Honing a Methodology for Computational Breast Cancer Drug Design

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The estrogen receptor (ERα) accounts for the up regulation and transcription of many breast cancers and therefore presents an ideal target for anti-cancer drugs. Experimental studies have shown osteoporosis-prevention drug, raloxifene, to be effective in preventing breast cancer through selective estrogen receptor modification (SERM). Raloxifene, however, is largely unavailable in the human body as it undergoes first-pass metabolism in the liver and intestine—leaving only 2% of the drug active. In the pursuit of an effective SERM which is also largely bioavailable, Grese et al. have developed a set of 76 raloxifene analogs, which we have studied in a computational context.

In order to create a more computationally-efficient methodology, we have developed a cut-system complex model—reducing the size of our ERα crystal structure from its entirety (4,000 atoms) to the 1,400 atoms within a 10 Å radius of the ligand binding domain (LBD). Within AMBER9, we first optimized each molecular structure using a HF/6-31G* geometry within Gaussian. Next, we assigned RESP charges to parts of the molecule with Antechamber and ran the molecule through AMBER9's LEaP module. We docked each Grese et al. analog into the cut ERα crystal structure using AutoDock Tools. After solvating the system in an octahedron of tip4p waters, we ran the entire complex, consisting of the solvated ERα and a raloxifene derivative, through sander in order to minimize its energy. Following this minimization, we ran the entire complex through MD for approximately 5000 ps, beginning with a 100 ps equilibration under constant volume. The rest of the simulation was run under constant pressure using the ff99SB force field for the protein and the GAFF for the ligand. We calculated semi-empirical Divcon single-pont calculations (SPCs) for snapshots from every 50 ps of the MD simulation. These SPCs were run in triplicate in order to obtain binding energy values for each ligand-receptor interaction [$\Delta H = H_{complex} - (H_{receptor} + H_{ligand})$].

Our aim with this project was to establish a reliable method for computational testing of raloxifene derivatives using a quantitative analysis of Divcon values for each ligand-ERα interaction. With the addition of explicit solvation to our system, we have recently found correlation between our computationally-determined and Grese et al.'s experimental results. We have been able to determine and assess the binding energies of these experimental anti-cancer drugs with the future direction of designing our own analogs to run through this system.