Three Leading Molecular Dynamics Simulation Packages

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Molecular dynamics - the computation of the motion of atoms within a molecular system using molecular mechanics - calculates the time dependent behavior of a molecular system, and allows the study of structure and key properties like stability, diffusion, binding between molecules, and vibration.

Molecular dynamics allows us to study the dynamics of large macromolecules, including biological systems such as proteins, nucleic acids (DNA, RNA), membranes. It is widely used for drug design which is very common today in the pharmaceutical industry for the testing of a molecule's properties at the computer without the need to synthesise it (which is far more expensive). Dynamic events may play a key role in controlling processes which affect functional properties of the biomolecule. Molecular dynamics are also widely used in the study of liquid, clusters, surfaces, defects, fracture and friction.

A few molecular dynamics software packages are available for life science research and simulations. Different software have different features and their own merits. Here is a brief introduction to three of the most popular molecular dynamics packages - Amber, CHARMm and Gromacs - which we have been supporting in recent years.

AMBER (Assisted Model Building and Energy Refinement)

Amber is the collective name for a suite of programs that allows users to carry out and analyse molecular dynamics simulations, particularly for proteins, nucleic acids and carbohydrates. It is also a family of force fields for molecular dynamics of biomolecules. Further development of both the force fields and software are now coordinated by David A. Case at The Scripps Research Institute.

The Amber software suite contains three kinds of programs: preparation programs, simulation programs and analysis programs.

The main preparation programs are **Antechamber** and **LEaP.** Antechamber automates the process of developing force field descriptors for most organic molecules. It starts with structures (usually in PDB format), and generates files that can be read into LEaP for use in molecular modeling. The force field description that is generated is designed to be compatible with the usual Amber force fields for proteins and nucleic acids. LEaP is an X-windows-based program that provides for basic model building and Amber coordinate and parameter/topology input file creation. It includes a molecular editor which allows for building residues and manipulating molecules.

The main molecular dynamics program is **Sander**. Sander simulates annealing with NMR-derived energy restraints. This allows for NMR refinement based on NOE-derived distance restraints, torsion angle restraints, and penalty functions based on chemical shifts and NOESY volumes.

Sander is the "main" program used for molecular dynamics simulations, and is also used for replica-exchange, thermodynamic integration, and potential of mean force (PMF) calculations. Sander also includes QM/MM capability.

The **ptraj** analysis program is used to analyse MD trajectories, computing a variety of things, like RMS deviation from a reference structure, hydrogen bonding analysis, time-correlation functions, diffusional behavior, and so on.

An overall view of Amber's strength and weaknesses is given in the following table, adopted from the article "The Amber Biomolecular Simulation Programs" published on Journal of Computational Chemistry, 26, 1668-1688, 2005.

Table 1. Strong and Weak Points of the Amber Biomolecular Simulation Programs.

Strengths	Weaknesses
Amber implements efficient simulations with periodic boundary conditions, using the PME method for electrostatic interactions and a continuum model for long-range van der Waals interactions.	One cannot do good simulations of just part of a system, such as the active site of an enzyme: stochastic boundary conditions for the water-continuum interface are missing, as are efficient means for handling long-range electrostatics and a reaction field.
Non-periodic simulations are supported, using a generalized Born or numerical Poisson-Boltzmann implicit solvent model.	The component programs lack a consistent user interface; there is only limited scripting capability to support types of calculations not anticipated by the authors.
Explicit support is provided for carbohydrate simulations, as well as for proteins, nucleic acids and small organic molecules.	There is limited support for force fields other than those developed by Amber contributors.
Free-energy calculations use thermodynamic integration or umbrella sampling techniques, and are not limited to pairwise decomposable potentials.	Missing features include: "dual topology" free energy calculations, reaction-path analysis, Monte Carlo sampling, torsion angle dynamics, and interactive steered molecular dynamics.
Convergence acceleration can use locally-enhanced sampling or replica exchange techniques.	QM/MM simulations are limited to semiempirical Hamiltonians, and cannot currently be combined with the PME or generalized Born solvation options.
There is a extensive support for trajectory analysis and energetic post-processing.	The codes were written by many authors over many years, and much of it is difficult to understand or modify.
Restraints can be very flexible, and can be based on many types of NMR data.	Efficient parallel scaling beyond about a dozen processors may required access to special hardware or the adoption of an implicit solvent model.
There is a large and active user community, plus tutorials and a User's Manual to guide new users. The source code is portable and is available for inspection and modification.	Users are required to compile the programs themselves, and it can be tedious to assemble the needed compilers and libraries.

***AMBER** software package is available at SVU on the alpha system cheetah and cheetah2, and Atlas0 Linux cluster.*

CHARMm (**Chemistry at HARvard Macromolecular Mechanics**)

CHARMm is a program for macromolecular dynamics and mechanics. It performs standard molecular dynamics in many different ensembles (for example NVE, NVT, NPT) using state-of-the-art algorithms for timestepping, long range force calculation (including Ewald and PME methods) and periodic images. CHARMm can be used for energy minimisation, normal modes and

crystal optimisations as well. The potential energy functions available for use with CHARMm have been extensively parameterised for simulations of proteins, nucleic acids and lipids. Free energy methods for chemical and conformational free energy calculations are also fully developed and available in CHARMm.

Key Features of CHARMm in Insight II

- Ability to generate PSF and RTF files for use with standalone CHARMm
- Typing using CHARMm, charmm19, charmm22, charmm27, and CFF
- Energy minimisation using all available methods
- Molecular Dynamics simulations: NVE, NVT
- Langevin Dynamics
- Generalised Born implicit solvent model
- Explicit solvation including the ability to use the Particle Mesh Ewald method for improved treatment (New in InsightII 2005)
- Constraints, assemblies, and integration with other powerful InsightII features
- Access to MMFP (The Miscelaneous Mean Field Potential Commands)
- Advanced trajectory analysis with DeCipher

*At SVU, we have the commercial version of **CHARMm,** which is interfaced from the InsightII software.*

GROMACS (Groningen Machine for Chemical Simulations)

Gromacs is primarily designed for biochemical molecules like proteins and lipids that have many complicated bonded interactions, but since it is extremely fast at calculating the nonbonded interactions (that usually dominate simulations) it is also used for research on non-biological systems, for example polymers.

GROMACS is user-friendly, with topologies, parameter files, and error messages written in clear text format. There is a lot of consistency checking, but no scripting language - all programs use a simple interface with command line options for input and output files.

Gromacs does not have a force field of its own, but it is compatible with Gromos, OPLS, Amber, and ENCAD force field. Interfaces with popular quantum-chemical packages (MOPAC, GAMES-UK, GAUSSIAN) are provided to perform mixed MM/QM simulations.

The aim of GROMACS is to provide a versatile and efficient MD program with source code, especially directed towards the simulation of biological macro molecules in aqueous and membrane environments, and is able to run on single processors as well as on parallel computer systems. It provides not only microcanomical Hamiltonian mechanics, but also stochastic dynamics (SD) including Langevin and Brownian dynamics, and energy minimisation (EM).

The highly optimised code makes GROMACS the fastest program for molecular simulations to date. Besides, the support of different force fields and the open source (GPL) character make

GROMACS very flexible. A notable use of GROMACS is in the distributed computing project Folding@home where it is used extensively in the simulation of protein folding.

Gromacs is available at SVU on the atlas0 Linux cluster.

Please email ccesvuhelp@nus.edu.sg should you have any queries on how to use these software.