# Employing Microsecond-Level Simulations of Membrane Proteins to Capture Their Millisecond-Level Behaviors Using Blue Waters


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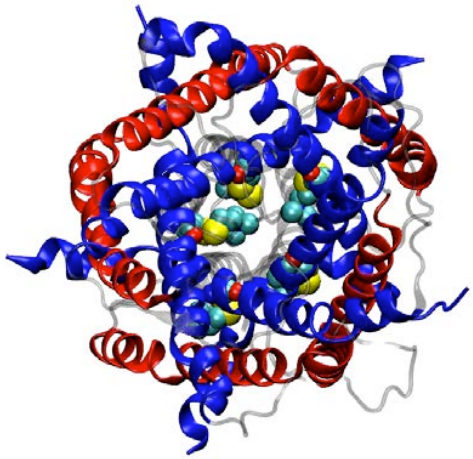

UNIVERSITY OF ARKANSAS

**Blue Waters Symposium 2019**
**Sunriver, OR**
**June 3, 2018**


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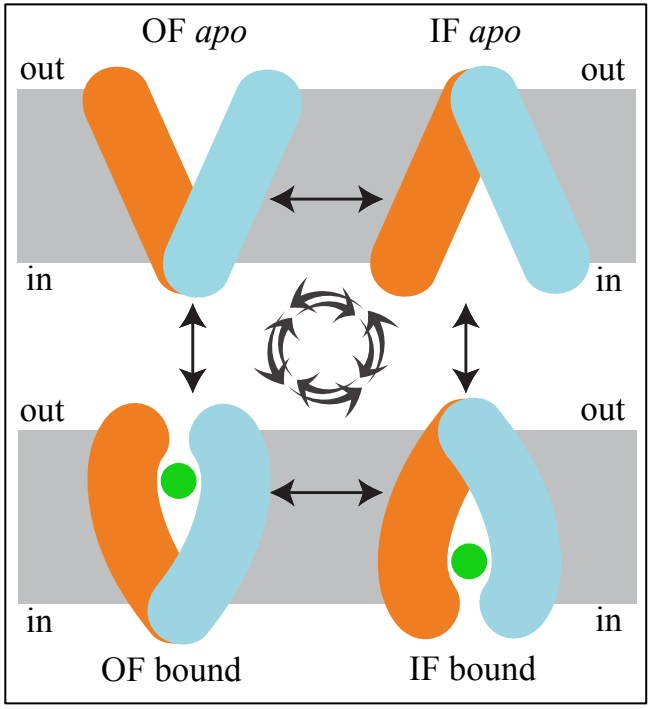
# Outline

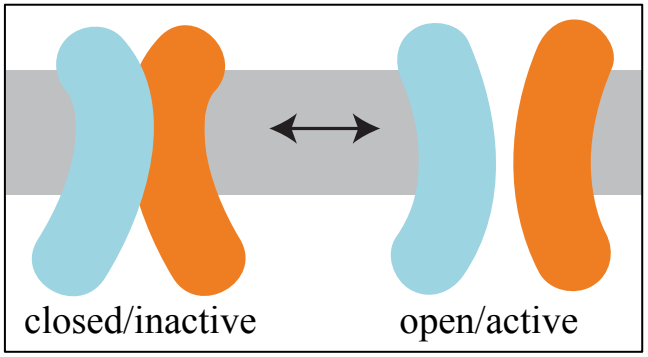
- Using **molecular dynamics** (MD) to study protein **large-scale conformational changes**
- Is the so-called **unbiased MD** reliable?
- How can we use **biased MD** to study large-scale conformational changes?
- Developing **loosely-coupled multiple-copy** (LCMC) MD algorithms within NAMD
- Applications to proton-coupled oligopeptide transporter **GkPOT** and mechanosensitive channel of large conductance **MscL**

# 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.



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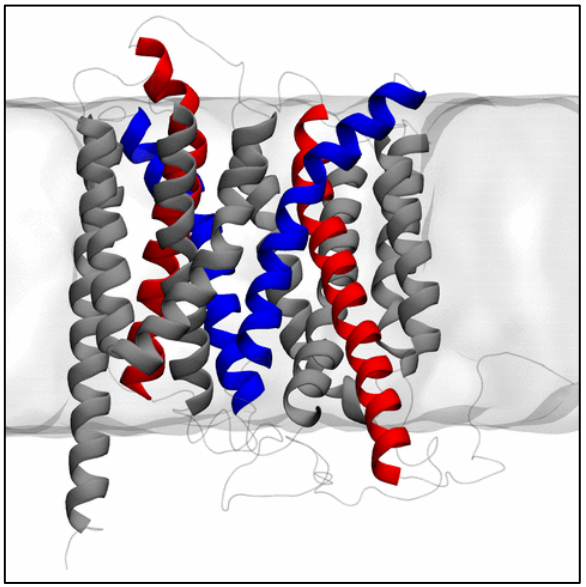

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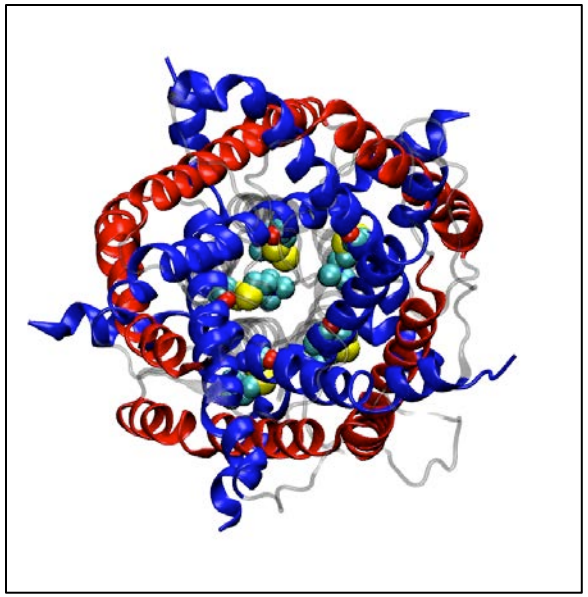
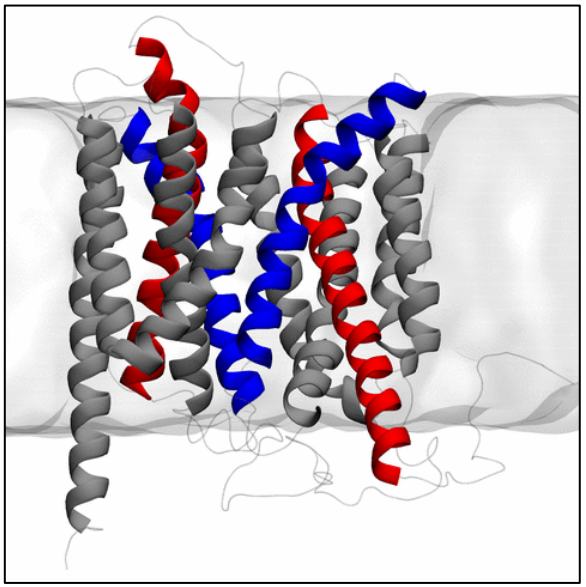


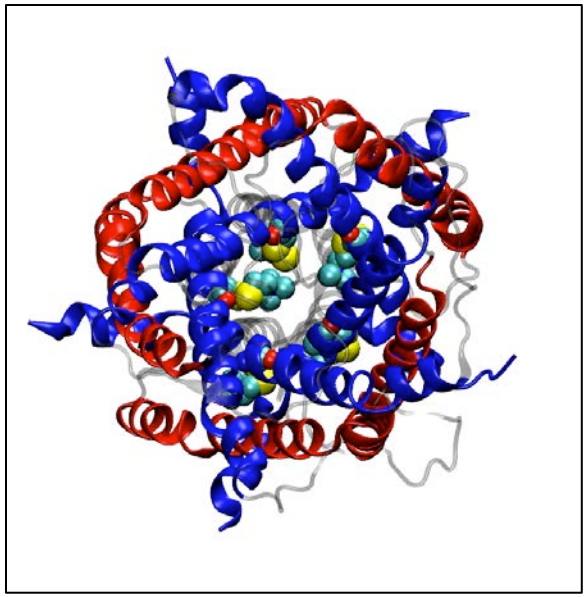
# Large-Scale Conformational Changes in Membrane Transport Proteins

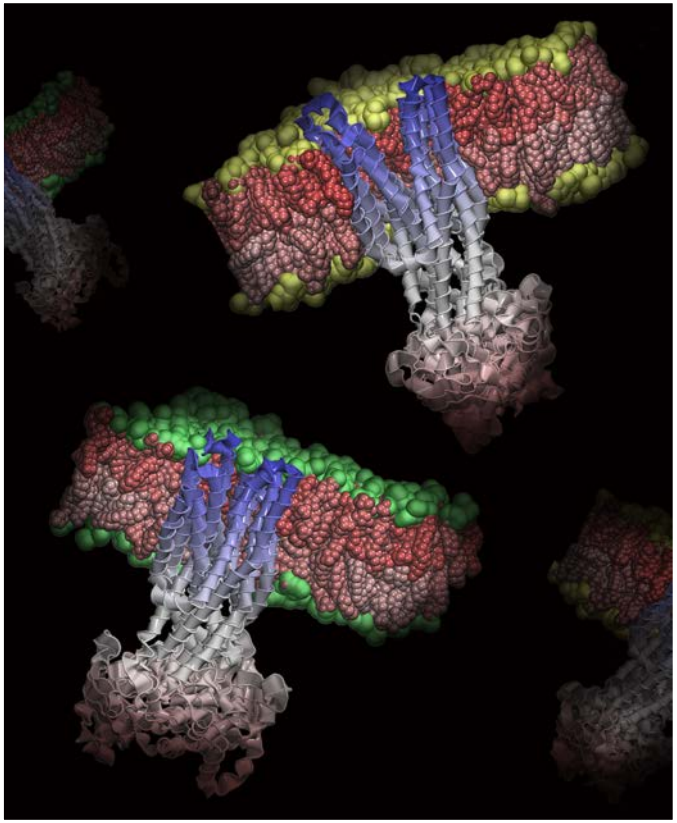
- Large-scale conformational changes require **concerted motions of thousands of atoms** whose motions are coupled by direct or indirect/allosteric interactions.

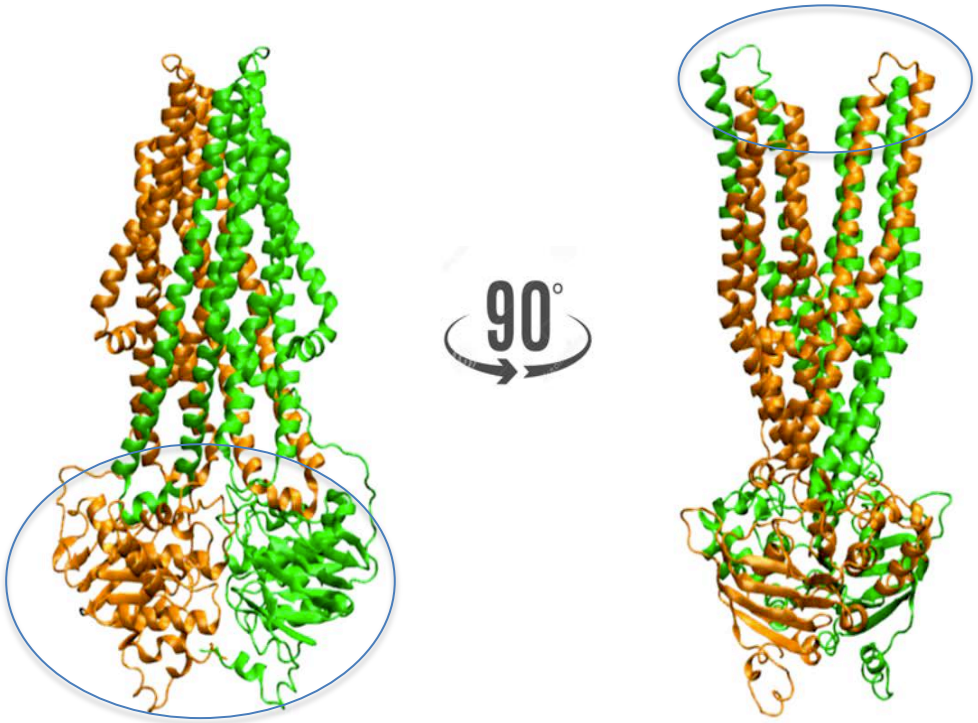
- It typically takes **several to thousands of microseconds** for a process like those described above to take place.

- These conformational changes are typically triggered by certain **chemical/mechanical changes** in the protein/environment.







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Research Article

Cite This: ACS Cent. Sci. 2019, 5, 43−56

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# Lipid-Dependent Alternating Access Mechanism of a Bacterial Multidrug ABC Exporter

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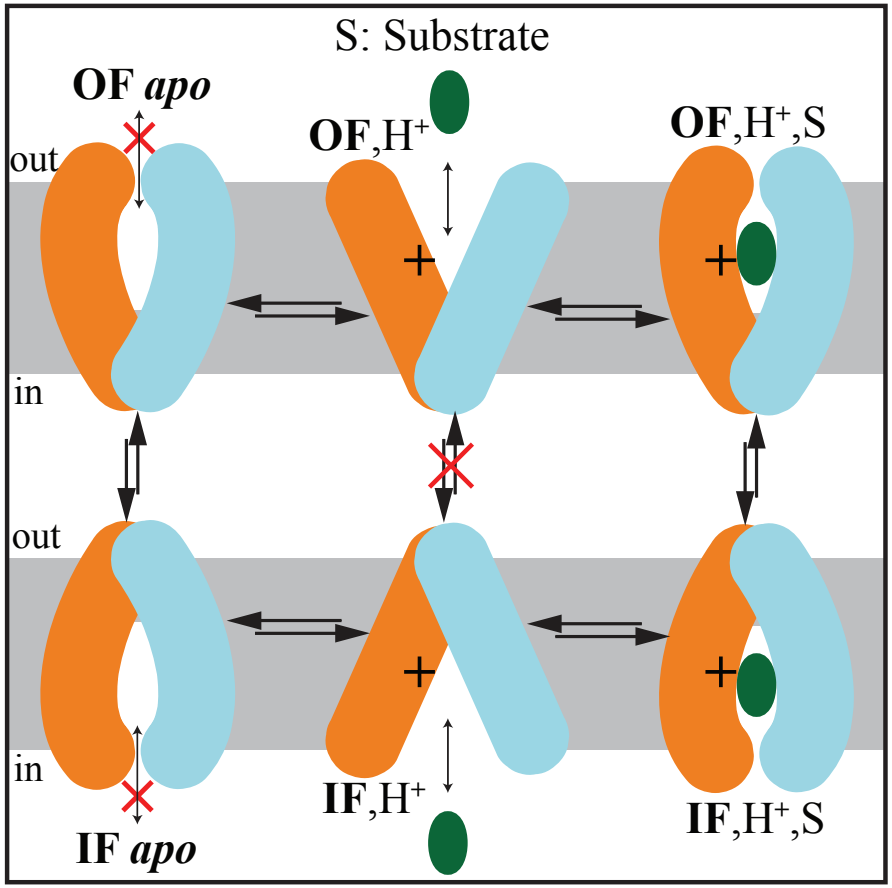
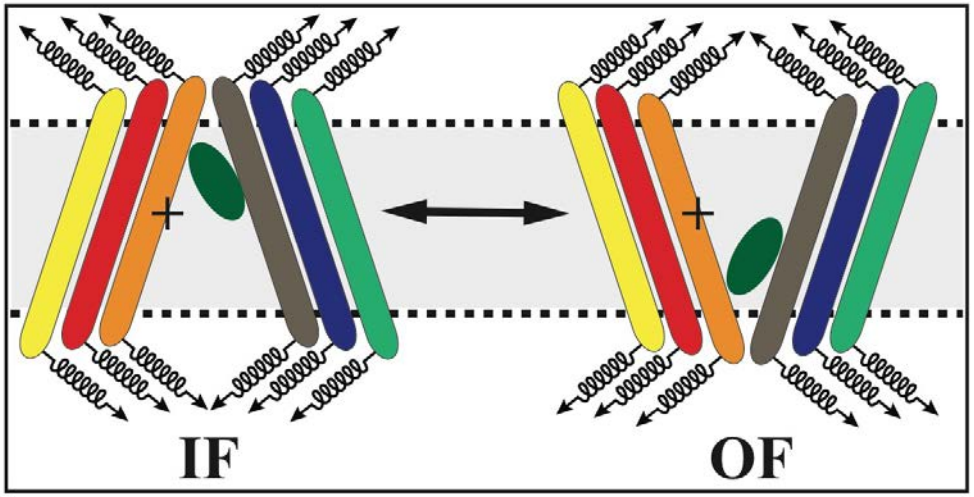
# Is the so-called unbiased MD reliable?

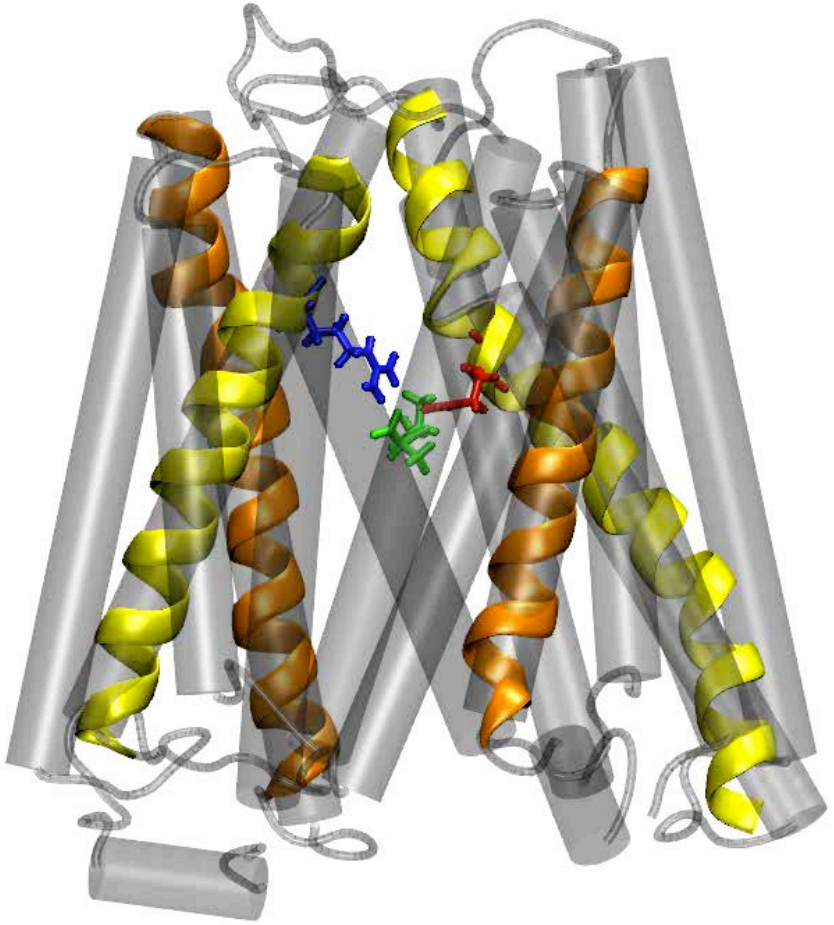
## A Case Study:
## Proton-coupled Oligopeptide Transporters (POTs)



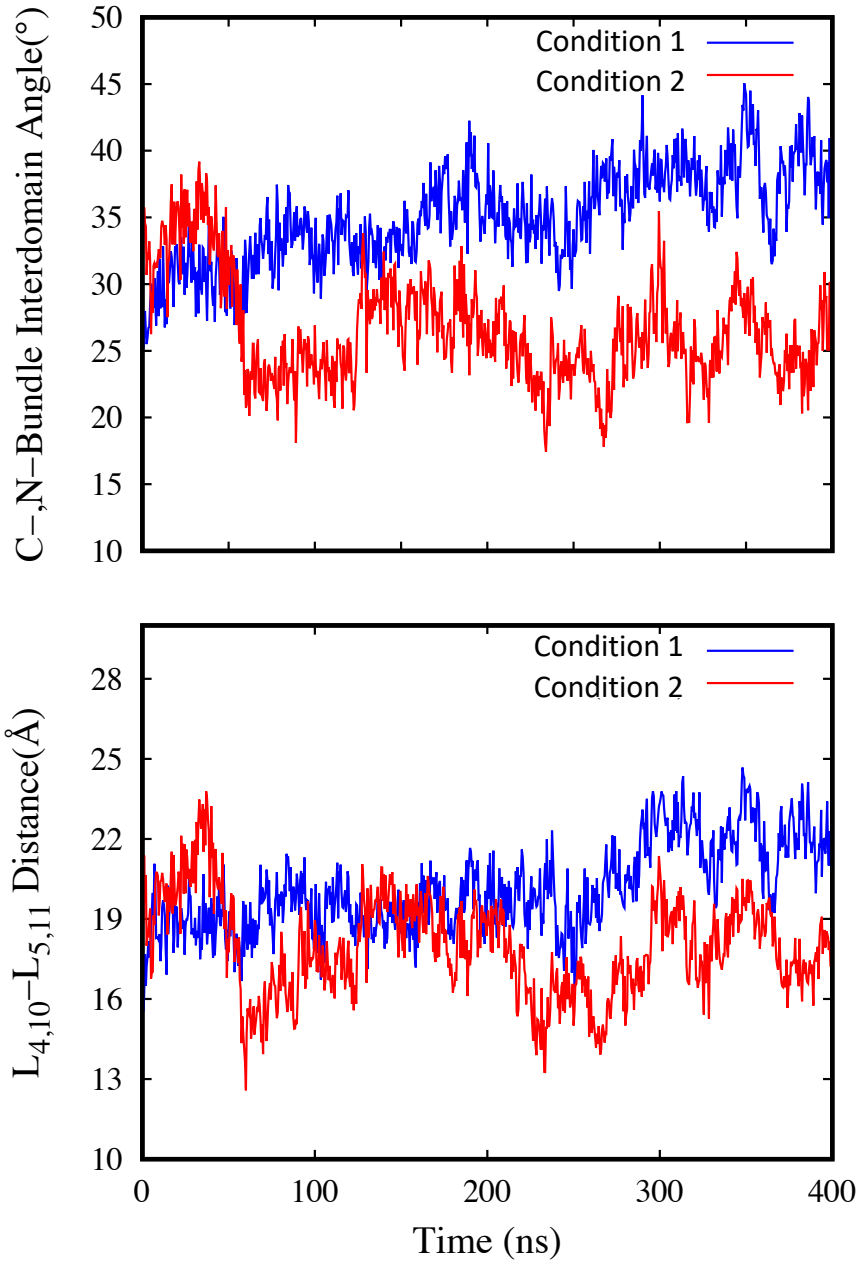
# A Case Study:
# Proton-coupled Oligopeptide Transporters (POTs)

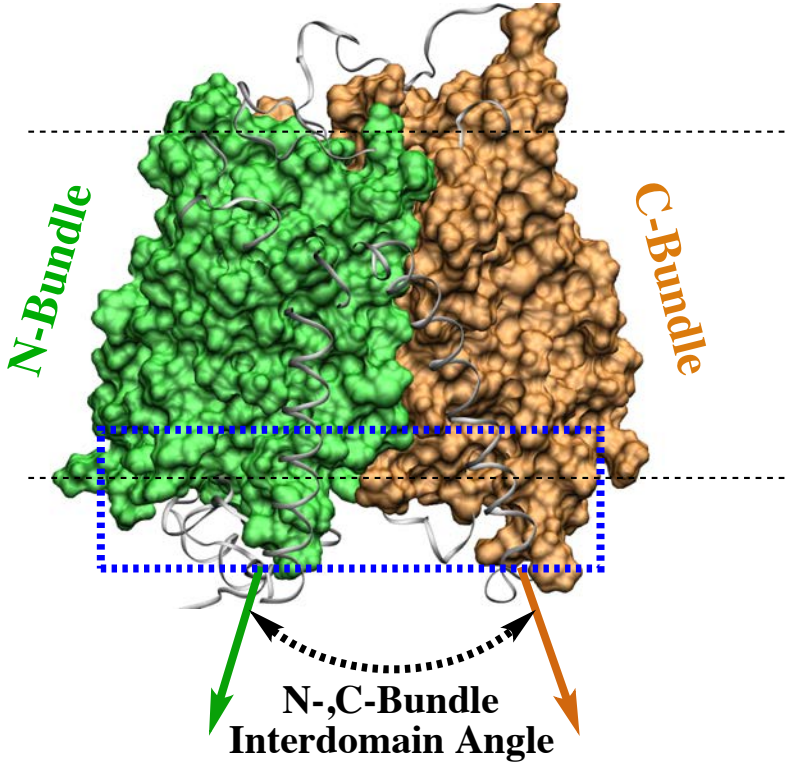
**GkPOT** (PDB:4IKV, 1.9 Å)
~100,000 atoms
Conventional unbiased MD simulations performed:
**8 conditions (different protonation states, substrates)**
**× 400 ns**
**× 2 repeats**

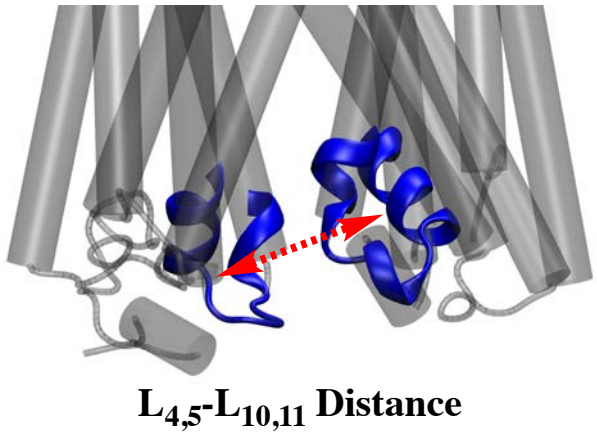


K Immadisetty, J Hettige, and M Moradi, ***What Can and Cannot Be Learned from Molecular Dynamics Simulations of Bacterial Proton-Coupled Oligopeptide Transporter GkPOT?*** J. Phys. Chem. B, **121**:3644-3656, 2017.

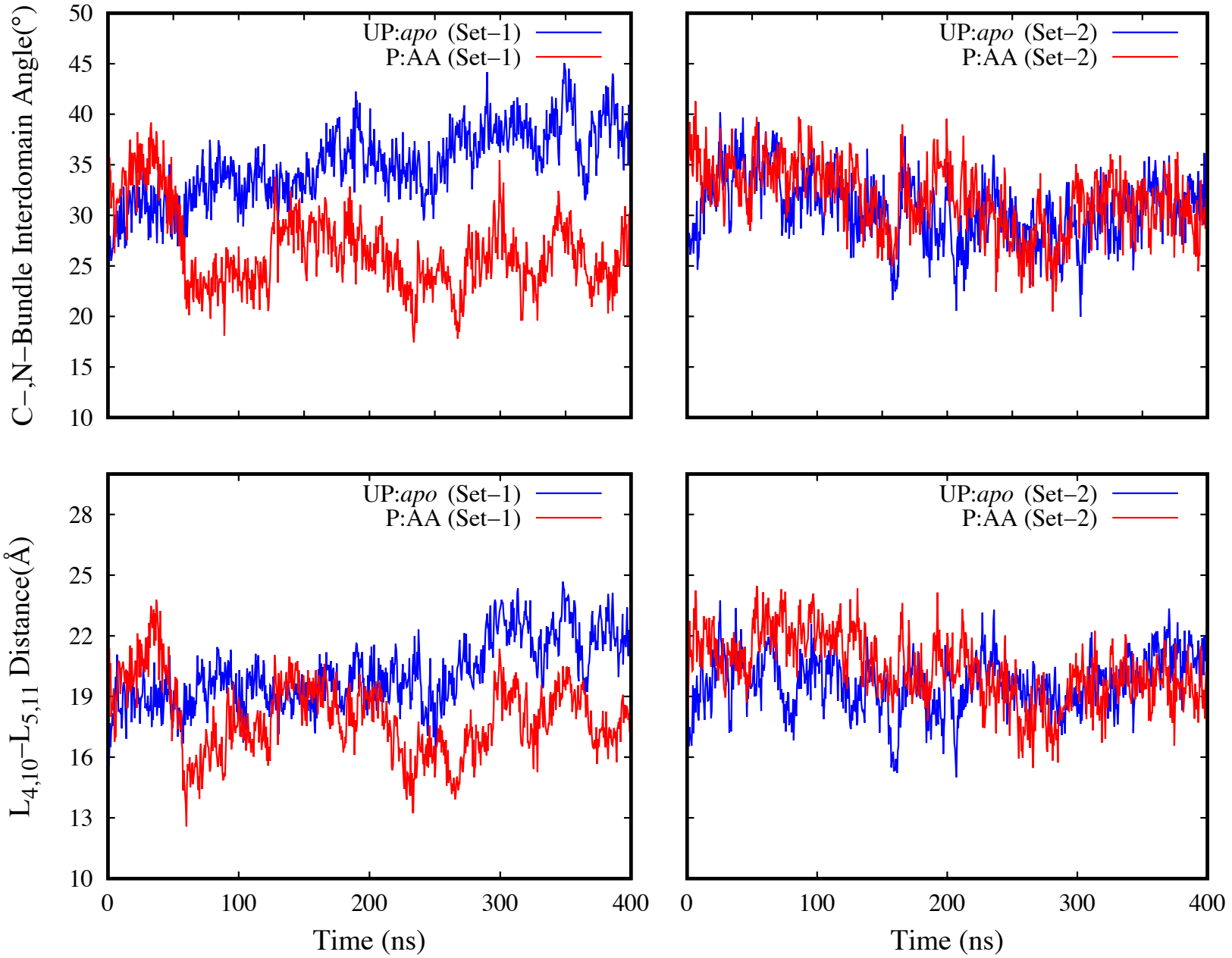
# Monitoring Global Conformational Changes



# Reproducibility Check



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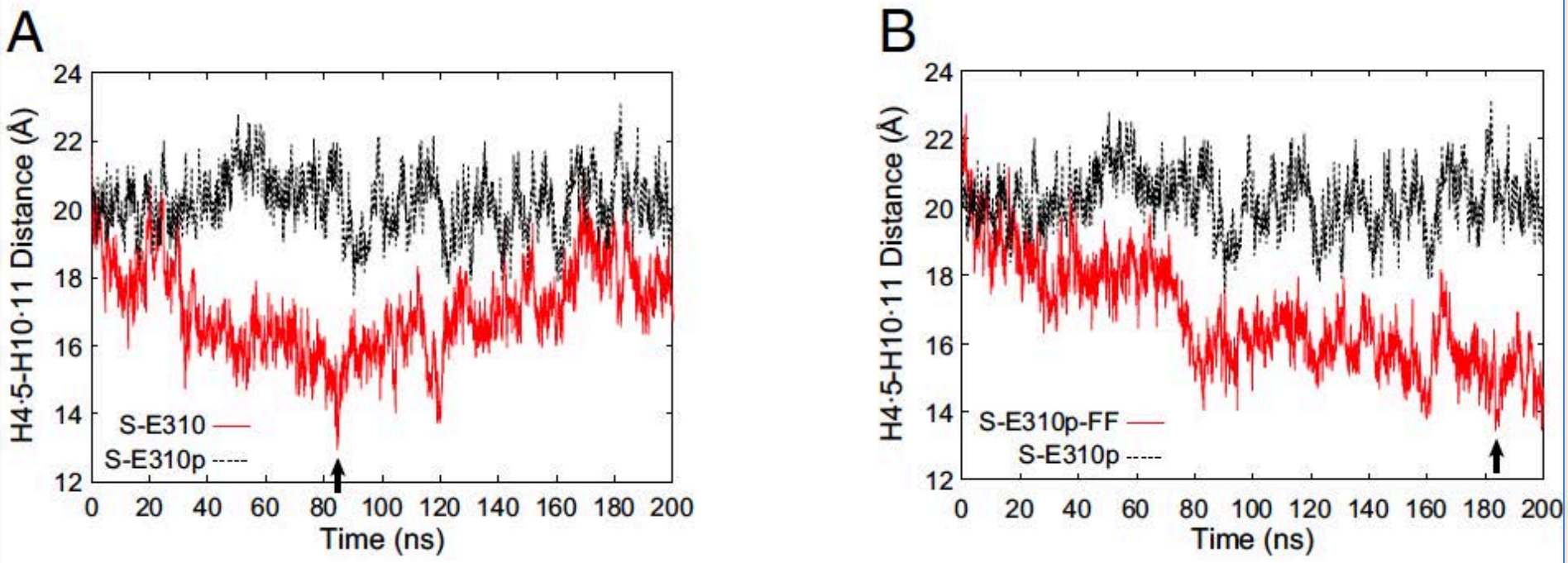
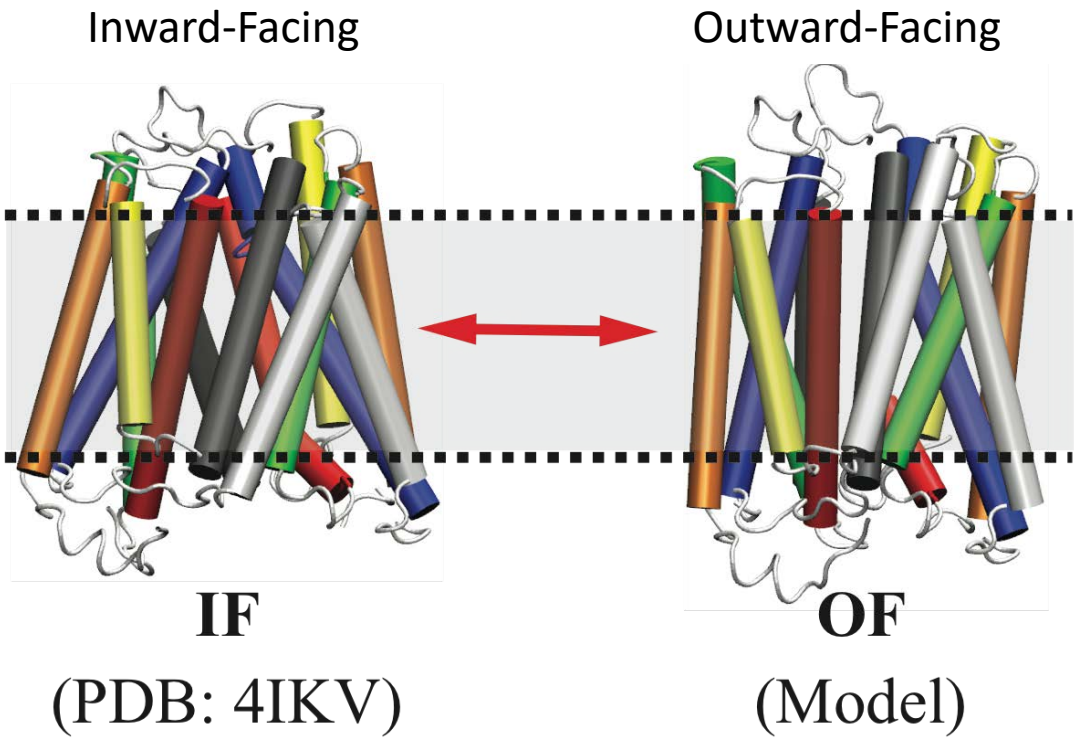



"Structural basis for dynamic mechanism of proton-coupled symport by the peptide transporter POT." **PNAS 2013** | vol. 110 | no. 28 | 11343–11348.

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

# How can we use biased MD to study large-scale conformational changes?



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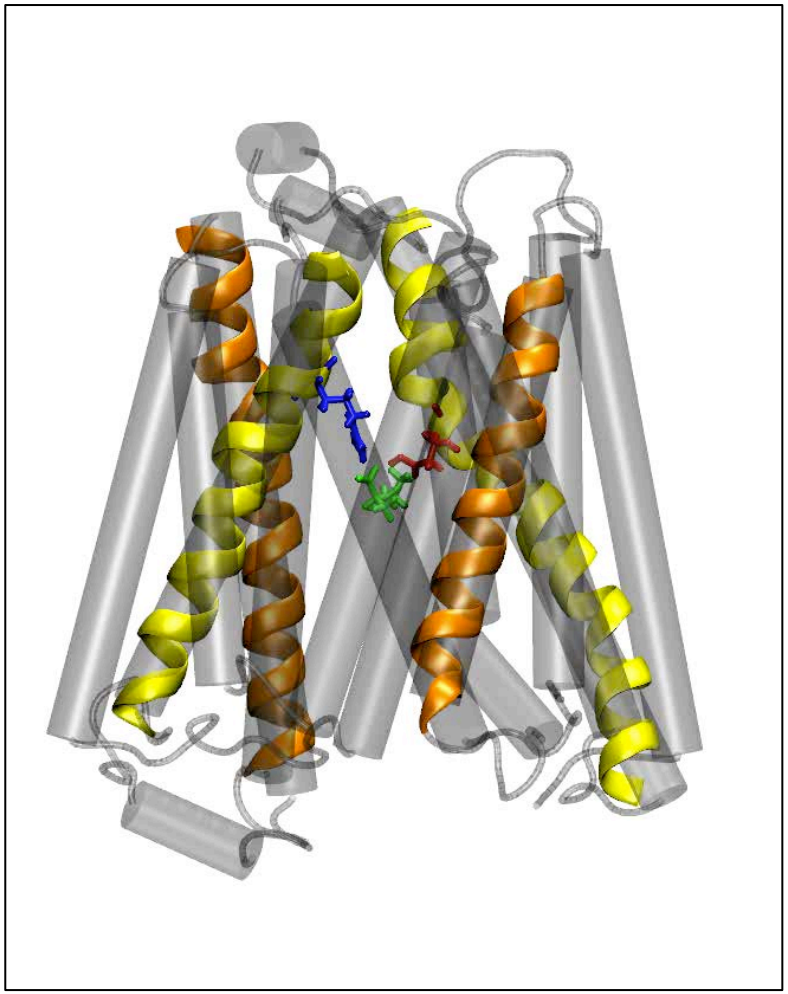
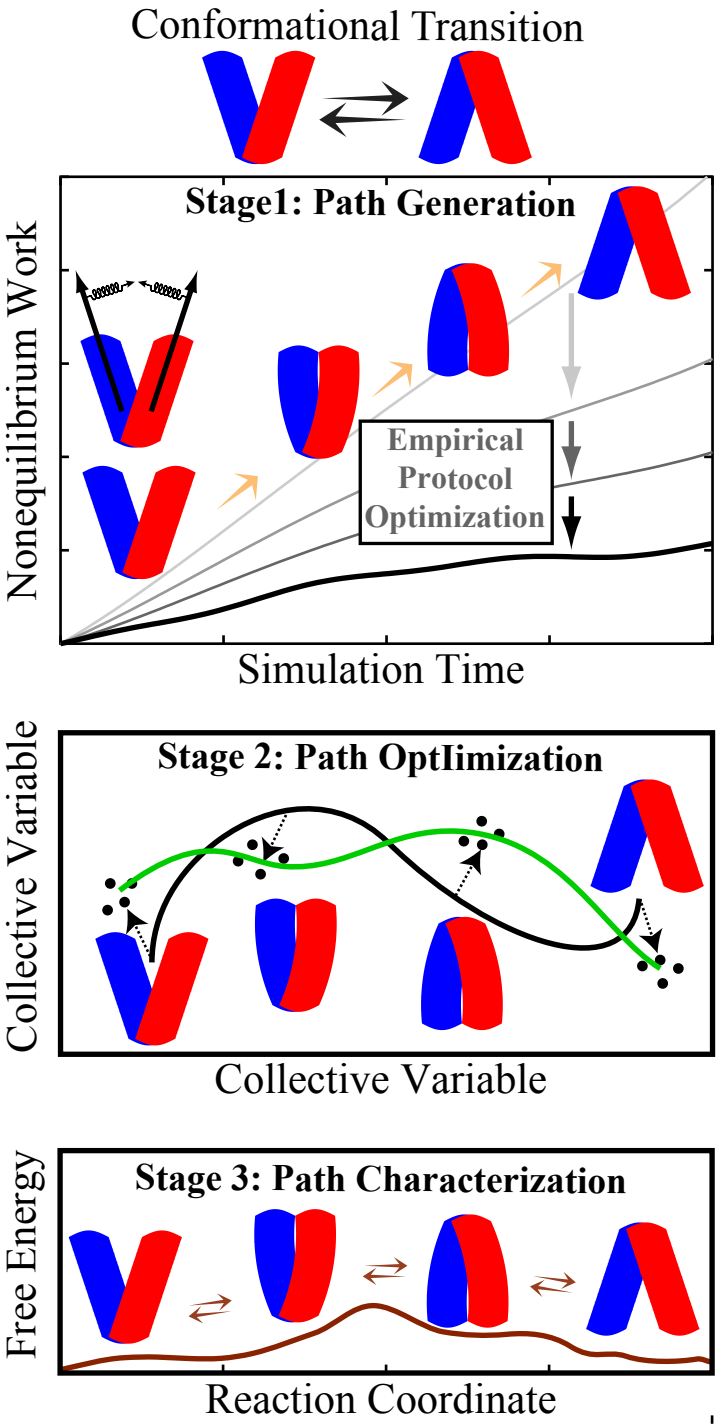




# Path-Finding Algorithms and Free Energy Calculations Based on Loosely-Coupled Multiple-Copy (LCMC) MD

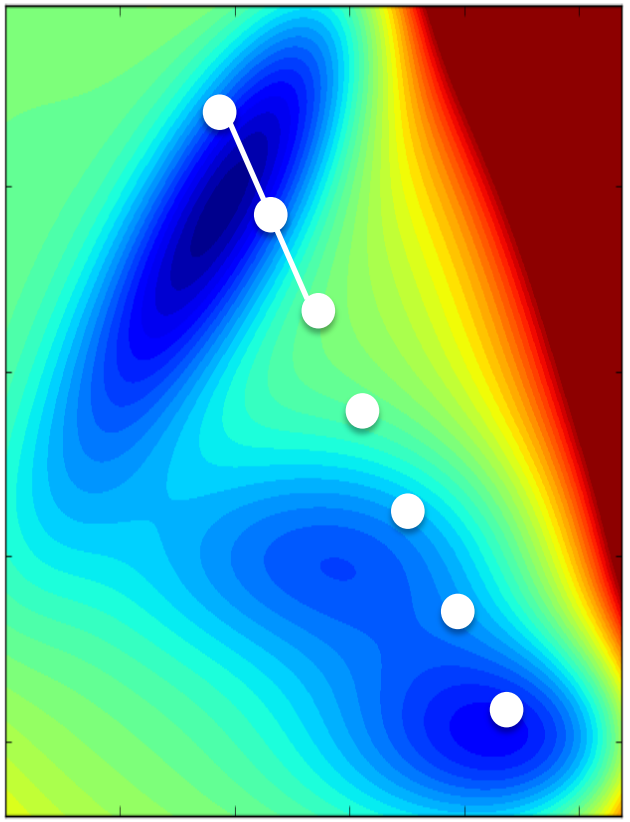
- Path-finding algorithms:

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

  - Start from an initial string of N images ($\zeta_i$)
  - Restrain M copies of each image for time $\Delta t$

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

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



- Free energy calculations:

  **e.g., umbrella sampling (US or BEUS):**

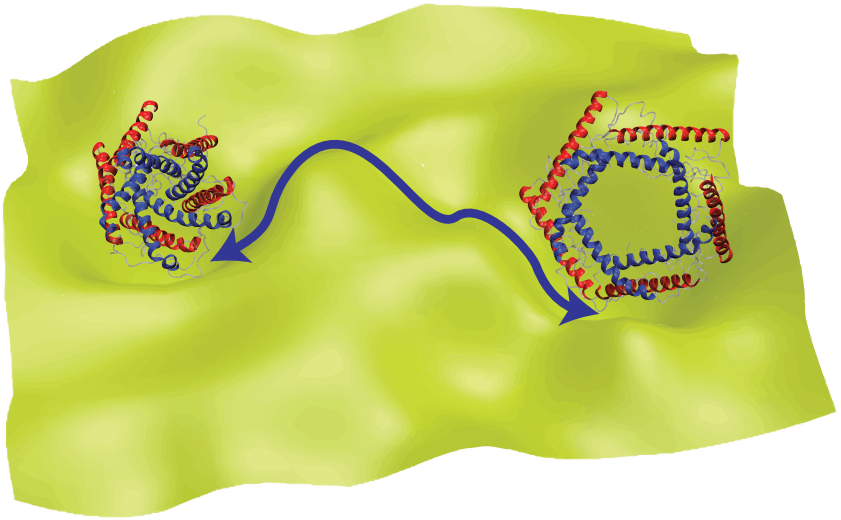
  - Bias one or more (e.g., M) copies: $U_i(\xi) = \frac{1}{2}k(\xi - \zeta_i)^2$
  - Use a reweighting scheme to unbias the data:

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

Shirts, Chodera, JCP, *129*, 124105 (2008)

# Riemannian Reformulation

- Riemannian reformulation of path-finding algorithms and free energy calculations methods such as SMwST/BEUS provides 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).

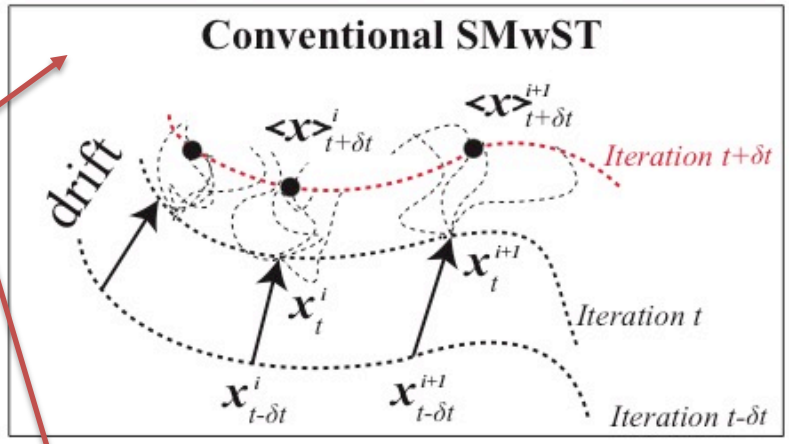
Fakharzadeh & Moradi, *Effective Riemannian diffusion model for conformational dynamics of biomolecular systems*. **J Phys Chem Lett.** 2016;7(24):4980-4987.

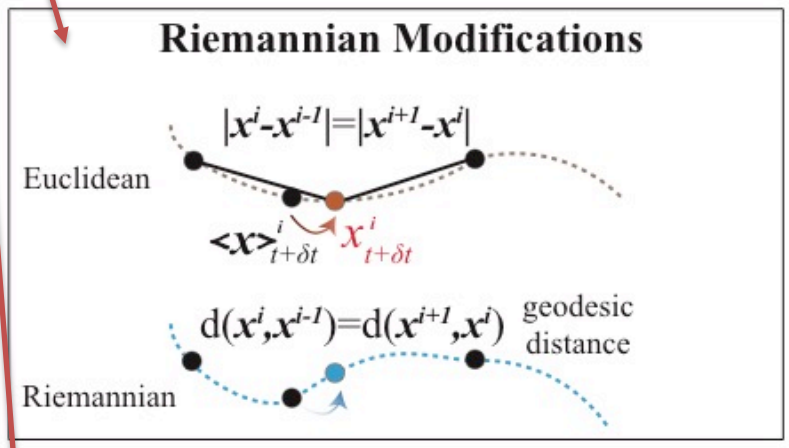
**Within the LCMC MD scheme, we have developed various improved variations of SMwST/BEUS**

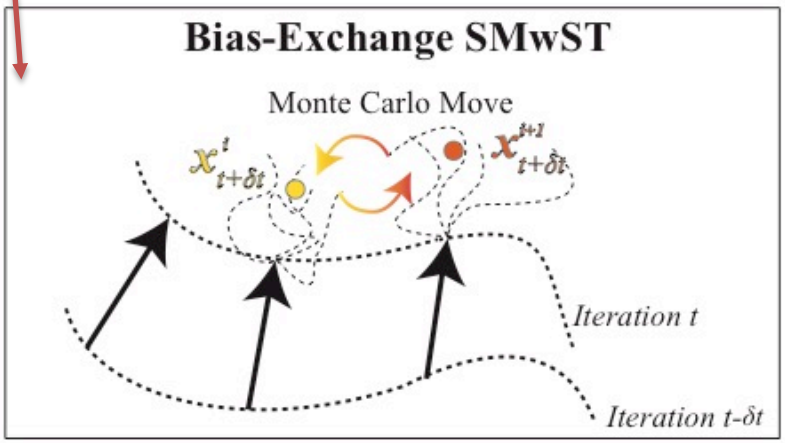
## LCMC MD with NAMD

Multiple **concurrent NAMD instances** are launched with internal partitions of Charm++ and located continuously **within a single communication world**. Messages between NAMD instances are passed by **low-level point-to-point communication functions**, which are accessible through **NAMD's TCL scripting interface**.

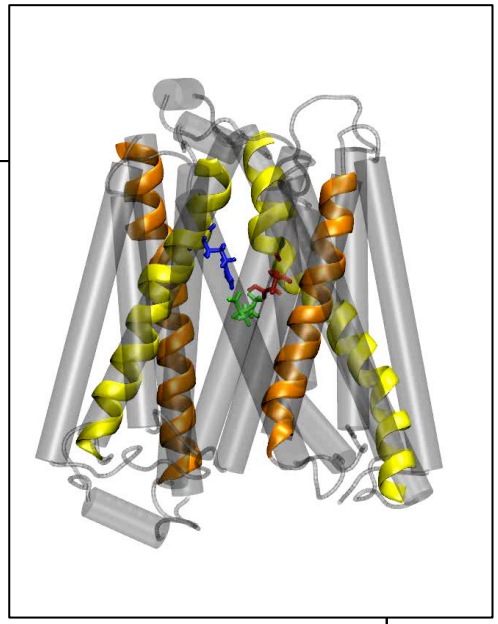
W. Jiang, J. Phillips, et al. Computer Physics Communications , 185, 908, 2014.

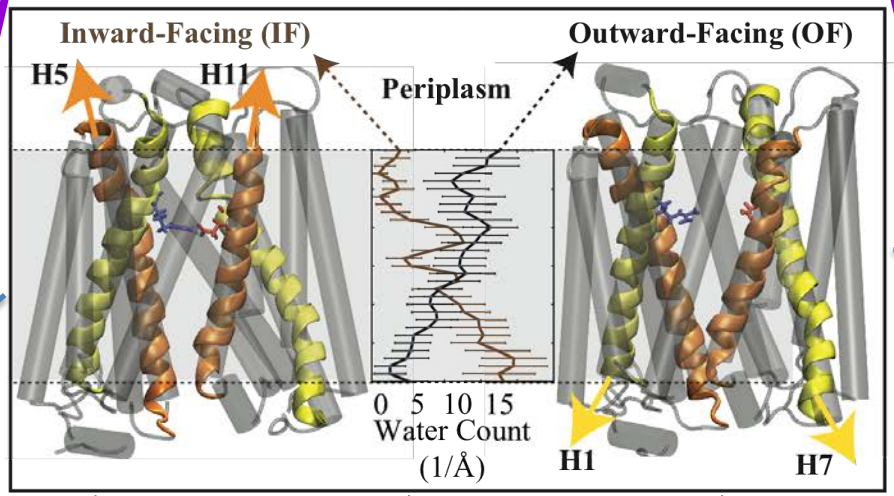


# Free Energy along the GKPOT IF-OF Transition Path





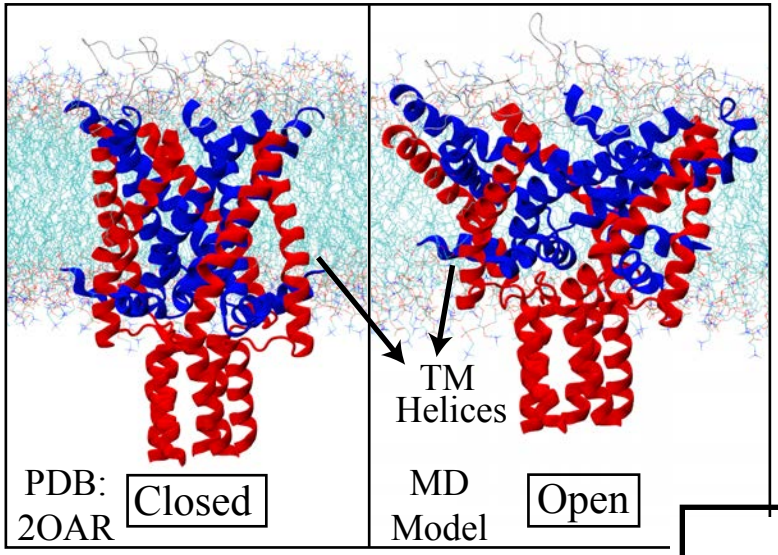

Free Energy (kcal/mol)

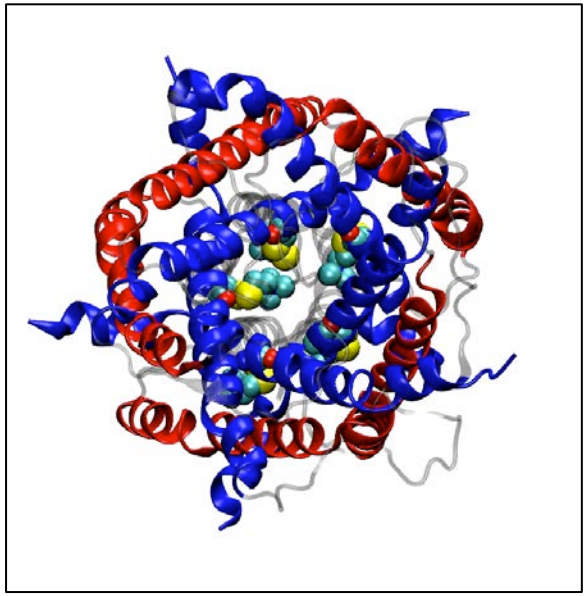
0 1 2 3 4 5 6 7 8

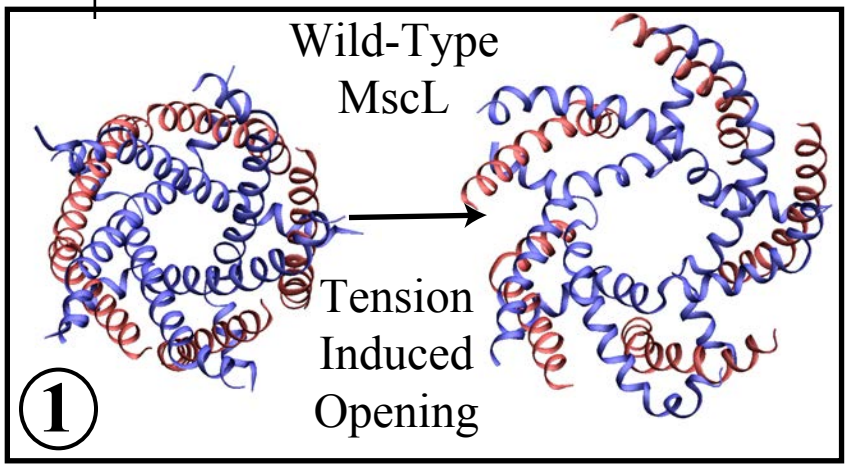
0 0.2 0.4 0.6 0.8 1

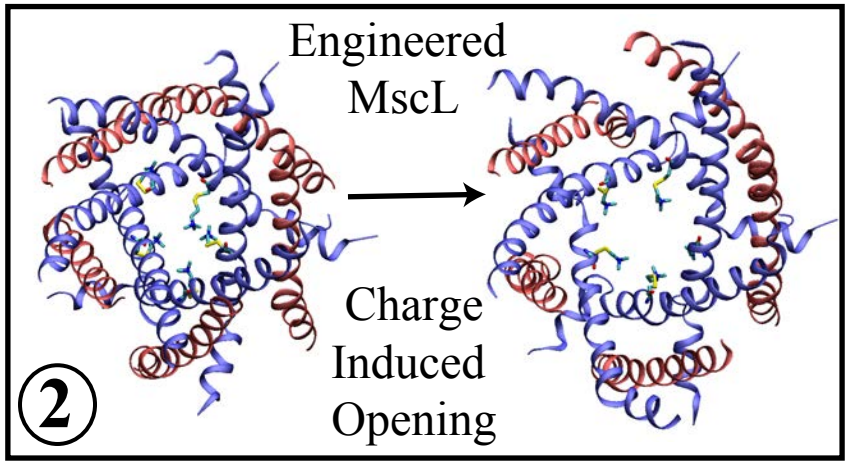
Reaction Coordinate

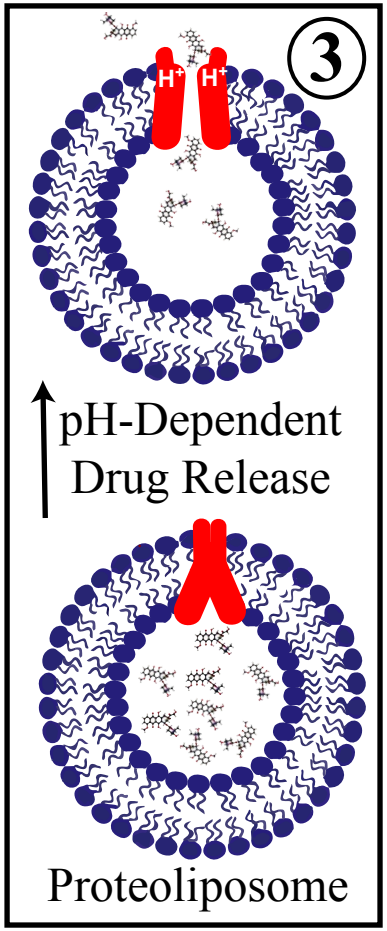
# pH-induced Activation of an Engineered Mechanosensitive Channel of Large Conductance (MscL)





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Dylan Ogden

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