BIOC404: Biochemical Methods – Introduction to Biomolecular Simulation

Lecture 1: Molecular dynamics and ensembles (Nov 20)
Lecture 2: Force fields and solvation (Nov 23)
Lecture 3: Enhanced sampling methods (Nov 27)

Overview:
Computational studies are becoming ubiquitious in molecular and cellular biology as supplement or validation of experimental findings. As such, it is important for students in these fields to be exposed to the basic concepts of molecular simulation and calculation while being able to identify what methods would be useful for their own research to increase impact and rigor. The lecture series will introduce many levels of molecular computation but will focus on molecular dynamics, as it represents the most relevant area for the widest range of students, with the aim of familiarizing the students to the concepts of molecular dynamics to aid in their understanding of studies in the current literature.

Lecture 1: Molecular dynamics and ensembles

- Computational methods in biochemistry
  - Bioinformatics
  - Systems biology/mathematical modeling
  - Molecular calculation and simulation
- General applications of molecular modeling and simulation
- Computational cost vs. resolution and accuracy
  - Introduction of “Hamiltonian”
  - Introduction of potential energy surface (PES)
    - Local minimums
    - Transition states
    - Reaction pathways
  - Degrees of freedom
    - Quantum chemical calculation vs simulation
  - Where to use tools
    - Quantum chemistry
    - All atom simulation (QM/MM, MD)
    - Coarse grain models
- What is molecular dynamics?
  - Define force
  - Separate kinetic and potential contributions
- The Ergodic hypothesis
  - Ensemble average vs time average
  - The sampling problem
- Introduce simulation ensembles
  - Minimization vs simulation
  - Equilibration vs production
- General molecular dynamics workflow
  - Introduce molecular dynamics integrators

    - Timestep limitations
    - Numerical chaos

Lecture 2: Force fields and solvation

- Reintroduce forces and Hamiltonian
- Detail molecular mechanics force fields
    - bonds
    - angles
    - torsions
    - non-bonded electrostatic
        - pairwise potentials
    - non-bonded, non-electrostatic (approximately vdW)
    - force field parameters and atom-typing
- Solvation models
    - Example protein folding problem, hydrophobic effect
    - Explicit water models
        - Detail commonly used models
        - Periodic Boundary conditions
            - Minimum image convention
            - Interaction cutoffs
    - Implicit water models
        - Definition of cavitation and interaction surface
        - Electrostatic screening
    - Comparison of advantages and limitations of the models

Lecture 3: Enhanced sampling methods

- Recall applications during first lecture
- Reintroduce the PES
    - Problems with native sampling and time
- Introduction to advanced sampling techniques
    - Potential of mean force
        - Protein folding
        - Ligand binding
    - Thermodynamic integration
        - Solvation
        - Mutations
        - Drug discovery
    - Replica Exchange Simulations
        - Intrinsically disordered proteins
        - Hamiltonian Replica Exchange