Enhanced Sampling of Protein Conformations for Cryptic Pocket Detection

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Summary:

- Enhanced sampling molecular dynamics to explore protein conformational space for a variety of tasks including cryptic pocket detection
- Physics-based methods to detect pocket formation
- Successful identification of cryptic pockets in multiple targets, including the difficult to drug K-RAS protein

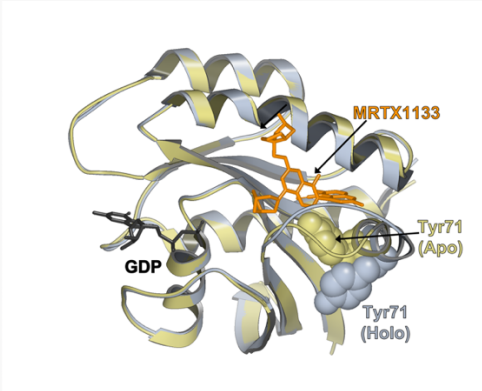
Product Keywords: Orion, Enhanced Sampling MD, Cryptic Pockets

Abstract:

Exploring new binding pockets in proteins is a key goal in early drug discovery. This effort broadens the scope of potential drug targets, creating opportunities to modulate protein activity. Discovering cryptic pockets, rarely seen in experimental structures, can reveal hidden ligand binding sites in static apo and holo structures, opening up new therapeutic possibilities.

To identify these cryptic pockets, we have implemented enhanced sampling molecular dynamics (ESMD) using the WESTPA package and a suite of analysis tools on our cloud-native platform, Orion. ESMD generates equilibrium ensembles of protein conformations in a variety of environments, including a mixed solvent with xenon atoms as probes for both hydrophobic and hydrophilic binding sites. Subsequently, these ensembles undergo diverse analysis methods to identify protein motions that may reveal a cryptic pocket.

Candidate pockets are analyzed using three complementary methods: 1) exposon formation, correlated changes in residue solvent exposure that may indicate pocket opening and closing; 2) dynamic probe binding, correlated changes in residue-co-solvent interaction; 3) probe occupancy mapping, stable binding locations for xenon atoms.



Cryptic Pocket identified in K-RAS led to Mirati's discovery of MRTX1133

In a cooperative project with Mirati Therapeutics the cryptic pocket tool was applied to K-RAS, a protein that has been very difficult to target (requiring over 30 years from discovery to first marketed drug). The project successfully identifying two adjacent cryptic pockets that are targeted by a new class of K-RAS inhibitors.

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