Everything you wanted to know about VAMP but were afraid to ask

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PyEMMA Workshop
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First of all

Variational

Approach for

Markov

Processes

Key papers:

Wu & Noé 2017, arXiv:1707.04659, "Variational approach…"
Paul et al, arXiv:1811.12551, "Identification of kinetic…"

First of all

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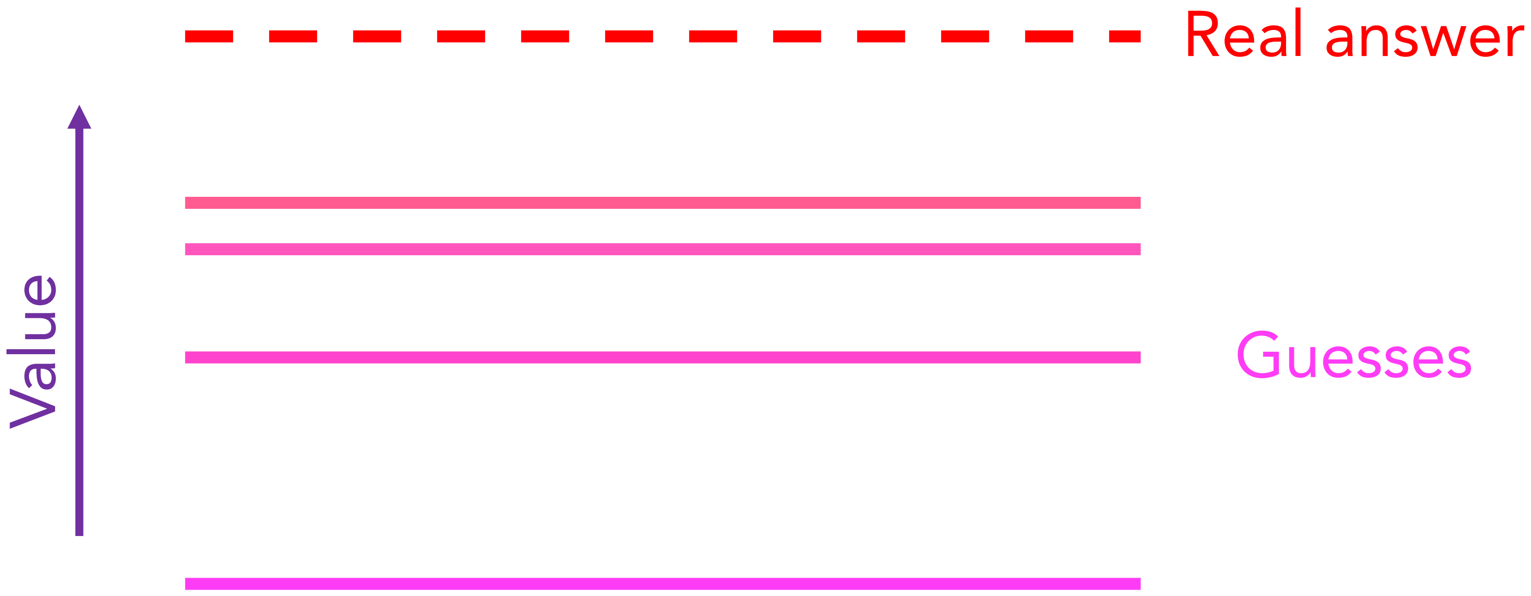
Processes



Key papers:

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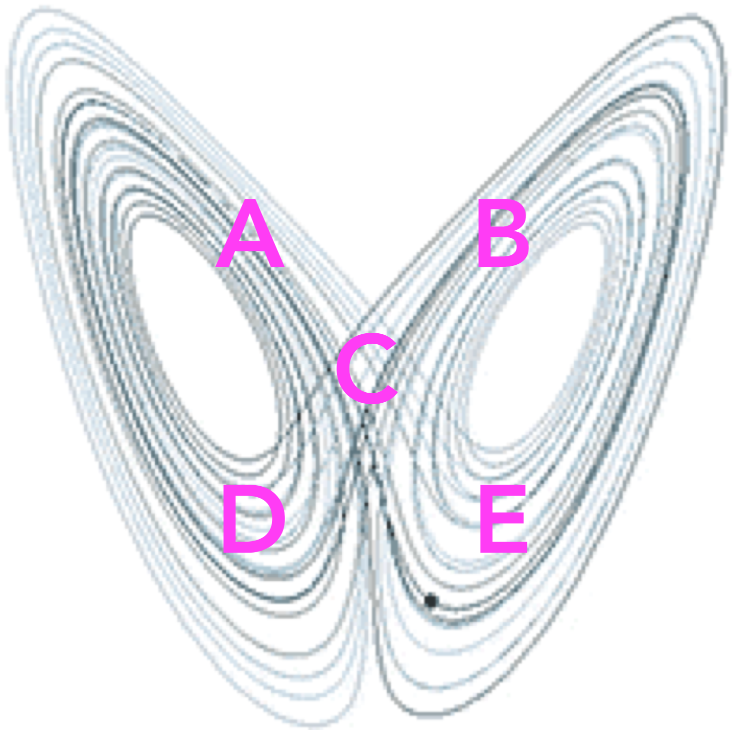
First of all

Variational
Approach for
Markov
Processes

Our data: $Z_1, Z_2, \ldots, Z_{t-2}, Z_{t-1}, Z_t, Z_{t+1}$

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \sigma(y - x),$$
$$\frac{\mathrm{d}y}{\mathrm{d}t} = x(\rho - z) - y,$$
$$\frac{\mathrm{d}z}{\mathrm{d}t} = xy - \beta z.$$



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Our data: $Z_1, Z_2, \ldots, Z_{t-2}, Z_{t-1}, Z_t, Z_{t+1}$

$[Z_t, Z_{t+1}]$

$[Z_t, Z_{t+\tau}]$

$$X = \begin{bmatrix} Z_1 \\ Z_2 \\ Z_3 \\ Z_4 \\ \\ Z_{t-1} \end{bmatrix} \qquad Y = \begin{bmatrix} Z_2 \\ Z_3 \\ Z_4 \\ Z_5 \\ \\ Z_t \end{bmatrix}$$

Key papers:

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Some history

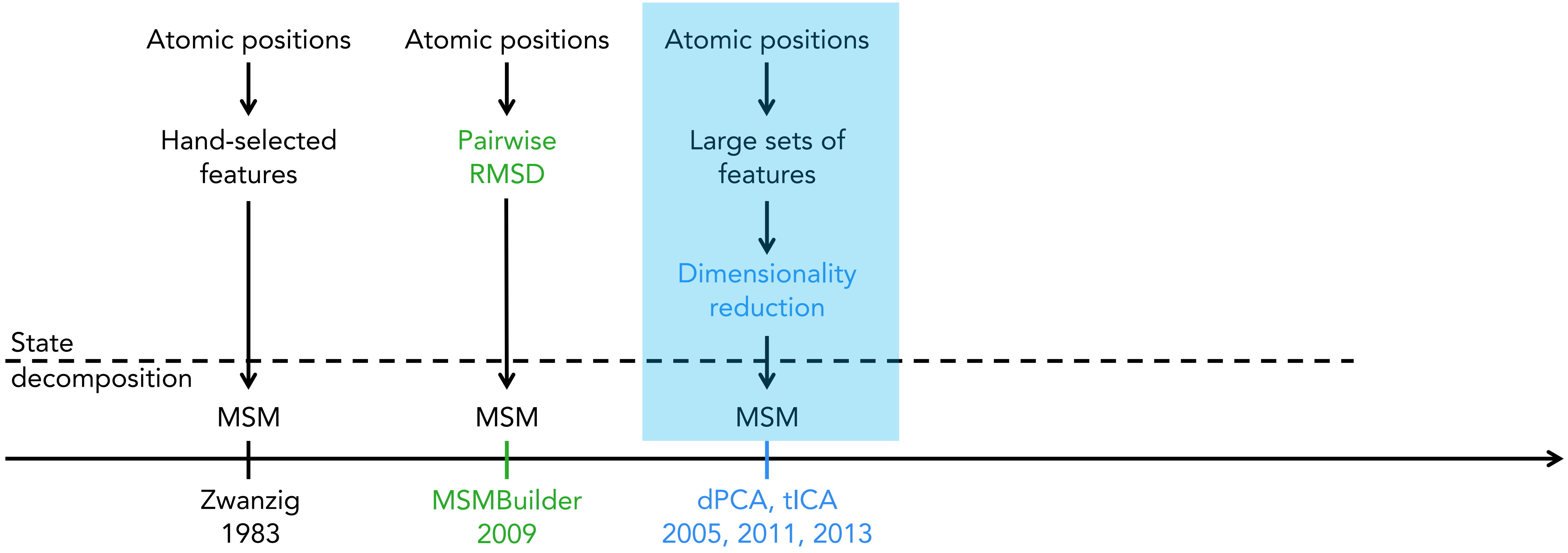
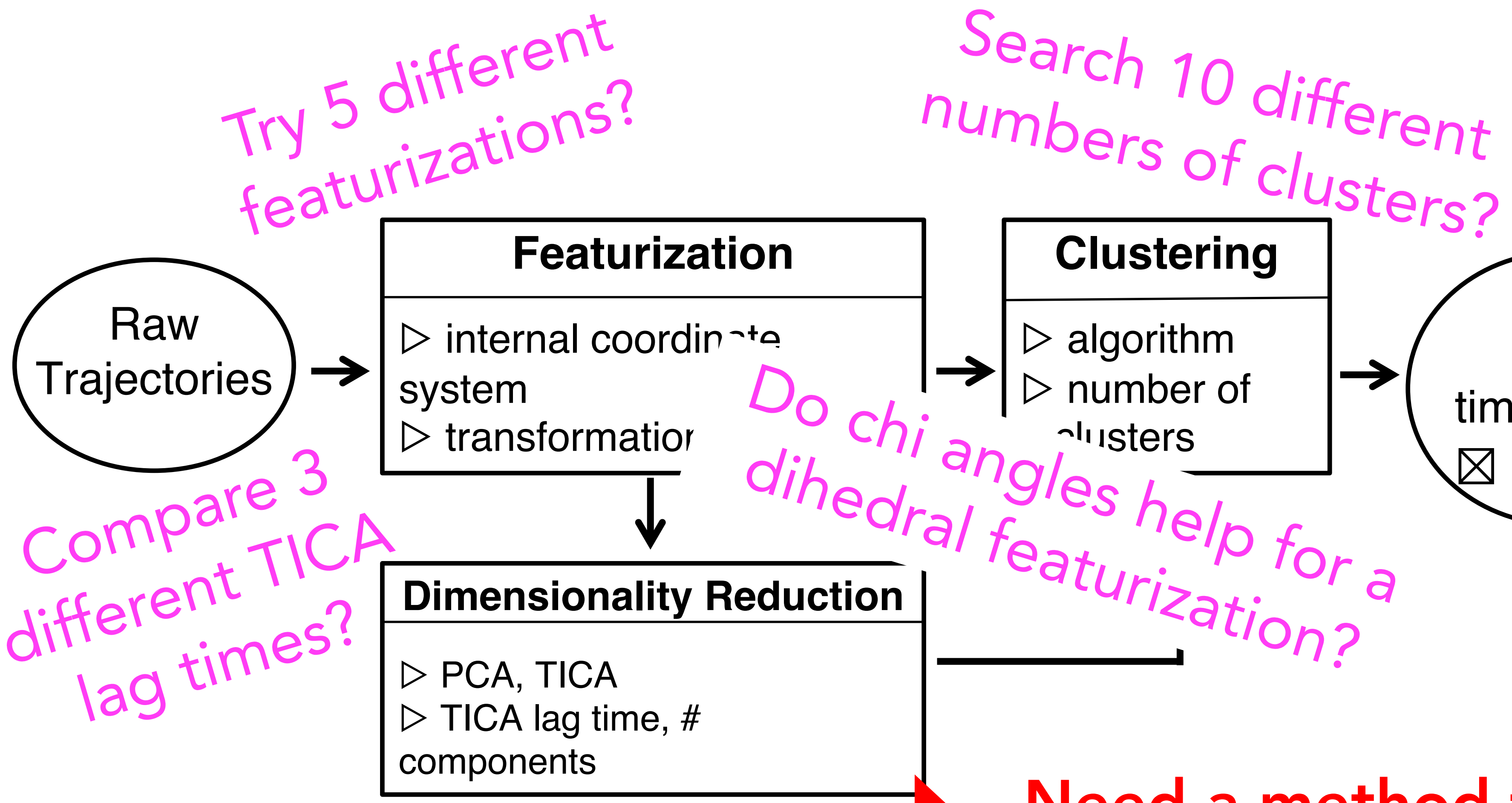


Figure from: Husic & Pande 2018, JACS, "Markov State Models: From an Art to a Science"

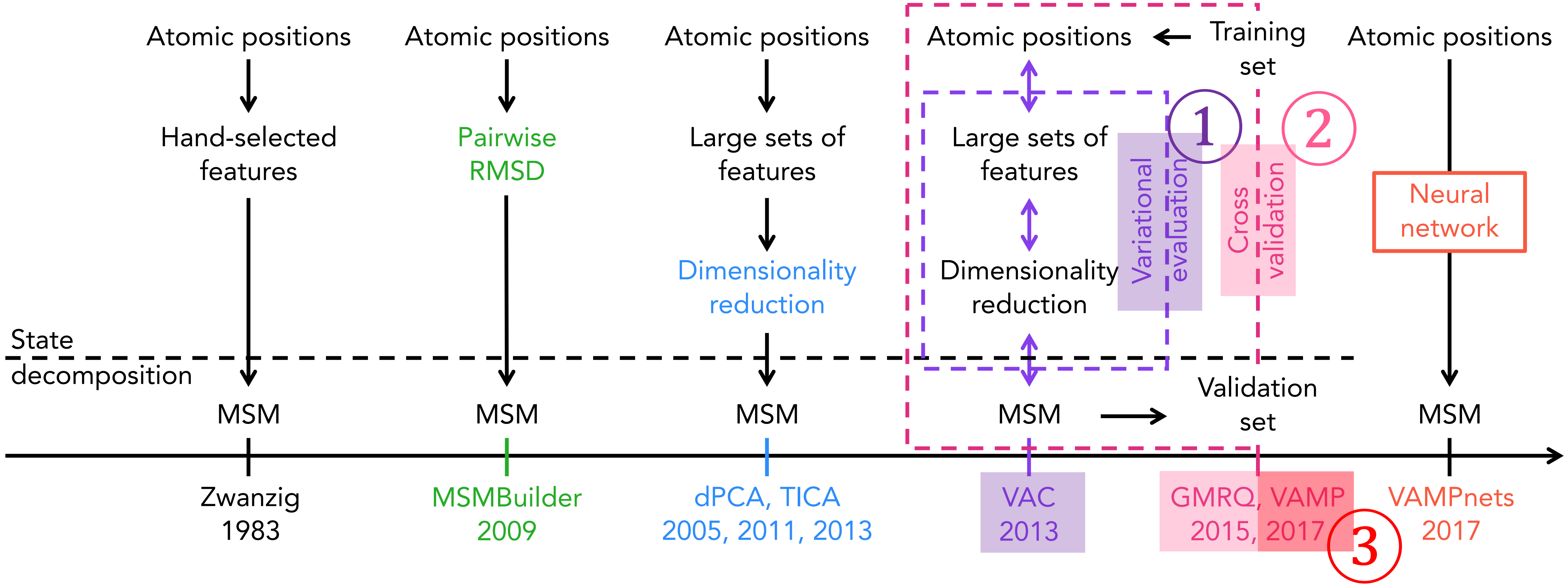
The problem



Need a method to objectively evaluate modeling choices!

Figure from: Husic & Pande 2017, J Chem Phys, "MSM lag time cannot be used for variational model selection"

Back to history



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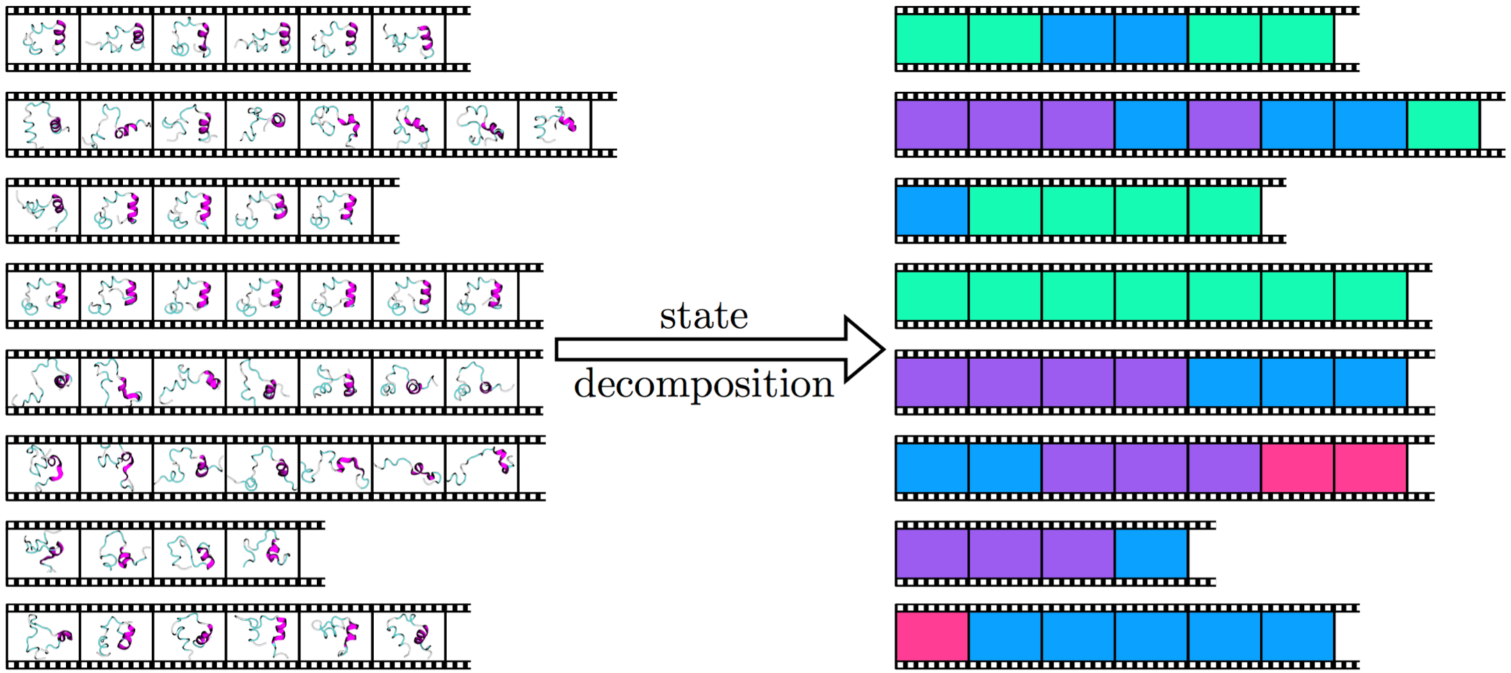
Let’s make sure we’re clear on MSMs



This is it! This *is* the MSM.

0.85	0.15	0	0
0.14	0.62	0.21	0.03
0	0.24	0.72	0.04
0	0.25	0.25	0.5

Transition matrix

- ★ Thermodynamics (populations!)
- ★ Kinetics (transition probabilities!)
- ★ Dynamical processes (eigenvectors!)
- ★ Pathways (TPT!)

Figure from: Husic & Pande 2018, JACS, “Markov State Models: From an Art to a Science”

The VAC

$$T(\tau)$$

	0.85	0.15	0	0
	0.14	0.62	0.21	0.03
	0	0.24	0.72	0.04
	0	0.25	0.25	0.5

Transition matrix

Key papers:

Noé & Nüske 2013, Multiscale Model Simul, "A Variational Approach…"
Nüske et al 2014, J Chem Theory Comput, "Variational Approach…"

The VAC

$$T(\tau)\psi_i = \lambda_i \psi_i \longrightarrow t_i = -\tau \,/\, \ln|\lambda_i|$$

Eigenvalues: related to timescales

Eigenvectors: dynamical processes

The eigenvalues have special properties according to the Perron-Frobenius theorem:

- They are real
- There is a unique maximum eigenvalue of 1
- All other eigenvalues have absolute values below 1

Key papers:

Noé & Nüske 2013, Multiscale Model Simul, "A Variational Approach…"
Nüske et al 2014, J Chem Theory Comput, "Variational Approach…"

The VAC

$$T(\tau)\psi_i = \lambda_i\psi_i \longrightarrow t_i = -\tau / \ln|\lambda_i|$$

The variational principle is for the ***eigenvalues***

Unknown true eigenvalues

$$\sum_{i=1}^{m} \hat{\lambda}_i \leq \sum_{i=1}^{m} \lambda_i$$

Eigenvalue predictions from MSM

Key papers:

Noé & Nüske 2013, Multiscale Model Simul, "A Variational Approach…"
Nüske et al 2014, J Chem Theory Comput, "Variational Approach…"

The VAC

$$T(\tau)\psi_i = \lambda_i \psi_i \longrightarrow t_i = -\tau / \ln|\lambda_i|$$

IMPORTANT: This score is only for the transition matrix defined at the given lag time τ

1

$$\text{SCORE} = \sum_{i=1}^{m} \hat{\lambda}_i \leq \sum_{i=1}^{m} \lambda_i$$

Unknown true eigenvalues

Eigenvalue predictions from MSM

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Reminder

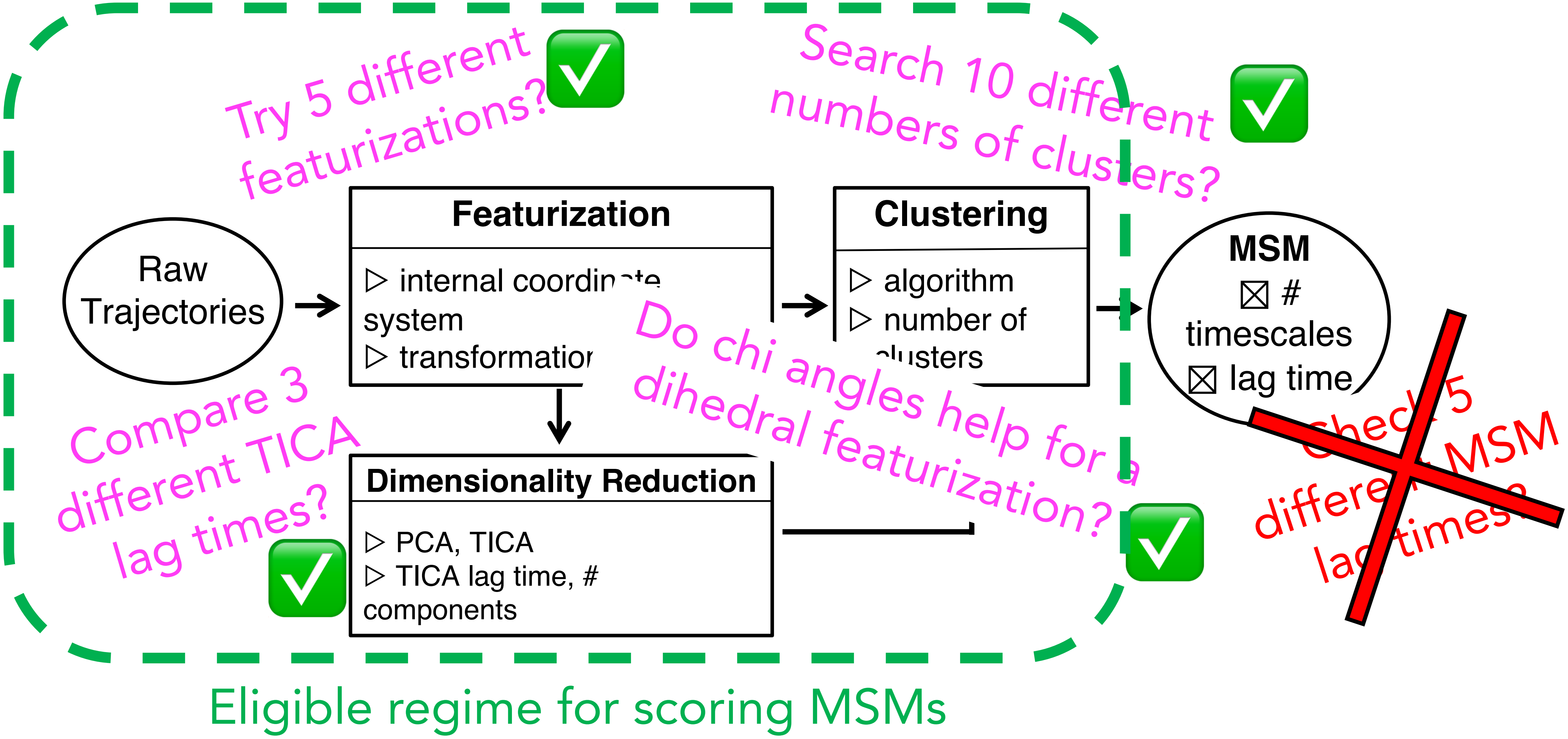

Figure from: Husic & Pande 2017, J Chem Phys, "MSM lag time cannot be used for variational model selection"

Cross validation

Unknown true eigenvalues

$$\text{SCORE} = \sum_{i=1}^{m} \hat{\lambda}_i \leq \sum_{i=1}^{m} \lambda_i$$

This method will have a problem with overfitting

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Eigenvalue predictions from MSM ***validation set***

Data:	Training set	Validation set

Make MSM

(is there enough sampling?)

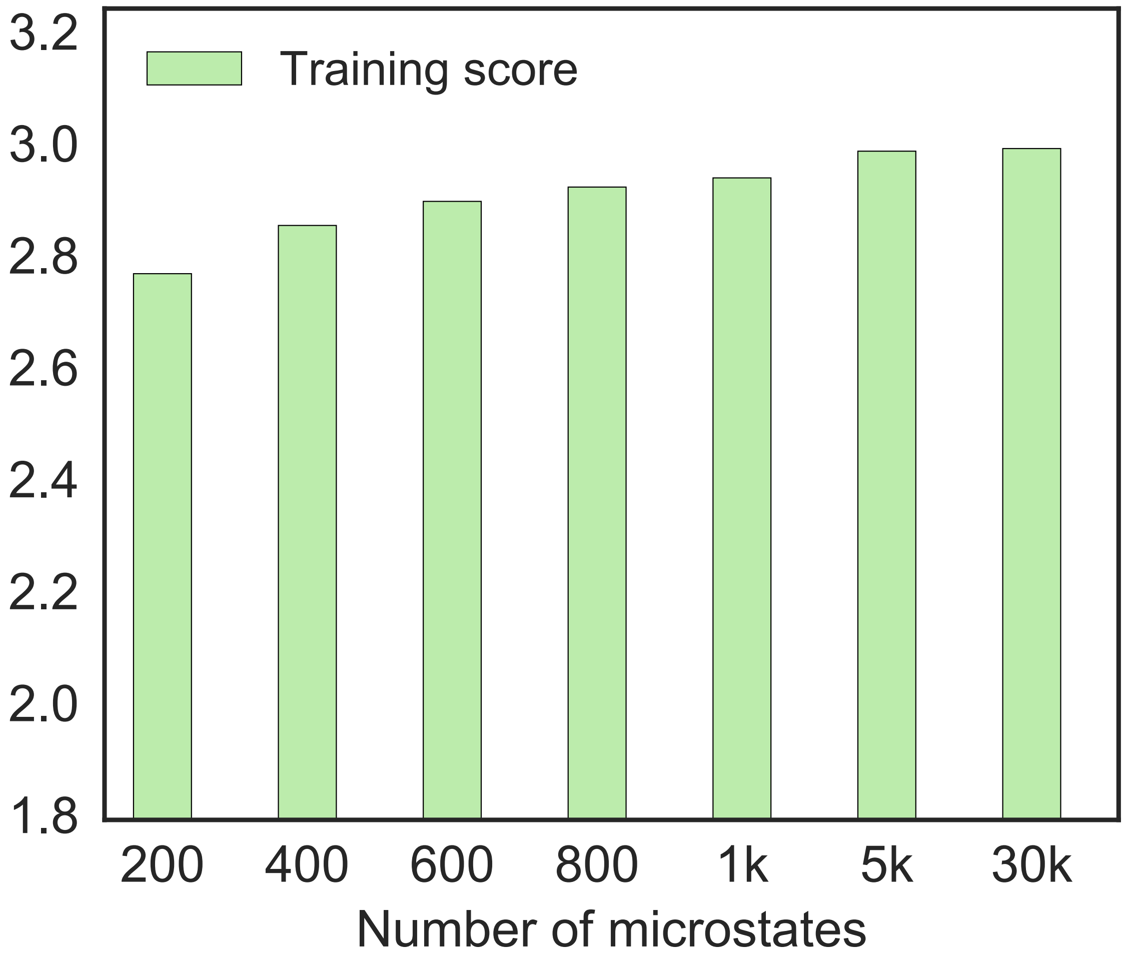
Apply MSM and score eigenvalues

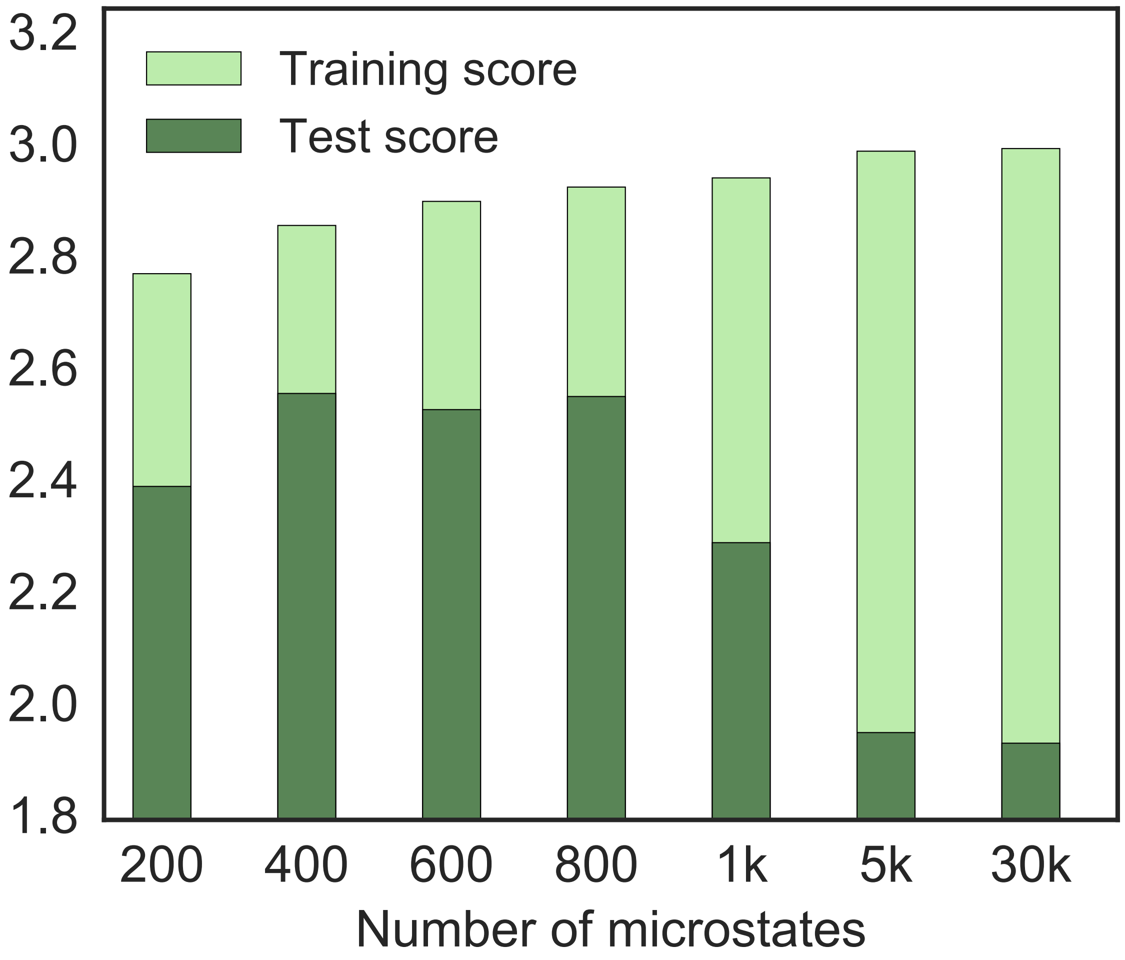
× some number of iterations with different sets

Key paper:

McGibbon & Pande 2015, J Chem Phys, "Variational cross-validation…"

An example





From Husic et al 2016, J Chem Phys, “Optimized parameter selection…”

Finally: the VAMP!

$$T(\tau)$$

	0.85	0.15	0	0
	0.14	0.62	0.21	0.03
	0	0.24	0.72	0.04
	0	0.25	0.25	0.5

Transition matrix

The transition matrix has certain properties due to the reversibility assumption.

This includes having an eigendecomposition.

Key papers:

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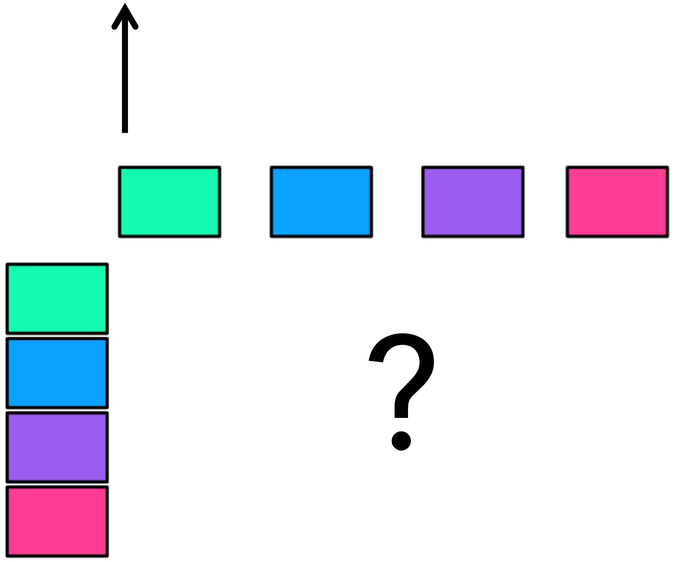
Finally: the VAMP!

$$K(\tau) \longrightarrow \{\ \varphi_i,\ \sigma_i,\ \varphi_i\ \}$$



Consider now a different matrix that is not necessarily reversible.
It may not have an eigendecomposition anymore, or its eigendecomposition may not be useful.

$$\text{SCORE} = \sum_{i=1}^{m} \hat{\sigma}_i \leq \sum_{i=1}^{m} \sigma_i$$

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However, it will always have a ***singular value decomposition***.

The VAMP uses more general math to score models that may not be reversible

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What we've learned…

- We have many choices when we make Markov state models
- Luckily, we have the VAC to evaluate different choices objectively
  - *But not the MSM lag time, of course.*
- We just have to do it under cross-validation to avoid overfitting
- We can use the VAMP in the more general, nonreversible case
  - *Which is the same as the VAC when we have an MSM!*
- With an objective metric, can't we just make models automatically..?
  - *Stay tuned!*

Paper highlights

VAC theory

Noé & Nüske 2013, Multiscale Model Simul, "A Variational Approach…"
Nüske et al 2014, J Chem Theory Comput, "Variational Approach…"

Cross-validation

McGibbon & Pande 2015, J Chem Phys, "Variational cross-validation…"

VAMP theory

Wu & Noé 2017, arXiv:1707.04659, "Variational approach…"
Paul et al, arXiv:1811.12551, "Identification of kinetic…"

General overview/history of MSMs

Husic & Pande 2018, JACS, "Markov State Models: From an Art to a Science"

General overview of ML methods

Noé 2018, arXiv:1812.07669, "Machine learning…"