Identification of active sites interaction of different protein molecules in case of formation Nap1-Nap1, Mdm2-Mdm2 and P53-Mdm2

T V Koshlan

Peter the Great St. Petersburg Polytechnic University, Russia

Abstract:

In this report, two algorithms are developed, algorithm 1 and algorithm 2. Algorithm 1 was developed in order to search for the interaction of a polypeptide chain of a full-length protein with short active region. Algorithm 2 was developed to determine the most active sites of interaction between full-length proteins when dimers are formed in the direction from the N terminus to C terminus. Numerical calculations were made using proteins Mdm2, Nap1, P53. For modern proteomics, research and prediction of protein interactions are very important tasks, since they determine the function of proteins at levels from the cell to the whole organism. For proteins whose structure is known, the search for intermolecular interactions according to known data on the conformation of their tertiary structure reduces to the problem of searching for geometric complementarity of the sections of two interacting molecular surfaces and modeling their contacts, the so-called molecular docking. The task of molecular docking is the task of a conformational search algorithm, which reduces to a search for the conformational space of the formed biological complex due to the variation of the torsion angles of protein molecules. Modern conformational search algorithms in most cases find conformations that are generally close to the experimentally found structures in a relatively short time. However, there are factors that also have a significant impact on the success of the docking, which are often not taken into account in standard algorithms. One such factor is the conformational mobility of the target protein. The mobility range can be different beginning with a small adjustment of the side chains and ending with scale domain movements. These movements play an important role. At first glance, the most logical solution to this problem is to take into account the mobility of the protein in a docking program. Unfortunately, modern computational tools do not allow such modeling to be performed in an acceptable time frame since a protein molecule is very large, and allowing for mobility over all degrees of freedom can lead to a so-called combinatorial explosion (an astronomical increase in the number of possible variants). Only in some programs is there a limited mobility of protein binding sites (usually at the level of a small adaptation of conformations of the side chains of the active center residues). Another approach to this problem consists in docking the same protein in several different conformations and then selecting the best solutions from each docking run. The third approach is to find a universal structure of the target protein in which docking would produce fairly good results for different classes of ligands. In this case, the number of missed (but correct) solutions decreases, but the number of incorrect options also increases significantly. It should also be noted that most programs for the theoretical docking of proteins work according to the following principle: one protein is fixed in space, and the second is rotated around it in a variety of ways. At the same time, for each rotation configuration, estimates are made for the evaluation function. The evaluation function is based on surface complementarity (the mutual correspondence of complementary structures (macromolecules, radicals), determined by their chemical properties), electrostatic interactions, van der Waals repulsion and so on. The problem with this approach is that calculations throughout the configuration space require a lot of time, rarely leading to a single solution, which in turn does not allow us to speak of the uniqueness of the target protein and ligand interaction variant. So in the work while modeling by the methods of molecular dynamics, from 200 to 10 000 possible combinations of the formation of a protein complex with a ligand were found. Such a large number of modifications, along with the lack of a criterion for selecting the most probable variants of the bound structures of biological complexes (which would allow a radical reduction in their number) makes it very difficult to interpret the theoretical results obtained for practical use, namely, the finding of catalytic centers and a qualitative assessment of the dissociation constant of interacting substances. In contrast to the above computer simulation algorithms, mathematical algorithms have been developed in this chapter that allow determining the detection of proteins active regions and detecting the stability of different regions of protein complexes (linear docking) by analyzing the potential energy matrix of pairwise electrostatic interaction between different sites of the biological complex, such as the homodimer of the histone chaperone Nap1-Nap1, the heterodimer of the p53 Mdm2 proteins, and the homodimer Mdm2 Mdm2, which are responsible for the entry of a whole protein molecule into biochemical reactions.

Biography:

T V Koshlan is currently working as a Professor at Peter the Great St. Petersburg Polytechnic University, Institute of Applied Mathematics and Mechanics, Department of Higher Mathematics. He has completed his PhD in Physics and Mathematics with Mathematical modeling of the optical properties of multilayer biological systems and structures in their heterogeneous conjugation. He has habilitation at the State Polytechnic University of St. Petersburg, Russia. His research

interests are diffraction theory, electrodynamics, physics of lasers, tissue optical methods of mathematical modeling in biological tissue optics and numerical method, biophysics.