

Introduction to CHARMM-GUI

Donghyuk Suh - Im Group @ Lehigh University
10th i-CoMSE Workshop
2025.06.26

6/26 Thursday Morning Session

CHARMM-GUI

- | | |
|---------------|--|
| 09:00 – 09:45 | Introduction to CHARMM-GUI (Enhanced Sampler, QM/MM Interfacer) |
| 09:45 – 10:30 | QMI Hands-on – playing with functionalities while building solvated lig |
| | |
| 10:30 – 10:50 | Coffee Break |
| | |
| 10:50 – 11:30 | QMI Hands-on – Building DHFR system (solvated protein+ligand) |
| 11:30 – 12:00 | MM minimization and equilibration of DHFR system @ PSC |
| 12:00 – 12:30 | Make QM/MM inputs for your own system of interest with QMI |

CHARMM-GUI – Since 2006



≡ Google Scholar

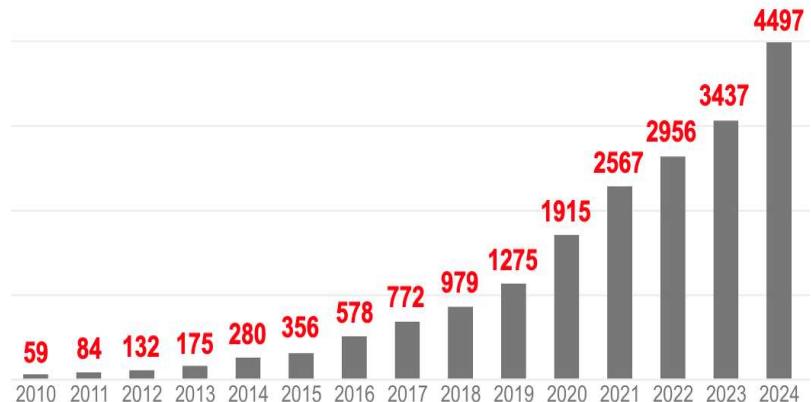


CHARMM-GUI

Im Lab, Biological Sciences, Chemistry, and Bioengineering, [Lehigh University](#).

Verified email at lehigh.edu - [Homepage](#)

Molecular Modeling and Si...

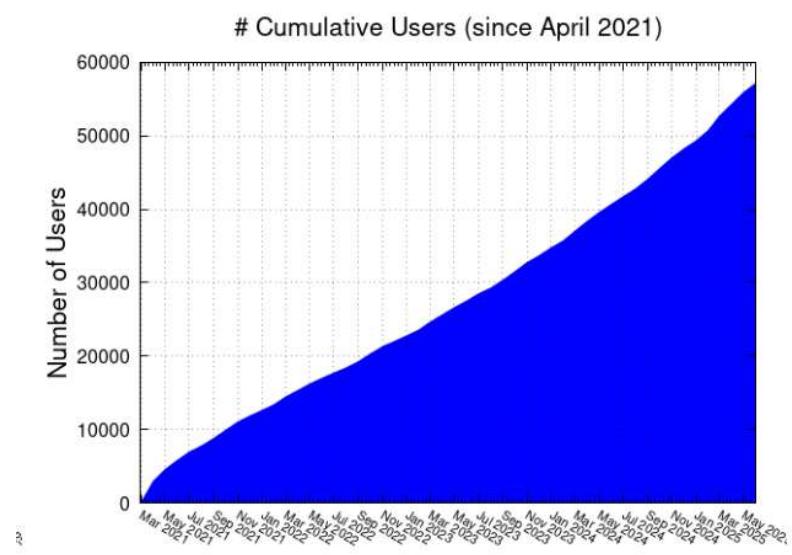
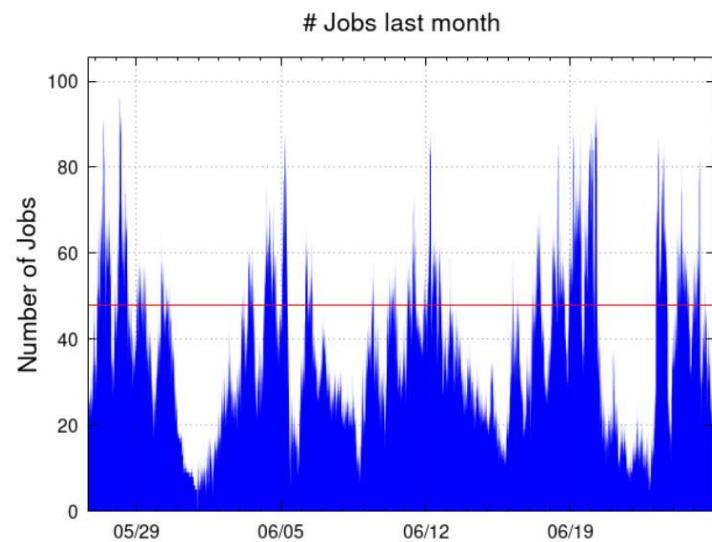


- A web-based graphical user interface (GUI) that prepares complex bimolecular systems/inputs.
- Gigantic cyberinfrastructure using C++, Python, Java, JS, CSS, php, html, sh, ...
- Developed originally for CHARMM;
 - Now + AMBER, NAMD, GENESIS, GROMACS, OpenMM, TINKER, Desmond, LAMMPS, ...
- Still CHARMM-GUI as system building is always done with CHARMM.

CHARMM-GUI – we're going to crash it today

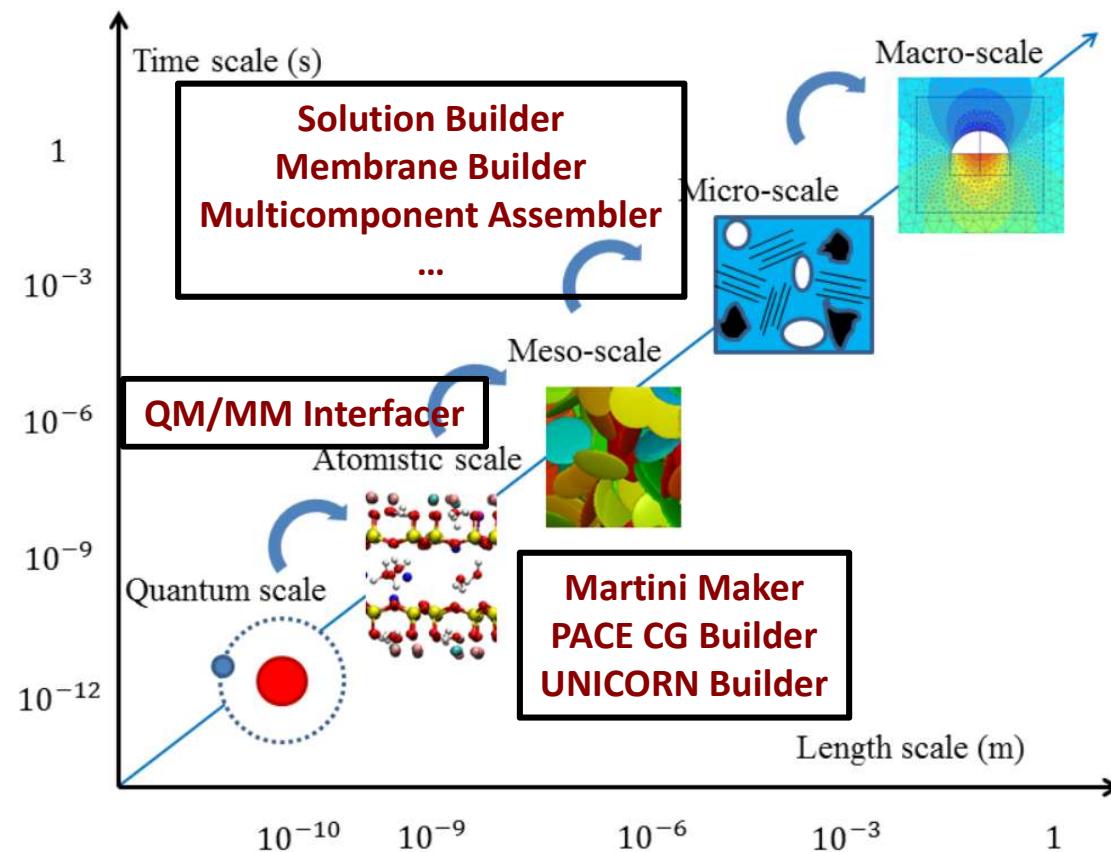
The CHARMM-GUI server is experiencing heavy load and may become randomly unresponsive. We are working on integrating job queueing and expanding our computing infrastructure, but it may take a few months to be ready.

If possible, please consider submitting jobs outside of 4 AM – 10 AM EST (GMT-04) on weekdays, which is currently our busiest time. Please excuse the inconvenience, and we thank you for your patience.



- We are experiencing a heavy load recently, mainly due to the increased number of users + some abusers...
- I'm sorry if you're experiencing a slow response from the server these days.
- We are purchasing more cpu/gpu/rams to support increased number of users.

CHARMM-GUI supports Multiscale modeling/simulation



- Based on timescale of interest,
- We're supporting different scale of simulation inputs.
- With the state-of-art force fields and methods as much as possible.

CHARMM-GUI – Key Modules

Modeling system

PDB
Reader & Manipulator

Ligand
Reader & Modeler

Glycolipid Modeler

Glycan
Reader & Modeler

LPS Modeler

Polymer
Builder

ST-Analyzer

LBS Finder & Refiner

Generating simulation input

FF-Converter

Solution Builder

Membrane Builder

Multicomponent Assembler

QM/MM Interfacer

Constant-pH Simulator

Free-energy Calculator

Nanomaterial Modeler

Martini Maker

EnzyDocker

Ligand Docker

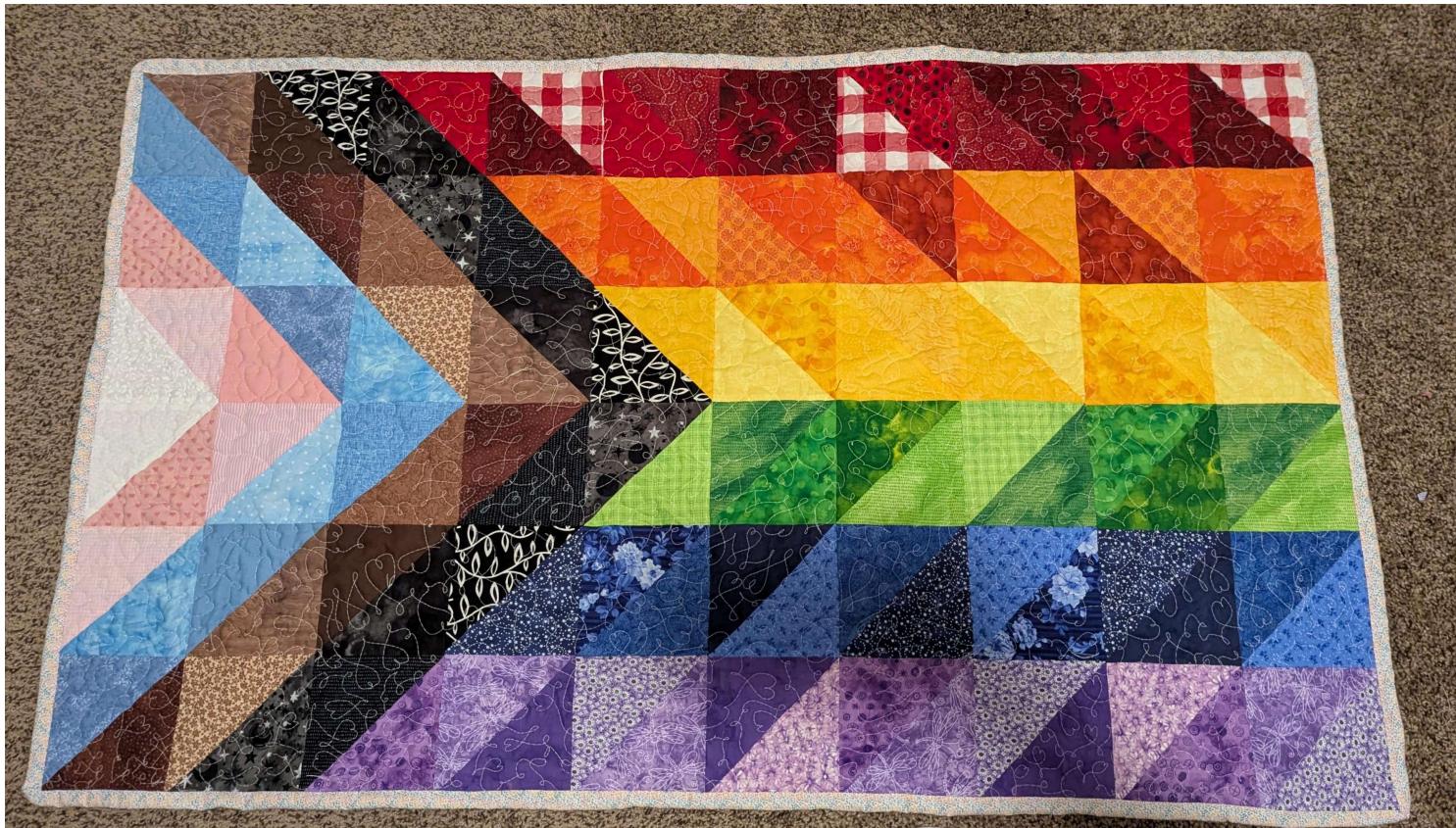
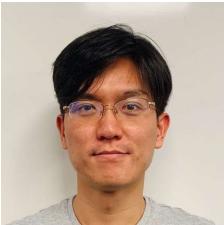
UNICORN Builder

Enhanced Sampler

Implicit Solvent Modeler

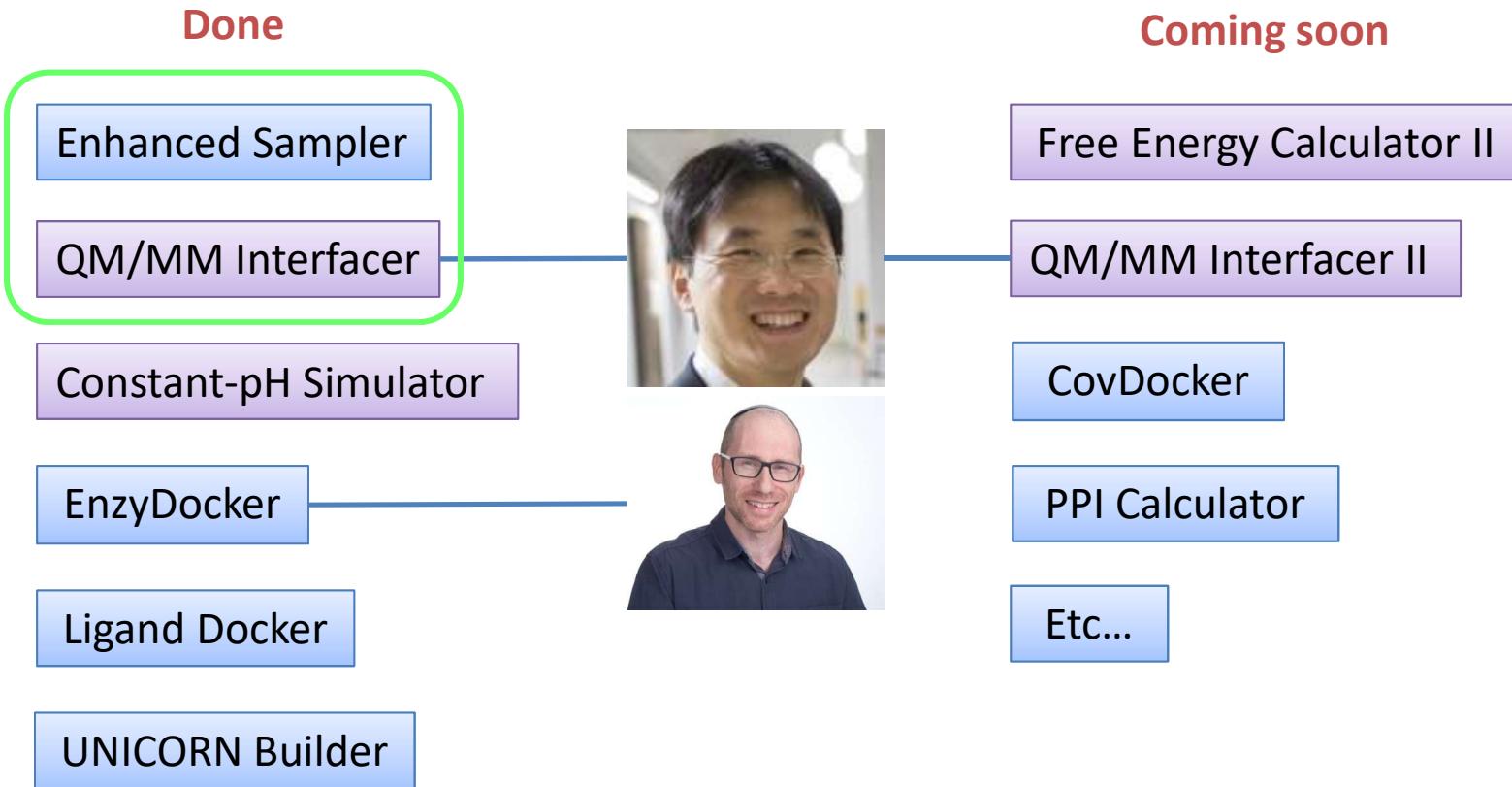
High-Throughput Simulator

CHARMM-GUI – just like Quilting



- Quite a few developers contributed during last 20 years.
- Students eventually graduate... postdocs last even shorter...
- Hard to maintain but hanging there.

CHARMM-GUI – my contributions



- You're welcome to ask me anything about these modules.
- I don't know much outside of what I built :P

CHARMM-GUI Enhanced Sampler (2022)

RESEARCH ARTICLE | JANUARY 02 2018

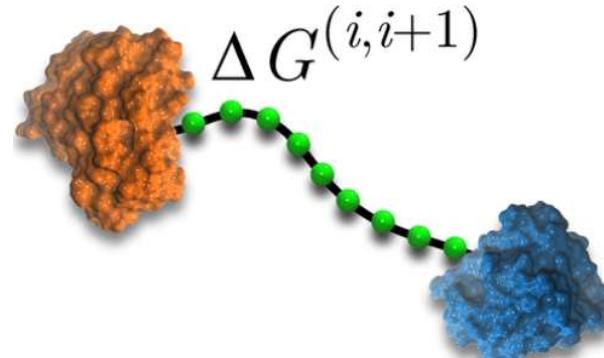
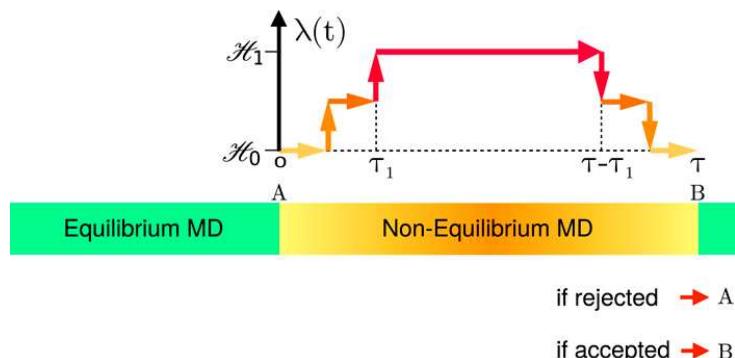
Enhanced configurational sampling with hybrid non-equilibrium molecular dynamics–Monte Carlo propagator

Journal of Chemical Theory and Computation > Vol 15/Issue 11 > Article

Subscribed

ARTICLE | October 8, 2019

String Method for Protein–Protein Binding Free-Energy Calculations



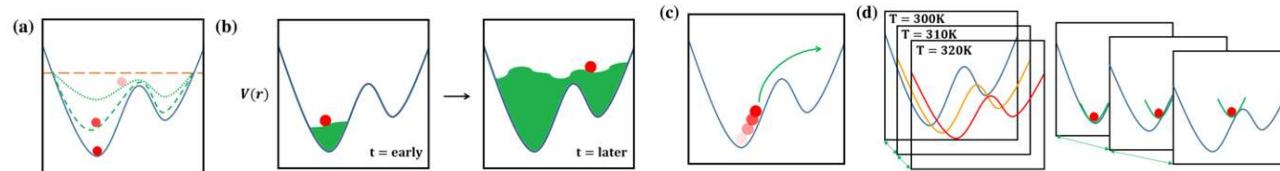
Received: 9 August 2022 | Revised: 6 September 2022 | Accepted: 7 September 2022

DOI: 10.1002/pro.4446

TOOLS FOR PROTEIN SCIENCE

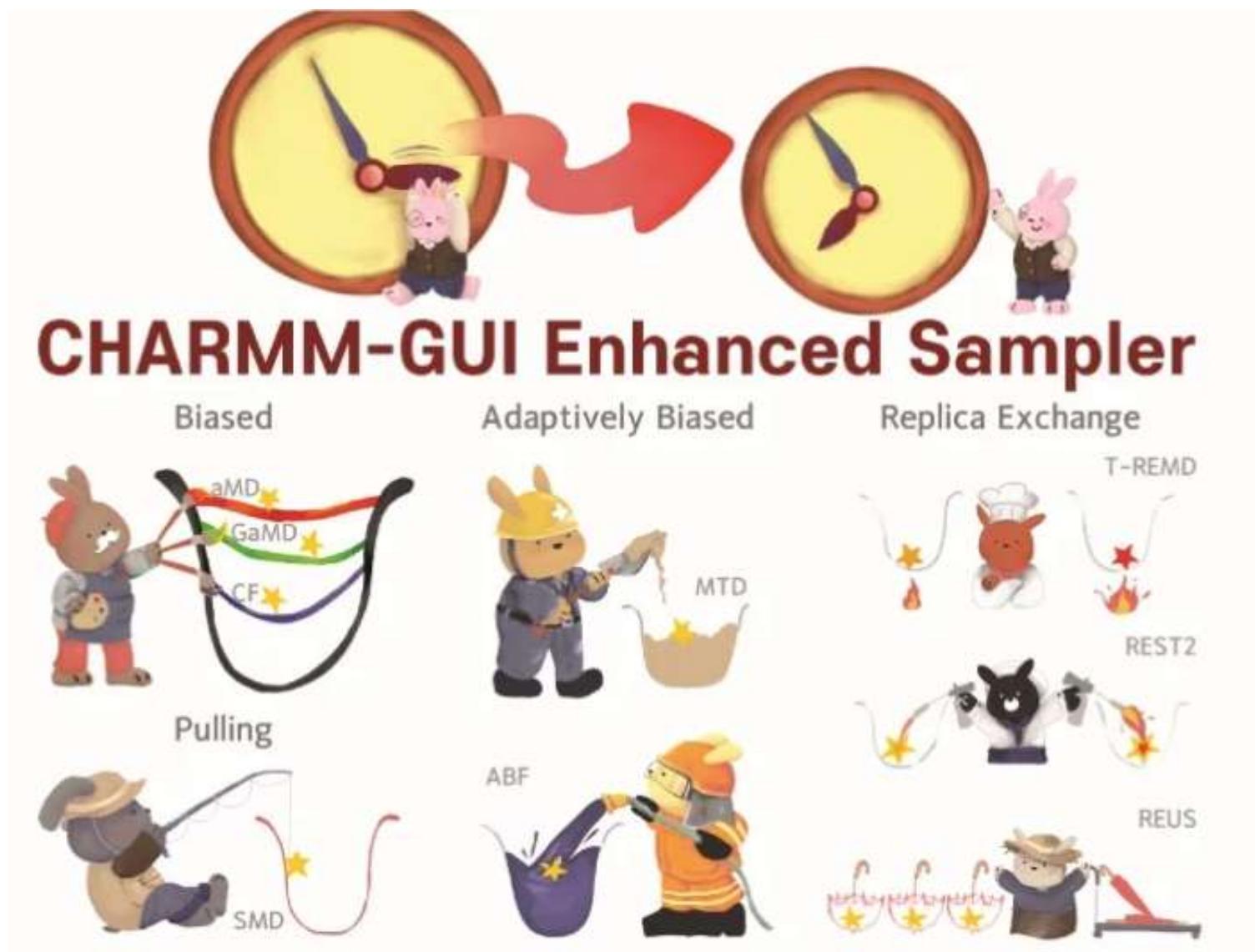


CHARMM-GUI Enhanced Sampler for various collective variables and enhanced sampling methods



J. Chem. Phys. 148, 014101 (2018) Journal of Chemical Theory and Computation 15 (11), 5829-5844
Protein Science. 2022; 31(11):e4446.

CHARMM-GUI Enhanced Sampler



- Many enhanced sampling methods available in the mainstream packages.
- But entry barriers present: Non-trivial simulation setup & Initial/optimized parameters

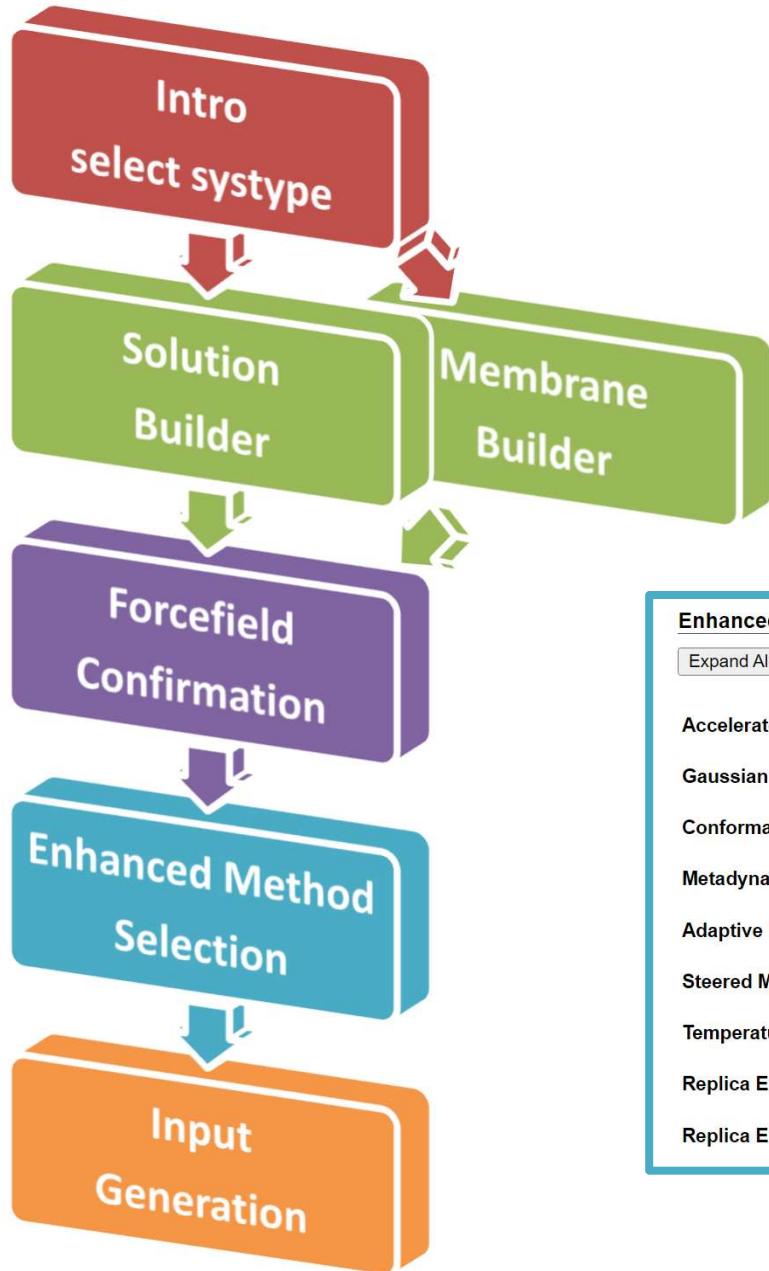
Protein Science. 2022; 31(11):e4446.

What Enhanced Sampler can do for you

Category	Enhanced Sampling Methods	Module(command) available in package						
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS	
Biasing potential energy	Accelerated MD	lamd	N/A	accelMD	N/A	AMDIintegrator	N/A	
	Gaussian aMD	lgamd	N/A	accelMDG	N/A	N/A	GAMD	
	Conformational flooding	N/A	N/A	N/A	Flood	N/A	N/A	
Adaptively biasing potential energy	Metadynamics	abmd flooding	N/A	metadynamics	Plumed	Plumed	N/A	
	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A	
Pulling	Steered MD	Jar rst	CONS PULL	SMD	Plumed	SMD	SMD	
Replica Exchange	Temperature	Temperature Replica Exchange	Rem	REPD	Tcl script	Replex	ParallelTempering Sampler	REMD
	Hamiltonian	Replica Exchange Umbrella Sampling	Rem	REPD	Tcl script	Plumed	Plumed	REMD
		Replica Exchange Solute Tempering 2	N/A	REPD/BLOCK	soluteScaling	Plumed	N/A	REST2

- Goal: csh README to run MD with enhanced sampling method

CHARMM-GUI Enhanced Sampler - Workflow



System Type: Solution
Solution
Download PDI Bilayer
Bilayer Only
Download Source: RCSB

Upload PDB File: Choose File No file chosen
PDB Format: PDB PDBx/mmCIF CHARM
Check/Correct PDB Format ?

Force Field Options:

CHARMM36m
CHARMM36m
AMBER
OPLS-AA/M

Confirm Force Field

Enhanced Method Input Options:

Expand All

Accelerated MD (aMD) +
Gaussian accelerated MD (GaMD) +
Conformational Flooding (CF) +
Metadynamics (MTD)
Adaptive Biasing Force (ABF) +
Steered MD (SMD) +
Temperature Replica Exchange MD (T-REMD) +
Replica Exchange Umbrella Sampling (REUS) +
Replica Exchange Solute Tempering2 (REST2) +

Metadynamics (MTD)

Hill height: 0.2 kcal / mol
Bias factor: 5
Colvar Type: Dihedral

SEGRID	RESID	RESID	AtomName
PROA	1	10	All
PROA	1	1	All
PROA	2	2	CD1
PROA	3	3	HN
PROA	4	6	Heavy atom
PROA	7	8	Sidechain
PROA	7	8	Backbone
PROA	9	10	Alpha carbon

AtomName

Add Atoms Remove Colvar

Colvar Type: Dihedral

Minum: -180
Maximum: 179

NAMD
AMBER
OpenMM
GROMACS

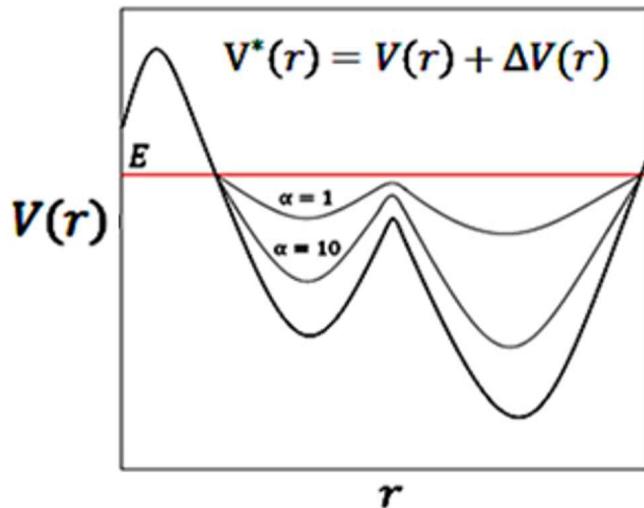
CHARMM-GUI Enhanced Sampler

- 6 MM packages: AMBER, CHARMM, GENESIS, GROMACS, NAMD, and OpenMM
- 9 Methods: aMD, GaMD, CF, MTD, ABF, SMD, T-REMD, H-REMD, and REST2
- 9 Collective Variables:

Collective variables	Description	Required selections
Distance	$\ \vec{r}_{ij}\ $	Two sets of atoms, range (min/max)
Angle	$\cos^{-1}\left(\frac{\vec{r}_{ji} \cdot \vec{r}_{jk}}{\ \vec{r}_{ji}\ \ \vec{r}_{jk}\ }\right)$	Three sets of atoms, range (min/max)
Dihedral	$\tan^{-1}\left(\frac{\ \vec{r}_{jk}\ \vec{r}_{ij} \cdot (\vec{r}_{jk} \times \vec{r}_{kl})}{(\vec{r}_{ij} \times \vec{r}_{jk}) \cdot (\vec{r}_{kl} \times \vec{r}_{ij})}\right)$	Four sets of atoms, range (min/max)
Root-mean-square deviation	$\sqrt{\frac{\sum_{i=1}^n \vec{r}_i - \vec{r}_{\text{ref}} ^2}{n}}$	A set of atoms, range (min/max)
Radius of gyration	$\sqrt{\frac{\sum_{i=1}^n m_i \vec{r}_i - \vec{r}_{\text{COM}} ^2}{\sum_{i=1}^n m_i}}$	A set of atoms, range (min/max)
Distance on axis	$e \cdot \ \vec{r}_{ij}\ $	Two sets of atoms, range (min/max), axis (xyz vector)
Rotation on axis	$2 \tan^{-1}\left(\frac{q_e}{q_0}\right)$	A set of atoms, range (min/max), axis (xyz vector)
Tilt on axis	$2 \left(\frac{q_0}{\cos\left(\frac{\tan^{-1} q_e}{q_0}\right)} \right)^2 - 1$	A set of atoms, range (min/max), axis (xyz vector)
Number of contacts	$\sum_i \sum_j \frac{1 - \left(\frac{ \vec{r}_i - \vec{r}_j }{\text{cutoff}}\right)^6}{1 - \left(\frac{ \vec{r}_i - \vec{r}_j }{\text{cutoff}}\right)^{12}}$	Two sets of atoms, range (min/max), cutoff

Accelerated MD (aMD)

- Boosts potential below threshold E to reduce barrier
- Two variables used to control the boost: threshold energy E & boosting constant α



$$V_{\text{aMD}}[x, \alpha, E] = \begin{cases} V[x], & V[x] \geq E \\ V[x] + \frac{(E-V[x])^2}{\alpha+(E-V[x])}, & V[x] < E \end{cases}$$

- Required parameters w/ rule of thumb:

- For dihedral mode,

$$V_d^* = V_d + 4 * N_{res}; \alpha = 4 * \frac{N_{res}}{5}$$

- For lipids in dihedral mode,

$$dV_d = 10 * N_{lip}; d\alpha = 3 * N_{lip}$$

- For total boost mode,

$$V_{tot}^* = V_{tot} + \frac{N_{atom}}{5}; \alpha = \frac{N_{atom}}{5}$$

- With this rule of thumb, csh README will collect parameters during 1 ns of Pre-run(MD) into the aMD input to run aMD.

J. Chem. Phys. 120(24):11919-11929, 2004.

J. Chem. Theory Comput. 7(10): 3199-3207, 2011

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Based potential energy	Accelerated MD	lambd	N/A	accelMD	N/A	AMDintegrator	N/A
	Gaussian aMD	lgand	N/A	accelMDG	N/A	N/A	GAMO
Adaptively biasing PT (MTD, ABF)	Conformational flooding	N/A	N/A	N/A	Flood	N/A	N/A
	Metadynamics	abmd Flooding	N/A	metadynamics	Plumed	Metadynamics	N/A
Pulling/targeted MD	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A
	Steered MD	jar rst	CONS PULL	SMD	pull-coord1	SMD	SMD
Replica Exchange	Temperature Replica Exchange	Rem	REPO	Td script	Replex	ParallelTempering Sampler	REMD
	Hemispherical	Rem	REPO/BLOCK	Td script	Plumed	ReplicaExchange Sampler	REMD
	Replica Exchange Umbrella Sampling	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REST2
	Replica Exchange Solute Temping 2						

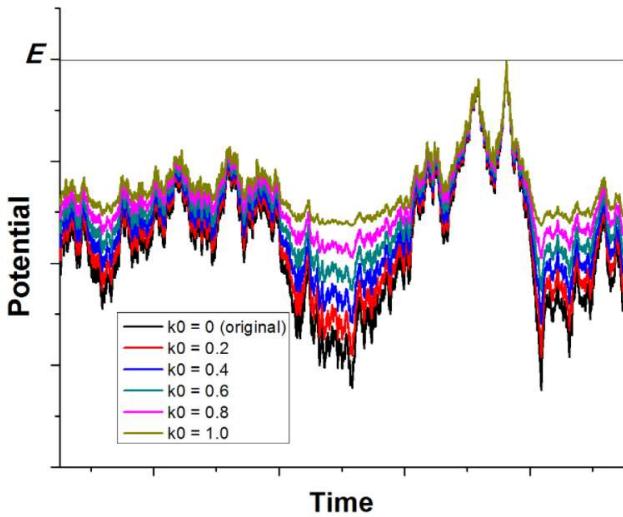
Gaussian accelerated MD (GaMD)

- Boosts potential below threshold E to reduce barrier
- Two variables used to control the boost: threshold energy E & boosting constant k

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD	lmd	N/A	accelMD	N/A	AMDintegrator	N/A
	Gaussian AMD	lgand	N/A	accelMD	N/A	N/A	GAMD
Conformational Sampling	Conformational Roofing	N/A	N/A	N/A	Roof	N/A	N/A
	Metadynamics	abmd Roofing	N/A	metadynamics	Plumed	Metadynamics	N/A
Adaptive biasing PE (MBT, ABE)	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A
	Pulling/Targeted MD	Steered MD	Jar rst	CONS PULL	SMD	pull-coord1	SMD
Replica Exchange	Temperature Exchange		Rem	REPD	Td script	Replex	ParallelTempering Sampler
			Rem	REPO/BLOCK	Td script	Plumed	ReplicaExchange Sampler
	Hamiltonian		N/A	REPO/BLOCK	soluteScaling	Plumed	N/A
							REST2

$$V^*(r) = V(r) + \Delta V(r),$$

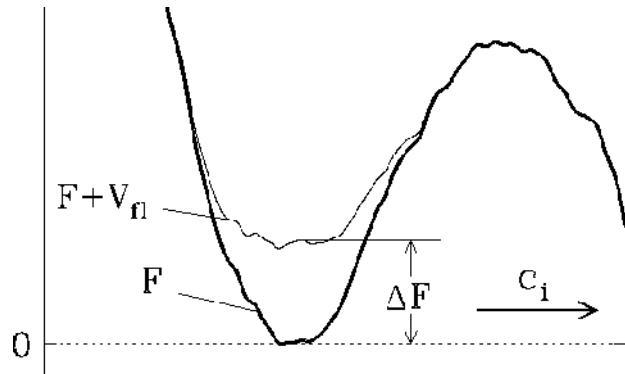
$$\Delta V(r) = \begin{cases} \frac{1}{2}k(E - V(r))^2, & V(r) < E \\ 0, & V(r) \geq E \end{cases}$$



- Required parameters: automatically selected from 2 pre-runs
 - Prerun1(MD) – collecting parameters
 - Prerun2(GaMD) – updating parameters
 - Production(GaMD) – fixed parameters
- V_{\max} , V_{\min} , V_{avg} , V_{dev} are detected for targeted potential in order to make dV nearly Gaussian shaped – advantageous for reweighting.
- csh README takes care of all pre-runs, updating parameters, and up to production.

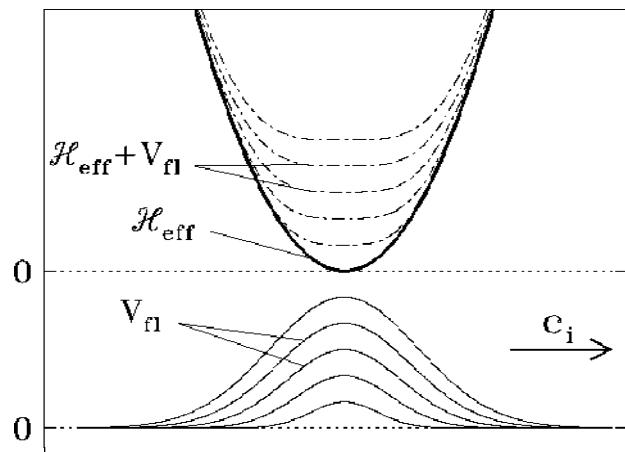
Conformational Flooding (CF)

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy							
Accelerated MD	lmd	N/A	accelMD	N/A	N/A	AMDintegrator	N/A
Gaussian AMD	lgand	N/A	accelMDG	N/A	N/A	N/A	GAMD
Conformational flooding	N/A	N/A	N/A	Flood	N/A	N/A	N/A
Adaptive biasing PE (MBD, ABD)							
Metadynamics	abmd Flooding	N/A	metadynamics	Plumed	Metadynamics	N/A	N/A
Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A	N/A
Pulling/Targeted MD	Steered MD	Jar rst	CONS PULL	SMD	pull-coord1	SMD	SMD
Replica Exchange	Temperature Exchange	Rem	REPD	Tcl script	Replex	ParallelTempering Sampler	REMDO
Hamiltonian	Replica Exchange Umbrella Sampling	Rem	REPO/BLOCK	Tcl script	Plumed	ReplicaExchange Sampler	REMDO
	Replica Exchange Solute Tempering 2	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REST2



$$\Delta V(r)_{\text{CF}} = k * \exp \left[-\frac{1}{2} r^T \Lambda r \right]$$

k=strength & Λ =shape
of flooding potential



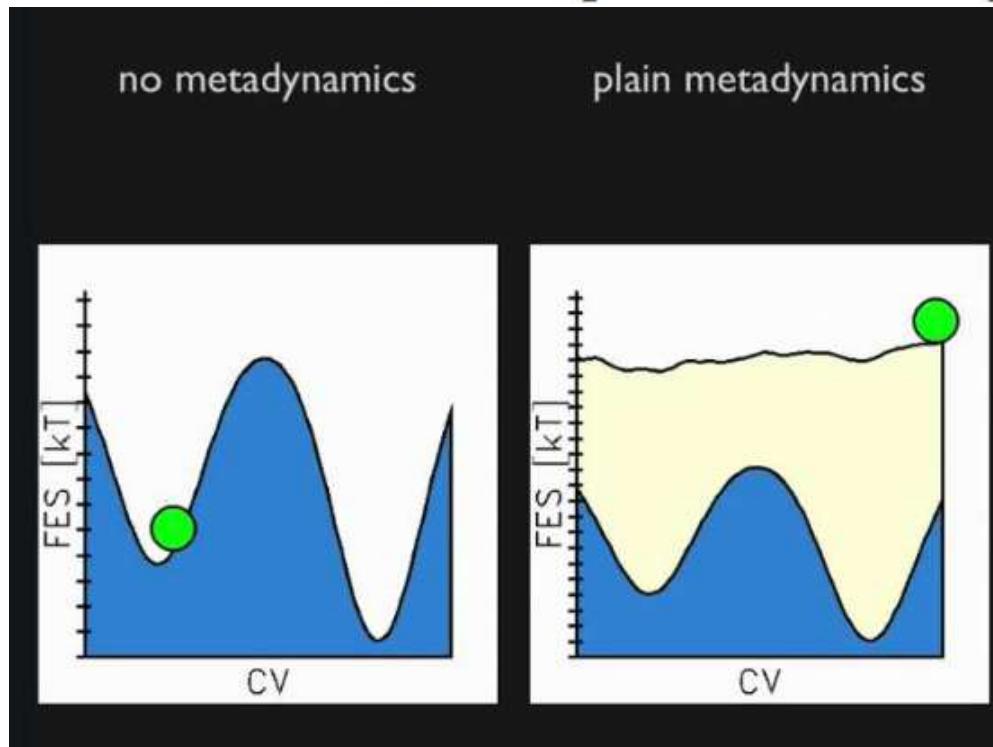
- Modifies FE landscape by designing a flooding potential
- Pre-run required for conformational flooding; requiring RC selection after the prerun.
- csh README

Metadynamics (MTD)

- One keeps adding potential where visited.
- Done once the system moves freely on the chosen reaction coordinate (with added potentials), and reweight based on cumulatively added PE for the desired PMF.

$$\Delta V_{\text{MTD}}^*(\xi(t)) = \sum_{n\delta t < t} W \exp \left[- \sum_{i=1}^n \frac{(\xi(t) - \xi(i\delta t))^2}{2\sigma^2} \right]$$

where ξ is a reaction coordinate, W is a Gaussian hill height, and δt is a hill depositing frequency.



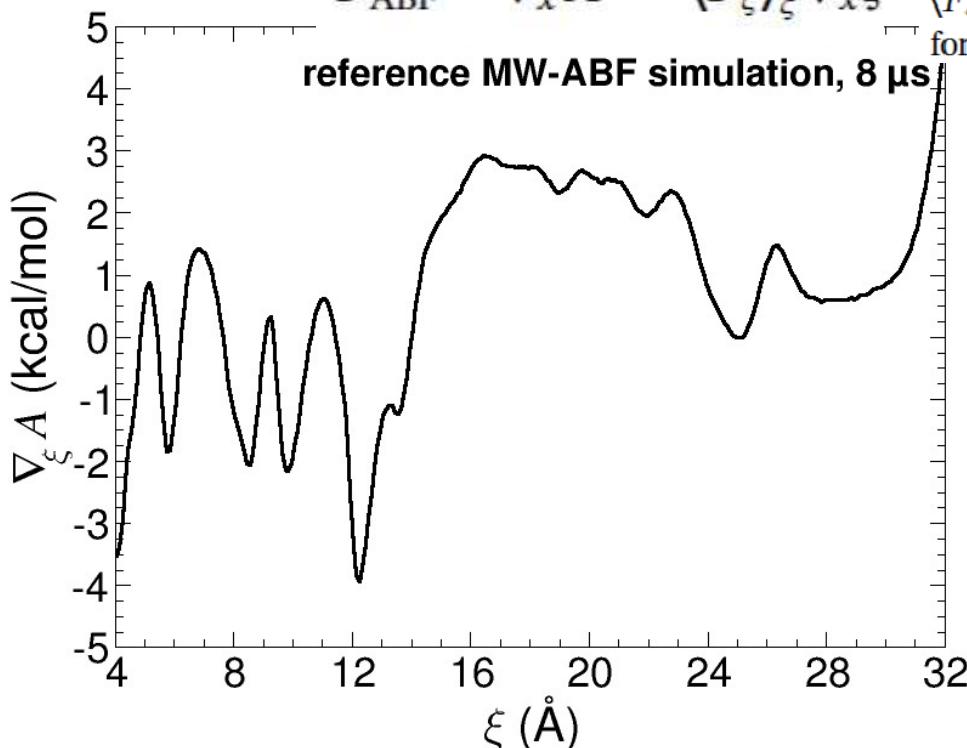
- Required: Colvars file representing
 1. Reaction Coordinate (any distance, dihedral, etc)
 2. MTD parameters
 - 1) Height of Gaussian hills
 - 2) The frequency of hills deposition
 - 3) Hill width
 - csh README

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD	lmd	N/A	accelMD	N/A	AMDEintegrator	N/A
	Gaussian AMD	lgand	N/A	accelMDG	N/A	N/A	GAMD
Conformational sampling	Conformational flooding	N/A	N/A	N/A	Flood	N/A	N/A
	Metadynamics	abmd Flooding	N/A	metadynamics	Plumed	Metadynamics	N/A
Adaptively biasing PE (MTD, ABF)	Adaptive biasing force	N/A	N/A	abf	N/A	N/A	N/A
	Pulling/Targeted MD	Steered MD	Jar rst	CONS PULL	SMD	pull-coord1	SMD
Replica Exchange	Temperature Exchange	N/A	Rem	REPD	Td script	Replex	ParallelTempering Sampler
		N/A	Rem	REPO/BLOCK	Td script	Plumed	ReplicaExchange Sampler
	Hamiltonian	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REST2

Adaptive Biasing Force (ABF)

- Another adaptively biasing method.
- Calculate the forces (negative gradients of P.E.), then accumulate gradients in local bin and update to end up with zero mean force.
- The integration of the gradient applied would generate free E landscape.

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMO	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD	lmd	N/A	accelMD	N/A	AMDintegrator	N/A
	Gaussian AMD	lgand	N/A	accelMDG	N/A	N/A	GAMD
Conformational Roofing	N/A	N/A	N/A	Roof	N/A	N/A	N/A
	Metadynamics	abmd Roofing	N/A	metadynamics	Plumed	Metadynamics	N/A
Adaptively biasing PE [MTD, ABF]	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A
	Pulling/Targeted MD	Steered MD	Jar rst	CONS PULL	SMD	pull-coord1	SMD
Replica Exchange	Temperature Exchange	N/A	Rem	REPD	Td script	Replex	ParallelTempering Sampler
		REPO/BLOCK	REPO/BLOCK	Td script	Plumed	ReplicaExchange Sampler	REMD
	Hamiltonian	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REMD



where A is the current estimate of the free energy and $\langle F_\xi \rangle_\xi$ is the mean force at ξ from averaging instantaneous forces, F_ξ

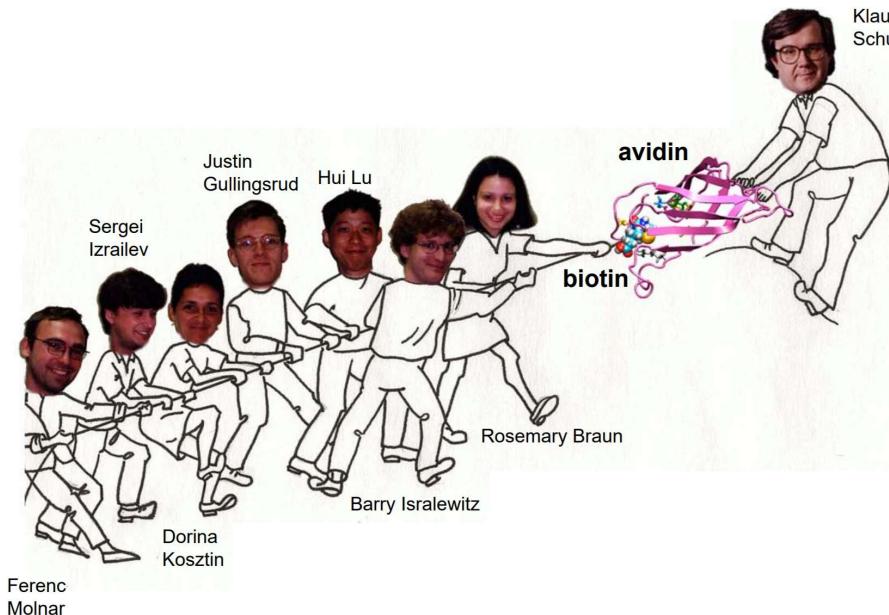
- Required: Colvars file representing
 1. Reaction Coordinate (any distance, dihedral, etc)
 2. ABF applied on that colvar with selected number of samples in the bin per update (fullSamples)
- csh README

Steered MD (SMD)

- Physically pulling subset of atoms during the simulation.
- Applying an external force to COM of selected atoms with constant force/velocity.

$$V(r, e, t) = \frac{k}{2} (r_{\text{COM}}(t) \cdot e - vt)^2$$

where k is the spring constant, v is the moving speed of the spring potentials (also called dummy atoms), $r(t)$ is the current position of the selected COM, and e is the pulling axis



- Required: Colvars file representing
 1. Subset selection
 2. Pulling vector
 3. Velocity/constant.
- csh README

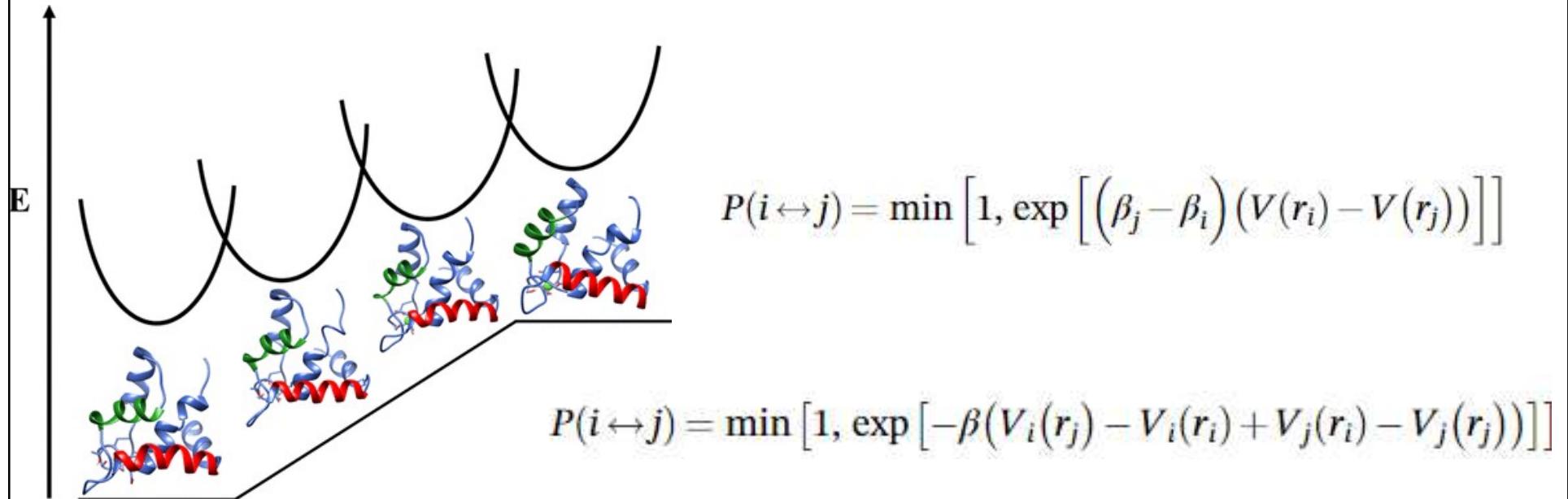
Science. 1996; 271(5251): 997-999
<https://www.ks.uiuc.edu/> for image

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD	lmd	N/A	accelMD	N/A	AMDintegrator	N/A
	Gaussian AMD	lgand	N/A	accelMDG	N/A	N/A	GAMD
Conformational sampling	Conformational Roofing	N/A	N/A	N/A	Roof	N/A	N/A
	Metadynamics	abmd Roofing	N/A	metadynamics	Plumed	Metadynamics	N/A
Adaptively biasing PE (MBD, ABF)	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A
	Steered MD	Jar est	CONS-PULL	SMD	pull-coordS	SMD	SMD
Replica Exchange	Temperature Exchange	Rem	REPD	Tcl script	Replex	ParallelTempering Sampler	REMDO
		REPO/BLOCK	REPO/BLOCK	Tcl script	Plumed	ReplicaExchange Sampler	REMDO
	Umbrella Sampling	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REST2
Hamiltonian	Replica Exchange Solute Tempering 2	N/A	REPO/BLOCK	N/A	N/A	N/A	N/A

REMD [T-REMD, H-REMD(REUS, REST2, ...)]

Category	Enhanced Sampling Methods	Module(s) (continued) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD	lambd	N/A	accelMD	N/A	AMBDintegrator	N/A
	Gaussian aMD	lgamd	N/A	accelMDG	N/A	N/A	GAMD
Conformational flooding	N/A	N/A	N/A	N/A	Flood	N/A	N/A
Adaptively biasing potential energy	Metadynamics	abmd flooding	N/A	metadynamics	Plumed	Metadynamics	N/A
	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A
Pulling/Ligated MD	Steered MD	Jar rot	CONS PULL	SMD	pull-coord	SMD	SMD
Replica Exchange	Temperature Replica Exchange	Rem	REPD	Tcl script	Repfix	ParallelTempering Sampler	REMDSampler
	Replica Exchange Umbrella Sampling	Rem	REPD/BLOCK	Tcl script	Plumed	ReplicaExchange Sampler	REMD
	Solute Exchange Solute Temperature 2	N/A	REPD/BLOCK	soluteScaling	Plumed	N/A	REST2

- Multiple replicas run concurrently with periodic exchanges.
 - Enables conformational/parameter swap between two windows using the metropolis criterion.
 - Sudden coordinate/parameter change causes rare event & reaching convergence faster at no cost of purity (Boltzmann equilibrium kept).

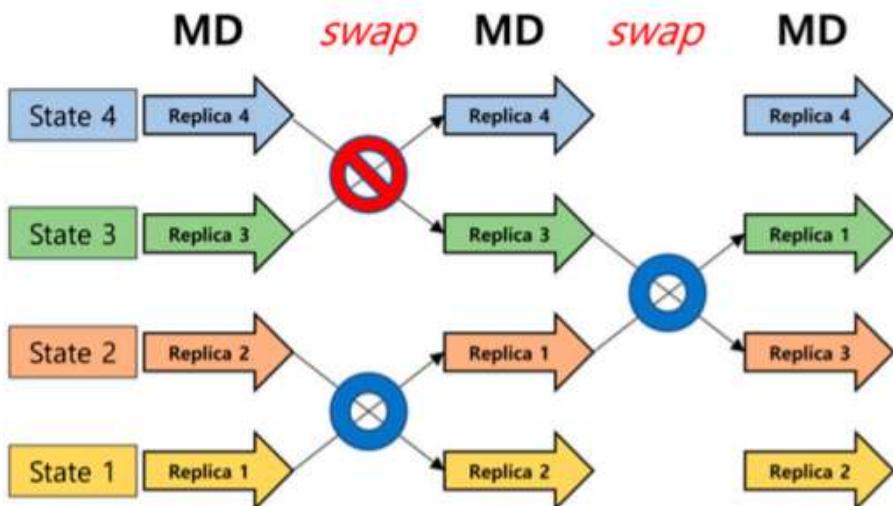


Chemical Physics Letters, 314, 141–151 (1999)
Methods Mol. Biol. 924, 153–195 (2013)

Replica Exchange Solute Tempering 2 (REST2)

- Not a T-REMD, but H-REMD.
- All replicas run on original temp while scaling solute-solute and solute-solvent interactions. (solvent-solvent untouched)
- Effective boosting > relatively small number of replicas compared to TREMD.
- REST2 (2011); $E_m^{REST2} = \frac{\beta_m}{\beta_0} E_{ss} + \sqrt{\frac{\beta_m}{\beta_0}} E_{sv} + E_{vv}$

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD Gaussian iMD	lmd	N/A	accelMD	N/A	AMDintegrator	N/A
	Conformational flooding	N/A	N/A	N/A	Flood	N/A	GAMO
Adaptive biasing PT (MTD, ABF)	Metadynamics Adaptive Biasing force	abmd flooding N/A	N/A	metadynamics abf	Plumed	Metadynamics N/A	N/A
Pulling/targeted MD	Steered MD	jar rst	CONS PULL	SMD	pull-coord1	SMD	SMD
Replica Exchanger	Temperature	Rem	REPO	Td script	Replex	ParallelTempering Sampler	REMD
	Hamiltonian	Rem	REPO/BLOCK	Td script	Plumed	ReplicaExchange Sampler	REMD
	Replica Exchange Umbrella Sampling	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REST2
	Replica Exchange Solute Tempering 2						



Why REST2 over REST1?

- REST1 required more replicas due to smaller conformational space overlap between higher temp vs. lower temp. Temp base different + smaller scaling Esv term helped in REST2.
- Higher temp running itself requires more cpu time due to fast motions > more freq neighboring list update or thicker shell req. (i.e. Desmond 600K vs. 300K > factor of 2)

ES on REMD

Category	Enhanced Sampling Methods	Module(command) available in package					
		AMBER	CHARMM	NAMD	GROMACS	OPENMM	GENESIS
Biased potential energy	Accelerated MD	lmd	N/A	accelMD	N/A	AMDintegrator	N/A
	Gaussian AMD	lgand	N/A	accelMDG	N/A	N/A	GAMD
Conformational sampling	Conformational Roofing	N/A	N/A	N/A	Roof	N/A	N/A
	Adaptively biasing potential energy	abmd Roofing	N/A	metadynamics	Plumed	Metadynamics	N/A
Pulling/Targeted MD	Adaptive Biasing force	N/A	N/A	abf	N/A	N/A	N/A
	Steered MD	Jar rst	CONS PULL	SMD	pull-coord1	SMD	SMD
Replica Exchange	Temperature Exchange	Rem	REPD	Td script	Replex	ParallelTempering Sampler	REMD
	Replica Exchange Umbrella Sampling	Rem	REPO/BLOCK	Td script	Plumed	ReplicaExchange Sampler	REMD
	Replica Exchange Solute Tempering 2	N/A	REPO/BLOCK	soluteScaling	Plumed	N/A	REST2

- What ES does for you:
 - T-REMD: Using a temperature predictor for T-REMD by Patriksson and Spoel, generating a temperature ladder based on user input of min/maxT and desired exchange ratio. System information of number of atoms, protein residues, water molecules, constraints, virtual sites ... are used to calculate this.
 - REUS: Using Park and Im's work, we provide a priori optimal REUS ladder, assuming a flat FES along RC.
 - REST2: we provide the exponential temp ladder based on user-chosen min/max temp and numreplicas.

$$d = \xi_{n+1} - \xi_n = z_{\text{opt}} \sqrt{\frac{2}{k\beta}}$$

$$T_i = T_{\min} \exp \left[\frac{i \ln \left(\frac{T_{\max}}{T_{\min}} \right)}{N_{\text{rep}} - 1} \right].$$

CHARMM-GUI QM/MM Interfacer (2024)

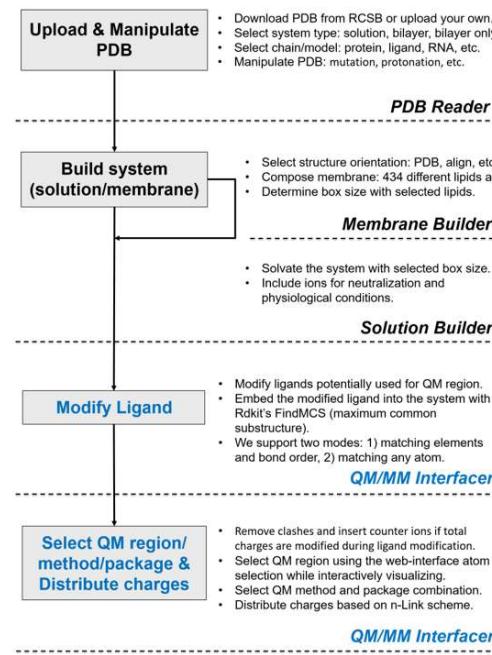
Journal of Chemical Theory and Computation > Vol 20/Issue 12 > Article

Open Access

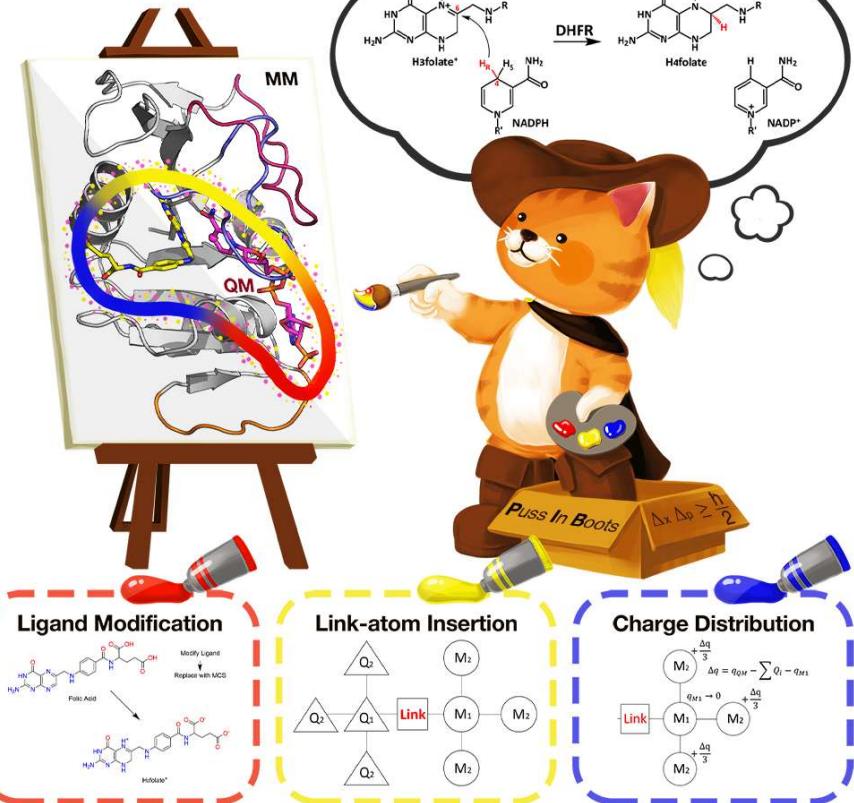
Cite Share

BIOMOLECULAR SYSTEMS | June 10, 2024

CHARMM-GUI QM/MM Interfacer for a Quantum Mechanical and Molecular Mechanical (QM/MM) Simulation Setup: 1. Semiempirical Methods



CHARMM-GUI QM/MM Interfacer



- QM/MM could be beneficial
 - For capturing electronic structure change at the site of reaction
 - While maintaining the computational cost at reasonable level.
 - But Hard to start with (especially with CHARMM)

What QM/MM Interfacer can do for you

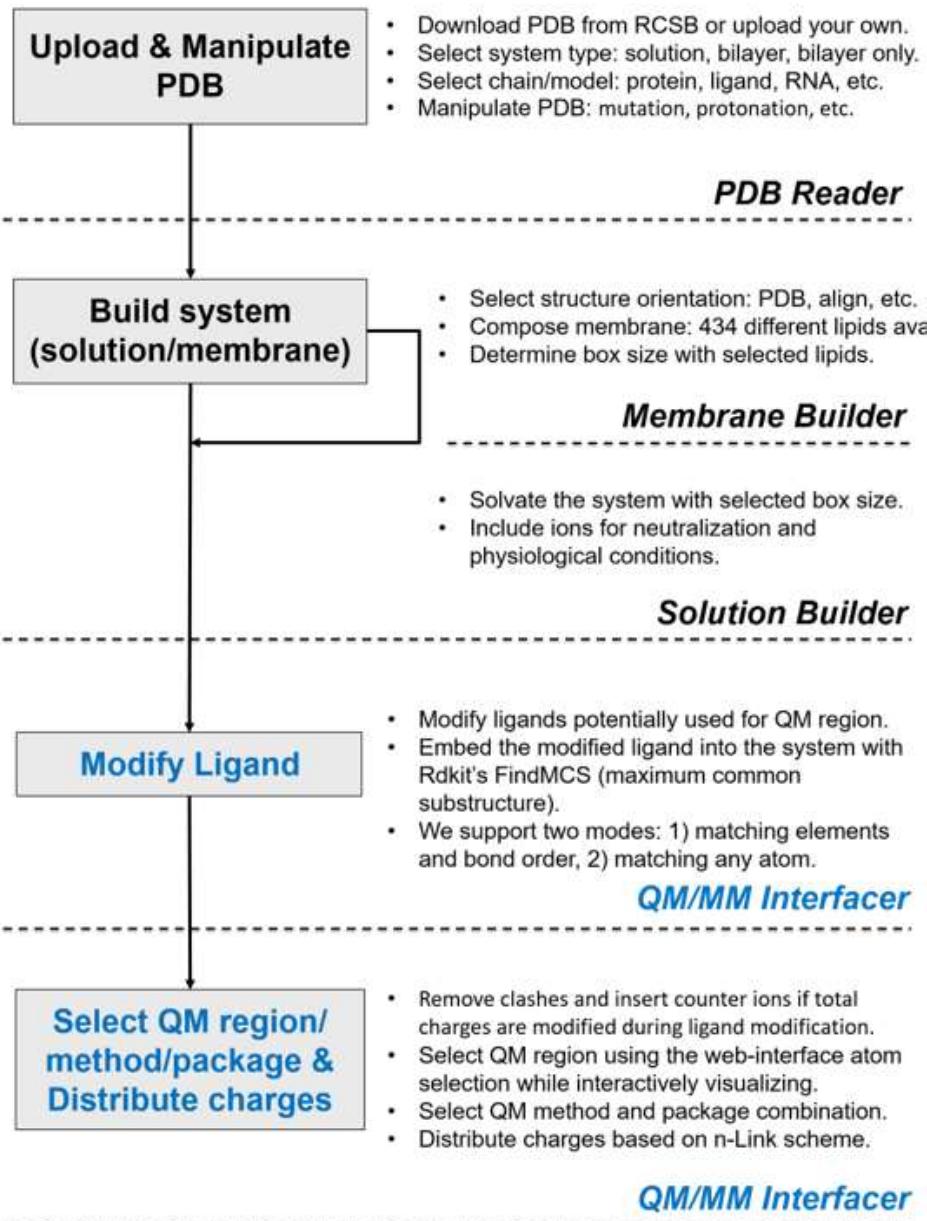
- Part 1

Package	Modules	Semi-Empirical Methods
CHARMM	SQUANTUM	AM1, PM3, MNDO, PDDG/MNDO, and PDDG/PM3
	MNDO97	AM1, PM3, MNDO, MNDO/d, and AM1/d
	SCC-DFTB	3ob and mio
AMBER	SQM	AM1, PM3, MNDO, MNDO/d, AM1/d, PDDG/MNDO, PDDG/PM3, RM1, and PM6
	SCC-DFTB	3ob, mio, matsci, ob2, and pbc

- Part 2



CHARMM-GUI QM/MM Interfacer - Workflow

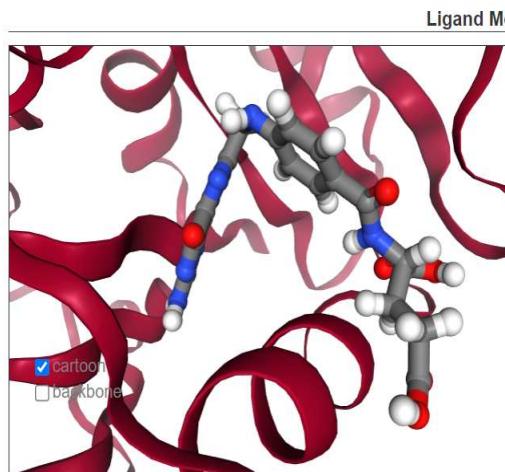


QMI's Ligand Modification

Modify Ligand

- Modify ligands potentially used for QM region.
- Embed the modified ligand into the system with Rdkit's FindMCS (maximum common substructure).
- We support two modes: 1) matching elements and bond order, 2) matching any atom.

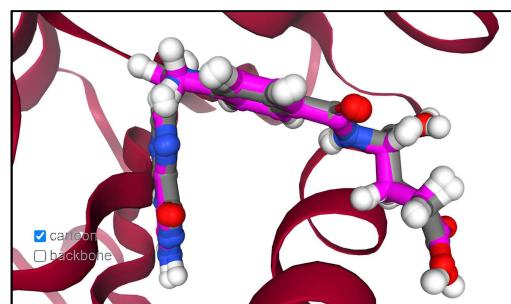
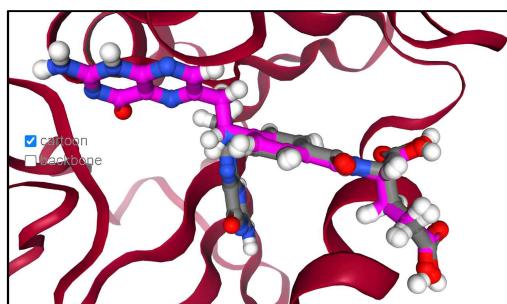
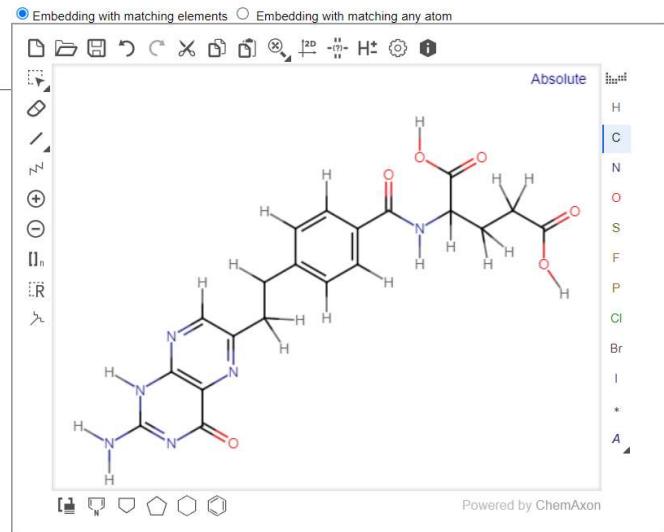
QM/MM Interfacer



Modify	Segid	Ligand	Modification	Parameterize	Run
<input checked="" type="checkbox"/>	HETB	FOL	open		
<input type="checkbox"/>	HETD	NAP	open		
<input type="checkbox"/>	WATA	HOH	open		

Modify and update ligand

Please use [R-group](#) buttons to generate combinatorial ligands: Smart R-group: [R](#) & R-group attachment: [R'](#)



1) Matching elements and bond order

2) Matching any atom (connectivity only)

QM Region Selection & Visualization



Select QM region/ method/package & Distribute charges

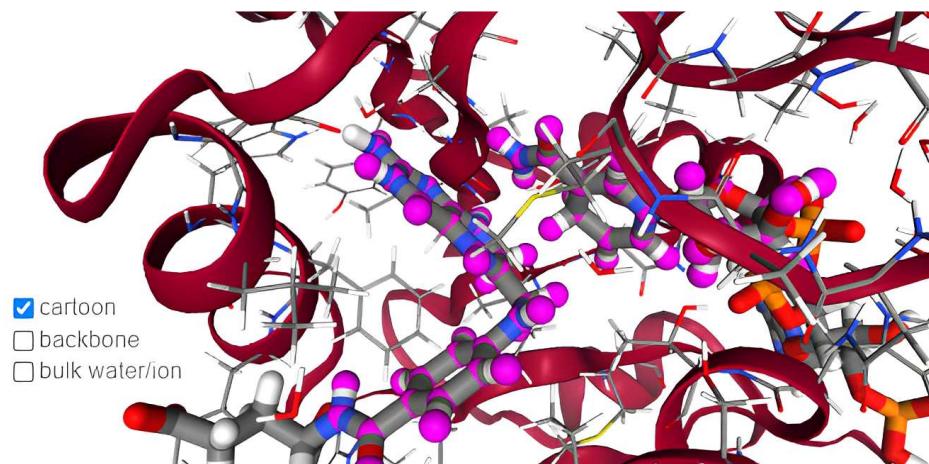
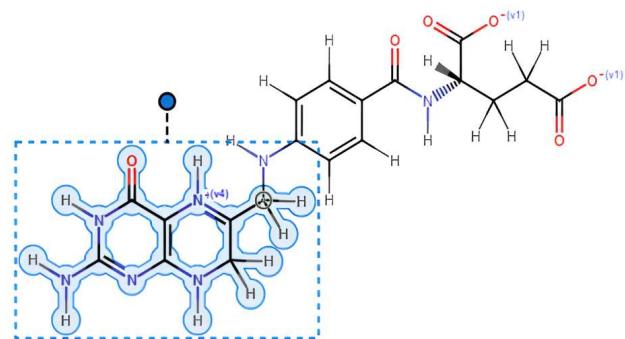
- Remove clashes and insert counter ions if total charges are modified during ligand modification.
- Select QM region using the web-interface atom selection while interactively visualizing.
- Select QM method and package combination.
- Distribute charges based on n-Link scheme.

QM/MM Interfacer

SEGID	RNAME	RESID	ATOM
PROA	LYS	32	Sidechain <input type="button" value="X"/>
WATA	TIP3	301	All <input type="button" value="X"/>
HETD	HETD	1	C20 <input type="button" value="X"/> C21 <input type="button" value="X"/> O17 <input type="button" value="X"/> N7 <input type="button" value="X"/> H26 <input type="button" value="X"/> H27 <input type="button" value="X"/>

Add Atoms

Show selected QM Region Total charge: 0.79400



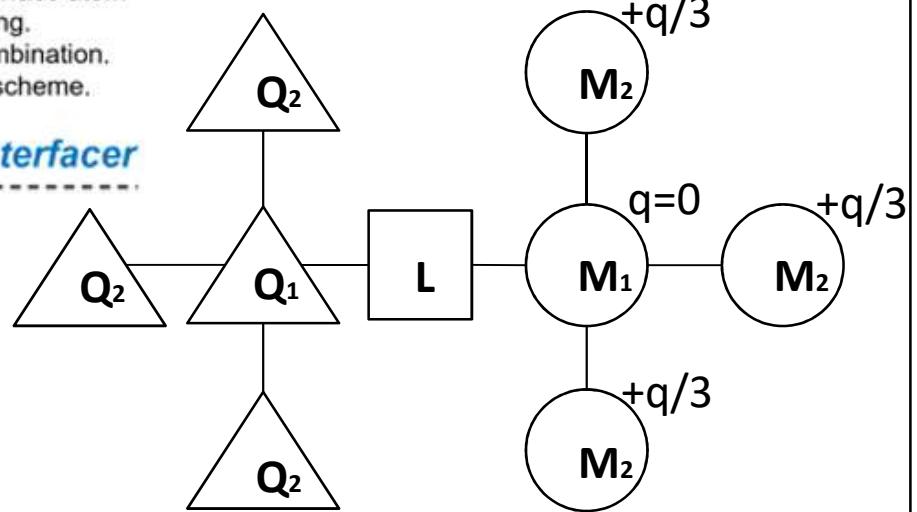
Link Atom Insertion & Charge Distribution

Select QM region/
method/package &
Distribute charges

- Remove clashes and insert counter ions if total charges are modified during ligand modification.
- Select QM region using the web-interface atom selection while interactively visualizing.
- Select QM method and package combination.
- Distribute charges based on n-Link scheme.

QM/MM Interfacer

QM charge:	<input type="text" value="1"/>	<input type="button" value="Distribute Charge"/>			
QM charge distribution:					
#Link	QM-Boundary	MM-Boundary	Connected to:		
Index ΔCharge	HETB-1-C12 [-0.06100]	HETB-1-N5 -0.37 → 0	HETB-1-CA -0.184 → -0.39950	HETB-1-H11 0.407 → 0.19150	
Index ΔCharge	HETD-1-C3 [-0.00300]	HETD-1-C4 -0.081 → 0	HETD-1-O3 -0.621 → -0.64900	HETD-1-H5 0.09 → 0.06200	HETD-1-H6 0.09 → 0.062
Index ΔCharge	PROA-6-CB 0	PROA-6-CA 0.07 → 0	PROA-6-N -0.47 → -0.44667	PROA-6-C 0.51 → 0.53333	PROA-6-HA 0.09 → 0.11334

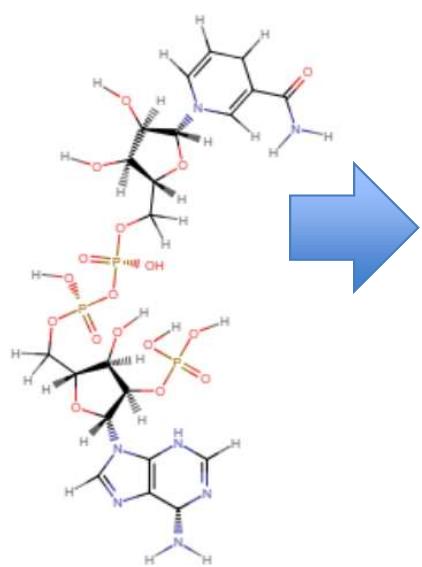
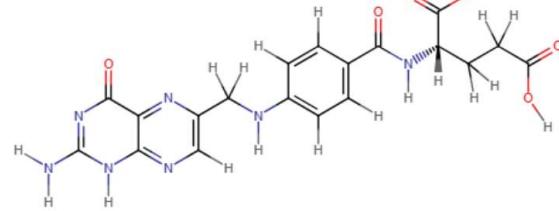
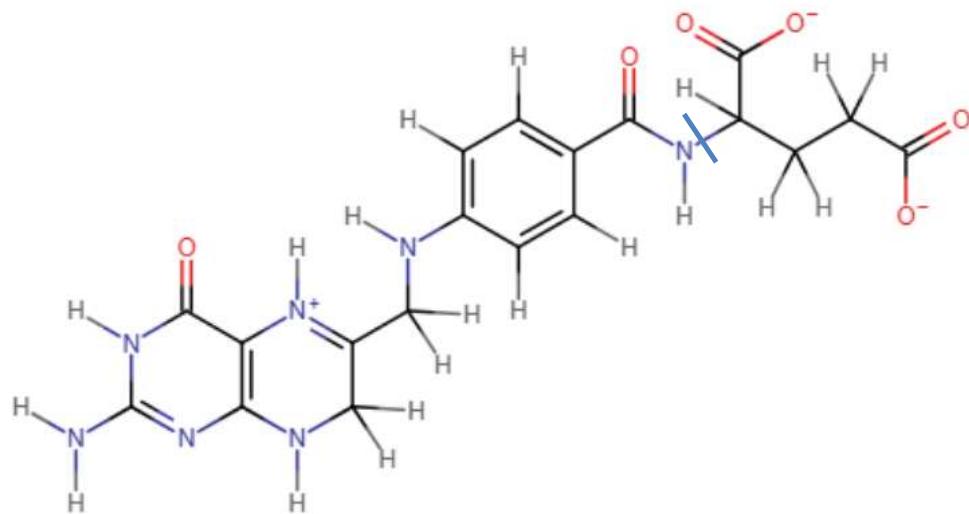


- We need to prevent over-polarization of QM density due to the closest MM atom, M1.
- Zeroing the charge of M1 (plus any residual charges from QM region) and evenly distributing among the connected M2 MM atoms => maintain total net charge.
- Based on the total charge of QM region, default QM charge will be the nearest integer.
- When users click 'Distribute Charge' button, the QM/MM covalent boundary will be detected, and each required linkage will be shown.
- The charge (residual + M1) distribution will be an even distribution as default, but users can modify in each box if they have a better plan.
- (All these things are for CHARMM... as it needs to be manually done by user)
- For AMBER package, user can select to evenly distribute either among M2 atoms or all MM atoms

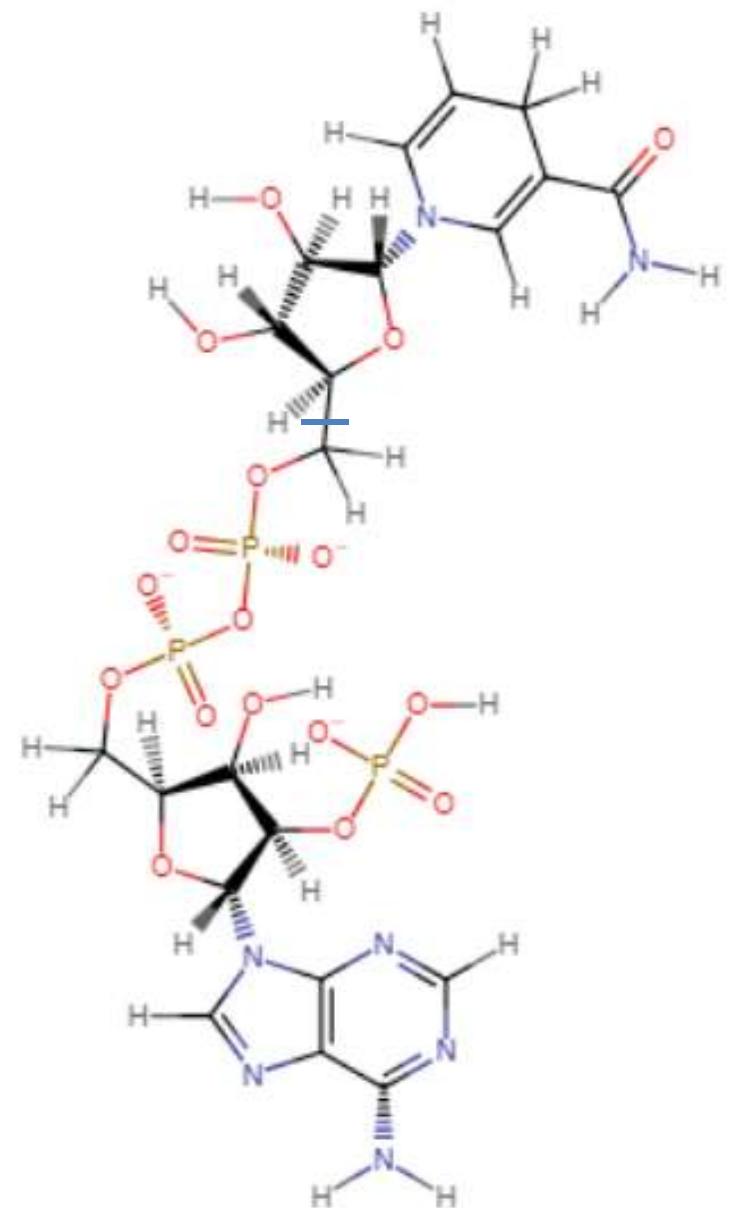
CHARMM-GUI QMI Hands on – playing with functionalities

- Go to: charmm-gui.org
- Login with the credentials
- Input generator > QM/MM Interfacer

CHARMM-GUI QMI Hands on - Ligand Modification



- FOL to H₃folate+ (TOP)
- NAP to NADPH (RIGHT)



MM minimization & equilibration

- Raafik prepared the DHFR system (with SCC-DFTB 3ob) for you.
 - cd into prepared folder
`10th_workshop_QM_MM_AIMD/04_thursday/knam_session02_thu_9am/01_build_system_with_charmmgui/`
 - Four .tgzs available;
 - 01-02 are amber & charmm inputs for ligands in water
 - 03-04 are amber & charmm inputs for DHFR system
 - Untar 02 and cd into the folder
 - tar xf 02_folate_water_charmm.tgz
 - cd charmm-gui-\$jobid/charmm
- However, if you want to proceed with what you've just prepared for any reason,
 - scp charmm-gui.tgz USERNAME@bridges2.psc.edu:~/
 - will put it in your home directory /jet/home/USERNAME
 - Untar and cd into the folder
 - tar xf charmm-gui.tgz
 - cd charmm-gui-\$jobid/charmm

MM minimization & equilibration

- vim (or any text editor you use) README
- On top of the file, replace the header so that it looks like...
 - `#!/bin/csh`
 - `#SBATCH --partition=RM-shared`
 - `#SBATCH --nodes=1`
 - `#SBATCH --ntasks-per-node=16`
 - `#SBATCH --export=ALL`
 - `#SBATCH -t 00:20:00`
 - `#SBATCH -A see220002p`
- # Generated blahblah...
- Replace set charmm = charmm with
- Set charmm =
`/ocean/projects/see220002p/shared/10th/charmm/charmm/c49b2_mdno97/bin/charmm`
- Comment out QM/MM input preparation & Production run by adding # in front of `#{charmm}`