Non-Markovian Dynamic Models of Protein Conformational Changes

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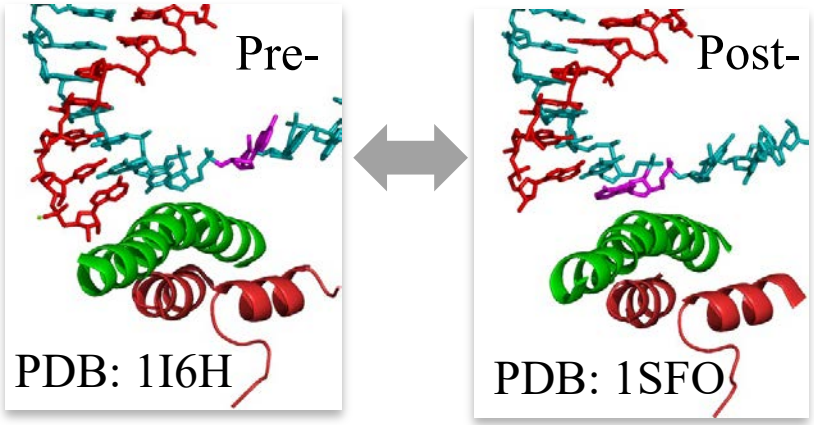
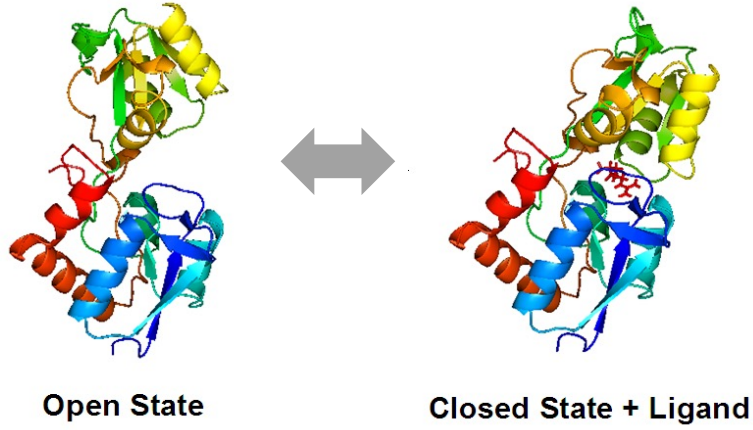
Dynamics of Conformational Changes are Crucial for Protein Function

Dynamic and localized transitions between pairs of conformational states:



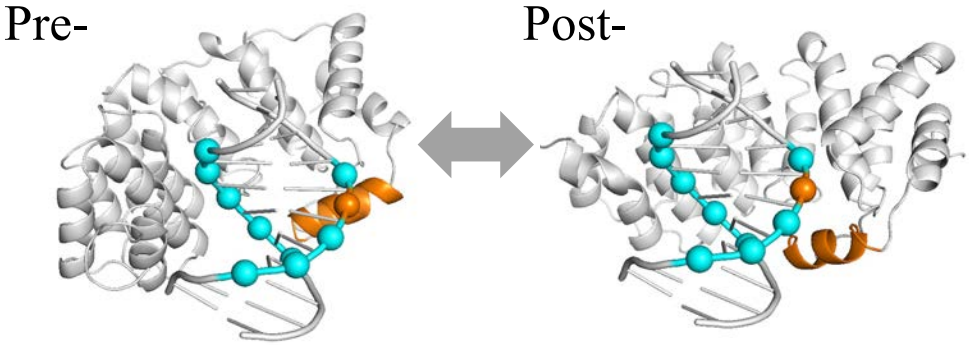
RNA Polymerase translocation

PNAS, 7665, (2014); ***Nat. Commun.***, 11244, (2016)



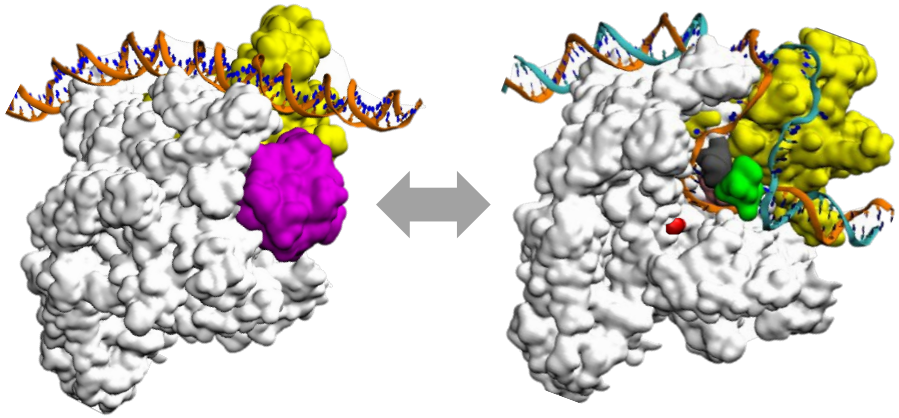
Protein-ligand recognition

PLOS. Comp. Bio., 7, e1002054, (2011)



DNA repair protein translocates on dsDNA

PNAS, 117, 21889, (2020)



DNA loading into RNA Polymerase

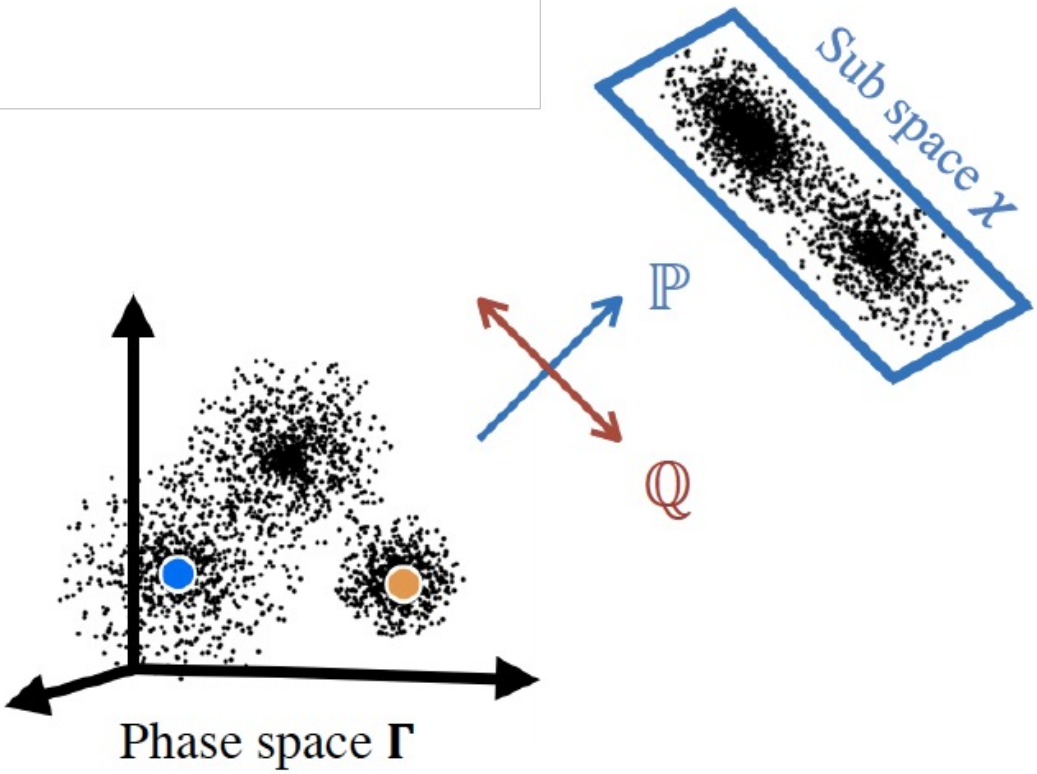
PNAS, 118(17), e2024324118, (2021)

Projection Operator Approach of Protein Dynamics

Evolution of density in phase space satisfies Liouville's Equation:

$$\frac{\partial \rho(\mathbf{\Gamma}, t)}{\partial t} = \mathcal{L}\rho(\mathbf{\Gamma}, t) \qquad \boldsymbol{\Gamma} = (\boldsymbol{x}; \boldsymbol{p})$$

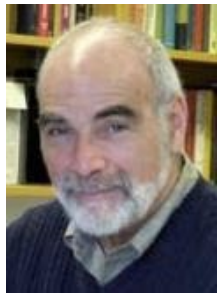
Mori-Zwanzig projection operator: $\boldsymbol{\Gamma} \rightarrow \boldsymbol{\chi}$



$\mathbb{P}$: slow variables $\boldsymbol{\chi}$

$\mathbb{Q}$: fast variables $\boldsymbol{\Gamma} \cap \bar{\boldsymbol{\chi}}$



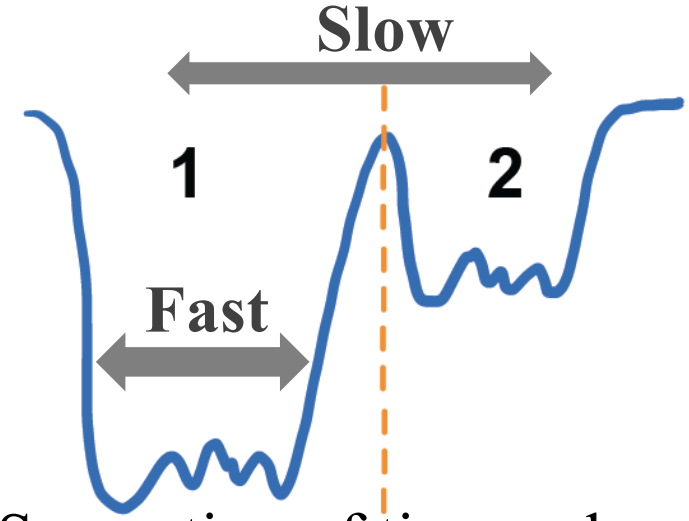


Zwangzig **Mori** **Berne**

Projecting Kinetics onto Coarse-grained States Introduces Memory

Hummer-Szabo projection operator:

$$\mathbb{P} := \sum_{j=1}^{n} \left|\rho(\boldsymbol{\Gamma};\ \mathrm{eq})\chi_j(\boldsymbol{x})\right\rangle \cdot \pi_j^{-1}\left\langle\chi_j(\boldsymbol{x})\right|$$



Separation of timescales

We choose $|\chi\rangle$ to be the state indicator function

$\chi_i(\boldsymbol{x}) = 1$: conformation $\boldsymbol{x}$ belongs to state i

- $\mathbb{P}$: Slow transitions between states
- $\mathbb{Q}$: Fast transitions within state

The projected kinetics satisfy a **Generalized Master Equation**:

$$\frac{\partial}{\partial t}\mathbf{T}(t) = \dot{\mathbf{T}}(0)\mathbf{T}(t) + \int_0^t \mathbf{K}(t')\mathbf{T}(t-t')dt'$$

Memory kernel: $\mathbf{K}(t) = \langle Le^{\mathbb{Q}Lt}\mathbb{Q}L\rangle_{\rho,\pi^{-1}}$

Hummer & Szabo, ***JPCB.*** 119, 9029, (2015)

Cao *et al.* ***J. Chem. Phys.***,153: 014105, (2020)

Projecting Kinetics onto Coarse-grained States Introduces Memory

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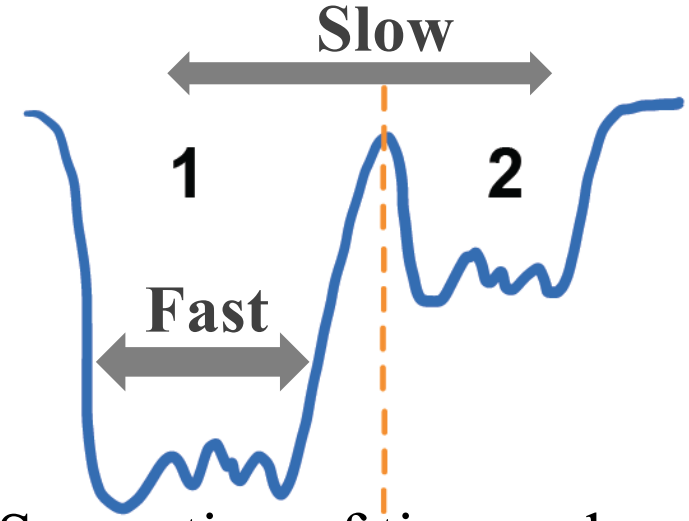

Separation of timescales

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- $\mathbb{P}$: Slow transitions between states
- $\mathbb{Q}$: Fast transitions within state

Discretion of time (lag time: τ) is sufficiently long so that: $\mathbb{P}e^{\mathcal{L}\tau}\mathbb{Q} \approx 0$

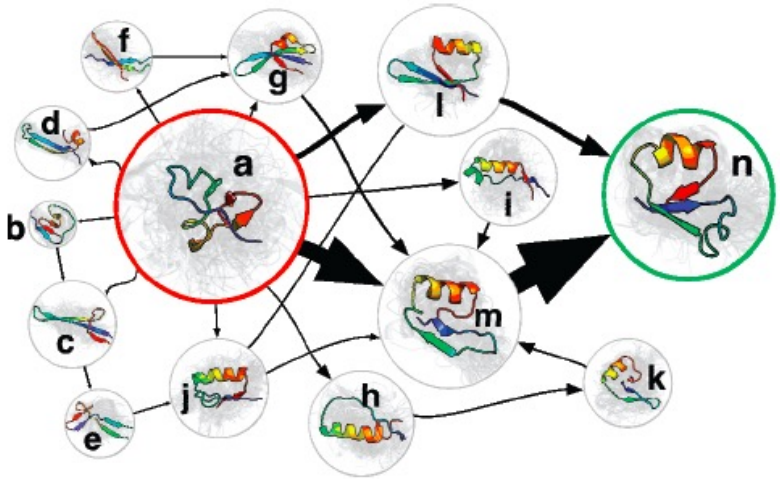
We obtain a **Markov State Model (MSM)**:

$$p(t+\tau) = \mathbf{T}\,p(t)$$

Wang, Cao, Zhu, Huang ***WIREs Comput. Mol. Sci.***, e1343, (2017)

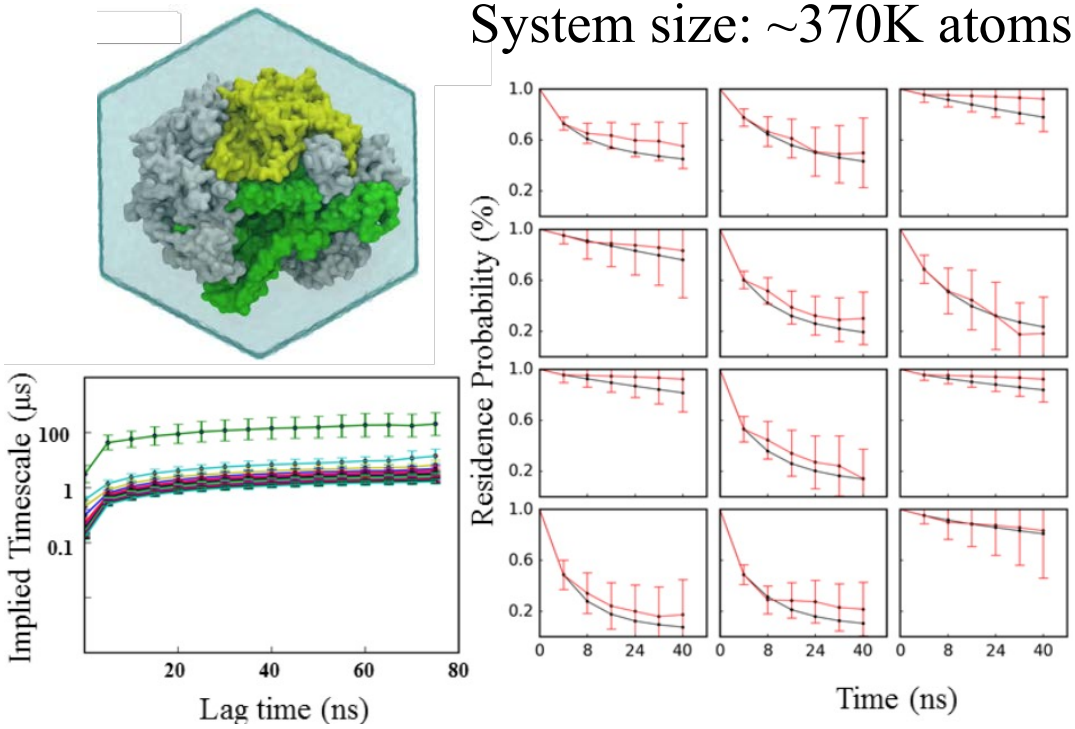
MSMs are often non-Markovian due to Limited Length of MD Simulations

NTL9 folding:



RNA Polymerase backtracking:

System size: ~370K atoms



2000-state MSM: lag time = 10ns.

14-state model: **Not Markovian**

Voelz *et al.* ***JACS***, 132,5, (2010)

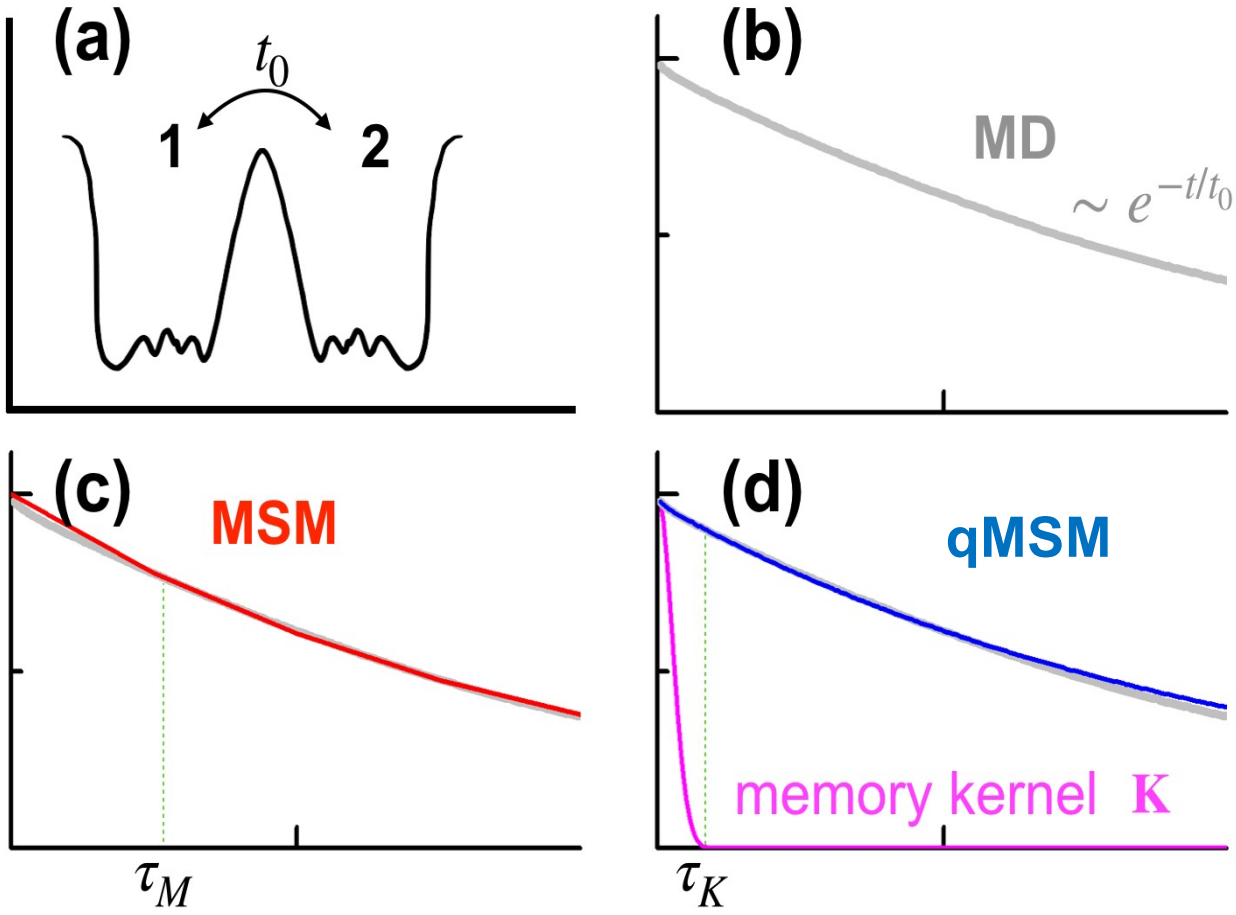
800-state MSM: lag time = 8ns (*480 100-ns MD simulations*)

4-state model: **Not Markovian**

Da,…, Huang, ***Nat. Communi.***, 7, 11244, (2016)

Quasi-Markov State Model (qMSM) Theory

Key Insights: Due to separation of timescales, the memory kernel (mainly reflecting intra-state transition) decays faster than the Markovian lag time.



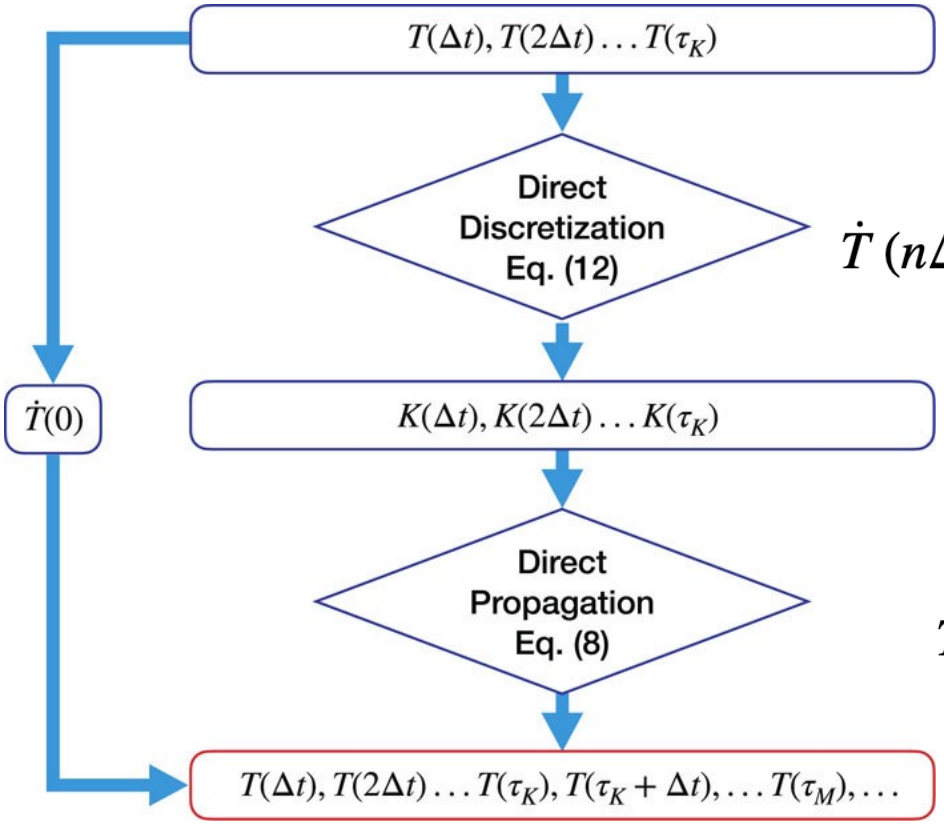
$\tau_K \ll \tau_M$

Our approach: Propagate dynamics using a Generalized Master Equation with memory kernel.

$\tau_K < \tau_M < t_0$

Cao *et al.* ***J. Chem. Phys.***,153, 014105, (2020)

Computing Memory Kernel for Protein Dynamics



Direct discretization of GME:

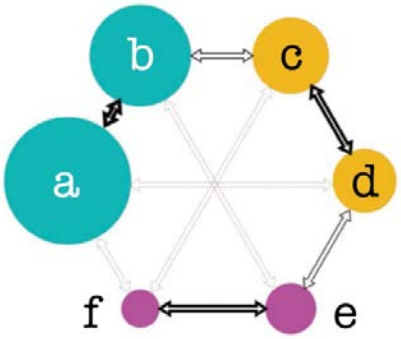
$$\dot{T}(n\Delta t) = \dot{T}(0)\,T(n\Delta t) + \Delta t \sum_{m=1}^{n} \mathscr{K}(m\Delta t)\,T((n-m)$$

GME:

$$\dot{T}(t) = \dot{T}(0)\,T(t) - \int_0^{\min[\tau_K, t]} d\tau\, \mathscr{K}(\tau)\,T(t-\tau)$$

Cao *et al.* ***J. Chem. Phys.***,153, 014105, (2020)

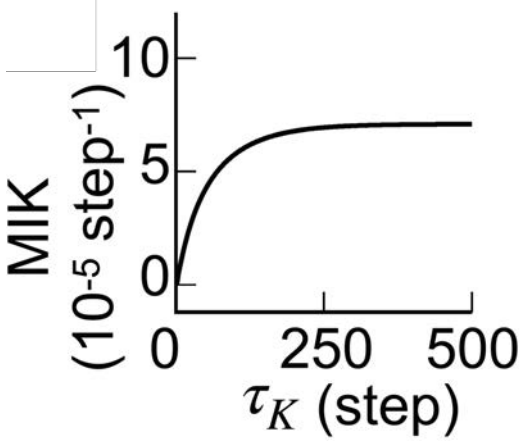
A Simple Kinetic Model

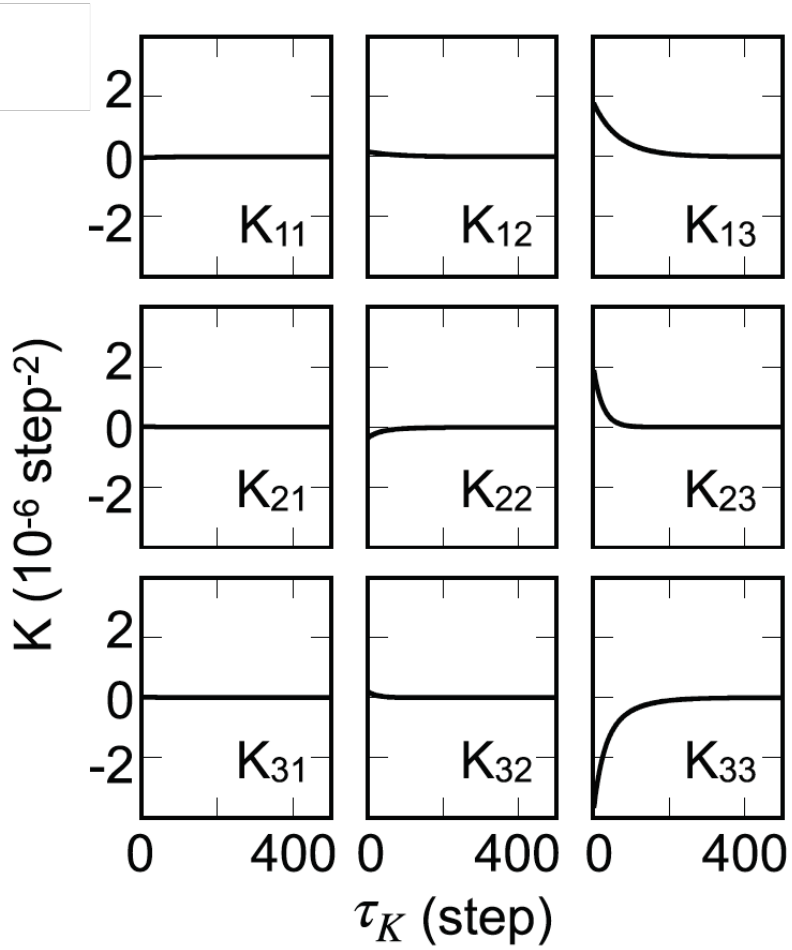


3-state

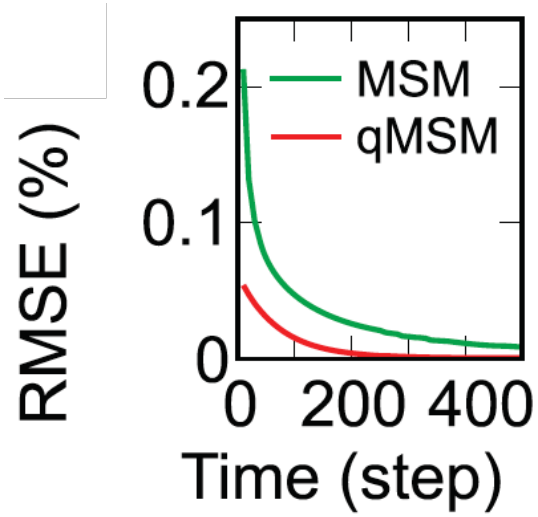
Good lumping

Memory Kernel Integral





Root mean square errors of TPM

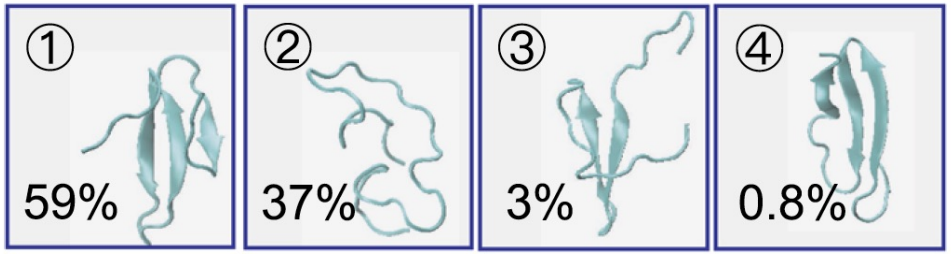


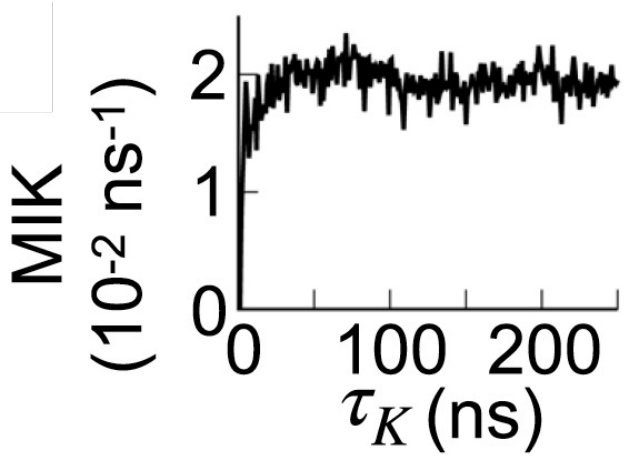
qMSM is more accurate than MSM.

Cao *et al.* ***J. Chem. Phys.***,153, 014105, (2020)

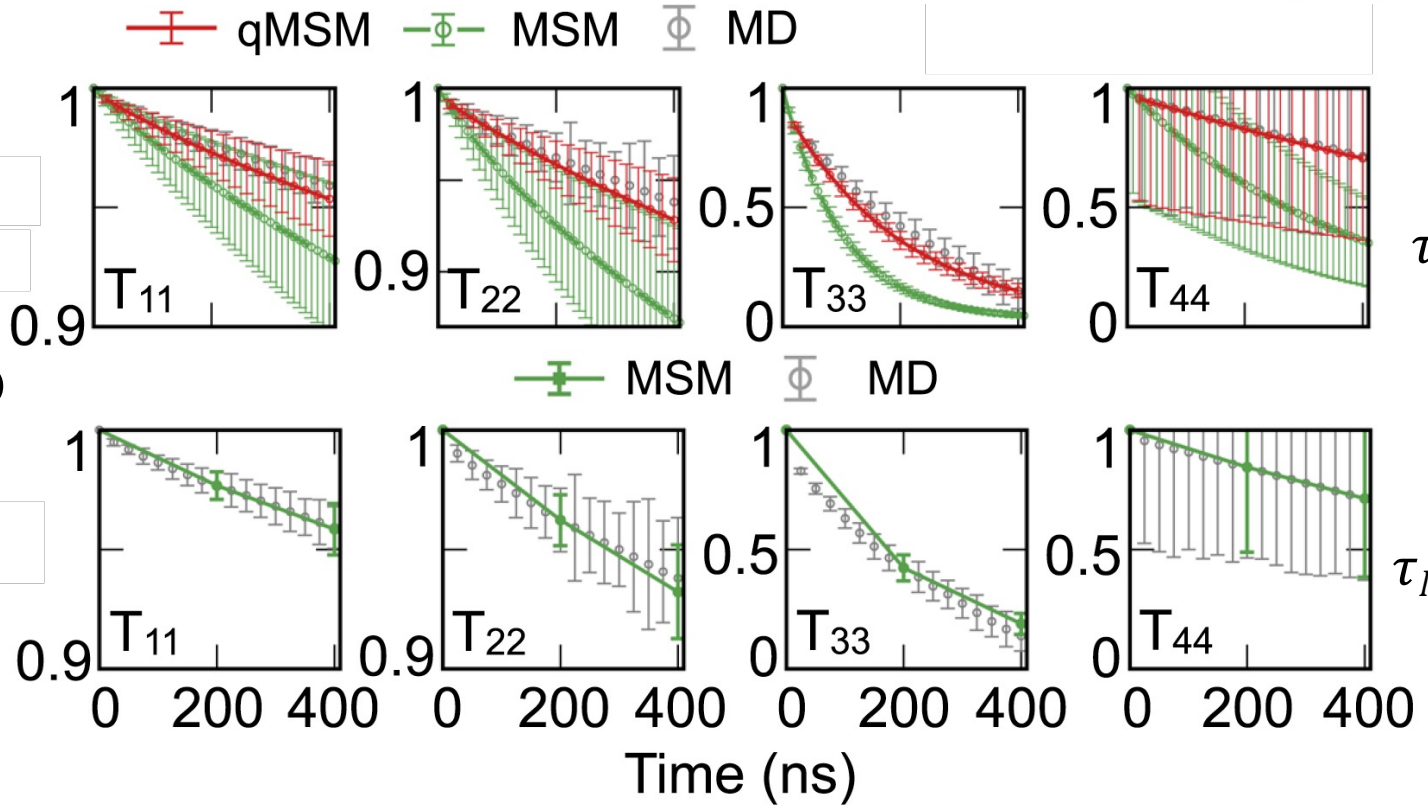
WW domain Folding

4-State





qMSM saves > **10 times in** MD length than MSM!

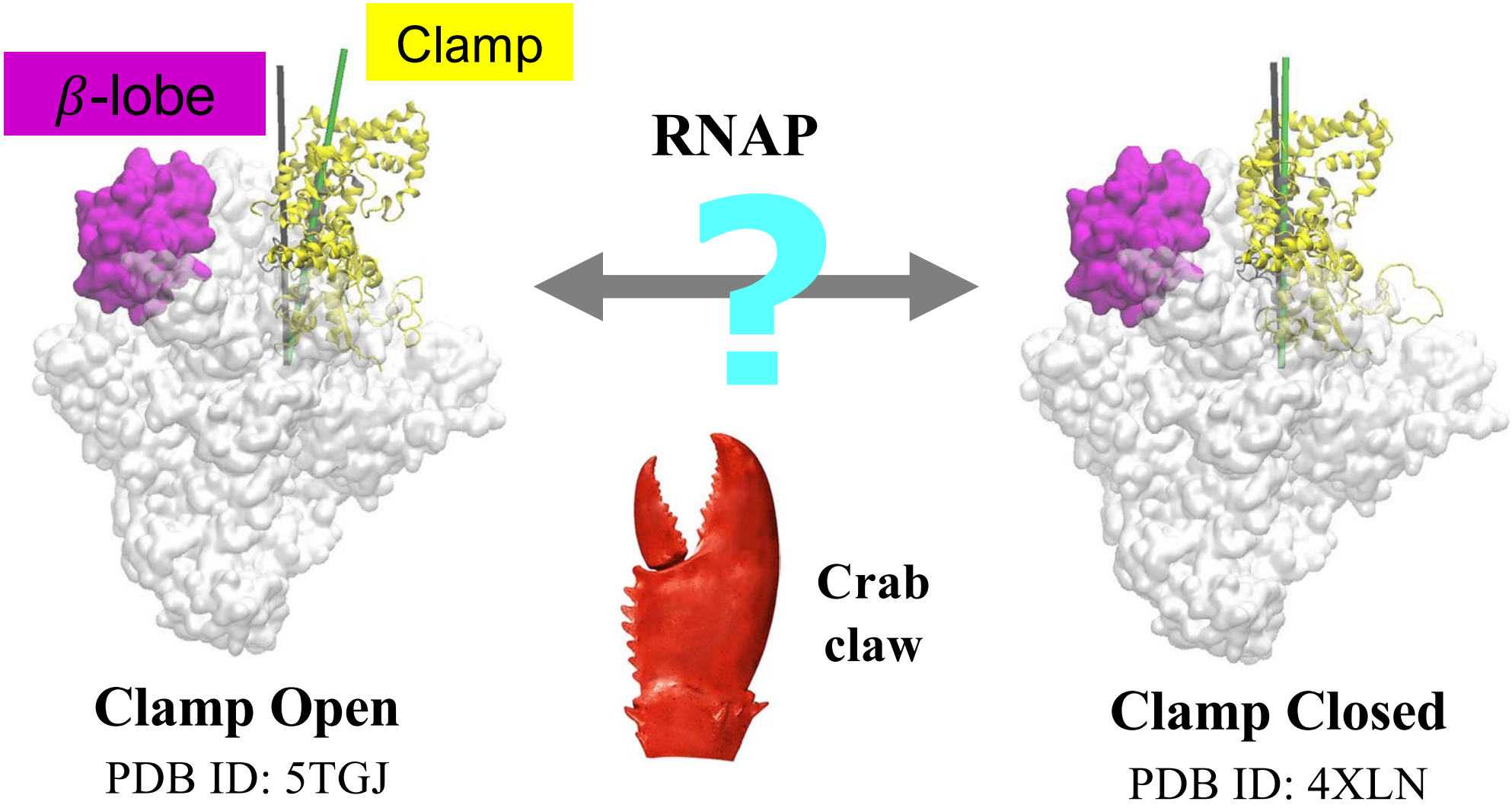


qMSM
$\tau_K = 15ns$

MSM
$\tau_M = 200ns$

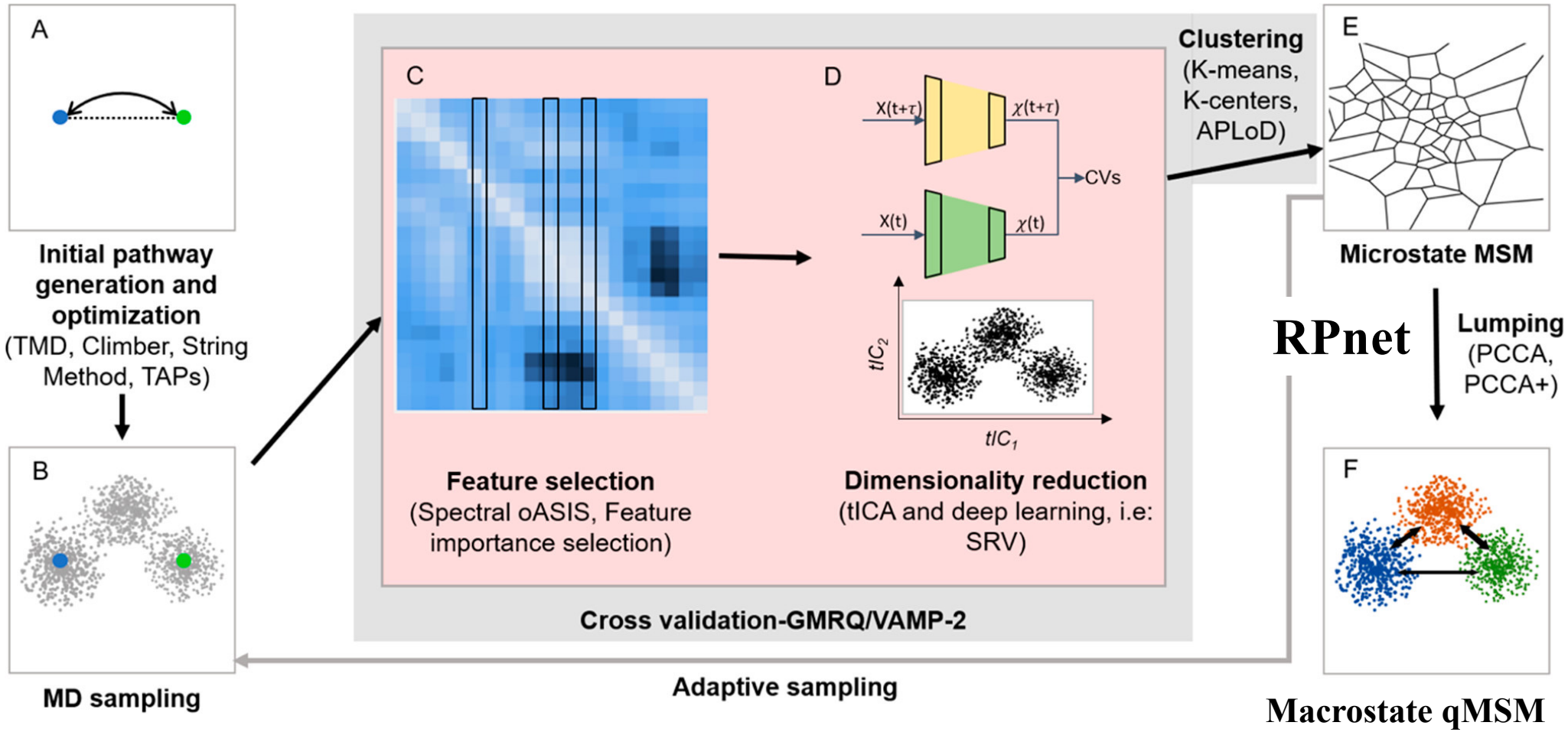
Cao *et al.* ***J. Chem. Phys.***,153, 014105, (2020)

Dynamics of RNAP Gate Opening is Crucial for DNA Promoter Loading



Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

Our Recipe for Constructing qMSMs to Study Functional Conformational Changes



JACS Au, 1, 1330-1341, (2021)

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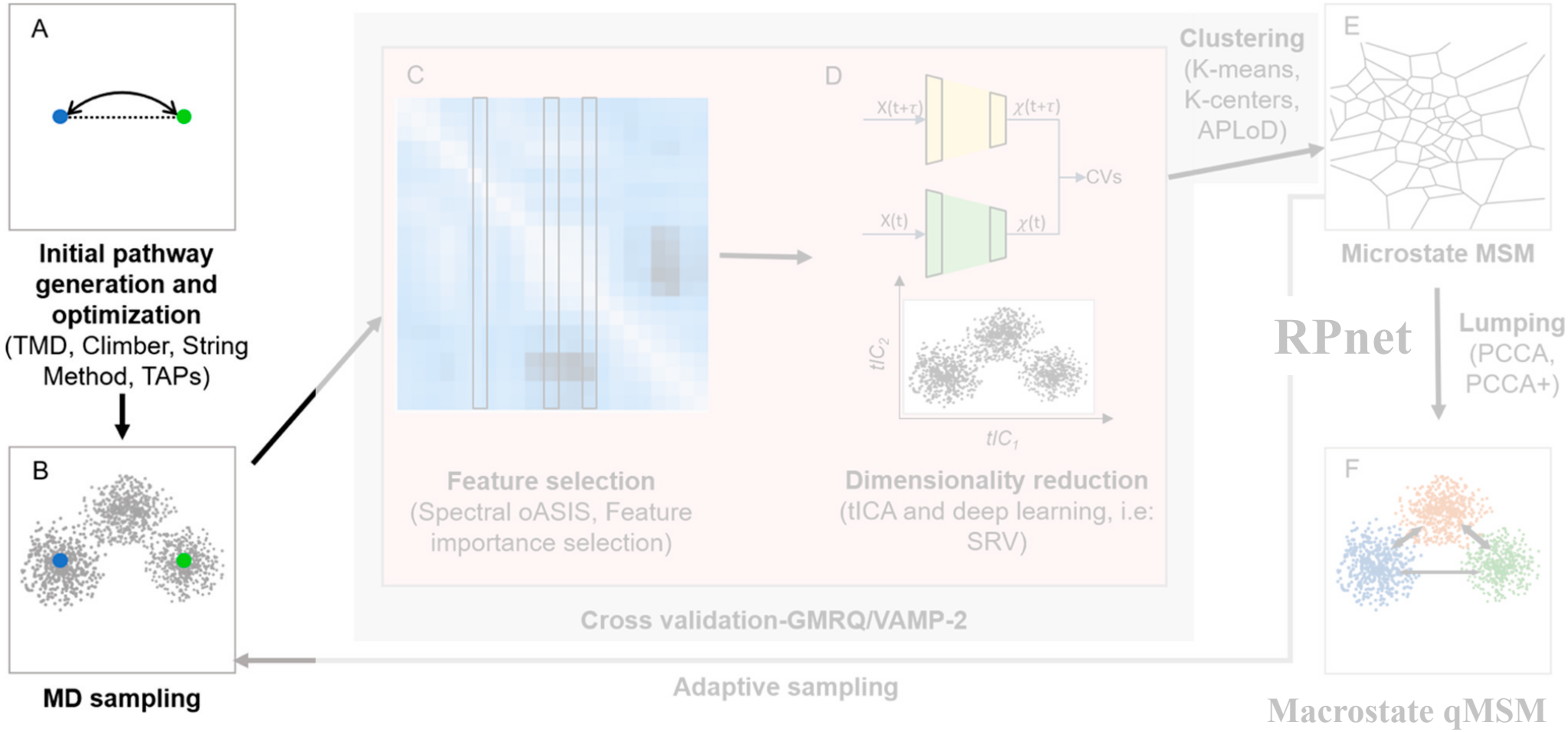
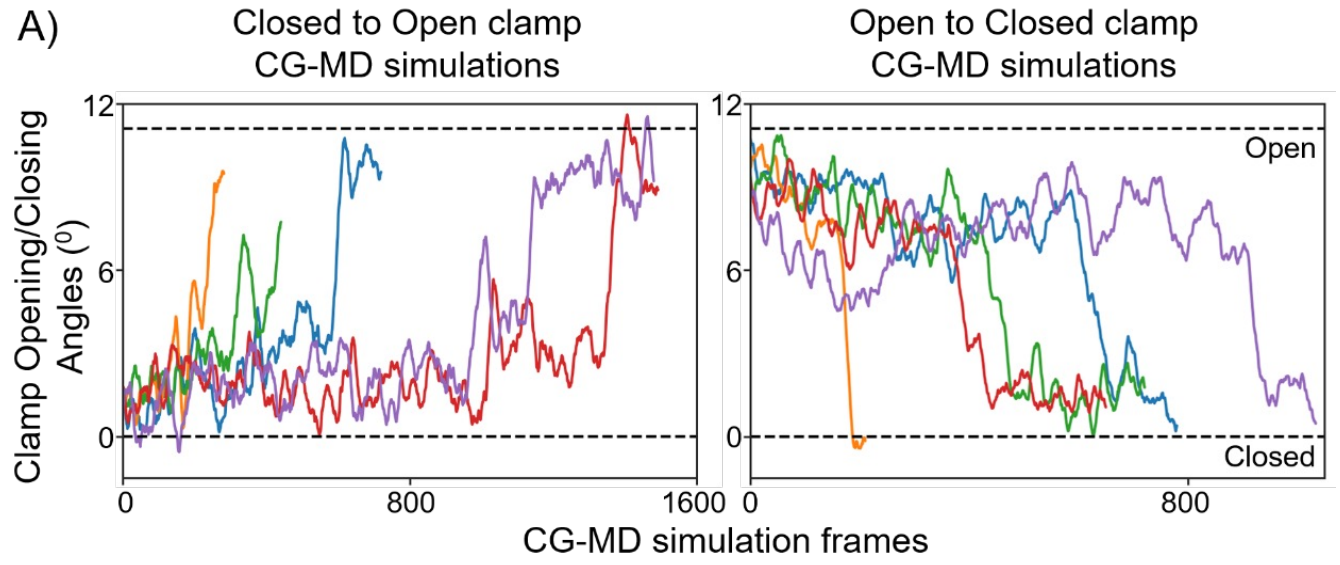
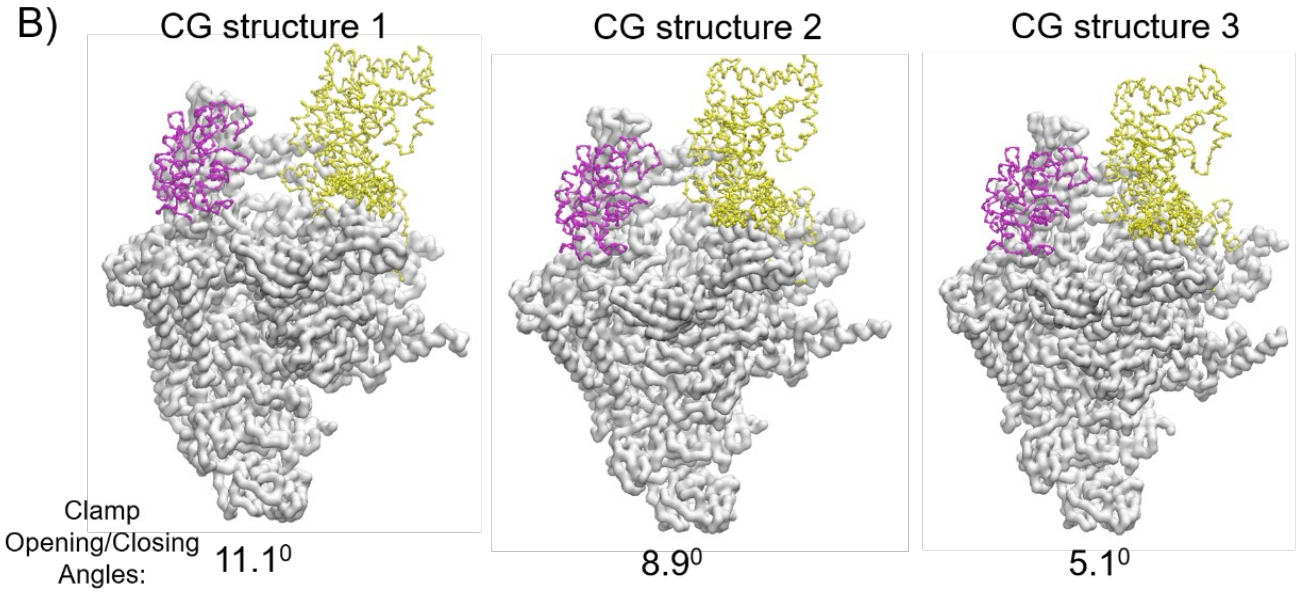


JACS Au, 1, 1330-1341, (2021)

Coarse-Grained MD Simulations to Generate Initial Path





Shoji Takada
Kyoto U

CafeMol

Back-map coarse–grained conformations to all-atom conformations.

Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

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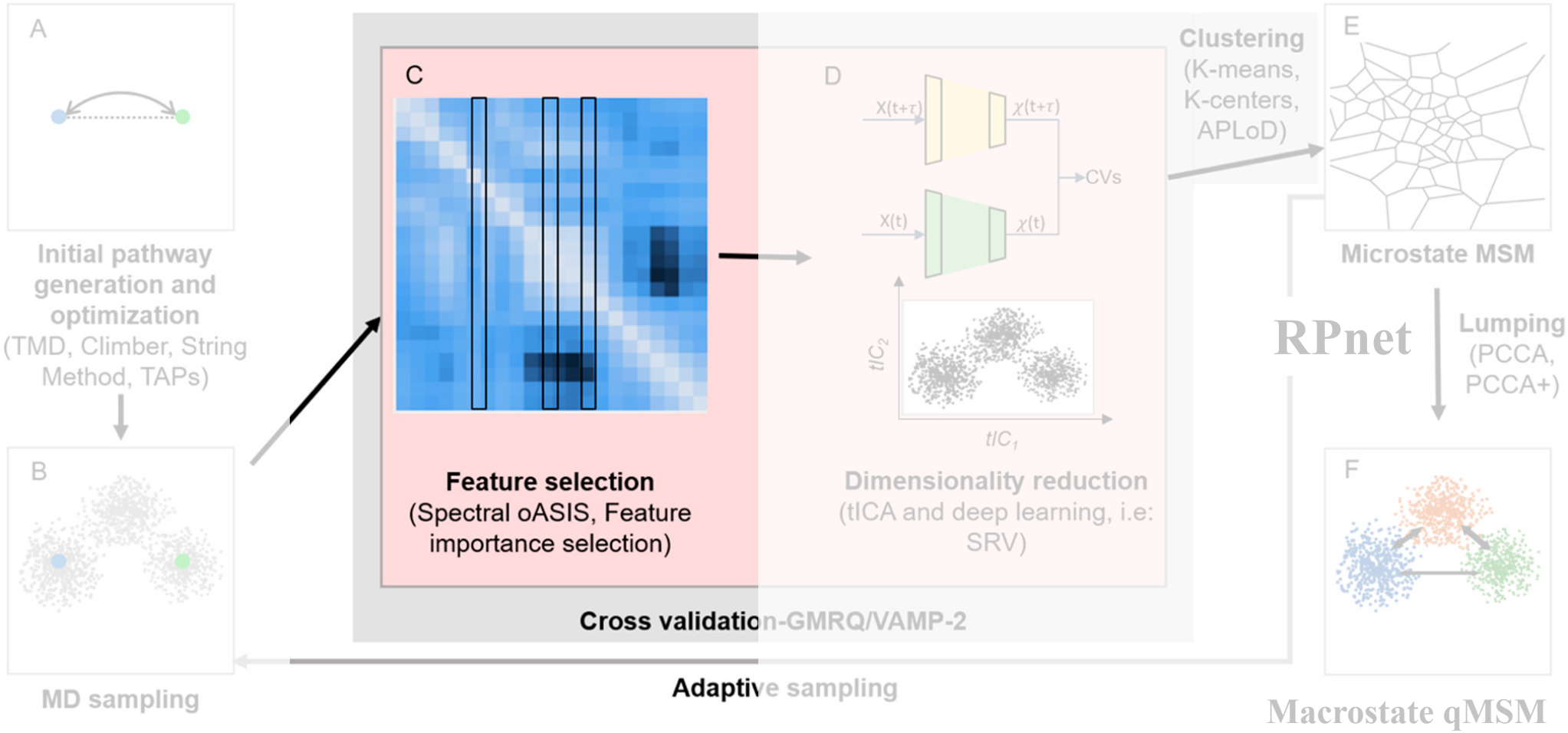
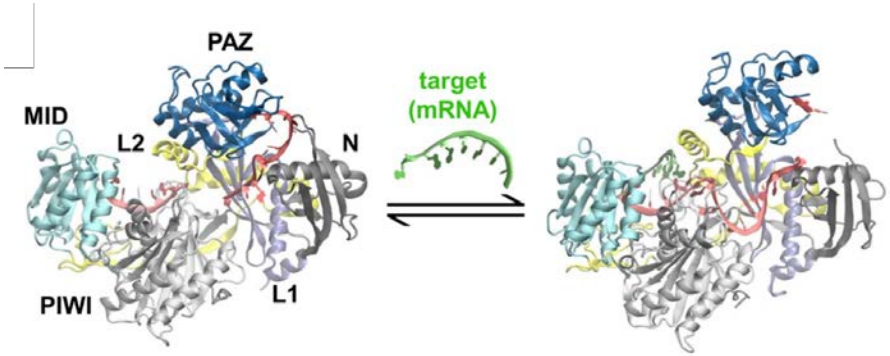


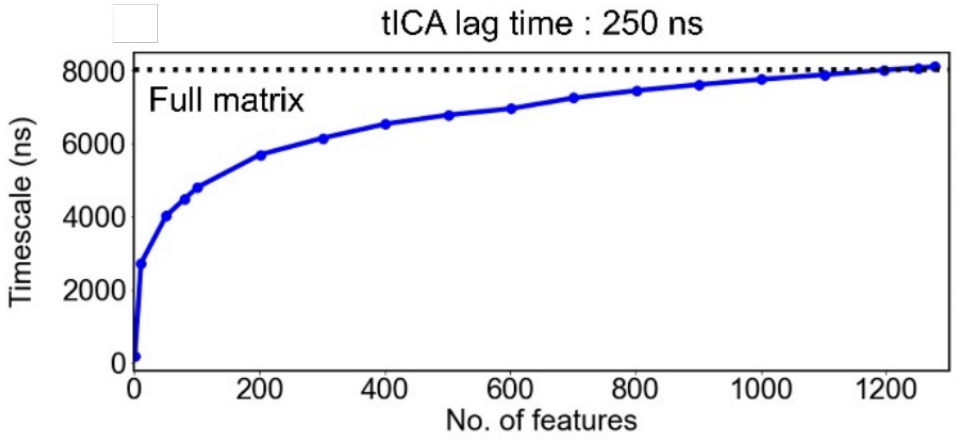
306 200-ns MD simulations

System size: 543K atoms

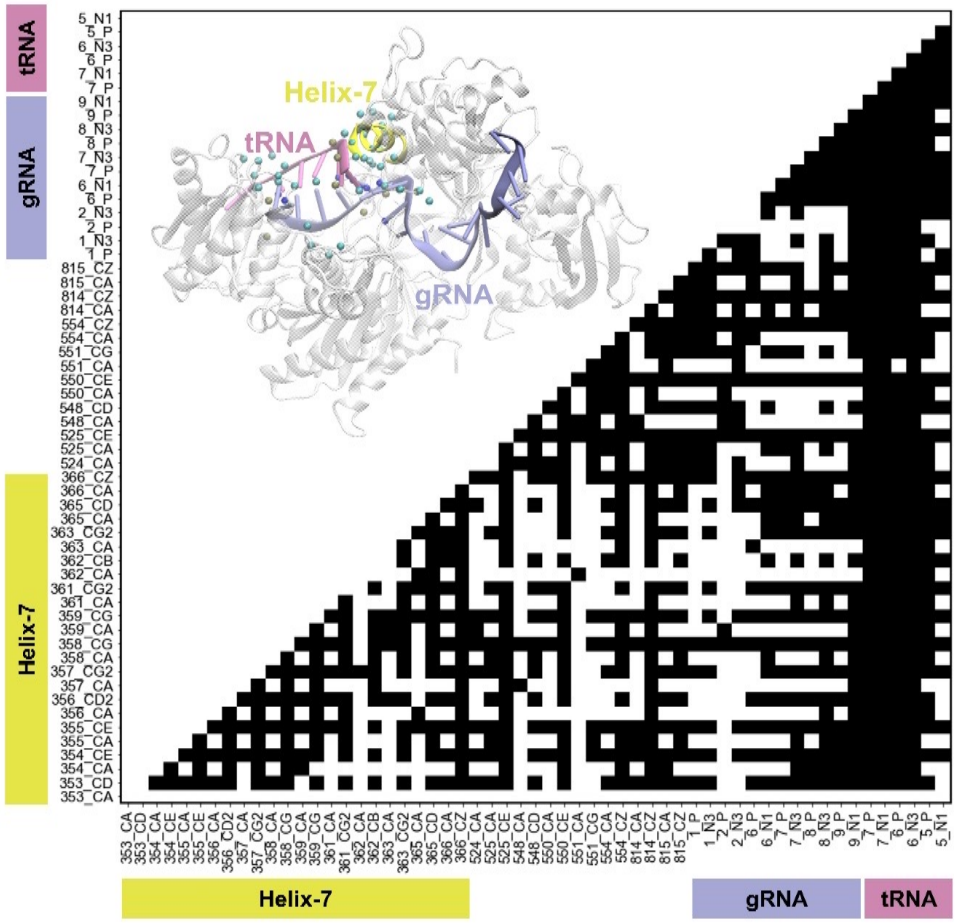
Automatic Selection of Features that can Describe Protein Conformational Changes



microRNA target recognition by
RNA induced silencing complex



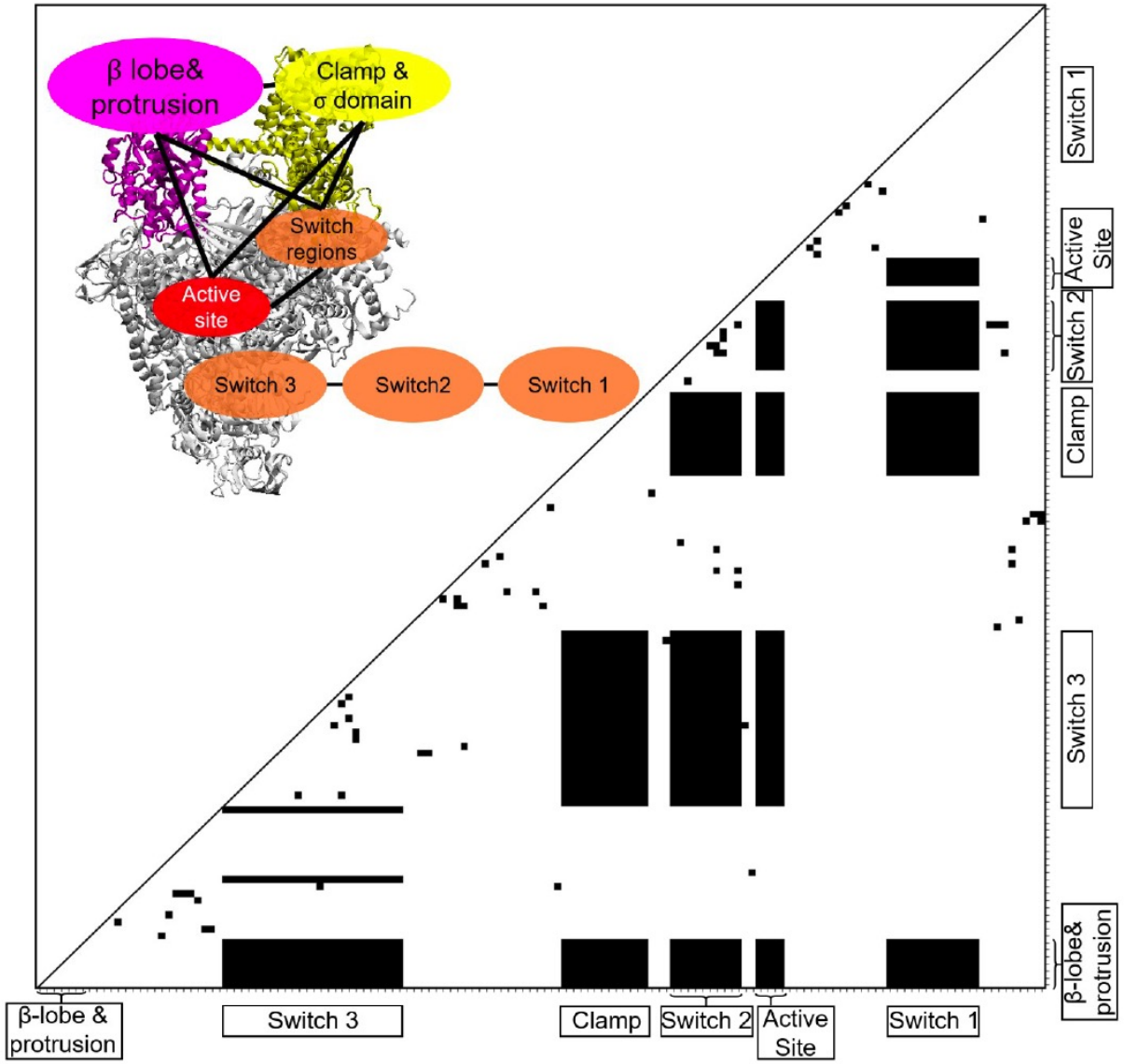
Spectral oASIS*: JCTC*, 14, 2771, (2018).



Spectral oASIS to choose 1,000
residue-residue distance features

Communications Biology 4 (1), 1345, (2021)

Automatic Selection of Features that can Describe Protein Conformational Changes



We selected 1770 residue-residue pairwise distances that can best describe the RNAP gate opening.

Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

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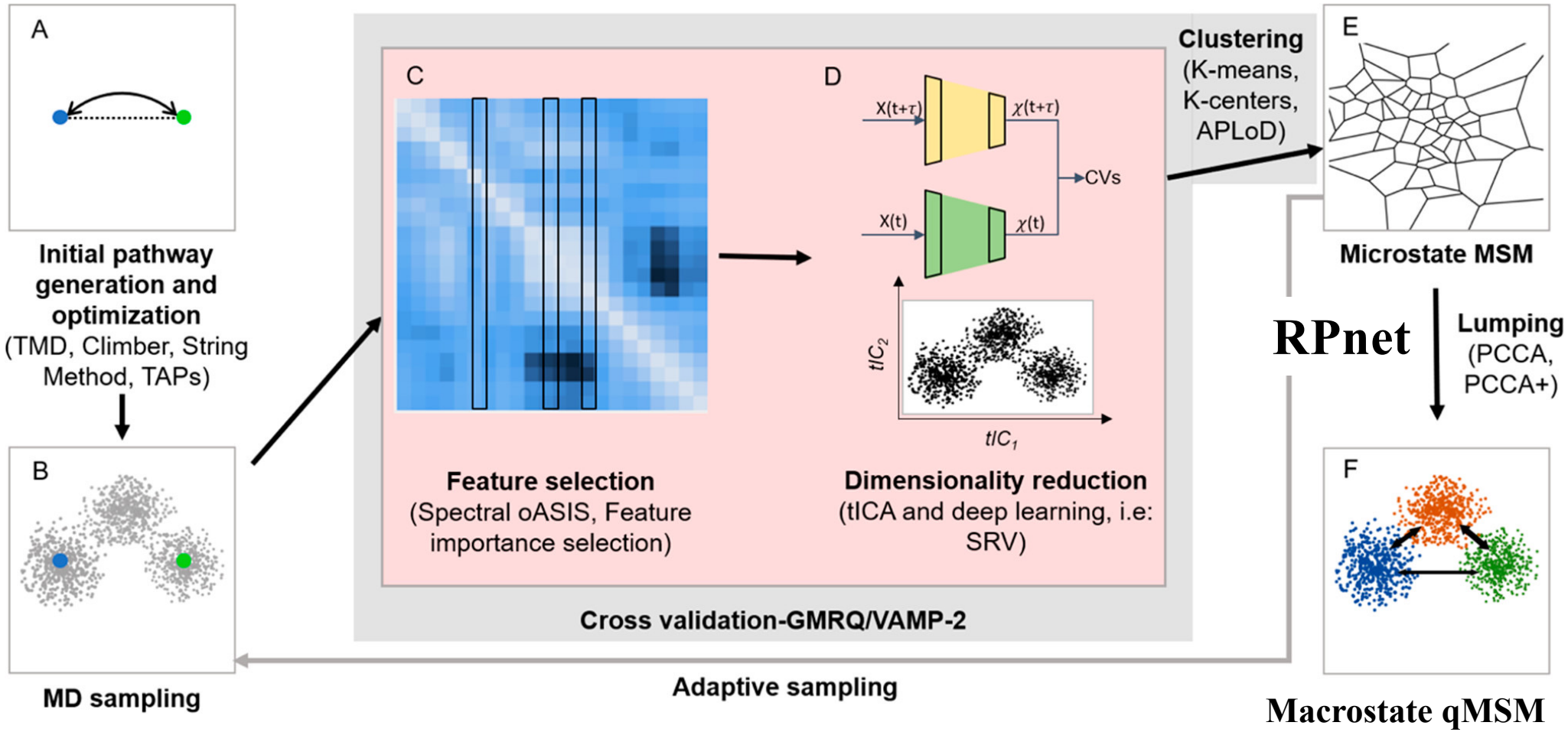
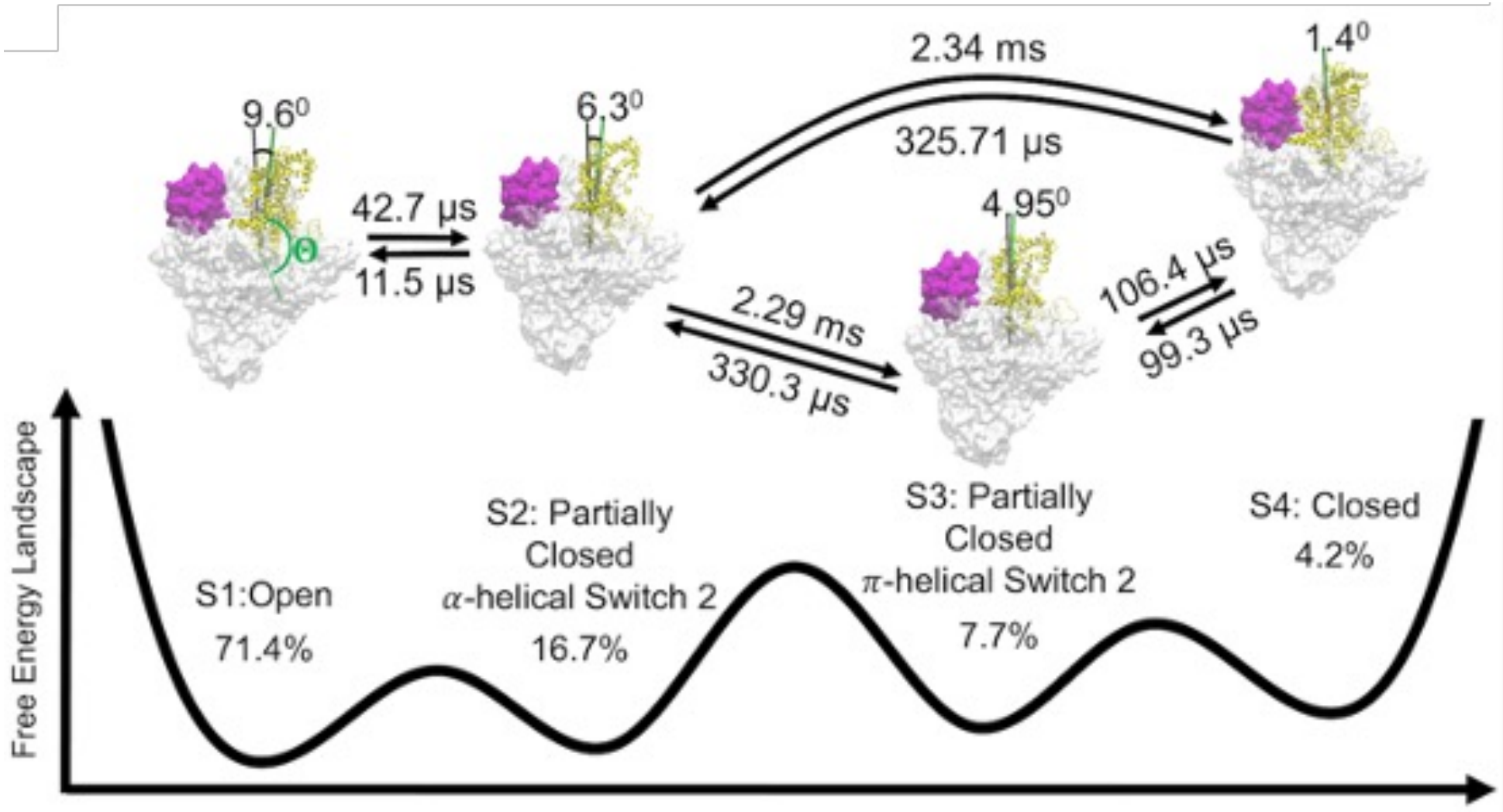


RNAP gate dynamics: a 4-state qMSM model

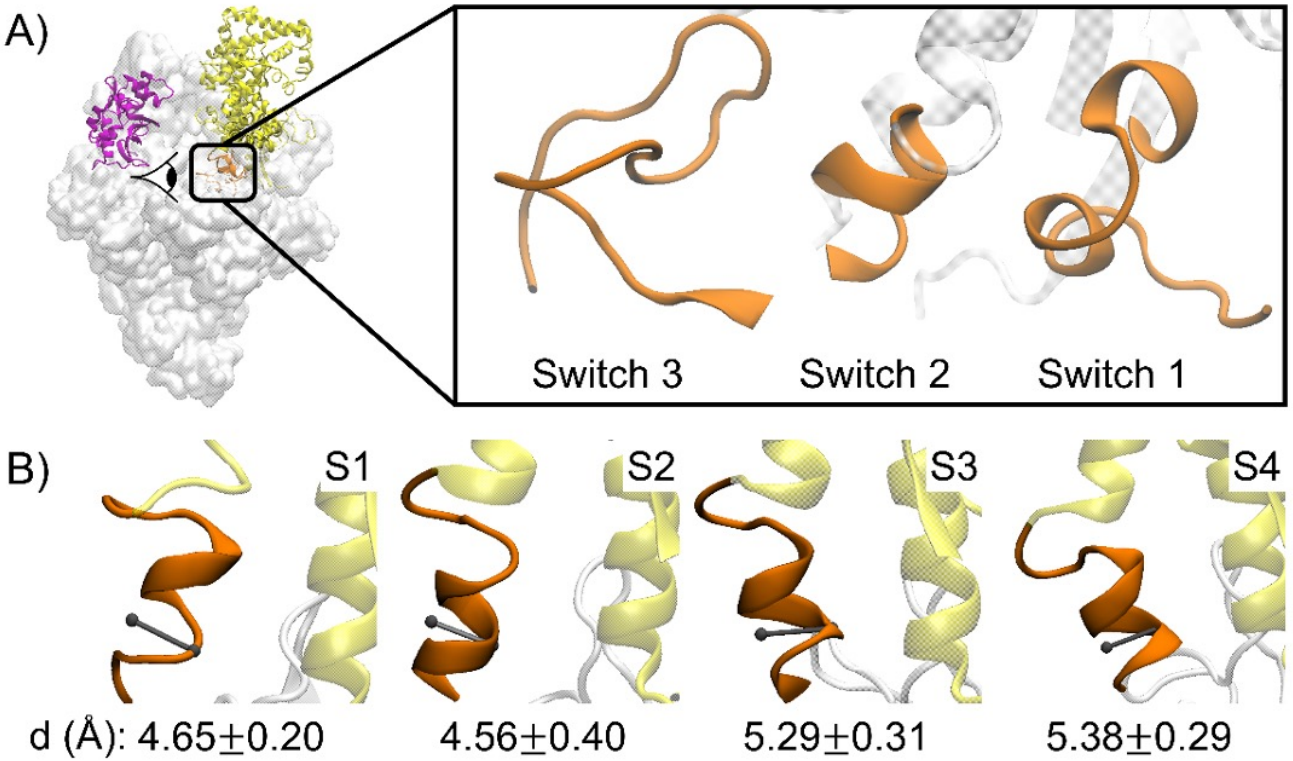
Clamp Closing is Rate-Limiting and Occurs at Milliseconds



Two intermediate states with different conformations of Switch 2.

Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

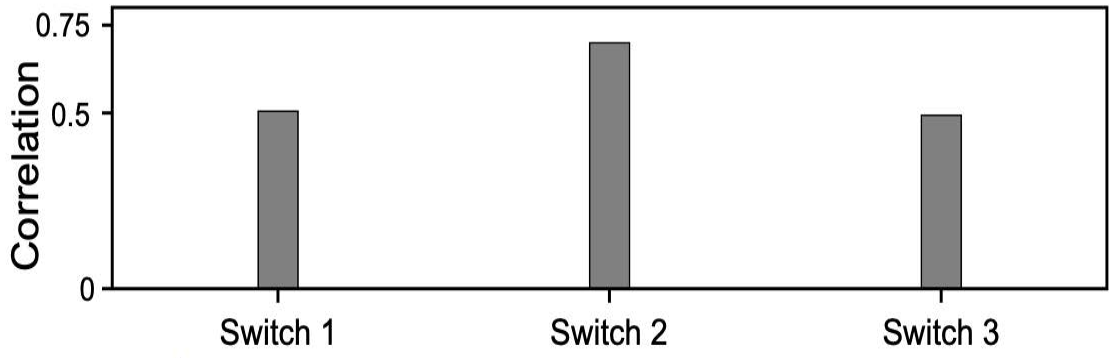
Clamp Closing is Dynamically Correlated with the Swtich-2 Region



Switch-2 conformation:

S1-S2: alpha-helix

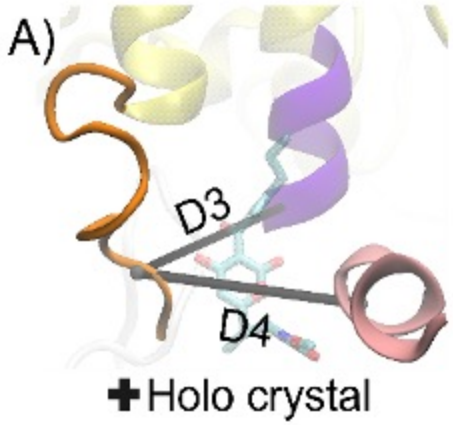
S3-S4: pi-helix

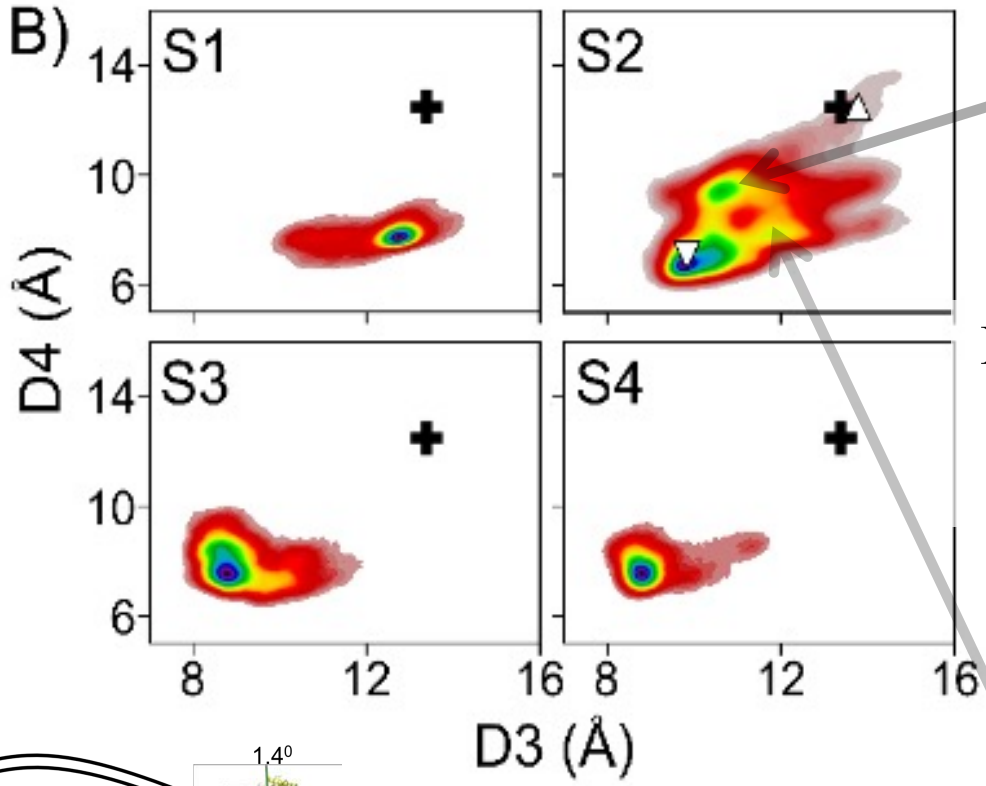


RNAP Clamp-Switch 2 has highest dynamic correlation.

Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

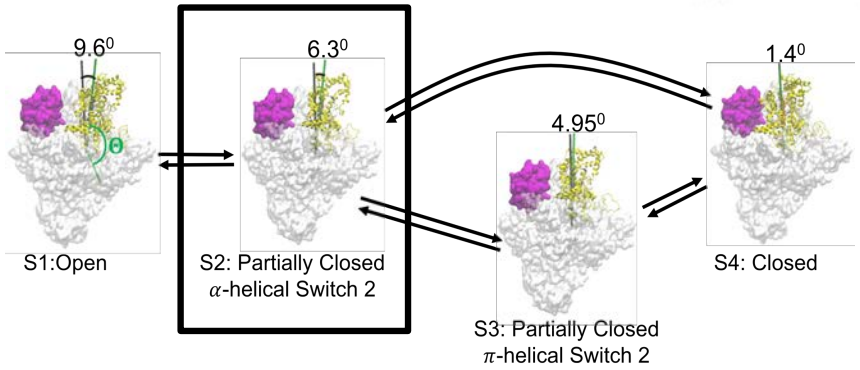
Unfolded Swtich-2 Conformations are Spontaneously Sampled by the Partially Closed Intermediate State





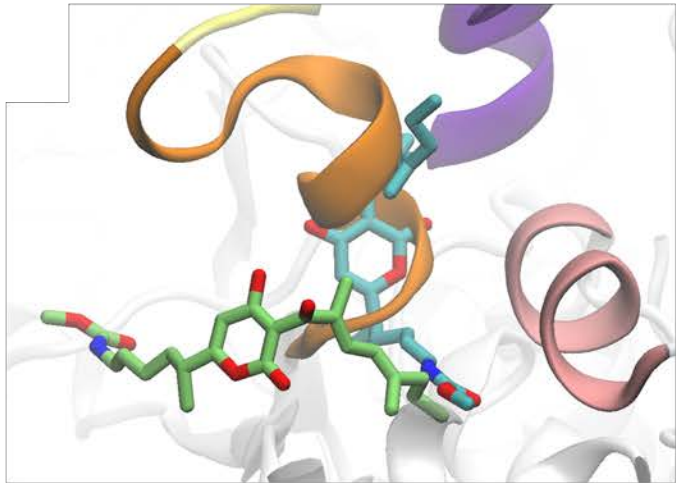
Partially unfolded and detached Switch-2

Unfolded Switch 2

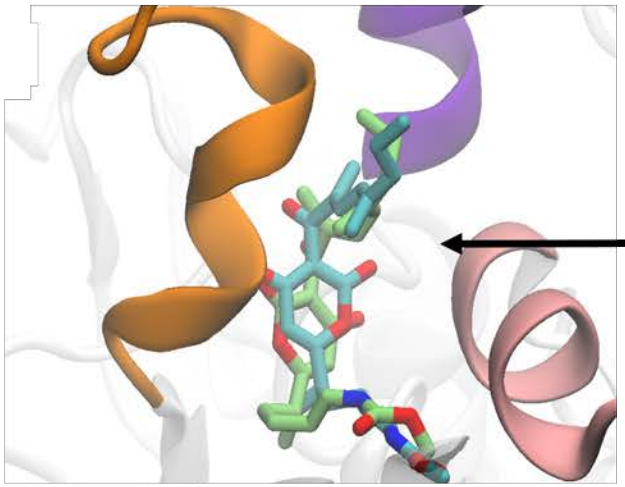


Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

Unfolded Swtich-2 Conformations Allow the Binding of Antibiotics Myx

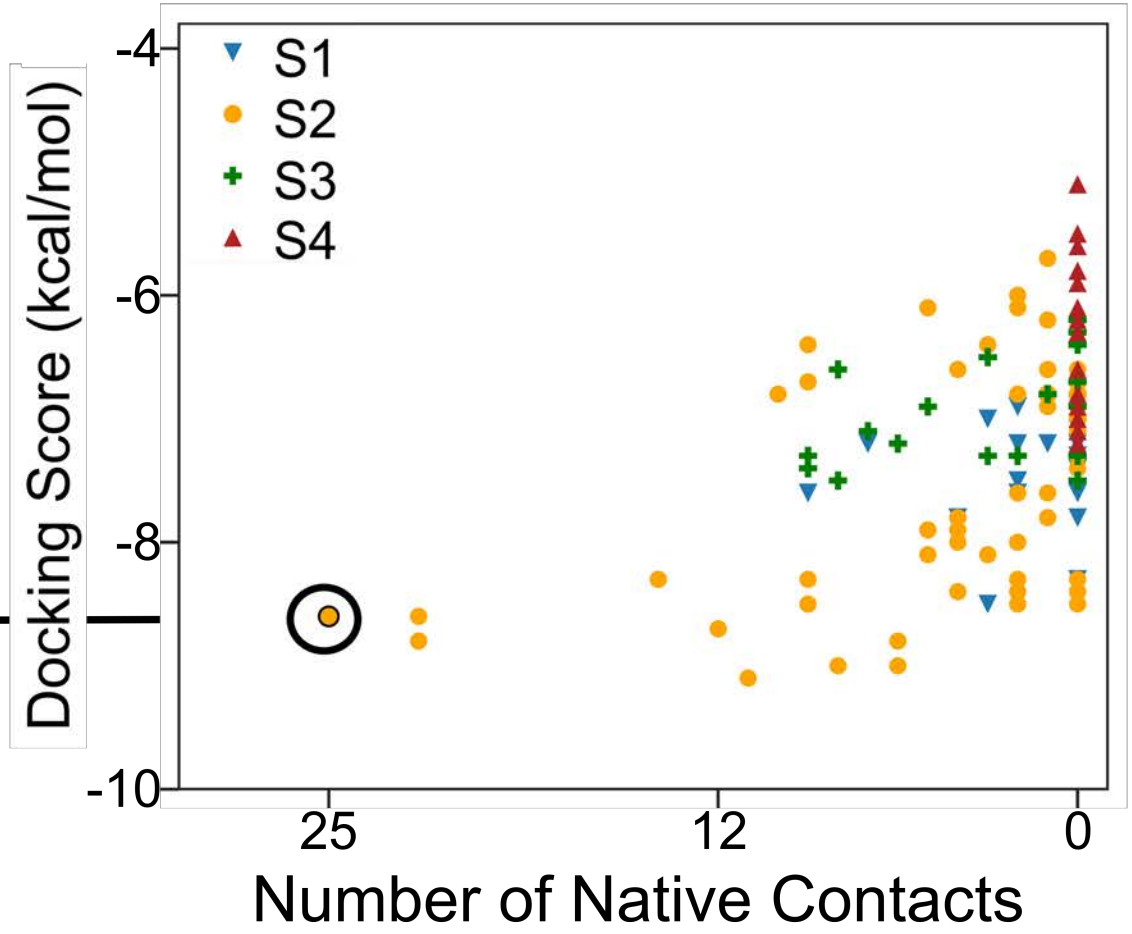


▽Folded



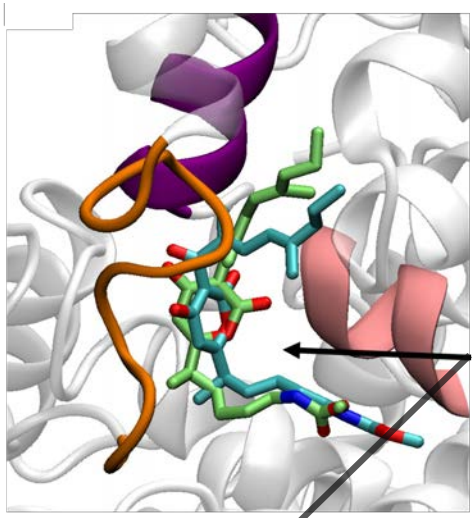
△Detached

Partially unfolded and detached Swtich-2 conformations allow sufficient space for the binding of antibiotics Myx



Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

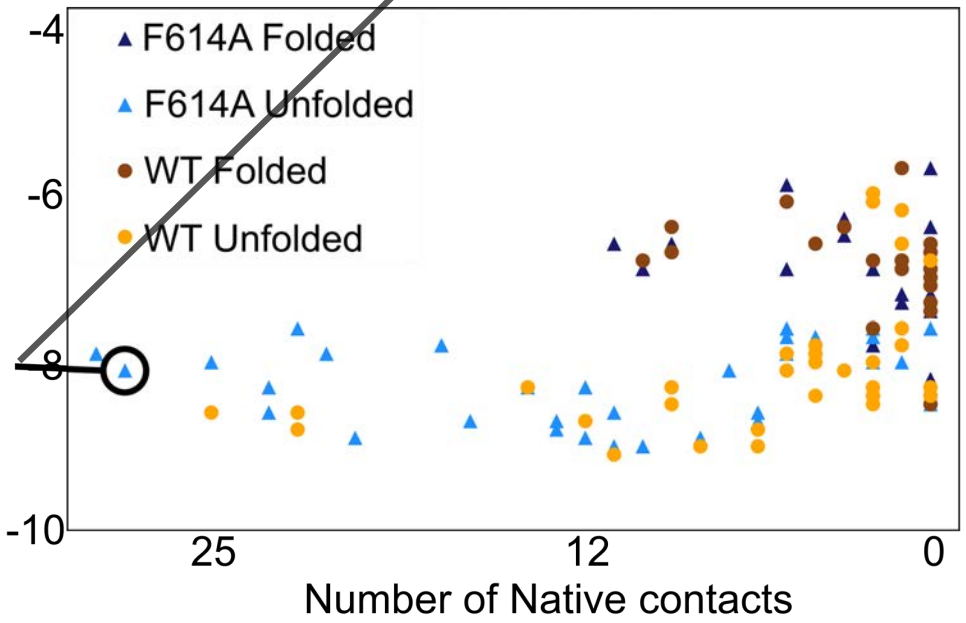
F614A Mutant Causes Hypersensitivity to Myx

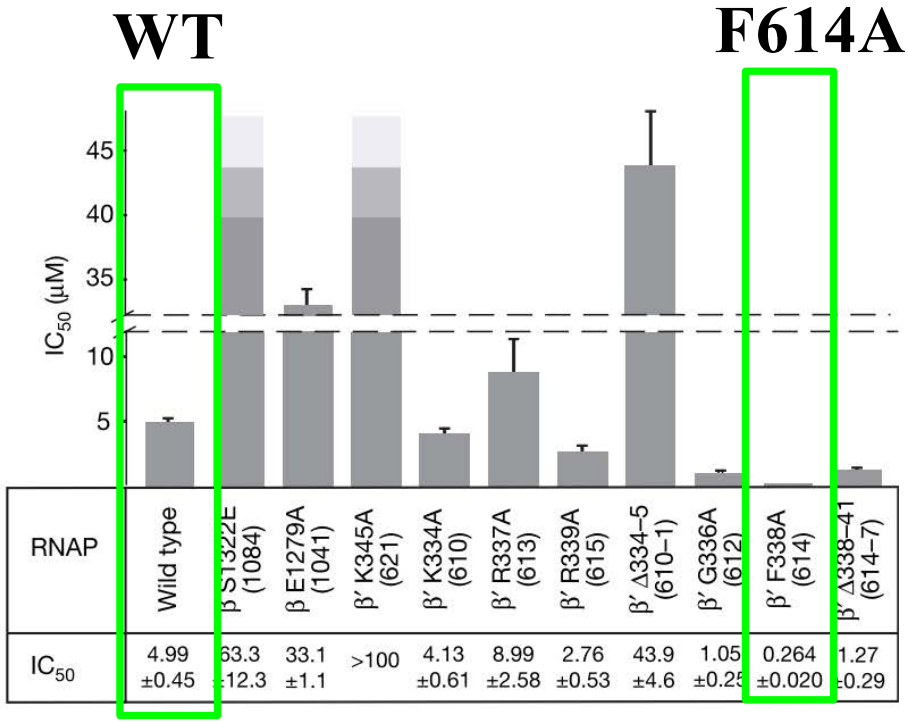


Lime: docking structure to F614A RNAP

Blue: Myx-bound Crystal structure

F614A allows for more favourable binding with Myx by providing more space in the binding pocket

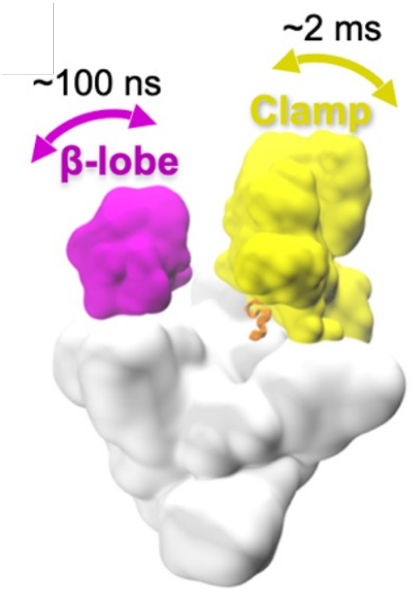


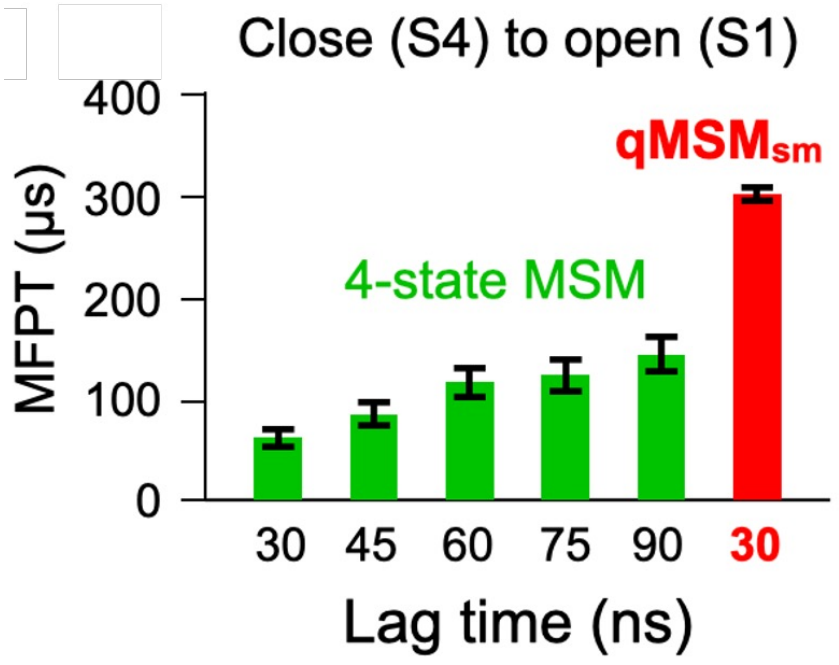


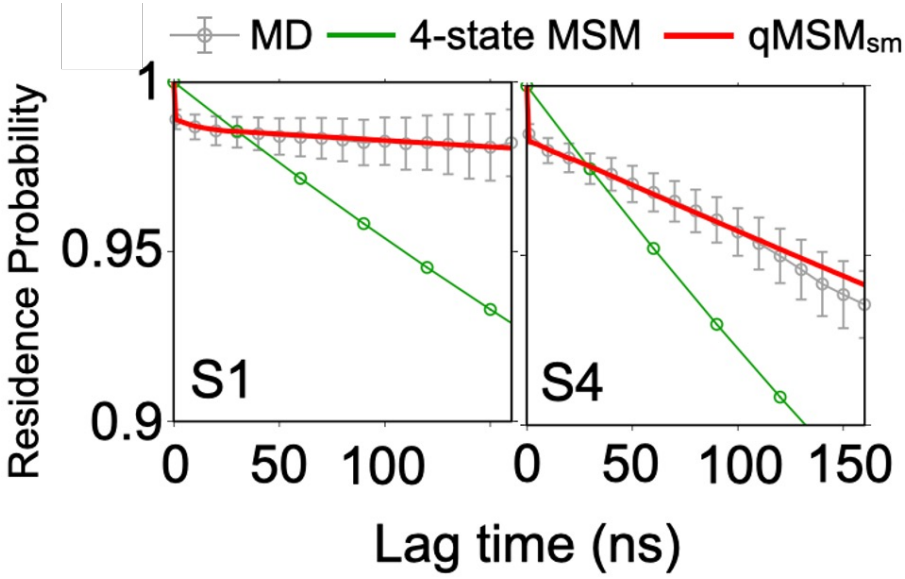
Thermus thermophilus RNAP

Belogurov et al. ***Nature,*** 457:332, (2009)

qMSMs Greatly Outperform MSMs







For MSM, it requires a lag time as long as 2000 ns in order to build a Markovian model (estimated by GME).

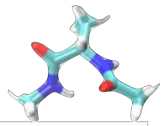
Proc. Nat. Acad. Sci. U.S.A., 118(17), e2024324118, (2021)

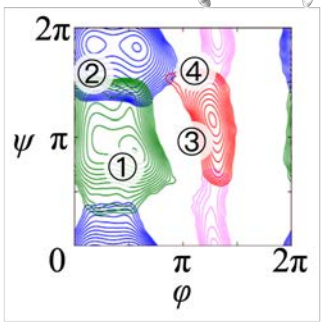
Overcoming the Challenges that still Face GME Models

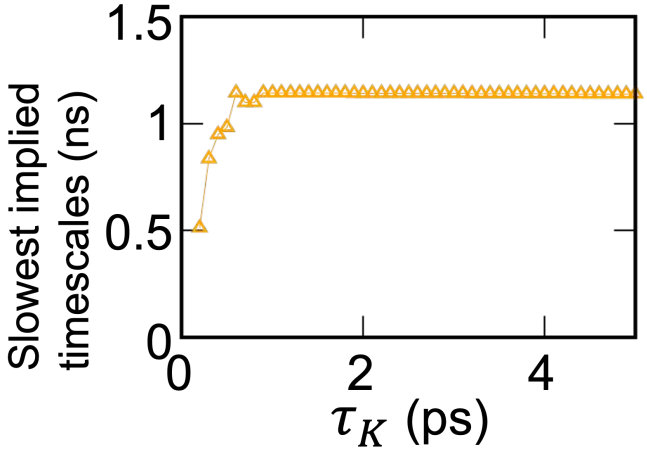
Numerical Instability of Memory Kernels for Complex Systems

qMSM

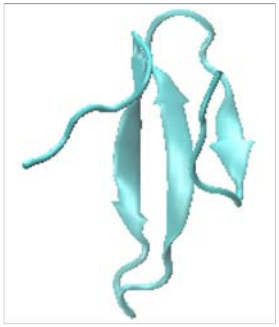
Alanine dipeptide

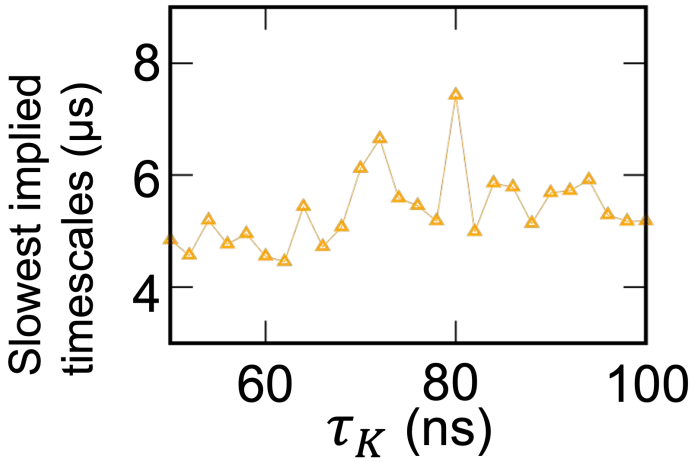




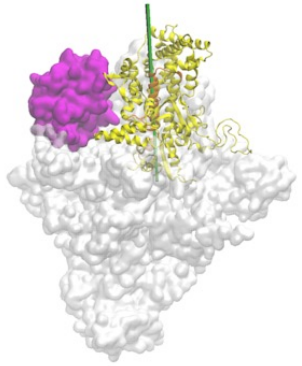


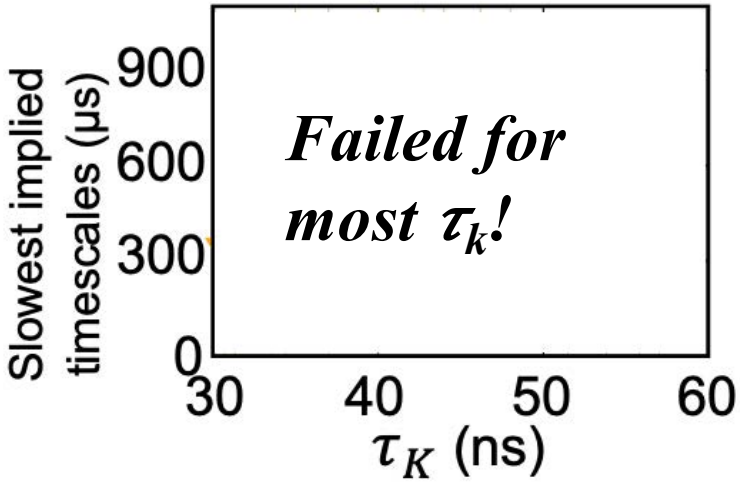
FIP35 WW domain





***Taq* RNAP**

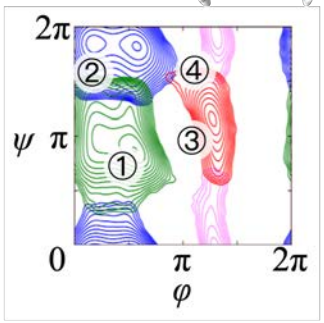


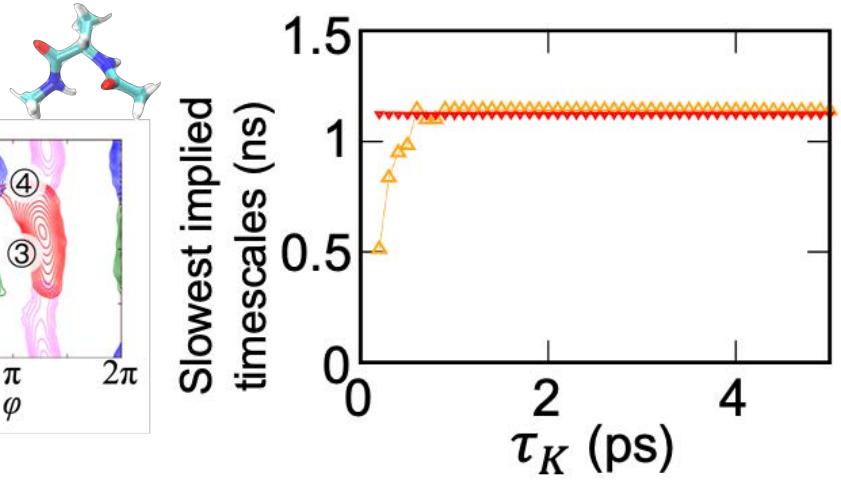


A Smoothing Scheme Improves Numerical Stability of Memory Kernels, but Not Enough!

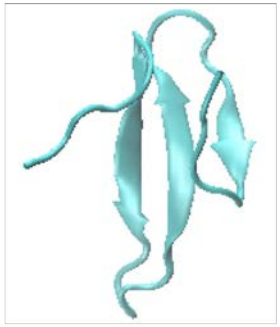
qMSM qMSM$_{sm}$

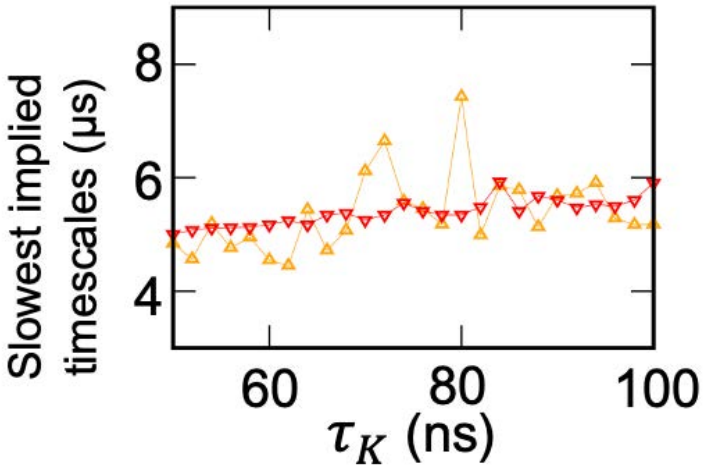
Alanine dipeptide



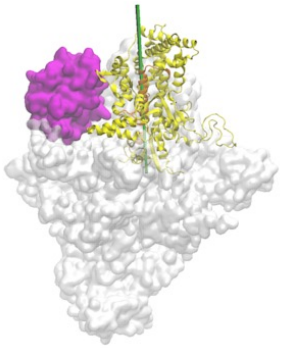


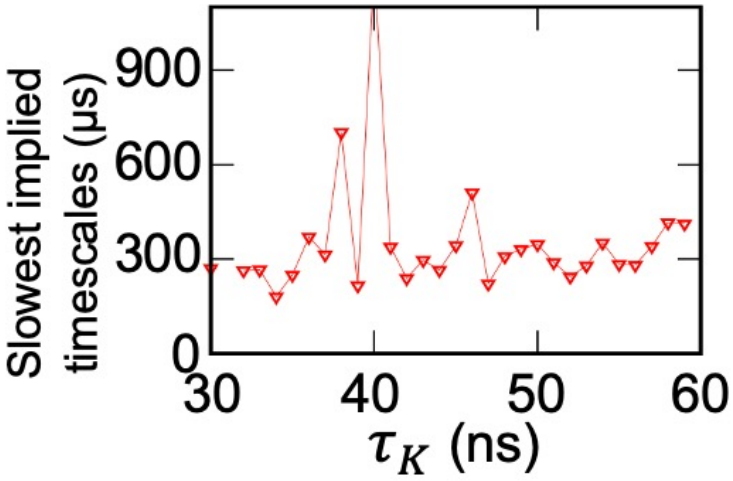
FIP35 WW domain





***Taq* RNAP**



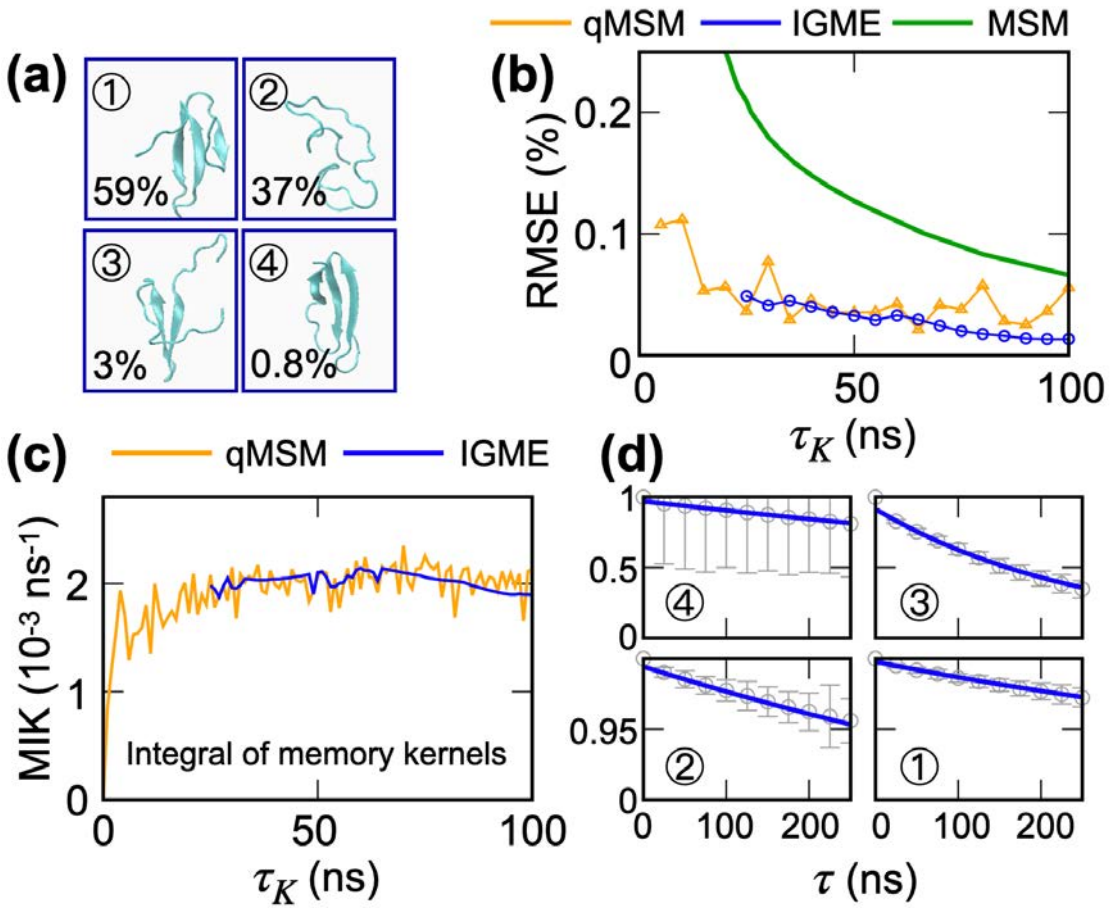


We fit time evolutions of TPM's eigenvalues to multiexponential functions and re-assemble TPMs based on smoothed eigenvalues.

Integrative-GME (IGME) Method

Taylor expansion of the memory term in GME:

$$\frac{d}{dt}\ln T(t) = \dot{T}(0) - M_0(t) - \left(T(t)^{-1} \sum_{m=1}^{n} \frac{(-1)^m}{m!} \frac{d^m}{dt^m} T(t) \right) M_m(t)$$



Integrals of memory:

$$M_m(t) = \int_0^t K(s) s^m ds$$

We solve this equation self-consistently.

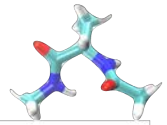
IGME substantially outperforms qMSM in yielding stable estimations of dynamics!

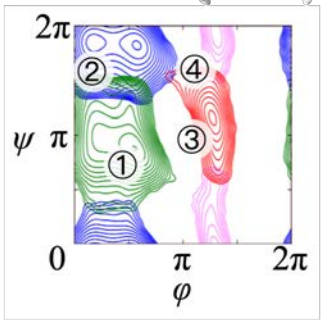
"Integrative Generalized Master Equation", ***Chemrxiv***: *DOI: 10.26434/chemrxiv-2022-0n9ld-v2*

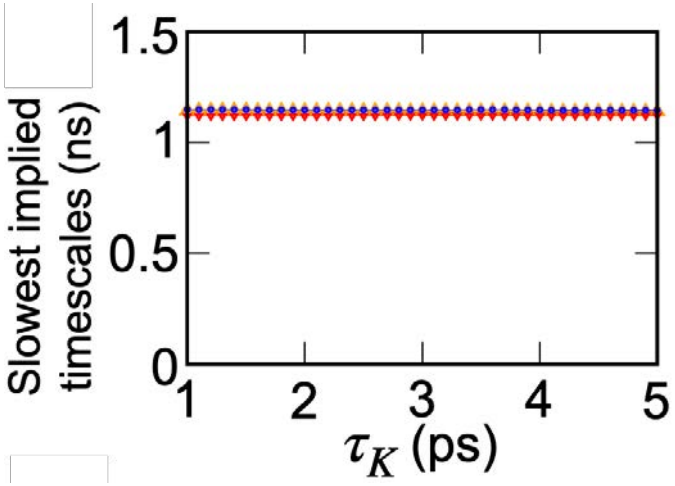
Integrative-GME (IGME) Models are Stable

qMSM qMSM$_{sm}$ IGME

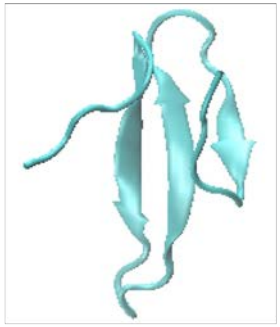
Alanine dipeptide

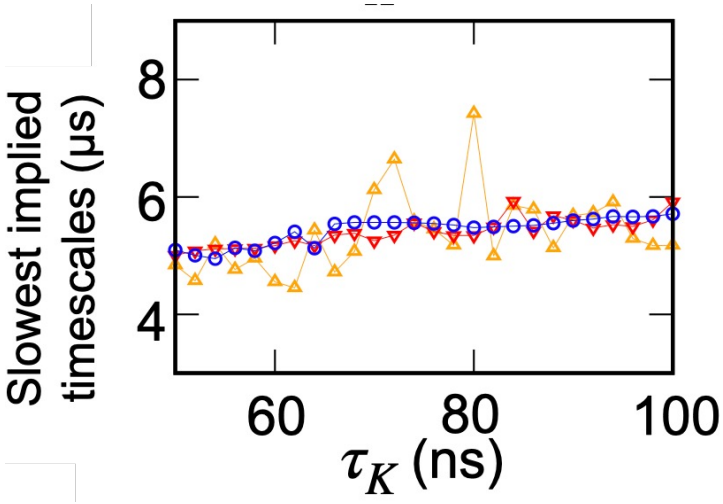




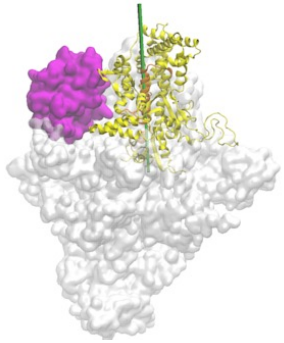


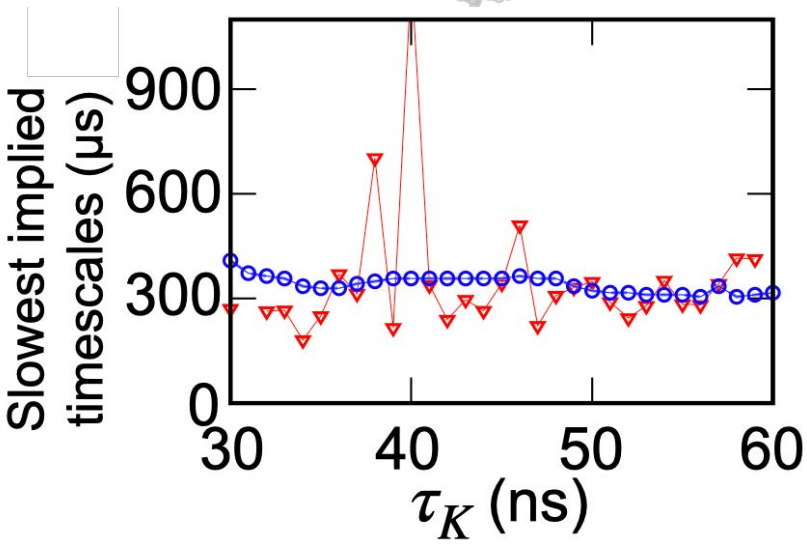
FIP35 WW domain





***Taq* RNAP**





IGME provides a numerically robust way to propagate the GME because it only considers the integrals of the memory kernels.

"Integrative Generalized Master Equation", ***Chemrxiv***: *DOI: 10.26434/chemrxiv-2022-0n9ld-v2*

Integrative Generalized Master Equation: A Theory to Study Long-timescale Biomolecular Dynamics via the Integrals of Memory Kernels

Working Paper

Siqin Cao University of Wisconsin–Madison,
Yunrui Qiu University of Wisconsin–Madison,
Michael Kalin University of Wisconsin–Madison,
Xuhui Huang University of Wisconsin–Madison

Abstract

The generalized master equation (GME) provides a powerful approach to study biomolecular dynamics via non-Markovian dynamic models built from molecular dynamics (MD) simulations. Previously, we have implemented the GME for biomolecular dynamics, namely the quasi Markov State Model (qMSM), where we explicitly calculate the memory kernel and propagate protein dynamics using a discretized GME. qMSM can be constructed with much shorter MD simulation trajectories than the Markov State Model (MSM). However, since qMSM needs to explicitly compute the time-dependent memory kernels, it is heavily affected by the

IGME: https://github.com/xuhuihuang/IGME

Acknowledgement

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Lizhe Zhu (CUHK)

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UNIVERSITY OF WISCONSIN–MADISON

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