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Site identification by ligand competitive saturation (SILCS): Computational approach for the identification and optimization of ligands targeting proteins, RNA and other macromolecules

Alexander D. MacKerell
University of Maryland, USA

Computational ligand design and optimization typically involve a single binding site, single ligand approach that is time and resource expensive. Fragment-based methods partially overcome this limitation, but current approaches include approximations with respect to the treatment of solvation and protein flexibility. To overcome these limitations we have developed the site identification by ligand competitive Saturation (SILCS) approach that uses explicit solvent all-atom molecular dynamics simulations to identify binding sites on protein surfaces for functional group classes based on rigorous free energy criteria that include protein flexibility and fragment desolvation. Information from the SILCS approach, termed Frag Maps, are produced in an upfront pre-computed calculation that may be rapidly accessed for the identification of novel ligands that bind to the target macromolecule, for *de novo* ligand design or for ligand optimization. Visualization of SILCS Frag Maps allows for qualitative ligand design by medicinal chemists while the Frag Maps also may be used for rapid, quantitative estimates of relative free energies of binding. Notably, the SILCS methodology may be applied to occluded binding sites such as those present in G-protein coupled receptors (GPCRs).

Biography

Alex D. MacKerell received a Ph.D. in Biochemistry in 1985 from Rutgers University, which was followed by postdoctoral fellowships in the Department of Medical Biophysics, Karolinska Institutet, Stockholm, Sweden and the Department of Chemistry, Harvard University. In 1992 he acquired his faculty position in the School of Pharmacy, University of Maryland where he is currently the Grollman-Glick Professor of Pharmaceutical Sciences and the Director of University of Maryland Computer-Aided Drug Design Center.

amackere@rx.umaryland.edu