Modern Molecular Simulations using Extended-Lagrangian Approaches

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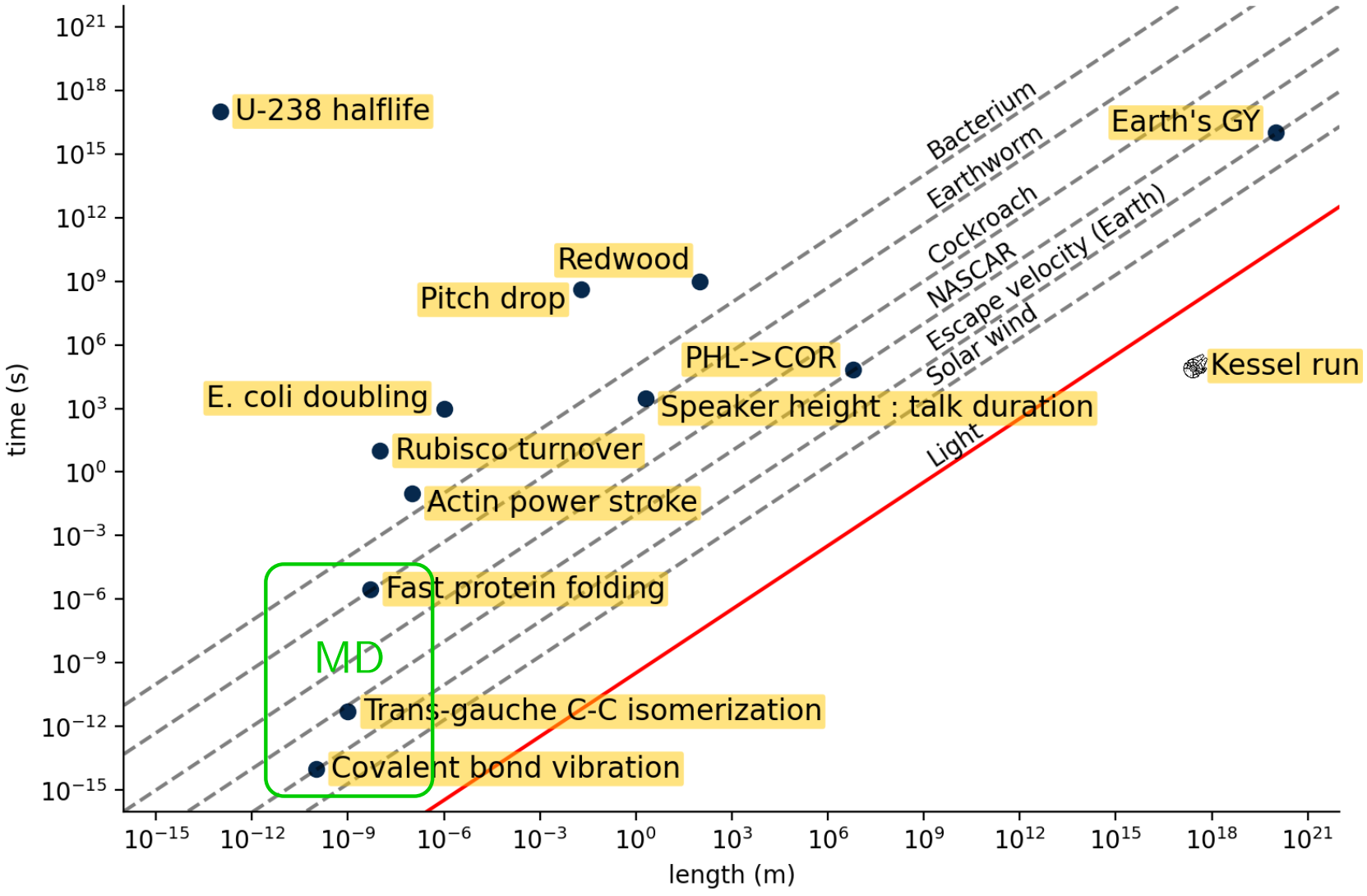
Outline

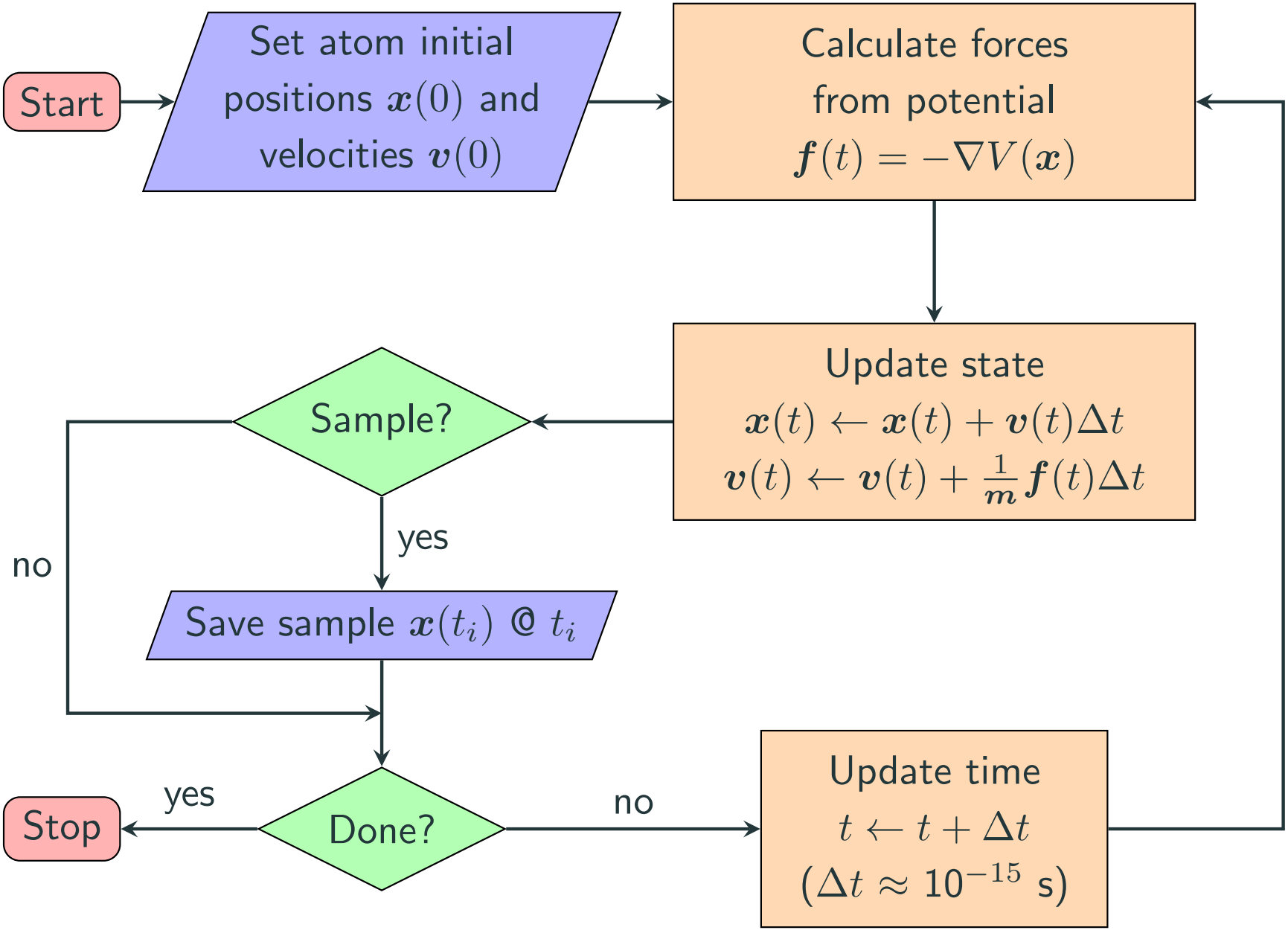
1. Introduction and Motivation
2. Temperature-Accelerated MD
3. On-the-Fly Parameterization
4. Summary

Introduction and Motivation

Time and Length Scales of Some Importance



Molecular Dynamics (MD)



MD and Ergodicity

Statistical mechanics:

$$P_\nu = \left\{ \begin{array}{l} \text{Probability of state } \nu \equiv (\boldsymbol{x}, \boldsymbol{v}) \\ \text{out of ensemble of states} \\ \text{at equilibrium} \end{array} \right\}$$

Observables as ensemble averages:

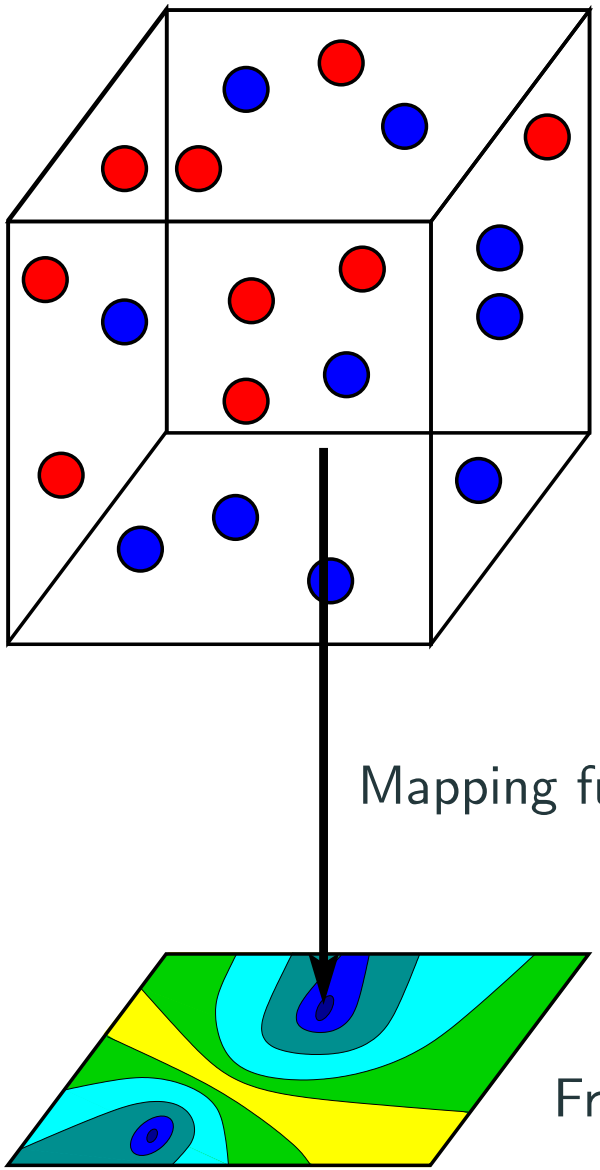
$$\langle G \rangle = \sum_\nu P_\nu G_\nu$$

Ergodic hypothesis: Infer P_ν via uniform random sampling

$$\langle G \rangle = \lim_{t \to \infty} \frac{1}{N} \sum_i^N G(\nu_{\mathrm{MD}}(t_i))$$

Ergodicity in MD is (usually) unattainable!

The Essential Problem: Poor Sampling of Feature Space



Configuration space $\boldsymbol{x} \equiv (x_1, y_1, z_1, \dots)$

MD $m_i \ddot{x}_i = -\nabla_i V(\boldsymbol{x}) +$ ensemble forces

Samples $\Rightarrow \ \boldsymbol{x}(t_1), \ \boldsymbol{x}(t_2), \ \dots$

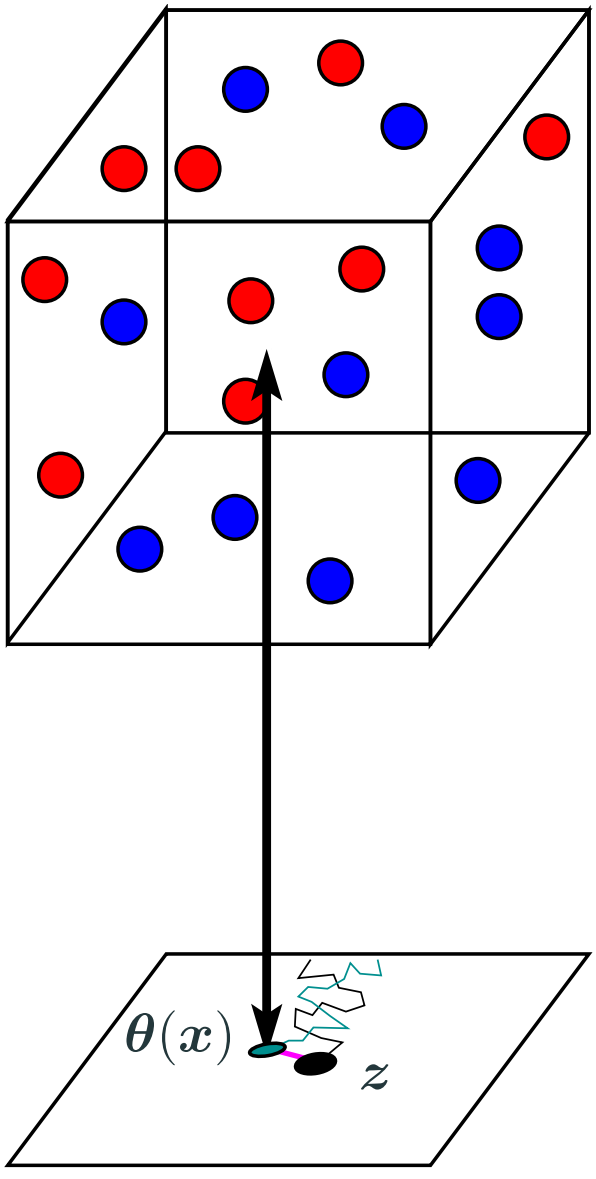
Ergodicity $\langle X \rangle \approx \dfrac{1}{n_\tau} \displaystyle\sum_{i=1}^{n_\tau} X[\boldsymbol{x}(t_i)]$

Mapping function $\boldsymbol{\theta}(\boldsymbol{x}) \mapsto \boldsymbol{z}$

Feature space $\boldsymbol{z}^M \equiv (z_1, z_2, \dots)$

Free energy $F(\boldsymbol{z}) = -k_\mathrm{B} T \ln \langle \delta \left[\theta(\boldsymbol{x}) - \boldsymbol{z} \right] \rangle$

Extended Lagrangian Formalisms



$$m_i \ddot{\boldsymbol{x}}_i = -\nabla_i V(\boldsymbol{x}) - \sum_{j=1}^{M} \kappa[\theta_j(\boldsymbol{x}) - z_j] \frac{\partial \theta_j}{\partial x_i} + \text{e.f.}$$

Forces link $\boldsymbol{x}$ and $\boldsymbol{z}$

Bias on $\boldsymbol{z}$: Enhanced sampling of feature space

$$\bar{m}_j \ddot{z}_j = \sum_{k=1}^{M} \mathcal{M}_{jk} \kappa[\theta_k(\boldsymbol{x}) - z_k] + \text{e.f.}$$

Temperature-Accelerated MD

Temperature-Accelerated MD (TAMD)

Maragliano and Vanden-Eijnden, *Chem Phys Lett* **426**:168 (2006)

Extended potential energy: $U(\boldsymbol{x}, \boldsymbol{z}) = V(\boldsymbol{x}) + \frac{1}{2}\kappa \sum_{j=1}^{M} [\theta_j(\boldsymbol{x}) - z_j]^2$

Dynamics of configurational variables $\boldsymbol{x}$ ("restrained MD"):

$$m_i \ddot{x}_i = -\frac{\partial V(\boldsymbol{x})}{\partial x_i} - \kappa \sum_{j=1}^{M} [\theta_j(\boldsymbol{x}) - z_j] \frac{\partial \theta_j}{\partial x_i} + \text{thermostat @ } \beta$$

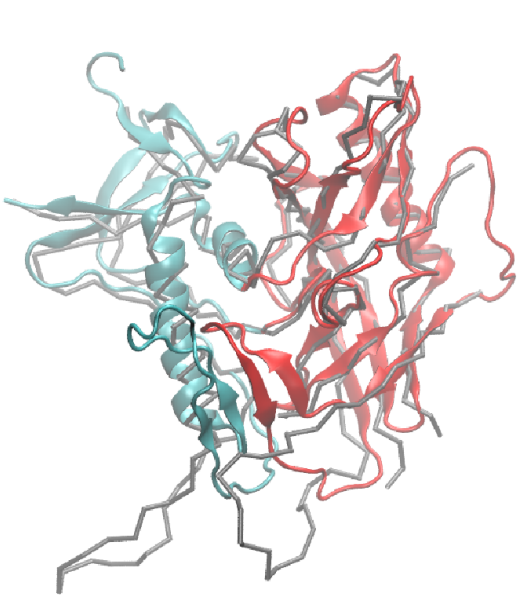
Dynamics of auxiliary variables $\boldsymbol{z}$ with enforced separation of time-scales:

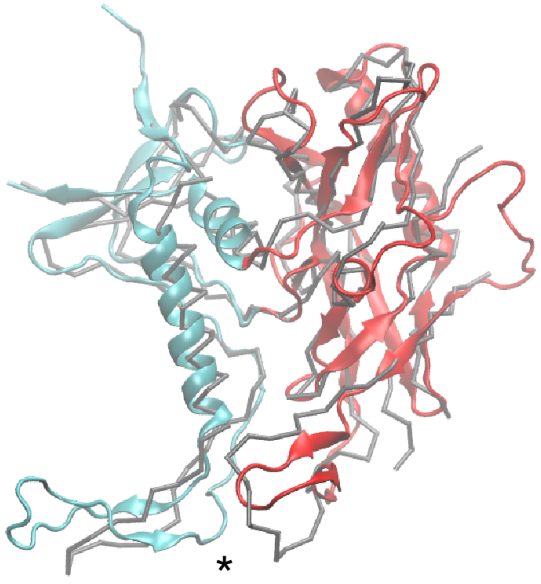
$$\bar{\gamma}\bar{m}_j \dot{z}_j = \kappa [\theta_j(\boldsymbol{x}) - z_j] + (\text{noise @ } \bar{\beta}) \approx -\frac{\partial F_\kappa}{\partial z_j} + \text{noise}$$

$\boldsymbol{z}$ responds to free energy like $\boldsymbol{x}$ responds to potential energy.
Taking $\bar{\beta} < \beta$ ($\bar{T} > T$) $\Rightarrow$ enhanced sampling in a chosen feature-space.

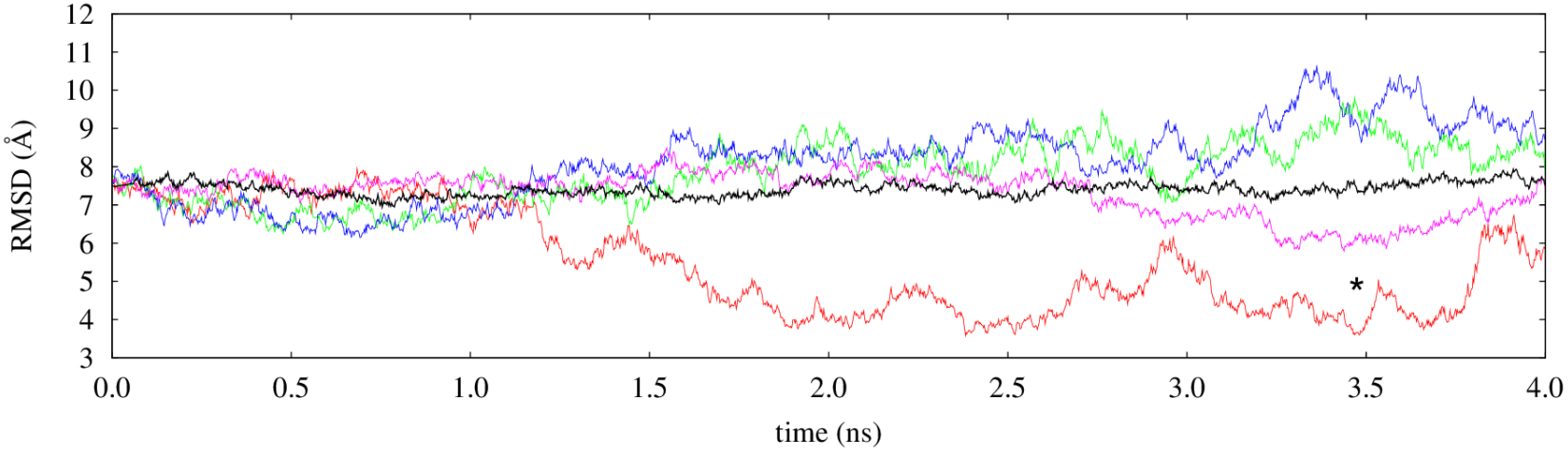
TAMD predicts HIV-1 gp120 conformational changes

CFA and E. Vanden-Eijnden *PNAS* **107**:4961 (2010).





- Ribbon: TAMD from 1GC1 (ground state) (inner/outer)
- Tube: Reference from 3HI1 (Ab-F105-bound)



On-the-Fly Parameterization

On-the-Fly Parameterization (OTFP) to Get F from TAMD

CFA and E. Vanden-Eijnden *Chem Phys Lett* **547**:114 (2012)

Basis-function expansion

$$\tilde{F}(\boldsymbol{z}) = \sum_k \lambda_k \phi_k(\boldsymbol{z})$$

Error as objective function

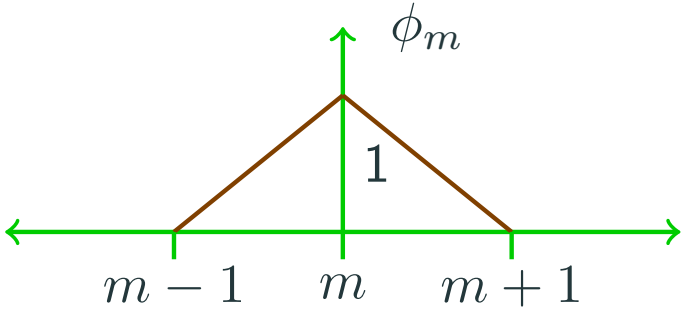
$$E(\boldsymbol{\lambda}) = \left\langle \sum_j \left[\kappa[z_j - \theta_j(\boldsymbol{x})] - \frac{\partial \tilde{F}(\boldsymbol{z})}{\partial z_j} \right]^2 \right\rangle_{\text{TAMD}}$$

$$A_{nm} = \frac{1}{2} \left\langle \sum_i \frac{\partial \phi_m(\boldsymbol{z})}{\partial z_i} \frac{\partial \phi_n(\boldsymbol{z})}{\partial z_i} \right\rangle_{\text{TAMD}}$$

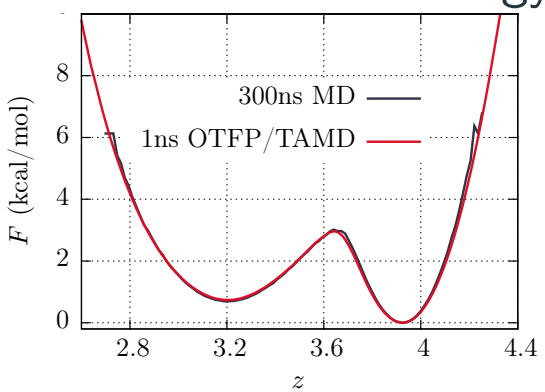
Minimize

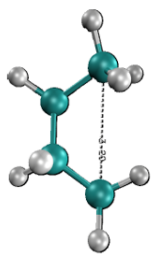
$$\boldsymbol{A\lambda} = \boldsymbol{b} \quad \leftarrow \quad \frac{\partial E}{\partial \boldsymbol{\lambda}} = 0$$

$$b_m = \left\langle \sum_i \frac{\partial \phi_m(\boldsymbol{z})}{\partial z_i} \kappa[z_i - \theta_i(\boldsymbol{x})] \right\rangle_{\text{TAMD}}$$

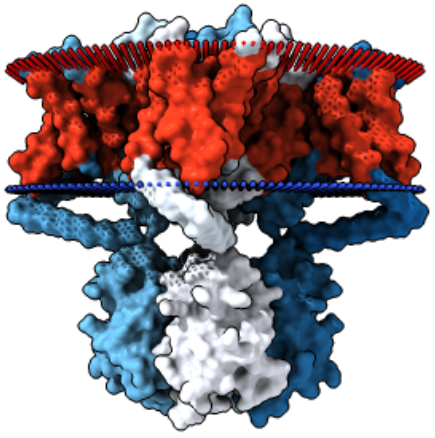


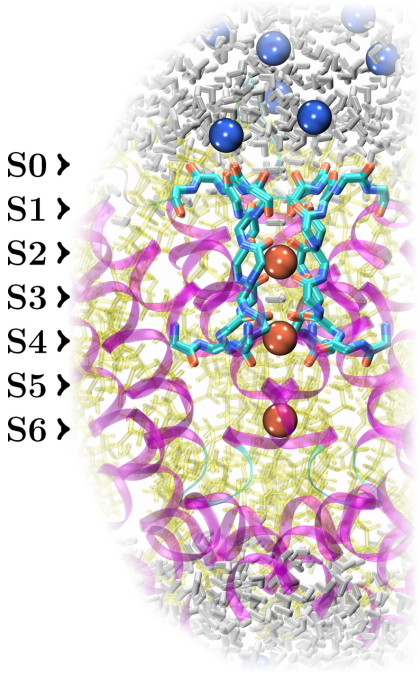
MD vs OTFP: Butane C_1-C_4 Distance Free Energy



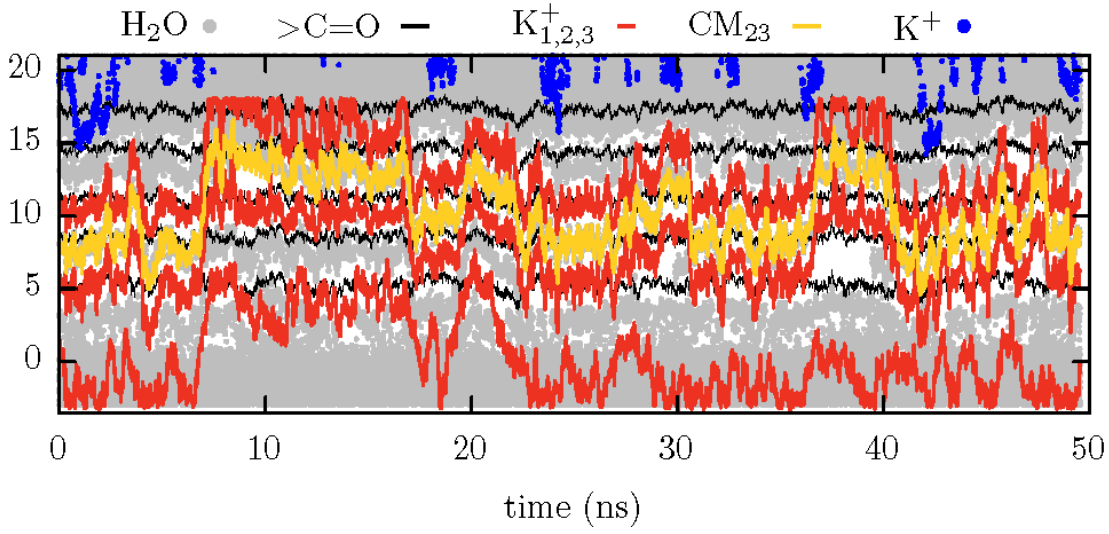


Potassium Channels

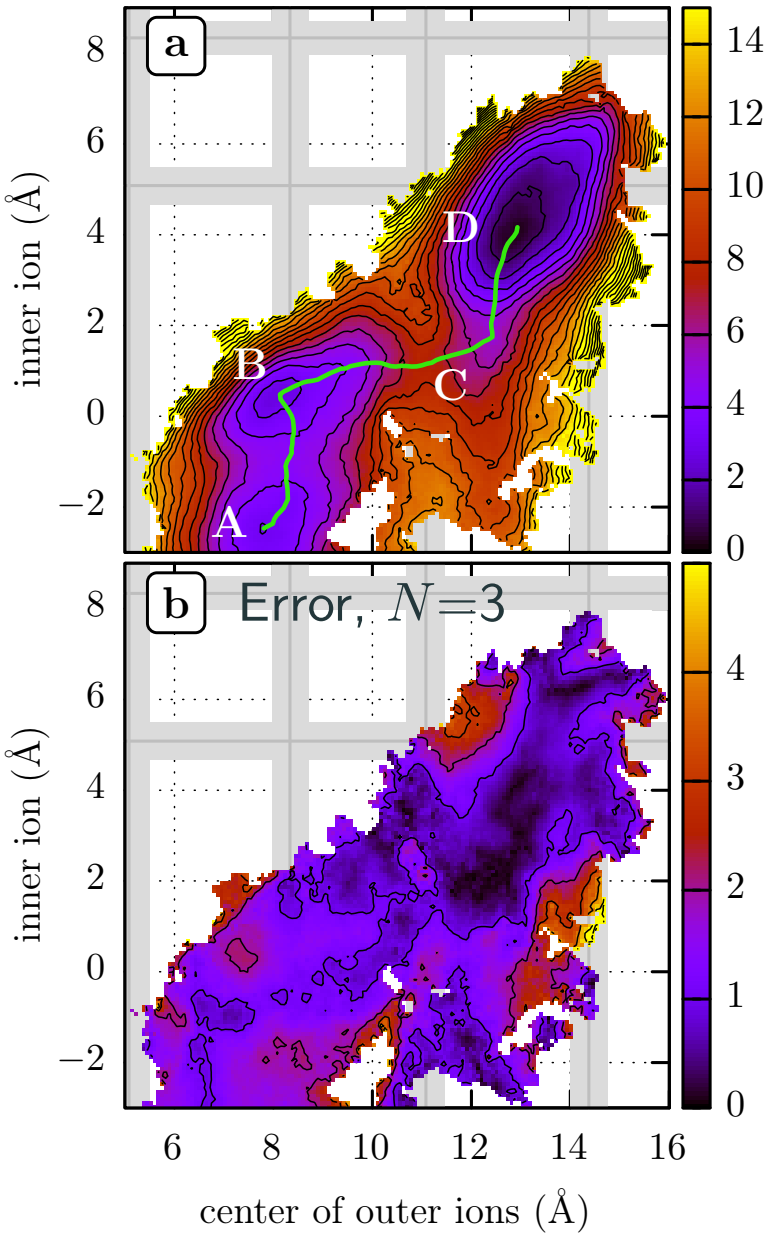




- Responsible for cell membrane *depolarization* in action-potential firing
- Malfunctions: "channelopathies" like episodic ataxia, neuromyotonia, seizure, and tinnitus
- Selectivity mechanism is not well-understood because the selectivity filter is complicated

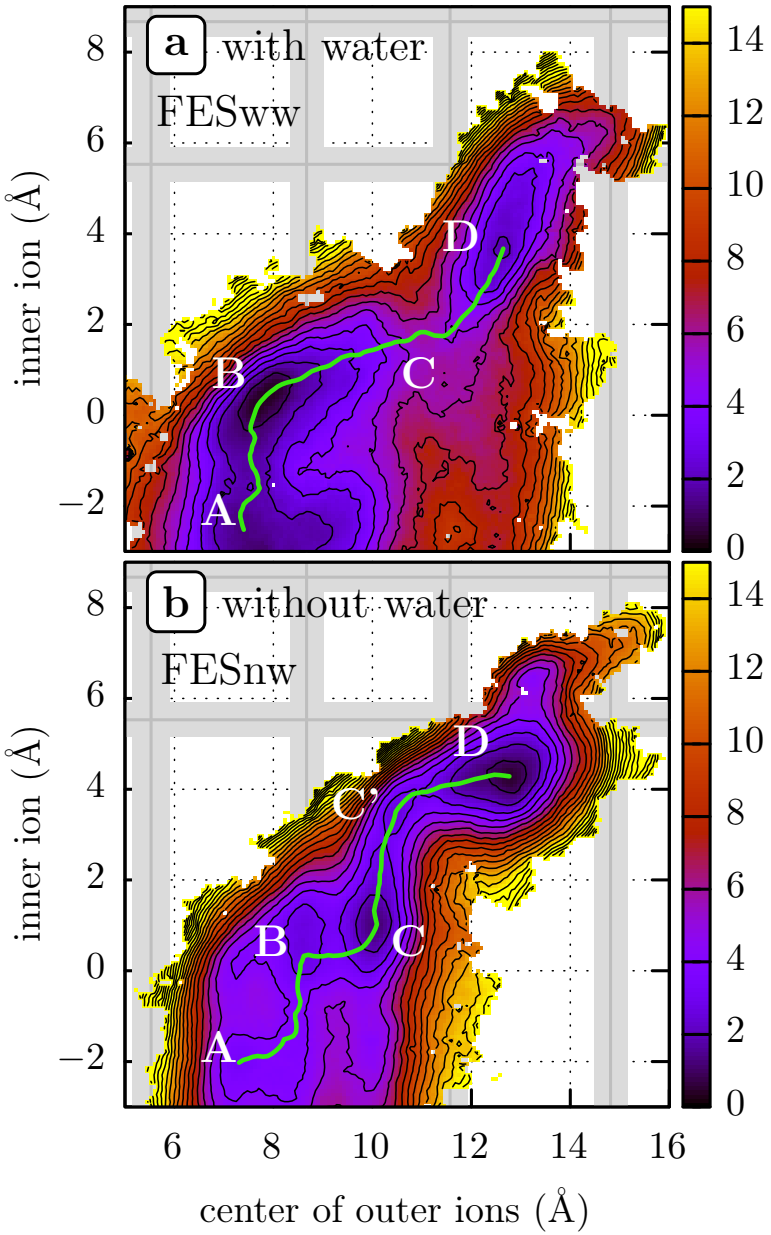


2D OTFP: Transport Minimum Free-Energy Pathways



- A→B: Innermost ion moves up one position
- B→C: $CM_{2,3}$ moves up one position, followed quickly by
- C→D: Innermost ion moves up one more position
- ⇒ Net translocation of one K^+
- What role is water playing?

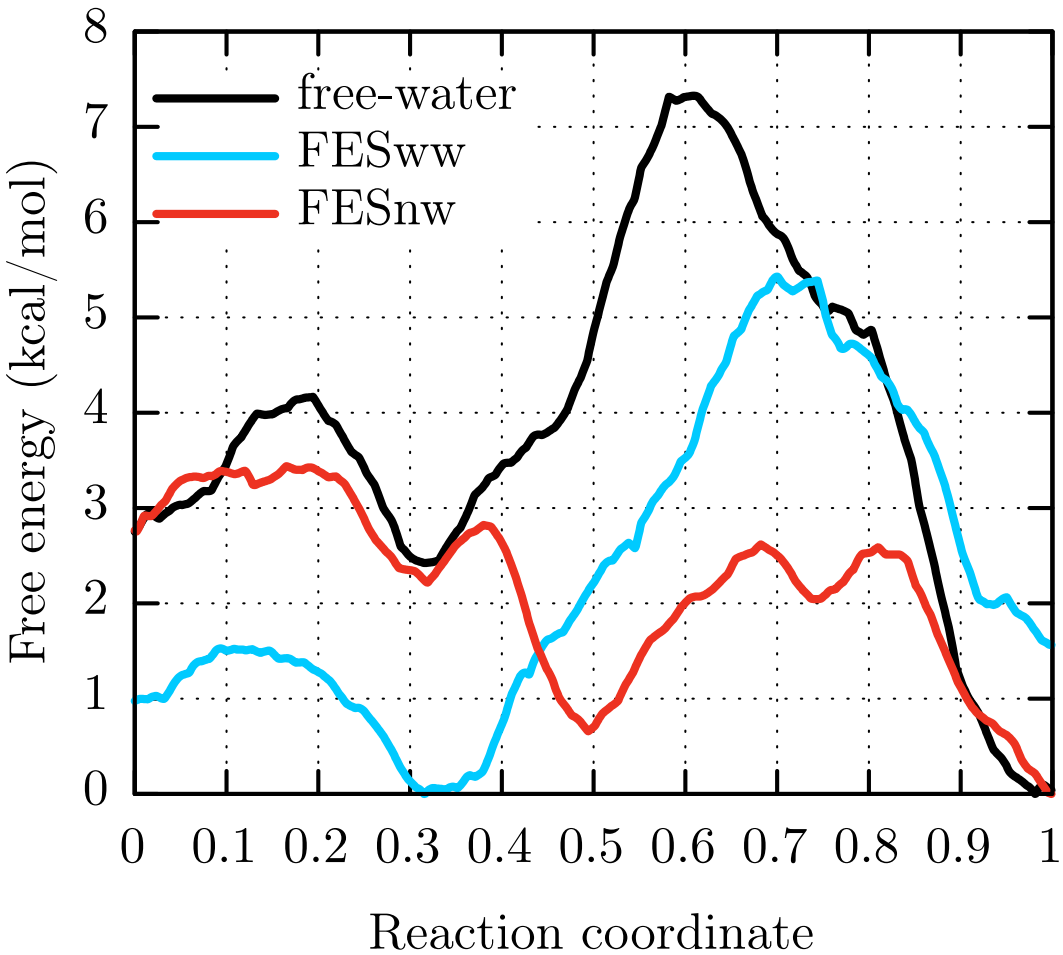
Water Restraints: Ion-Tethered vs. Excluded-from-Filter



- With one water tethered to each K^+, FES resembles unrestrained one
- With water excluded from channel, ion motion is less concerted, more "hard-knock" like

Free-Energy Profiles along MFEP's

S. A. Paz, L. Maragliano, and CFA *J. Chem. Theory. Comput.* **14**:2743-2750 (2018)



- Energy barriers for unrestricted and ion-tethered water systems are similar; suggests intercalated water is preferred
- Dry filter shows shallower barriers; dry transport might be faster if water could be actively excluded

Summary

Summary

- OTFP combines enhanced sampling and free-energy-profile generation to provide deeper understanding of biomolecular mechanisms
- We recapitulate water-mediated "knock-on" transport of multiple K^+ ions in Kv1.2, but also predict reduced barriers for dry transport
- Demonstrated Markovian milestoning along minimum free-energy pathways to estimate entry and exit rates of O_2 in MSOX
- MSOX: Simulations agree with experiment that modified ping-pong mechanism is more likely than ping-pong because substrate influences O_2 entry and exit kinetics
- MSOX: Substrate-induced gatekeeper closing and active-site desolvation likely underly the substrates effect on O_2.

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- **Climbing String:** Dr. Gourav SHRIVASTAV ()
- **Other projects:**
  - Steven GOSSERT (2021): HIV-1 Entry Inhibitor Design
  - Natasha VERGARA (2022): HIV-1 Entry Inhibitor Design
  - Ming HUANG (2023): Molecular modeling of thermosets
  - Dr. Salman ZARRINI: Molecular modeling of thermoset/glass sizing fluid
  - Dr. Mohammadjavad MOHAMMADI: HIV-1 Entry Inhibitor Design
- **Collaborators**
  - Prof. Eric VANDEN-EIJNDEN (NYU; Mathematics)
  - Prof. Irwin CHAIKEN (DUCOM; Biochemistry)
  - Prof. Amos SMITH III (UPenn; Organic Chemistry)
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- **Resources:** `www.github.com/cameronabrams/cfacv`, `www.github.com/cameronabrams/pestifer`