Quantification of Binding Free Energies in Amyloid-Antibody Systems Related to Alzheimer's and Enhancement of Antibody Binding Affinities

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Amyloids comprise of the amino acids that are the primary cause of Alzheimer's; an antibody that binds with high affinity to the amyloid has great potential of being an improved drug candidate. Current calculations of binding energies remain inaccurate and inefficient; this project proposes a novel approach to quantify binding energies and optimize mutations for enhanced drug targeting. I developed a new thermochemical and computational model using implicit solvent models and the Generalized Born equation derived from the linearized Poisson-Boltzmann equation. The energy difference between the bound and unbound state of solvated molecules is found by computing binding energies in vacuum and solvating each step. This model was validated by comparing calculated binding energies with a dataset of known energy values. Visualization software and molecular docking were applied to program amino acid properties so that the nature of amyloid interactions could be predicted; I created a machine learning algorithm based on finding the global minimum in the energy graph generated by the new model to determine optimal antibody mutations as it interacts with the amyloid of given properties. The results of selected antibodies were compared with nuclear magnetic resonance data from the Protein Data Bank for similarity validation. The results show high accuracy in numerical comparisons between the simulated and actual binding mechanism. Also, >92% of optimized mutations proposed by the algorithm decreased binding energies by thousands of joules/mole, enhancing antibody affinities and specificity. This can improve drug design by revealing the most favorable modifications of antibody receptors while reducing side effects such as mental impairment caused from lack of drug specificity.

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