Two Rules on Protein-ligand Interactions

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Motivation

- Understanding ruling principles of interactions between a target protein and a ligand is of paramount importance in drug discovery efforts.
- However, we still lack a clear molecular mechanism to explain the protein-ligand interaction on the basis of electronic structure of a protein and guide novel molecules designing.
- We present two new rules on protein-ligand interactions.

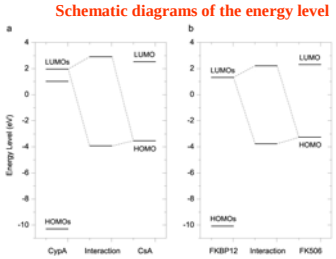
Simulation Method

- Molecular Dynamics simulation, using the CHARMm potential: $V = V_B + V_a + V_{imp} + V_D + V_{nonbond}$
- Full electronic structure calcualtion:

$$\begin{cases} \psi = \sum_{n=1}^{N} \sum_{j=1}^{m_n} C_j(n)\varphi_j(n) \\ (H - \lambda S)C = 0 \\ NE(x) = \sum_{n=1}^{N} NNE[U_n(x)] \end{cases}$$

- Take a peptides composed of n residues as a Markov Chain, then its probability: $P(S) = P(S_1)P(S_2 \mid S_1)P(S_3 \mid S_2)\cdots P(S_n \mid S_{n-1})$
- Bayes formula tells us that we can calculate the HOMO one pair resdiues by one pair resdiues. $P(S_i \mid S_{i-1}) = P(S_{i-1}S_i)/P(S_{i-1})$

Schematic diagrams of the energy level



(**a**) Protein CypA interacts with ligand CsA at ground state. (**b**) Protein FKBP12 interacts with ligand FK506 at 300 K.

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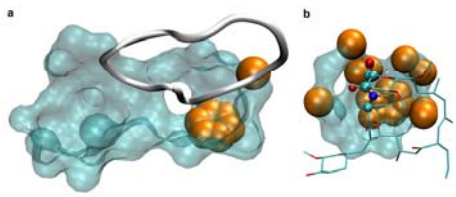
Rule 1: The interaction only occurs between the lowest unoccupied molecular orbitals (LUMOs) of a protein and the highest occupied molecular orbital (HOMO) of its ligand, not between the HOMOs of a protein and the LUMO of its ligand.

Spatial configurations of binding pockets and activity atoms



The binding pocket and actvity atoms of CypA/CsA (**a**) and FKBP12/FK506 (**b**).

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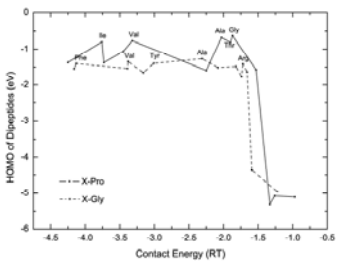
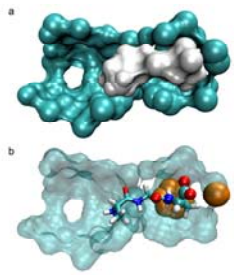
Rule 2: Only those residues or atoms located both on the LUMOs of a protein and in a surface pocket of a protein are activity residues or activity atoms of the protein and the corresponding pocket is the ligand binding site.

The HOMO energies of dipeptide X-Pro and X-Gly



The dipeptide Gly-Pro has the highest HOMO energy among X-Pro. The dipeptide Ala-Gly has the highest HOMO energy among X-Gly. Therefore, Ala-Gly-Pro is the best tripeptied to bind to CypA.

Comformation of predicted ligand Ala-Gly-Pro (AGP)



(**a**) Both the ligand AGP and the binding site of CypA are represented in combined model of VDW and Surf, colored in white and gray respectively.

(**b**) The seven activity atoms of AGP are represented in CPK model, Gly: C, Pro: N, CA, HA, C, OT1 and OT2 (left to right), and the rest of AGP are represented in Licorice model. The seven activity atoms of CypA are represented in VDW model and colored in orange.

Conclusion

◆ **These two rules are derived from the characteristics of energy levels of a protein and might be one of important criterions of drug design.**

◆ **They were validated on complex CypA/CsA and FKBP12/FK506. A tripeptide Ala-Gly-Pro (AGP) was predicted to bind to CypA as an application of our two rules by using HMM/MCMC of stochastic process.**

◆ **Therefore, this new method might greatly assist drug design industry to save time and money during the process of looking for potential drugs.**

References

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