Development of SILCS kinetics methodology for the determination of ligand dissociation pathways and free energy barriers

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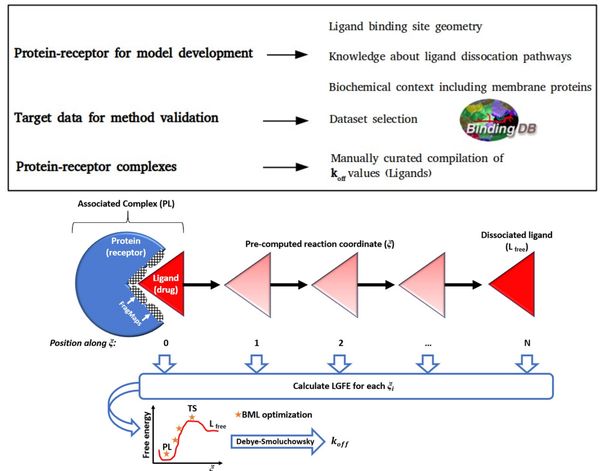
COMPUTER-AIDED DRUG DESIGN SYMPOSIUM

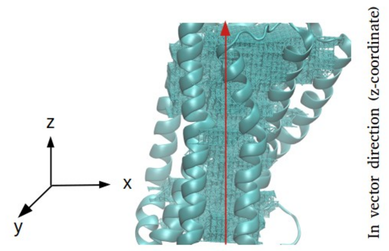
Abstract

The fast and accurate assessment of unbinding kinetics of ligands from proteins remains challenging due to high computational requirements and the lack of the information about the molecular transition states due to limited conformational sampling. Therefore, in the present study we investigate the extension of the site-identification by ligand competitive saturation (SILCS) methodology towards estimation of ligand unbinding kinetics. The proposed SILCS-kinetics (SILCS-KIN) method is implemented to sample the free-energy landscape of drug dissociation pathways. SILCS-KIN methodology will be expected as a potential tool for the discovery and design of drug-like compounds with optimized ligand dissociation properties.

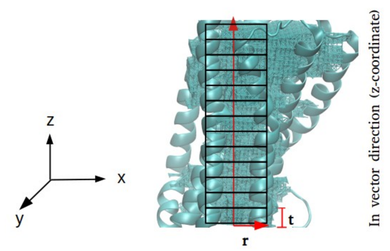
Methodology



Steps implemented in the SILCS-KIN methodology

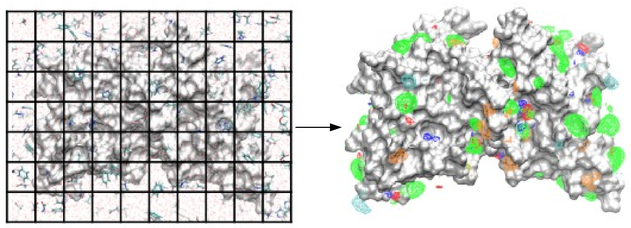


Exhaustive sampling SILCS MC method



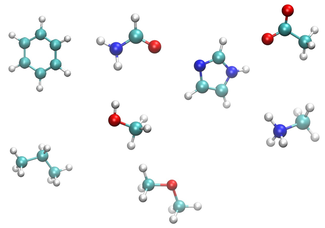
Slab based SILCS MC method

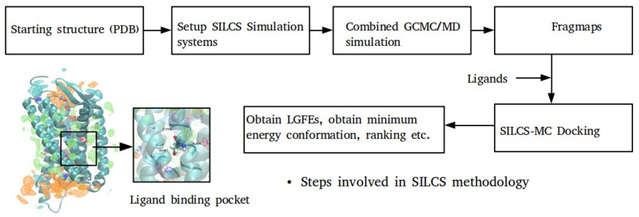
SILCS Strategy



Map Functional Groups

- Benzene
- Propane
- Methanol
- Imidazole
- Formamide
- Dimethylether
- Methylammonium
- Acetate

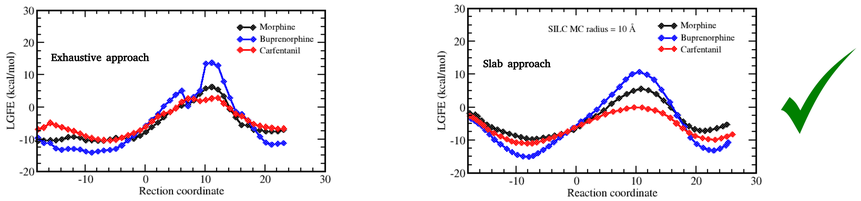




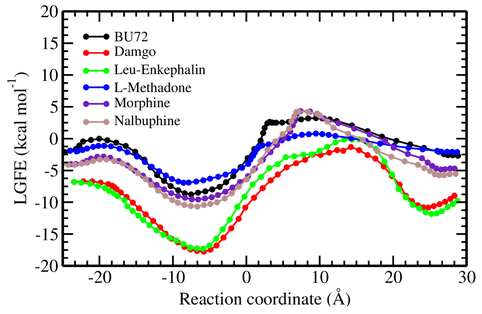
• Steps involved in SILCS methodology

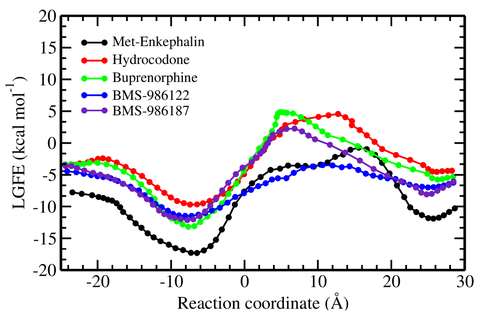
μ-opioid receptor (membrane protein)

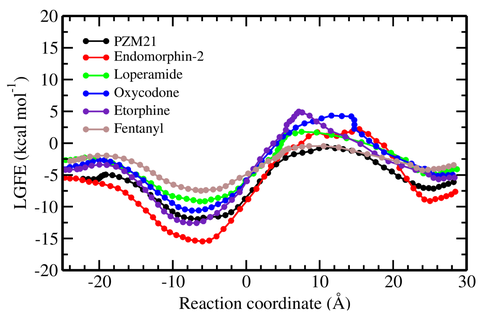
Results

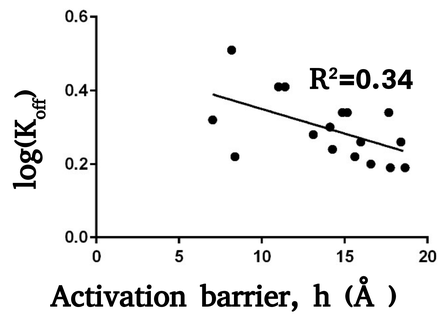


Exhaustive vs Slab based SILCS MC sampling









Activation barrier, h (Å)

Summary

- Slab based SILCS MC approach is better and accurate than Exhaustive SILCS MC
- SILCS-KIN approach will be tested for other proteins in the dataset
- BML method will be further used to maximize the predictibility of SILCS-KIN model

References

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2. PLoS Comput Biol 2009, 5(7):e1000435; J Chem Inf Model 2011, 51(4):877–896; J Chem Inf Model 2013, 53(12):3384–3398

Acknowledgments

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