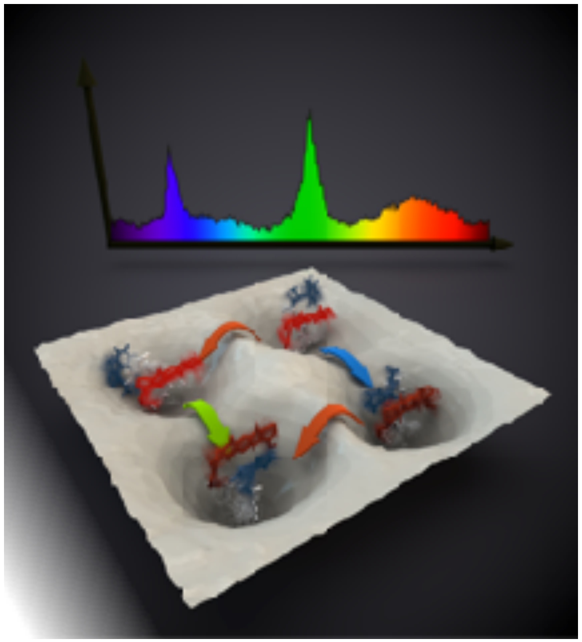
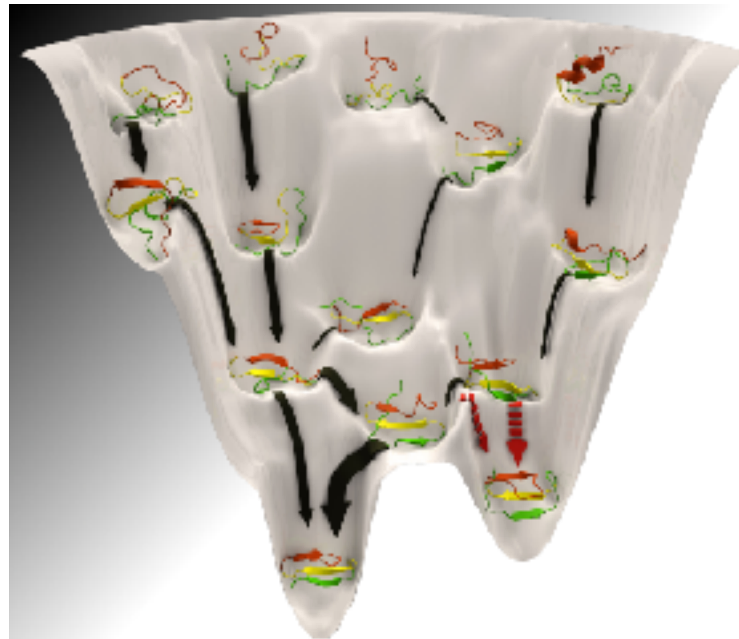
Model optimization and selection:
Variational Approach for Markov Processes (VAMP)





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Computational Molecular Biology

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Motivation

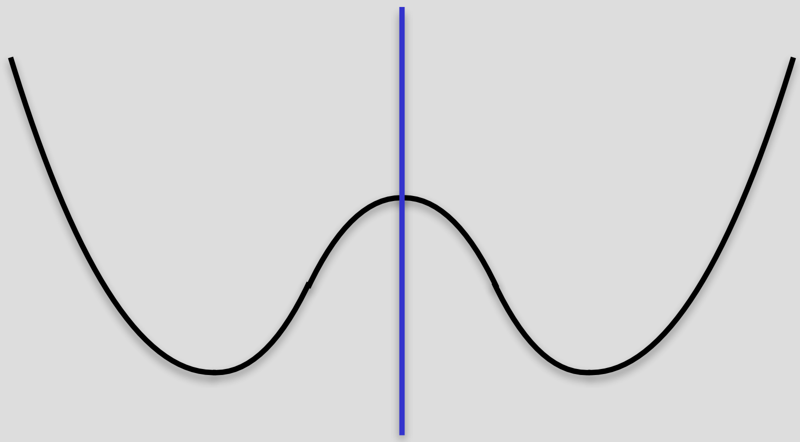
Which parameters?

$(x_1, x_2, \ldots, x_T)$

$(s_1, s_2, \ldots, s_T)$

transition matrix?

How many states?



2 ?
10 ?
1000 ?

Which features?

Ca-coordinates ?
distances ?
contacts ?

Parameter optimization problem

Hyperparameter optimization / model selection problem

Solving model selection problem requires two ingredients:

1) A **score** to rank models (MSMs, TICA, etc) by goodness

    ==> Variational principle

2) A **statistical validation method** to avoid overfitting

    ==> Cross-validation https://en.wikipedia.org/wiki/Cross-validation_(statistics)

Slow processes

Backward propagator

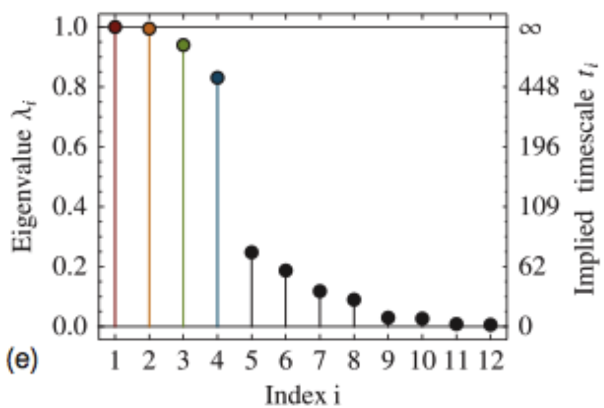
$$\rho_\tau = \mathcal{T}(\tau)\rho_0$$

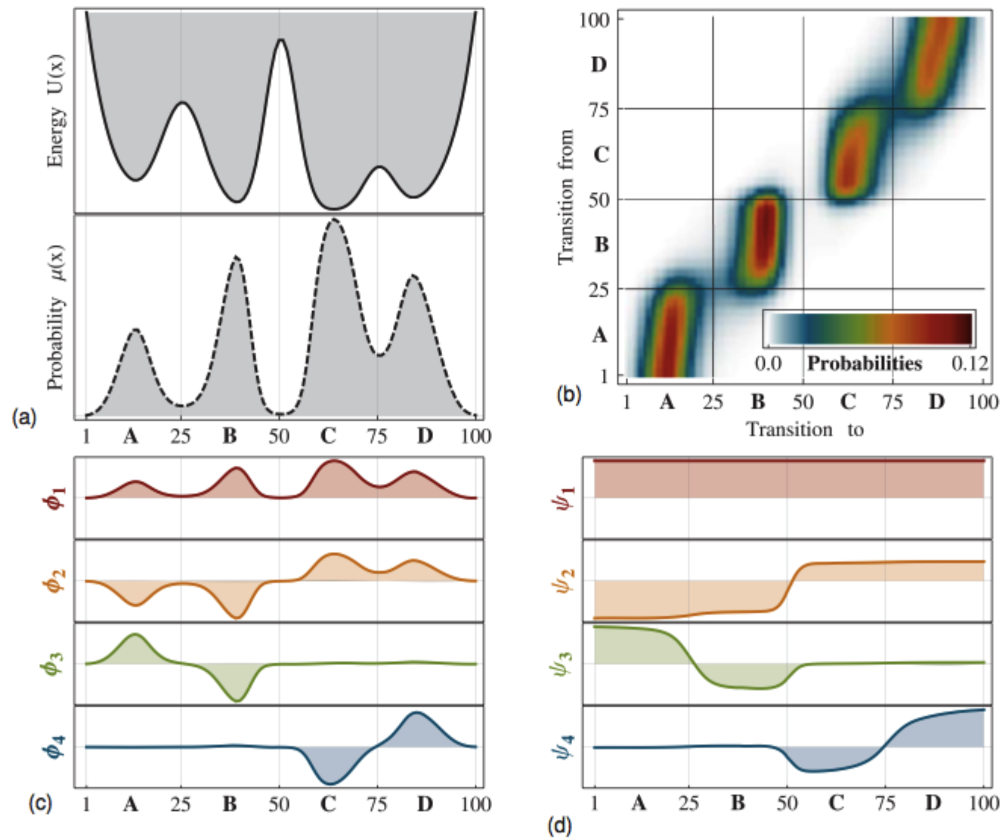
Spectral decomposition

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

Processes:

Eigenvalues / timescales κ_i^{-1}





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

Part I : Variational score

***Variational theorem**: For any $m \geq 1$, the first m eigenfunctions $\psi_1, \ldots, \psi_m$ are the solution of the following optimization problem*

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

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

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

where $\mathbf{E}_\mu[\cdot]$ denotes the expected value with $\mathbf{x}_t$ sampled from the stationary density μ and the maximum value is the generalized Rayleigh quotient, or Rayleigh trace $R_m = \sum_{i=1}^{m} \lambda_i$.

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

Part I : Variational score

Variational theorem: *For any $m \geq 1$, take a set of functions $f_1, ..., f_m$ and the covariance matrices $\mathbf{C}(0)$ and $\mathbf{C}(\tau)$ with elements:*

$$c_{ij}(0) = \mathbb{E}_t\left[f_i(\mathbf{x}_t)\, f_j(\mathbf{x}_t)\right]$$
$$c_{ij}(\tau) = \mathbb{E}_t\left[f_i(\mathbf{x}_t)\, f_j(\mathbf{x}_{t+\tau})\right]$$

where $\mathbb{E}_t[\cdot]$ denotes the ergodic time average. Now perform an eigenvalue decomposition

$$\mathbf{C}(\tau)\mathbf{b}_k = \mathbf{C}(0)\mathbf{b}_k\hat{\lambda}_k$$
$$\mathbf{K}\mathbf{b}_k = \mathbf{b}_k\hat{\lambda}_k,$$

where we have used the abbreviation $\mathbf{K} = \mathbf{C}(0)^{-1}\mathbf{C}(\tau)$.

Then, the maximization of the Rayleigh trace:

$$R_m = \max_{f_1,\ldots,f_m} \sum_{k=1}^{m} \hat{\lambda}_k = \sum_{i=1}^{m} \lambda_i.$$

solves the first m eigenfunctions $\psi_1, \ldots, \psi_m$ of the transfer operator by

$$\psi_k(\mathbf{x}) = \sum_i b_{ki} f_i(\mathbf{x}).$$

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

Part I : Variational score

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$$\mathbf{K}\mathbf{b}_k = \mathbf{b}_k \hat{\lambda}_k,$$

where we have used the abbreviation $\mathbf{K} = \mathbf{C}(0)^{-1}\mathbf{C}(\tau)$.

Then, the maximization of the kinetic variance:

$$K_m = \max_{f_1,...,f_m} \sum_{k=1}^{m} \hat{\lambda}_k^2 = \sum_{i=1}^{m} \lambda_i^2.$$

solves the first m eigenfunctions $\psi_1, \ldots, \psi_m$ of the transfer operator by

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Noé and Nüske, **MMS** 11, 635-655 (2013)
Nüske et al, **JCTC** 10, 1739-1752 (2014)
*Noé and Clementi, **JCTC** 11, 5002—5011 (2015)

Variational Approach for Markov processes (VAMP)

We have the trajectory

$$\mathbf{X} = (\mathbf{x}_1, ..., \mathbf{x}_T)$$

We define features $f_1, ..., f_n$ that are candidates for the eigenfunctions or singular functions. For each configuration we thus get a n-dimensional feature vector:

$$\mathbf{f}(\mathbf{x}) = (f_1(\mathbf{x}), ..., f_n(\mathbf{x}))$$

We estimate covariance matrices, for example using the direct estimator:

$$\mathbf{C}_{\mathbf{f}}^{00}(\mathbf{X}) = \frac{1}{T-\tau}\sum_t^{T-\tau} \mathbf{f}(\mathbf{x}(t))\, \mathbf{f}^\top(\mathbf{x}(t))$$

$$\mathbf{C}_{\mathbf{f}}^{0\tau}(\mathbf{X}) = \frac{1}{T-\tau}\sum_t^{T-\tau} \mathbf{f}(\mathbf{x}(t))\, \mathbf{f}^\top(\mathbf{x}(t+\tau))$$

$$\mathbf{C}_{\mathbf{f}}^{\tau\tau}(\mathbf{X}) = \frac{1}{T-\tau}\sum_t^{T-\tau} \mathbf{f}(\mathbf{x}(t+\tau))\, \mathbf{f}^\top(\mathbf{x}(t+\tau)).$$

and $\mathbf{C}_\tau$ (either TICA or MSMs).

The estimates of $\mathbf{C}^{00}$ and $\mathbf{C}^{\tau\tau}$ are sometimes regularized by adding $\lambda\mathbf{I}$, an identity matrix scaled by a small parameter λ (also called Shrinkage or Ridge estimator). This is to ensure that $\mathbf{C}^{00}$ and $\mathbf{C}^{\tau\tau}$ are invertible.

Variational Approach for Markov processes (VAMP)

VAMP-2 Score

$$R_2(\mathbf{f}, \mathbf{X}, k) = \left\| \mathbf{C}_{\mathbf{f}}^{00}(\mathbf{X})^{-\frac{1}{2}} \; \mathbf{C}_{\mathbf{f}}^{0\tau}(\mathbf{X}) \; \mathbf{C}_{\mathbf{f}}^{\tau\tau}(\mathbf{X})^{-\frac{1}{2}} \right\|_{V(k)}$$

Where

$$\|\mathbf{A}\|_{V(k)}^2 = \sum_{i=1}^{k} \sigma_i^2$$

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

where $\mathbf{\Sigma} = (\sigma_1, ..., \sigma_n)$ are the singular values (in descending order) of the matrix decomposition

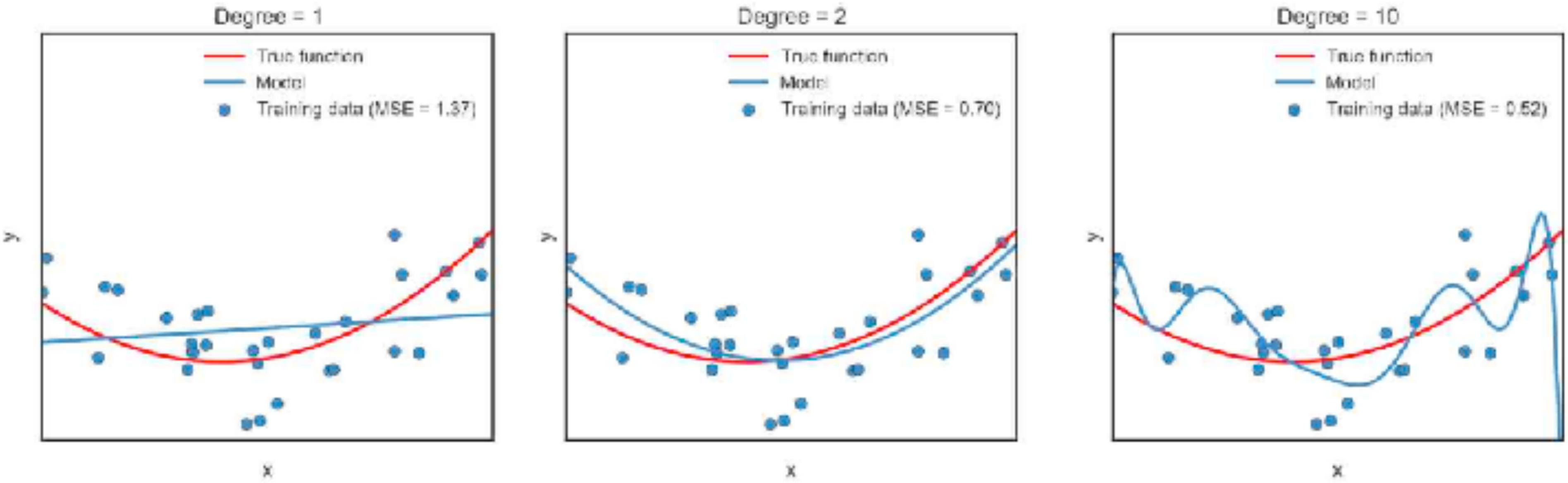
$$\mathbf{A} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^\top$$

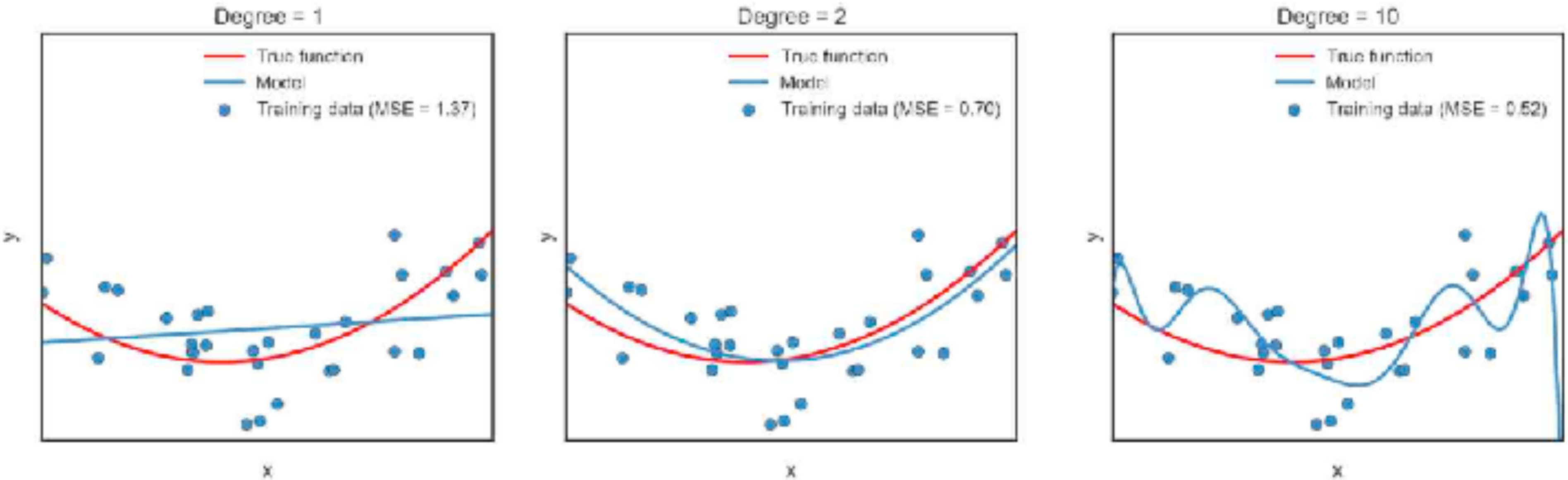
If dynamics are **reversible** (detailed balance), $\mathbf{C}_{\mathbf{f}}^{0\tau}$ is symmetric, $\mathbf{U} = \mathbf{V}$, the singular values are equal to the eigenvalues $\sigma_i = \lambda_i$, and the VAMP-2 norm is the kinetic distance:

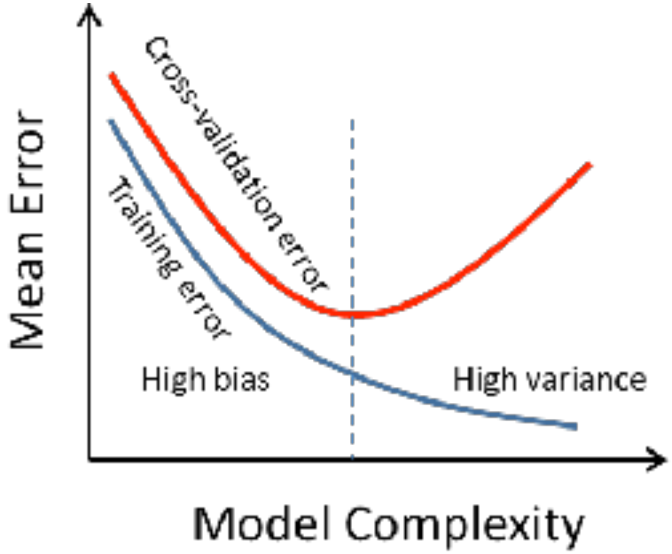
$$\|\mathbf{A}\|_{V(k)}^2 = \sum_{i=1}^{k} \lambda_i^2$$

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

Part II : Statistical validation




Degree = 1
True function
Model
Training data (MSE = 1.37)
y
x
Degree = 2
True function
Model
Training data (MSE = 0.70)
y
x
Degree = 10
True function
Model
Training data (MSE = 0.52)
y
x


Mean Error
Cross-validation error
Training error
High bias
High variance
Model Complexity

Cross-validation

Training:

Use data $\mathbf{X}_{\text{train}}$ and optimize $\mathbf{f}$:

$$\mathbf{f} = \arg\max_{\boldsymbol{f}} R_2(\boldsymbol{f}, \mathbf{X}_{\text{train}}, k)$$

The training score is then given by

$$R_2^{\text{train}}(\mathbf{f}, k) = R_2(\mathbf{f}, \mathbf{X}_{\text{train}}, k)$$

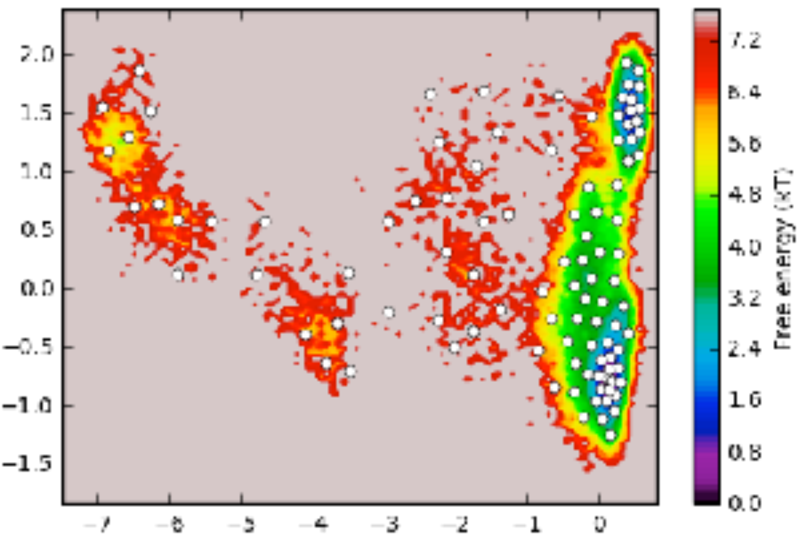
Validation:

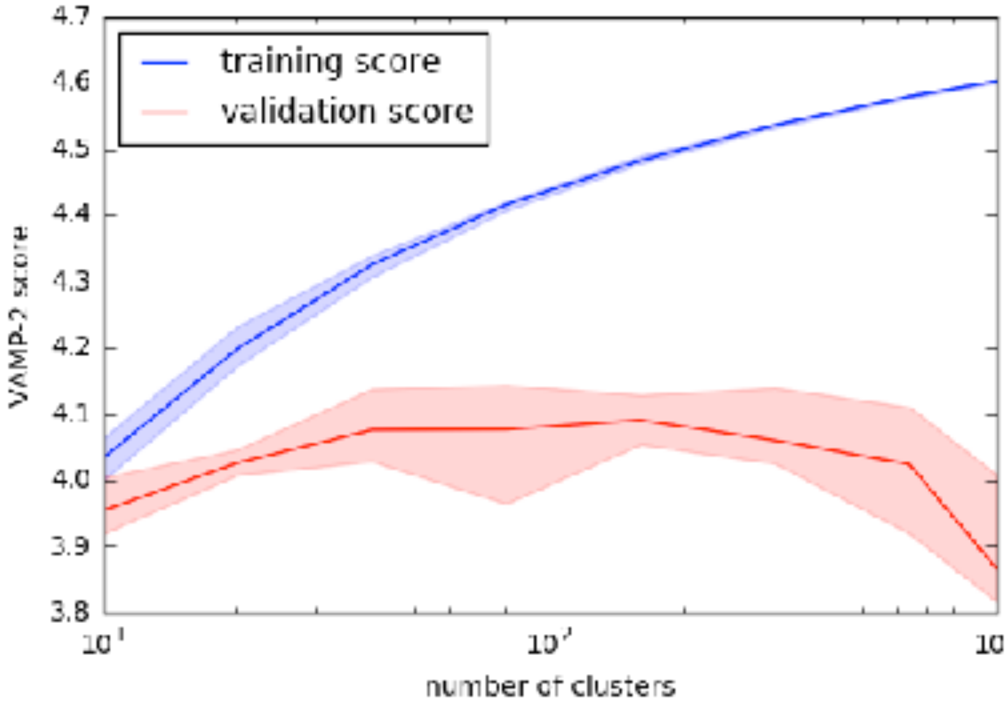
Use independent data $\mathbf{X}_{\text{val}}$ and compute validation score:

$$R_2^{\text{val}}(\mathbf{f}, k) = R_2(\mathbf{f}, \mathbf{X}_{\text{val}}, k)$$

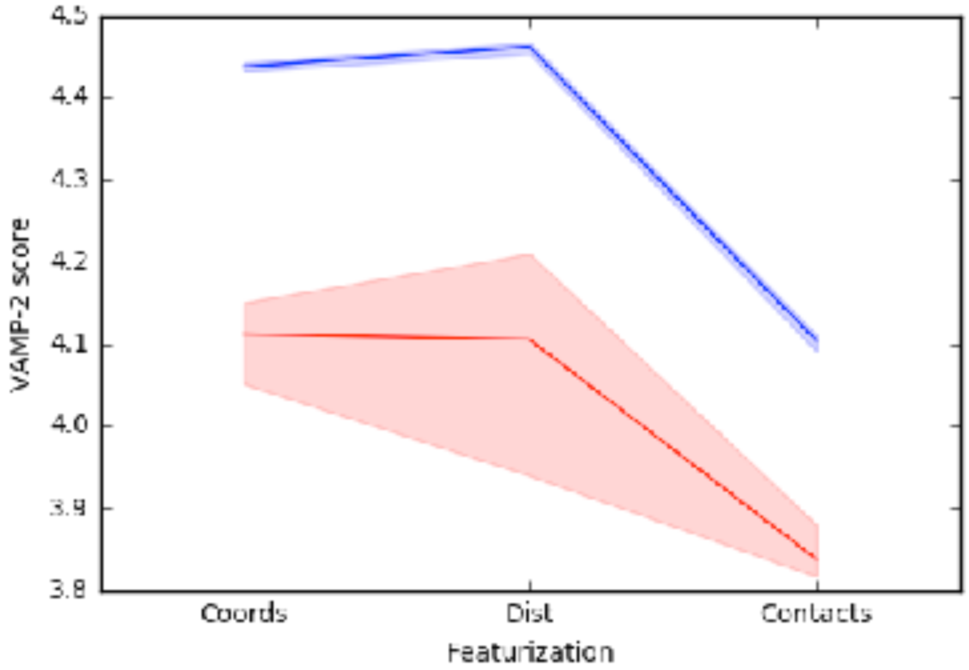
Note that we keep the transformation $\mathbf{f}$ learned in training, but we apply it on new data $\mathbf{X}_{\text{val}}$. $R_2^{\text{val}}(\mathbf{f}, k)$ can be used to score different models, e.g. compared different sets of functions.

How many states in BPTI?

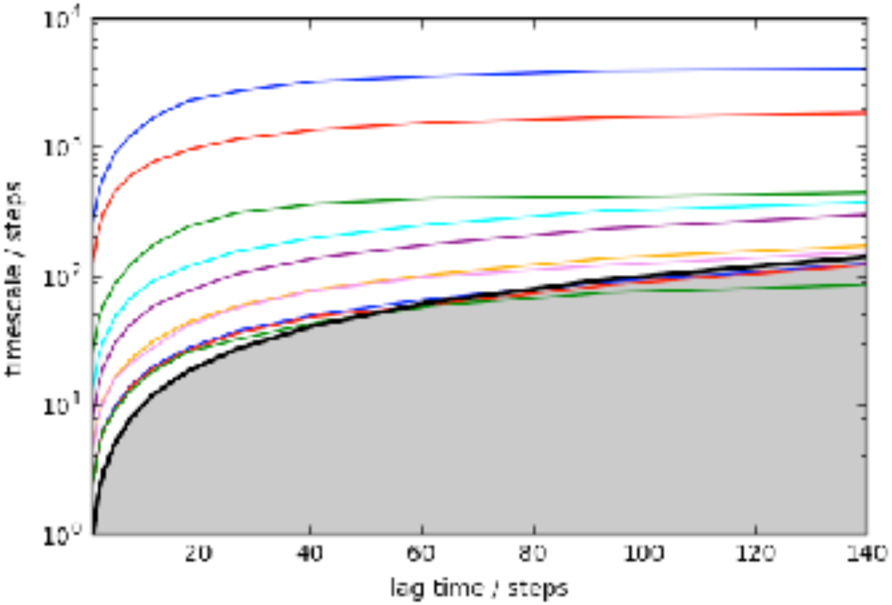




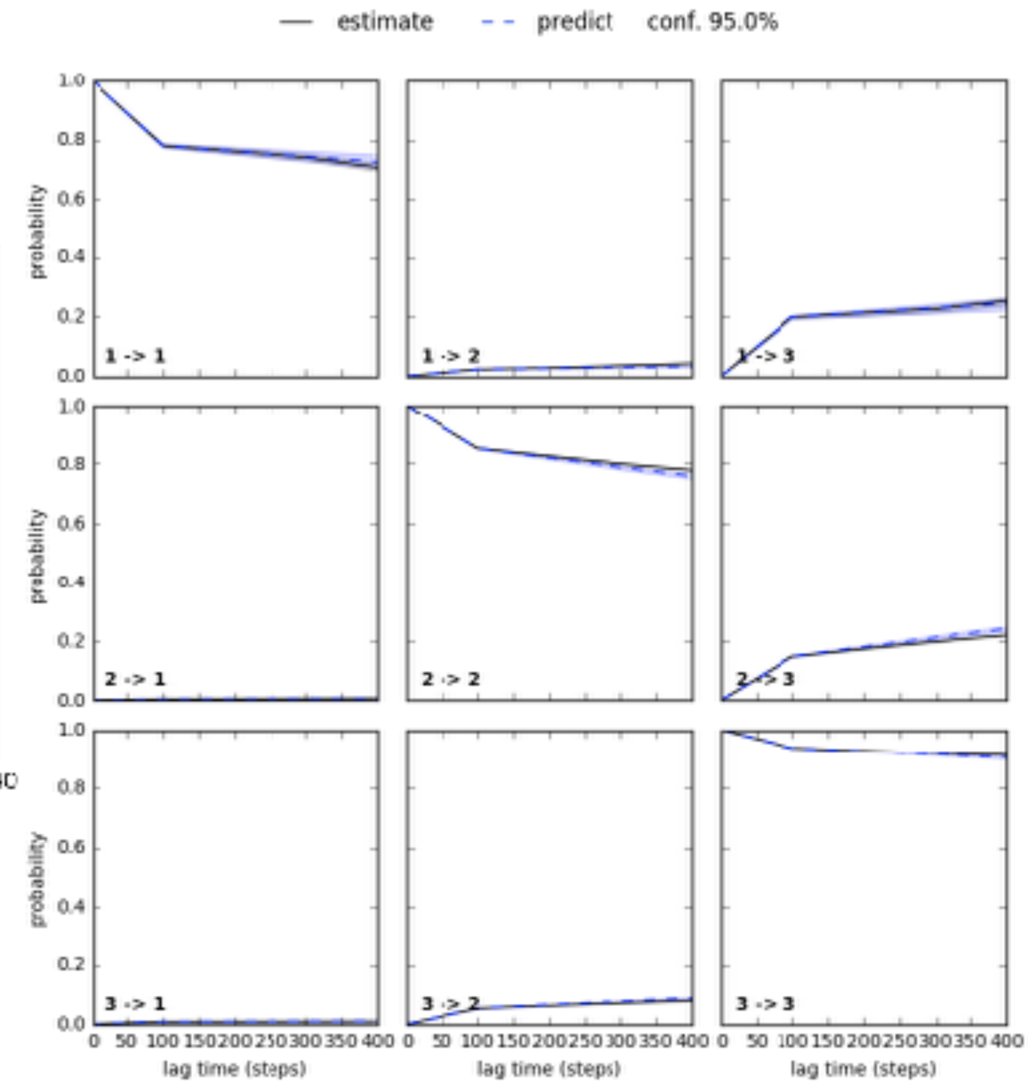
Which features for BPTI?



Validation

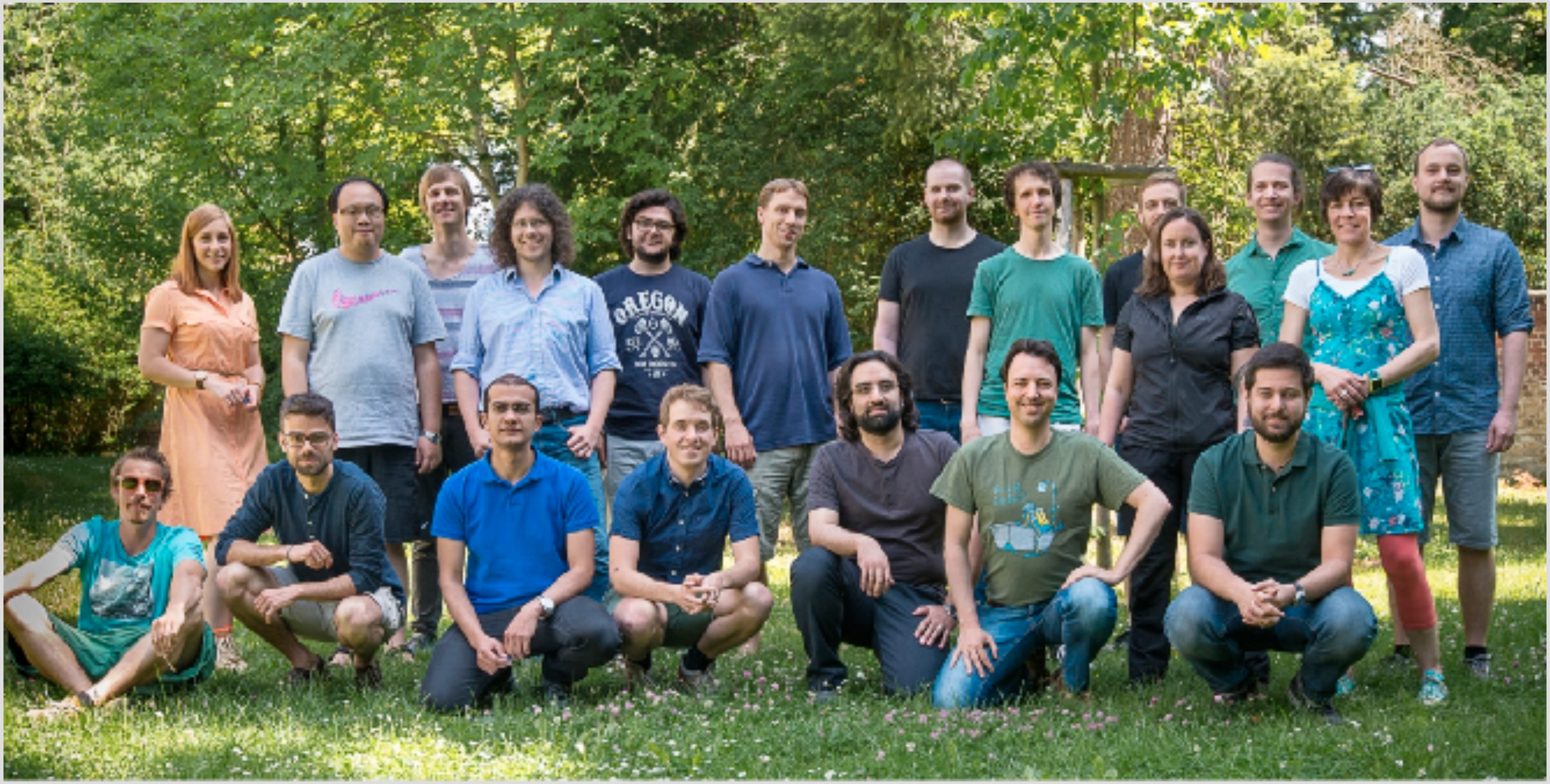


timescale / steps
20
40
60
80
100
120
140
lag time / steps



estimate
predict
conf. 95.0%
probability
1 -> 1
1 -> 2
1 -> 3
2 -> 1
2 -> 2
2 -> 3
3 -> 1
3 -> 2
3 -> 3
lag time (steps)

Acknowledgements



Collaborations

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