An Analysis of the Difference between the Generalized Born Solvent Model and the Distance Dependent Dielectric Model for Normal Mode Analysis

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The binding of receptors and ligands is the principal device for activity at the molecular level in biological systems.[1] Molecular binding is dependent upon the free energy differences between an unbound receptor and ligand pair and a bound receptor-ligand complex. Large contributions to this free energy difference, and thus to the overall binding affinity, arise from vibrational entropy changes of the systems.[2] These contributions are by and large neglected in simple scoring functions for receptor-ligand binding, but can be estimated using computational approaches. At present, Normal Mode Analysis (NMA) is considered to be the gold standard for this. So far, NMA on biomacromolecules has been performed using a distance dependent dielectric (DDD) solvent model. Recently, second derivatives in generalized Born theory have been introduced. [3] This allows NMA to be performed using a Generalized Born (GB) solvent model and, hence, a more realistic solvent representation.

In the present study, we determined vibrational entropy changes by NMA upon receptor-ligand binding for 27 protein-ligand and 4 protein-polypeptide complexes using either the DDD or GB model, as implemented in AMBER Tools. [4] Aside from differences in computation time, this comparison revealed a surprising and significant difference between the two methods: the NMA-GB predicted that, for the majority of our test systems, vibrational entropy contributions disfavor binding, whereas NMA-DDD predicted the opposite. Due to the lack of validation by experiment, it is important to identify which method is a more realistic representation of these systems and so we present possible reasons for the difference here.

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