Thermodynamic Characterization of Conformational Landscape in Proton-Coupled Oligopeptide Transporters

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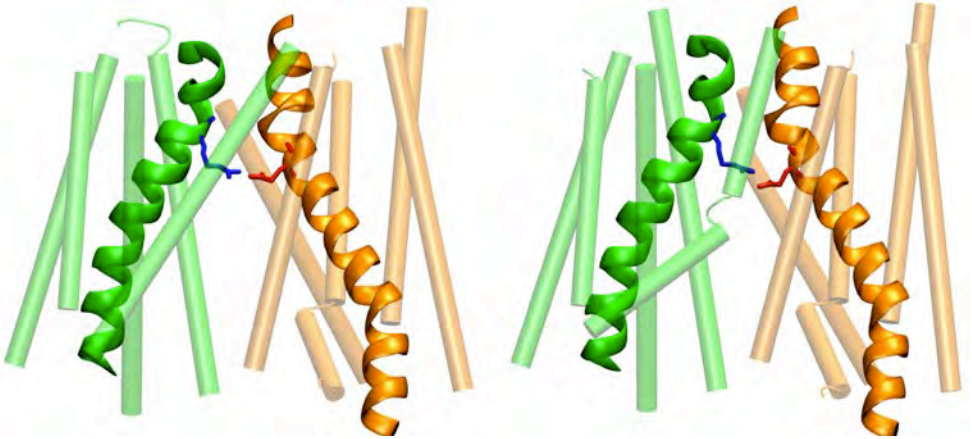

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Sunriver, OR
June 5, 2018

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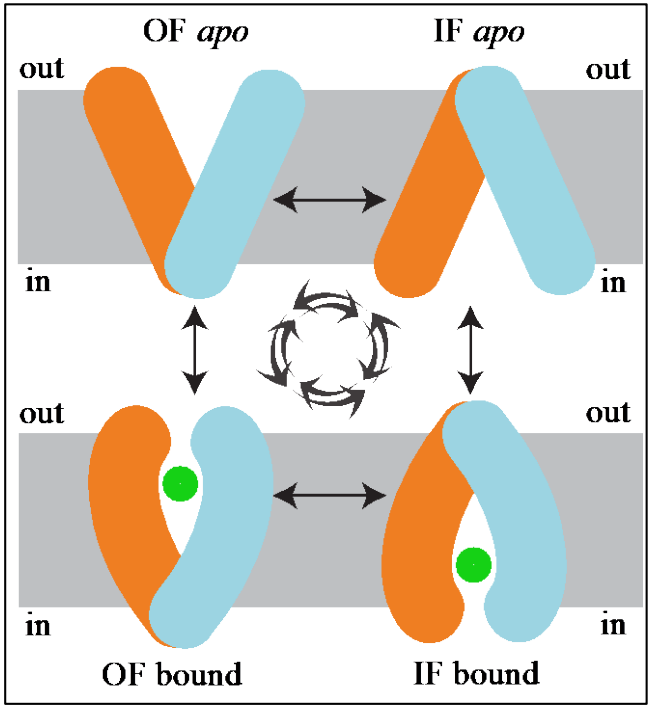
Outline

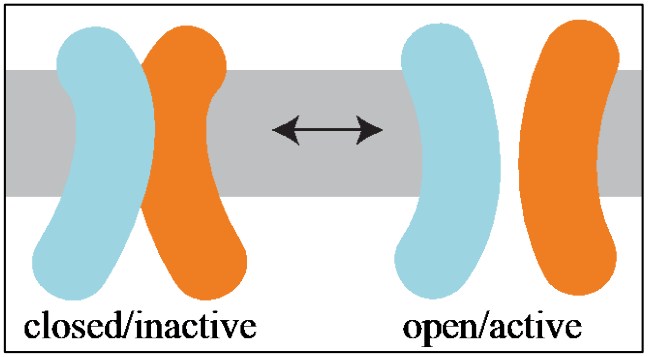
- **Introduction**
  - Large-scale protein conformational changes
- **Methodology**
  - Path-finding algorithms and free energy calculation methods
- **Theoretical Framework**
  - Effective Riemannian diffusion model
- **Applications**
  - Membrane transport proteins

Large-Scale Conformational Changes in Membrane Transport Proteins

- **Membrane transporters** rely on large-scale conformational changes between **inward-facing (IF)** and **outward-facing (OF)** states (**alternating access mechanism)**

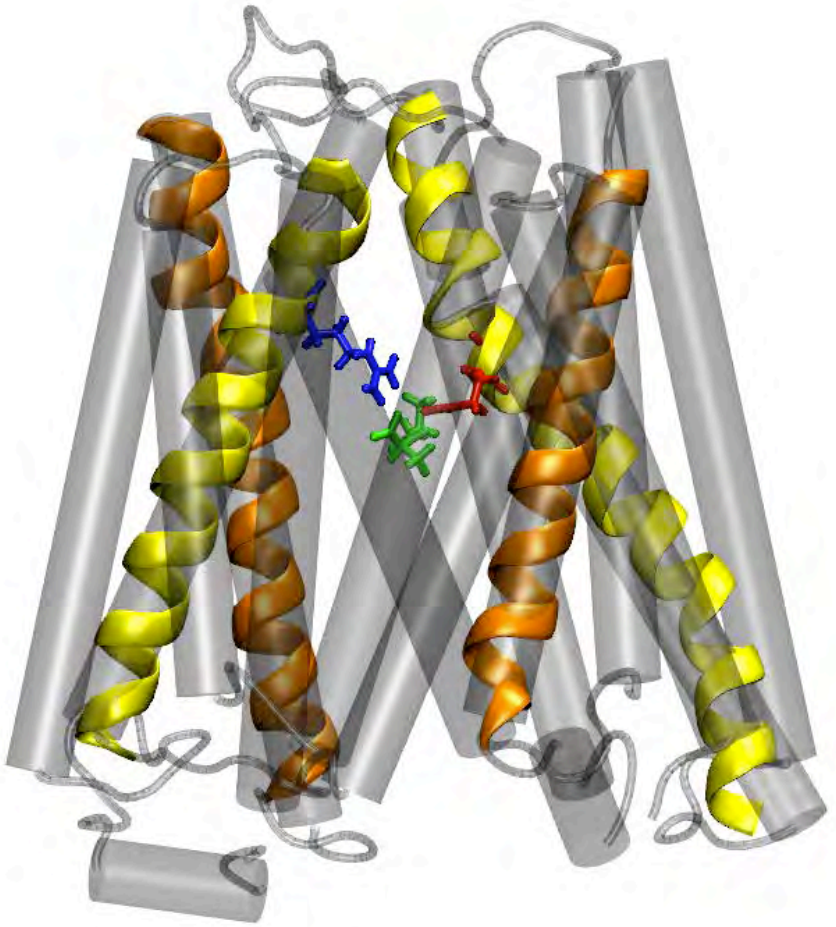


- **Channels** may require large-scale conformational changes between their **open/active** and **closed/inactive** states.



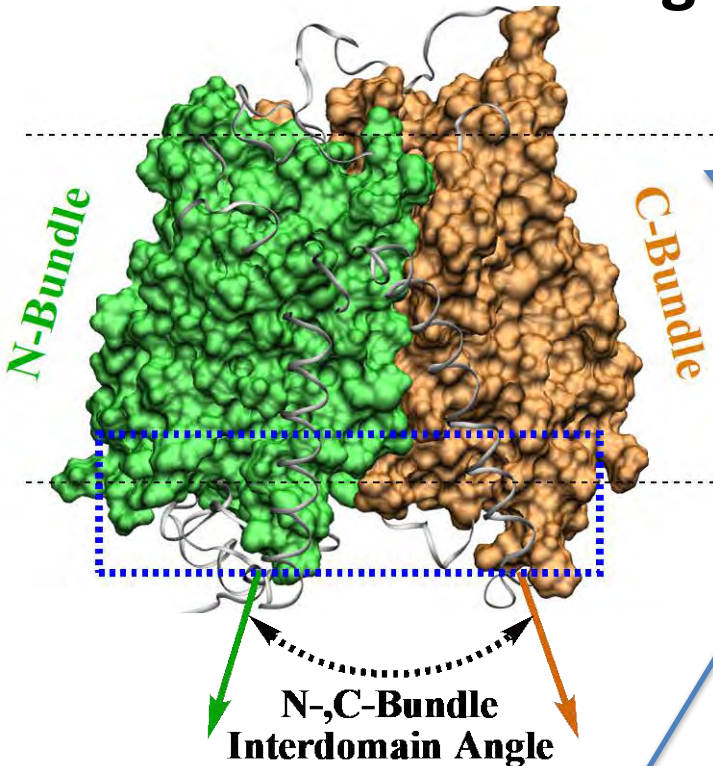
A Case Study:
Proton-coupled Oligopeptide Transporters (POTs)

GkPOT (PDB:4IKV, 1.9 Å)
~100,000 atoms
Conventional unbiased simulations performed:
8 conditions (protonated/unprotonate, different substrates)
× **400 ns**
× **2 repeats**

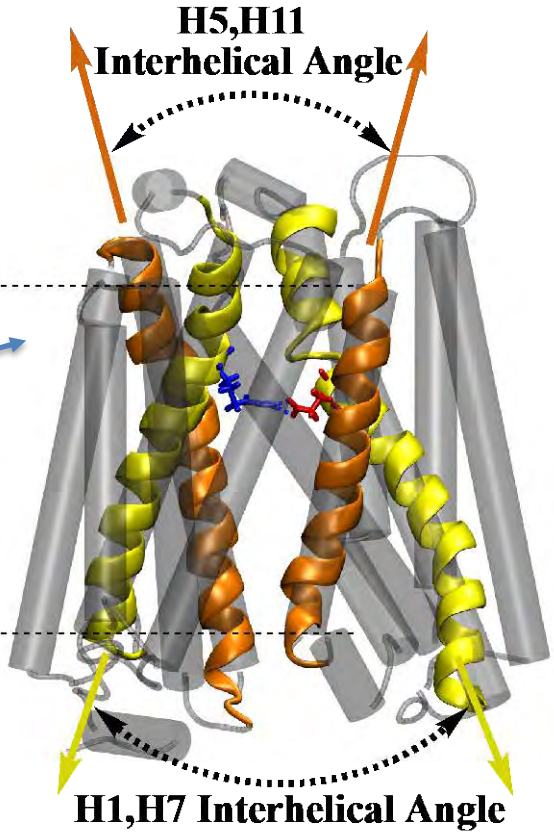


K Immadisetty, J Hettige, and M Moradi, ***What Can and Cannot Be Learned from Molecular Dynamics Simulations of Bacterial Proton-Coupled Oligopeptide Transporter GkPOT?*** J. Phys. Chem. B, **121**:3644-3656, 2017.

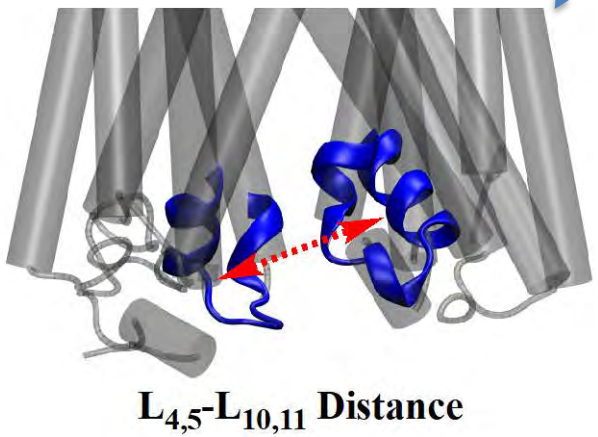
Monitoring Global and Local Conformational Changes

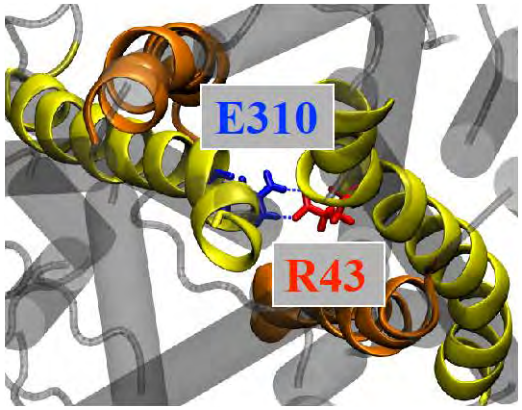


Global

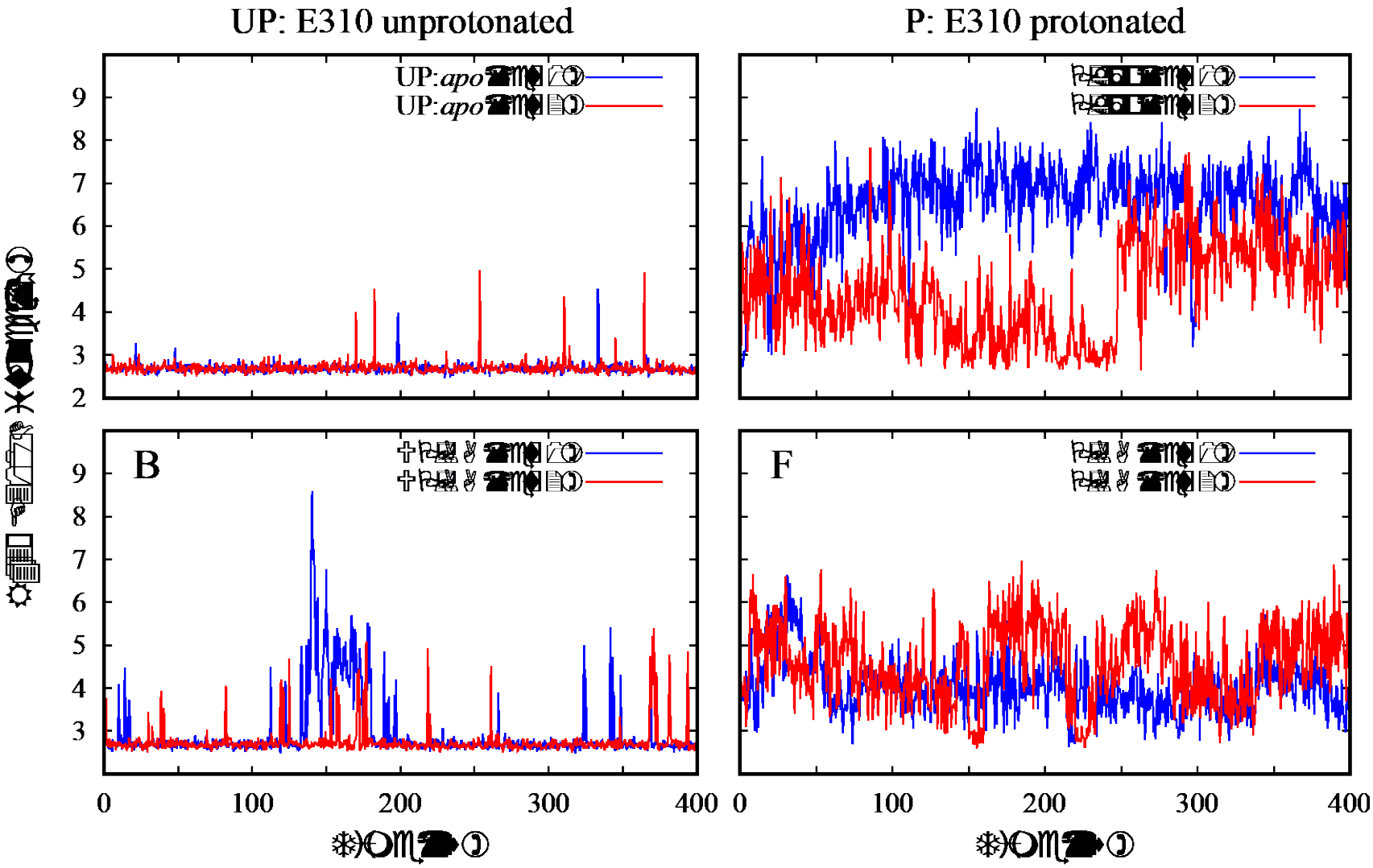


Local
(Salt Bridge)



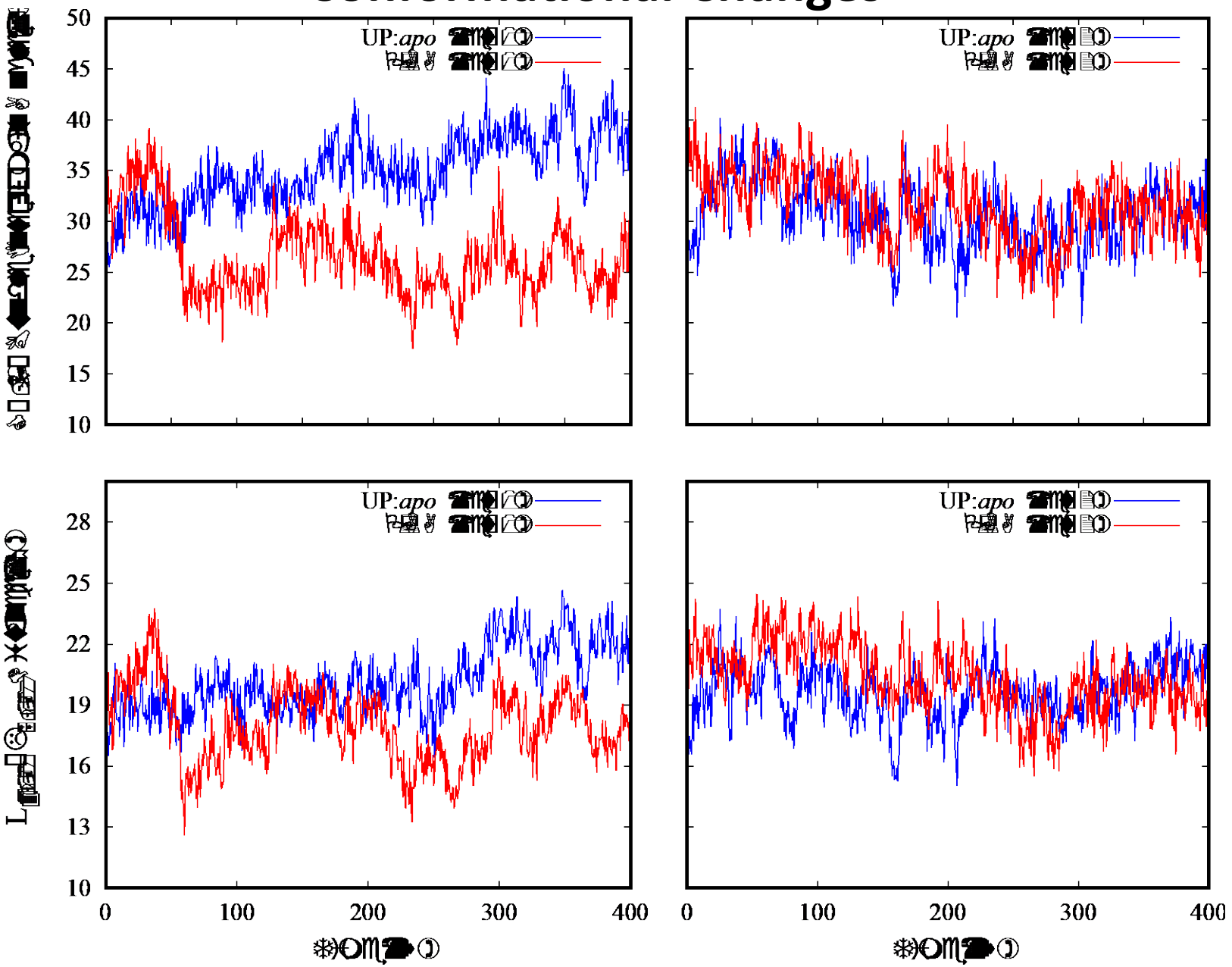


Local Conformational Changes

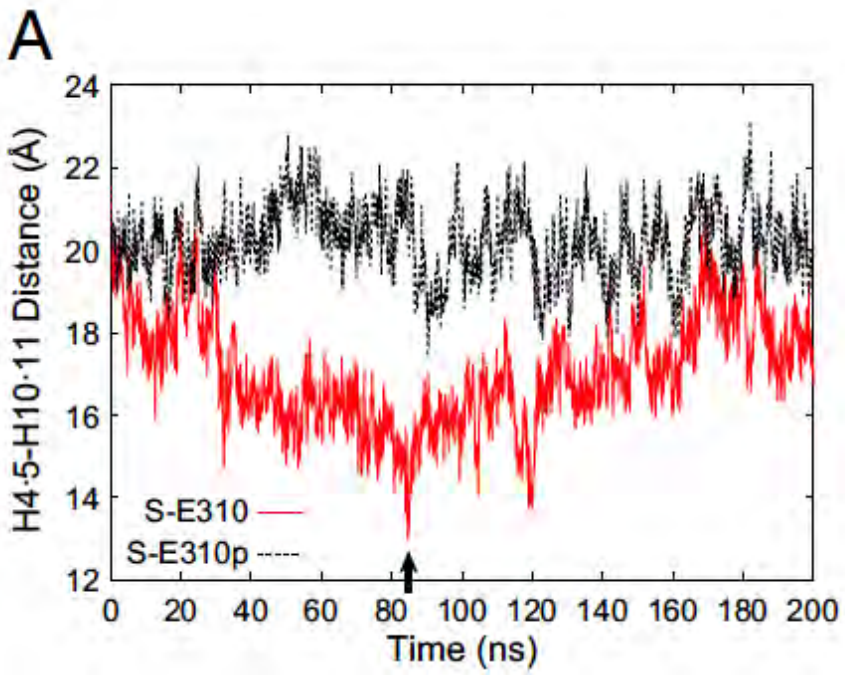


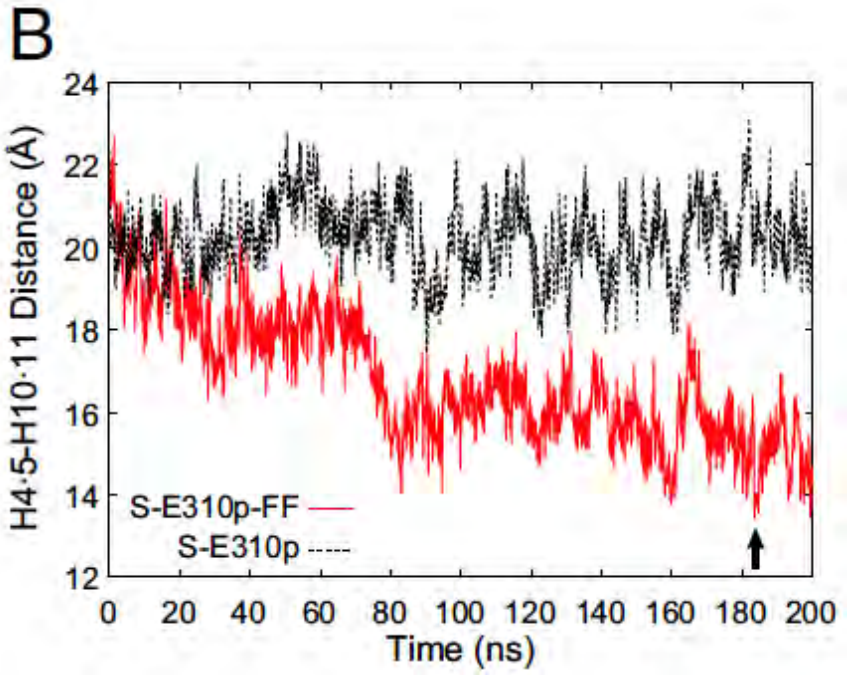
There is a clear distinction between different conditions.

Global Conformational Changes



Global Conformational Changes

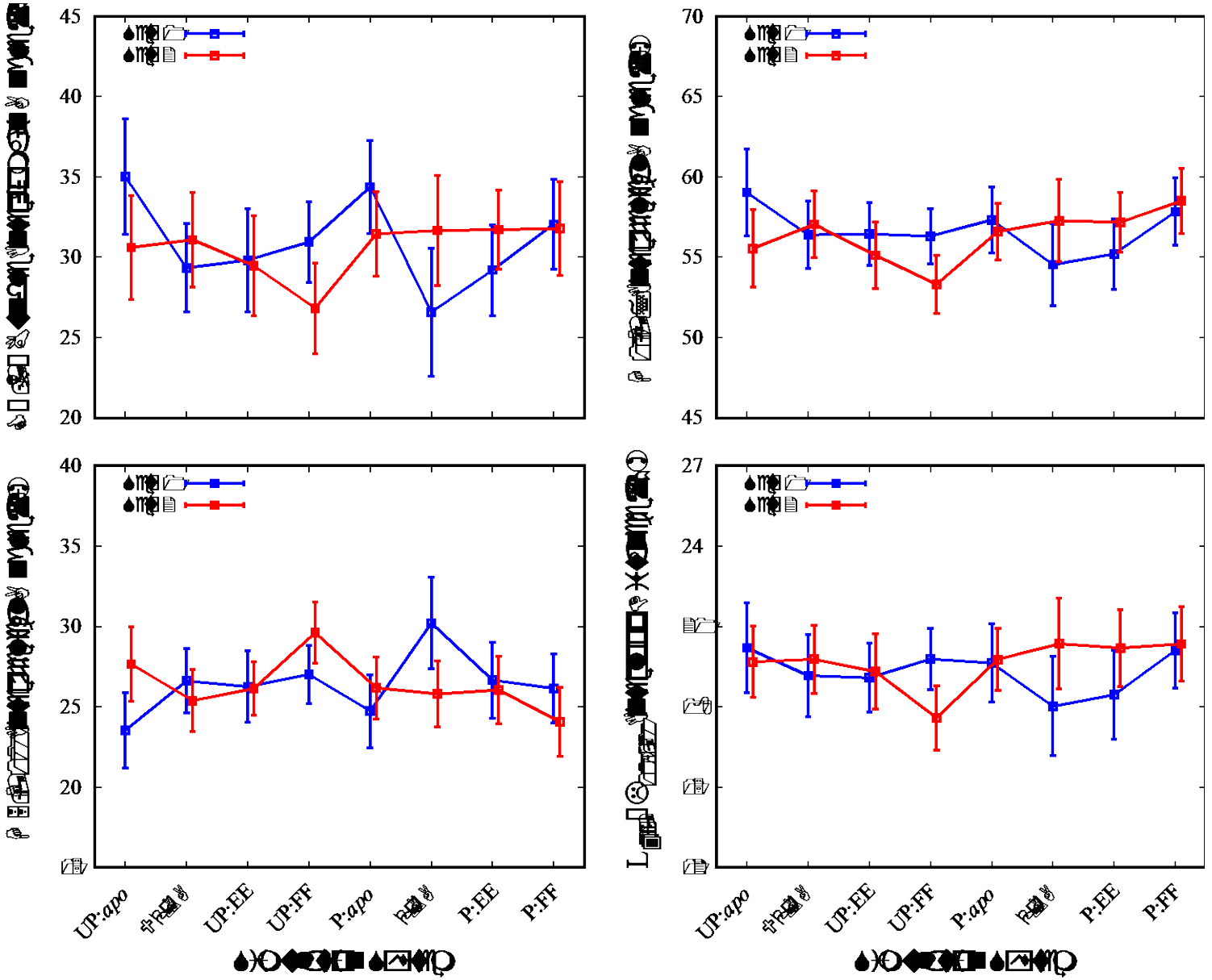




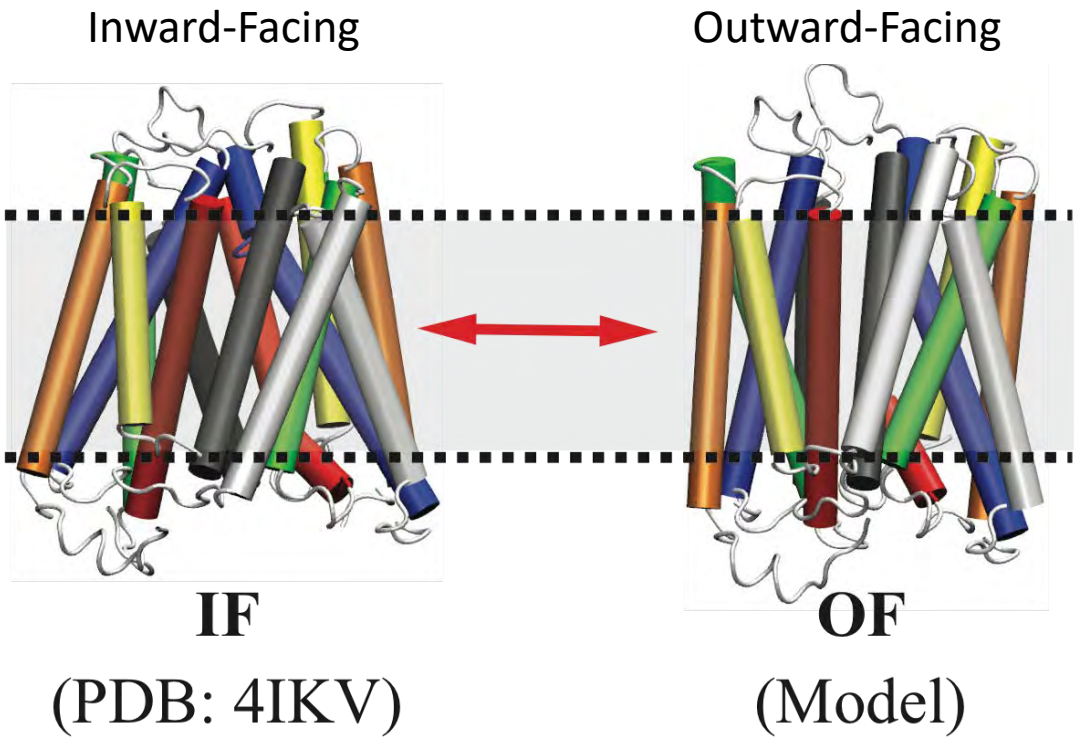
"Structural basis for dynamic mechanism of proton-coupled symport by the peptide transporter POT." **PNAS 2013** | vol. 110 | no. 28 | 11343–11348.

Although a common practice, statements made about millisecond-level biomolecular events based on sub-microsecond level simulations are not reliable.

Global Conformational Changes

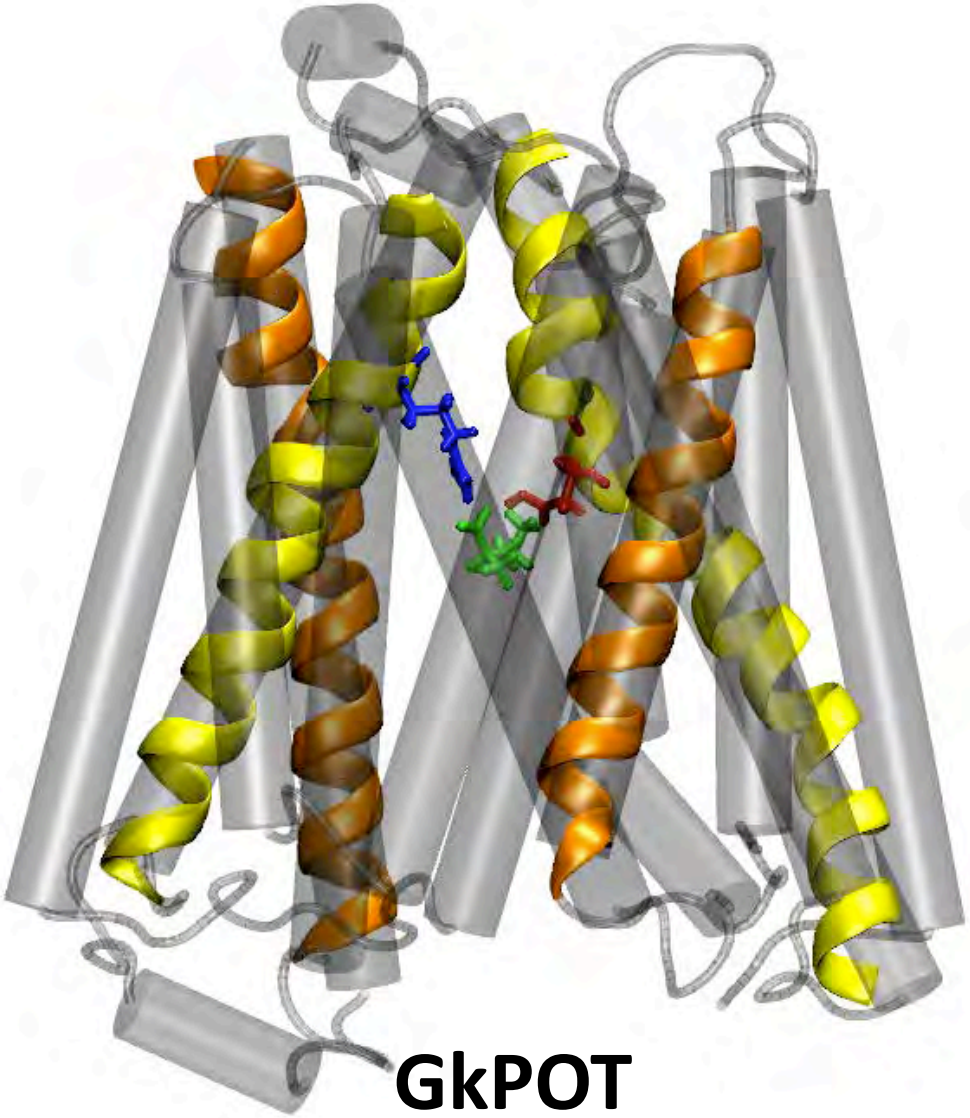


How to study large-scale conformational changes?



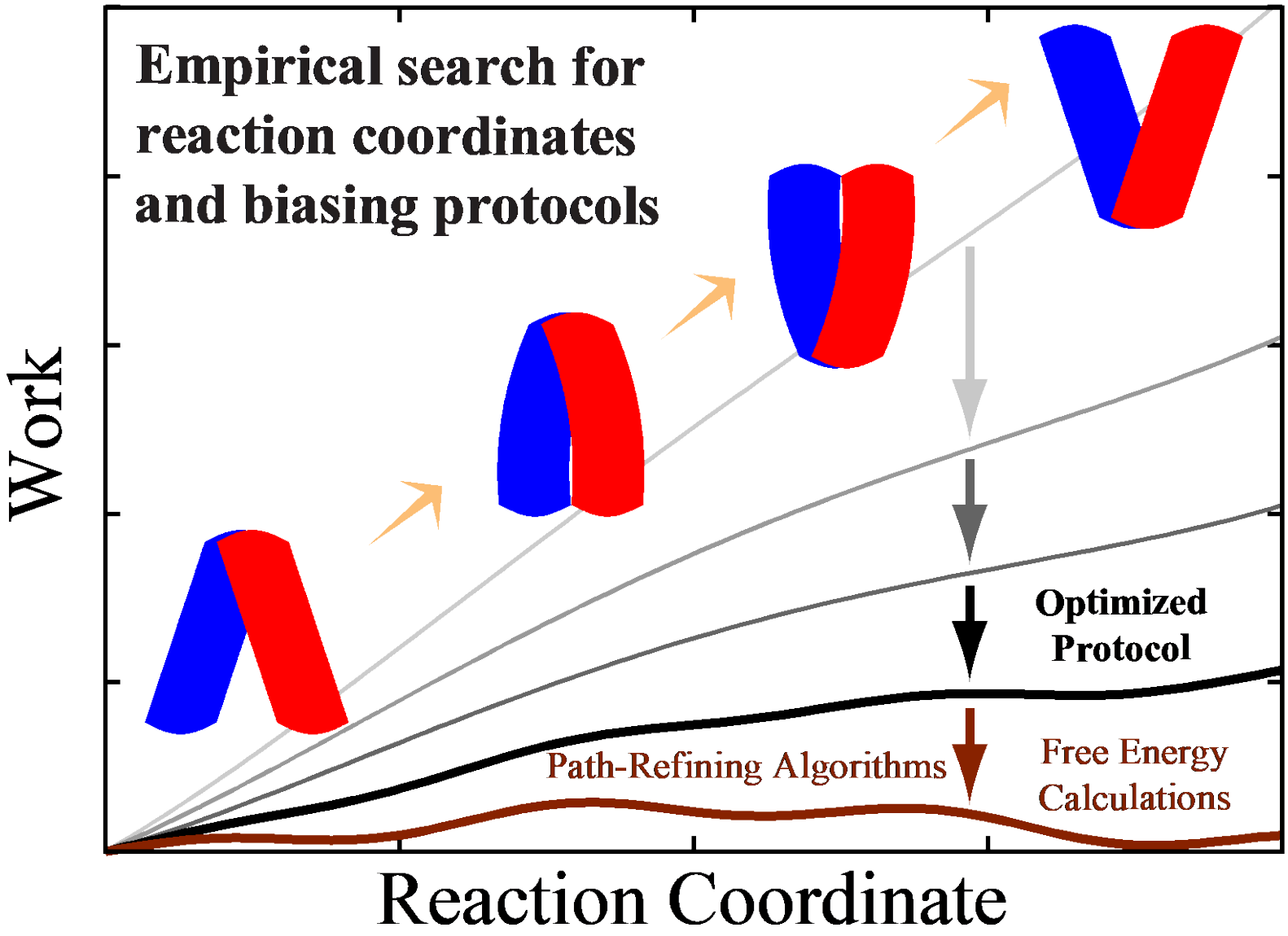
GkPOT

How to study large-scale conformational changes?

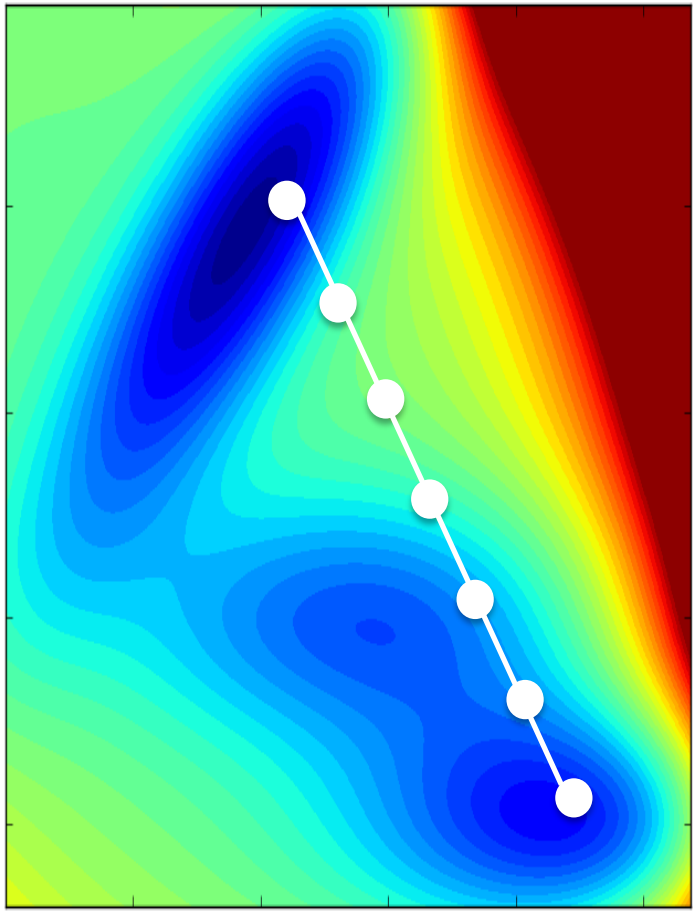


GkPOT

Our Sampling Strategy



Iterative path-finding algorithms and free energy calculations



- Path-finding algorithms:

  e.g., string method (SM or SMwST)

  - Start from an initial string of N images (ζ_i)
  - Restrain M copies of each image for time Δt

$$U_i(\xi) = \frac{1}{2}k(\xi - \zeta_i)^2$$

  - Release the restraints and run for time $\Delta t'$
  - New string (ζ_i) is determined from $\langle\xi\rangle_i$'s
  - Iterate until converged

- Free energy calculations:

  e.g., umbrella sampling (US or BEUS): Shirts, Chodera, JCP, ***129***, 124105 (2008)

  - Bias one or more (e.g., M) copies

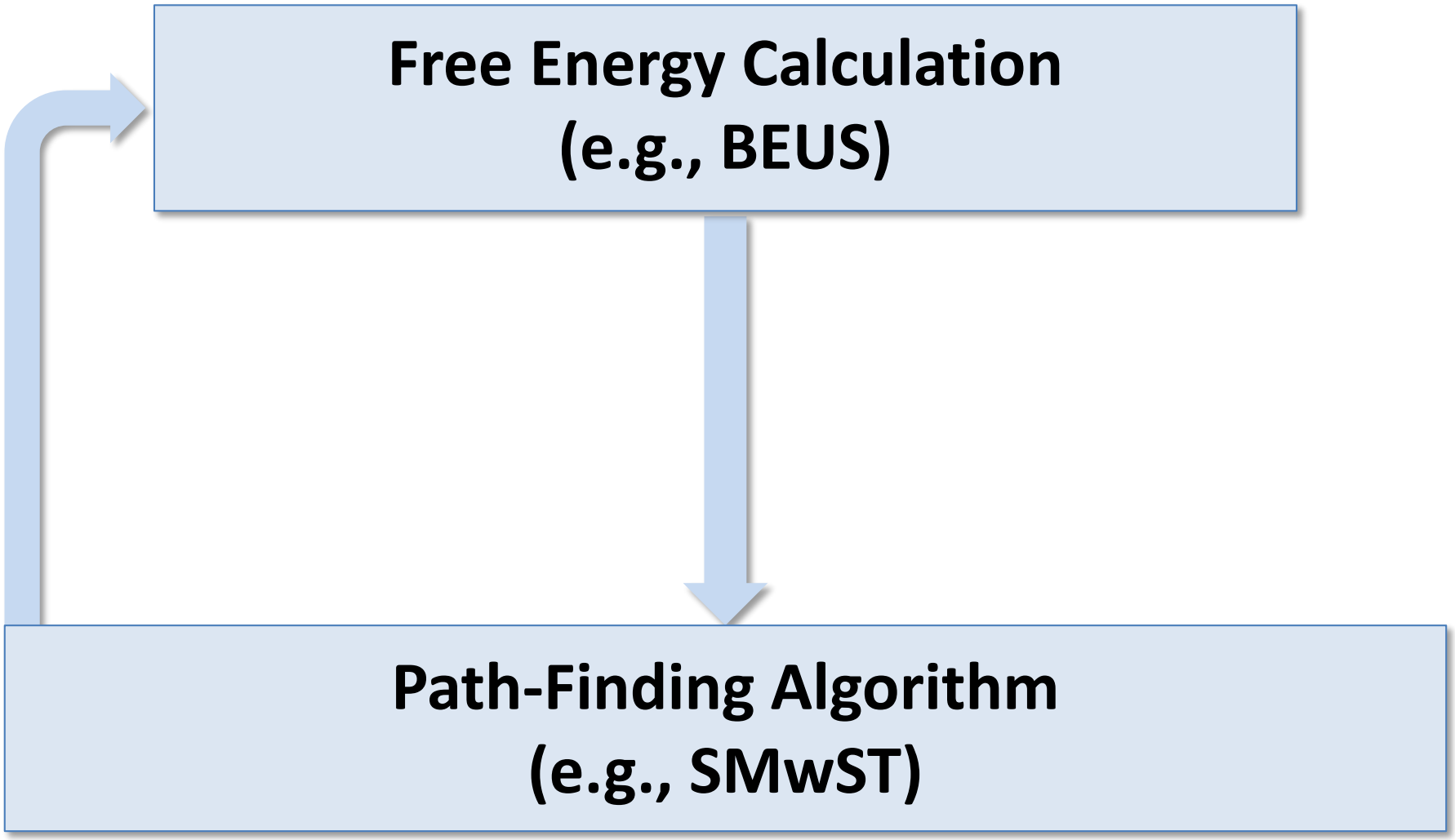
$$U_i(\xi) = \frac{1}{2}k(\xi - \zeta_i)^2$$

$$e^{-\beta F_i} = \left\langle \frac{e^{-\beta U_i(\xi^t)}}{\sum_j n_j e^{-\beta(U_j(\xi^t) - F_j)}} \right\rangle$$

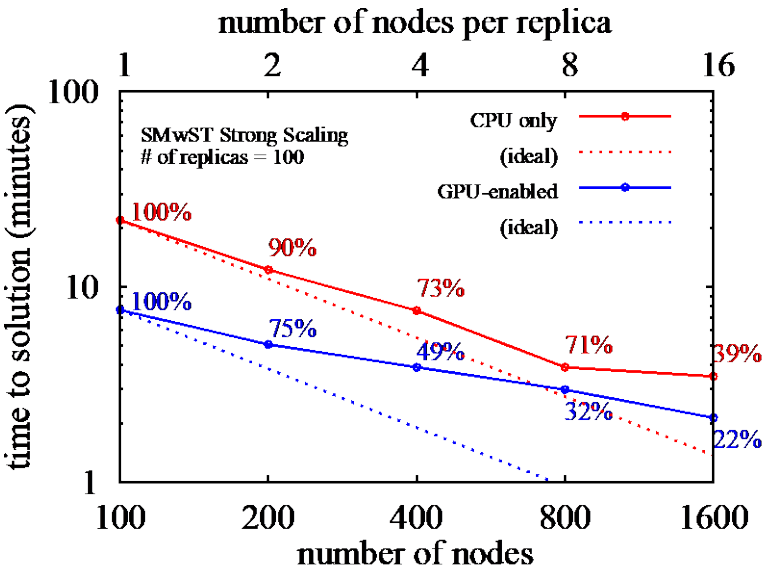
all samples

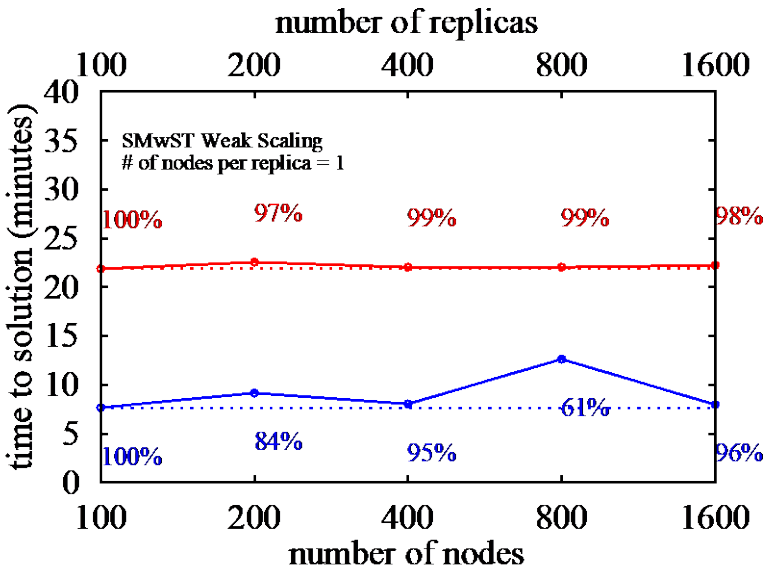
PMF is related but not the same as the "perturbed free energy"

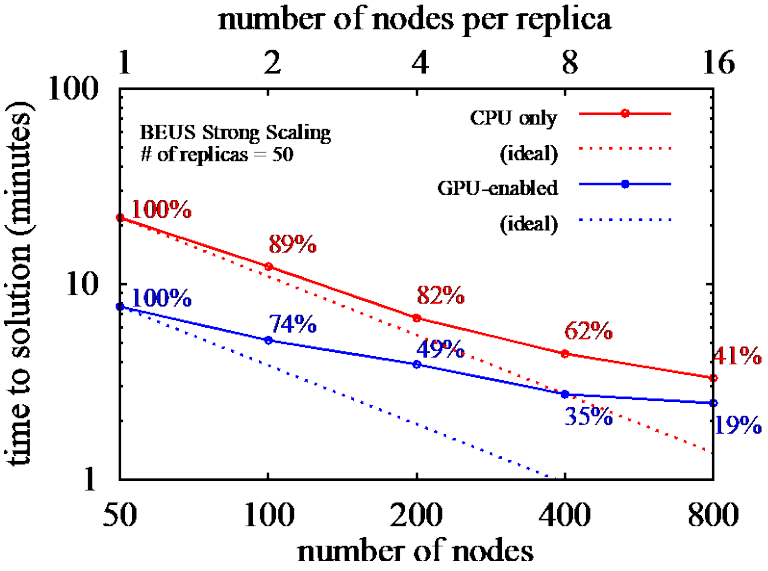
Iterative path-finding algorithms and free energy calculations

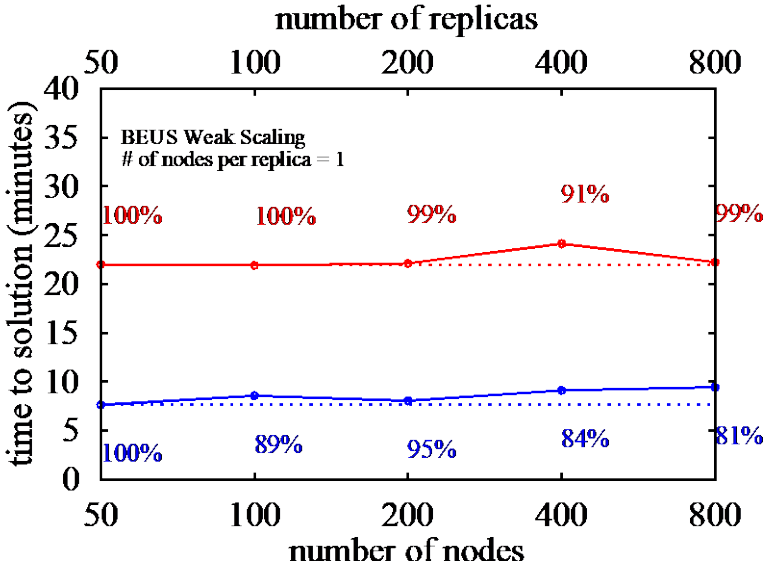


BEUS and SMwST are both loosely-coupled multiple-copy (LCMC) algorithms

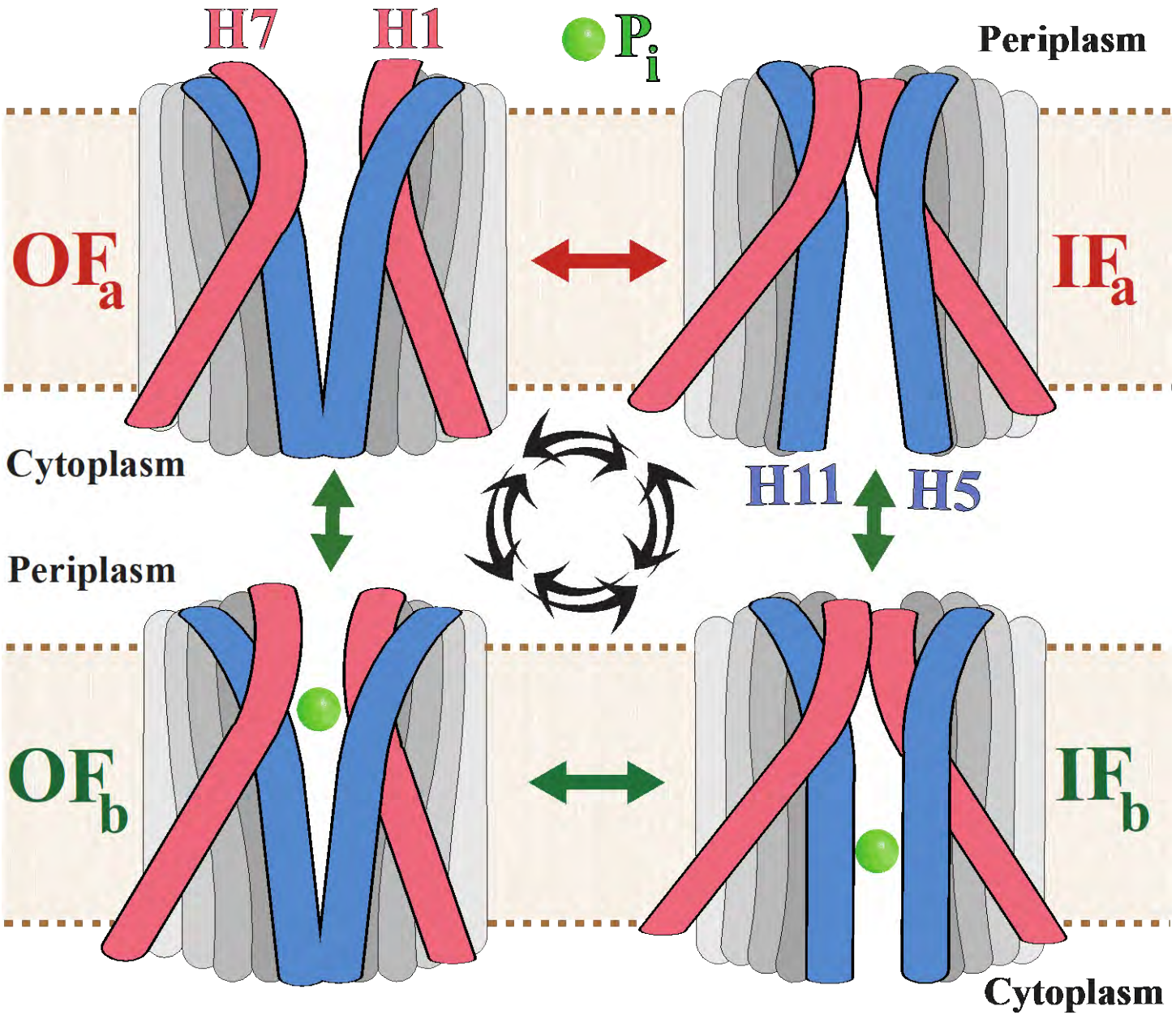




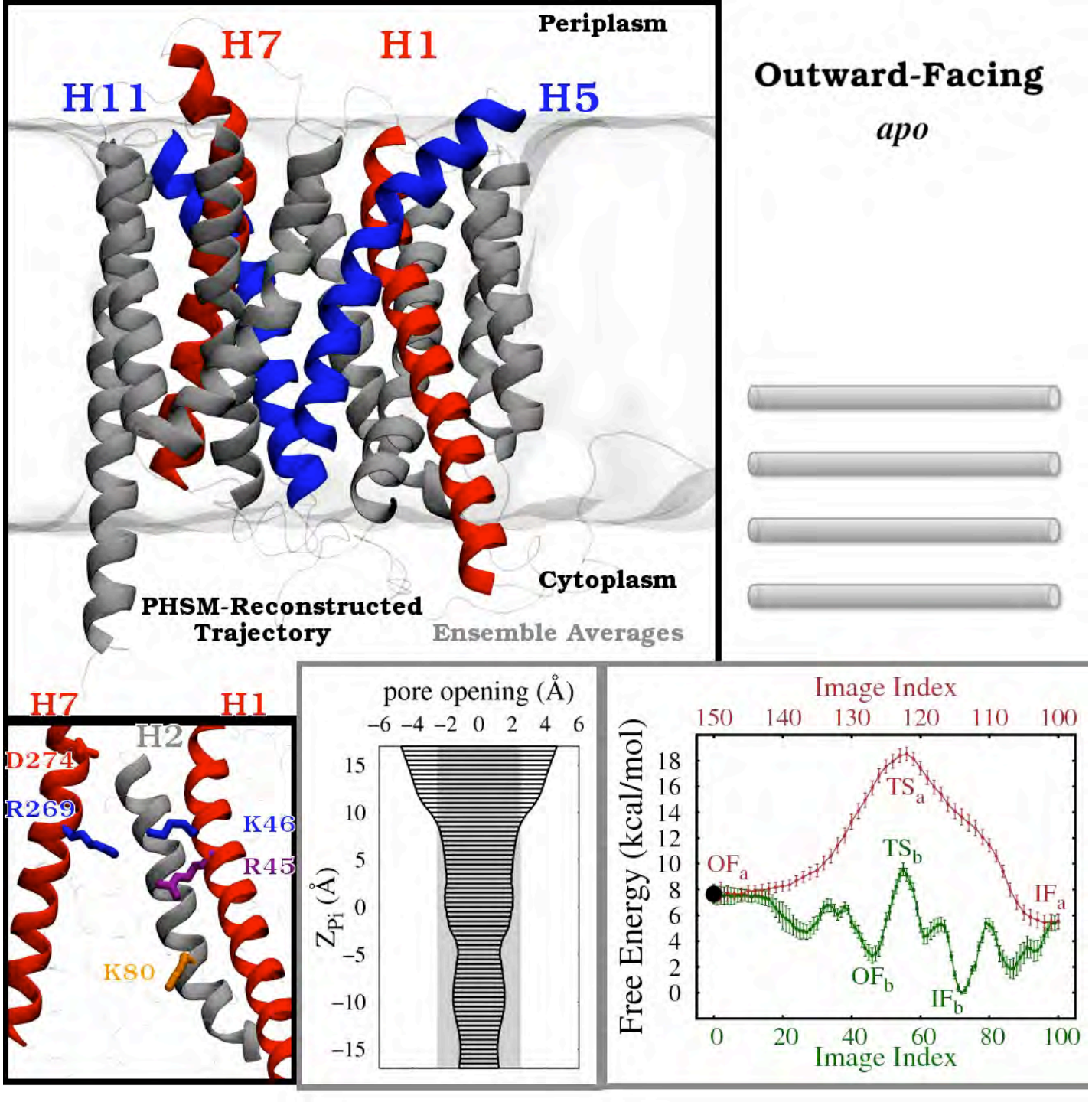




Example: Transport Cycle of GlpT

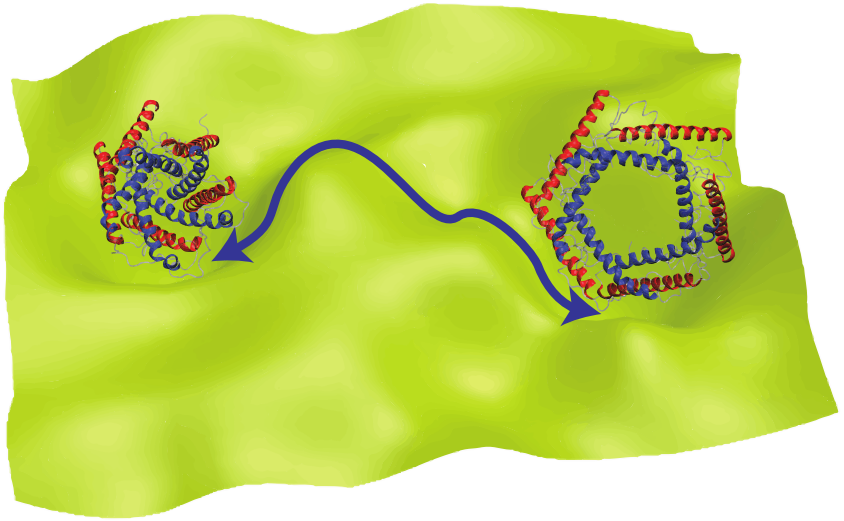


Moradi M., Enkavi G., and Tajkhorshid E., **Nature Communications 6** 8393 (**2015**)


Periplasm
H7
H1
H11
H5
Cytoplasm
PHSM-Reconstructed Trajectory
Ensemble Averages
Outward-Facing
apo
H7
H1
H2
D274
R269
K46
R45
K80
pore opening (Å)
−6 −4 −2 0 2 4 6
15
10
5
0
−5
−10
−15
Z_{Pi} (Å)
Image Index
150 140 130 120 110 100
Free Energy (kcal/mol)
18 16 14 12 10 8 6 4 2 0
TS_a
TS_b
OF_a
IF_a
OF_b
IF_b
0 20 40 60 80 100
Image Index

Riemannian Reformulation

- Riemannian reformulation of path-finding algorithms and free energy calculations methods such as SMwST/BEUS provide solutions for the minimum free energy path and its free energy that are **invariant under coordinate transformation.**



- The Riemannian formulation allows for developing **more robust** free energy calculation methods and path-finding algorithms (due to the **"invariance"** feature).

Fakharzadeh & Moradi, *Effective Riemannian diffusion model for conformational dynamics of biomolecular systems*. **J Phys Chem Lett.** 2016;7(24):4980-4987.

Riemannian Reformulation

- There is an **exact analytical relationship** between the PMF and estimated perturbed free energy:

Perturbed free energy

$$e^{-\beta G(\xi)} = \left(\frac{2\pi}{\beta k}\right)^{-\frac{n}{2}} e^{-\frac{1}{2\beta k}\Delta} e^{-\beta f(\xi)}$$

Riemannian PMF

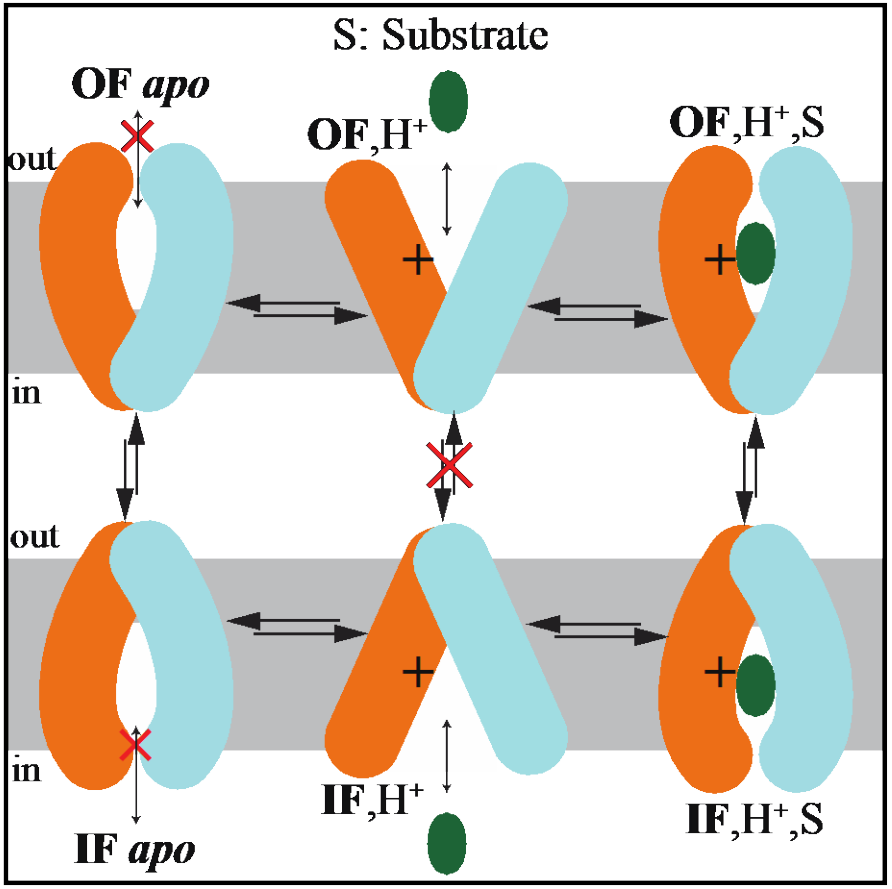
- Methods such as BEUS and SMwST can be modified by using **geodesic distance** instead of **Euclidean distance,** etc.
- For certain collective variables, the geodesic distance can be approximated by analytic expressions, e.g., for **orientation quaternions**:

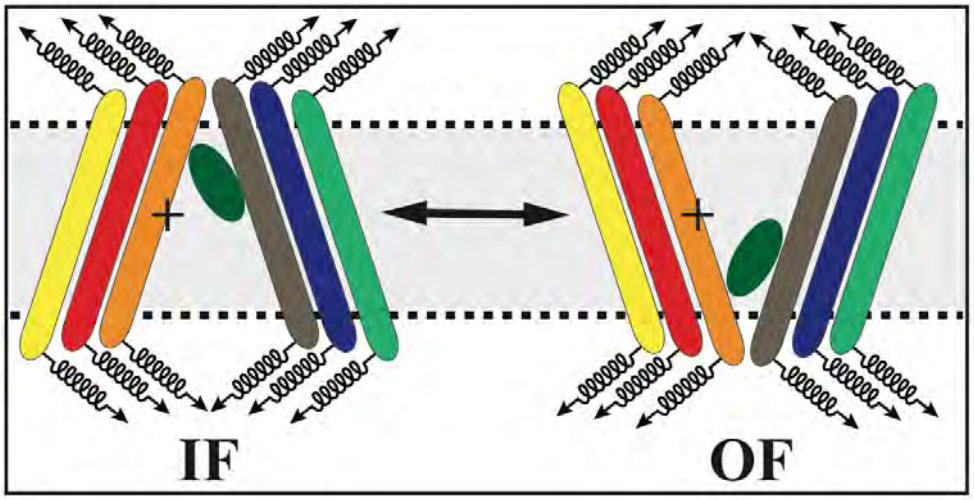
$$d(\boldsymbol{q}_1, \boldsymbol{q}_2) \approx \cos^{-1}(\boldsymbol{q}_1 . \boldsymbol{q}_2)$$

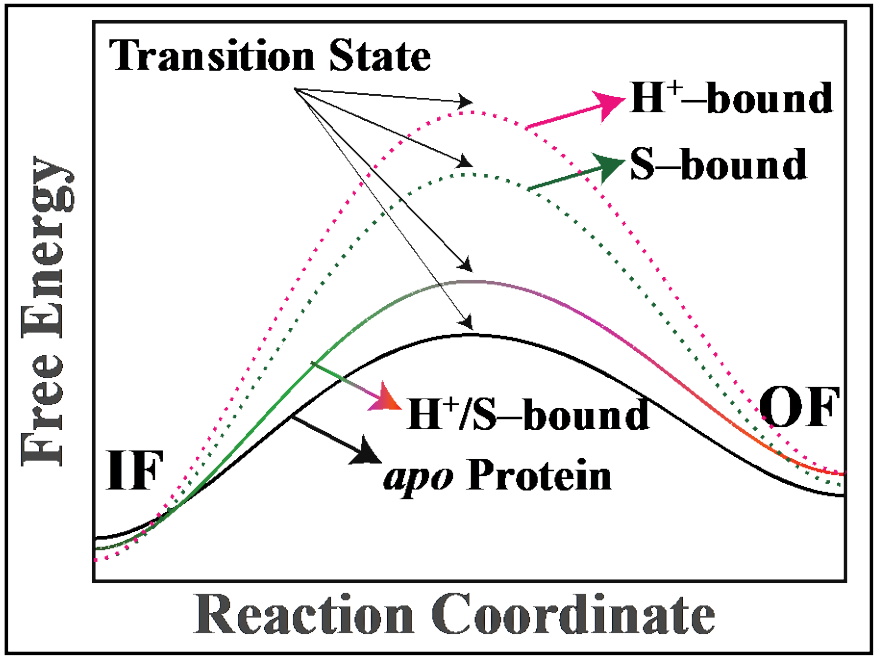
- For other collective variables, on-the-fly metric calculations maybe necessary.

Fakharzadeh & Moradi Effective Riemannian diffusion model for conformational dynamics of biomolecular systems**. J Phys Chem Lett.** 2016;7(24):4980-4987.

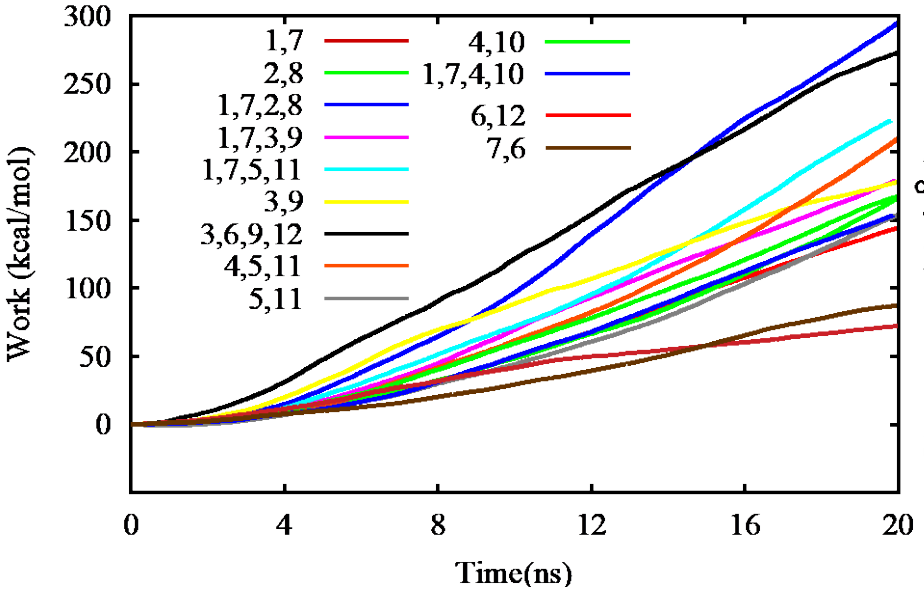
Bacterial POT transporter GkPOT

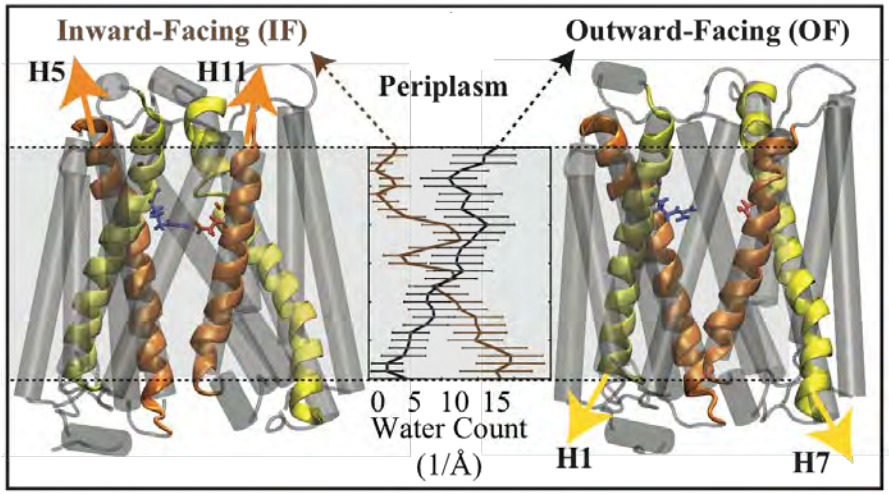


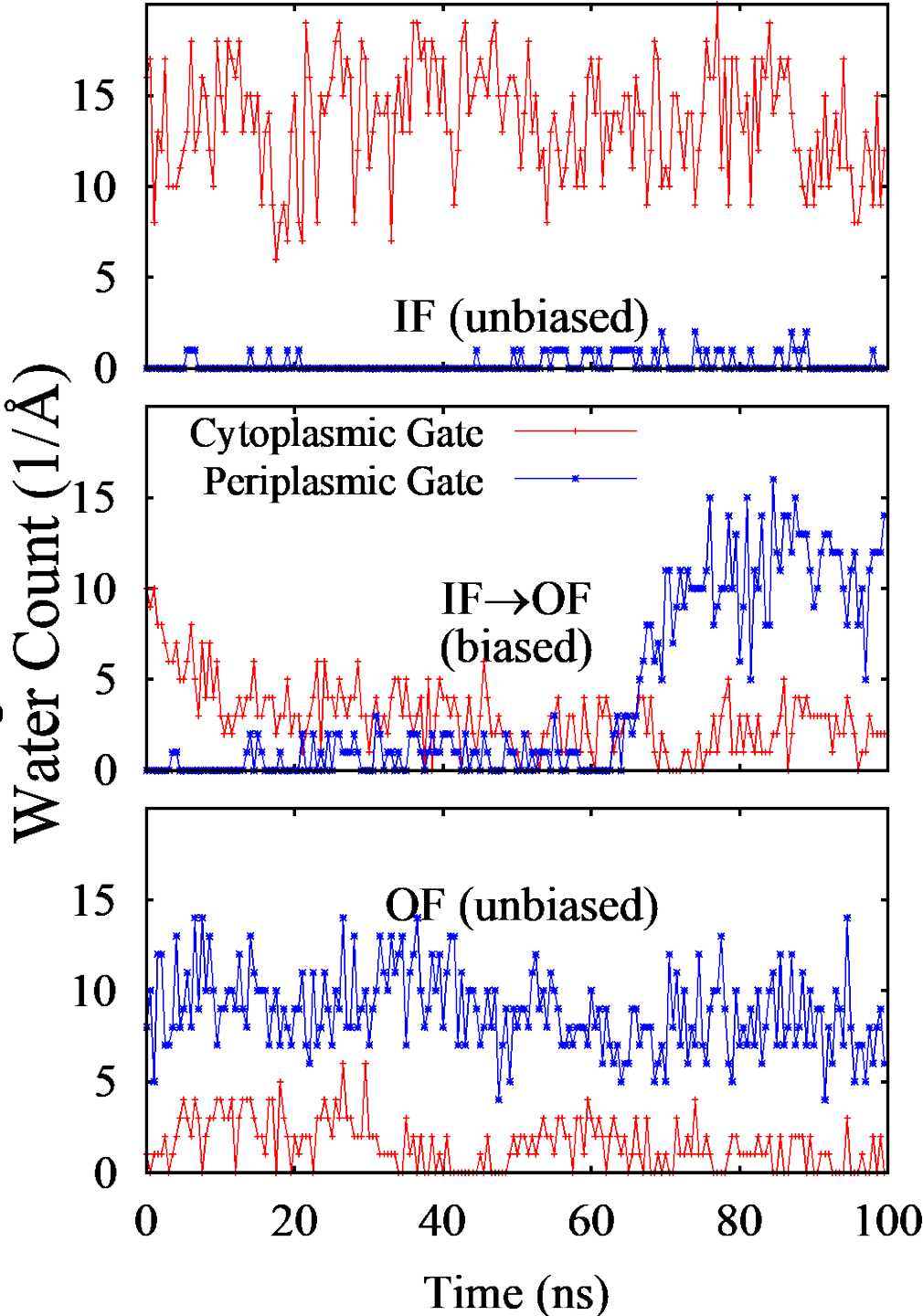


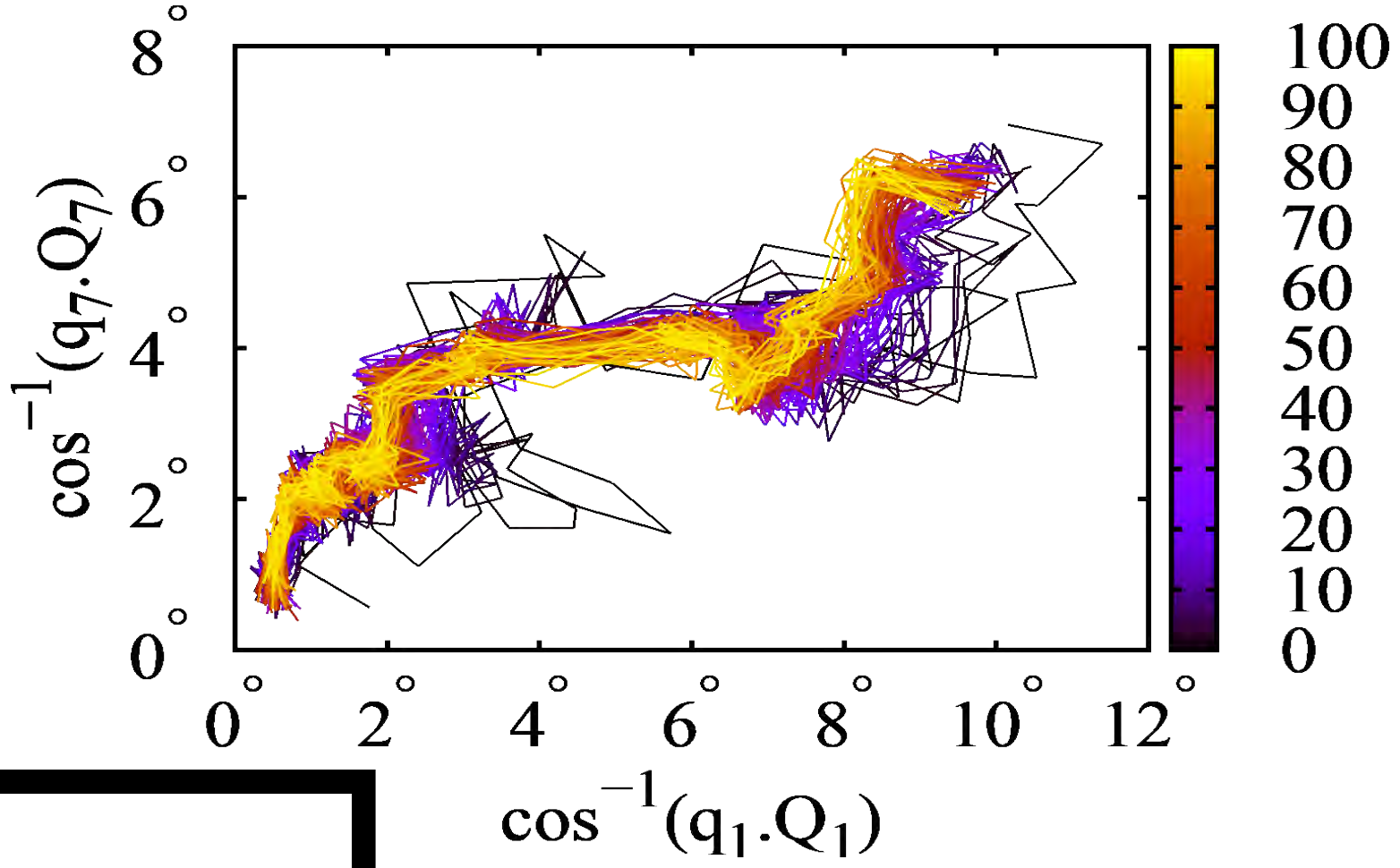


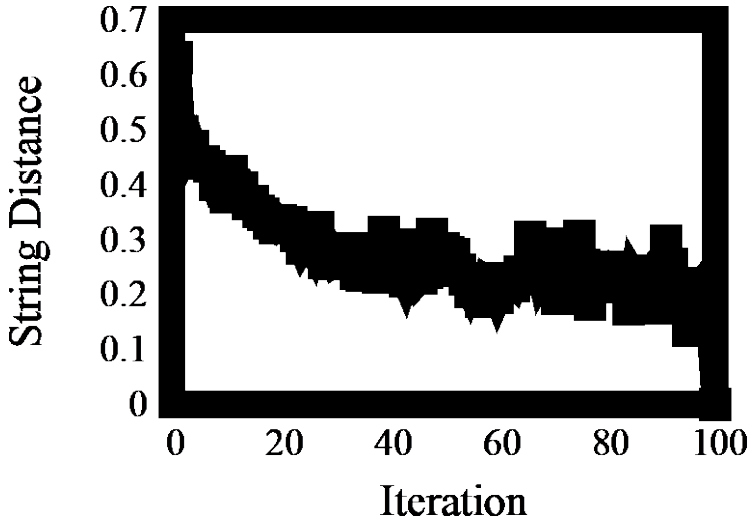
Search for biasing protocols





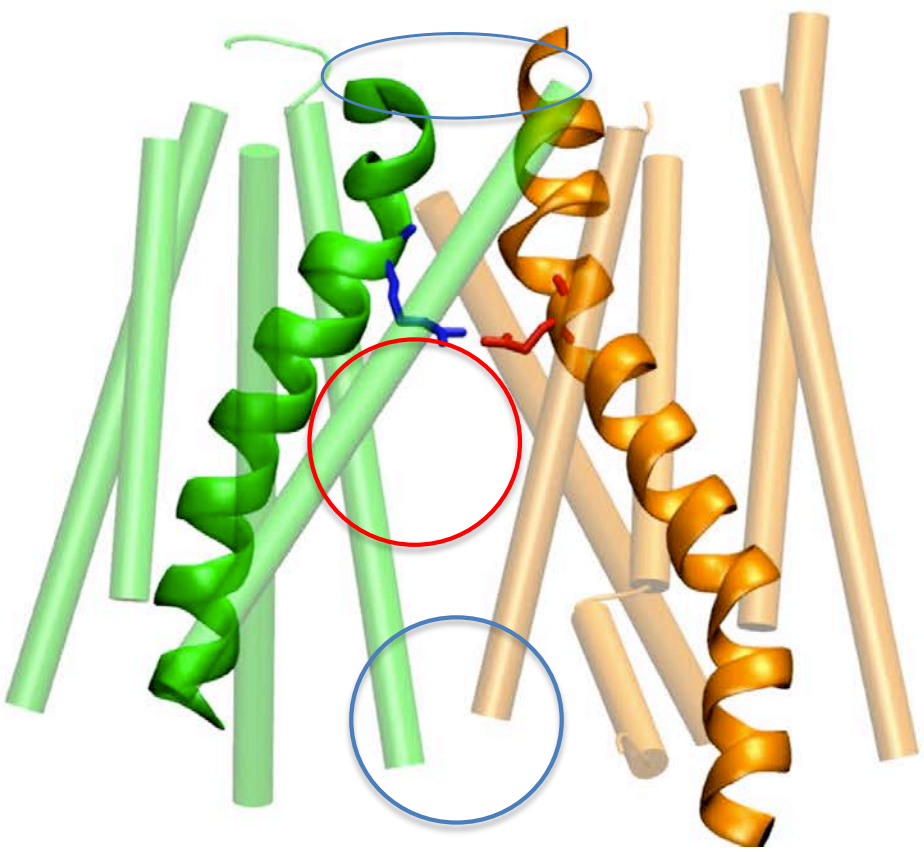




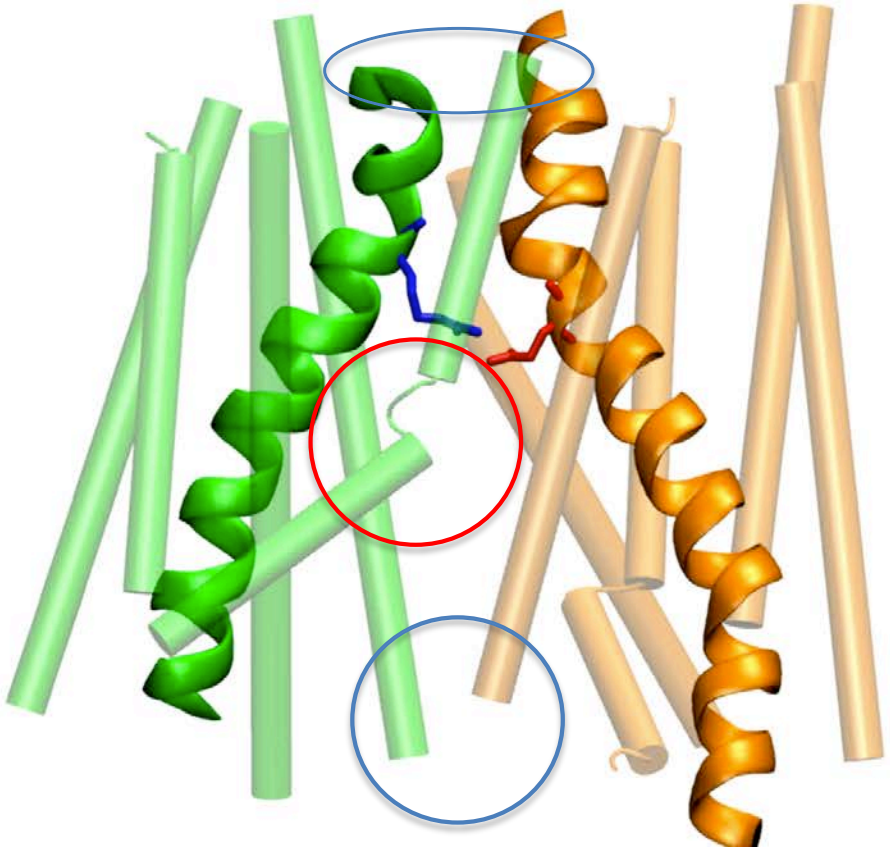


SMwST Convergence

Inward- ↔outward-facing transition



Nonequilibrium Pulling



SMwST

Great Lakes Consortium for Petascale Computation

NCSA BLUE WATERS SUSTAINED PETASCALE COMPUTING

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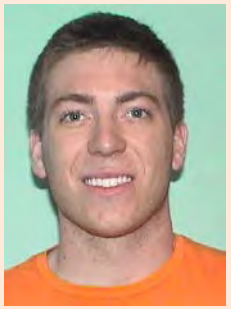
Curtis Goolsby



Dylan Ogden

Kalyan Immadisetty

Hamid Tabari

Vivek Govind Kumar

Adithya Polasa

AHPCC Arkansas High Performance Computing Center

PITTSBURGH SUPERCOMPUTING CENTER

XSEDE Extreme Science and Engineering Discovery Environment