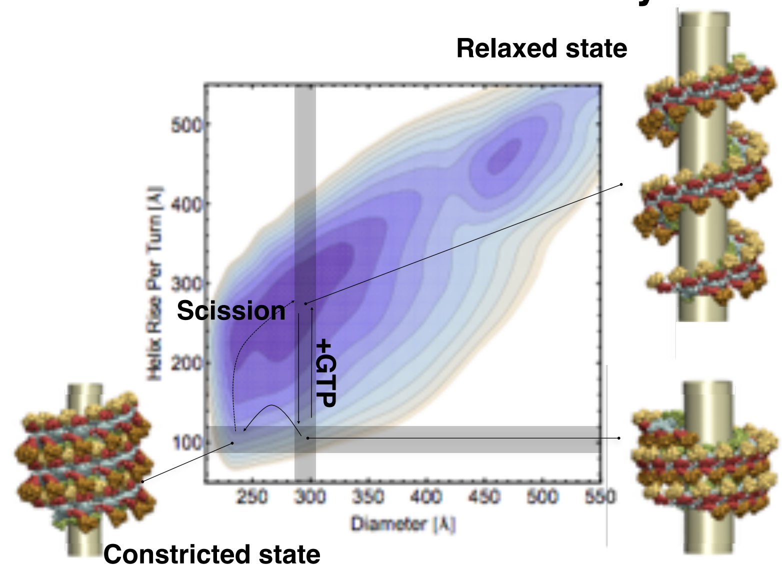
Sadiq, Noé, De Fabritiis, **PNAS** (2012)

Single molecule experiments



Keller, Kobitski, Jäschke, Nienhaus, Noé, **JACS** (2014)

Domain interaction in Dynamin



Faelber et al., **Nature** (2011)
Reubold et al.,**Nature** (2015)

Slow processes

Backward propagator

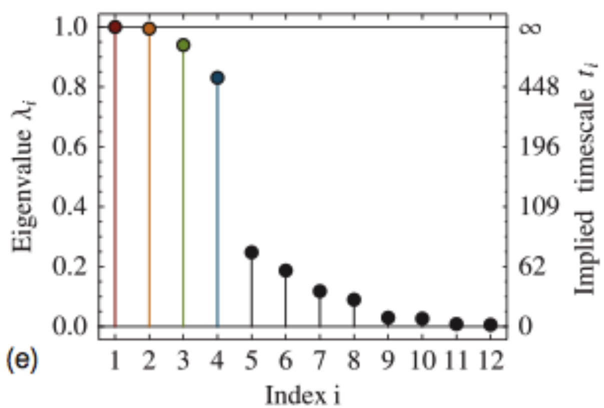
$$\rho_\tau = \mathcal{T}(\tau)\rho_0$$

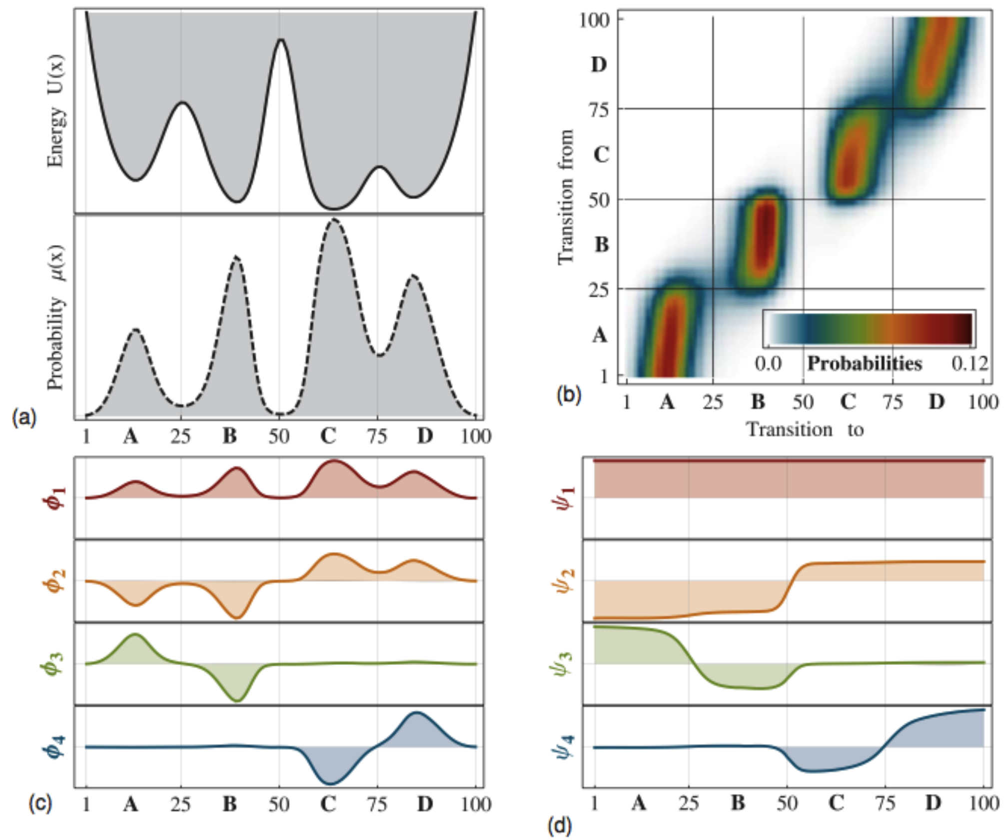
Spectral decomposition

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

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 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)

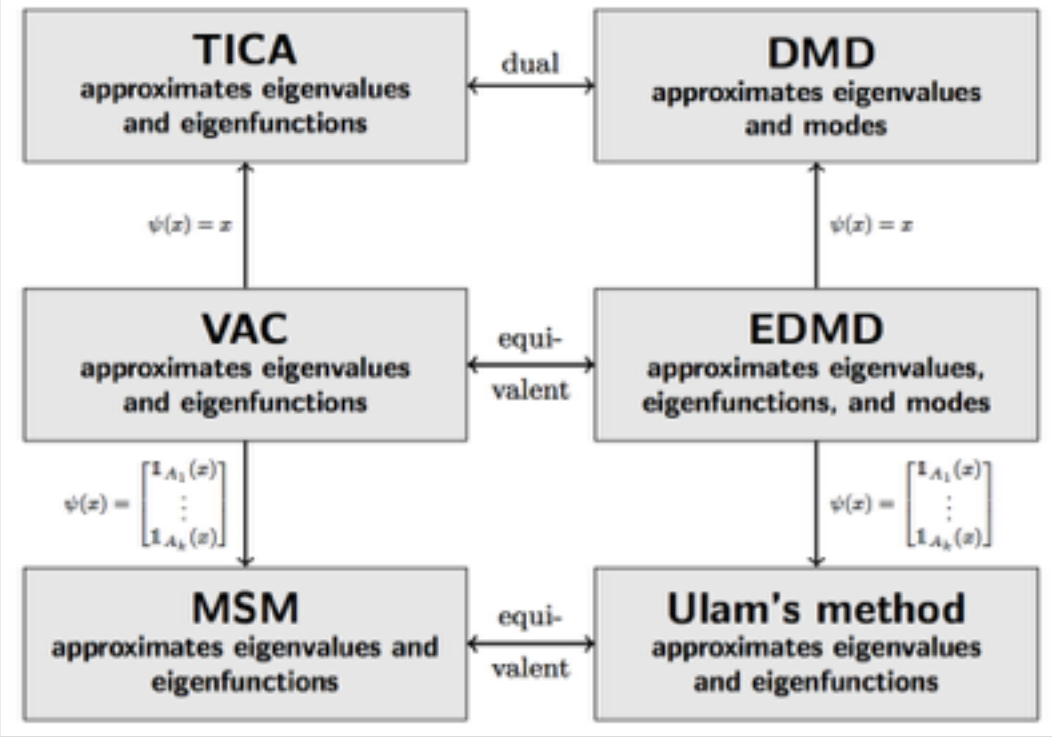
Comparison between methods

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, …

Klus, Nüske, Koltai, Wu, Krevrekidis, Schütte, Noé: Data-driven model reduction and transfer operator approximation (**J. Nonlin. Sci.** 2018 / **arXiv**:1703.10112)

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)

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

Singular value decomposition:

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

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

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

Singular value decomposition:

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

- 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:*

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

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

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

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)

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with

$$\begin{aligned} \mathbf{X} &= \left(\chi_0(\mathbf{x}_1), \chi_0(\mathbf{x}_2), \ldots, \chi_0(\mathbf{x}_{T-\tau})\right)^\top \\ \mathbf{Y} &= \left(\chi_1(\mathbf{x}_{1+\tau}), \chi_1(\mathbf{x}_{2+\tau}), \ldots, \chi_1(\mathbf{x}_T)\right)^\top \end{aligned}$$

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 $\hat{\mathbf{\Sigma}}_k$, $\psi = \mathbf{U}_k^\top\mathbf{C}_{00}^{-\frac{1}{2}}\chi_0$ and $\phi = \mathbf{V}_k^\top\mathbf{C}_{11}^{-\frac{1}{2}}\chi_1$

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

$$
\begin{aligned}
\mathbf{X} &= \left(\chi_0(\mathbf{x}_1), \chi_0(\mathbf{x}_2), \ldots, \chi_0(\mathbf{x}_{T-\tau})\right)^\top \\
\mathbf{Y} &= \left(\chi_1(\mathbf{x}_{1+\tau}), \chi_1(\mathbf{x}_{2+\tau}), \ldots, \chi_1(\mathbf{x}_{T})\right)^\top
\end{aligned}
$$

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 $\hat{\mathbf{\Sigma}}_k$, $\psi = \mathbf{U}_k^\top\mathbf{C}_{00}^{-\frac{1}{2}}\chi_0$ and $\phi = \mathbf{V}_k^\top\mathbf{C}_{11}^{-\frac{1}{2}}\chi_1$

For the choice $\chi_0 = \chi_1$, TCCA is consistent with EDMD:

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

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

VAMP: Koopman approximation error

Theorem (Koopman approximation error): For an operator $\hat{\mathcal{K}}_\tau$ defined by

$$\hat{\mathcal{K}}_\tau h = \sum_i \hat{\sigma}_i \left\langle g_i, h \right\rangle_{\rho_1} f_i$$

we have

- R_E (VAMP-E score)

$$\left\| \hat{\mathcal{K}}_\tau - \mathcal{K}_\tau \right\|_{\mathrm{HS}}^2 = \mathrm{tr}\left[\hat{\mathbf{\Sigma}} \mathbf{C}_{00} \hat{\mathbf{\Sigma}} \mathbf{C}_{11} - 2 \hat{\mathbf{\Sigma}} \mathbf{C}_{01} \right] + \sum_i \sigma_i^2$$

where $\|\cdot\|_{\mathrm{HS}}$ denotes the Hilbert-Schmidt norm, $\hat{\mathbf{\Sigma}} = \mathrm{diag}\left(\hat{\sigma}_1, \hat{\sigma}_2, \ldots\right)$, and

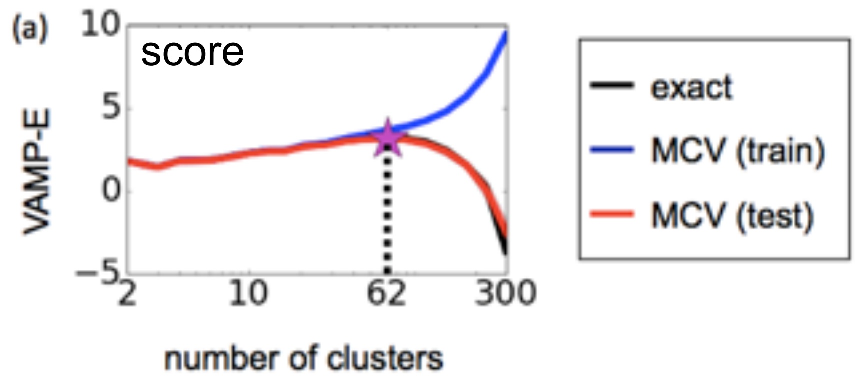
$$\begin{aligned} \left[\mathbf{C}_{00}\right]_{ij} &= \mathbb{E}_{\rho_0}\left[f_i\left(\mathbf{x}\left(t\right)\right) f_j\left(\mathbf{x}\left(t\right)\right)\right] \\ \left[\mathbf{C}_{01}\right]_{ij} &= \mathbb{E}_{\rho_0}\left[f_i\left(\mathbf{x}\left(t\right)\right) g_j\left(\mathbf{x}\left(t+\tau\right)\right)^\top\right] \\ \left[\mathbf{C}_{11}\right]_{ij} &= \mathbb{E}_{\rho_1}\left[g_i\left(\mathbf{x}\left(t\right)\right) g_j\left(\mathbf{x}\left(t\right)\right)^\top\right]. \end{aligned}$$

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

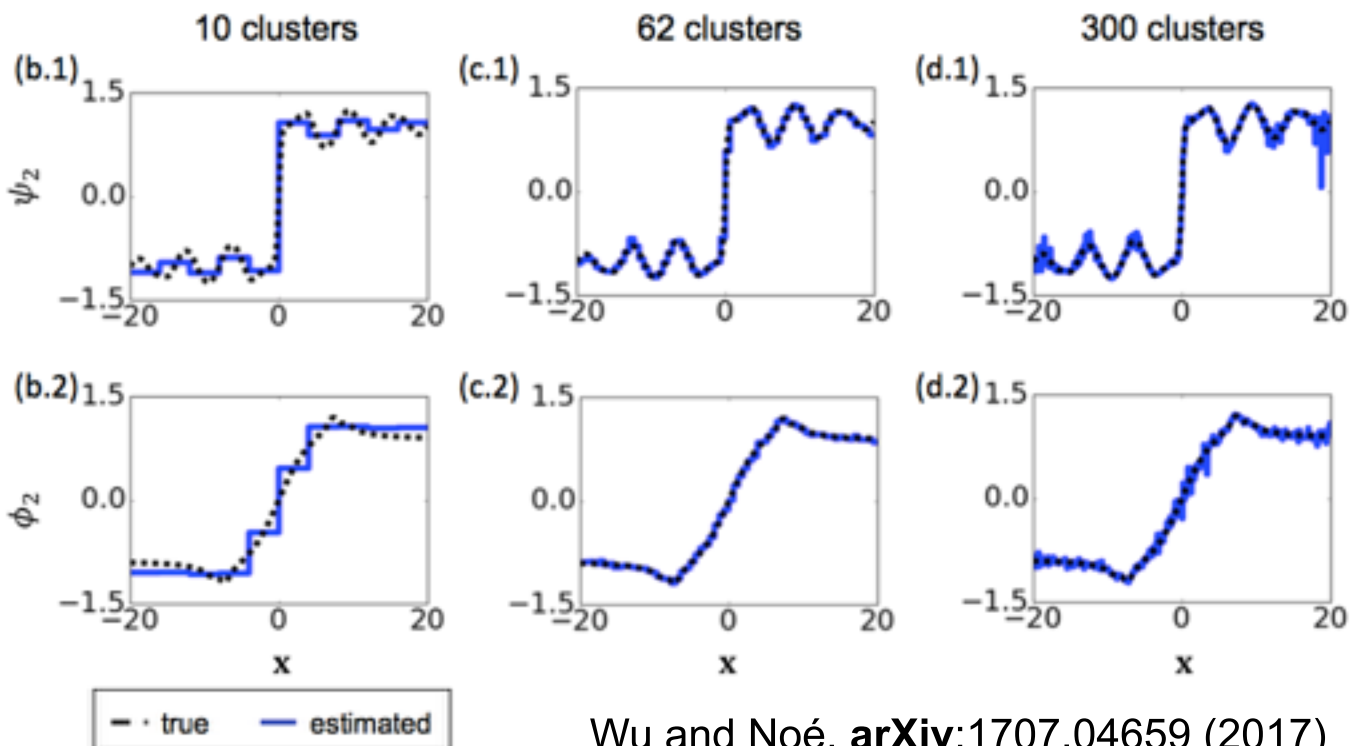
1D-Example

Markov process with Gaussian noise w_t

$$x_{t+1} = \frac{x_t}{2} + \frac{25x_t}{1+x_t^2} + \sqrt{10}\,(1.1 + \cos(x_t))\,w_t$$



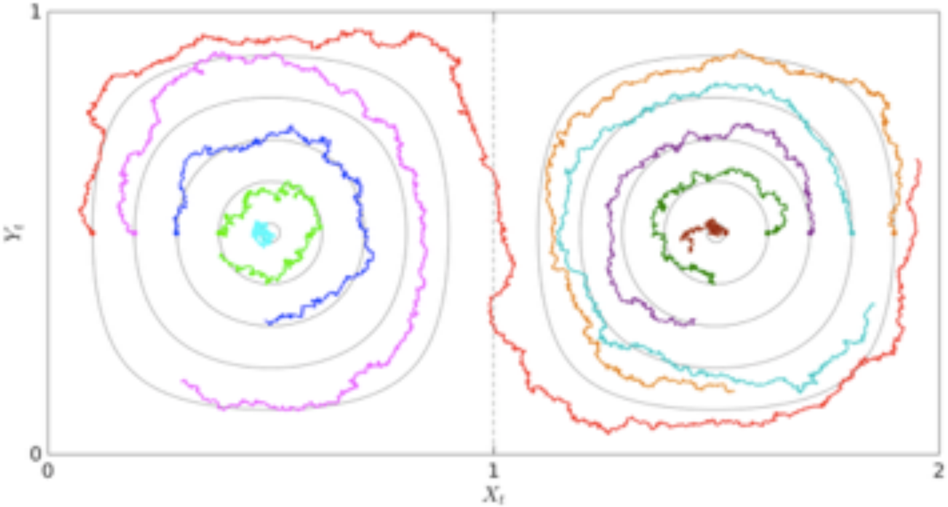
Eigenfunctions

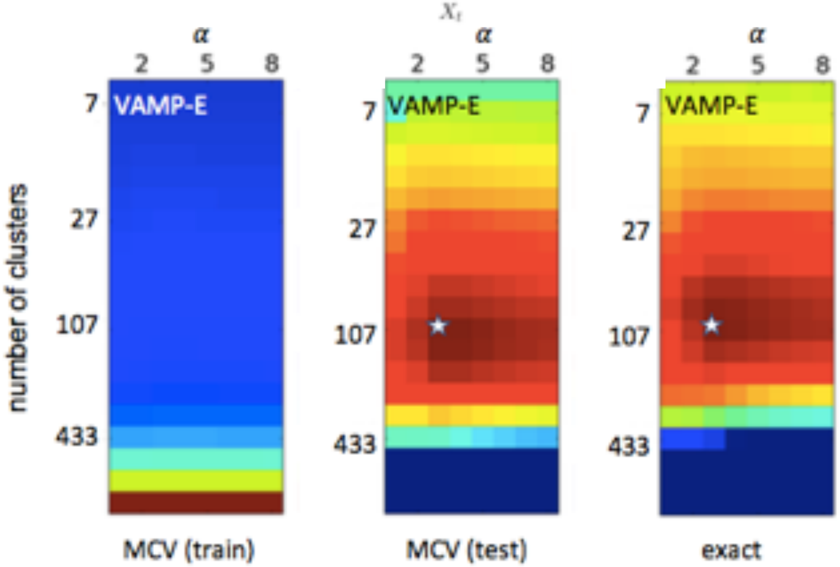


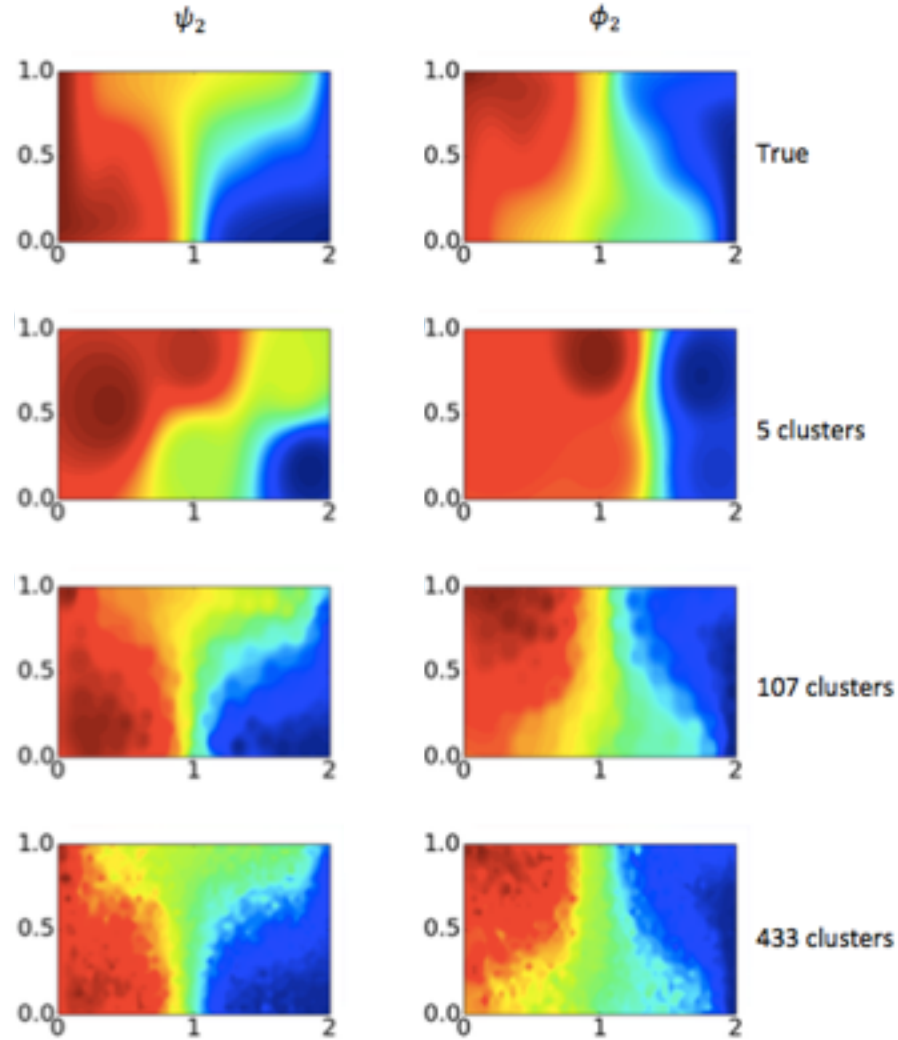
Wu and Noé, **arXiv**:1707.04659 (2017)

Generalization: VAMP reduces nonequilibrium processes

$$dx_t = -\pi A \sin(\pi x_t) \cos(\pi y_t) - \epsilon(2y_t - 1) + \varepsilon \, d\mathbf{W}_{t,1},$$
$$dy_t = \pi A \cos(\pi x_t) \sin(\pi y_t) - \epsilon(2x_t - 3) + \varepsilon \, d\mathbf{W}_{t,2}$$

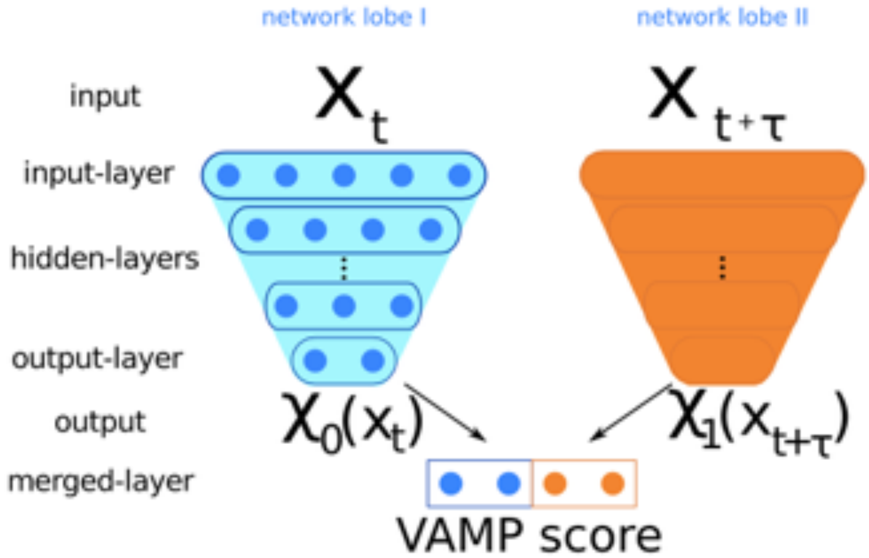






Wu and Noé, **arXiv**:1707.04659 (2017)

VAMPnets



VAMP variational principle (subspace version)

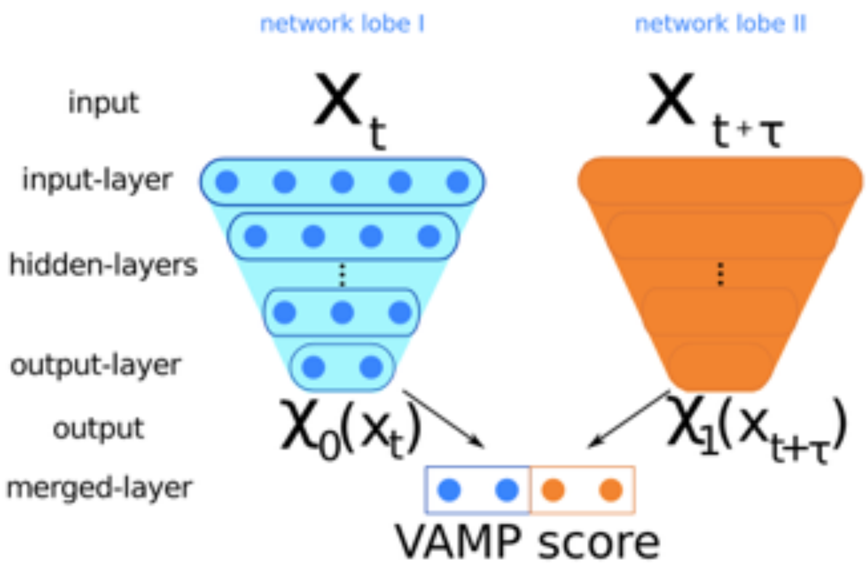
For any two sets of linearly independent functions $\boldsymbol{\chi}_0(\mathbf{x}) = (\chi_{01}(\mathbf{x}), ..., \chi_{0n}(\mathbf{x}))$ *and* $\boldsymbol{\chi}_1(\mathbf{x}) = (\chi_{11}(\mathbf{x}), ..., \chi_{1n}(\mathbf{x}))$, *let us call*

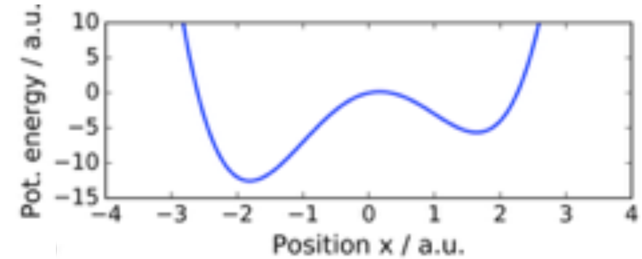
$$\hat{R}_2[\boldsymbol{\chi}_0, \boldsymbol{\chi}_1] = \left\| \mathbf{C}_{00}^{-\frac{1}{2}} \mathbf{C}_{01} \mathbf{C}_{11}^{-\frac{1}{2}} \right\|_F^2$$

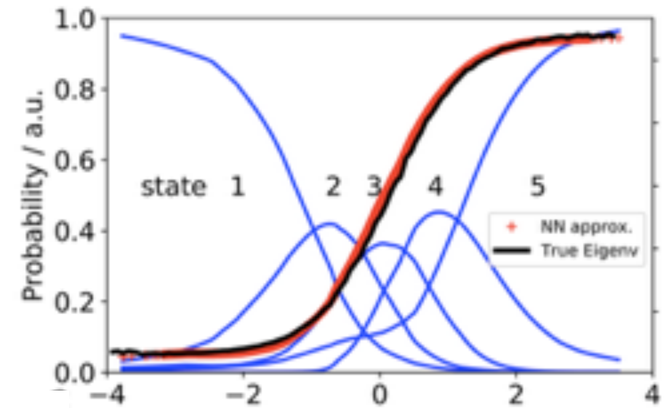
their VAMP-2 score, where $\mathbf{C}_{00}$, $\mathbf{C}_{01}$, $\mathbf{C}_{11}$ *are the feature correlation matrices as defined earlier and* $\|\cdot\|_F$ *indicates the Frobenius norm. The maximum value of the VAMP-2 score is achieved when the top* n *left and right Koopman singular functions belong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

Mardt, Pasquali, Wu, Noé **Nat. Commun.** 9, 5 (2018)

VAMPnets



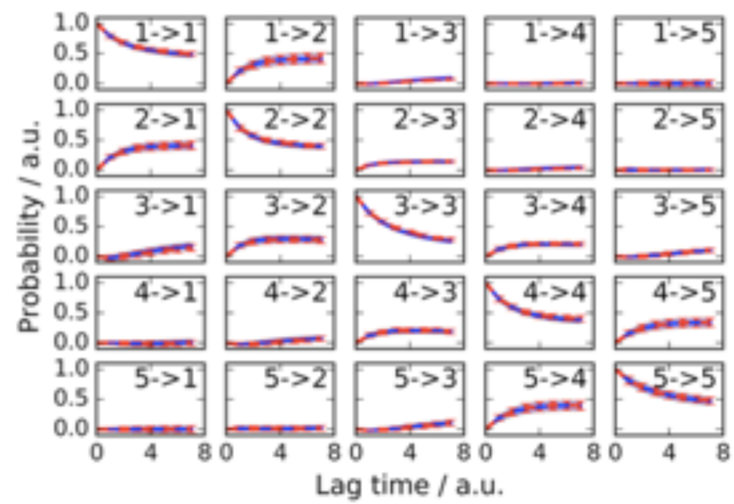




Resulting Markov model: $$\mathbf{K} = \mathbf{C}_{00}^{-1}\mathbf{C}_{01}.$$

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

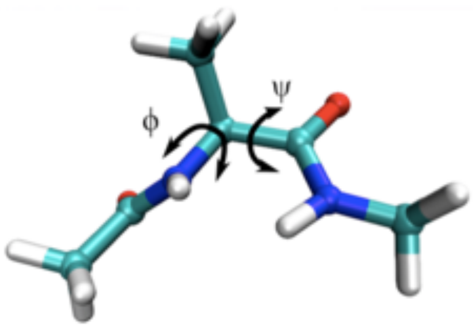
Validate (Chapman-Kolmogorov test): $$\mathbf{K}(n\tau) = \mathbf{K}^n(\tau),$$

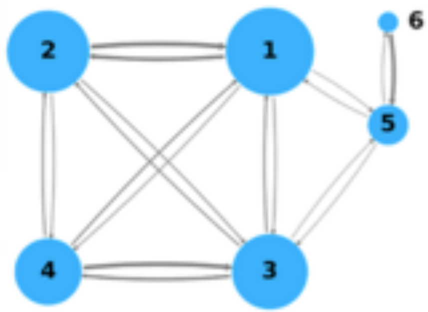


Mardt, Pasquali, Wu, Noé **Nat. Commun.** 9, 5 (2018)

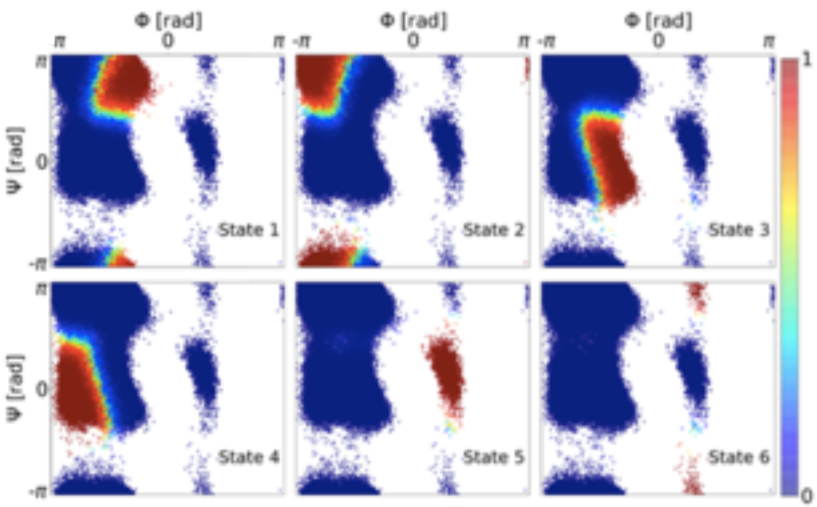
VAMPnets

Alanine dipeptide

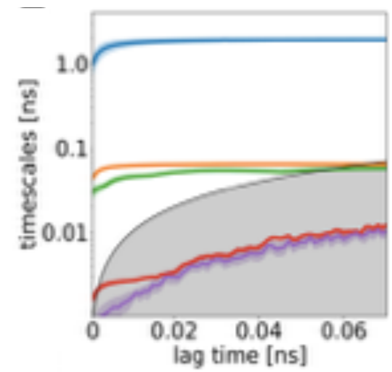


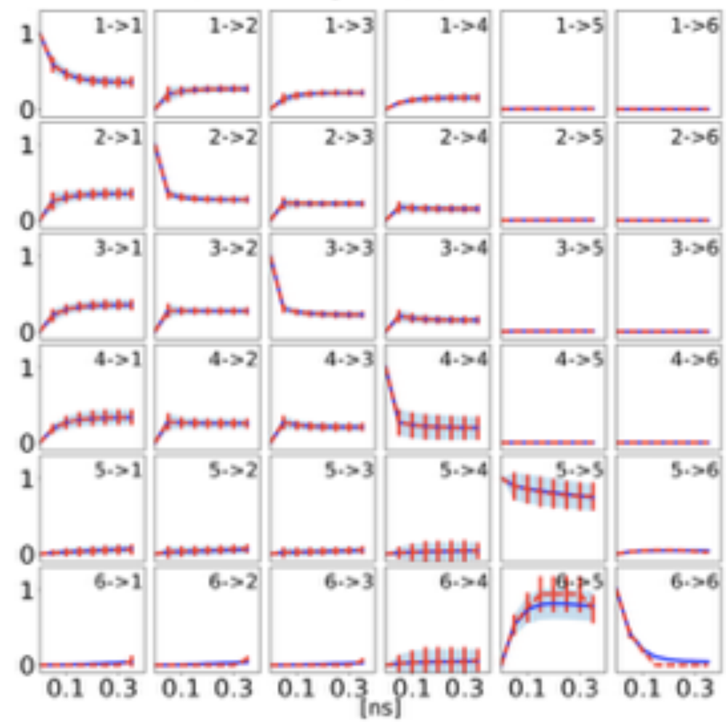


Max. transition probability: 41%
Min. transition probability: 0.5%



Validation





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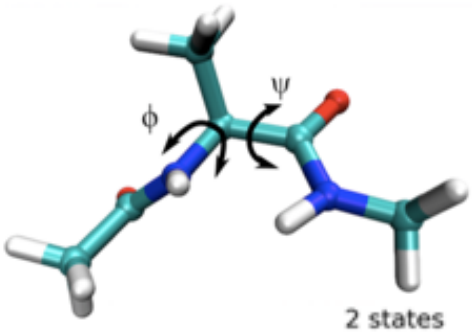
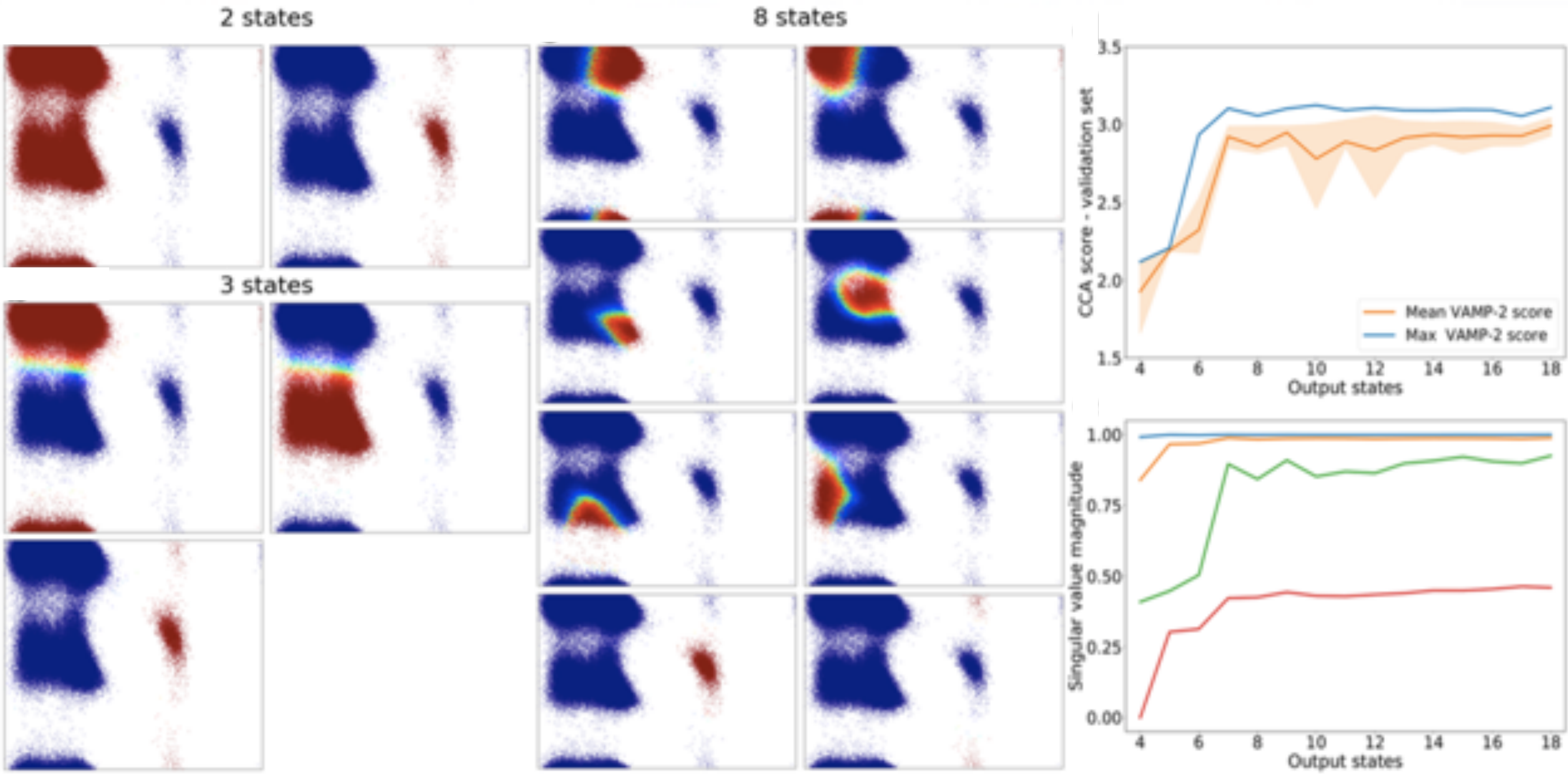
VAMPnets



Results as a function of the number of states



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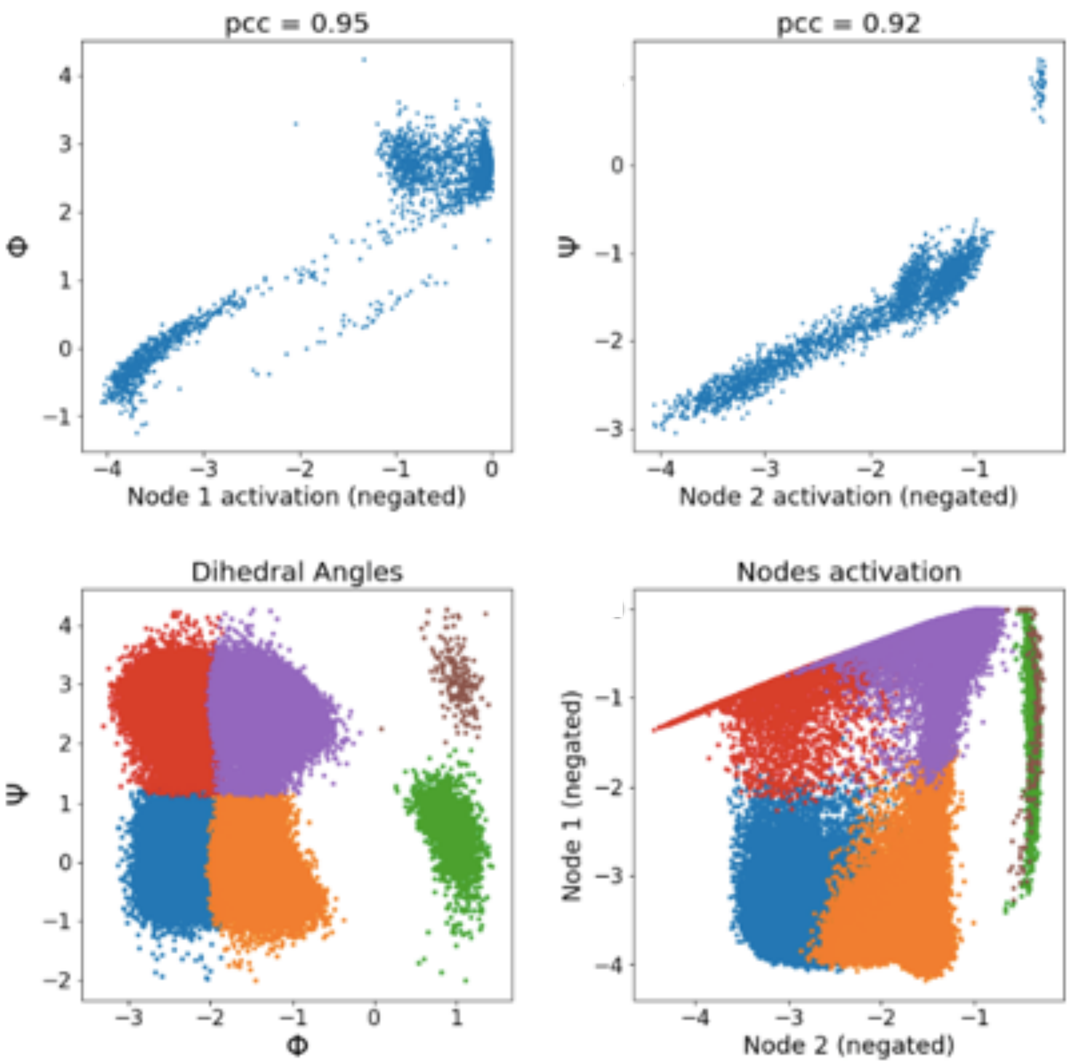
Freie Universität Berlin

VAMPnets

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



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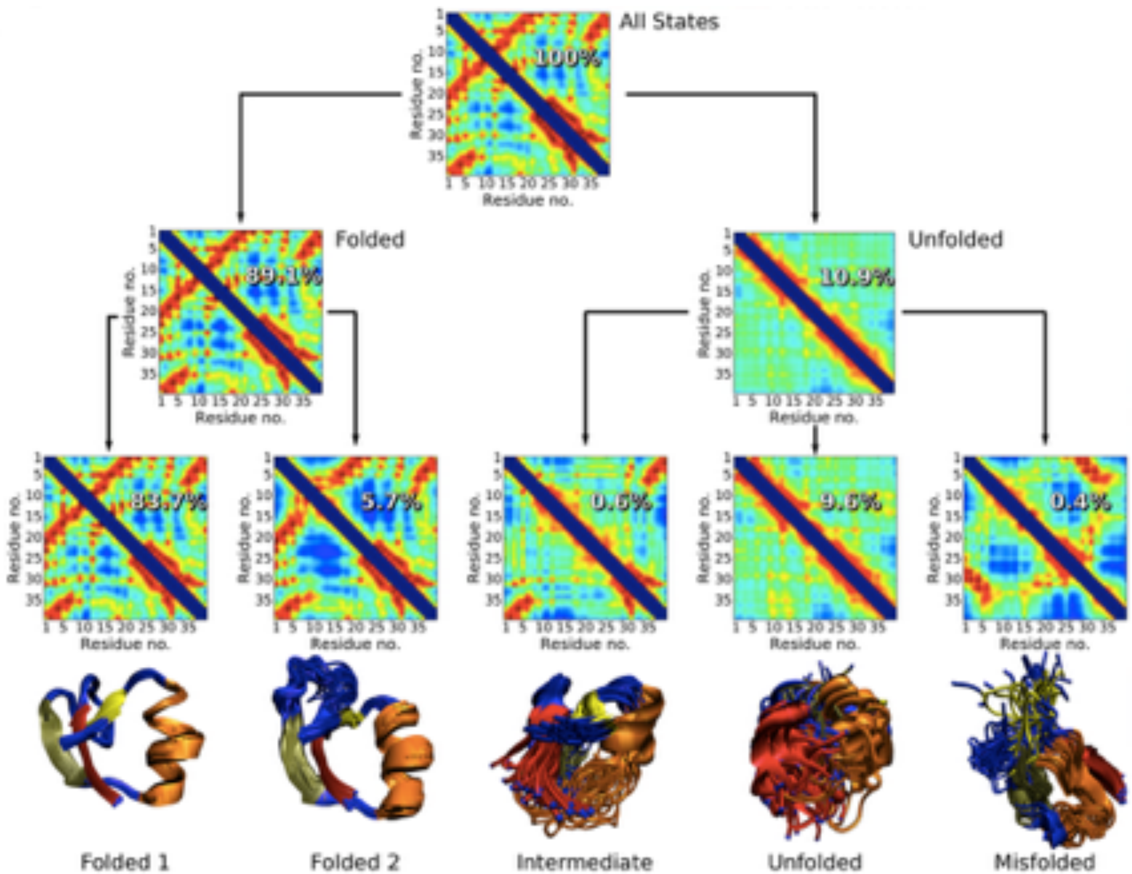
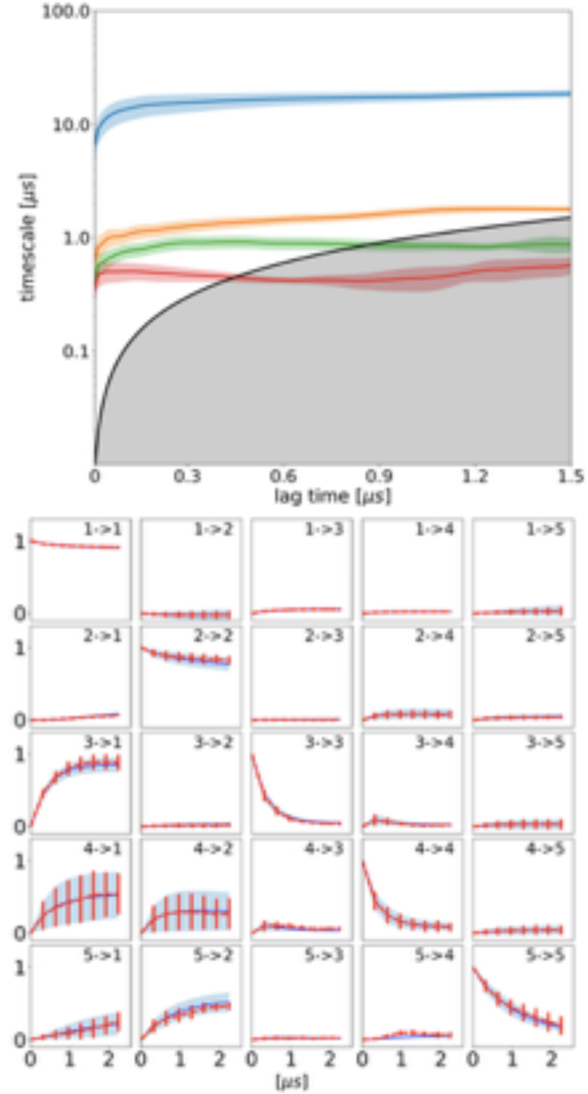
VAMPnets

NTL9 Protein folding



Validation



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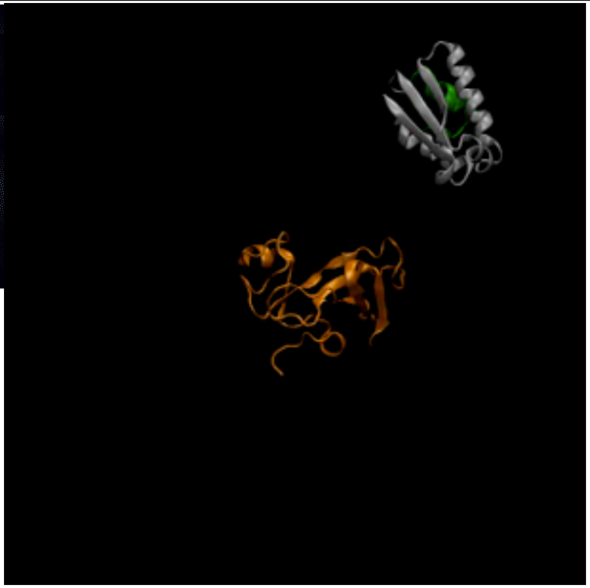
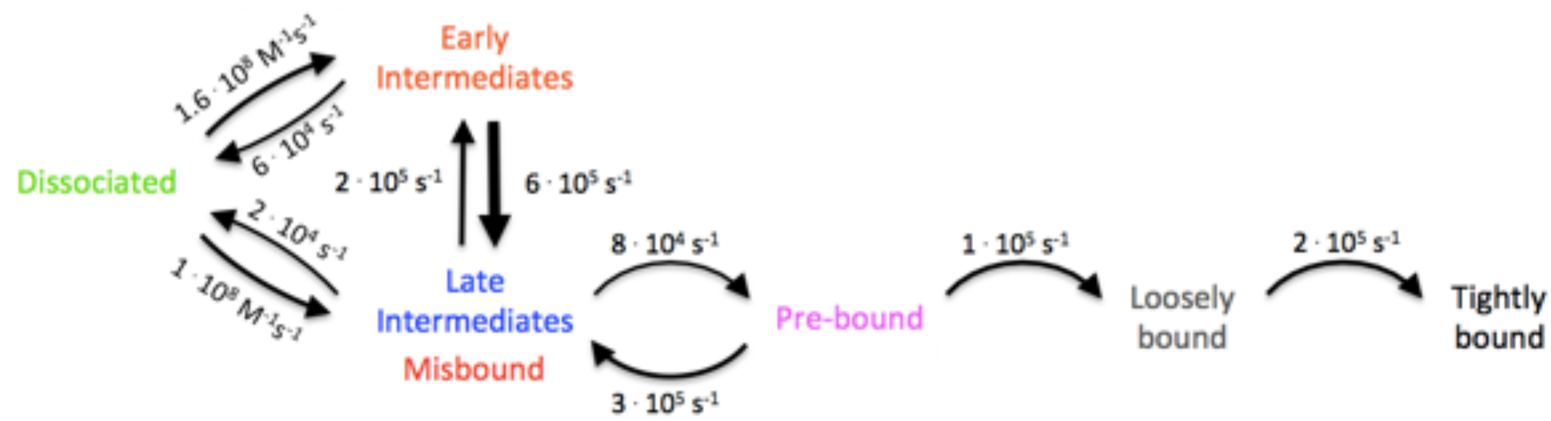
Simulating biological timescales at atomic resolution

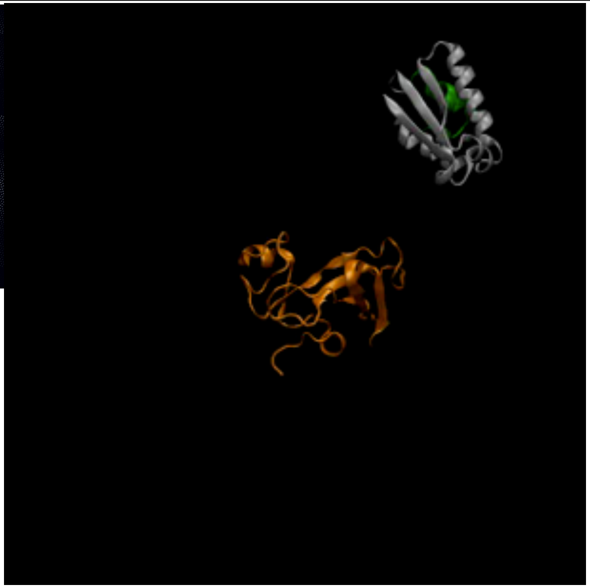
1000's of **Microsecond** MD Trajectories



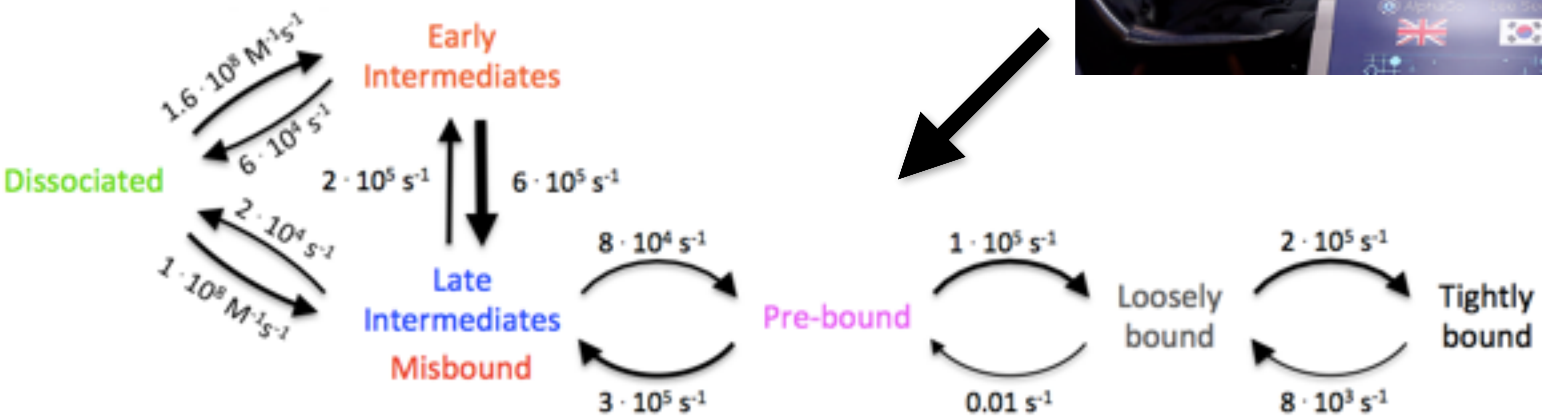


Markov State Model — **Millisecond kinetics**

Simulating biological timescales at atomic resolution

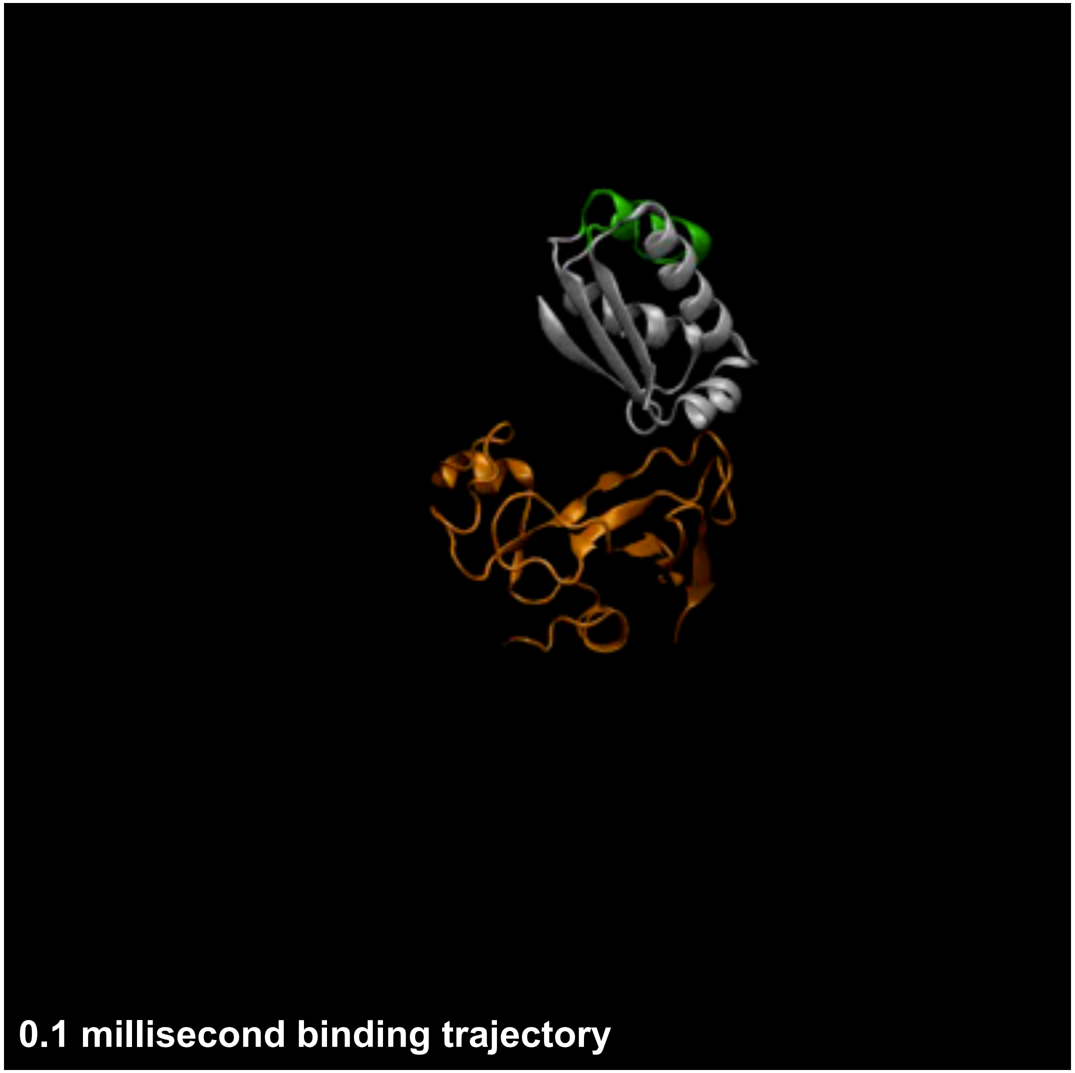


Reinforcement learning



Adaptive Markov State Model — **seconds to hours kinetics**

Sampling biological timescales at atomic resolution



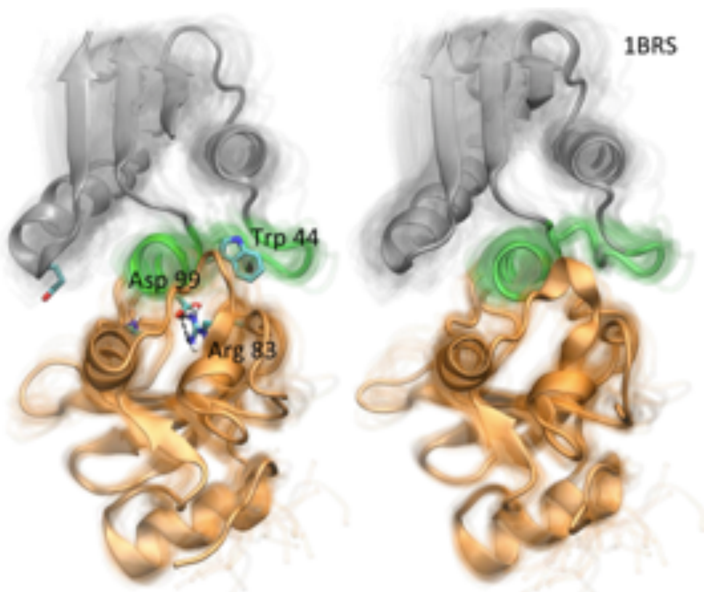
Plattner, Doerr, De Fabritiis, Noé
Nature Chemistry 9, 1005 (2017)

Validation

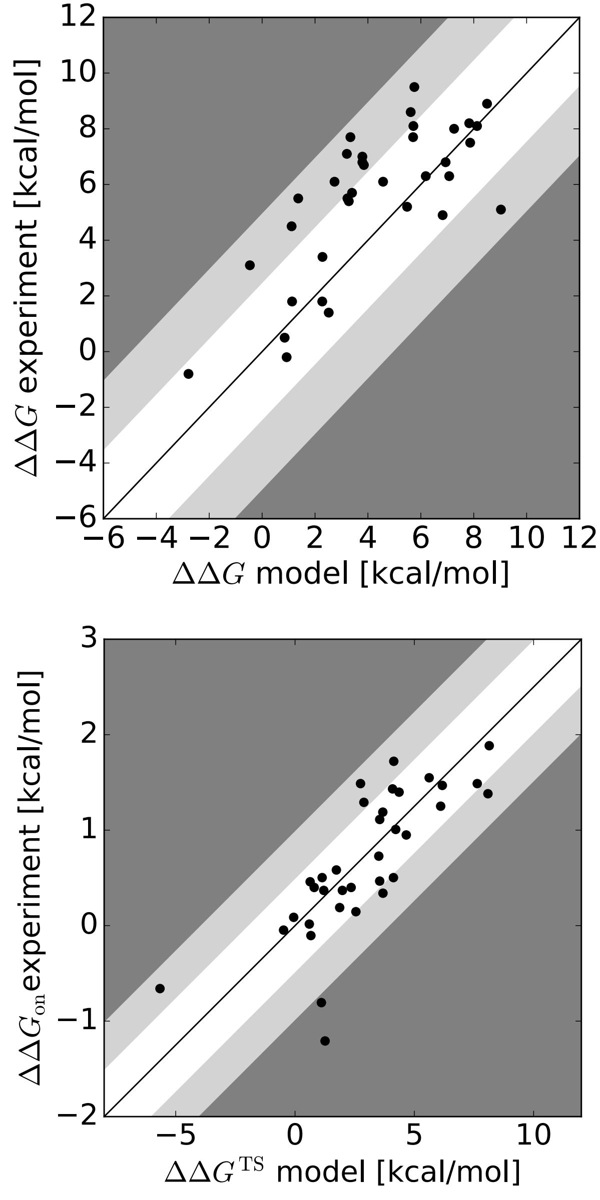
	Markov Model	Experiment
Binding energy	**14.8 +- 2.5** kcal / mol	**16.8** kcal/mol
Association rate	**0.74 +- 0.05 10^8** $s^{-1}M^{-1}$	**$1 \cdot 10^8$** $s^{-1}M^{-1}$

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

average heavy-atom RMSD 2.1 A



Mutants (first order perturbation theory vs experiment)

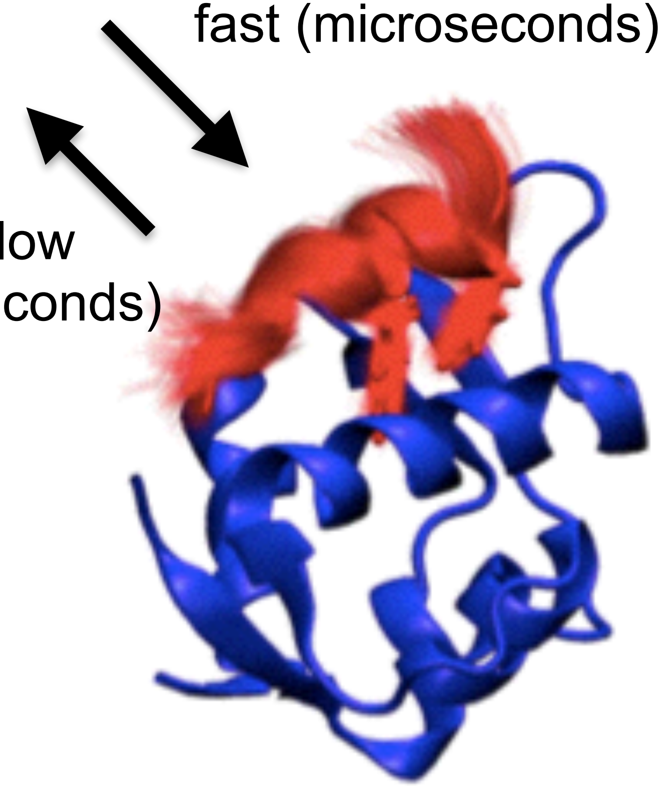


Plattner, Doerr, De Fabritiis, Noé **Nature Chemistry** 2017

Other issues…

Rare Events vs. High Precision

Multi-Ensemble Markov Models



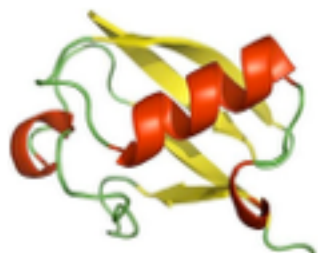
Wu, Paul, Wehmeyer and Noé
PNAS 113, E3221-E3230 (2016)

Paul, …, Clarke, Freund, Weikl, Noé,
Nature Communications 8, 1095 (2017)

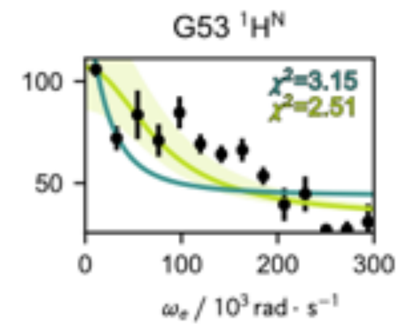
Force Fields vs. High Accuracy

Augmented Markov Models

MD Simulation data



Experimental observa



estimate

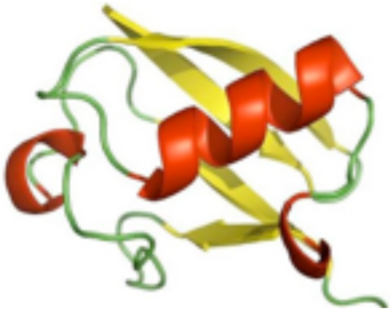
estimate

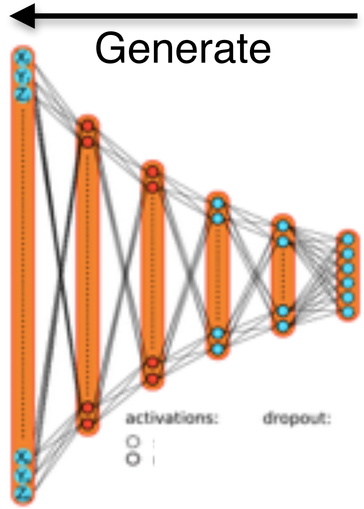
Markov Model

Olsson, Wu, Paul, Clementi, Noé
PNAS 114, 8265-8270, 2017

Generative learning and molecular design

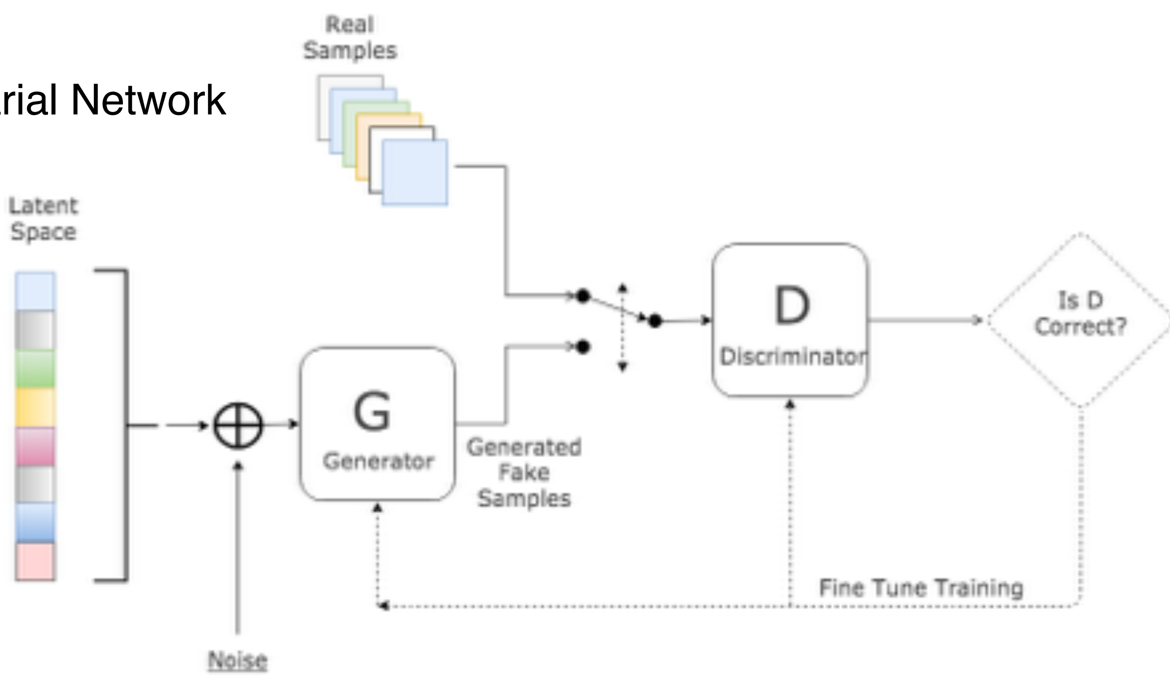
Structure and dynamics
from MD Simulation data
Experimental data …



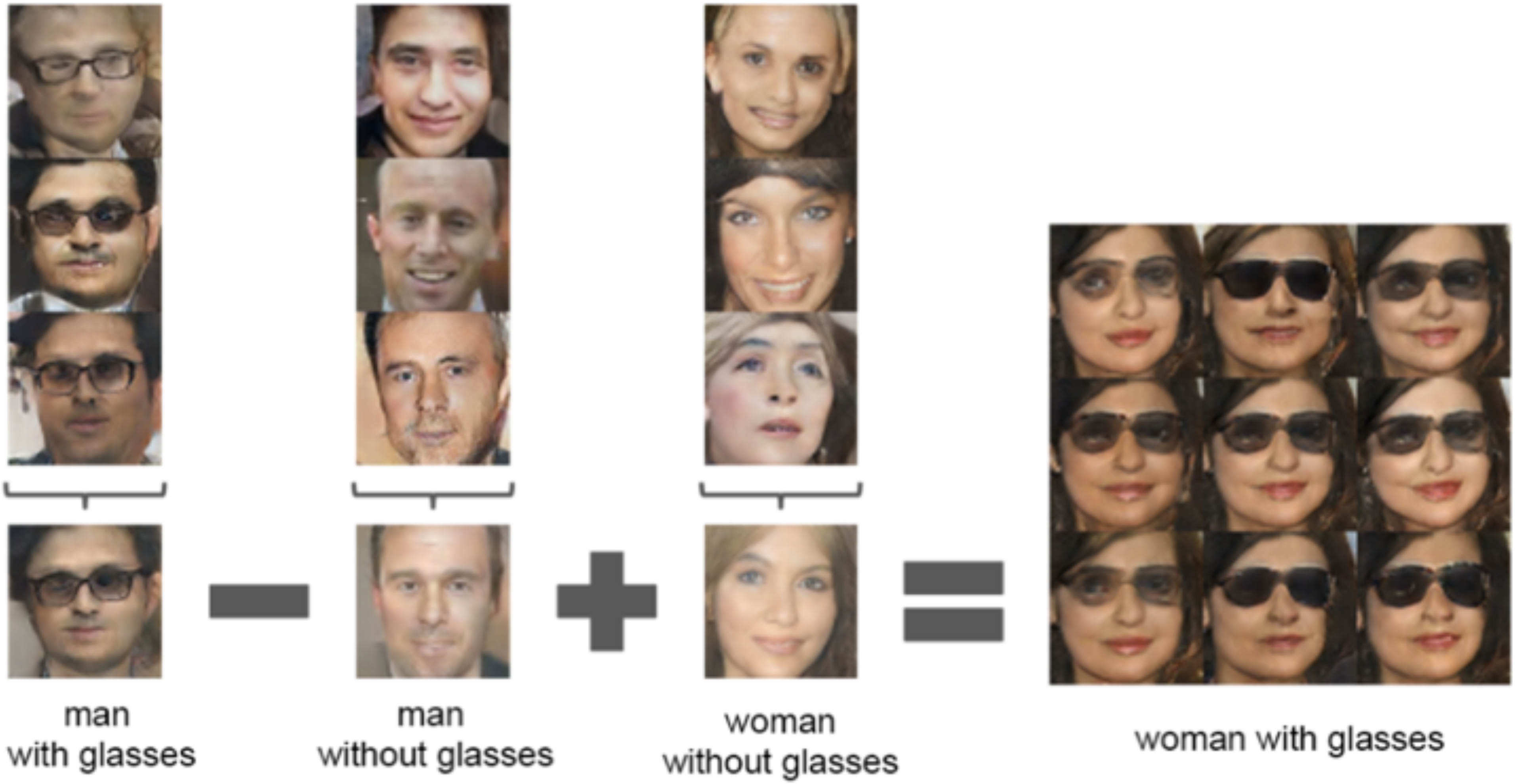


“Latent” variables
(states, kinetics, properties…)

Example:
Generative Adversarial Network

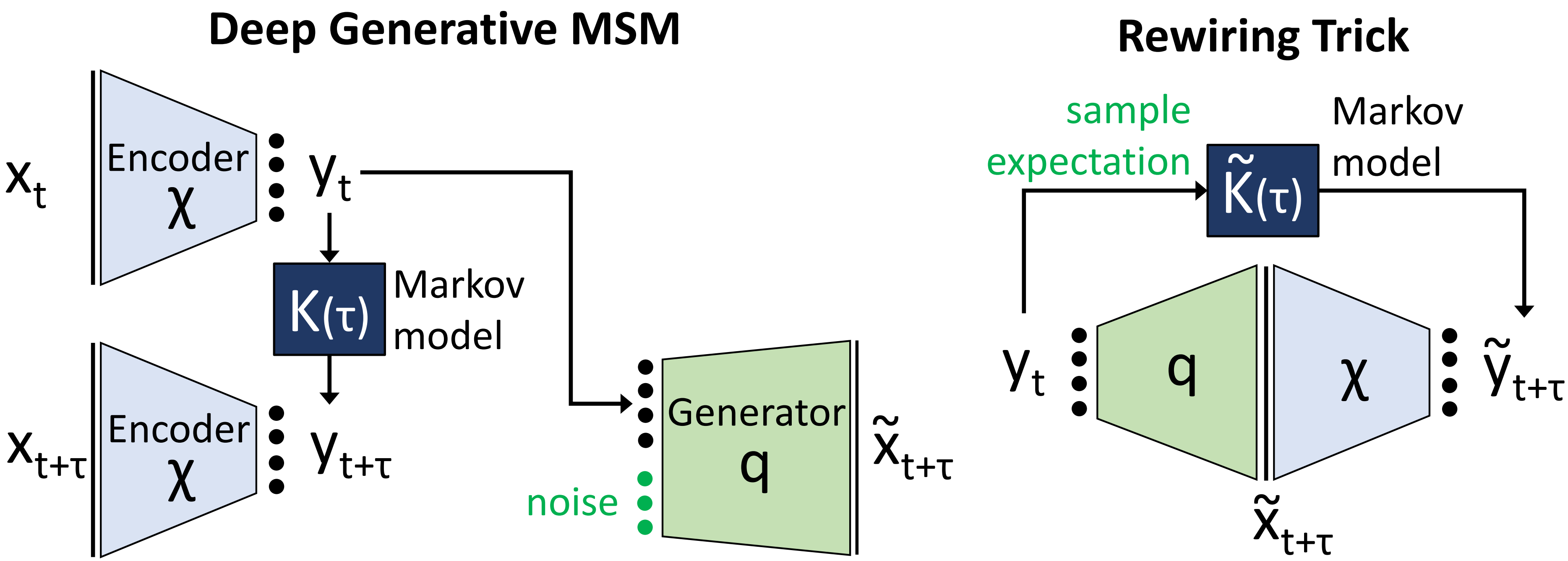


Generative Adversarial Network



Radford et al: Unsupervised Representation Learning with Deep Convolutional Generative Adversarial Networks arXiv:1511.06434 (2015)

Deep Generative Markov State Models

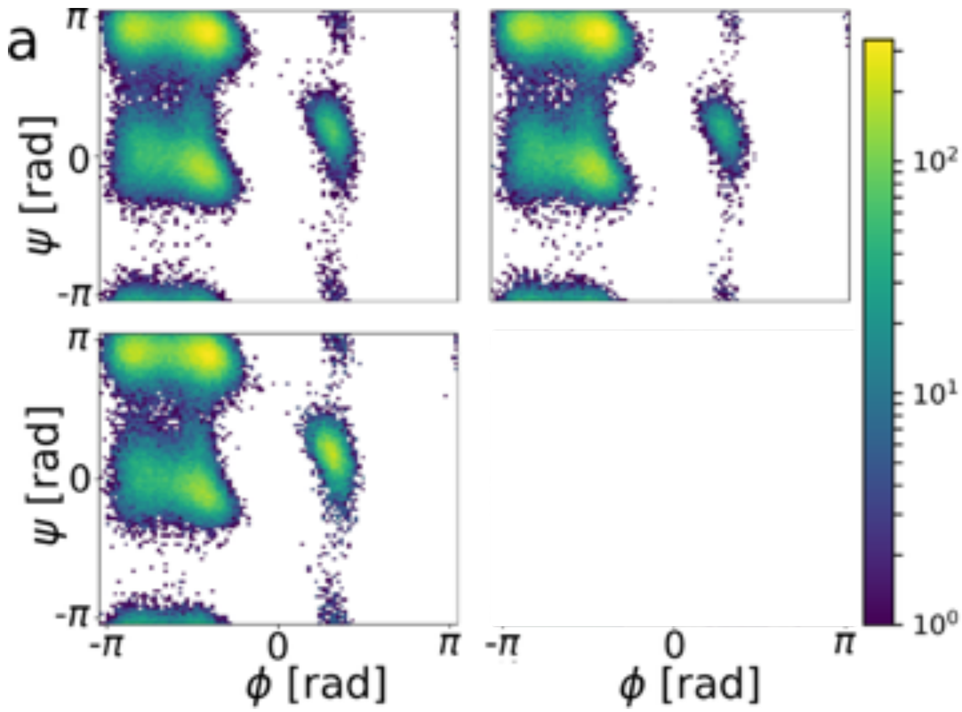


Wu, Mardt, Pasquali, Noé **NIPS** 2018 — arXiv:1805.07601

Deep Generative Markov State Models

Data

Deep MSM, resampled



"good" classical MSM

Wu, Mardt, Pasquali, Noé **NIPS** 2018 — arXiv:1805.07601

Deep Generative Markov State Models

Energy distance between distributions:

$$D_E\left(\mathbb{P}(x),\mathbb{P}(y)\right)=\mathbb{E}\left[2\left\|x-y\right\|-\left\|x-x'\right\|-\left\|y-y'\right\|\right]$$

with

$$x,x'\sim\mathbb{P}(x)$$

$$y,y'\sim\mathbb{P}(y)$$

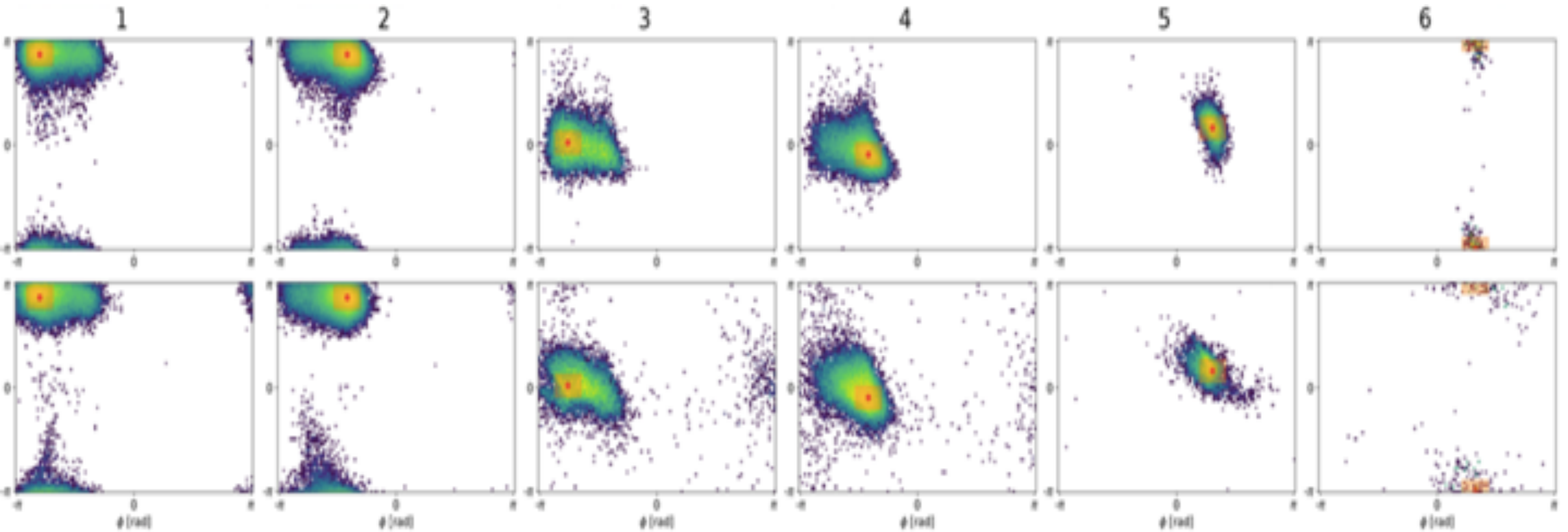
D_E = 0 only if distributions are equal

—> Train Generator Network by minimizing Energy Distance

Wu, Mardt, Pasquali, Noé **NIPS** 2018 — arXiv:1805.07601

Deep Generative Markov State Models

Learning transition densities

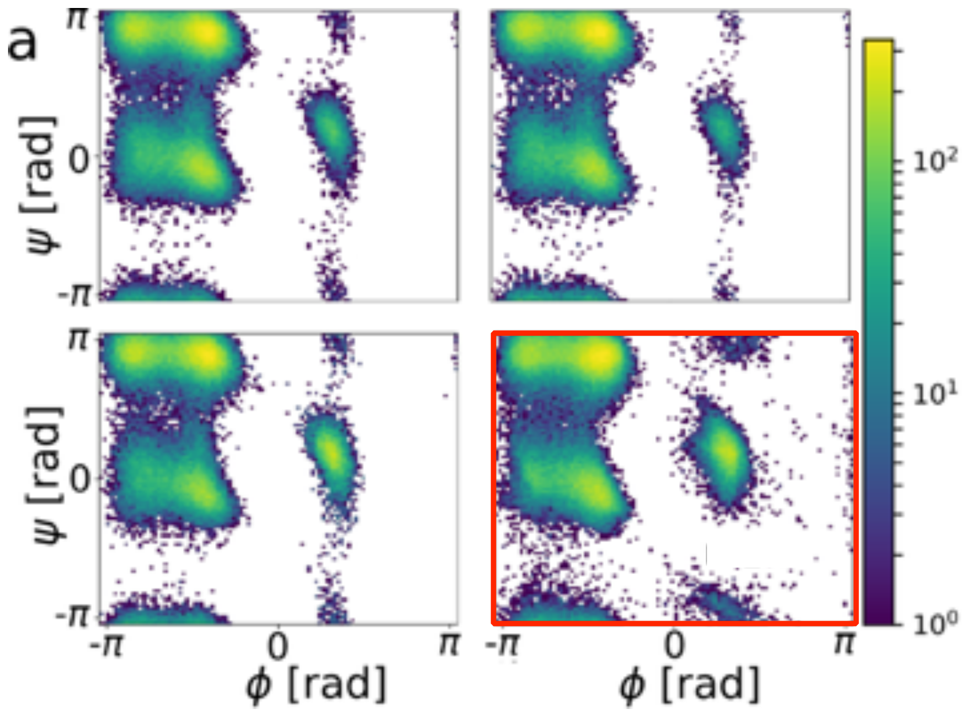


Wu, Mardt, Pasquali, Noé **NIPS** 2018 — arXiv:1805.07601

Deep Generative Markov State Models

Data

Deep MSM, resampled

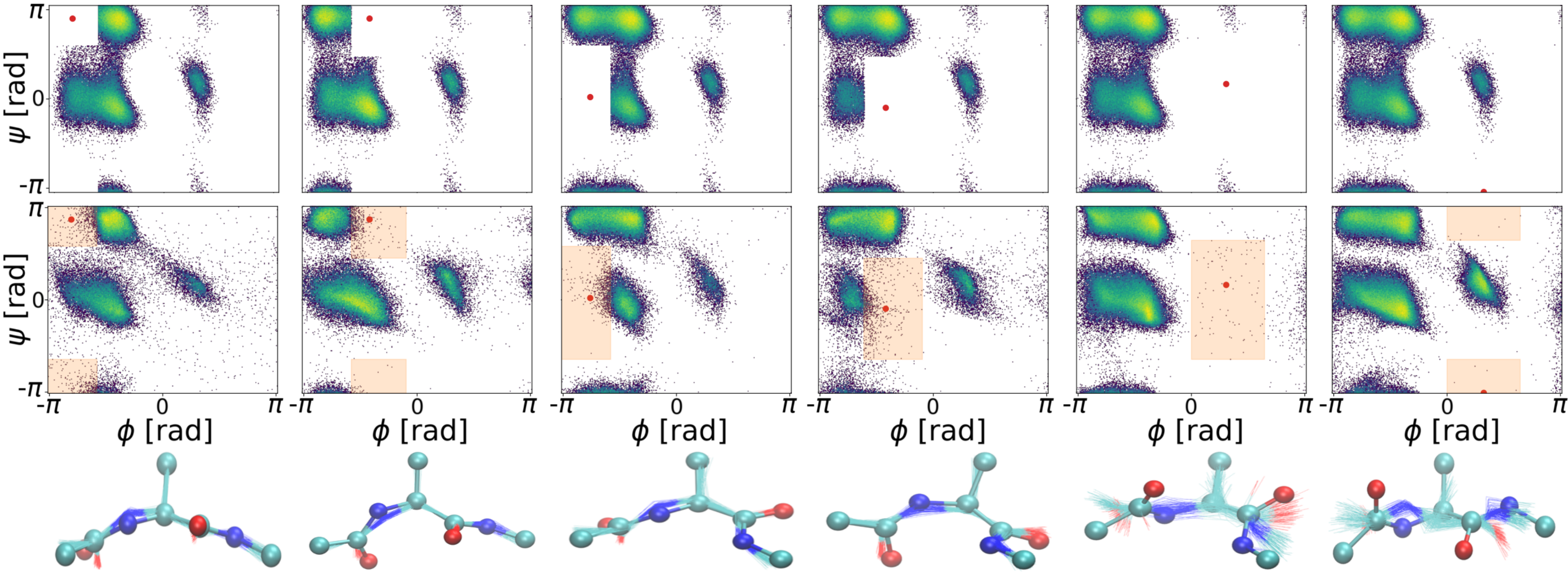


"good" classical MSM

Deep generative MSM

Wu, Mardt, Pasquali, Noé **NIPS** 2018 — arXiv:1805.07601

Deep Generative Markov State Models



Wu, Mardt, Pasquali, Noé **NIPS** 2018 — arXiv:1805.07601

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Collaborations

Cecilia Clementi (Rice University)
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erc

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DFG Deutsche Forschungsgemeinschaft

Freie Universität Berlin

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)

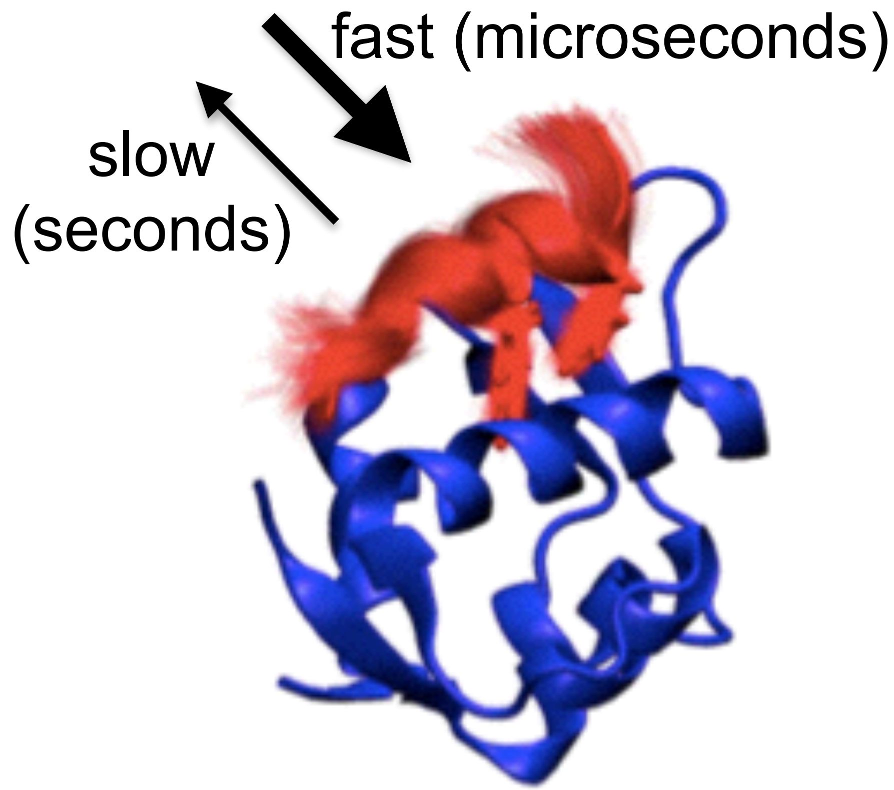
Hao Wu
Theory

Christoph Wehmeyer
Software and Methods

Fabian Paul
Theory and Methods

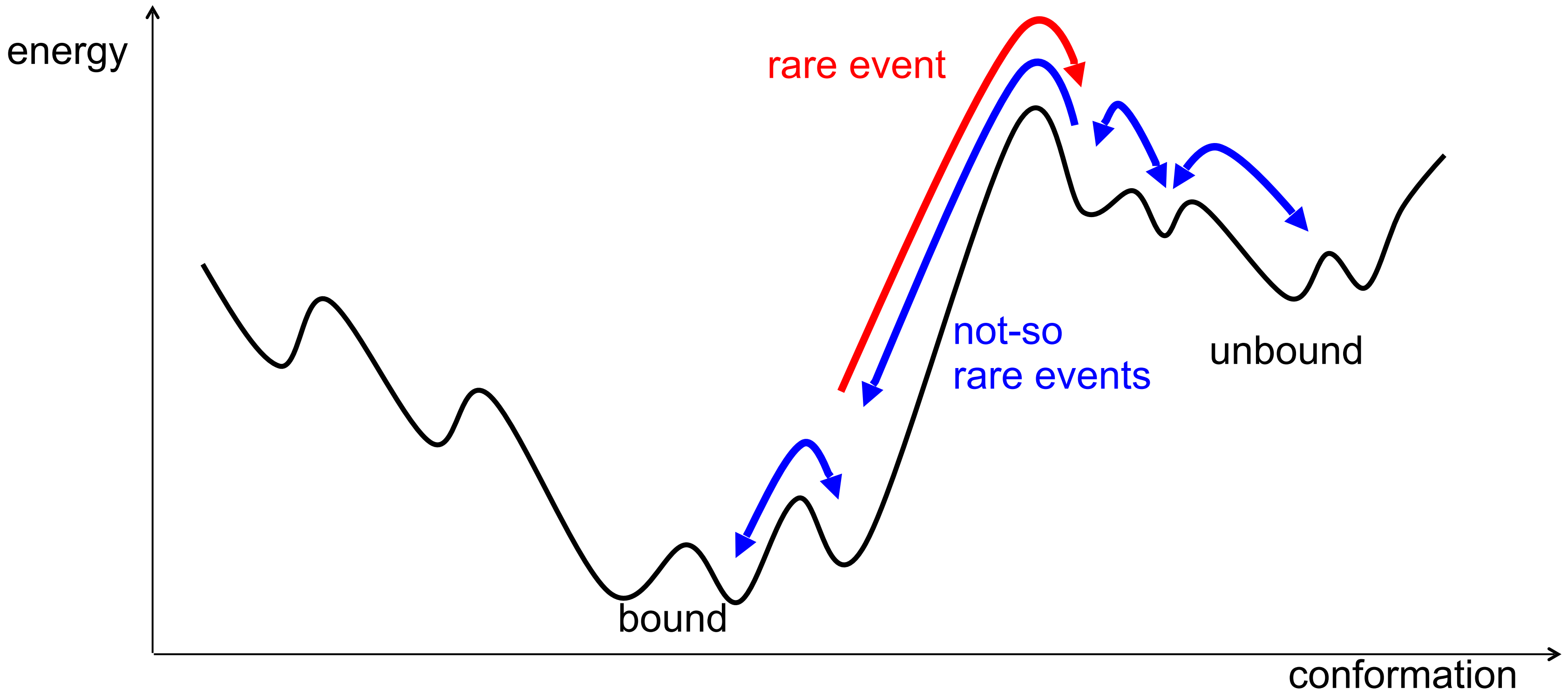
Esam Abualrous
Experiments

Example: binding and folding of PMI to MDM2

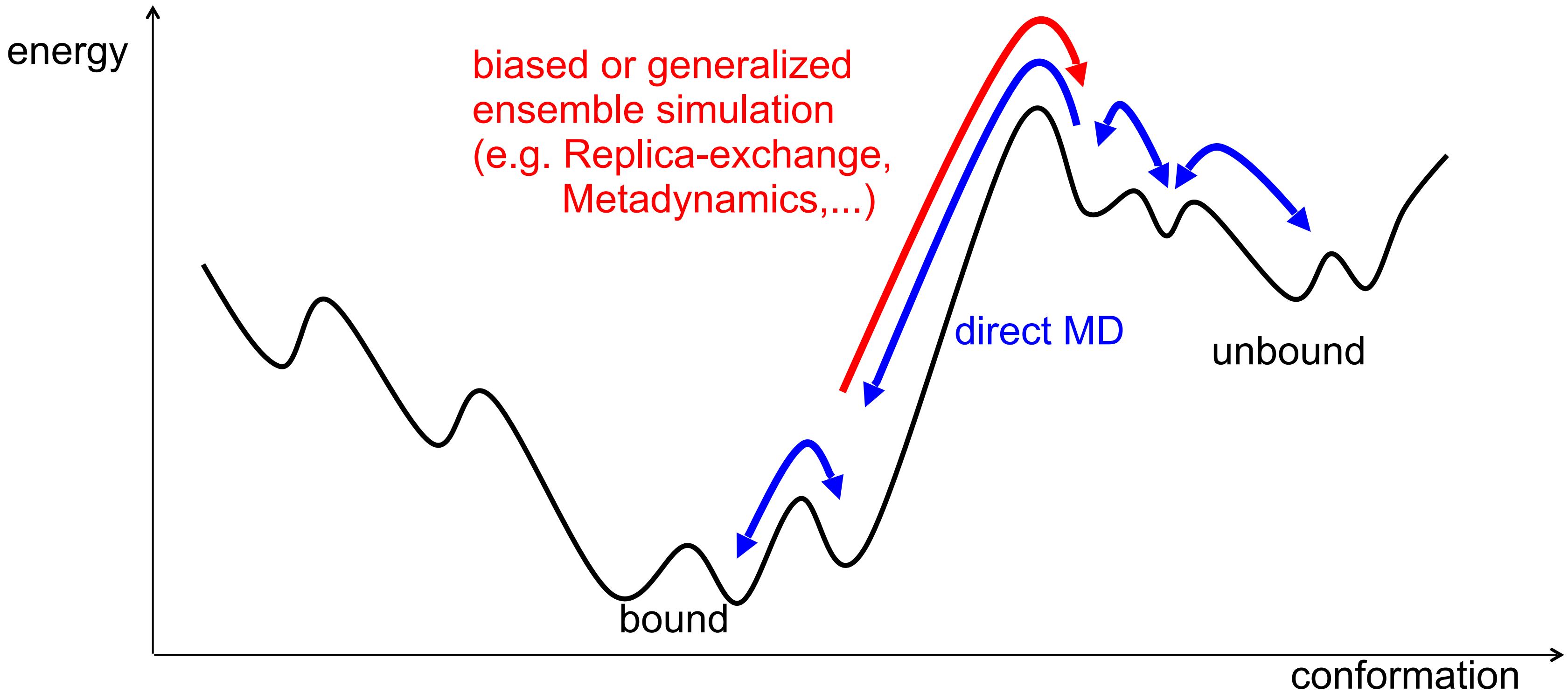


nanomolar binder

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



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



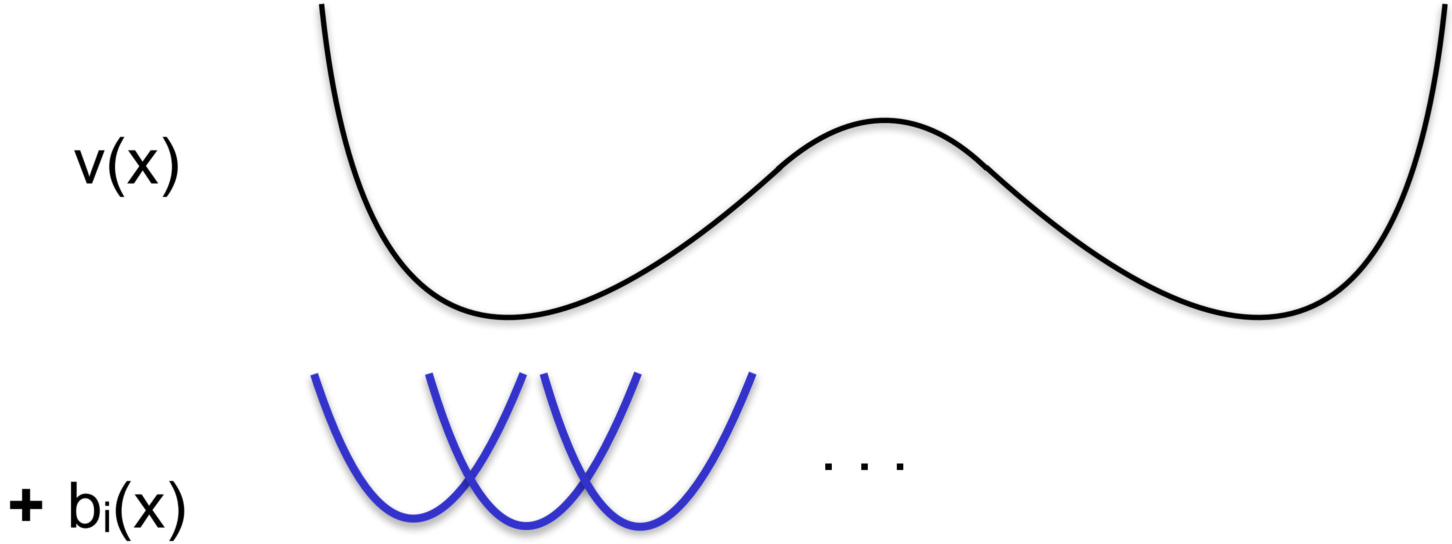
direct molecular dynamics

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)

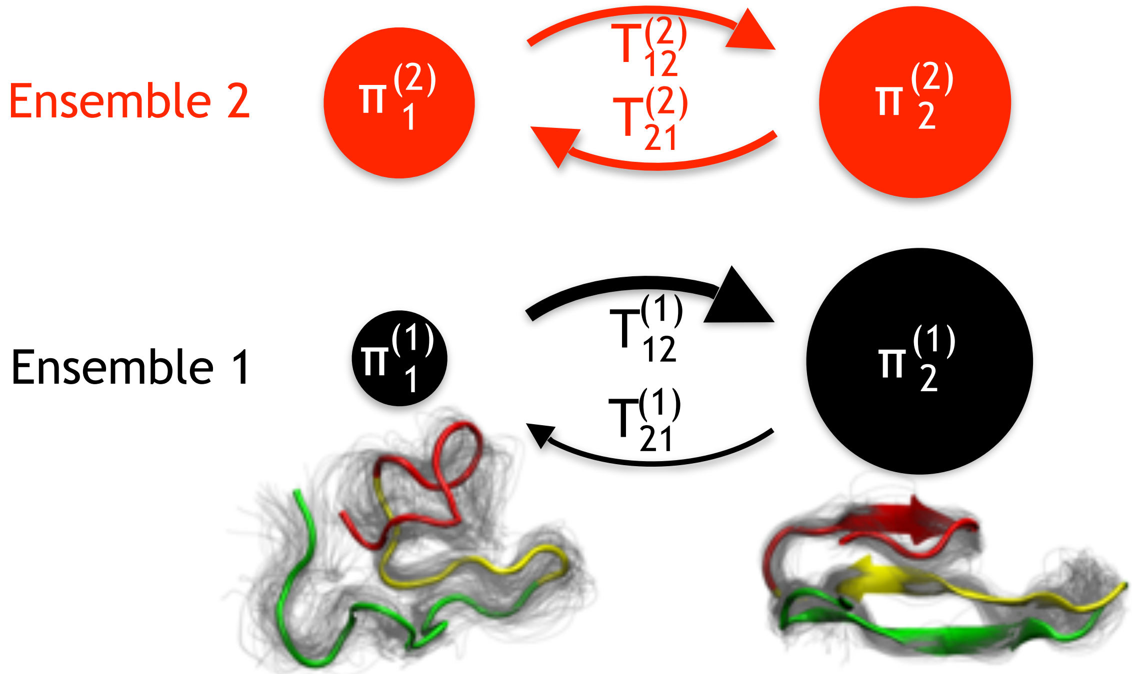
$$\begin{pmatrix} T_{11}^{(1)} & \cdots & T_{1n}^{(1)} \\ \vdots & \ddots & \vdots \\ T_{n1}^{(1)} & \cdots & T_{11}^{(1)} \end{pmatrix}$$

Thermodynamic state / Ensemble

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

Configuration state

$$\ddots$$



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

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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

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

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

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

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

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

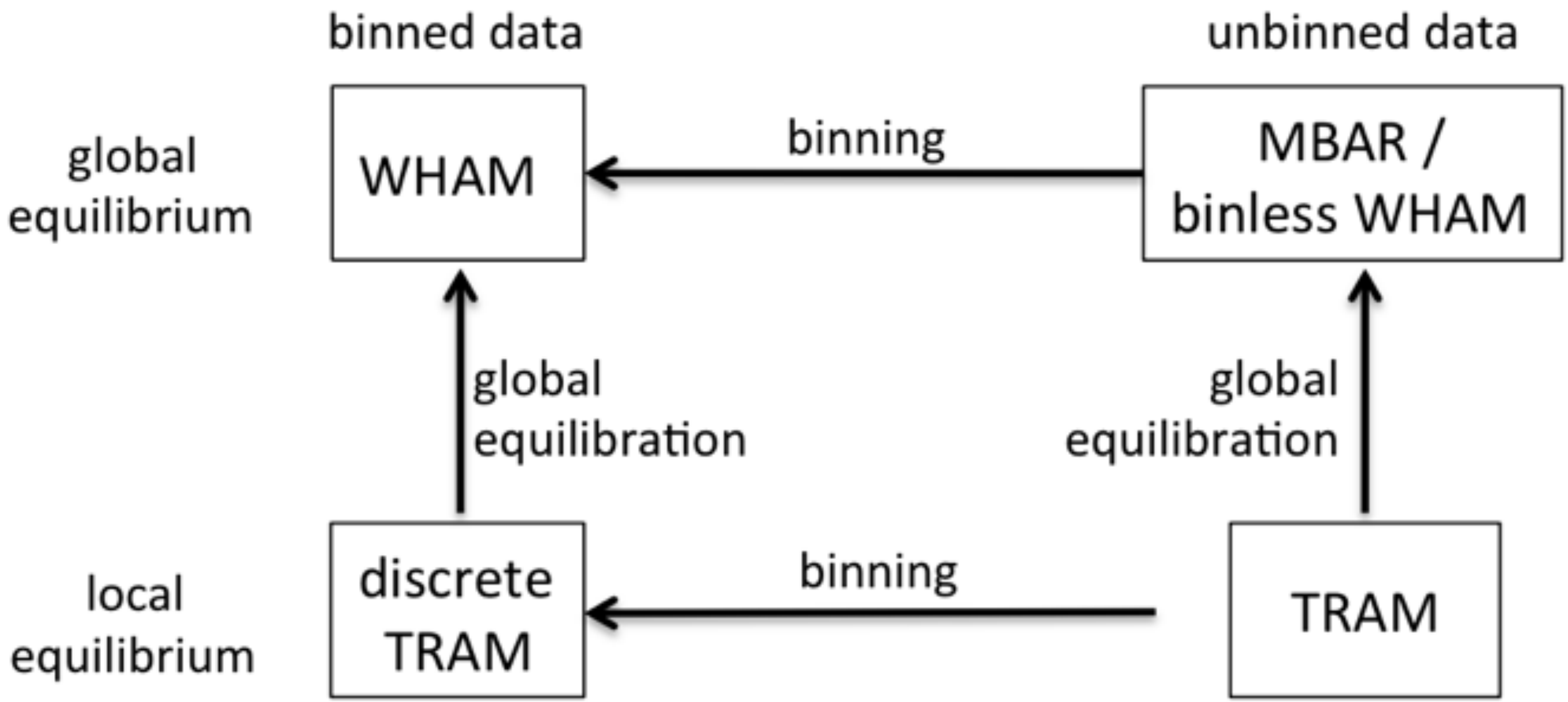
$$R_i^k = \sum_j \frac{\left(c_{ij}^k + c_{ji}^k\right) v_j^k}{v_j^k + \exp\left[f_i^k - f_j^k\right] v_i^k} + N_i^k - \sum_j c_{ji}^k$$

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)



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

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

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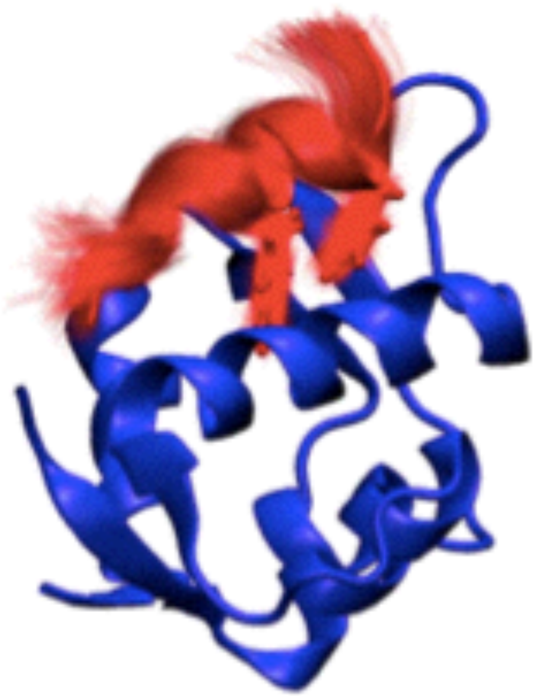
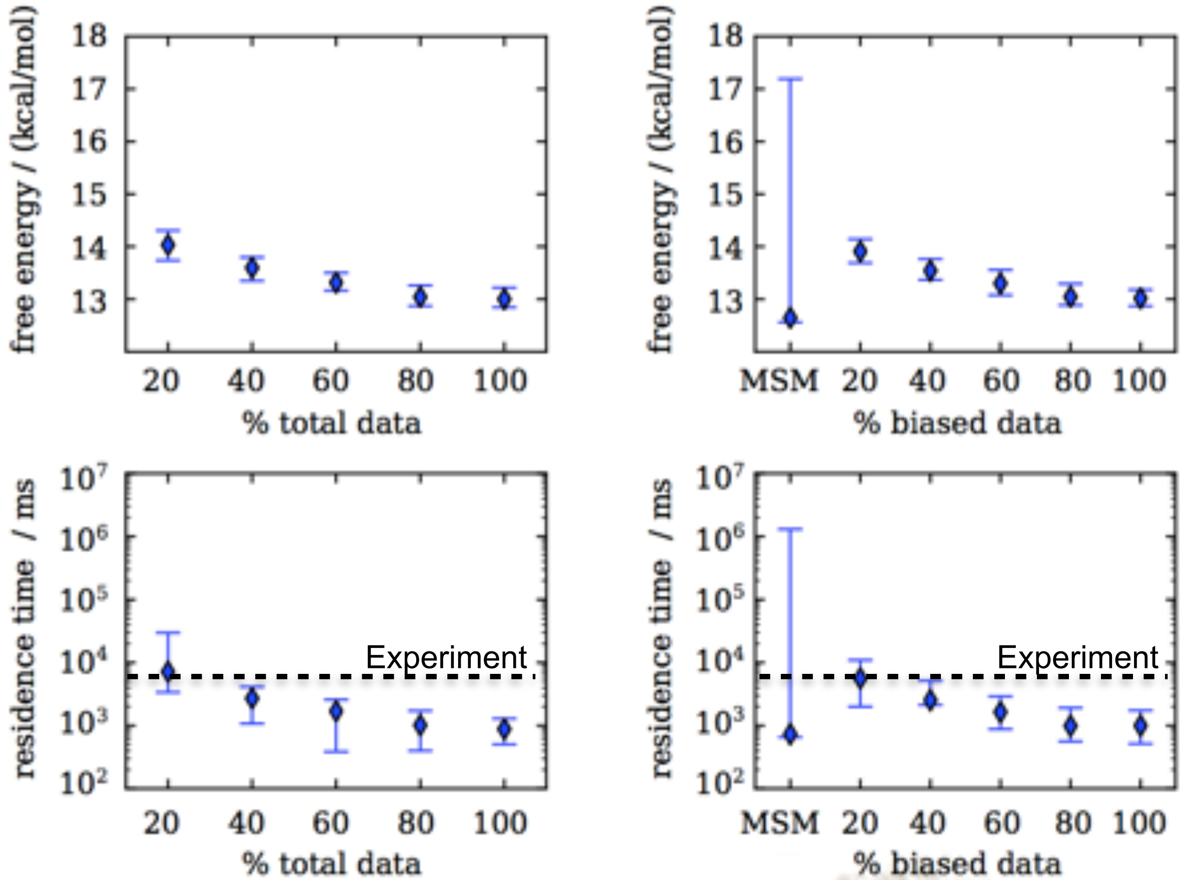
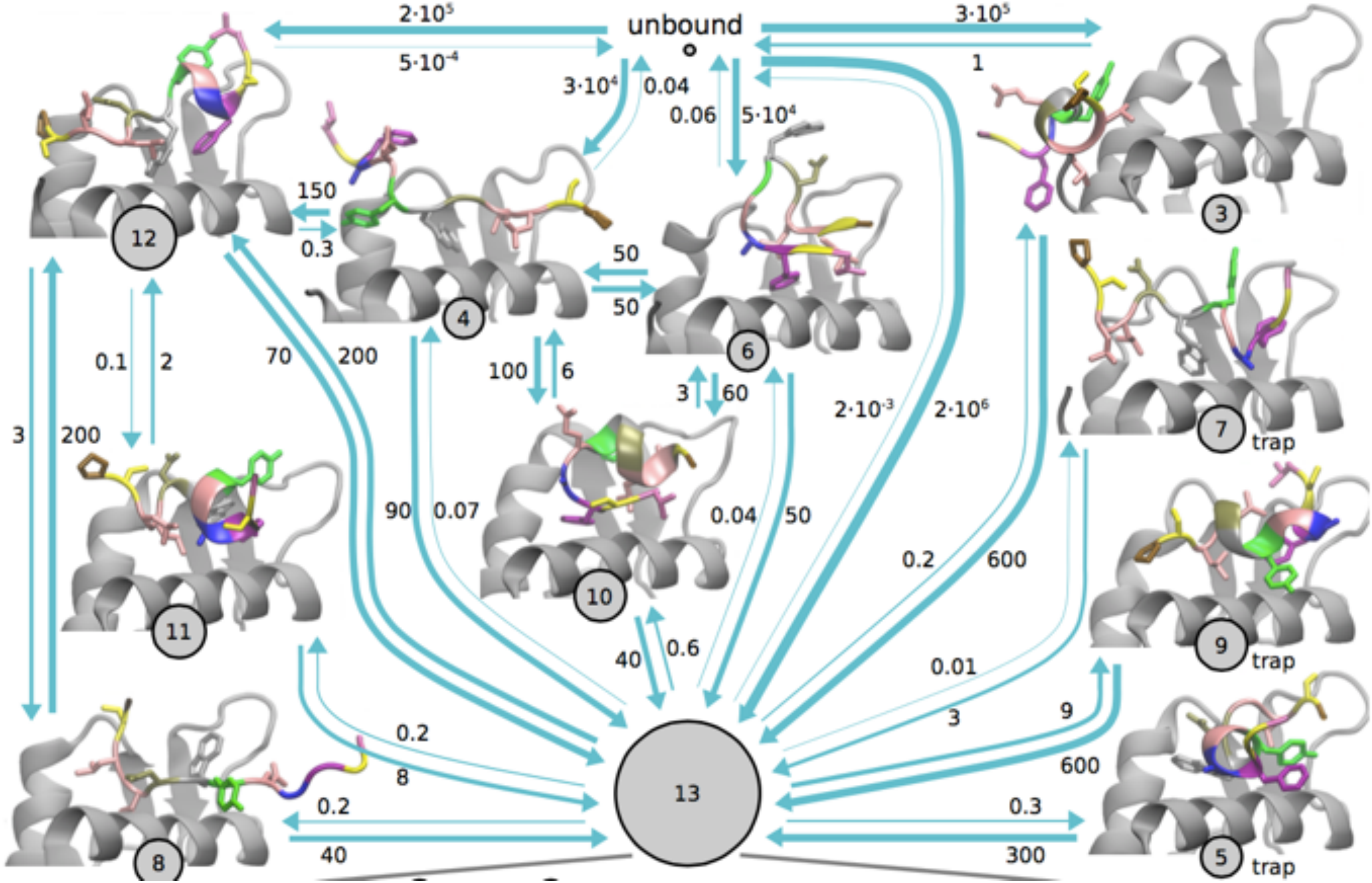
PMI-MDM2: rates and affinities





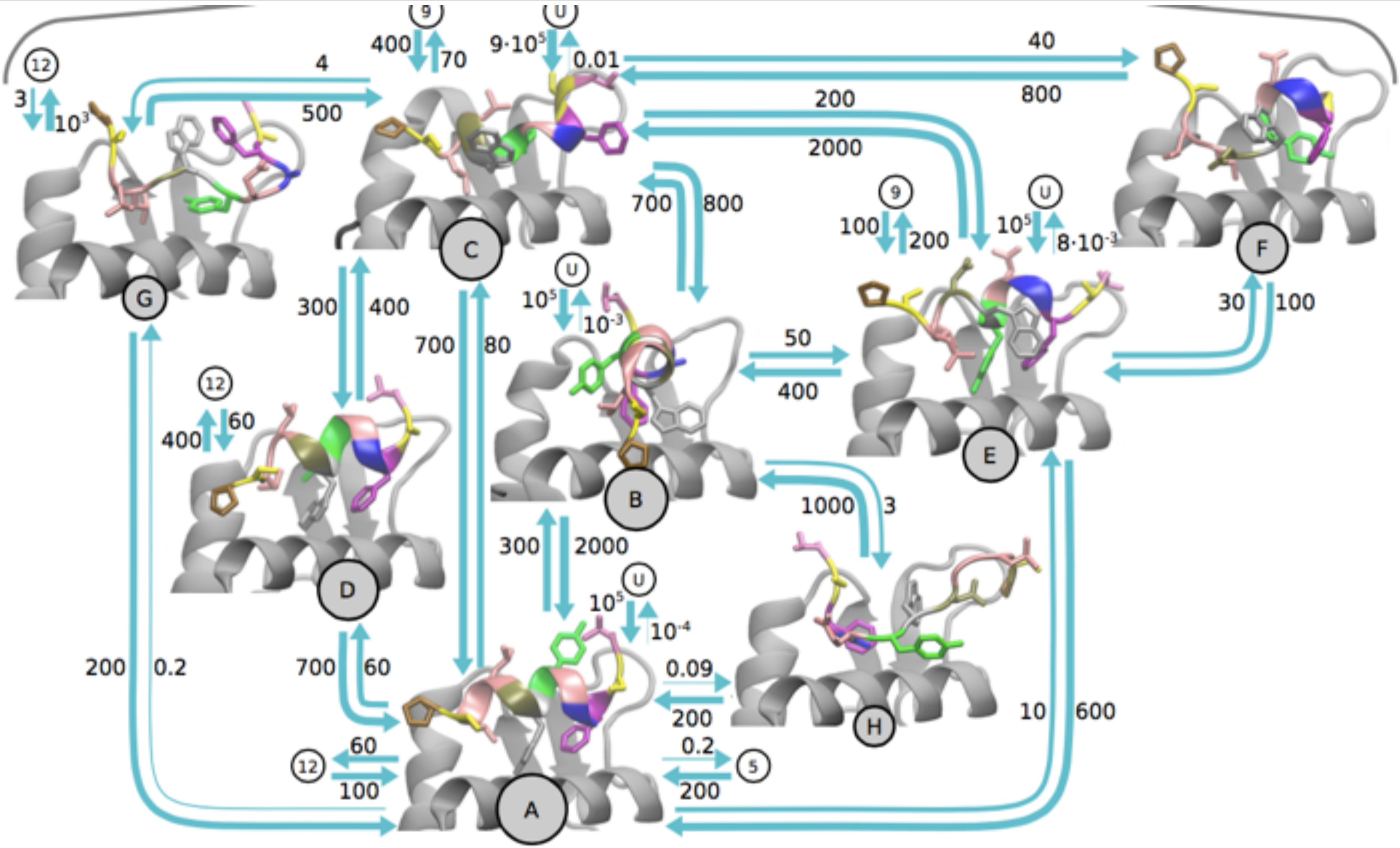
Paul et al., **Nature Communications** 8, 1095 (2017)

PMI-MDM2: mechanism 1



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

PMI-MDM2: mechanism 2



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

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