Using a Mechanistic Perspective to Simulate Protein Backbone Motion

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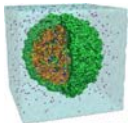
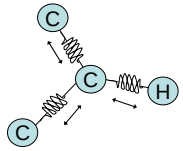
1. Simulating Protein Motion

The majority of proteins perform their function by changing their conformation. In an effort to better understand a protein's function and to facilitate efficient drug design methods, we desire to model these motions.



All atoms and their interactions are calculated in an MD Simulation[1]



Molecular Dynamics (MD)
Model all atoms & forces
Compute detailed motions
Computationally Expensive

Normal Mode Analysis (NMA)
Model connections as springs
Compute coarse motions
Computationally Efficient

MD cannot simulate protein motions that are longer than ~200ns, while NMA provides only a coarse analysis.

Protein Motions and MD Simulations		
Protein Phenomena Simulation	**Simulation Duration**	**Required Computation Time***
Peptide-Membrane Interaction[2]	110 ps ($1x10^{-12}$ sec)	160 CPU Hours
Side Chain, Ligand Interaction[3]	150 ps ($1x10^{-12}$ sec)	3000 CPU Hours
Phl p 6 Allergen Motion[4]	10 ns ($1x10^{-9}$ sec)	4000 CPU Hours
Protein Folding & Unfolding	Up to ms (10^{-3} sec)	Not feasible
Protein Ligand Docking	Up to 100+ seconds	Not feasible

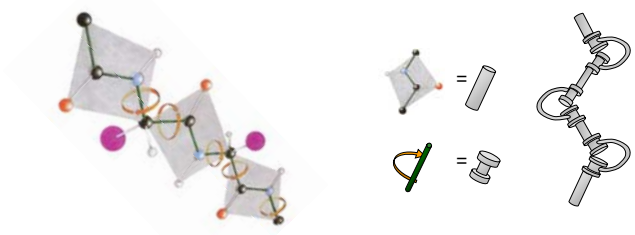
* CPU hour = 1 hour of computation time on a single computer

2. Rationale & Scope

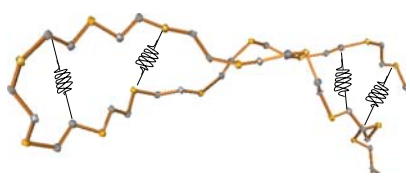
We want to devise a method that can simulate backbone motion without the need to calculate all intermolecular forces. As a first step towards such a computationally efficient method, we use operational space control principles from robotics and kinematics principles from mechanics to simulate the motion of a protein's backbone at interactive rates.

3. Kinematic Simulation of Backbone Motion

Covalent bonds are fixed in length, and we model these bonds as links in a kinematic chain. Dihedral angles reflect rotations around these links.

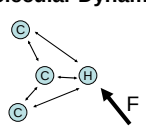


We model intermolecular forces, such as hydrogen bonds, as springs so that we can easily calculate the backbone motions caused by these forces.

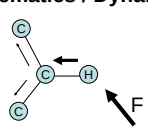


We use operational space control methods to efficiently transform information about the interactions of individual atoms of a protein into valid conformational changes of the entire kinematic structure.

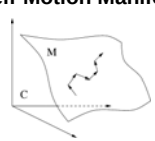
Molecular Dynamics



Kinematics / Dynamics

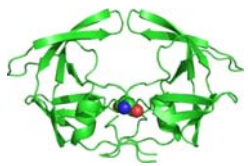


Self-Motion Manifold



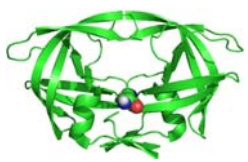
The underlying kinematic structure of the mechanistic model constrains the movement of the protein to kinematically feasible conformations.

4. Experiments & Results



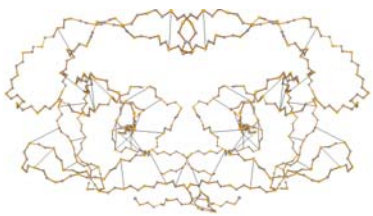
PDB: 1HHP
open conformation

HIV1 Protease transitions between two main conformations, characterized by the location of the flaps.



PDB: 1HVR
closed conformation

1. We model the open conformation of HIV1 Protease as a kinematic chain.
2. We apply a force on the flap to drive the protein towards the known closed conformation.



The kinematic structure and hydrogen bonds constrain the movement of the backbone in near real-time, at interactive rates, and at a fraction of the computation cost of an MD simulation. The resulting conformation of the kinematic chain is similar to the known biological closed conformation of HIV1 Protease.

Model Constraints	RMSD to 1HVR
Mechanistic Model Only (MM)	1.86 Å
MM + 10 Hydrogen Bonds	1.09 Å
MM + 20 Hydrogen Bonds	0.96 Å
MM + 30 Hydrogen Bonds	0.78 Å

This experiment demonstrates that our representation is computationally efficient and allows coarse simulation of biologically relevant protein motion.

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