PhD Thesis's Title: Navigating Protein Conformational Landscapes: An AI and Molecular Dynamics Approach

Abstract

Despite significant advancements in structural biology techniques, capturing diverse energy states and transition pathways of macromolecules remains an unmet challenge. Computational modeling, and especially Molecular Dynamics (MD) simulations, have been pivotal in studying complex biological macromolecules. However, traditional MD simulations grapple with issues such as slow and or inadequate sampling of their conformational transitions.

The thesis introduces a novel approach leveraging Machine Learning, Artificial Intelligence, and enhanced Molecular Dynamics (MD) sampling techniques. The method developped significantly expedites MD simulations and offers more effective and efficient sampling of conformational landscapes, as demonstated for few model and molecular systems. It has been applied as well to study the activation of the Voltage Sensor Domain of the Kv 1.2 potassium channel. The algorithm, together with state-of-the-art techniques applied to Markov State Modeling, revealed substantial insights on the kinetics involved.

All together this work paves the way for developpement of an automated pipeline that offers an exhaustive and holistic tool for sampling conformational landscales and revealing kinetics, with the ultimate characteristics of drasctically reducing human bias.

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