Analysis of Complementarity of Protein-Protein and Protein-DNA Interactions Using the Molecular Surface Database, eF-site

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1 Introduction

Structural genomics project now producing a large number of protein 3D structures, and the structural information will give us a lot of information on the protein molecular functions. On the other hand, it is not an easy task to solve the structure of protein complexes especially when the complexes are transient, even though the formation of such transient complexes has critical roles to express the biological function of proteins. Thus, some techniques to know or predict the structure of transient complexes of proteins is now required.

2 Method and Results

To develop a method to predict protein-protein interactions, as the first step, we carried out the analyses of the interface of protein-protein complexes from the view point of complementarity of physicochemical properties of protein molecular surfaces.

Proteins are interacting with the other proteins through their molecular surfaces with several kinds of physicochemical interactions. Among them electrostatic interactions and hydrophobic interactions are considered to be major factors to stabilize the complexes. Thus we focus our attention on the molecular surface of proteins [2], electrostatic potential [5] and hydrophobicity [6] on the surface, and analyze the complementarity of the interface. For this purpose, at first we have constructed a database named eF-site, which contains the information of electrostatic-surface of functional site of known proteins.

2.1 eF-site Database

The *e*F-site database visualizes molecular surfaces of proteins with the electrostatic potential and the hydrophobicity on the surface in interactively by chime plug-in [8] and Java3D (Fig. 1). The database consists of five parts: *e*F-site/antibody, *e*F-site/prosite, *e*F-site/P-site, *e*F-site/ActiveSite and eF-site/Membrain, each of which is oriented to the functional site of antibody, sequence motifs [1], phosphate binding site in mononucleotide-protein complexes [4], and active site of enzyme proteins [7], respectively. As a total, about 2000 entries have already been registered. The {UNKNOWN CHARACTER}-version of *e*F-site database is now available at http://pi.protein.osaka-u.ac.jp/eF-site [3].

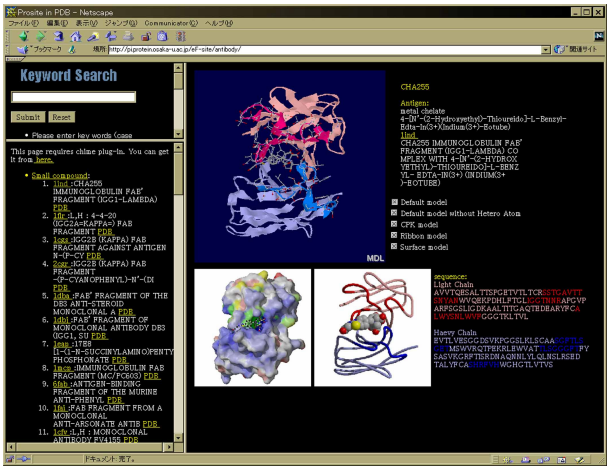

Figure 1: An example of eF-site database.

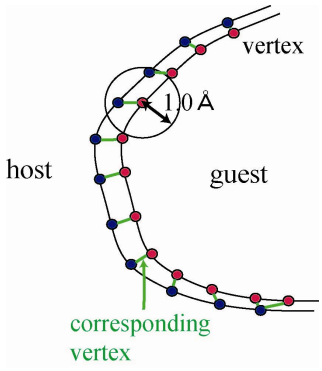

Figure 2: Definition of corresponding vertexes.

2.2 Analysis of Complementarity of the Properties on the Molecular Surface

Molecular surface generated by Connolly's algorithm [2] was represented by a set of triangle meshes with a normal vector to the surface at each vertex, and the electrostatic potential at each vertex was calculated by solving the Poisson-Boltzmann equations numerically for a precise continuum model [5], and the hydrophobic scale [6] of the nearest functional group was mapped onto the vertex. With this representation, to analyze the complementarity of properties and geometries of molecular surface of proteins, we first define such a pair of vertexes, one from larger protein (host protein) and the other from smaller protein (guest protein) whose distance is no more than a certain threshold (1Å was used in this analysis), as a corresponding vertex (Fig. 2). Then visualize the complementarity with a scatter plot of the properties whose x-axis is the properties of guest protein and whose y-axis is that of host protein (Fig. 3). So far, we have applied this method to the antibody-peptide complexes, antibody-protein complexes, and enzyme-inhibitor complexes (19 complexes as a total), then found the similar tendency of the complementarity plot. One typical case is shown in Fig. 3, which is showing the complementarity of electrostatic potential (upper figure) and hydrophobicity (lower figure) for the Caspase-activated DNase (CAD, host protein) and its inhibitor (ICAD, guest protein). The same procedure can be applied to the DNA-protein complexes. Analyses of the representative 25 DNA-protein complexes are now under progress. More detailed results and the result of the DNA-protein complexes are described in the workshop.

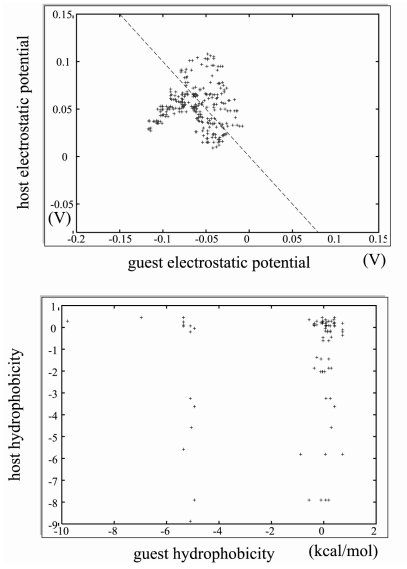

Figure 3: An example of complementarity plot.

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