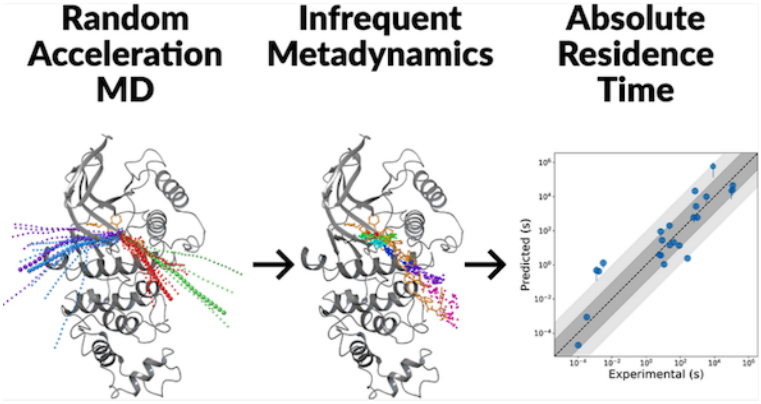
Let it go: exploring and learning from unbinding pathways

Jonas Kaindl

Schrödinger GmbH, Mannheim, Germany

The estimation of drug-target residence time has been widely adopted in drug discovery and lead optimization campaigns as a metric to control and modulate in vivo drug efficacy. Over the years, several computational approaches have been developed to simulate unbinding kinetics and calculate dissociation rates. In addition to accurately predicting residence time, understanding the molecular basis of the unbinding event is crucial to support and drive the design of drugs with optimized kinetic profiles. Here, we present the application of the unbinding kinetics workflow developed by Schrödinger to accurately predict the residence time and to study the unbinding mechanism of a set of drug-target systems [1]. We applied the presented approach to different target classes and modalities, looking at the details of the dissociation process and understanding the determinants of such an event. Overall, the results demonstrate the applicability of the workflow in assisting drug design with minimal human intervention and a computational cost compatible with drug design cycle timeline.



[1] Z. Smith, et al., *J. Chem. Inf. Model*, **2025**, *65 (24)*, 13360-13373.