Exploring Local Shape Space with Fragment Replacement

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Fragment-based design offers the ability to search much larger regions of chemical or physical property space for new molecules with certain desired properties than can be searched with techniques that focus on the whole molecule (be they ligand-based or structure-based). Those desired properties are often a combination of biological (good potency) and physical (good solubility). We present a method for searching fragment space that relies on matching a query fragment to fragments in a database using both shape and electrostatic similarity methods. Only those fragments in the database with a desirable physical property profile, as judged by the user, are scored using the shape and electrostatic methods. The high scoring fragments are then assembled into a whole molecule and this molecule is assigned a probability of potency using a belief model (a joint probability can also be assigned to a set of new molecules). In this way we provide the user with the ability to assign a risk, based on the probability of potency, to selecting a given hit fragment or molecule for further project activity (purchase, synthesis, screening) while ensuring that any fragment or molecule selected will have an appropriate physico-chemical profile. A theoretical background to this approach will be presented, along with case studies of its application in drug discovery.