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## Docking-based comparative intermolecular contacts analysis as new structure-based drug design approach

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The significant role played by docking algorithms in drug discovery combined with their serious pitfalls prompted us to envisage a novel concept for validating docking solutions, namely, Docking-Based Comparative Intermolecular Contacts Analysis (dbCICA). This novel approach is based on the number and quality of contacts between docked ligands and amino acid residues within the binding pocket. It assesses a particular docking configuration on the basis of its ability to align a set of ligands within a corresponding binding pocket in such a way that potent ligands come into contact with binding site spots distinct from those approached by low-affinity ligands and vice versa. In other words, dbCICA evaluates the consistency of docking by assessing the correlation between ligands' affinities and their contacts with binding site spots. Optimal dbCICA models can be translated into valid pharmacophore models that can be used as 3-D search queries to mine structural databases for new bioactive compounds. dbCICA was implemented to search for new inhibitors of candida N-myristoyl transferase as potential antifungal agents and Glycogen Phosphorylase (GP) inhibitors as potential antidiabetic agents. The process culminated in five selective micromolar antifungal leads and nine GP inhibitory leads.

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## Prediction of plasma protein binding and the corresponding determination of the applicability domain by using an artificial neural networks ensemble

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**Purpose:** To develop a QSAR model, based on calculated molecular descriptors and an Artificial Neural Networks Ensemble (ANNE), for the estimation of plasma protein binding (as fraction of unbound drug in plasma-fup) of drugs in human, rat, dog and monkey plasma, as well as the assessment of the applicability domain (AD) of the model.

**Methods:** A total of 680 individual fup values (75% train and 25% validation), were collected in the literature from human, rat, dog and monkey plasma concentrations. A correlation between simple molecular descriptors for lipophilicity, ionization, size and hydrogen bonding capacity and fup data was attempted by using an ANNE.

**Results:** A degradation of the correlations was observed for predicted values with high uncertainty, as judged by the standard deviations of the ANNE outputs. Based on this, a "cut-off" SD<0.0857 was established to consider that a particular drug is inside the AD of the model. Similar statistics were observed between the train and validation group of data, when inside the AD, with correlations between the observed values and the predicted average ANNE values, of 0.951 and 0.854, respectively. 82% of the drugs were well predicted with diference of less than 0.2 in the validation group of data, again when inside the AD (93% in the train dataset).

**Conclusion:** This model may be a valuable tool for simulation and prediction in early drug development, allowing the *in silico* estimation of fup in different pre-clinical models and in the human, that may be used for PBPK purposes.

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**Notes:**