Computing Potentials of Mean Force in GROMACS

Dissociation of an Amyloid Protofibril

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Objectives

• Understand the basic concepts of the pull code

• Learn the protocol for calculating PMF for the dissociation of a protein complex

• Understand the analysis methods associated with PMF
Background

- GROMACS manual, section 6.4
- PMF theory
- WHAM algorithm
- GROMACS g_wham
- Today’s example
**Background**

- Virtual particle attached to some molecule in the system via a “spring” (harmonic potential)

\[ F = -k(x - x_0) \]

- Virtual particle moves, extending the spring and increasing the force

- Pulled molecule responds to this applied force
Background

- To calculate PMF, we define a reaction coordinate, $\xi$
  - A path along which the system evolves
  - Can be:
    • A direction (vector)
    • An angle (dihedral rotation)
    • Other abstract things

- Generate a series of configurations along $\xi$, conduct individual simulations at chosen intervals
Background

Harmonic potential allows for oscillation within each window, overlap with neighboring sampling windows.

References

Theory
Background

Sampling window \{ \}

\begin{align*}
x_1 &\rightarrow E_1 \\
x_2 &\rightarrow E_2 \\
x_3 &\rightarrow E_3
\end{align*}

\[ \Delta G \]

References
Theory
Tutorial Exercise

- Steered MD (SMD) for path-dependent quantities
- Umbrella sampling (US) for ΔG calculation

Tutorial Exercise

• Tutorial files provided

  pmf_tutorial/conf
  /mdp
  /pull_data
  /scripts
  /tpr

  Starting configurations
  Run parameters
  Sample data
  Accessory scripts
  Run input files

• Protocol online

http://www.bevanlab.biochem.vt.edu/Pages/Personal/justin/gmx-tutorials/umbrella/index.html
Tutorial Exercise

• Constructing the box
  – Caveats of using pull_geometry = distance
Tutorial Exercise

• Notes on pull geometries
  – distance (uses pull_dim)
    • Simple to use, intuitive
  – direction (pull_vec)
    • Also very simple, could be used here
  – direction_periodic (pull_vec)
    • Eliminates PBC issue, but problems with NPT
  – position (pull_vec)
    • Could be used here, more complex
  – cylinder (pull_vec)
    • Useful for membranes and surfaces
Tutorial Exercise

• Generate configurations
  – Starting coordinates for each window
  – Can be done manually
    • editconf or trjconv to place molecules
  – Use pull code (steered MD)
    • Can provide path-specific insight

• Determine adequate spacing for windows
• Equilibrate within each window
Tutorial Exercise

• Pull rates and force constants during SMD
  – No hard and fast rules, sorry!
  – Both pull_k1 and pull_rate1 affect outcome
  – Try multiple values

• Determine source of any artifacts
Tutorial Exercise

• Pull rates and force constants during US
  – Pull rate is zero
    • Not producing net displacement
  – pull_k1 determines width of windows
    • How far molecule can deviate from center of window
    •Extent of overlap between neighboring windows

Too strong

Too weak?

Perfect!
Tutorial Exercise

• Main outcome of umbrella sampling is the PMF
  – WHAM algorithm via \texttt{g\_wham} in GROMACS
    • Calculates PMF, produces profile
    • Outputs histograms to show sampling
    • Conducts error analysis and calculates autocorrelations
    • Convenient symmetry and shifting operations
      – Options \texttt{-sym/-cycl} and \texttt{-zprof0}
Tutorial Exercise

• Input files for \texttt{g\_wham}
  – \texttt{tpr-files.dat}
    • List of .tpr file names
  – \texttt{pullf\_files.dat/pullx\_files.dat}
    • List of pullf.xvg or pullx.xvg file names
Tutorial Exercise

- Output files
  - profile.xvg (from –o option)
    - PMF profile
  - bsResult.xvg (from –bsres option)
    - Average PMF profile, with σ from boostrapping
  - bsProfs.xvg (from –bsprof option)
    - All PMF profiles from bootstrapping
  - histo.xvg (from –hist option)
    - Sampling histograms
    - Plot with xmgrace -nxy
Tutorial Exercise

g_wham -it tpr/tpr-files.dat -if pull_data/pullf-files.dat -o profile.xvg -hist histo.xvg -bsprof bsProfs.xvg -bsres bsResult.xvg -temp 310 -nBootstrap 200

Bootstrap Profiles

Average PMF Profile