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COMPUTER-AIDED DRUG DISCOVERY: FROM TARGET PROTEINS TO DRUG CANDIDATES

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Computer-aided drug design (CADD) is an exciting and diverse discipline where various aspects of applied and basic research merge and stimulate each other. The latest technological advances (QSAR/QSPR, structure-based design, combinatorial library design, cheminformatics & bioinformatics); the growing number of chemical and biological databases; and an explosion in currently available software tools are providing a much improved basis for the design of ligands and inhibitors with desired specificity.

The CADD track of PSB ‘99 was organized to reflect the diversity of the field, and to provide a forum for the presentation and discussion of the most modern concepts, algorithms, and drug design techniques. Drug discovery typically starts with an analysis of binding sites in target proteins, or an identification of structural motifs common to active compounds. It ends with the generation of small molecule "leads" suitable to further chemical synthetic work. Focal points of our session included, but were not limited to, modeling and analysis of protein-ligand complexes (database searching, docking, and de novo design), quantitative assessment of binding interactions (free energy calculations and scoring functions), development of pharmacophores, and analog design.

Six manuscripts were accepted for publication in this journal. Each contribution introduces a new computational approach and reports at least one application example. Three papers address, in rather different ways, the important problem of molecular similarity.

Gerry Maggiora and colleagues of Pharmacia & Upjohn describe an extension of the molecular field-based similarity program MIMIC to align flexible molecules, while taking conformational energy of the compared structures into account. Jonathan Mason and Daniel Cheney, Bristol-Myers Squibb, discuss 4-point, three-dimensional pharmacophores and beautifully illustrate their advantages compared to the more conventional 3-point, planar pharmacophores. Paul Labute of the Chemical Computing Group introduces a novel 2D QSAR-like method termed Binary QSAR. The method predicts compounds to be either active or inactive using a probability distribution function calculated from a learning set. This set of active/inactive compounds, for a given target, could be the result of a screening experiment.

Other contributions cover selected topics from cheminformatics & bioinformatics, and the theory of docking. Peter Gund of Pharmacopeia outlines, for the first time, an integrated software/database environment combining the design, administration, and evaluation of large combinatorial libraries. In so doing, he also assesses relative merits of the so called "rational" and "empirical" elements of the drug discovery process. Gennadi Verkhivker and his colleagues from Agouron Pharmaceutical demonstrate, using weighted histogram analysis, that the shape of a force field-based binding free energy profile is a critical determinant of the success of protein-ligand docking simulations. When compared to calculations using a standard force field, softened short-range repulsive interactions result in a smooth energy landscape, which yields better agreement between predicted and X-ray structures. Finally, Shkel and Kim of the University of Wisconsin-Madison and Parke-Davis report on the use of weighted-ensemble Brownian dynamics to simulate interactions between proteins in 2D space.

Our thanks are due to all of our colleagues who contributed to the organization of this session, and especially to those who helped us as referees of the printed papers.