Novel Nudged Elastic Band (NEB) Approach for Minimum Energy Pathway Modeling in Protein Binding for Efficient Drug Discovery

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Current drug design methods treat proteins as rigid structures, failing to capture functional high-energy states. This contributes to 40–50% of clinical-stage drug failures. Mapping continuous, low-energy transition pathways between states is therefore critical for drug discovery. I optimized a Nudged Elastic Band (NEB) protocol using AmberTools 2023 to map the transition pathways of two Benchmark 5.5 Dataset proteins classified as "difficult" docking targets: 1J57 (NuiA nuclease A inhibitor) and 1CKV-A(9) (regulatory protein B). My modified NEB model reduced computational time by 20% and prevented protein unfolding and denaturation. Simultaneously, it identified intermediate conformational changes, and captured converging, reproducible global minimum energy paths (MEPs) with less than 5% uncertainty (over seven runs) for both proteins. The MEPs revealed distinct conformational mechanisms due to different types of motion (loop vs. hinge and large domain vs. local movements): even at high potential energy, 1J57 exhibited structural rearrangement while 1CKV-A(9) remained relatively static. Docking ~4000 ZINC small molecules to the transition state (TS) yielded candidates that lowered potential energy (up to 3.5% in 1J57), showing higher binding success rates. These results prove that targeting intermediate, high-energy states, rather than only the bound structure, supports the strategy of transition-state stabilization to improve hit identification and discover allosteric modulators in structure-based drug design. Future studies will characterize energy curves of diverse motions, define reaction coordinates to boost TS-specificity, and apply this pipeline to disease-relevant proteins, shifting from screening to de novo drug design.

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