

W0242

Computational Studies at the Micromolecule/Macromolecule Interface. William B. Gleason^{1,3,4}, Eric R.A. Johnson³, Derek Straka^{1,2}, Jane Shvelidze³, Caroline Nibbel¹, David MacDonald², Jack Anderson¹, Depts. of Chemistry¹, Biochemistry², Biomedical Engineering³, and Laboratory Medicine & Pathology⁴, Univ. of Minnesota, Minneapolis, MN 55406 USA.

Docking remains a popular technique in drug design business, because it is believed that it may help to constrain the enormous cost of drug development. Docking requires either models (macro and micro) derived from experimental data or, preferably, real structures of ligand/macromolecular complexes. Various authors, e.g. Gerard Kleywegt, have reviewed the situation from the small molecule perspective. We will present from our own work (“tips and tricks”) that may be useful. Examples of the binding of sulfated model compounds to heparin-binding proteins will be given. Using AUTODOCK3 we have found that the implementation of rotational constraints leads to much better results for ligands with many degrees of rotational freedom. We will also present examples of docking involving HIV protease inhibitors as well as work with docking inhibitors of the EGFR receptor kinase. A brief discussion of how these inhibitors relate to the very useful empirical rules of Lipinsky will be given.



1M17.pdb + DS101

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