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Virtual experiments — A modern alchemy ?

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In the absence of an experimental receptor structure, biomedical research often relies on QSAR techniques for estimating binding energies of potential drug candidates. While 3D-QSAR is widely used in the drug design community, such concepts would seem to be limited by two approximations: the use of an averaged receptor model to represent the flexible bioregulator and the pharmacophore hypothesis. A 4D-QSAR concept developed at our laboratory not only takes local induced fit into account but also allows for the representation of the ligand molecules by an ensemble of conformation, orientations, and protonation states.

Toxic agents, particularly those that exert their actions with a great deal of specificity, sometimes act via receptors to which they bind with high affinity. Our laboratory is currently establishing a virtual laboratory on the Internet to predict harmful effects triggered by drugs or chemicals and their metabolites *in silico.* This database shall be continuously extended to include surrogates for any bioregulator known or presumed to mediate toxicity or being associated with other harmful effects. Free access to this virtual laboratory shall allow any interested party (academic, industrial, government) to quickly estimate the harmful potential of any given substance prior to its synthesis. This is achieved by generating the three-dimensional structure of a given compound and all its possible metabolites in the computer, followed by calculating their binding affinity towards each receptor surrogate in the database.

Optimization of the distribution of a therapeutic compound between oral or gastrointestinal resorption and the target receptor site is a critical component in the drug-design process. Computational methodologies used for the identification and optimization of such molecules are particularly efficient in enhancing their affinity towards a given bioregulator — a powerful approach for the prediction of the associated bioavailability, however, has yet to be identified. A very challenging undertaking for the next decade involves the extension of our 4D-QSAR concept to allow for a computational prediction of the oral bioavailability of drug candidates based on their three-dimensional topology, conformational flexibility, and physicochemical properties. This task may be addressed by simulating their distribution among five quasi-atomistic surrogates, representing compartments relevant with respect to drug pharmacokinetics: *resorption, first pass, passive* and *active transport* as well as *retention in the fatty tissues.*

Computer-based simulations ("virtual experiments") may not be capable of replacing complex biological experiments in the near future. But their impact on chemical engineering and biomedical research is substantial, thereby contributing to the analysis, understanding and design of real experiments, helping to save energy and resources, and reducing animal testing. Advantages of virtual over real experiments include the capability to simulate hypothetical substances, to analyze experiments step by step, and to screen large structural databases in short time and at low cost.

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