Developing a Methodology for Computational Drug Design

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Computational methods are beneficial to drug design due to increased control over experimental conditions, as well as significant reduction in the time and expense required to identify potential drug candidates for therapeutic use. Ligand docking allows us to closely observe ligand-receptor interactions in the context of estrogen receptor (ER) and anti-breast cancer compounds. In our experiments, we have docked analogues of a promising cancer drug, raloxifene, into an ER-α crystal structure and have calculated binding energies for each ligand-receptor interaction. The size and complexity of our biological system presents several obstacles in modeling both the dynamics and energetics of the receptor-ligand complex. We have examined protonation states of the ligands in order to better match previous experiments and reduced the size of the ER in order to increase our experiment's efficiency. To obtain data points on these interactions, we first optimized each raloxifene analogue using a HF/6-31G* level of theory. Next, we assigned RESP charges to parts of the molecule with Antechamber and ran the molecule through AMBER8's LEaP module using the ff99SB force field for the protein and the GAFF force field for the ligand. The entire complex, consisting of the ER and a ligand, was then minimized in sander. Following this minimization, we ran the complex through an MD simulation for 2000 ps. We used RMS plots to determine the equilibration point for each ligand within its complex, then ran MMGBSA calculations in order to obtain values changes in free energy of binding over the whole trajectory. After obtaining MMGBSA values, we calculated semi-emperical DivCon single-pont calculations (SPCs) for snapshots from every 50 ps of the MD simulation. These SPCs were run in sets of three in order to obtain the binding enthalpy for each snapshot: $\Delta H = H_{complex} - (H_{receptor} + H_{ligand})$.