Contribution ID : **87** Type : **Poster Presentation**

EuCompChem2025 – Suwala – Oral

Cytochrome P450-mediated mechanisms play a significant role in drug metabolism, with estimates indicating that 75% of commercially available drugs are metabolized by only 6 of the 57 human CYP enzymes [1]. These heme-containing cytochromes P450 display a broad spectrum of ligand specificity [2], a property enabled in part by the flexible protein region adjacent to the binding site. Consequently, this flexibility challenges docking methodologies that rely on a rigid protein approximation, resulting in reduced reliability [2],[3]. This work [4] evaluates open-source docking engines in a high-throughput manner on a dataset of 128 ligands. We employ four notably different engines: RosettaFold-AllAtoms [5] (rfaa), GalaxyDock2 HEME [6] (gdock), AutoDock VINA [7,8] and GNINA [9]. Redocking and crossdocking simulations were employed to assess the docking protocols. In redocking, the ligand is docked into a protein that possesses the optimal binding conformation, whereas in crossdocking, the ligand is docked into a folded protein lacking the binding-specific conformational information, thereby necessitating adjustments. Consequently, crossdocking offers a more realistic representation of practical applications. To compare the engines, we introduced system-specific metrics focused on the heme iron atom and evaluated model performance using the mean absolute error. We report significant improvement for flexible rfaa full sequence prediction and during the presentation, we will outline our simulation workflow, elaborate on our system-specific metrics, benchmark results, and conclude with a discussion on the current challenges.

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