Investigation of protein inter- and intramolecular interactions with a simple graphics tool

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An interactive protein-structure investigation program, called Pimig, running on the Evans & Sutherland PS340, is presented. The main purposes of the program are visual inspection and handy simulation of the protein–protein interaction. Simplifying an intrinsically complicated problem, Pimig provides a graphics tool for rather instinctive aspects of the study. As an extension of Alpha, the program is also useful in the construction of a three-dimensional model of a protein based on subunit structures.

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INTRODUCTION

The interaction between biological molecules is a fundamental process of the biological function and has been investigated in atomic detail since three-dimensional (3D) structures of several protein complexes became available.[1] Recently, 3D structures of complexes between antigens (lysozyme and neuraminidase) and Fab fragments of antibodies have been determined and refined by X-ray crystallographic technique.[2,3] Even such a highly selective antigen–antibody recognition was found not to be an exception from other known protein–protein interactions, in which hydrophobicity is the major stabilizing factor and complementarity plays a selective role.

Several methods of analysis of protein–protein interactions have already been described.[4–11] Some of the methods use known properties and restrict the problem to a study of the interactions for a given protein–protein orientation.[4,5] The development of those kinds of studies is an automatic generation of possible complex structures.[6] In other methods, two-dimensional (2D) projections of protein surface properties were employed.[7,8] The most recent contribution in this field may be the introduction of surface fractality.[9,10] Interactive computer graphics methods have also been used in simulation of the protein–protein interactions.[10,11] However, no single, satisfactorily reliable method exists because of the intrinsic complicatedness of the problem. On the other hand, even visual inspection has been viewed as helpful in a protein–protein interaction study.[6] In this article, a computer graphics program that offers an aid for such a study is presented.

Although the final interaction structure must be determined by precise atomic interactions, an approximate image of a protein structure may be useful in visual inspection of the protein–protein interaction. Simulation of protein complex formation could also be performed employing such a method. Pimig (Protein InterMolecular Interaction with Graphics) was developed for this purpose. It is basically an extension of Alpha toward a two or more protein structure problem. Its application is not limited to intermolecular interaction; it is also useful in the study of the intramolecular interaction of a protein and in investigating model building.

IMPLEMENTATION

Pimig was developed using VAX-11/780 as a host computer and an Evans & Sutherland PS340, which has calligraphic and raster displays, as a graphic terminal connected by a DMR-11 communication line. The calligraphic display was used as a structure-manipulation terminal, and a Leeds liquid crystal 3D viewer of Millennium was employed in the stereoviewing version. The raster display was used as a CPK-like representation of molecules in which the CPK modeling firmware of Evans & Sutherland was employed. The program was written in VAX-FORTRAN and PS340 programming language.

BACKGROUND

In Pimig, proteins are represented by a α-carbon models and amino acid information color-coded CPK-like models as in Alpha.[12] These graphics methods have two fundamental advantages in a protein–protein interaction study: simplicity, and correspondence with the intrinsic motility of side-chain conformation in a protein. A similar idea has already been introduced into the protein–protein interaction analysis with considerable success, although a 2D projection method was used in that study.[7]

In Precise, the basic factor dominating the protein complex structure is the interatomic interaction. However, a detailed atomic model gives a rather complicated image of a protein, which makes visual inspection difficult. In Pimig, physicochemical characters of amino acid

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are seen as color in the sphere, centered at α-carbon position of each residue, as each amino acid represents roughly the composition of atoms that form each residue. This method gives rather simplified representation of the character of the surface of a protein.

Recent studies using X-ray crystallography have shown that conformational heterogeneity exists in the same protein, especially among side-chains, on the proteins surface.[13,14] Furthermore, there is direct evidence that a protein has a different conformation in complex from that in monomer.[3] These facts indicate that a protein may change its conformation in the process of interaction and that the exact positions of atoms in monomeric structure are not as important. If this conformational motility is taken into consideration, a spherical representation of amino acid residues may reflect an aspect of a protein structure better than an ordinal all-atom model.

Pimig is also applicable in the study of the protein intramolecular interaction because protein folding has common features with the protein–protein interaction. This is evident in the protein complex, which is originally synthesized as a single polypeptide and processed into subunits afterward.

Overview of Pimig function

Model transformation and construction are performed on the calligraphic display. There are two versions: two-eye-point version (the same as Alpha) and a stereoviewing version. In the two-eye-point version, two proteins are shown in red and blue α-carbon models (see Color Plate 1). The stereoviewing version is superior in the construction of a model because it gives a realistic 3D image of a protein model. Two structures are manipulated simultaneously. More than two structures can also be handled with simple file manipulation on the host computer because an α-carbon model needs comparatively fewer coordinates than an all-atom model.

Real-time rotation, translation and scaling of overall structure or rotation and translation of each structure with dials are available. In the independent structure transformation mode, each structure rotates around the center of mass of each protein to acquire visually smooth movement. The relative spatial orientation of proteins can be written back to the host computer after an interactive session is over. The transforming object can be changed with a press of function button. The object name appears in the right-bottom box of the screen and on the dial board LED display. The residue name is shown on the screen if an amino acid point is hit with the tablet pen. All residue names are erased with a press of function button.

An amino acid information color-coded CPK-like model corresponding to an α-carbon model on the calligraphic display is shown on the raster screen with a press of function button; an informative view of any orientation can thus be obtained. There are choices of color codes according to physicochemical and sequence dependent information (as in Alpha). The variety of structural information of known proteins that can be used in CPK-like models has increased in combination with the database of conformational elements of protein, which has been constructed on the same host computer.[15] Another selection concerning the display object is also available in Pimig. Two proteins can be shown simultaneously, one with a dark color (see Color Plate 2), or independently (see Color Plates 3 and 4). A cross-section view, which is obtained by setting the model across the clipping plane, is useful in a detailed investigation of the interaction surface.

APPLICATIONS

Several examples of Pimig applications are briefly discussed in this section. All of the studies are in progress, and the details will be presented later.

Dimer, oligomer and complex proteins in the Protein Data Bank[16] have been inspected using Pimig. The dimer of beef liver catalase[17] is shown as an example in Color Plates 1 through 4. As far as the investigation has progressed, the importance of the arrangement of hydrophobic residues is properly simulated by Pimig representation. Other factors, like electrostatic field, have also been found meaningful in the protein–protein interaction.

A protein is usually constructed from some subunits, like domains[18] and modules.[19] If structure files are adequately separated and prepared, the interaction between domains and modules can be visualized. A modular structural unit in chicken lysozyme is shown in Color Plate 6 as an example. The intramolecular interaction that determines the protein folding can be investigated using this method. In this example, the importance of hydrophobicity is visually demonstrated.

Some of membrane proteins have been proposed to be constructed from several α-helix membrane–spanning units. Although most reports concern only the prediction of such domains in the sequence from hydropathy plots, a 3D image of α-helix arrangement of such a protein can be constructed using Pimig. Color Plate 6 shows a predicted model of photosystem II herbicide–binding protein membrane–spanning region,[20] in which five α-helices were arranged by matching hydrophilic residues.

CONCLUSION

In a previous paper,[12] the usefulness of the α-carbon model in the predictive study of the 3D structure of a protein was described. Therein the hierarchical nature of protein was discussed in reasoning the basic concept of Alpha. Another step toward a higher level of the hierarchy would be the protein–protein interaction. The present study demonstrates that the α-carbon model is also applicable in such investigations. A combination of a colorful visualizing method and an interactive graphics model, Pimig is a useful tool for the study of protein–protein interaction.

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