How to obtain statistically converged MM/GBSA results

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Background
An important task in the process of drug design is to accurately calculate the binding free energy, $\Delta G$, of a ligand to its receptor. The Molecular Mechanics and Generalized Born-Surface Area (MM/GBSA) method offers a simplified, yet an attractive way to do this.

Problems with MM/GBSA:
- Large standard errors (~20-150 kJ/mol)
- Possibly incomplete sampling

Aim: Devise a protocol that gives results with a statistical precision of 1 kJ/mol

Methods
- Amber 99SB force field for protein and TIP4P-Ewald waters
- Amber 10 was used for the simulations
- $\Delta G$ was calculated according to
  \[
  \Delta G_{\text{bind}} = \langle G_{RL} \rangle - \langle G_R \rangle - \langle G_L \rangle
  \]
  and
  \[
  G = E_{\text{MM}} + G_{\text{solv}} - T S_{\text{MM}}
  \]
- Where $RL$ is the protein-ligand complex, $R$ is the receptor, $L$ is the ligand, $E_{\text{MM}}$ is the molecular mechanics energy, $G_{\text{solv}}$ is the solvation energy and $T S_{\text{MM}}$ is the entropy.
- Solvation method was generalized Born method of Onufriev et al. (model I)

Results
Simulation protocol
- With one long simulation results were different for the 4 subunits, i.e. results were not converged
- With 20 independent simulations the results were converged
- The $\Delta G$ estimates in the 20 independent simulations have a range of ~50 kJ/mol
- The sampling frequency should be 5 ps
- The equilibration time should be 100 ps
- The optimal protocol varies depending on the system

Best protocol applied to 7 biotin analogs
- Required 20-50 simulations to obtain errors of 1 kJ/mol
- $\Delta G$ estimates systematically too low, owing to the solvation method
- Mean absolute difference 15±0.3 kJ/mol
- Correlation coefficient 0.59±0.01
- Predictive index 0.85±0.03

Conclusions
- We have a statistically valid estimate of the MM/GBSA results
- A statistically valid estimate of the true accuracy
- Possible to compare with other force fields and methods

Publication