Hamilton Institute

A Point-Based Algorithm for Multiple 3D Surface Alignment of Drug-Sized Molecules

Daniel Baum

Zuse Institute Berlin (ZIB)

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Abstract:

One important step in virtual drug design is the identification of new lead structures with respect to a pharmacological target molecule. The search for new lead structures is often done with the help of a pharmacophore, which carries the essential structural as well as physico-chemical properties that a molecule needs to have in order to bind to the target molecule. In the absence of the target molecule, such a pharmacophore can be established by comparison of a set of active compounds. To identify their common features, a multiple alignment of all or most of the active compounds is needed. Since the molecular shape plays a major role in the interaction between drug and target, an alignment algorithm aiming at the elucidation of a pharmacophore should consider the molecule's `outer shape', which can be approximated best by some kind of molecular surface.

This talk presents a new approach to molecular surface alignment which is based on a discrete representation of shape as well as physico-chemical properties using points. To distribute points regularly on a molecular surface w.r.t. a smoothly varying point density given on that surface, we developed a new point distribution method based on centroidal Voronoi tesselation. For the computation of pairwise surface alignments, we can then apply an efficient point matching scheme, which we extended to surface points. Due to the discrete representation of the molecules' shapes and properties, multiple alignments can be computed from pairwise alignments in a straight forward way. One hurdle that needs to be overcome, however, is the large number of surface points that we consider. In this talk, the application of the presented pairwise as well as multiple surface alignment algorithms will be demonstrated on two sets of molecules: a set of eight thermolysin inhibitors, and a set of seven HIV-1 protease inhibitors.

Venue: Seminar Room, Hamilton Institute, Rye Hall, NUI Maynooth

Time: 2.00 - 3.00pm (followed by tea/coffee)

Travel directions are available at www.hamilton.ie

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