

Modeling Biomolecular Systems II

BME 540

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Introduction

- Why do we perform simulations?
- What makes simulations possible?
- How do we perform simulations?
- What types of things/systems do we simulate?
- Engineering aspects of simulations

Why do we perform simulations?

- Simulations are experiments performed on a computer
- (Repeat) Simulations are experiments performed on a computer
- Simulations represent a controlled environment
- Probe length and time scales not accessible by other means

Advantages of Simulations

- Simulations are not limited by the laws of physics – we define the laws and basis of interaction, dynamics, etc. – whether they be physical or nonphysical
 - Ignore forces – gravity, viscosity
 - Use of simple, effective potentials that give the correct dynamics (simple harmonic oscillator)
 - Increase time rate – slow reactions, diffusion limited reactions
 - Sampling – explore interesting regions of phase space that may only be periodically visited

Connection to Wet Lab Experiments

- Confirm, extrapolate and predict wet lab experimental results – simulations represent just one more experimental tool, just like EM, AFM, Stopped Flow, ...
- Can be cheaper, faster and easier than wet-lab experiments
 - No protein expression, purification, ...
 - Mutations, combinatorial chemistry, etc. is now easy
 - Drug libraries – high throughput screening
- Provides details not available in typical experiment
 - Single molecule dynamics – like laser tweezers
 - Reaction pathways
 - Atomic/ Molecular level dynamics – similar to neutron scattering or NMR

Disadvantages of Simulations

- A simulation is only as realistic as you make it – since you control the physics, the physics must be correct
- Can be time consuming and approximate
- Does not have wide based support from the experimental community (changing slowly)

What makes simulations possible?

- All sciences are based primarily on numbers, except for biology – this has started to change in the past few decades.
- Simulations have become possible since biological information is able to be expressed as data useful for computing (discrete objects)
- Protein sequence and structures
 - Sequence information (genome, protein)
 - Fold types
 - Secondary structure elements (alpha helices, beta sheets, ...)
 - Tertiary structure (structure of folded protein)
 - Quaternary structures (filaments, polymers)

Biomolecular Function

- An important part of function is interaction
 - Bound or co-crystal structures
 - NOE, FRET, x-ray footprinting, deuterium exchange – *areas that interact*
 - Rate constants – *how fast things interact*
 - Free energy calculations – *how strongly biomolecules interact*

Required Technology

- Increase in computational speed has come at the same time as the biological information
- Computer Simulations will be required !!
 - Too time consuming and costly to get structures for all the proteins – the protein folding problem will have to be solved.
 - Once we get protein structures, we need to be able to figure out the physical basis for their interaction in order to understand protein complexes

How do we perform simulations?

- This is not theoretical work (most times) since we are not proposing new physical laws or interactions. All we are trying to do is recreate or mimic the physical environment and the interactions between the molecules/proteins involved (**remember it's an experiment**)
- We use *exotic* principles such as
 - Newton's laws – kinematics
 - Coulomb's law – electrostatics
 - Fluid dynamics
 - Polymer dynamics
 - Schrödinger equation

How do we perform simulations?

- Simulation does not mean programming! Most simulations techniques, methods, programs, algorithms exist in the public domain. Experimentalists can and do perform good simulations.
- Simulations tend to produce lots of data and not just one simple answer. You must understand in detail the physics of a system in order to design a simulation, and you must understand just as much in order to interpret the results.
- Simulations can be serial or parallel. Today, most people use PCs for serial jobs and Beowulf clusters or supercomputers for parallel applications

What do we simulate?

- Historically, simulations were very simple – molecules were spheres, no solvent, ... now we can simulate as much detail as we want (if we are willing to pay the price)
- Now, we are starting to simulate large biomolecular systems, but challenges still exist
- All simulations present a challenge to balance the detail of a simulation with the length of time it takes to run – we can't afford to simulate everything

Engineering Aspects

- Simulations make it easy to test theories and ideas
- Allows for the design and testing of small molecules, proteins or biomaterials
 - Drugs
 - Drug delivery systems
 - Issues of biocompatibility

Scope of BME 540

- We will be focusing on several aspects of proteins at different time and length scales
 - Quantum calculations
 - QM/MM hybrid methods
 - Molecular Mechanics – MD and MC
 - Electrostatics
 - Brownian Dynamics and Diffusion