From Undruggable to Actionable: Unlocking Hidden Binding Sites with Advanced Protein Dynamics

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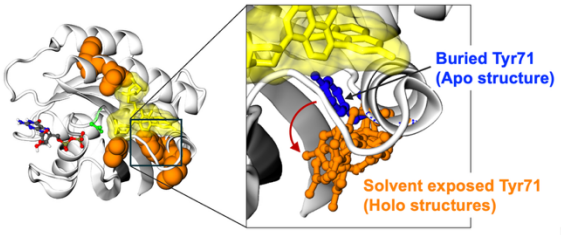
Summary:

- Many therapeutically relevant binding sites are transient and not observed in static protein structures.
- Enhanced molecular dynamics sampling enables systematic discovery of cryptic pockets across diverse protein motions.
- Cryptic pocket detection expands drug discovery beyond previously established binding sites.
- Early identification of cryptic pockets enables alternative and allosteric drug discovery strategies.

Product Keywords: Target X, Weighted Ensemble MD, Cryptic Pocket, Orion®

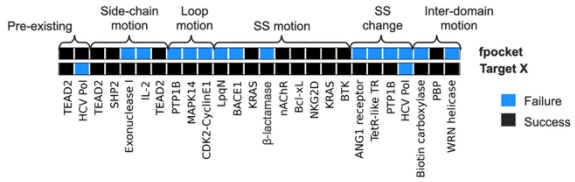
Abstract:

The discovery of cryptic binding pockets has transformed drug discovery for targets long considered difficult or undruggable. These pockets often emerge from rare conformational states and are often absent from experimental structures. Capturing such states require explicit sampling of protein dynamics across broad range of motions and timescales.



In a cooperative project with Mirati Therapeutics, Target X predicts the known cryptic pockets in K-Ras oncoprotein (yellow - inhibitor, orange - pocket residues).

OpenEye's Target X uses weighted ensemble molecular dynamics (WEMD) driven by normal modes and has successfully predicted known cryptic pockets in the K-Ras oncoprotein. This approach efficiently and unbiasedly explores protein conformational landscapes by sampling collective intrinsic motions that may give rise to cryptic pockets; from large interdomain rearrangements to localized structural fluctuations. Mixed-solvent simulations with small, non-specific probes further reveal emergent binding sites through probe occupancy analysis.



Applied to a dataset of 26 pockets across 21 diverse proteins, Target X method outperforms fpocket and successfully identified cryptic pockets starting from only the apo structure in over 90% of cases.

When applied across a diverse set of proteins, Target X helps scientists identify binding sites suitable for orthosteric, allosteric, and alternative inhibition strategies. Insights into cryptic pockets enable drug discovery teams to proactively explore new binding modes rather than relying on retrospective experimental findings.

Reference: Vithani et. al. Preprints. Research Square. Feb 15, 2026. DOI: https://doi.org/10.21203/rs.3.rs-8854093/v1

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