Seeing is retrieving

Combinations of docking (pose prediction) and scoring methods (prediction of binding affinity) were recently performed by Forino and Jung *et al*. [1] within the Sybyl software environment to predict Akt1 kinase inhibition. Akt1 (protein kinase B) participates in cell signaling between human tumor cells and has been co-crystallized with AMP–PNP. Whereas only one marketable Akt1 inhibitor (H-89) is known, this *in silico* investigation unearthed three new Akt1 inhibitors.

Two docking methods were used: FlexX and GOLD. FlexX essentially builds the ligand directly in the receptor by attaching new fragments to a pre-docked anchor fragment with a greedy conformational search algorithm. Receptor-ligand interactions are estimated from a lookup table derived from the PDB. GOLD uses genetic optimization to dock a flexible ligand to a semiflexible receptor. Its chromosomes represent the bond rotation angles in the ligand and the protein. Three scoring functions (calculated by CSCORE) were used. DrugScore is a knowledge-based scoring function distilled from the observed inter-atomic contacts in crystal structures of protein-ligand complexes. ChemScore takes lipophilic interactions, metal-ligand binding, H-bonding, and loss of ligand flexibility into account. GoldScore emphasizes H-bonding and the internal conformational energies of the ligand.

The investigation screened the ChemBridge 50000-compound drug-like database, which was prepared by adding hydrogens with Sybyl and then by '3D-izing' with Concord and Corina. All screening hits were assayed with a kit from Invitrogen. The first approach docked the 50000 compounds with FlexX. The top 2000 compounds from FlexX were scored with ChemScore, GoldScore, and DrugScore and the top 100-200 hits from each were assayed. The same active was found by GoldScore and ChemScore, but DrugScore found none. A second approach used the top 4000 compounds from FlexX but redocked them with GOLD. The assay of the top 200 GOLD compounds found the same active again. A third approach scored the top 4000 FlexX/DrugScore molecules with GoldScore and ChemScore, then determined the top 200 hits common to the top 700 hits of each scoring function. Half of the 200 hits were eliminated by manually viewing the docking results. An assay of the remaining hits revealed two more actives which were as potent as H-89. The authors went on to experimentally determine the three actives to be specific and competitive inhibitors to Akt1. This finding strongly suggested that a similar binding mode occurs between the three new inhibitors and AMP-PNP, prompting the authors to include H-bonding patterns of AMP-PNP in their final screen.

The authors credit the 10% hit rate of their new screening procedure to their consensus scoring and consideration of H-bonding patterns. However, they make no comments about the applicability of their final screen method to other targets, and leave it to the readers to reach their own conclusions. At a minimum, this investigation indicates that human perception and decision-making should not be completely removed from a data mining screen.

1 Forino, M. *et al.* (2005) Virtual docking approaches to protein kinase B inhibition. *J. Med. Chem.* 48, 2278–2281

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