2O03

Robotic Path Planning and Dynamics of Protein-Ligand Interaction

○Carlos A. Del Carpio[1]、坪井 秀行[1]、古山通久[1]、畠山 望[1]、
遠藤 明[1]、高 羽洋充[1]、久保 百司[1]、宮本 明[1,2]

[1]東北大学大学院工学研究科応用化学専攻(〒980-8579 仙台市青葉区荒巻字青葉 6-6-11-1302)
[2]東北大未来未来科学技術共同研究センター(〒980-8579 仙台市青葉区荒巻字青葉 6-6-10)

【Introduction】

One of the biggest challenges in computational drug design is to take into account the dynamic behavior of the receptor protein. Using a single conformation for a protein, i.e., a rigid structure as registered in X ray crystallographic data bases, limits the success achieved by screening compounds towards the receptor. On the other hand, screening a series of compounds with a series of conformations for the receptor rapidly becomes a combinatorial explosive problem difficult to solve with hitherto computational technologies. Methodologies considering the effects of the flexibility of the receptor on the docking process of small ligands have been attracting attention in recent years. Here we implement a new methodology to deal with this problem.

【Method】

In this study we propose the implementation of a flexibility analysis program and a subsequent protein dynamic behavior analyzer implemented for the case of protein-protein interactions[1] to the problem of protein-small organic compound interaction. Docking processes are performed within the MIAX[2] framework. The main technique underlying the analyzer is based on a robotic path planning algorithm developed for then protein-protein interaction case. The main characteristics of the system is the recognition of flexible loops for the receptor from graph theoretical instances and the generation of probable paths of interaction on the complex conformational space.

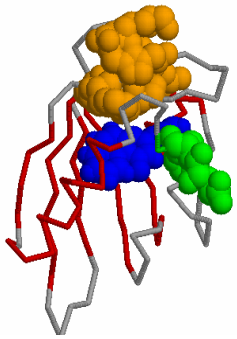

Fig.1 Position of PHE318,ILE319 and HIS320 in the AhR model respect to β NF

【Results and Discussion】

The methodology is applied to a series of receptor-ligand systems, and here the results for DHFR-MTX and AhR-β NF are presented. Figure 1. shows the analysis for the second case, where the flexible loop shown in light color, plays the critical role in the binding of the ligand. This loop is constituted by PHE318, ILE319 and HIS320. Mutations of any of these amino acids affect the flexibility of this loop in the complex and consequently the binding mode of the ligand in the groove of the protein. We have performed flexibility and dynamical studies for the mutants: F318A, F318Y, ILE319A, HIS320A and A375R. Results of the calculations are in good agreement with experimental mutagenesis studies reported in the literature[3].

【References】

[1]. Del Carpio et al.," Robotic Path Planning and Protein Complex Modeling Considering Low Frequency Intra-molecular Loop and Domain Motions", Genome Informatics 2006.

[2] Del Carpio et al.,"MIAX: A New Paradigm to Model Bio-Molecular Interaction and complex formation in condensed phases PROTEINS: Structure, Function and Genetics (2002), 48(4):696-732.

[3] Goryo et al., Identification of amino acid residues in the Ah receptor involved in ligand binding Biochem Biophys Res Commun. 2007.