ACCELERATING QUANTUM-CHEMICAL MULTILIGAND SIMULTANEOUS DOCKING WITH DEEP REINFORCEMENT LEARNING

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This study employs quantum-chemical multiligand simultaneous docking (MLSD) to identify potent single or joint inhibitors of human acetylcholinesterase (hAChE), human butyrylcholinesterase (hBChE), and/or equine butyrylcholinesterase (eqBChE). Moving beyond traditional single-molecule docking, we adopted a fragment-based paradigm, docking multiple small molecular scaffolds designed for subsequent assembly *via* modular organic synthesis. To navigate the high-dimensional configurational space and the computational complexity associated with translational, rotational, and conformational degrees of freedom, we developed a parallelized Monte Carlo algorithm to enhance sampling efficiency.[1] This framework incorporates a smart structure generator for pre-screening and input optimization. Binding enthalpies were determined using the PM7 semiempirical Hamiltonian,[2] which has been shown to outperform other semiempirical methods for organic molecules.[3] To overcome the computational bottleneck of PM7 calculations, particularly in multiligand systems, we integrated deep neural networks (DNNs) trained on-the-fly *via* deep reinforcement learning.[4] These DNNs accurately approximate potential energy surfaces (PESs), substantially reducing the computational cost of energy determinations. Finally, active-site coverage was monitored dynamically throughout the simulations using probability density functions to ensure optimal ligand placement throughout the active site.

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REFERENCES

[1] T. Hrenar, ***qcc***, *Quantum Chemistry Code*, rev. 0.6826, Zagreb, Croatia, 2026.

[2] J. J. P. Stewart, Optimization of parameters for semiempirical methods VI: More modifications to the NDDO approximations and re-optimization of parameters. *J. Mol. Model.* **2013**, 19, 1–32.

[3] J. Hostaš, J. Rezač, P. Hobza, On the performance of the semiempirical quantum mechanical PM6 and PM7 methods for noncovalent interactions. *Chem. Phys. Lett.* **2013**, 568, 161–166.

[4] T. Hrenar, ***moonee***, *Program for Manipulation and Analysis of Multi- and Univariate Data*, rev. 0.68268, Zagreb, Croatia, 2026.