GPU Accelerated Molecular Dynamics Enabling Transformative Drug Development

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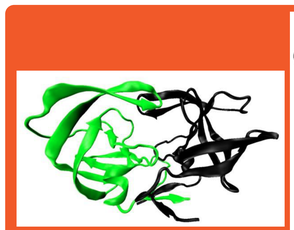
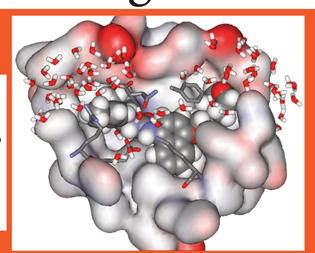
GPU acceleration is crucial for all facets of molecular dynamics development and workflow for drug discovery

One powerful computational technique for the science of drug development has been the use of molecular dynamics (MD) simulations. MD simulations can simulate the interactions and dynamics between small-molecule drugs and membrane-bound proteins on an atomic level. With this method, it is possible to understand the biological function of drug targets through their structural motions. GPU computing is revolutionizing the field of MD, with GPU accelerated MD code competing with national supercomputers. Our research goal is to use GPU technology to not only improve MD performance, but to improve MD development and workflow for drug development.

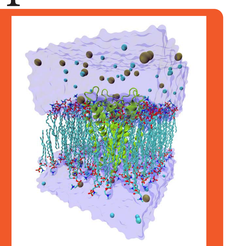
1. The Science of Drug Development



HIV-1 protease



p38 protein kinase*

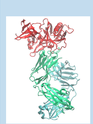


KcsA channel and POPC membrane+

2. Computational Drug Development

Structure based drug design

1. Biological identification of a biomolecular target



HIV glycoprotein gp120 and antibody b12

2. Generation of small molecules or biologicals that bind or influence activity

3. Library screening and optimization

4. Structure determination of biomolecular complexes

Computational drug development

Identification of interaction site

Prediction of docking and affinity

Structure and dynamics refinement

Amber Molecular Dynamics

3. Molecular Dynamics

Amber Molecular Dynamics (MD)
A suite of computational chemistry programs and force fields for molecular dynamics

Force fields and molecular dynamics
Amber includes force fields designed for the simulation of nucleic acids, proteins, and lipids in solvent.

Poisson-Boltzmann solvation calculations

Accelerated molecular dynamics

QM/MM calculations coupled to a variety of external quantum chemistry programs

About Amber
Originally developed by Peter Kollman at UCSF

Currently developed by an international collaboration of computational chemistry groups

Used by thousands of researchers, cited widely in literature

4. GPU Accelerated Molecular Dynamics

One major problem for molecular dynamics simulations is the limit in the timestep size.

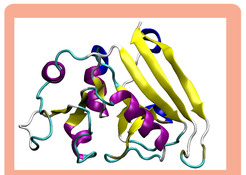
1-2 fs timestep

Previously, molecular dynamics simulations were not able to simulate biomolecular processes that take place on long time scales.

1 ns = 1000000 fs

6.47 ns per day, 8 CPUS

Another problem with molecular dynamics is many studied systems are not converged.



Dihydrofolate Reductase
23558 atoms

However, there are still new methods in molecular dynamics that do not yet take advantage of GPU acceleration.

It is now possible to run simulations on timescales on biological timescales, at a fraction of the cost.

58.28 ns per day, 2x NVIDIA Tesla M2090

5. Supercomputing and GPUs

Several US supercomputers include NVIDIA GPUs and are used for Amber Molecular dynamics

Keeneland

GIT, NICS, Oak Ridge, UT-Knoxeville
Keeneland

NCSA
Forge

However, as the amount of molecular dynamics data increases massively, the tools for analysis need to be adapted correspondingly.

New, fast methods to analyze molecular dynamics data with GPUs will be crucial.

Methods to mine and refine small-molecule and protein target dynamics data rapidly will be valuable for drug development.

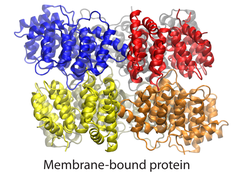
Trypsin inhibitor#

6. GPU Accelerated Force Field Development

One critical issue in molecular dynamics of small molecule drug and protein interactions is the quality of the force field used.

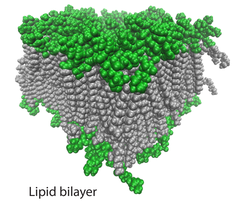
Force fields consist of an energy function and parameters that govern the interactions and motions of atoms in molecular dynamics.

Most proteins that are drug targets are found in a lipid bilayer membrane.



Membrane-bound protein

Studying lipid bilayer systems is difficult because the lipid force fields do not accurately describe lipid dynamics

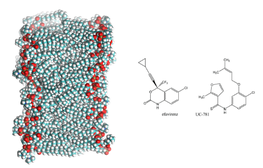


Lipid bilayer

Improving the lipid force field will enable better simulations of potential drugs interacting with drug targets, as well as other crucial drug properties

Because force fields play such an important role in molecular dynamics, new ways to systematically and rapidly improve force fields parameters are needed

Some approaches may require the massively parallel architechture of GPUs to fit many force field parameters at the same time



Non-nucleoside reverse-transcriptase inhibitors#

Future

Molecular dynamics has been at the forefront of scientific high performance computing. We will continue to develop applications that use the latest technologies and hardware, including GPU computing. As time-scales increase, more direct comparisons with experiments will be possible.

ACKNOWLEDGEMENTS:
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FIGURES:
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+ Aksimentiev, et al. Membrane Proteins Tutorial, 2012
# Okimoto, et al. PLoS Comp. Bio., 2009