Modern Molecular Simulations using Extended-Lagrangian Approaches

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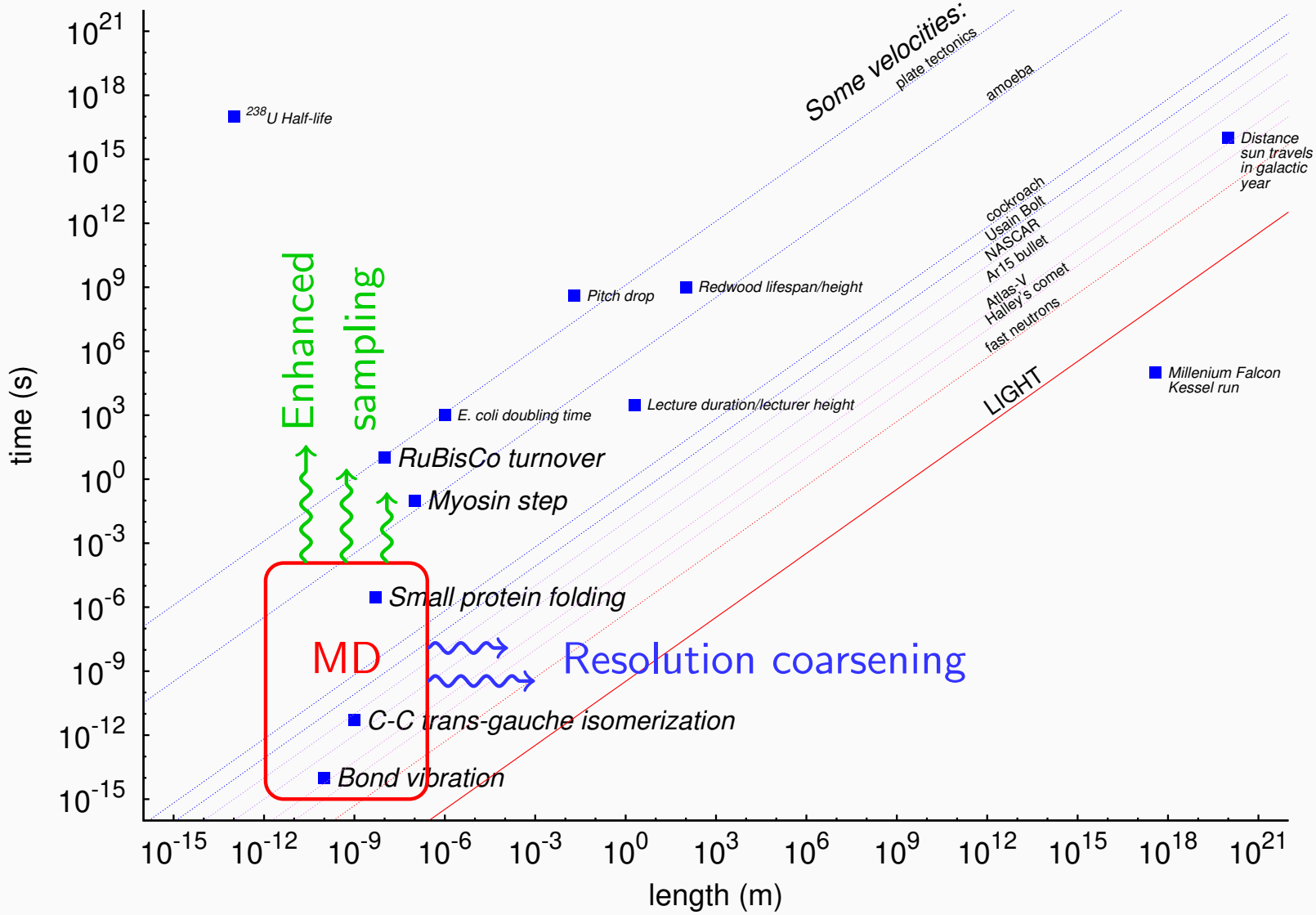
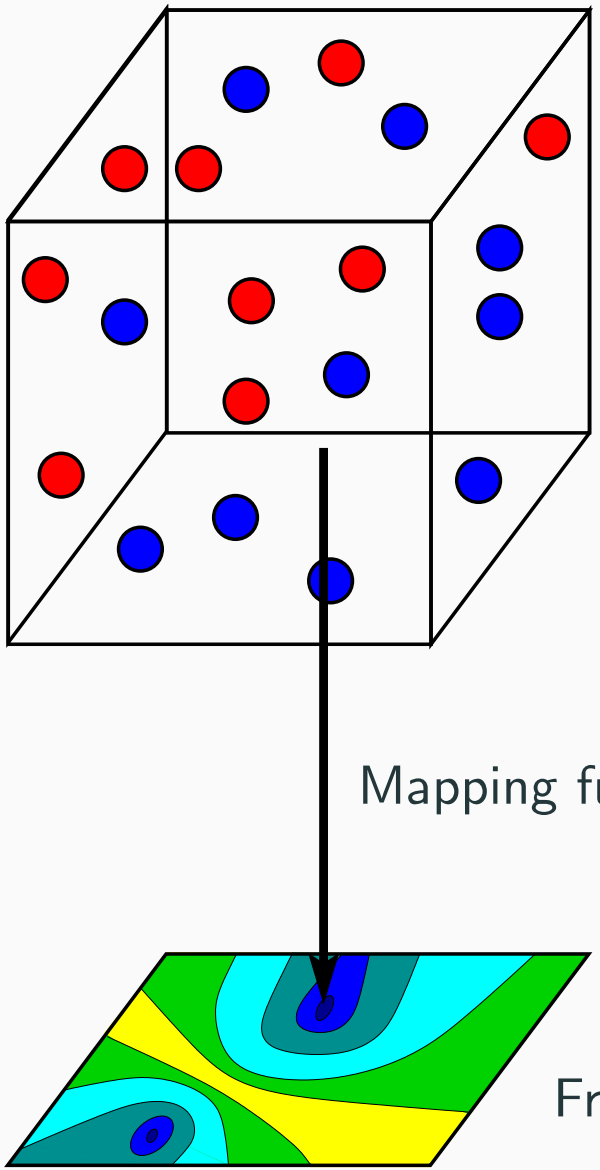
Outline

Introduction and Motivation

Lengthening the Reach of Molecular Dynamics Simulations



The Essential Problem: Poor Sampling of Feature Space



Configuration space $\boldsymbol{x}^{3N} \equiv (x_1, y_1, z_1, \dots)$

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

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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- **Milestoning:** Dr. Anthony BUCCI (West Pharma)
- **Other current 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. Gourav SHRIVASTAV: Milestoning and advanced methods
  - 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/psfgen`