Automated Identification of Cryptic Pockets for Drug Discovery

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The pharmaceutical industry is always on the lookout for new therapeutic targets. Many proteins found in signaling pathways have historically been considered “undruggable” as no points of attack for classical drug development work can be identified. The proteins do not show obvious “active sites” that can be targeted with e.g. classic virtual screening techniques due to their smooth protein surface or large inherent protein motion.

In recent years, many advances have been made in MD (Molecular Dynamics) simulations algorithms as well as compute power that drives them, to allow the study of the dynamic behavior of such undruggable proteins. Long timescale protein motions can, in many cases, reveal pockets that typically do not exist in an apo form where a ligand is not present, but can open during simulations. These so-called “cryptic pockets” have been studied and exploited so that now the first drugs binding to cryptic pockets are on the market.

OpenEye's cloud-native computing platform provides scientists with unprecedented scalability for parallel computing that can detect and classify such cryptic pockets through embarrassingly parallel simulations. The integration of the Weighted Ensemble toolkit WESTPA [1] allows for automated simulation of these slow and rare pocket opening events in reasonable time scales to identify potential cryptic pockets. We will discuss examples how we can identify cryptic pockets in proteins that were thought to be undruggable.

[1] Russo, John D., et al. "WESTPA 2.0: High-performance upgrades for weighted ensemble simulations and analysis of longer-timescale applications." Journal of chemical theory and computation 18.2 (2022): 638-649.