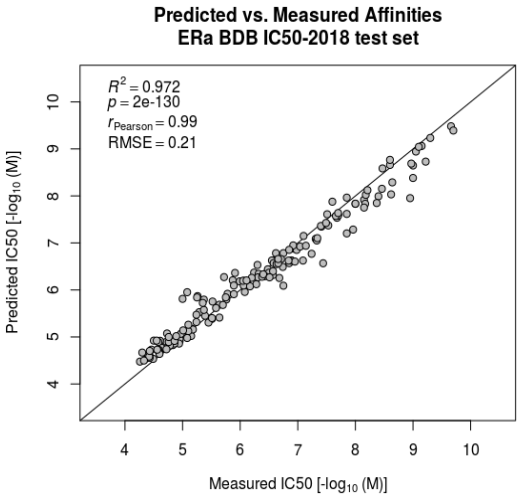
[P27] Improving ligand screening by exploiting structure ensembles and machine learning

Melanie Schneider[1], Jean-Luc Pons[1], William Bourguet[1], Gilles Labesse[1]

[1]*Centre de Biochimie Structurale, CNRS UMR 5048, INSERM U 1054, Université de Montpellier, 34090 Montpellier, France*



Nuclear receptors (NRs) are DNA-binding transcription factors and one of the most important cellular mediators for sensing (hormones, drugs, xenobiotics) and signal transduction. Therefore, their dysfunction and the subsequent aberrant signaling is associated with many diseases concerning cancer or reproduction and metabolism disorders. Due to their ligand binding ability they are of interest for a broad scientific field, in particular for the pharmaceutical industry as potential pharmaceutical targets and for drug development and in toxicology and environmental science for risk assessment. In particular the Estrogen Receptor alpha (ERα) is an important target for medical treatment and among the most studied NRs.

Predicting the interactions between small molecules and receptors plays a critical role in drug discovery and development.

During our study, exhaustive docking for all known ERα ligands present in BindingDB was achieved using parallel docking on conformational ensembles, which also result in more precise pose predictions. This result enables us to employ a random forest (RF) machine learning algorithm on a large high quality data set in order to predict precise binding affinities (R^2=0.97, figure 1). Here, the “sampling problem” is tackled by using structure ensembles, while taking advantage of numerous scoring schemes for virtual screening to better evaluate ligand conformation and protein-ligand interactions.

These results pave the way for a web server dedicated to rapid and high-accuracy docking into the estrogen receptors.