OLD DOG, NEW TRICKS: FREE ENERGY CALCULATIONS WITH GRAND CANONICAL MONTE CARLO

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Water molecules often form an integral part of membrane pores and protein-drug complexes. They can stabilise complexes by bridging the interaction between ligands and proteins, and their displacement upon the binding of a ligand can contributed favourably to the affinity of the complex. When water molecules are buried within proteins, or are tightly bound, molecular dynamics (MD) simulations lasting many microseconds may be required to achieve sufficient sampling [1]. In contrast, grand canonical Monte Carlo (GCMC) methods can completely bypass the need for excessively long MD simulations via the application of alchemical insertion and deletion moves [2]. This is accomplished by imposing a constant chemical potential – a user defined parameter – on the simulations. Previously, *a priori* knowledge was required to determine the correct value of the chemical potential for a system of interest [3].

By expanding the theory underpinning GCMC, we show that the optimal chemical potential can be calculated directly from the simulations themselves. We also introduce and validate a new free energy calculation method based on GCMC, which, among other uses, allows one to efficiently calculate the binding free energy of entire networks of water molecules to protein-ligand binding sites; calculations which otherwise would require multiple technically demanding simulations.

[1] Ostmeyer J. et al., *Nature* 501 (2013) 121-214.

[2] D. J. Adams, *Molecular Physics* 28 (1974) 1241-1252.

[2] Resat H., Mezei M., *Biophysical Journal* 71 (1996) 1179-1190.

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