

Shape Signatures: A Powerful New Technology for Risk Assessment

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Tools in bioinformatics, chemical informatics (cheminformatics), and molecular modeling are making a profound impact in a large and growing number of applications including drug discovery and toxicology. Our laboratory has been active in the development and application of informatics tools to accelerate the screening and prioritization of chemical compounds for prospective in vitro and in vivo testing of hazardous chemicals including endocrine disrupting chemicals (EDCs). Here we introduce a powerful new computational tool called Shape Signatures that rapidly matches small-molecule compounds (e.g., suspected EDCs) with each other or against target receptor sites/subsites. The method uses customized ray-tracing techniques to explore the volume enclosed by a ligand molecule or, alternatively, by a receptor pocket; the resulting “signatures” are compact descriptors of molecular shape and polarity. Shape Signatures, while highly complementary to quantitative structure-activity relationships (QSAR) -based models, avoids a major problem with QSAR-based models: the need for complete reformulation of the models as new biological data become available. Since the method compares molecules based on fundamental molecular properties (viz., shape, electrostatic properties) rather than on chemical composition, it can find matches between molecules belonging to different chemical families. This feature is often critically important in risk assessment applications, where molecules from different chemical families may bind the same receptor (e.g., estrogen receptor). Our poster will illustrate the utility of the method in realistic scenarios and introduce a prototype Shape Signatures website under development that is geared to non-expert users.

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