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COMPUTATIONAL TOOLS FOR PROTEIN-LIGAND BINDING KINETICS IN PERSONALIZED MEDICINE

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Patients with the fusion oncoprotein BCR-ABL develop chronic myeloid leukaemia, where the kinase domain of ABL is constitutively active instead of auto-inhibited. Tyrosine kinase inhibitors (TKIs) have been developed that competitively bind to the ATP binding site of ABL, minimizing ABL's enzymatic function of transferring phosphate groups to substrate proteins. Mutations in the kinase domain of ABL can reduce – or completely block – the binding activity of known TKIs, to which the need of novel and personalized drug molecules arises. s

In this study, state-of-the-art molecular dynamics simulation techniques are being used to extract both thermodynamical and kinetical information of ABL-inhibitor complexes, for multiple inhibitors, and for multiple ABL mutations. Kinetic descriptors of protein-drug complexes, such as drug residence time, have recently been shown to be important for predicting the *in vivo* efficacy of candidate drug molecules. Computational tools to predict binding kinetics are therefore needed in the screening stages of the drug-design pipeline; however, the time-dependent nature of kinetics makes it a challenging subject for current computational resources.

Replica Exchange Transition Interface Sampling (RETIS) is used to calculate drug (un)binding rates and residence times, where it is currently set up for imatinib and wildtype ABL as a proof of concept. Unlike biasing techniques, RETIS delivers trajectories with the intrinsic dynamics untouched, allowing also qualitative comparisons between different inhibitors/mutations. In the future, we will extend the RETIS method to the general case of protein-ligand binding, where it can be a useful tool in precision medicine and drug design.