I-L Development of Techniques for Prediction of Conformations and Applications to Proteins and Organic Compounds

Various techniques of prediction of conformations have been developed in this decades including proteins and organic compounds. Furthermore, the analysis of genome sequences from various species including human have been performed quite rapidly. The next significant problem is to clarify 3D structures and functions of proteins coded by genome sequences. Since the experimental techniques to determine 3D structures of proteins are still time-consuming, a predictive technique is desired. However, a prediction of protein 3D strcutures is still unsolved and difficult problem in the area of molecular biophysics. Currently, we are attempting to predict location of 3D strcuture units, so-called domains, in genome sequences by means of a kind of contact map based on the statistics of average distances between amino acids in proteins. This information can be helpful to determine the 3D structure of each structural unit. On the other hand, development of a modeling technique of organic compounds in terms of the interactions with a protein is also important especially in the field of drug design. We have applied a 3D search method to find a new potent inhibitor of an enzyme for development of a new herbicide. We also made the MD simulation of some polysacchalydes, chitosan and amylose, to clarify the relationship between their dynamical properties and the coloring bahavior with iodine.

I-L-1 Contact Maps Derived from the Statistics of Average Distances between Residues in Proteins. Application to the Prediction to the Prediction of Structiures and Active-Sites of Protein and Peptides

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Information on various 3D structural features of proteins is extractable from statistics of protein 3D stuctures, using the method we review here. The main tool for the method is a contact map, called an average diatance map (ADM), constructuted from the statistics of average distances between residues. In spite of their simplicity, theese maps proveide various predictions on 3D structures of proteins, *e.g.*, location of domains, structural similarity between proteins, proteins structural classes, active sites in bioactive peptides, and so on. The present method is useful for practical problems encountered in protein engineering and drug design. We also demonstrate a practical application of the present method to the structure-activity relationship prediction of an insect peptidic hormone; the results have ramifications for the future development of new types of insecticides. Further, ADM can be applied for identification of functional units on genome sequences in the post-genome era.

I-L-2 Prediction of Protein 3D Folding Properties in Genome Sequences Based on the Statistics of Average Distances between Residues

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The analyses of human genome has been proceeded quite rapidly and whole human genome will be uncovered in very near future. The next significant step is to predict the 3D structure and function of domains in an Open Reading Frame (ORF) derived from a genome analysis, *i.e.* to clarify which region in an ORF corresponds to what kind of functional domain. The average distance (ADM) method is useful and adequate for the step of prediction of domain locations on ORFs. The ADM method also gives several predictions on 3D structures of proteins. In the present work, we report the recent progress of the ADM method to treat ORFs derived from genome analyzes especially focusing on the prediction of location and folding properties of domains. The results show that the ADM method predicts folding units in a protein sequence and it corresponds to a functional domain in many cases.

I-L-3 Identification of Novel Potent Inhivitors for ATP-Phosphoribosyl Transferase Using Three-Dimensional Structural Database Search Technique

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An efficient method to search potent inhibitors of an enzyme or a receptor is required in the process of drug design. One simple but effective strategy is to search compounds fit to the cavity of a receptor from the compound 3D database. We identified new potent inhibitors for ATP-phosphoribosyl transferase, which acts at the first step of histidine biosynthesis pathway, using a 3D database search technique. The 3D search was based on the structure of the product molecule, N-1-(5'-phosphoribosyl-1-pyrophosphate), *i.e.* bi-substrate

mimicking. Four compounds with three different chemical classes were examined. Among them, amino-(chlorophenyl)-triazolopyrimidine compounds, which are the simplest and smallest ones, showed potent activity. The structural comparison with the product molecule suggests that the simultaneous occupation of two substrate-binding sites likely enhances the enzyme inhibition. The most potent compound examined in this study was a disulfide-bond containing molecule, whose mode of action seems to be different from others.

I-L-4 Complex Formation of Chitosan with Iodine and Its Structure and Spectroscopic Properties—Molecular Assembly and Thermal Hysteresis Behavior

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To elucidate the factors responsible for the complexation of chitosan with iodine and to gain insight into the structures and spectroscopic properties of chitosan-iodine (CI) complexes, extensive studies were performed on the effects of iodine/chitosan concentrations and temperature on the CI complexation. That is, the several physicochemical properties of the complex in acidic solutions containing excess KI were examined by means of various spectroscopic (absorption, CD, *etc.*) and structural analyses (SAXS, *etc.*) and molecular dynamics (MD) simulations. The CI complex exhibited absorption spectra with a peak at around 500 nm, regardless of the iodine/chitosan concentrations and temperature. Correspondingly, the CI complexes exhibited mutually split CD bands with opposite signs (+, –) at around 500 nm. The CI complex showed thermal hysteresis, *i.e.*, an irreversible reaction process involved in complexation and color formation. MD calculations predicted that the irreversibility and thermal hysteresis behavior of the CI complexes are due to a crystalline-like extended compact folded conformational transition.