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Exploring the entire medicinal chemistry space on the hybrid computational platform with quantum annealer and gate-based quantum circuits

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***Abstract*—There are at least 10^{60} small organic molecules in the chemical space relevant for drug discovery. Target identification and validation is considered as the first step for modern drug discovery. Thanks to the emergence of several AI-empowered structural prediction tools, e.g., AlphaFold, RosettaFold, ESMFold, etc., the structures of many novel drug target can be predicted with high accuracy. Once the structure of the drug target can be obtained with good quality, the so-call molecular docking calculation can be harnessed to conduct the structure-based virtual screening in a rational fashion for discovering the lead candidates. Key ingredients of the molecular docking calculation include accurate estimation of the binding free energy between the small organic molecule and its target protein, and efficient exploration of the possible position, orientation, and conformations of the small molecule with respect to the target protein. Currently, with the cloud computing and by using rather inexpensive machine learned methods to estimate the binding free energies for screening, it is possible to explore the so-called "ultra-large" chemical library of about 10^8 chemical molecules within just one day. Although this is an impressive speed, it can easily be understood that we are still far from exploring the medicinal chemistry space of about 10^{60} molecules. Universal gate-based quantum computers hold the promise to explore the entire space of medicinal chemistry. In this presentation, we will show how we constructed the quantum circuits to evaluate the binding free energies between small molecules and their target proteins of a myriad of protein-ligand complex structures simultaneously. Besides, we will also present how the molecular docking calculations can be implemented with the quadratic unconstrained binary optimization (QUBO) scheme, so that the high-dimensional search for optimal pose with the minimal predicted binding free energy can be carried out robustly and efficiently.**

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