Molecular Modeling to Predict and Understand Chemical Toxicity
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Science Question
There is a paucity of relevant experimental information available for the evaluation of the potential health and environmental effects of many new made chemicals. Therefore, there is a compelling need to develop information that would enable the screening of the potential health and environmental effects of large numbers of man-made chemicals. Knowledge of the potential pathways for activity in a rational basis for the computations inherent in the preliminary evaluation of risk and the establishment of priorities for obtaining needed data for environmental chemicals. The differential step in many mechanisms of toxicity may be the generation as the interaction between the small molecule (a potential toxicant) and one or more macromolecular targets. The small molecule may be the chemical itself or one of its degradation products. A computation approach based on the interaction between a potential molecular toxicant and a library of macromolecular targets for toxicity (The Toxicant-Target approach) has been proposed as a tool for chemical screening and testing prioritization. In order to use a library of this type, a rapid method to evaluate interaction between the small molecule and a (macromolecular) target is needed. Molecular “docking” has been developed to screen large chemical libraries for molecules that interact strongly with specific sites on proteins and therefore are potential pharmacological agents. This approach has subsequently been applied to investigate the potential activity of weaker agents.

Can “docking” and other molecular modeling approaches be applied to screen for chemicals that interact with a macromolecular target? Can the results of this approach be used in conjunction with experimental assays in a screen for potential toxicity? Using experimental results for the rat estrogen receptor, will “docking” separate agents that bind weakly to inactive chemicals? For any chemical screening approach that depends on a data base and molecular parameters, how is its range of applicability determined?

Research Goals
1. To develop an approach for applying “docking” and other molecular modeling methods to problems of screening and prioritizing chemicals for potential toxicity.
2. To test two “docking” methods for their capacity to identify chemicals that compete weakly with E2 for the active site of the estrogen receptor.
3. To develop methods for determining the domain of applicability of any relationship that predicts chemical toxicity from other molecular parameters (experimental or computational).

Methods/Approach

Structurally Based Computational Screening

Docking

Results/Conclusions

The potential ligands are then introduced into the computational target and the most stable target-scaner pairs identified using two different approaches.

- Considering the entire molecule as flexible (FRED)
- Decomposing the molecule into substructures (eHiTS)

(a) Docking each substructure separately
(b) Reconstructing the substructures in the target

The energy of each potential ligand-target pose is calculated from the energy of interaction of the ligand with each specific protein or class of potential targets.

This approach has been successfully applied to aid in the discovery of novel pharmacological agents (strong binders). However, it has not often been used to separate potential weak binders from nonbinders, more like the problem of screening environmental chemicals.

A Data Set
A library of 281 environmentally relevant chemicals was tested in the same laboratory with the same protocol for their capacity to compete with unlabeled 17-β-estradiol for their binding to the rat ER. The advantage of comparing computational molecular “docking” results to the experimental results in this library is

- First, there are a number of excellent crystal structures of both α and β estrogen receptors available in the Protein Data Bank that can be used to synthesize macromolecular targets for computer “docking”.

- Second, the data set is mostly inactive chemicals. Only 15 chemicals were found to be active and most only weakly so.

- Third, the experiments yield a relatively direct measure of what is modeled in computational “docking”, the energy of interaction between the two chemicals and the receptor compared to the energy of interaction of the receptor with 17-β-estradiol.

A simplified Pharmacophore

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A Data Set

FRED 2 constraints

FRED no constraints

FRED 2 constraints

References


Impact and Outcomes
It has been demonstrated that an approach developed for enriching chemical libraries for likely candidate pharmaceuticals (strongly active molecules) is also capable of separating weak active chemicals from inactive ones. The relative energies for chemicals interacting at specific targets for toxicity may be used by themselves or in conjunction with other parameters to predict chemical toxicity or prioritize chemicals for further testing. This approach may be used for targets where crystal structures are available and also for targets similar to macromolecules where the structures are known.

Future Directions
The Toxicant chemicals have been docked in 150 targets. Pharmacophores for as many of the targets as possible are being developed and the docking poses will be filtered by the pharmacophores. The evaluation of the capability of computational methods to predict toxicity or any other multiple-parameter method for chemical screening, requires an understanding of the position of an ontological chemical in chemical and biological space. A method is being developed for evaluating the domain of applicability for any multiparameter method of this type.