Replica-exchange in molecular dynamics

Part of 2014 SeSE course in Advanced molecular dynamics

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Frustration in MD
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- different motions have different time scales
  - bond vibration, angle-vibration, side-chain rotation, diffusion, secondary structure (de)formation, macromolecular events, . . .
  - need a short enough time step
- a model that doesn’t get enough fine detail right will struggle with higher-level things, too
Barriers in MD
Frustration in MD

- barriers more than a few $kT$ exist, and are hard to cross
- need extremely large amount of brute-force sampling to get over them
- makes solving problems like protein folding exceedingly expensive
Ways to grapple with the problem

- give up on fine detail, and use a coarse-graining approach
- accelerate the sampling (work smarter!)
- throw more hardware at it (e.g. Folding@Home)
- write faster software (hard, very hard)
Accelerating the sampling

- if the problem is that $kT$ is too small..
  1. increase $T$
  2. sample widely
  3. . . .
  4. profit!

- unless the landscape changes...
Accelerating the sampling - heating it up
Simulated tempering

- use Monte Carlo approach to permit system to move in control parameter space
- typical control parameter is temperature (but not essential)
- typically sample the system only when at temperature of interest
- correct if the (Metropolis) exchange criterion is constructed correctly
  - how? For a state $s$

$$P((\beta, s) \rightarrow (\beta', s)) = \min(1, \frac{w(\beta', s)}{w(\beta, s)})$$

where $\beta = \frac{1}{kT}$ and $w(\beta, s) = \exp[-\beta U + g(\beta)]$
Simulated tempering (2)

- correct if the exchange criterion is constructed correctly
  - the optimal $g(\beta)$ is the free energy... 
  - so you’re good if you already know the relative likelihood of each conformation at each temperature
- works great if you already know the answer to a harder problem than the original
- (but you can use an iterative scheme to converge on the answer)
Parallel tempering (a.k.a. replica exchange)

- side-steps the prior-knowledge problem by running an *independent copy* of the simulation at each control parameter
- (note, throwing more hardware at the problem!)
- now the exchange is between copies at different control parameters, each of which is known to be sampled from a correct ensemble already
- this eliminates $g(\beta)$ from the generalized exchange criterion...
Parallel tempering - the exchange criterion

\[ P((\beta, s) \leftrightarrow (\beta', s')) = \min(1, \frac{w(\beta, s') w(\beta', s)}{w(\beta, s) w(\beta', s')}) \]

which for Boltzmann weights reduces to

\[ = \min(1, \exp[(\beta' - \beta)(U' - U)]) \]
Parallel tempering - understanding the exchanges

Distribution

Figure: Potential energy distributions of alanine dipeptide replicas
Parallel tempering - is this real?

- recall that $P(\beta s) \propto \exp[-\beta U(x)]$
- any scheme that satisfies detailed balance forms a Markov chain whose stationary distribution is the target (generalized) ensemble
- so we require only that $P((\beta, s))P((\beta, s) \rightarrow (\beta', s)) = P((\beta', s'))P((\beta', s') \rightarrow (\beta, s'))$
- ... which is exactly what the exchange criterion is constructed to do
Parallel tempering - is this real? (2)

- high temperature replicas hopefully can cross barriers
- if the conformations they sample are representative of lower-temperature behaviour, then they will be able to exchange down
- if not, they won’t
Ensembles used

- natural to use the NVT ensemble with an increasing range of $T$ and constant $V$
- there’s a hidden catch - must rescale the velocities to suit the new ensemble in order to construct the above exchange criterion
- probably this should use a velocity-Verlet integrator ($x$ and $v$ at same time)
- in principle, can use other ensembles like NPT
Ensembles used (2)

- NVT at constant volume must increase $P$ with $T$
- that seems unphysical
- worse, the force fields are parameterized for a fixed temperature
- but the method doesn’t require that the ensembles correspond to physical ones
- merely need overlap of energy distribution
- how much overlap determines the probability of accepting an exchange
Problems with replica exchange

- Molecular simulations typically need lots of water
- Thus lots of degrees of freedom
- Energy of the system grows linearly with system size
- Width of energy distributions grow as $\sqrt{\text{size}}$
- Need either more replicas or accept lower overlap
Unphysics is liberating

- if there’s no need to be physical, then may as well be explicit about it
- large number of schemes proposed
- example: resolution exchange
  - run replicas at different scales of coarse graining
  - at exchange attempts, not only rescale velocities, but reconstruct the coordinates at the higher/lower grain level
Hamiltonian replica exchange

- replicas can be run varying some other control parameter
  - e.g. gradually turn on some biasing potential
- can construct higher-dimensional control-parameter schemes also
  - in a free-energy calculation, exchange between both alchemical transformation parameter $\lambda$ and temperature
Replica exchange with solute tempering

- selectively “heat” only a small region of the system
- modify the parameters to scale the energy, rather than heating
  - remember $P(\beta s) \propto \exp[-\beta U(x)]$
- advantage that the energy distribution of only part of the system increases over control parameter space
- needs many fewer replicas for a given control parameter space
- implemented in GROMACS with PLUMED plugin
Questions?