Variational Coarse-graining and Mean First Passage Times in Markov State Models

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Outline

1 Introduction
   • Motivation
   • Constructing Markov State Models

2 Clustering Methods
   • Perron Cluster Cluster Analysis
   • Effective rates
   • Projection techniques
   • Variational coarse-graining
   • MFPT in variational Coarse-graining
   • Limiting relaxation times

3 Conclusions
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Often governed by rare transitions between metastable states: slow $O(1 \times 10^{-3})$ sec

Time step in MD set by molecular vibrations and collisions: fast $O(10^{-14})$ sec

⇒ too many integrations needed!

Statistical description of dynamics from relatively short simulations?

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State-space: $S = \{1, \ldots, n\}$

Key assumption: memoryless

$$dp_i dt = \sum_{j \neq i} \left( K_{ij} p_j - K_{ji} p_i \right)$$

$$d p dt = K p \Rightarrow p(t + \tau) = Q(\tau) p(t)$$

Propagator $Q(\tau) = e^{K \tau}$:

$$Q_{ij}(\tau) = P(i, \tau | j, 0)$$

Maximum Likelihood:

$$L = \prod_{ij} Q_{ij}^{T_{ij}(\tau)}$$

$$\frac{d}{d \tau} Q_{ij}(\tau) \left[ \log L - \sum_i \lambda_i (1 - \sum_j Q_{ji}) \right] = 0 \Rightarrow Q_{ij}(\tau) = T_{ij}(\tau) \sum_k T_{kj}(\tau)$$

Caveat: aggregation of states may hide barriers

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Dependence on the lag-time $\tau$

Choice of lag-time?

Smallest $\tau$ that ensures Markovianity

Chapman-Kolmogorov test:

$Q_n(\tau) = Q_n(\tau) \quad \text{[Recall:]} \quad Q(\tau) = e^{K\tau}$

In practice:

$\tau = -\frac{1}{\ln |\lambda|^{2}(\tau)} = -\frac{n\tau}{\ln |\lambda|^{2}(n\tau)}$

Rather subjective test, especially when dealing with finite statistics

necessary but not sufficient: should also test eigenvectors...

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![Relaxation time vs. Lag time graph](image)

![Molecular structure diagram](image)
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Dimensionality Reduction?

Often coarse-graining needed to gain physical intuition:

\[
S = \{1, \ldots, i, j, \ldots, n\} \quad \Rightarrow \quad S' = \{1, \ldots, I, J, \ldots, N\} \quad \text{with} \quad N < n
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\[
\begin{pmatrix}
1 & 0 & 0 \\
\vdots & \vdots & \vdots \\
1 & 0 & 0 \\
0 & 1 & 0 \\
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P = A^T p
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Clustering via PCCA

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\[ \phi_i^{(n)} = p_{i\text{eq}} \psi_i^{(n)} \]

\[ \sum_{j} \phi_j^{(n)} = 0 \quad \forall n > 1 \]

\[ t_i = -\tau \ln |\lambda_i| \]

Often no clear spectral gap: How many important states? Only targeted at metastable states i.e. states with high occupation probability.
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![Potential energy vs Reaction coordinate diagram](image)
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![Potential energy diagram with Reactants, Transition state, Activated complex, and Products labeled along the reaction coordinate.]

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- **Algorithms** to automatically and reliably detect TSs?
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- MSMs defined in discrete time \( \Rightarrow \) Markov matrix
  \[ Q_{CG}^{i,j}(\tau)P_{J}^{eq} = \sum_{i \in I, j \in J} Q_{ij}(\tau)p_{j}^{eq} \]
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  C_{ij}(\tau) = \langle \theta_{i}(\tau)\theta_{j}(0) \rangle, \quad \theta_{i}(t) = \begin{cases} 1 & n(t) \in i \\ 0 & n(t) \text{ otherwise} \end{cases}
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  \[ C_{ij}(\tau) = \langle \theta_i(\tau) \theta_j(0) \rangle, \quad \theta_i(t) = \begin{cases} 1 & n(t) \in i \\ 0 & n(t) \text{ otherwise} \end{cases} \]
Enforcing Markovian description

\[ \frac{dP}{dt} = RP \]

- Minimal requirement: \( RP^{eq} = 0 \) for \( P_I^{eq} = \sum_{i \in I} p_i^{eq} \)
- Impose detailed balance:
  \[ R_{IJ} P^eq_J = R_{JI} P^eq_I \implies \text{leaves freedom!} \]
- Local equilibrium:
  \[ R_{IJ} P^eq_J = \sum_{i \in I, j \in J} K_{ij} p_j^{eq} \]
- MSMs defined in discrete time \( \implies \) Markov matrix

\[ C^{CG}_{IJ}(\tau) = Q^{CG}_{IJ}(\tau) P^{eq}_J = \sum_{i \in I, j \in J} Q_{ij}(\tau) p_j^{eq} = \sum_{i \in I, j \in J} C_{ij}(\tau) \]

\[ C_{ij}(\tau) = \langle \theta_i(\tau) \theta_j(0) \rangle, \quad \theta_i(t) = \begin{cases} 1 & n(t) \in i \\ 0 & \text{otherwise} \end{cases} \]
Enforcing Markovian description

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\]

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\[
R_{IJ}P_{J}^{\text{eq}} = \sum_{i \in I, j \in J} K_{ij}p_{j}^{\text{eq}}
\]

- MSMs defined in discrete time \( \Rightarrow \) Markov matrix

\[
C_{IJ}^{CG}(\tau) = Q_{IJ}^{CG}(\tau)P_{J}^{\text{eq}} = \sum_{i \in I, j \in J} Q_{ij}(\tau)p_{j}^{\text{eq}} = \sum_{i \in I, j \in J} C_{ij}(\tau)
\]

\[
C_{ij}(\tau) = \langle \theta_{i}(\tau)\theta_{j}(0) \rangle, \quad \theta_{i}(t) = \begin{cases} 1 & n(t) \in i \\ 0 & n(t) \text{ otherwise} \end{cases}
\]

exact correlations at chosen lag-time
Hummer-Szabo method

- Occupancy-number connected correlator

\[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \]

\[ Q(t) = e^{Kt}C_{ij}(t) = [e^{Kt}]_{ij}p_{eq}^j - p_{eq}^i p_{eq}^j \]

\[ \hat{C}_{ij}(s) = (sI_n - K)^{-1}_{ij}p_{eq}^j - p_{eq}^i \]

Equate areas underneath correlations:

\[ \hat{f}(s) = \int_0^\infty dt f(t) e^{-st} \]

\[ \hat{C}_{CGIJ}(0) = \sum_{i \in I, j \in J} \hat{C}_{ij}(0) \]

\[ \hat{p}(s) = (sI_n - \hat{R}(s))^{-1} p(0) \]

\[ \hat{C}_{CGIJ}(s) = [(sI_n - \hat{R}(s))^{-1} - 1]_{IJ}p_{eq}^J - 1_s p_{eq}^I p_{eq}^J \]

Hummer-Szabo method

- Occupancy-number connected correlator

\[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]

\[ C_{ij}(t) = [e^{Kt}]_{ij} p_j^{eq} - p_i^{eq} p_j^{eq} \]
Hummer-Szabo method

- Occupancy-number connected correlator
  \[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]

  \[ C_{ij}(t) = [e^{Kt}]_{ij} p_{eq}^j - p_{eq}^i p_{eq}^j \]

- Equate areas underneath correlations:
  \[ \int_0^\infty dt \ C_{IJ}^{CG}(t) = \sum_{i \in I, j \in J} \int_0^\infty dt \ C_{ij}(t) \]
Hummer-Szabo method

- Occupancy-number connected correlator

\[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]

\[ C_{ij}(t) = [e^{Kt}]_{ij} p_{eq}^j - p_{eq}^i p_{eq}^j \]

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Hummer-Szabo method

- Occupancy-number connected correlator

\[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]

\[ C_{ij}(t) = [e^{Kt}]_{ij}p_{eq}^j - p_{eq}^i p_{eq}^j \quad \Rightarrow \quad \hat{C}_{ij}(s) = [(sI_n - K)^{-1}]_{ij}p_{eq}^j - \frac{1}{s}p_{eq}^i p_{eq}^j \]

- Equate areas underneath correlations: \( \hat{f}(s) = \int_0^\infty dt f(t)e^{-st} \)

\[ \int_0^\infty dt \ C_{I,J}^{CG}(t) = \sum_{i \in I, j \in J} \int_0^\infty dt \ C_{ij}(t) \quad \Rightarrow \quad \hat{C}_{I,J}^{CG}(0) = \sum_{i \in I, j \in J} \hat{C}_{ij}(0) \]
Hummer-Szabo method

- Occupancy-number connected correlator
  \[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]
  \[ C_{ij}(t) = [e^{Kt}]_{ij}p_{j}^{\text{eq}} - p_{i}^{\text{eq}}p_{j}^{\text{eq}} \implies \hat{C}_{ij}(s) = [(sI_n - K)^{-1}]_{ij}p_{j}^{\text{eq}} - \frac{1}{s}p_{i}^{\text{eq}}p_{j}^{\text{eq}} \]

- Equate areas underneath correlations:
  \[ \hat{f}(s) = \int_0^\infty dt f(t)e^{-st} \]
  \[ \int_0^\infty dt C_{1J}^{\text{CG}}(t) = \sum_{i \in I, j \in J} \int_0^\infty dt C_{ij}(t) \implies \hat{C}_{1J}^{\text{CG}}(0) = \sum_{i \in I, j \in J} \hat{C}_{ij}(0) \]
  \[ \frac{dp}{dt} = Kp \implies \hat{p}(s) = (sI_n - K)^{-1}p(0) \]
Hummer-Szabo method

- Occupancy-number connected correlator

\[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]

\[ C_{ij}(t) = [e^{Kt}]_{ij}p^\text{eq}_j - p^\text{eq}_i p^\text{eq}_j \Rightarrow \hat{C}_{ij}(s) = [(sI_n - K)^{-1}]_{ij}p^\text{eq}_j - \frac{1}{s}p^\text{eq}_i p^\text{eq}_j \]

- Equate areas underneath correlations:

\[ \hat{f}(s) = \int_0^\infty dt f(t)e^{-st} \]

\[ \int_0^\infty dt C_{I,J}^{CG}(t) = \sum_{i \in I, j \in J} \int_0^\infty dt C_{ij}(t) \Rightarrow \hat{C}_{I,J}^{CG}(0) = \sum_{i \in I, j \in J} \hat{C}_{ij}(0) \]

\[ \frac{dp}{dt} = Kp \Rightarrow \hat{p}(s) = (sI_n - K)^{-1}p(0) \]

- Clustered dynamics non-Markovian:

\[ \frac{dP}{dt} = \int_0^t R(t - \tau)P(\tau)d\tau \]
Hummer-Szabo method

- Occupancy-number connected correlator
  \[ C_{ij}(t) = \langle \theta_i(t) \theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]
  \[ C_{ij}(t) = [e^{Kt}]_{ij} p_{eq}^j - p_{eq}^i p_{eq}^j \quad \Rightarrow \quad \hat{C}_{ij}(s) = [(sI_n - K)^{-1}]_{ij} p_{eq}^j - \frac{1}{s} p_{eq}^i p_{eq}^j \]

- Equate areas underneath correlations:
  \[ \hat{f}(s) = \int_0^\infty dt f(t) e^{-st} \]
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- Clustered dynamics non-Markovian:
  \[ \frac{dP}{dt} = \int_0^t R(t - \tau) P(\tau) d\tau \quad \Rightarrow \quad \hat{P}(s) = (sI_N - \hat{R}(s))^{-1} P(0) \]
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- Occupancy-number connected correlator

\[ C_{ij}(t) = \langle \theta_i(t)\theta_j(0) \rangle - \langle \theta_i(t) \rangle \langle \theta_j(0) \rangle, \quad Q(t) = e^{Kt} \]

\[ C_{ij}(t) = [e^{Kt}]_{ij}p_{eq}^i - p_{eq}^i p_{eq}^j \quad \Rightarrow \quad \hat{C}_{ij}(s) = [(sI_n - K)^{-1}]_{ij}p_{eq}^i - \frac{1}{s}p_{eq}^i p_{eq}^j \]

- Equate areas underneath correlations: \( \hat{f}(s) = \int_0^\infty dt f(t)e^{-st} \)

\[ \int_0^\infty dt \, C_{iJ}^{CG}(t) = \sum_{i \in I, j \in J} \int_0^\infty dt \, C_{ij}(t) \quad \Rightarrow \quad \hat{C}_{iJ}^{CG}(0) = \sum_{i \in I, j \in J} \hat{C}_{ij}(0) \]

\[ \frac{dp}{dt} = Kp \quad \Rightarrow \quad \hat{p}(s) = (sI_n - K)^{-1}p(0) \]

- Clustered dynamics non-Markovian:

\[ \frac{dP}{dt} = \int_0^t R(t-\tau)P(\tau)d\tau \quad \Rightarrow \quad \hat{P}(s) = (sI_N - \hat{R}(s))^{-1}P(0) \]

\[ \hat{C}_{iJ}^{CG}(s) = [(sI_n - \hat{R}(s))^{-1}]_{iJ}P_{eq}^i p_{eq}^j - \frac{1}{s}P_{eq}^i p_{eq}^j \]

1 Introduction
   • Motivation
   • Constructing Markov State Models

2 Clustering Methods
   • Perron Cluster Cluster Analysis
   • Effective rates
   • Projection techniques
     • Variational coarse-graining
     • MFPT in variational Coarse-graining
     • Limiting relaxation times

3 Conclusions
Projection method

Projection on to some sub-space via operator $\mathcal{P}$ ($Q = I_n - \mathcal{P}$):

\[
\frac{dp}{dt} = Kp \quad u = \mathcal{P}p, \quad v = p - u = Qp
\]

\[
\frac{du}{dt} = \mathcal{P}Ku + \mathcal{P}Kv
\]

\[
\frac{dv}{dt} = QKu + QKv
\]
Projection method

Projection on to some sub-space via operator $\mathcal{P}$ ($Q = I_n - \mathcal{P}$):

$$\frac{dp}{dt} = Kp \quad \text{u} = \mathcal{P}p, \quad \text{v} = p - u = Qp$$

$$\frac{du}{dt} = \mathcal{P}Ku + \mathcal{P}Kv$$

$$\frac{dv}{dt} = QKu + QKv$$

Solve for $v$ (with $v(0) = 0$), and sub into eqn for $u$:

$$\frac{du}{dt} = \int_0^t M(t - \tau)u(\tau)d\tau,$$

with memory kernel

$$M(t - \tau) = \mathcal{P}K\delta(t - \tau) + \mathcal{P}Ke^{QK(t-\tau)}QK$$
Projection method

Projection on to some sub-space via operator $\mathcal{P}$ ($Q = I_n - \mathcal{P}$):

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Solve for $v$ (with $v(0) = 0$), and sub into eqn for $u$:

$$\frac{du}{dt} = \int_0^t M(t - \tau)u(\tau) d\tau,$$

with memory kernel

$$M(t - \tau) = \mathcal{P}K\delta(t - \tau) + \mathcal{P}Ke^{QK(t-\tau)}QK$$

or

$$\hat{M}(s) = s\mathcal{P}K(sI - K + \mathcal{P}K)^{-1}$$
Def macrostates: $P = A^T p$

$$\frac{dP}{dt} = \int_{0}^{t} R(t - \tau)P(\tau)d\tau$$
Def macrostates: $\mathbf{P} = \mathbf{A}^T \mathbf{p}$

$$\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t-\tau)\mathbf{P}(\tau) d\tau \quad \Rightarrow \quad s\hat{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s)\mathbf{P}(s)$$
Def macrostates: \( P = A^T \mathbf{p} \)

\[
\frac{dP}{dt} = \int_0^t R(t - \tau)P(\tau)d\tau \quad \Rightarrow \quad s\hat{P}(s) - P(0) = \hat{R}(s)P(s)
\]

- Projection corresponding to clustering protocol \( A \)?
Def macrostates: \( \mathbf{P} = \mathbf{A}^T \mathbf{p} \)

\[
\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t - \tau)\mathbf{P}(\tau)d\tau \quad \Rightarrow \quad s\hat{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s)\mathbf{P}(s)
\]

- Projection corresponding to clustering protocol \( \mathbf{A} \)?
- Relation between \( \hat{\mathbf{R}}(s) \) and \( \mathbf{K} \)?
Def macrostates: \( P = A^T p \)

\[
\frac{dP}{dt} = \int_0^t R(t - \tau) P(\tau) d\tau \quad \Rightarrow \quad s\hat{P}(s) - P(0) = \hat{R}(s)P(s)
\]

- Projection corresponding to clustering protocol \( A \)?
- Relation between \( \hat{R}(s) \) and \( K \)?
- \( u = \mathcal{P} p, \quad s\hat{u}(s) - u(0) = \hat{M}(s)\hat{u}(s) \)
Def macrostates: \( \mathbf{P} = \mathbf{A}^T \mathbf{p} \)

\[
\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t - \tau)\mathbf{P}(\tau)d\tau \quad \Rightarrow \quad s\hat{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s)\mathbf{P}(s)
\]

- Projection corresponding to clustering protocol \( \mathbf{A} \)?
- Relation between \( \hat{\mathbf{R}}(s) \) and \( \mathbf{K} \)?
- \( \mathbf{u} = \mathcal{P}\mathbf{p}, \quad s\hat{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s)\hat{\mathbf{u}}(s) \)
- Assume \( n \times N \) matrix \( \mathbf{H} \): \( \mathbf{u} = \mathbf{H}\mathbf{p} \quad \Rightarrow \quad \mathcal{P} = \mathbf{HA}^T \)
Def macrostates: $\mathbf{P} = \mathbf{A}^T \mathbf{p}$

$$\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t - \tau)\mathbf{P}(\tau) d\tau \Rightarrow s\hat{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s)\mathbf{P}(s)$$

- Projection corresponding to clustering protocol $\mathbf{A}$?
- Relation between $\hat{\mathbf{R}}(s)$ and $\mathbf{K}$?

$$\mathbf{u} = \mathcal{P}\mathbf{p}, \quad s\hat{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s)\hat{\mathbf{u}}(s)$$

- Assume $n \times N$ matrix $\mathbf{H}$: $\mathbf{u} = \mathbf{H}\mathbf{p}$ $\Rightarrow$ $\mathcal{P} = \mathbf{H}\mathbf{A}^T$

- Also, $\mathcal{P}^2 = \mathcal{P}$ $\Rightarrow$ $\mathbf{A}^T\mathbf{H} = \mathbf{I}_N$
Def macrostates: $\mathbf{P} = \mathbf{A}^T \mathbf{p}$

$$\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t - \tau) \mathbf{P}(\tau) d\tau \quad \Rightarrow \quad s\mathbf{P}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s) \mathbf{P}(s)$$

- Projection corresponding to clustering protocol $\mathbf{A}$?
- Relation between $\hat{\mathbf{R}}(s)$ and $\mathbf{K}$?

$\mathbf{u} = \mathcal{P}\mathbf{p}, \quad s\hat{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s)\hat{\mathbf{u}}(s)$

Assume $n \times N$ matrix $\mathbf{H}$: $\mathbf{u} = \mathbf{H}\mathbf{p} \quad \Rightarrow \quad \mathcal{P} = \mathbf{H}\mathbf{A}^T$

- Also, $\mathcal{P}^2 = \mathcal{P} \quad \Rightarrow \quad \mathbf{A}^T \mathbf{H} = \mathbf{I}_N \quad \Rightarrow \quad \hat{\mathbf{R}}(s) = \mathbf{A}^T \hat{\mathbf{M}}(s) \mathbf{H}$

Retrieve local equilibrium
Def macrostates: \( \mathbf{P} = \mathbf{A}^{T} \mathbf{p} \)

\[
\frac{d\mathbf{P}}{dt} = \int_{0}^{t} \mathbf{R}(t - \tau)\mathbf{P}(\tau)d\tau \Rightarrow s\hat{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s)\mathbf{P}(s)
\]

- Projection corresponding to clustering protocol \( \mathbf{A} \)?
- Relation between \( \hat{\mathbf{R}}(s) \) and \( \mathbf{K} \)?

\( \mathbf{u} = \mathcal{P}\mathbf{p} \), \( s\hat{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s)\hat{\mathbf{u}}(s) \)

Assume \( n \times N \) matrix \( \mathbf{H} \): \( \mathbf{u} = \mathbf{H}\mathbf{p} \) \( \Rightarrow \) \( \mathcal{P} = \mathbf{H}\mathbf{A}^{T} \)

Also, \( \mathcal{P}^{2} = \mathcal{P} \) \( \Rightarrow \) \( \mathbf{A}^{T}\mathbf{H} = \mathbf{I}_{N} \) \( \Rightarrow \) \( \hat{\mathbf{R}}(s) = \mathbf{A}^{T}\hat{\mathbf{M}}(s)\mathbf{H} \)

\[
\hat{\mathbf{R}}(s) = s\mathbf{A}^{T}\mathbf{K}(s\mathbf{I}_{n} - \mathbf{K} + \mathbf{H}\mathbf{A}^{T}\mathbf{K})^{-1}\mathbf{H}
\]
Def macrostates: \( P = A^T \mathbf{p} \)

\[
\frac{dP}{dt} = \int_0^t \mathbf{R}(t - \tau)P(\tau)d\tau \quad \Rightarrow \quad s\hat{P}(s) - P(0) = \hat{\mathbf{R}}(s)P(s)
\]

- Projection corresponding to clustering protocol \( A \)?
- Relation between \( \hat{\mathbf{R}}(s) \) and \( \mathbf{K} \)?

\( \mathbf{u} = \mathcal{P}\mathbf{p}, \quad s\hat{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s)\hat{\mathbf{u}}(s) \)

Assume \( n \times N \) matrix \( \mathbf{H} \): \( \mathbf{u} = \mathcal{P}\mathbf{p} \quad \Rightarrow \quad \mathcal{P} = \mathbf{H}A^T \)

Also, \( \mathcal{P}^2 = \mathcal{P} \quad \Rightarrow \quad A^T \mathbf{H} = \mathbf{I}_N \quad \Rightarrow \quad \hat{\mathbf{R}}(s) = A^T \hat{\mathbf{M}}(s) \mathbf{H} \)

\[
\hat{\mathbf{R}}(s) = sA^T \mathbf{K}(s\mathbf{I}_n - \mathbf{K} + \mathbf{H}A^T \mathbf{K})^{-1} \mathbf{H}
\]

DB:

\[
\hat{\mathbf{R}}(s)\mathbf{D}_N = \mathbf{D}_N \hat{\mathbf{R}}^T(s), \quad (\mathbf{D}_N)_{IJ} = \mathbf{P}^\text{eq}_I \delta_{IJ}
\]

\[
\mathbf{H} = \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \quad \text{with} \quad (\mathbf{D}_n)_{ij} = \mathbf{p}^\text{eq}_i
\]
Def macrostates: \( P = A^T p \)

\[
\frac{dP}{dt} = \int_0^t R(t - \tau)P(\tau)d\tau \Rightarrow s\hat{P}(s) - P(0) = \hat{R}(s)P(s)
\]

- Projection corresponding to clustering protocol \( A \)?
- Relation between \( \hat{R}(s) \) and \( K \)?

\[
u = Pp, \quad s\hat{u}(s) - u(0) = \hat{M}(s)\hat{u}(s)
\]

Assume \( n \times N \) matrix \( H \):

\[
u = HP \Rightarrow P = HA^T
\]

Also, \( P^2 = P \Rightarrow A^T H = I_N \Rightarrow \hat{R}(s) = A^T \hat{M}(s)H
\]

\[
\hat{R}(s) = sA^T K(sI_n - K + H A^T K)^{-1} H
\]

DB:

\[
\begin{align*}
\hat{R}(s)D_N &= D_N \hat{R}^T(s), \\
(D_N)_{IJ} &= P_{I}^{eq} \delta_{IJ}
\end{align*}
\]

\[
H = D_n A D_n^{-1}
\]

with \((D_n)_{ij} = p_{i}^{eq}\)

for \( s \to \infty \):

\[
\hat{R}(\infty) = A^T K H
\]

\[
\hat{R}(\infty)D_N = A^T K D_n A
\]
Def macrostates: \( \mathbf{P} = \mathbf{A}^T \mathbf{p} \)

\[
\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t - \tau) \mathbf{P}(\tau) d\tau \quad \Rightarrow \quad s\hat{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s) \mathbf{P}(s)
\]

- Projection corresponding to clustering protocol \( \mathbf{A} \)?
- Relation between \( \hat{\mathbf{R}}(s) \) and \( \mathbf{K} \)?

\( \mathbf{u} = \mathcal{P} \mathbf{p}, \quad s\hat{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s) \hat{\mathbf{u}}(s) \)

Assume \( n \times N \) matrix \( \mathbf{H} \):

\[ \mathbf{u} = \mathbf{H} \mathbf{p} \quad \Rightarrow \quad \mathcal{P} = \mathbf{H} \mathbf{A}^T \]

Also,

\[ \mathcal{P}^2 = \mathcal{P} \quad \Rightarrow \quad \mathbf{A}^T \mathbf{H} = \mathbf{I}_N \quad \Rightarrow \quad \hat{\mathbf{R}}(s) = \mathbf{A}^T \hat{\mathbf{M}}(s) \mathbf{H} \]

\[ \hat{\mathbf{R}}(s) = s \mathbf{A}^T \mathbf{K} (s \mathbf{I}_n - \mathbf{K} + \mathbf{H} \mathbf{A}^T \mathbf{K})^{-1} \mathbf{H} \]

DB:

\[
\begin{align*}
\hat{\mathbf{R}}(s) \mathbf{D}_N &= \mathbf{D}_N \hat{\mathbf{R}}^T(s), \\
(\mathbf{D}_N)_{IJ} &= P_{I}^{eq} \delta_{IJ}
\end{align*}
\]

\[ \mathbf{H} = \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \quad \text{with} \quad (\mathbf{D}_n)_{ij} = P_{i}^{eq} \]

for \( s \to \infty \):

\( \hat{\mathbf{R}}(\infty) = \mathbf{A}^T \mathbf{K} \mathbf{H} \)

\[ R_{IJ} P_{J}^{eq} = [\hat{\mathbf{R}}(\infty) \mathbf{D}_N]_{IJ} = [\mathbf{A}^T \mathbf{K} \mathbf{D}_n \mathbf{A}]_{IJ} = \sum_{i \in I, j \in J} K_{ij} P_{j}^{eq} \]
Def macrostates: \( \mathbf{P} = \mathbf{A}^T \mathbf{p} \)

\[
\frac{d\mathbf{P}}{dt} = \int_0^t \mathbf{R}(t - \tau) \mathbf{P}(\tau) d\tau \Rightarrow s\dot{\mathbf{P}}(s) - \mathbf{P}(0) = \hat{\mathbf{R}}(s) \mathbf{P}(s)
\]

- Projection corresponding to clustering protocol \( \mathbf{A} \)?
- Relation between \( \hat{\mathbf{R}}(s) \) and \( \mathbf{K} \)?

\( \mathbf{u} = \mathcal{P} \mathbf{p}, \quad s\dot{\mathbf{u}}(s) - \mathbf{u}(0) = \hat{\mathbf{M}}(s) \mathbf{u}(s) \)

- Assume \( n \times N \) matrix \( \mathbf{H} \): \( \mathbf{u} = \mathbf{H} \mathbf{p} \quad \Rightarrow \quad \mathcal{P} = \mathbf{H} \mathbf{A}^T \)

- Also, \( \mathcal{P}^2 = \mathcal{P} \quad \Rightarrow \quad \mathbf{A}^T \mathbf{H} = \mathbf{I}_N \quad \Rightarrow \quad \hat{\mathbf{R}}(s) = \mathbf{A}^T \hat{\mathbf{M}}(s) \mathbf{H} \)

\[
\hat{\mathbf{R}}(s) = s \mathbf{A}^T \mathbf{K}(s\mathbf{I}_n - \mathbf{K} + \mathbf{H} \mathbf{A}^T \mathbf{K})^{-1} \mathbf{H}
\]

- DB:
  \[
  \hat{\mathbf{R}}(s) \mathbf{D}_N = \mathbf{D}_N \mathbf{R}^T(s), \quad (\mathbf{D}_N)_{IJ} = P_{IJ}^{\text{eq}} \delta_{IJ}
  \]

\[
\mathbf{H} = \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \quad \text{with} \quad (\mathbf{D}_n)_{ij} = p_{ij}^{\text{eq}}
\]

- for \( s \rightarrow \infty \): \( \hat{\mathbf{R}}(\infty) = \mathbf{A}^T \mathbf{K} \mathbf{H} \)

\[
R_{IJ} P_{J}^{\text{eq}} = [\hat{\mathbf{R}}(\infty) \mathbf{D}_N]_{IJ} = [\mathbf{A}^T \mathbf{K} \mathbf{D}_N \mathbf{A}]_{IJ} = \sum_{i \in I, j \in J} K_{ij} p_{j}^{\text{eq}}
\]

Retrieve local equilibrium
general $s$: $A^T (sI_n - K)^{-1} D_n A = (sI_N - \hat{R}(s))^{-1} D_N$
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Subtract off $s^{-1} A^T D_n D_n^T A = s^{-1} D_N D_N^T$

$A^T \left( (sI_n - K)^{-1} D_n - \frac{1}{s} D_n D_n^T \right) A = (sI_N - \hat{R}(s))^{-1} D_N - \frac{1}{s} D_N D_N^T$
general $s$: $A^T(sI_n - K)^{-1}D_nA = (sI_N - \hat{R}(s))^{-1}D_N$

Subtract off $s^{-1}A^TD_nD_{n}^TA = s^{-1}D_ND_N^T$

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Equating **Laplace transformed correlations** naturally arises!

$$\sum_{i \in I} \sum_{j \in J} \hat{C}_{ij}(s) = \hat{C}_{IJ}^{CG}(s) \quad \hat{f}(s) = \int_0^\infty dt \, f(t)e^{-st}$$

when **projections preserve detailed balance**
general $s$: $A^T(sI_n - K)^{-1}D_nA = (sI_N - \hat{R}(s))^{-1}D_N$

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$$\sum_{i \in I} \sum_{j \in J} \hat{C}_{ij}(s) = \hat{C}_{IJ}^G(s) \quad \hat{f}(s) = \int_0^\infty dt f(t)e^{-st}$$

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LE and HS correspond to $s \to \infty$ and $s \to 0$, same

$$\mathcal{P} = D_nAD_N^{-1}A^T$$
general $s$: $A^T(sI_n - K)^{-1}D_nA = (sI_N - \hat{R}(s))^{-1}D_N$

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$$A^T((sI_n - K)^{-1}D_n - \frac{1}{s}D_nD_n^T)A = (sI_N - \hat{R}(s))^{-1}D_N - \frac{1}{s}D_ND_N^T$$

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LE and HS correspond to $s \to \infty$ and $s \to 0$, same

$$\mathcal{P} = D_nAD_N^{-1}A^T$$

$s \to 0$:

$$\hat{R} = P^{eq}1_N^T - D_N[A^T(p^{eq}1_n^T - K)^{-1}D_nA]^{-1}$$
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3 Conclusions
In fact, can build Markovian approximations that preserve other properties of correlation functions:

$$\sum_{i \in I} \sum_{j \in J} \int_{\tau_1}^{\tau_2} C_{ij}(\tau) d\tau = \int_{\tau_1}^{\tau_2} C_{IJ}^{CG}(\tau) d\tau$$
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\]

A variational principle applies to the second largest eigenvalue of \( R \)

\[
|\mu_2| \geq |\lambda_2|
\]

with

\[
\begin{align*}
K \phi^{(i)} &= \lambda_i \phi^{(i)} \\
R \Phi(I) &= \mu_I \Phi(I)
\end{align*}
\]
In fact, can build Markovian approximations that preserve other properties of correlation functions:

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A variational principle applies to the second largest eigenvalue of $R$

$$|\mu_2| \geq |\lambda_2|$$

with

$$\begin{cases} K\phi^{(i)} = \lambda_i \phi^{(i)} \\ R\Phi(I) = \mu_I \Phi(I) \end{cases}$$

Second eigenvalue as a variational parameter

- Second eigenvalue has been shown to decrease with increasing lag-time and finer discretization

[Prinz et al, JCP (2011); Sarich, Noe, Schütte MMS (2010), Djurdjevac, Sarich, Schütte (2012), Noe & Nüske, MMS (2013)]

"In contrast to previous practice, it becomes clear that the best MSM is not obtained by the most metastable discretization, but the MSM can be much improved if non-metastable states are introduced near the transition states"
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Variational coarse-graining

- Idea: choose $A$ that minimizes $|\mu_2|$
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[Image of three graphs showing potential energy functions]

[Martini et al., PRX 7, 031060 (2017)]
Variational coarse-graining

- **Idea:** choose $A$ that minimizes $|\mu_2|$

- Minimization of $|\mu_2|$ correctly identifies **key metastable states & transition states**, as one increases the number of clusters.

---

[Martini et al., PRX 7, 031060 (2017)]
Variational coarse-graining

- Idea: choose $A$ that minimizes $|\mu_2|$

Minimization of $|\mu_2|$ correctly identifies key metastable states & transition states, as one increases the number of clusters.

Aim: define minimal variationally optimal transition network consisting of key metastable & transition states.

[Source: Martini et al., PRX 7, 031060 (2017)]
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3 Conclusions
Can we understand optimal position of the boundaries and width of TS in a quantitative way?

First look at optimal position of first boundary $a \Rightarrow 2$-state clustering:

$$\tau_2(a) = \int_0^\infty C_{11}(t) C_{11}(0) dt = \int_0^\infty \langle \delta \theta_1(0) \delta \theta_1(t) \rangle \langle \delta \theta_1(0) \rangle dt,$$

$$\theta_1(x) = \begin{cases} 1 & x \leq a \\ 0 & x > a \end{cases}$$

[Chandler, JCP (1978), Skinner & Wolynes, JCP (1978), Perico et al., JCP (1993)]

Can expand integral of correlation in terms of potential

$$\int_0^\infty \langle \delta \theta_i(0) \delta \theta_i(t) \rangle dt = \int_{-\infty}^\infty dx \ De^{-\beta v(x)} \left[ \int_\infty^x \delta \theta_i(y) e^{-\beta v(y)} dy \right]^2 \int_{-\infty}^\infty e^{-\beta v(x)} dx$$

[Szabo, Shulten and Shulten, JCP (1980), Bicout & Szabo, JCP (1997)]
Can we understand optimal positions of the boundaries and the width of TS in a quantitative way?

First look at optimal position of first boundary $a$

$\tau_2(a) = \int_0^\infty C_{11}(t)C_{11}(0) dt = \int_0^\infty \langle \delta \theta_1(0) \delta \theta_1(t) \rangle dt, \quad \theta_1(x) = \begin{cases} 1 & x \leq a \\ 0 & x > a \end{cases}$

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Can we understand optimal position of the boundaries?
Optimal boundary positions

- Can we understand optimal position of the boundaries?
- & width of TS in a quantitative way?

- First look at optimal position of first boundary
- $\tau_2(a) = \int_0^\infty C_{11}(t) C_{11}(0) dt = \int_0^\infty \langle \delta \theta_1(0) \delta \theta_1(t) \rangle dt$, $\theta_1(x) = \{ 1 \text{ if } x < a, 0 \text{ if } x > a \} [\text{Chandler, JCP (1978), Skinner & Wolynes, JCP (1978), Perico et al., JCP (1993)}]

- Can expand integral of correlation in terms of potential $\int_0^\infty \langle \delta \theta_i(0) \delta \theta_i(t) \rangle dt = \int_{-\infty}^\infty dx D e^{-\beta v(x)} \left[ \int_0^x \delta \theta_i(y) e^{-\beta v(y)} dy \right]^2 \int_{-\infty}^\infty e^{-\beta v(x)} dx [\text{Szabo, Shulten and Shulten, JCP (1980), Bicout & Szabo, JCP (1997)}]$
Can we understand optimal position of the boundaries?

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First look at optimal position of first boundary $a$
Optimal boundary positions

- Can we understand optimal position of the boundaries?
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First look at optimal position of first boundary $a$

$\Rightarrow$ 2-state clustering:

$$\tau_2(a) = \int_0^\infty \frac{C_{11}(t)}{C_{11}(0)} dt = \int_0^\infty \frac{\langle \delta \theta_1(0) \delta \theta_1(t) \rangle}{\langle \delta \theta_1(0)^2 \rangle} dt,$$

$$\theta_1(x) = \begin{cases} 
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[Chandler, JCP (1978), Skinner & Wolynes, JCP (1978), Perico et al., JCP (1993)]
Optimal boundary positions

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First look at optimal position of first boundary $a$

$\Rightarrow$ 2-state clustering:

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- Can expand integral of correlation in terms of potential

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mean first passage time to reach barrier at $a$ starting in 2

$$t_{a2} = \int_a^\infty \frac{dx}{Dp_2(x)} \left[ \int_x^\infty dy p_2(y) \right] , \quad \text{with} \quad p_2(x) = \frac{e^{-\beta v(x)}}{\int_a^\infty e^{-\beta v(x)} dx}$$
mean first passage time to reach barrier at $a$ starting in 2

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Use properties of step functions and some algebra

$$\tau_2(a) = P_{1eq} t_{a2} + P_{2eq} t_{a1}$$
**mean first passage time** to reach barrier at \( a \) starting in 2

\[
t_{a2} = \int_a^\infty \frac{dx}{Dp_2(x)} \left[ \int_x^\infty dy \, p_2(y) \right], \quad \text{with} \quad p_2(x) = \frac{e^{-\beta v(x)}}{\int_a^\infty e^{-\beta v(x)} dx}
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- Use properties of step functions and some algebra

\[
\tau_2(a) = P_{1}^{eq} t_{a2} + P_{2}^{eq} t_{a1}
\]

- Can explicitly differentiate!

\[
\frac{d\tau_2(a)}{da} = 0 \quad \Rightarrow \quad P_{1}^{eq} t_{a2} = P_{2}^{eq} t_{a1}
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\]


• Combine with DB & \( \tau_2 = 1/(R_{12} + R_{21}) \) get **effective rates**

\[
R_{12} + R_{21} = \frac{1}{2P_{1eq}^t a_2} \quad \Rightarrow \quad R_{12} = \frac{1}{2t_{a2}}, \quad R_{21} = \frac{1}{2t_{a1}}
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mean first passage time to reach barrier at \( a \) starting in 2

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t_{a2} = \int_{a}^{\infty} \frac{dx}{Dp_{2}(x)} \left[ \int_{x}^{\infty} dy p_{2}(y) \right], \quad \text{with} \quad p_{2}(x) = \frac{e^{-\beta v(x)}}{\int_{a}^{\infty} e^{-\beta v(x)} dx}
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Transparent interpretation: fluxes crossing the boundary in each direction must equate!
• mean first passage time to reach barrier at \( a \) starting in 2

\[
t_a^2 = \int_a^\infty \frac{dx}{Dp_2(x)} \left[ \int_x^\infty dy \, p_2(y) \right], \quad \text{with} \quad p_2(x) = \frac{e^{-\beta v(x)}}{\int_a^\infty e^{-\beta v(x)} \, dx}
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\]

• Transparent interpretation: fluxes crossing the boundary in each direction must equate!

• for 3-state clustering, symmetric potential (boundaries \( \pm a \))

\[
P_1^{eq} t_{-aa} = t_{-a1}
\]
Test on analytical potential

Arrhenius rates:

$$K_{ij} = \frac{A e^{-\left( \frac{V_i - V_j}{2kBT} \right)}}{i = j}$$

MFPT computed via Meyer method

$$t_{ji} = \tau_{Q_{ji}}(\tau) + \sum_{k \neq j} Q_{ki}(\tau)(t_{jk} + \tau)$$

Test on analytical potential

Arrhenius rates:

\[ K_{ij} = A e^{- \frac{(V_i - V_j)}{2k_B T}} \]
**Test on analytical potential**

Arrhenius rates:

\[ K_{ij} = A e^{-\frac{(V_i - V_j)}{2k_B T}} \]

[Kells, Mihálka, Annibale, Rosta, J. *Chem. Phys.* (2019)]

MFPT computed via Meyer method

\[ t_{ji} = \tau Q_{ji}(\tau) + \sum_{k(\neq j)} Q_{ki}(\tau)(t_{jk} + \tau) \]
Test on symmetric potentials

Two-state clustering


Three-state clustering
Simulations of Alanine Pentapeptide (Ala$_5$)

Martini, et al., PRX (2017)


Estimating MFPT: $T_1, \ldots, T_k$ crossing times

\[
\sum_i \frac{k/2}{\sum_i^N_i} = \frac{\sum_i^k (N_i + 1)N_i/2}{\sum_i^k N_i}
\]

$k$ crossing events

\[
N_i = (T_{i+1} - T_i)/\tau
\]
Simulations of Ala$_5$

Error bars are obtained from 4 equal segments of the MD simulation trajectory. [Kells et al., JCP (2019)]
Boundary position dependence on lag-time

- With one boundary, LE and HS give the same result
- With two boundaries, LE converge to HS at large lag-time

Martini et al., PRX (2017)

Can we use functional dependence of eigenvalue on the lag-time, to infer the true relaxation time?
Boundary position dependence on lag-time

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Limiting relaxation time

\[ Q \phi^{(i)} = \lambda_i \phi^{(i)} \quad \psi^{(i)} Q = \lambda_i \psi^{(i)} \quad \phi_n^{(i)} = p_{n}^{eq} \psi_n^{(i)} \]
Limiting relaxation time

\[ Q \phi^{(i)} = \lambda_i \phi^{(i)} \quad \psi^{(i)} Q = \lambda_i \psi^{(i)} \quad \phi^{(i)} = p_{eq} \psi^{(i)} \]

- Normalised correlation function of \( f, g \) in MSM \( Q^{CG} \)

\[ C(f, g, \tau, Q^{CG}) = \frac{\sum_{I=2}^{N} e^{\mu I \tau} (g \cdot \Phi^{(I)})(f \cdot \Phi^{(I)})}{\sum_{I=2}^{N} (g \cdot \Phi^{(I)})(f \cdot \Phi^{(I)})} \]
Limiting relaxation time

\[ Q\phi^{(i)} = \lambda_i \phi^{(i)} \quad \psi^{(i)} Q = \lambda_i \psi^{(i)} \quad \phi^{(i)}_n = p_{n_{eq}} \psi^{(i)}_n \]

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- Set \( f = g = \Psi^{(2)} \): \( C(\Psi^{(2)}, \Psi^{(2)}, \tau, Q^{CG}) = e^{\mu_2 \tau} \)
Limiting relaxation time

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- Set \( f = g = \Psi^{(2)} \):

\[
C(\Psi^{(2)}, \Psi^{(2)}, \tau, Q^{CG}) = e^{\mu_2 \tau}
\]

- Project MSM eigenvector onto full dimensional space \( \Psi^{(2)} A^T \)

\[
C(\Psi^{(2)} A^T, \Psi^{(2)} A^T, \tau, Q) = \frac{\sum_{i=2}^{\infty} e^{\lambda_i \tau} (\Psi^{(2)} A^T \cdot \phi^{(i)})(\Psi^{(2)} A^T \cdot \phi^{(i)})}{\sum_{i=2}^{\infty} (\Psi^{(2)} A^T \cdot \phi^{(i)})(\Psi^{(2)} A^T \cdot \phi^{(i)})} = \sum_{i=2}^{\infty} A_i e^{\lambda_i \tau}
\]
Limiting relaxation time \[\text{[Kells, Annibale, Rosta, JCP (2018)]}\]

\[Q \phi^{(i)} = \lambda_i \phi^{(i)} \]
\[\psi^{(i)} Q = \lambda_i \psi^{(i)} \]
\[\phi_n^{(i)} = \rho_n \psi_n^{(i)} \]

- Normalised correlation function of \(f, g\) in MSM \(Q^{\text{CG}}\):

\[C(f, g, \tau, Q^{\text{CG}}) = \frac{\sum_{I=2}^{N} e^{\mu I \tau} (g \cdot \Phi(I)) (f \cdot \Phi(I))}{\sum_{I=2}^{N} (g \cdot \Phi(I)) (f \cdot \Phi(I))} \]

- Set \(f = g = \Psi^{(2)}\):

\[C(\Psi^{(2)}, \Psi^{(2)}, \tau, Q^{\text{CG}}) = e^{\mu_2 \tau} \]

- Project MSM eigenvector onto full dimensional space \(\Psi^{(2)} A^T\):

\[C(\Psi^{(2)} A^T, \Psi^{(2)} A^T, \tau, Q) = \frac{\sum_{i=2}^\infty e^{\lambda_i \tau} (\Psi^{(2)} A^T \cdot \phi^{(i)})(\Psi^{(2)} A^T \cdot \phi^{(i)})}{\sum_{i=2}^\infty (\Psi^{(2)} A^T \cdot \phi^{(i)})(\Psi^{(2)} A^T \cdot \phi^{(i)})} = \sum_{i=2}^\infty A_i e^{\lambda_i \tau} \]

- \(\tau \gg 1\):

\[e^{\mu_2 \tau} \approx A_2 e^{\lambda_2 \tau} \quad \Rightarrow \quad \mu_2 = \lambda_2 + \frac{\epsilon}{\tau} \quad \text{with} \quad \epsilon = \log A_2 \]
\[ Q \phi^{(i)} = \lambda_i \phi^{(i)} \quad \psi^{(i)} Q = \lambda_i \psi^{(i)} \quad \phi_n^{(i)} = p_{eq}^{(i)} \psi_n^{(i)} \]

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\]

- Set \( f = g = \Psi^{(2)} \): \( C(\Psi^{(2)}, \Psi^{(2)}, \tau, Q^{CG}) = e^{\mu_2 \tau} \)

- Project MSM eigenvector onto full dimensional space \( \Psi^{(2)} A^T \)

\[
C(\Psi^{(2)} A^T, \Psi^{(2)} A^T, \tau, Q) = \frac{\sum_{i=2}^{\infty} e^{\lambda_i \tau} (\Psi^{(2)} A^T \cdot \phi^{(i)})(\Psi^{(2)} A^T \cdot \phi^{(i)})}{\sum_{i=2}^{\infty} (\Psi^{(2)} A^T \cdot \phi^{(i)})(\Psi^{(2)} A^T \cdot \phi^{(i)})} = \sum_{i=2}^{\infty} A_i e^{\lambda_i \tau}
\]

- \( \tau \gg 1: \) \( e^{\mu_2 \tau} \approx A_2 e^{\lambda_2 \tau} \implies \mu_2 = \lambda_2 + \frac{\epsilon}{\tau} \) with \( \epsilon = \log A_2 \)

\[
\lambda_2^{-1} = t_{\text{relax}}, \quad \mu_2^{-1} = t_{\text{relax}}^{\text{MSM}}, \quad t_{\text{relax}}^{\text{MSM}} = \frac{\tau t_{\text{relax}}}{\tau + \epsilon t_{\text{relax}}}
\]
Limiting relaxation time \[ \text{[Kells, Annibale, Rosta, JCP (2018)]} \]

\[
Q\phi^{(i)} = \lambda_i \phi^{(i)} \quad \psi^{(i)} Q = \lambda_i \psi^{(i)} \quad \phi_n^{(i)} = p_{n\text{eq}} \psi_n^{(i)}
\]

- Normalised correlation function of \( f, g \) in MSM \( Q^{CG} \)

\[
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\]

\[
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\]

- fit to data \( \Rightarrow \) get \( t_{\text{relax}} \) and \( \epsilon \)
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- fit to data \( \Rightarrow \) get \( t_{\text{relax}} \) and \( \epsilon \)

- \( \epsilon \) useful indicator of how Markovian selected variable is!
Test on analytical potential [Kells, Annibale, Rosta, JCP (2018)]

2-state MSM: 100 trajectory length $\alpha t_{\text{relax}}$: left $\alpha = 0.5$, right $\alpha = 2$

3-state MSM
Simulation of Ala$_5$

<table>
<thead>
<tr>
<th>LT=1</th>
<th>LT=1000</th>
<th>EPSILON LIMITING RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.5</td>
<td>516.1</td>
</tr>
<tr>
<td>2</td>
<td>952.2</td>
<td>2700.7</td>
</tr>
<tr>
<td>3</td>
<td>25.5</td>
<td>567.7</td>
</tr>
<tr>
<td>4</td>
<td>687.2</td>
<td>3353.6</td>
</tr>
<tr>
<td>5</td>
<td>33.9</td>
<td>515.8</td>
</tr>
<tr>
<td>6</td>
<td>653.2</td>
<td>2813.0</td>
</tr>
<tr>
<td>7</td>
<td>65.8</td>
<td>424.7</td>
</tr>
<tr>
<td>8</td>
<td>490.0</td>
<td>1929.3</td>
</tr>
<tr>
<td>9</td>
<td>27.1</td>
<td>302.9</td>
</tr>
<tr>
<td>10</td>
<td>189.5</td>
<td>740.5</td>
</tr>
</tbody>
</table>

[Kells, Annibale, Rosta, JCP (2018)]
Simulation of Ala5

Data: four 250ns simulations, started at different initial conditions, $\Delta = 1$ps

Results for $\phi_3$
Simulation of Ala5

Data: four 250ns simulations, started at different initial conditions, $\Delta = 1$ps

$\epsilon$ may help discriminate between "good" and "bad" RC

Results for $\phi_3$

<table>
<thead>
<tr>
<th>COORDINATE</th>
<th>LT=1</th>
<th>LT=1000</th>
<th>EPSILON</th>
<th>LIMITING RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ($\Phi_1$)</td>
<td>6.5</td>
<td>516.1</td>
<td>1.81</td>
<td>6976.3</td>
</tr>
<tr>
<td>2 ($\Psi_1$)</td>
<td>952.2</td>
<td>2700.7</td>
<td>0.23</td>
<td>4711.3</td>
</tr>
<tr>
<td>3 ($\Phi_2$)</td>
<td>25.5</td>
<td>567.7</td>
<td>1.75</td>
<td>6042.0</td>
</tr>
<tr>
<td>4 ($\Psi_2$)</td>
<td>687.2</td>
<td>3353.6</td>
<td>0.17</td>
<td>6571.1</td>
</tr>
<tr>
<td>5 ($\Phi_3$)</td>
<td>33.9</td>
<td>515.8</td>
<td>2.01</td>
<td>6875.1</td>
</tr>
<tr>
<td>6 ($\Psi_3$)</td>
<td>653.2</td>
<td>2813.0</td>
<td>0.22</td>
<td>5101.8</td>
</tr>
<tr>
<td>7 ($\Phi_4$)</td>
<td>65.8</td>
<td>424.7</td>
<td>2.47</td>
<td>9421.1</td>
</tr>
<tr>
<td>8 ($\Psi_4$)</td>
<td>490.0</td>
<td>1929.3</td>
<td>0.47</td>
<td>5325.4</td>
</tr>
<tr>
<td>9 ($\Phi_5$)</td>
<td>27.1</td>
<td>302.9</td>
<td>3.43</td>
<td>11303.5</td>
</tr>
<tr>
<td>10 ($\Psi_5$)</td>
<td>189.5</td>
<td>740.5</td>
<td>1.06</td>
<td>5594.0</td>
</tr>
</tbody>
</table>
Simulation of Ala5

Data: four 250ns simulations, started at different initial conditions, \( \Delta = 1 \text{ps} \)

Results for \( \phi_3 \)

\[\begin{array}{c|cccc}
\text{COORDINATE} & \text{LT}=1 & \text{LT}=1000 & \text{EPSILON} & \text{LIMITING RT} \\
1 (\Phi_1) & 6.5 & 516.1 & 1.81 & 6976.3 \\
2 (\Psi_1) & 952.2 & 2700.7 & 0.23 & 4711.3 \\
3 (\Phi_2) & 25.5 & 567.7 & 1.75 & 6042.0 \\
4 (\Psi_2) & 687.2 & 3353.6 & 0.17 & 6571.1 \\
5 (\Phi_3) & 33.9 & 515.8 & 2.01 & 6875.1 \\
6 (\Psi_3) & 653.2 & 2813.0 & 0.22 & 5101.8 \\
7 (\Phi_4) & 65.8 & 424.7 & 2.47 & 9421.1 \\
8 (\Psi_4) & 490.0 & 1929.3 & 0.47 & 5325.4 \\
9 (\Phi_5) & 27.1 & 302.9 & 3.43 & 11303.5 \\
10 (\Psi_5) & 189.5 & 740.5 & 1.06 & 5594.0 \\
\end{array}\]

\( \epsilon \) may help discriminate between "good" and "bad" RC

[Kells, Annibale, Rosta, JCP (2018)]
1 Introduction
   • Motivation
   • Constructing Markov State Models

2 Clustering Methods
   • Perron Cluster Cluster Analysis
   • Effective rates
   • Projection techniques
   • Variational coarse-graining
   • MFPT in variational Coarse-graining
   • Limiting relaxation times

3 Conclusions
Suggested Markovian Approximations of Coarse-grained descriptions based on projections
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