Poster K-19

Construction of Scoring Functions using Neural Network for Determination of Affinities Constants Receptor-Ligand.

Authors:
Thaís Gaudencio do Rêgo (*Laboratório Nacional de Computação Científica*)
Marco Antônio Vilela (*Laboratório Nacional de Computação Científica*)
Hélio José Corrêa Barbosa (*Laboratório Nacional de Computação Científica*)
Laurent Emmanuel Dardenne (*Laboratório Nacional de Computação Científica*)

Short Abstract: One of the most important challenges of molecular modeling is provide quantitative or semiquantitative information, using a low computational cost, about ligand-receptor affinities. Have as main objective in this work for the solution that problem, the construction of empirical functions of free energy with neural networks.

Long Abstract:
One of the most important challenges in the structure based rational drug design area is to provide a quantitative or semiquantitative information, using a low computational cost, about ligand-receptor affinities based on the results obtained in docking studies. One of the objectives is to determine which are the best lead candidates, amongst a great compound set, or to predict the correct ligand-receptor bind mode.
From a theoretical point of view, one of the main objectives of receptor-ligand docking studies is to predict the free energy differences ΔG between two thermodynamic states: complexed and non-complexed ligand-receptor situations (delta G can be directly associated with the inhibition constants Ki experimentally determined); a same ligand in complex with distinct receptors; or to evaluate the affinity of distinct ligand conformations in respect to the same receptor.
The theoretical determination of accurate free energy differences through computational methodologies involves a computational cost extremely high, involving long simulations of systems with biological macromolecules immersed in explicit solvent. One of the possible solutions for this problem is the application of faster methodologies that involve the construction of free energy empirical functions to estimate ligand-receptor binding affinities.
The use of empirical free energies scoring functions assumes that the associated receptor-ligand geometry is known or correctly predicted. From this ligand-receptor geometry several physical-chemical quantities are calculated and used as independent variables in the scoring function. The coefficients associated to the independent variables are pre-optimized to reproduce a set of experimental results (i.e., receptor-ligand structures and their respective constants of inhibition Ki). In the scoring function, the functional dependence of variables is determined a priori and usually considered as linear.
The objective of this work is the construction of an artificial neural network (ANN) to predict receptor-ligand binding affinities. The ANN was trained to reproduce the results obtained by Oliveira et al. [1], in a docking study involving ten protein-ligand structures, using an empirical free-energy function with a quadratic term in the solvation free energy. The independent variables in the ANN are: (i) the ligand-receptor interaction enthalpy calculated at the PM3 semi-empirical quantum level; (ii) ligand solvation energy term; (iii) the number of

the ligand rotatable bonds that were frozen as a result of the ligand interaction with the atoms of the active site. The experimental binding data were taken from the work of Dal Piaz et al. [2]. The compounds studied in the work of Oliveira et al. [1], were chosen because they present an adequate structural variability with a large activity range.

The neural network architecture applied has 3 neurons in the input layer, 3 neurons in the hidden layer and 1 output neuron. The neurons of the input and hidden layers have a tangent sigmoid activation function and the output neuron has a linear activation function. The ANN weights of this network are adjusted through a backpropagation learn algorithm. For training of the neural network, we normalized the data set in range [-1,1]. The ANN converged with about two thousand epochs with a mean square error (MSE) of 1e-5 using a learning rate of 0,01. The results showed the great potential of the method as an useful tool for the ligand-receptor affinities prediction with a low computational cost and with a great versatility due to the fact that is not necessary to impose a priori any kind of functional relation between the independent variables.

Dal Piaz, V.; Giovannoni, M.P.; Castellana, C.; Palacios, J.M.; Beleta, J.; Doménech, T.; Segarra, V. Eur. J. Med. Chem. 1998, 33, 789-797.

Oliveira, F.G.; Sant'Anna, C.M.R.; Caffarena, E.R.; Dardenne, L.E.; Barreiro, E.J. Bioorganic and Medicinal Chemistry. In press.