Docking and QSAR

BT 305

Docking

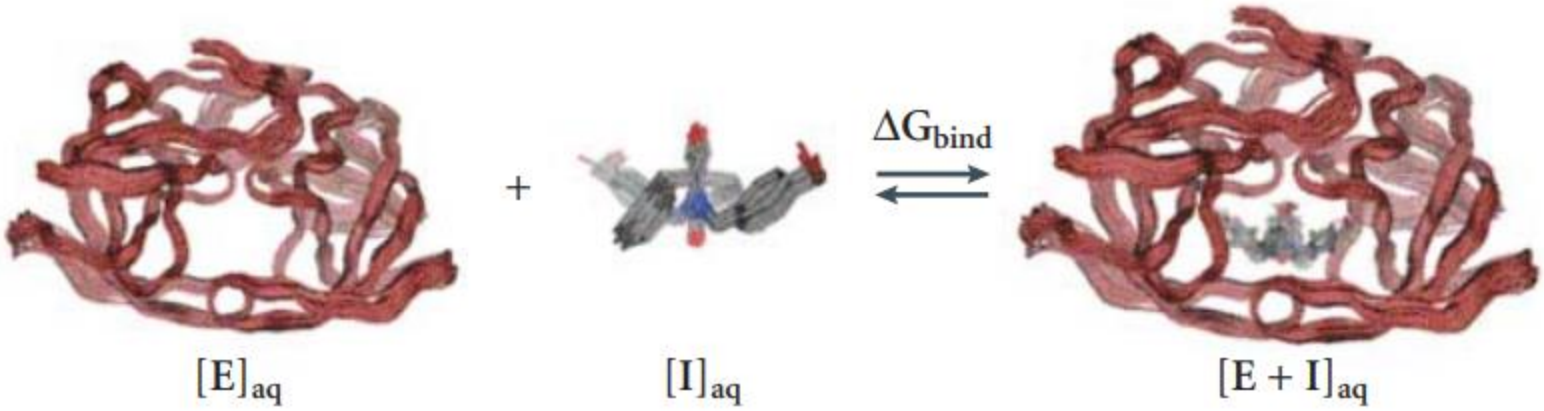
What is docking?

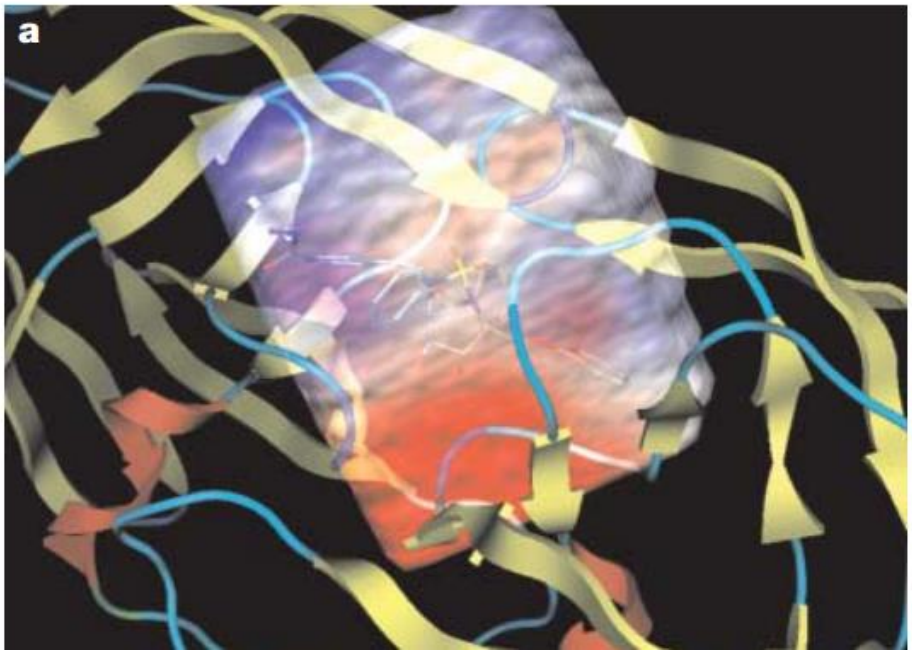
- Molecular modeling method
- Predicts the preferred orientation of one molecule to a second when to each other to form a stable complexes.
- Rational of design of drugs

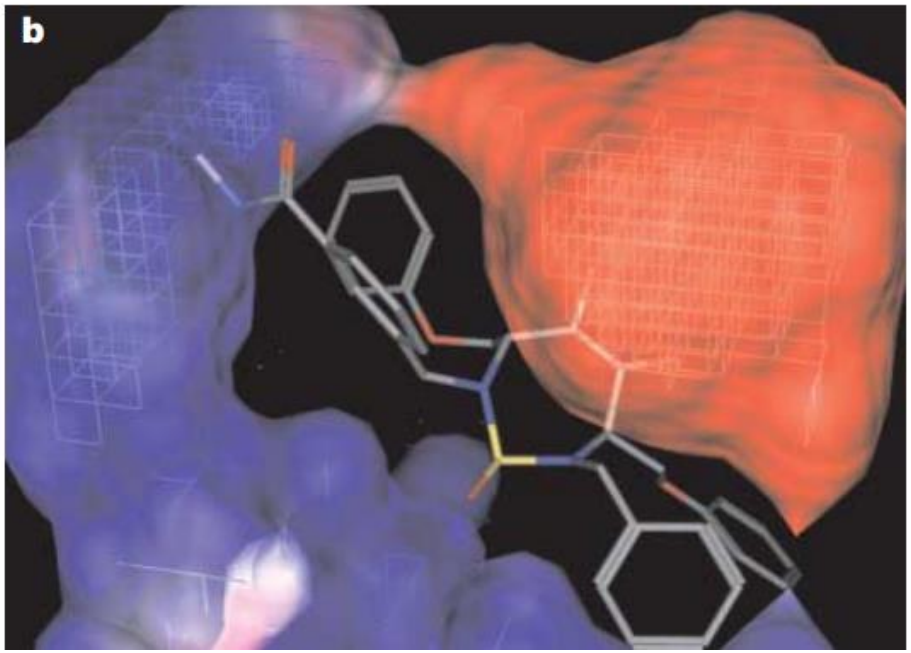
Initially,molecular docking was used to predict and reproduce_protein-ligand complexes.

For an enzyme and inhibitor, docking aims at correct prediction of the structure of the complex [E+I] = [EI] under equilibrium conditions (see figure and equation 1).

$$[EI]_{aq} \rightleftharpoons [E]_{aq} + [I]_{aq} \qquad (1)$$







- Potential energy grids was pioneered by Goodford

- The basic idea is to store information about the receptor's energetic contributions on grid points so that it only needs to be read during ligand scoring. In the most basic form, grid points store two types of potentials: electrostatic and van der Waals.

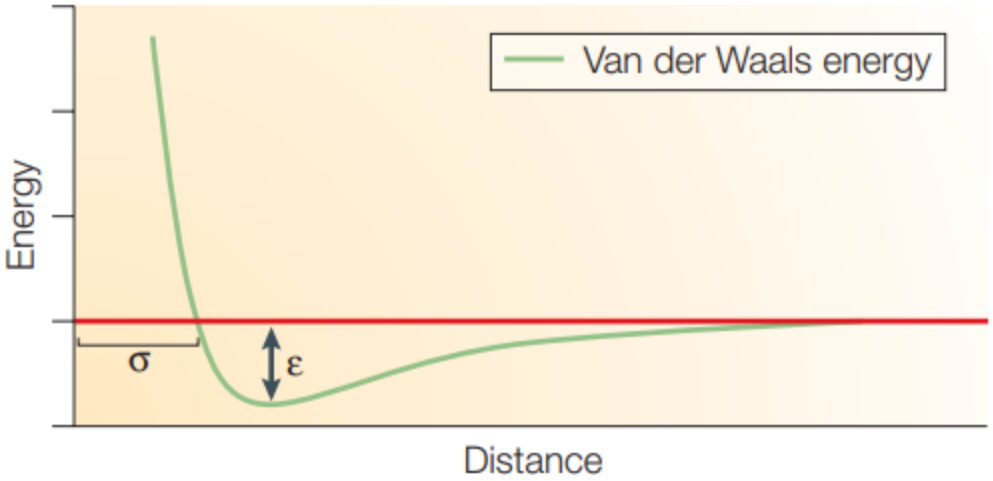
The electrostatic potential energy is represented as a pair-wise summation of Coulombic interactions, as described in equation 1:

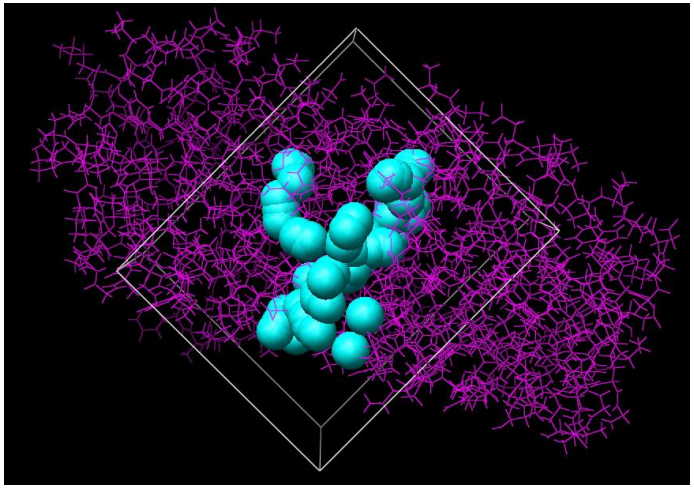
$$E_{coul}(r) = \sum_{i=1}^{N_A} \sum_{j=1}^{N_B} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \qquad (1)$$

In equation 1, N is the number of atoms in molecules A and B, respectively, and q the charge on each atom.

The van der Waals potential energy for the general treatment of non-bonded interactions is often modelled by a Lennard–Jones 12–6 function, as shown in equation 2:

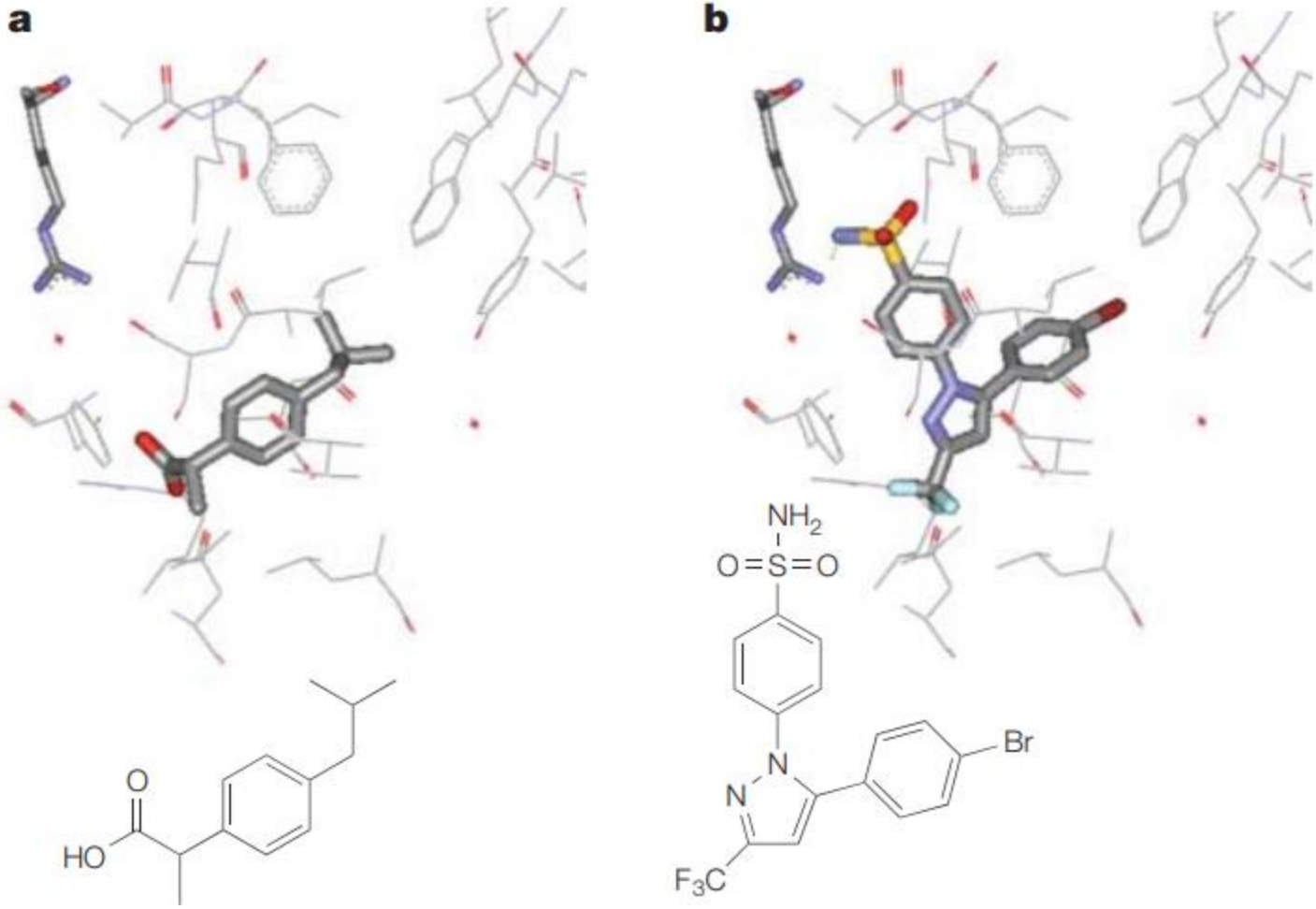
$$E_{vdW}(r) = \sum_{}^{N} \sum_{}^{N} 4\varepsilon \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] \qquad (2)$$



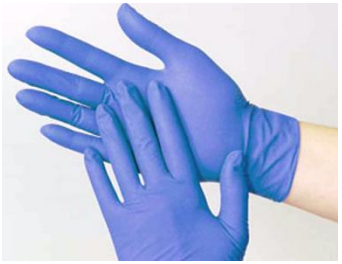


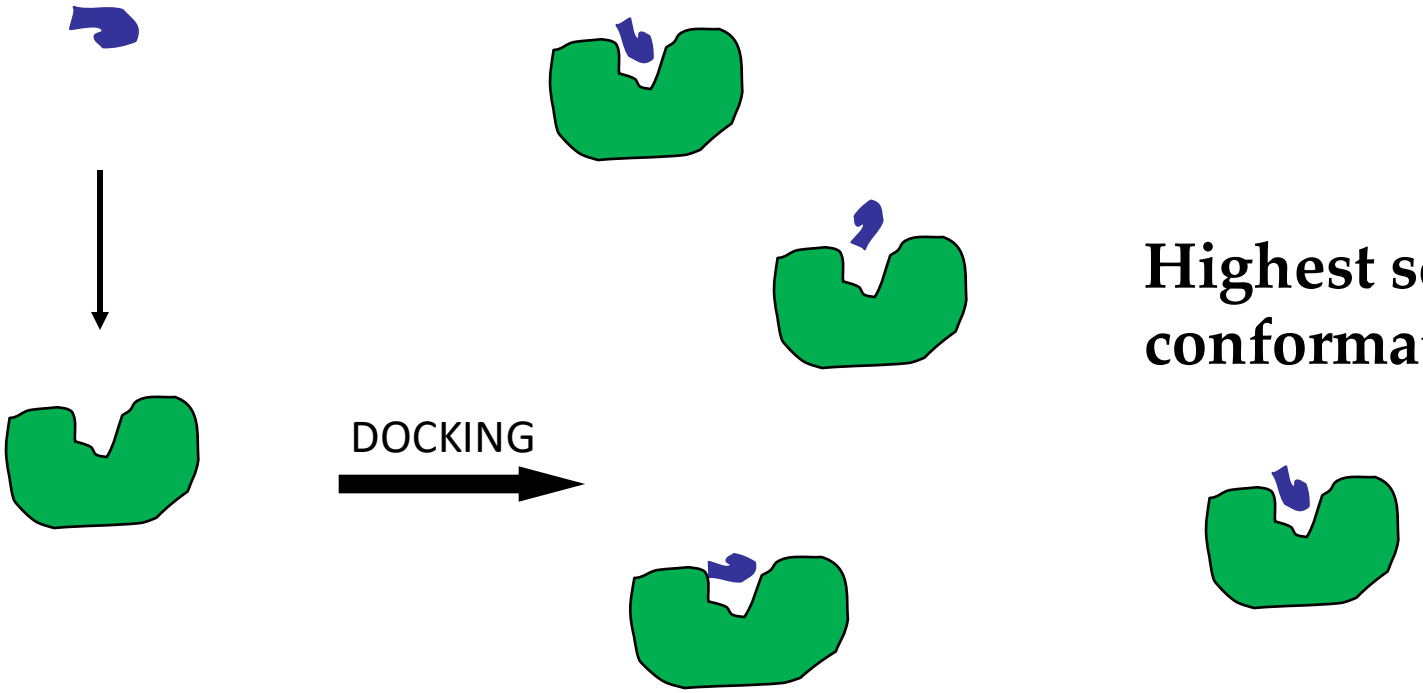
When docking, each scoring function is applied independent of the others and the results are written to separate output files.

Grid also computes a bump grid which identifies whether a ligand atom is in severe steric overlap with a receptor atom


a
b
HO
O
NH2
O=S=O
N
N
Br
F3C

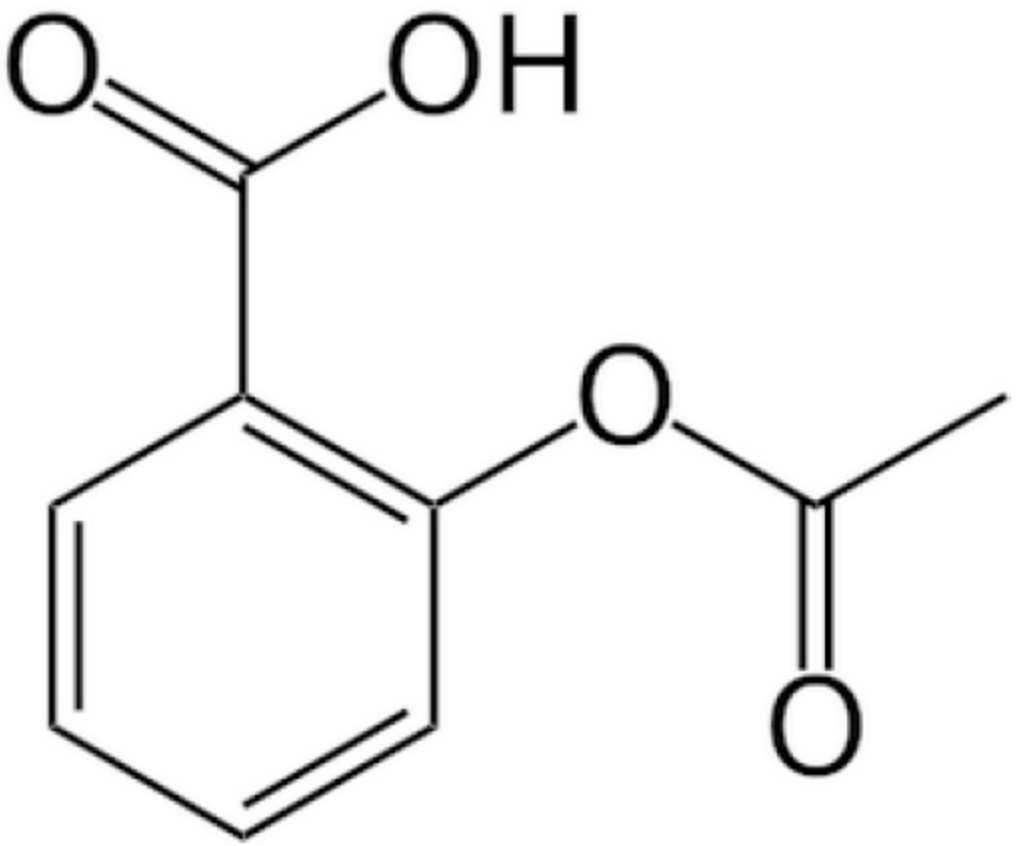
Best Fit ??????



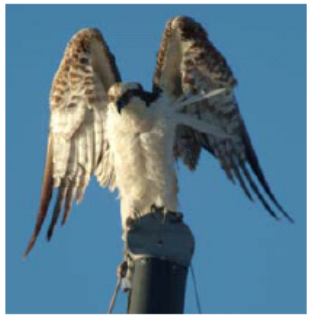


- *Focus of molecular docking is to achieve an optimized conformation for both the protein/DNA/RNA/etc and ligand and relative orientation between target and ligand*

Topological Molecular Graph

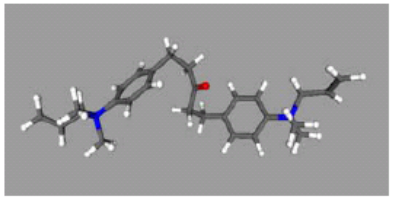


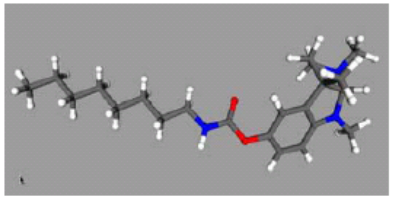
QSAR (of birds):



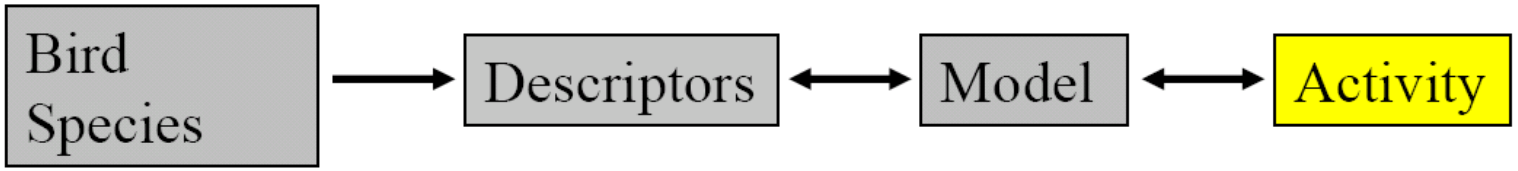
QBSPR: What is flight performance? Performance = muscle efficiency * flight time as

(P = Efficiency*Time)

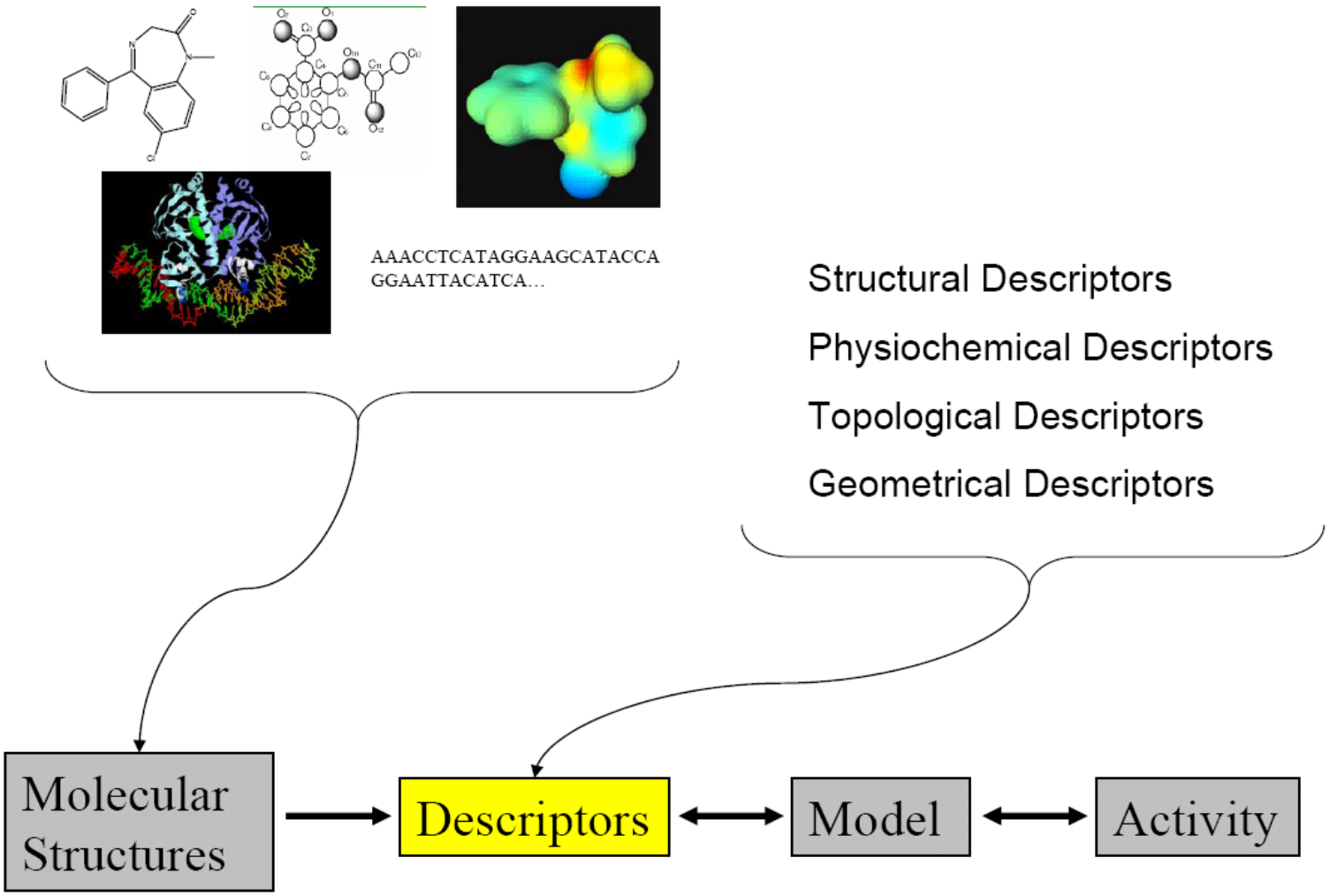




QSAR: What is AChE inhibition? IC50 is a measure of the concentration required for 50% inhibition.



Courtesy: Matt Sundling, RECCR Troy NY.



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