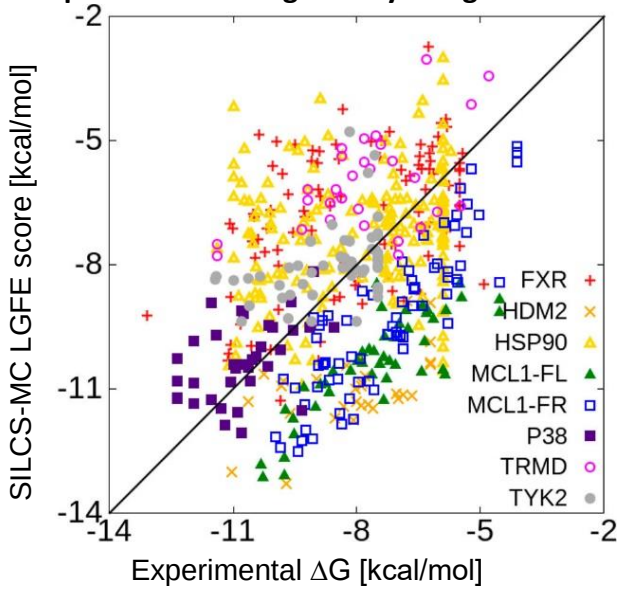
SILCS-MC Accurately Ranks Affinities Across 7 Diverse Proteins and 551 Ligands

Site-identification by ligand competitive saturation (SILCS™) is a cosolvent sampling technique that maps binding affinity patterns of chemical fragments on a protein as free energy fields called FragMaps. SILCS offers significant advantages over simple co-solvent methods by simultaneously evaluating a range of functional groups by including multiple probe types in the same simulation system. SILCS simulations offer improved accuracy of FragMaps and the ability to identify hidden pockets on both the surface and interior of the protein using Grand-Canonical Monte Carlo (GCMC) sampling of the probes and water in conjunction with Molecular Dynamics. SILCS FragMaps for a protein target enable rapid analysis of ligands to predict their binding conformations and relative binding affinities using the SILCS-Monte Carlo (SILCS-MC) approach.

In a recently published study in the *Journal of Chemical Information and Modeling* (10.1021/acs.jcim.9b00210), the SILCS-MC approach was applied to seven protein targets and 551 ligands. Across the protein–ligand sets, the rank ordering of the affinity of ligands was initially predicted correctly an average of 69% of the time. Investigators then optimized the ligand scoring scheme using available experimental data and a new machine learning (ML) approach, increasing the number of correct relative affinity predictions. After optimization, an average overall predictability of 76% is achieved, with predictability rates of over 80% attained for select data sets. The ML optimization algorithm was shown to be effective with a small training set, allowing for reliable target-specific SILCS-MC scoring with limited experimental data input.

Correlation between experimental and predicted binding affinity using SILCS-MC



SILCS Achieves a 76% Correct Relative Prediction Rate Across These Seven Protein Targets

This rate is similar to or better than the significantly more compute-intensive industry standard free energy perturbation (FEP) method. SILCS-MC protocols can accommodate ligands in a congeneric series, scaffold changes, and a variety of larger chemical modifications, expanding the diversity of ligand modifications available for consideration, including those not accessible by FEP. These results further support the utility of SILCS as a powerful tool to support lead compound optimization and development in drug discovery.

SILCS FragMaps and software have been used in computer-aided drug design (CADD) efforts by chemists and drug designers in the US, Europe, Japan and the UK. SILCS-MC provides a much faster alternative to FEP methods, the current CADD industry standard, as the FragMaps do not need to be recomputed for each ligand modification.

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Find out how SILCS can improve and accelerate your computational drug design efforts.

MORE INFO

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