How can we estimate the slowest dynamics of a Markov process?

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Modeling & simulation group, April 2019

Interesting things happen slowly.

Chemistry is dominated by slow processes.
We need an algorithm to identify these slow processes.

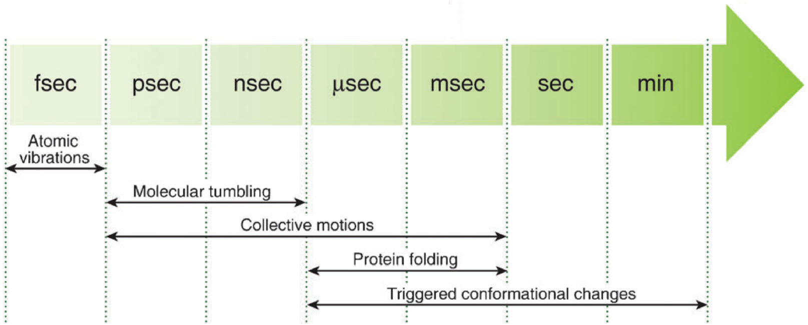


Figure: Interesting things happen slowly (Ben-Nissan & Simon, 2011)

Interesting things happen slowly

We want to identify the slow dynamics of a Markov process $(X_t)_{t \geq 0} \in \mathbb{R}^d$.

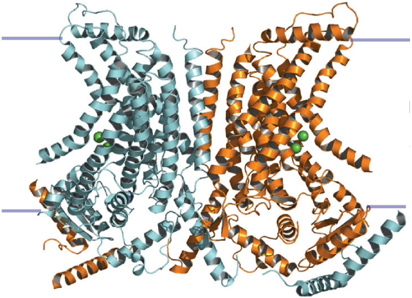


Figure: Molecular dynamics model for gating protein in the lipid bilayer (Lee et al., 2018)

Interesting things happen slowly

We want to identify the slow dynamics of a Markov process $(X_t)_{t \geq 0} \in \mathbb{R}^d$.

1. Diffusion process in $\mathbb{R}^d$

$$dX_t = \mu(X_t)\,dt + \sigma(X_t)\,dW$$

2. Discretization of a diffusion

$$X_{t+h} = X_t + \mu(X_t)\,h + \sigma(X_t)\sqrt{h}Z_t$$

3. MCMC algorithm to sample π

$$X_{t+1} = \begin{cases} X_t + Z_t, & \text{w.p.}\ \frac{\pi(X_{t+1})}{\pi(X_t)} \wedge 1 \\ X_t, & \text{otherwise} \end{cases}$$

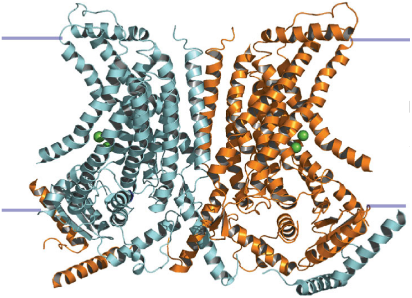


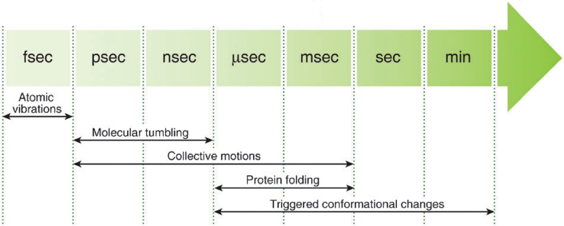
Figure: Molecular dynamics model for gating protein in the lipid bilayer (Lee et al., 2018)

Overview of talk

1. We need an algorithm to identify slow dynamics
   - Interesting things happen slowly
   - How can we define slow dynamics mathematically?
2. How can we estimate slow dynamics?
   - The variational approach to conformation dynamics (VAC)
   - Applications in chemistry
3. New results: mathematical analysis of VAC error
   - Convergence proof for VAC eigenfunctions.
   - Error bounds for VAC
   - Numerical examples
4. Conclusions

Maximizing autocorrelations (Math 1/3)

Let's look for the functions of X_t that decorrelate most slowly.



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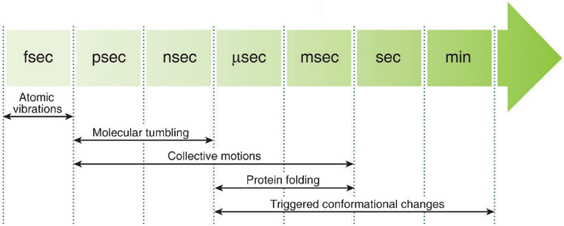

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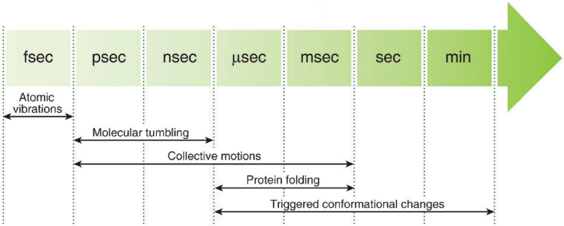
- Search for mean-zero functions $\eta \in L^2\left(\mu\right)$ that maximize

$$\mathrm{corr}_{\mu}\left[\eta\left(X_0\right), \eta\left(X_{\tau}\right)\right] = \frac{\mathrm{E}_{\mu}\left[\eta\left(X_0\right)\eta\left(X_{\tau}\right)\right]}{\mathrm{E}_{\mu}\left|\eta\left(X_0\right)\right|^2}.$$



Operator theory (Math 2/3)

Define the transition operator $T_\tau : L^2(\mu) \to L^2(\mu)$ as

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$\implies$ T_τ is a self-adjoint operator in $L^2(\mu)$, because

$$\langle f, T_\tau g \rangle_\mu = E_\mu\left[f(X_0)\, g(X_t) \right] = E_\mu\left[f(X_\tau)\, g(X_0) \right] = \langle T_\tau f, g \rangle_\mu .$$

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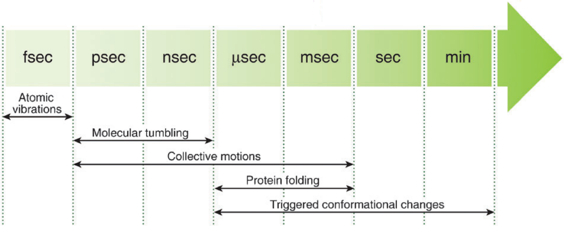
$\implies$ Under some assumptions (including compactness), T_t has a spectral decomposition

$$T_\tau = \sum_{i=1}^{\infty} e^{-\sigma_i \tau} \eta_i \langle \eta_i, \cdot \rangle$$

where $0 = \sigma_1 < \sigma_2 < \sigma_3 < \cdots$ and where $\eta_1, \eta_2, \ldots$ are orthonormal eigenfunctions. The first eigenfunction is the trivial eigenfunction $\eta_1 \equiv 1$.

Courant-Fischer min-max principle (Math 3/3)



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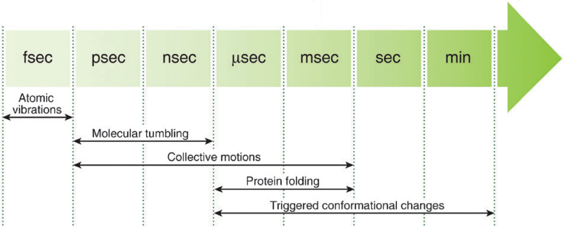
$\eta_1, \ldots, \eta_k$ span all the most slowly decorrelating functions of the system.



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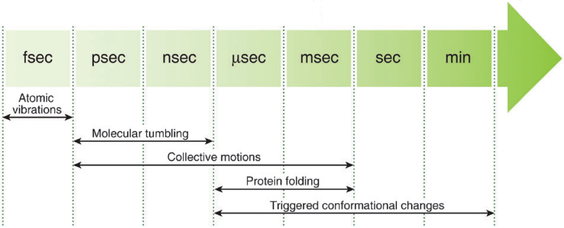
$\eta_1, \ldots, \eta_k$ span all the most slowly decorrelating functions of the system.

- If η belongs to the linear span of $\eta_2, \ldots, \eta_k$, then

$$\mathrm{corr}_\mu \left[\eta\left(X_0\right), \eta\left(X_\tau\right)\right] = \frac{\langle \eta, T_\tau \eta \rangle_\mu}{\langle \eta, \eta \rangle_\mu} \geq e^{-\sigma_k \tau}.$$



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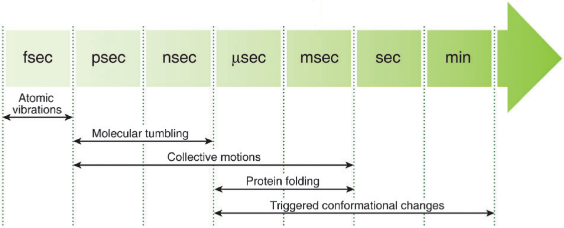
- If u is orthogonal to η_i for $1 \leq i \leq k$ then,

$$\text{corr}_\mu \left[u\left(X_0\right), u\left(X_\tau\right)\right] = \frac{\langle u, T_\tau u \rangle_\mu}{\langle u, u \rangle_\mu} \leq e^{-\sigma_{k+1} \tau}.$$



VAC (1/3)

The variational approach to conformation dynamics (Noé & Nüske, 2013) approximates eigenvalues and eigenfunctions of T_τ using a set of basis functions $\phi_1, \phi_2, \ldots, \phi_n$.

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Using VAC in practice

simulation: complete lots of short, independent simulations ($\sim 100 - 1000$) or a few longer simulations ($\sim 1 - 10$).

preparation: choose a set of basis functions ($\sim 10 - 1000$) and estimate expectations $\mathrm{E}_\mu \left[\phi_i \left(X_0 \right) \phi_j \left(X_\tau \right) \right]$.

spectral estimation: apply VAC to estimate eigenvalues and eigenfunctions.

post-processing: look at top eigenfunctions ($\sim 1 - 10$) to find meaningful and interpretable patterns.

VAC (2/3)

VAC algorithm at lag time τ.

1. Form matrix $\hat{C}(0)$ with entries $\hat{C}_{ij}(0) \approx \mathrm{E}_\mu [\phi_i(X_0)\, \phi_j(X_0)]$.
2. Form matrix $\hat{C}(\tau)$ with entries $\hat{C}_{ij}(\tau) \approx \mathrm{E}_\mu [\phi_i(X_0)\, \phi_j(X_\tau)]$.
3. Solve eigenvalue problem $\hat{\lambda}_i^\tau\, \hat{v}^i(\tau) = \hat{C}(0)^{-1}\, \hat{C}(\tau)\, \hat{v}^i(\tau)$.
4. Return estimated eigenvalues $\hat{\lambda}_i^\tau$ and eigenfunctions $\hat{\gamma}_i^\tau = \sum_j \hat{v}_j^i(\tau)\, \phi_j$.

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$\tau =$ lag time parameter

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Examples of VAC include

1. *Markov state models (MSMs)*: basis functions are indicator functions on disjoint sets.
2. *Time-lagged independent component analysis (TICA)*: basis functions are the coordinate axes.

VAC (3/3)

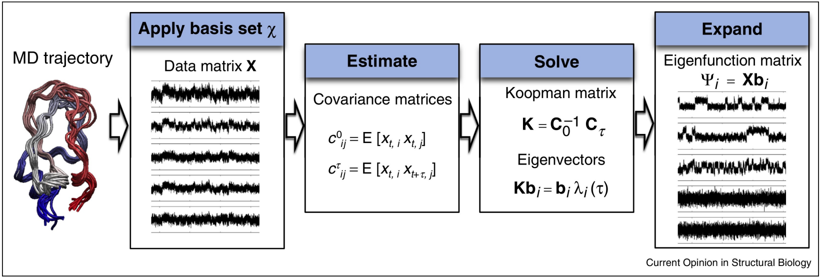

Figure: Schematic of how VAC is used in practice (Noé and Clementi, 2018)

Applications in chemistry

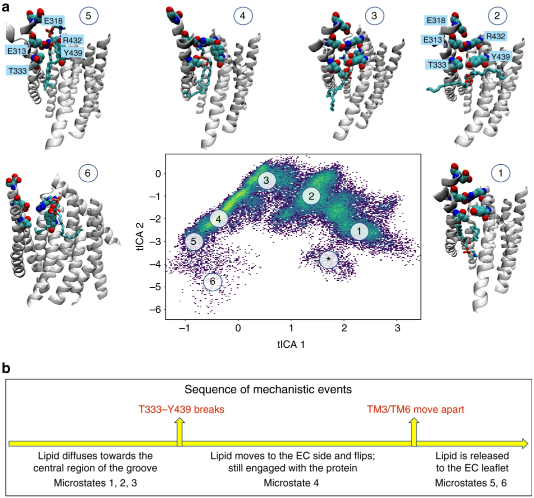

Figure: Lee et al. (2018) use VAC to understand protein dynamics.

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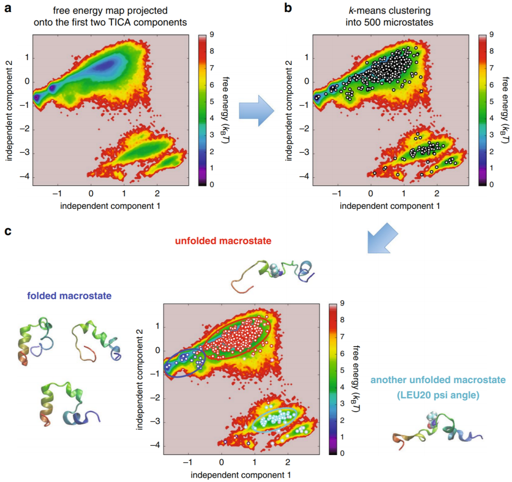

Figure: Chong & Ham (2018) use VAC to identify folded and unfolded states.

Problems with VAC

Problems.

1. No one has proved convergence of VAC eigenfunctions.
2. No one knows how to choose a lag time.
3. How do we know if VAC is accurate?

No one has proved convergence of VAC eigenfunctions.

Djurdjevac, Sarich & Schütte (2012) proved convergence of eigenvalues.

Theorem (eigenvalue convergence)

Assume $\hat{C}_{ij}(\tau) \approx \mathrm{E}_{\mu}\left[\phi_i(X_0)\,\phi_j(X_\tau)\right]$ *terms are evaluated perfectly, and set* $\Phi = \mathrm{span}_{1 \leq i \leq n}\,\phi_i$. *Then, VAC eigenvalues converge*

$$\hat{\lambda}_k^{\tau} \to e^{-\sigma_k \tau}$$

provided that $\mathrm{proj}_{\Phi}\,\eta_i \to \eta_i$ *for each* $1 \leq i \leq k$.

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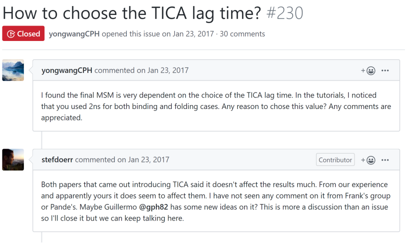
- What about convergence of VAC eigenfunctions?
- What if matrix entries $\hat{C}_{ij}(\tau) \approx \mathrm{E}_{\mu}[\phi_i(X_0)\,\phi_j(X_\tau)]$ are evaluated imperfectly because of the finite data set?

No one knows how to choose a lag time.

A reasonable setting of the lag-time parameter is critically important... (Naritomi & Fuchigami, 2011)



How to choose the TICA lag time? #230

Closed yongwangCPH opened this issue on Jan 23, 2017 · 30 comments

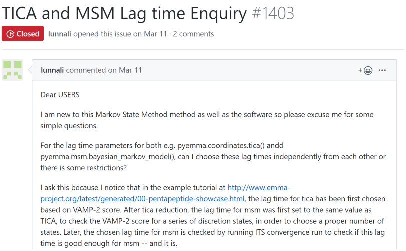
yongwangCPH commented on Jan 23, 2017

I found the final MSM is very dependent on the choice of the TICA lag time. In the tutorials, I noticed that you used 2ns for both binding and folding cases. Any reason to chose this value? Any comments are appreciated.

stefdoerr commented on Jan 23, 2017 Contributor

Both papers that came out introducing TICA said it doesn't affect the results much. From our experience and apparently yours it does seem to affect them. I have not seen any comment on it from Frank's group or Pande's. Maybe Guillermo @gph82 has some new ideas on it? This is more a discussion than an issue so I'll close it but we can keep talking here.

Figure: VAC results were sensitive to lag time, issue was never resolved



TICA and MSM Lag time Enquiry #1403

Closed lunnali opened this issue on Mar 11 · 2 comments

lunnali commented on Mar 11

Dear USERS

I am new to this Markov State Method method as well as the software so please excuse me for some simple questions.

For the lag time parameters for both e.g. pyemma.coordinates.tica() andd pyemma.msm.bayesian_markov_model(), can I choose these lag times independently from each other or there is some restrictions?

I ask this because I notice that in the example tutorial at http://www.emma-project.org/latest/generated/00-pentapeptide-showcase.html, the lag time for tica has been first chosen based on VAMP-2 score. After tica reduction, the lag time for msm was first set to the same value as TICA, to check the VAMP-2 score for a series of discretion states, in order to choose a proper number of states. Later, the chosen lag time for msm is checked by running ITS convergence run to check if this lag time is good enough for msm -- and it is.

Figure: VAC user unsure how to select a lag time

How do we know if VAC is accurate?

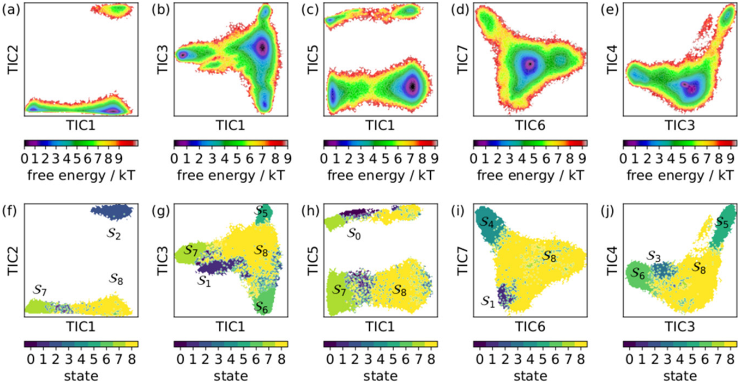


Figure: Sidsky et al. (2019) identify 7 nontrivial eigenfunctions for trp-cage protein – are all 7 eigenfunctions accurate?

Goals of our work

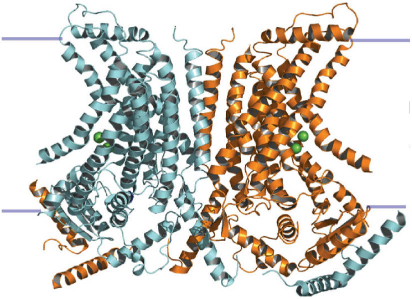


Figure: Molecular dynamics model for gating protein in the lipid bilayer (Lee et al., 2018)

Goal 1: prove convergence of VAC eigenfunctions

Goal 2: determine how error depends on lag time

Goal 3: provide examples assessing accuracy of VAC

Proving convergence (1/3)

1. Colloquially, VAC is an algorithm for estimating eigenfunctions. Really, VAC estimates eigenspaces and other invariant subspaces.

$$\operatorname*{span}_{j \leq i \leq k} \hat{\gamma}_i^{\tau} \approx \operatorname*{span}_{j \leq i \leq k} \eta_i,$$

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$$d_F(\mathcal{U}, \mathcal{W}) = \left\| \text{proj}\left[\mathcal{W}^{\perp}\right] \text{proj}\left[\mathcal{U}\right] \right\|_F$$

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   where $\mathcal{W}^\perp$ is the orthogonal complement of $\mathcal{W}$ and $\|\cdot\|_F$ is the Hilbert-Schmidt/Frobenius norm.
4. The definition also works if $\dim \mathcal{U} < \dim \mathcal{W} \leq \infty$. Then, $d_F(\mathcal{U},\mathcal{W})$ measures the distance between $\mathcal{U}$ and the nearest $\dim \mathcal{U}$-dimensional subspace of $\mathcal{W}$.

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Idealized VAC involves $C(\tau)$, λ_i^τ, and γ_i^τ.
VAC involves $\hat{C}(\tau)$, $\hat{\lambda}_i^\tau$, and $\hat{\gamma}_i^\tau$.

Proving convergence (3/3)

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Theorem (Rayleigh-Ritz bound)

1. Idealized VAC eigenfunctions converge

$$\gamma_k^\tau \to \eta_k \qquad \text{as } \operatorname*{proj}_{\Phi} \eta_i \to \eta_i \text{ for } 1 \leq i \leq k.$$

2. Idealized VAC error is bounded by

$$1 \leq \frac{d_F^2\left(\operatorname{span}_{1\leq i\leq k}\gamma_i^\tau, \operatorname{span}_{1\leq i\leq k}\eta_i\right)}{d_F^2\left(\operatorname{span}_{1\leq i\leq k}\eta_i, \Phi\right)} \leq 1 + \frac{\left\|\operatorname{proj}\left[\Phi^\perp\right]\; T_\tau \operatorname{proj}\left[\Phi\right]\right\|_2^2}{\left|e^{-\sigma_k \tau} - \lambda_{k+1}^\tau\right|^2}.$$

Limitations of Rayleigh-Ritz bound

Rayleigh-Ritz bound explains how error depends on the basis set Φ.

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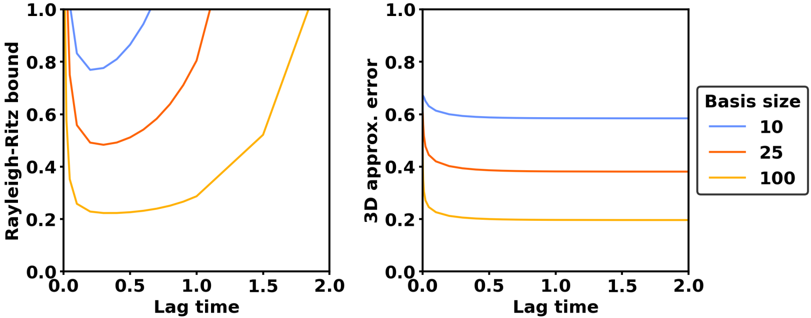

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Limitations of Rayleigh-Ritz bound

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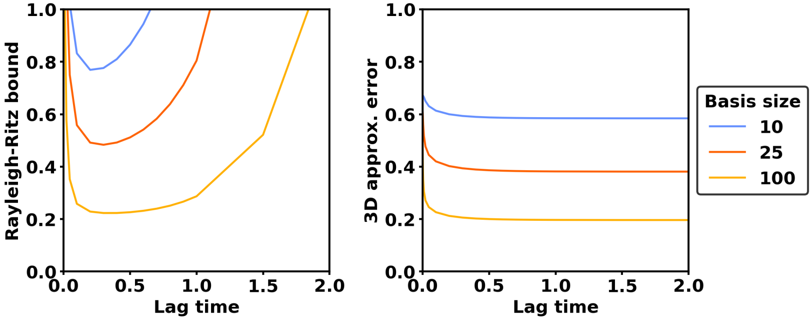

Figure: The Rayleigh-Ritz bound asymptotes to infinity at long lag times (left). The true error decreases and then stabilizes at long lag times (right).

To understand lag time, we need to prove a new error bound.

Analyzing lag time

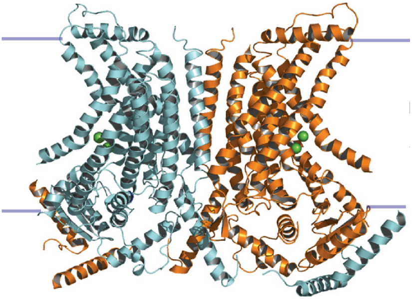

Figure: Molecular dynamics model for gating protein in the lipid bilayer (Lee et al., 2018)

Goal 1: prove convergence of VAC eigenfunctions

Goal 2: determine how error depends on lag time

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Analyzing lag time

Decompose the error into two parts

$$\underbrace{d_F\left(\operatorname{span}_{1\le i\le k} \hat{\gamma}_i^\tau, \operatorname{span}_{1\le i\le k} \eta_i\right)}_{\text{total error}}$$

$$\le \underbrace{d_F\left(\operatorname{span}_{1\le i\le k} \gamma_i^\tau, \operatorname{span}_{1\le i\le k} \eta_i\right)}_{\text{approximation error}} + \underbrace{d_F\left(\operatorname{span}_{1\le i\le k} \hat{\gamma}_i^\tau, \operatorname{span}_{1\le i\le k} \gamma_i\right)}_{\text{estimation error}}.$$

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- Estimation error = difference between idealized VAC and VAC

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- Approximation error = difference between idealized VAC and true eigenfunctions η_i.
- Estimation error = difference between idealized VAC and VAC
- VAC is error-prone at short lag times due to approximation error and at long lag times due to estimation error

Approximation error (1/2)

New result: idealized VAC eigenfunctions converge at long lag times.

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Theorem (The $\tau \to \infty$ limit)

1. Idealized VAC eigenfunctions converge

$$\operatorname*{span}_{1 \leq i \leq k} \gamma_i^\tau \to \operatorname{proj}[\Phi] \operatorname*{span}_{1 \leq i \leq k} \eta_i \qquad \textit{as} \qquad \tau \to \infty.$$

2. The rate of convergence is exponentially fast, asymptotically proportional to $\lambda_{k+1}^\tau / \lambda_k^\tau$.

3. Lastly, approximation error is bounded by

$$1 \leq \frac{d_F^2\left(\operatorname{span}_{1 \leq i \leq k} \gamma_i^\tau, \operatorname{span}_{1 \leq i \leq k} \eta_i\right)}{d_F^2\left(\operatorname{span}_{1 \leq i \leq k} \eta_i, \Phi\right)} \leq 1 + \left|\frac{e^{-\sigma_{k+1}\tau}/2}{\lambda_k^\tau - e^{-\sigma_{k+1}\tau}}\right|^2,$$

provided that $\lambda_k^\tau > e^{-\sigma_{k+1}\tau}$.

Approximation error (2/2)

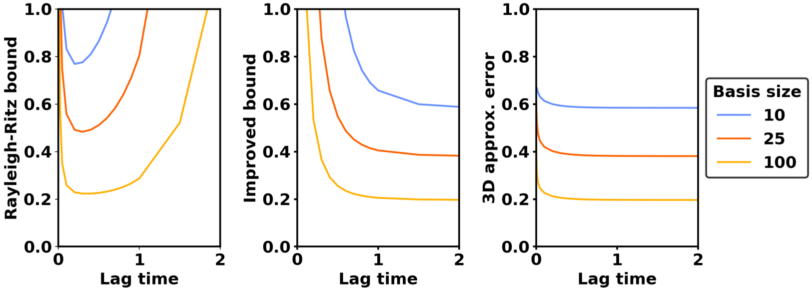

Figure: The Rayleigh-Ritz bound asymptotes to infinity at long lag times (left). The true error decreases and then stabilizes at long lag times (right). Our improved bound becomes sharp at long lag times (center).

Estimation error (1/2)

New result: there is a precise asymptotic formula for the estimation error.

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$$d_{\mathrm{F}}\left(\operatorname*{span}_{1\leq i\leq k}\hat{\gamma}_i^{\tau},\operatorname*{span}_{1\leq i\leq k}\gamma_i^{\tau}\right)^2 = \sum_{i=k+1}^{n}\sum_{j=1}^{k}\left|\frac{v^i(\tau)^T\left[\hat{C}(\tau)-\lambda_j^{\tau}\hat{C}(0)\right]v^j(\tau)}{\lambda_i^{\tau}-\lambda_j^{\tau}}\right|^2(1+o(1))$$

in the limit as $\hat{C}(\tau)\to C(\tau)$ *and* $\hat{C}(0)\to C(0)$.

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in the limit as $\hat{C}(\tau) \to C(\tau)$ *and* $\hat{C}(0) \to C(0)$.

Condition number = maximum change in VAC eigenfunctions as $\hat{C}(0)$ and $\hat{C}(\tau)$ become corrupted by small errors $= \left(\lambda_k^\tau - \lambda_{k+1}^\tau\right)^{-1}$

Estimation error (2/2)

Step 1: using trajectory data, estimate statistical error in $\hat{C}(0)$ and $\hat{C}(\tau)$.

Step 2: using the asymptotic formula, approximate the mean-squared estimation error.

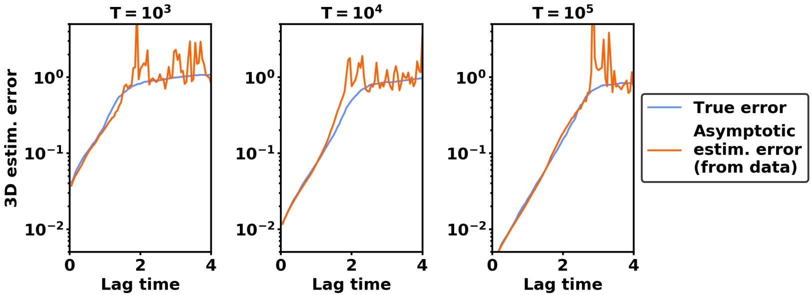
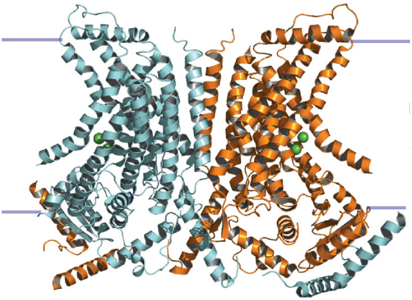


Figure: For a range of trajectory lengths T, the asymptotic formula gives accurate predictions for the the mean squared estimation error.

Assessing accuracy



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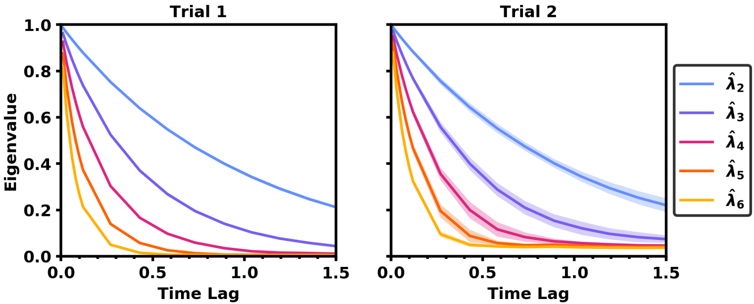

Figure: VAC eigenvalues for the OU process

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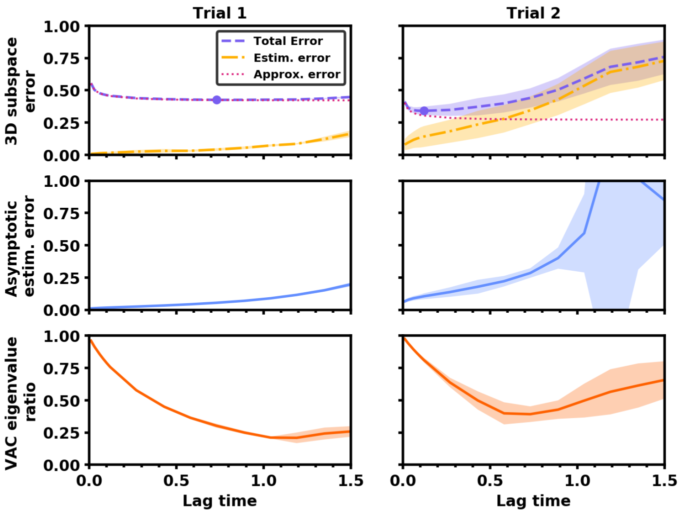

Assessing accuracy - dependence on condition number

Consider the diffusion process

$$dX = -\frac{1}{2}\sigma\sigma^T \nabla U(X)\, dt + \sigma\, dW$$

where

$$U(x_1, x_2) = 4x_1^4 - 8x_1^2 + x_1 + 0.5x_2^2,$$

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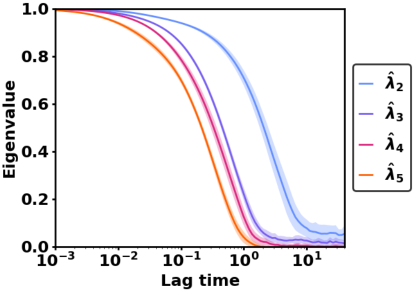


Figure: VAC eigenvalues for the double well potential

Assessing accuracy - dependence on condition number

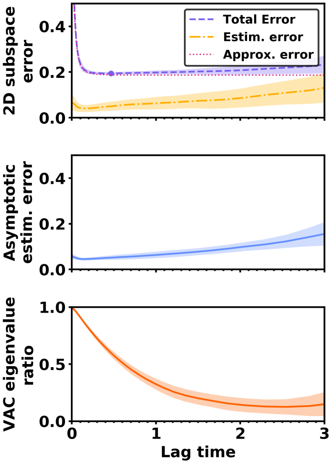


Figure: Subspace $\{\eta_1, \eta_2\}$, condition number ≈ 2.0

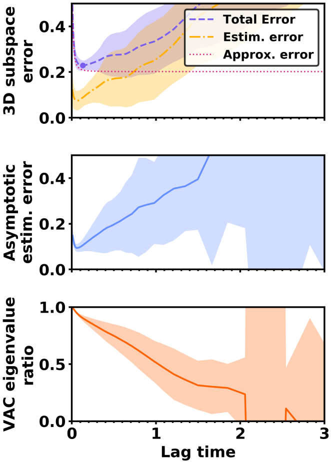
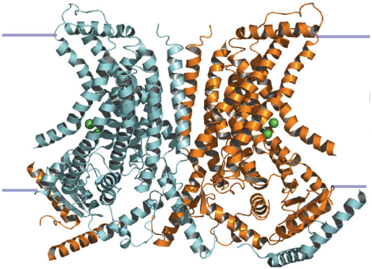


Figure: Subspace $\{\eta_1, \eta_2, \eta_3\}$, condition number ≈ 9.5

Conclusions



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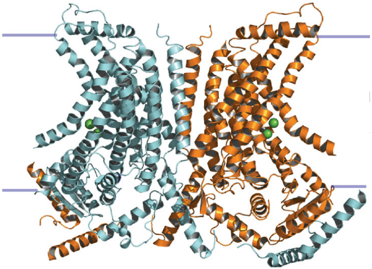

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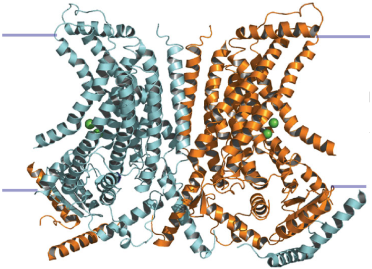

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1. We proved convergence of VAC eigenfunctions.
2. We determined how error depends on lag time.
3. We provided diagnostic tools to gauge error.
   - VAC eigenvalue ratio
   - condition number
   - asymptotic estimation error