Structural Biology: Modeling applications and techniques at a glance

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ABSTRACT

As recent advancements in biology shows, the molecular machines specially proteins, RNA and complex molecules play the main role of the so called cell functionality. It means a very big part of the system biology is concerned with the interactions of such molecular components. Drug industries and research institutes are trying hard to better understand the concepts underlying these interactions and are highly dependent on the issues regarding these molecular elements. However the costs for such projects are so high and in many cases these projects will be funded by governments or profit making companies. With this in mind it has to be said that the techniques like stimulation are always a very good candidate to decrease such costs and to provide scientists with a bright future of the project results before undergoing costly experiments. However the costs involved projects that determine an approximation for the problem is not that much high but they are also costly. So it is of utmost importance to invent special techniques for the concept of stimulation that can also decrease the project costs and also predict much accurately. Since the system biology and proteomics as the study of the proteins and their functions are in the center of consideration for the purpose of drug discovery, understanding the cell functionalities and the underlying causes behind diseases; so we need advance software and algorithms that can predict the structure of the molecular components and to provide researchers with the computational tools to analyze such models. In this paper we make review of the importance of molecular modeling, its limitations and applications.

Keywords: Molecular modeling; Homology modeling; Drug design; Molecular component; Molecules structure

INTRODUCTION

In recent years specially since the completion of the Human Genome Project (HGP) in 2003[1] a huge amount of data on the concepts of the genomics has been revealed which also opened a very big door for the researchers in industries and institutions to understand the concepts of life. Since then many articles have been published every day regarding health issues. As it can be depicted from these articles a very big part of them are the concepts of modeling molecular components due to the fact that all the interactions of these elements specially proteins, the interaction between these elements and newly discovered drugs and also their functionalities are highly dependent with their structure. It means there is a close relationship between the function and the structure of molecules like proteins and drugs [2, 3]. Accordingly, molecular modeling has become a valuable and essential tool to medicinal chemists in the drug design process [4-7].

Therefore the development of the useful algorithms for the determination of the physical structure of the molecular components is so important in a way that today a very big and important part of the computational sciences is

concerned with the development of these computational algorithms which lead to the advent of interdisciplinary projects and majors like computational biology.

Also it has to be mention that the process of the development of such algorithms is highly dependent on the biological data which are published every day[8]. Moreover due to fact that here we are concerning with the concepts of modeling so algorithms in this area have many limitations and also they are time consuming due to the nature of the modeling problems.

Modeling: concepts and limitations

As described before molecular modeling is very important to our knowledge of molecules structure specially proteins [9] and to determine the binding sites where drugs can bind and interact with them[10, 11]. To achieve this we should know that there are different techniques to model a molecule. Some of the techniques are highly dependent on the crystal structures of the proteins that had been X-rayed before. In this sense the protein that we want to determine and model its structure or the better say subject protein should have some homology with the object protein [the protein that had been X-rayed before][12]. Therefore in many cases there would be no significant templates for the process of modeling or those which are present in the protein structure banks are not homologue enough for this process. As it is clear from the concepts of this technique, it is called homology modeling[13]. If for the homology modeling, there exist any homologue X-rayed proteins so one can perform the task using homology modeling servers like Swiss-Prot[14] http://swissmodel.expasy.org and other bioinformatics' servers [1, 15-26] that provide tools for the process or one can use special software that do the same thing. It means one can either do it in on-line mode or off-line mode. After the completion of the modeling task, there are also a number of operations that should be carried out in order to improve the structural quality up to the acceptable level. These quality factors are the energy of the structures, polarization of the molecules, the distribution of the elements of the molecules in Ramachandran plot and so on which all can be tested using special programs like What_if [25]. It is also of utmost importance to know that all these improvements will be made by the special computational algorithms specifically designed and developed for this matter. In figure 1 you can see the crystal structure of a RAD51-BRCA2 BRC repeat complex that had been X-rayed[26, 27] and is also accessible with 1n0w accession number. In figure 2 you can also see the crystal structure of the Yeast Rad51 H352Y Filament Interface Mutant[26, 28] that are also accessible with the 3lda accession number.

By understanding the pivotal idea of homology modeling, one can see the extreme limitations of the technique explained. These limitations involve the very low number of proteins that had been undergone the process of crystallography in comparison with the number of detected proteins and the situation in which there would be some homologues for the subject proteins but do not share a good percentage of homology with the object protein. There are also numbers of other limitations regarding homology modeling but the technique is very useful and can play a very significant role in the discovery of the secondary and tertiary structures of the proteins and molecular machines [29, 30].

Besides homology modeling there are a number of other techniques that are used to predict the structure of the molecular machines by putting the atoms of the molecules besides each other in order to make the molecule. In this case the scientist will make the structure and put the elements in the best coordination and then will do the same improvements on the template and will also test the structure against quality factors using the same algorithms and programs.

This technique is more being used when the object molecule has no suitable homologues presented in the protein data banks. Like when one may want to predict the structure of an unknown protein, enzymes and so on.

Although this technique can solve some problems of the homology modeling but it is time consuming in comparison with homology modeling and one should know the knowledge of the structural biology very well to handle this method [Table 1].

One of the most promising strategies which has provided a valuable means for simulating And consequently predicting the construction, nature and mechanism of biological systems and

actions is molecular dynamics [31] and MD simulation [32].

Figure 1. The crystal structure of a RAD51-BRCA2 BRC repeat complex

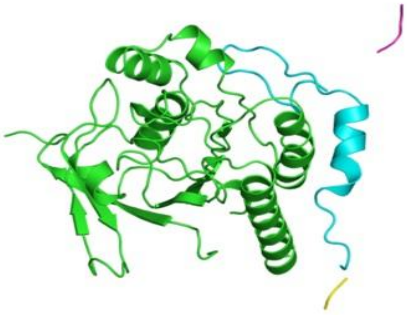

Figure 2. The crystal structure of the Yeast Rad51 H352Y Filament Interface Mutant

Due to invaluable information which can be obtained from a molecular dynamic simulation [31], the MD methodology has founded applications in various areas and has successfully been used to simulate different biological and bio-molecular systems such ligand-DNA systems [33-38], enzymes and enzyme kinetics [39-49], genetic and gene expression [50-52], proteins and protein folding [53-72], DNA-protein interactions [73-83], peptides [84-97] and cells [31, 98-103].

The fast development in computer technology and creation of powerful molecular dynamics or mechanics software during the past decade has opened novel possibilities for simulating and modeling aspects of the complex biological process. Consequently, it is noticeable [as example shown in figures 3 and 4[104]] that computational techniques shall play an ever-increasing role in the design and investigation of structural biology systems. Furthermore, it is anticipated that these progresses shall have direct impact on the progression of new application areas for biological systems, especially DNA[figure 5[104]], RNA proteins [figure 6[105]], and complex molecules for use in therapeutics and medical researches and advances.

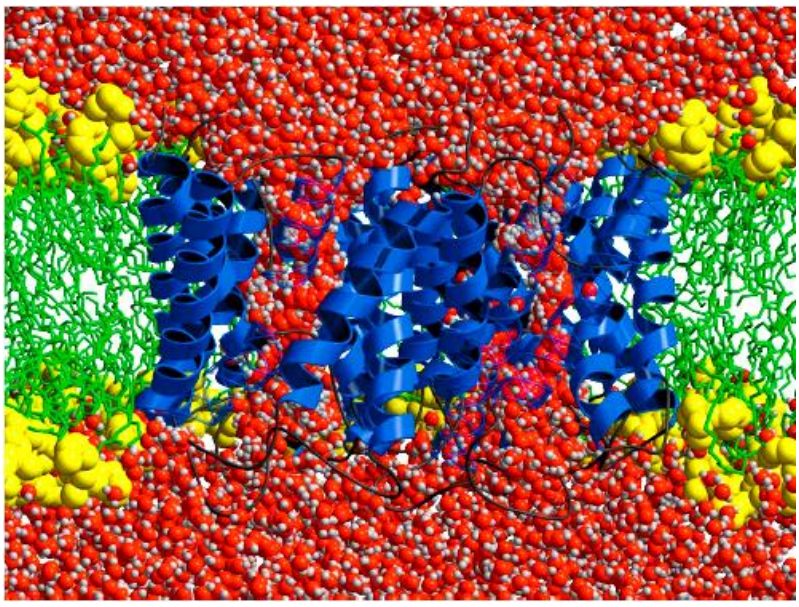

Figure 3. The permeation of water through a model of aquaporin [blue] in a lipid bilayer membrane [head groups in yellow molecules [red and gray] through the aquaporin tetramer during the 10 ns simulation is indicated by an overlay of 100 snapshots [112]

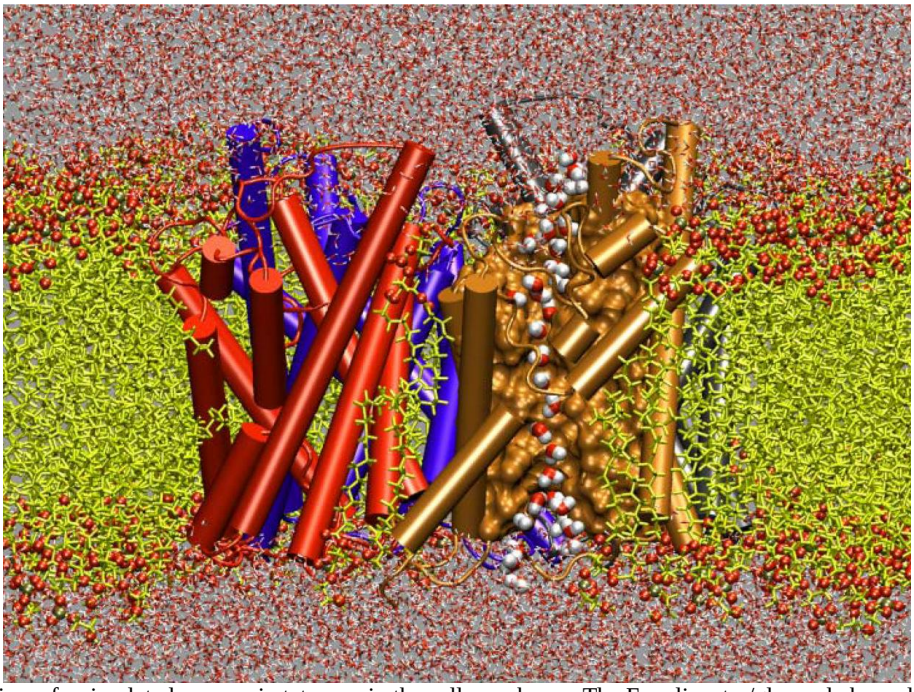

Figure 4. Side view of a simulated aquaporin tetramer in the cell membrane. The E. coli water/glycerol channel GlpF is embedded in a patch of POPE lipid bilayer and fully hydrated by water on both sides. Lipid head groups are shown in CPK and the hydrophobic tail region is drawn using licorice representation. The four AQP monomers, each forming an independent water pore, are shown in different colors. The single file of water formed inside the pores is shown in one of the monomers. The characteristic conformational inversion of water at the center of the channel that contributes to the barrier against proton transfer is discernible [113].

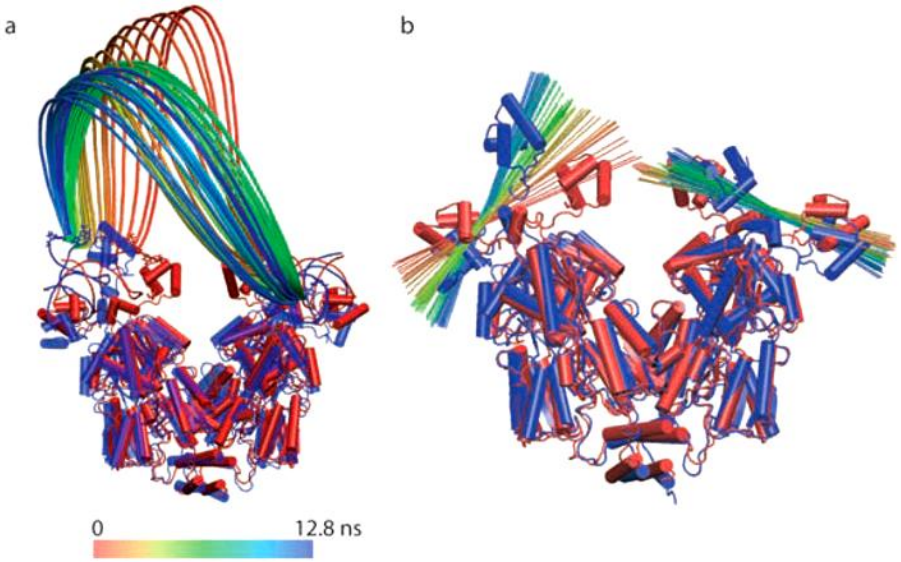

Figure 5. Snapshots taken over the course of the LacI-DNA complex multiscale simulation: [a] The evolution of the structure of the DNA loop; [b] The structure of LacI remains unchanged, with the exception of the rotation of the head groups, which allows the DNA loop to adopt a more relaxed configuration [113].

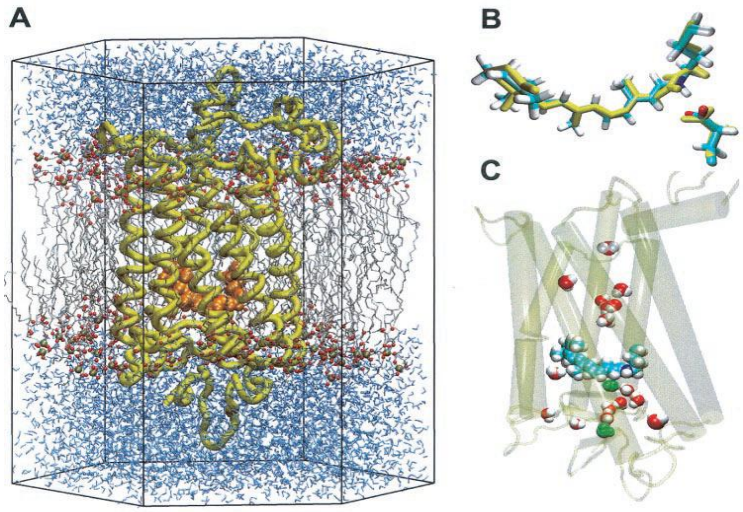

Figure 6. [A] Rhodopsin [yellow] with retinal in orange, embedded in membrane [gray, red]. The system is solvated in water [blue] and was simulated using hexagonal periodic boundary conditions [unit cell marked by black lines]. [B] Retinal with protonated Schiff base and the counterion, Glu-113. The refined crystal structure [yellow] is highly distorted between the Schiff base nitrogen and C14, and the Schiff base points to the wrong direction. After minimization we obtain a more planar retinal [blue, white], which is very similar to the one found in the first crystal structure [114]. [C] Equilibrated rhodopsin with water molecules suggested by DOWSER in red, and the crystal water molecules in green [115].

Modeling Applications

As it has been pictured, industries and research institutes are highly dependent on the structure of the molecular components[106, 107]. Therefore modeling the structure of the molecules is a very useful technique and can play a very important role in the process of drug design[108], understanding molecular interactions and also can reveal some information of the molecules that had not been known yet [109].

Drug design companies invest a huge amount of money every year on the modeling projects in which they can be able to predict the structure of the newly made drugs and the molecular components that will providing biding sites for them. They also invest on the invention of systems that can predict binding operation of the discovered drugs and molecular components.

It is also of utmost importance for research institutes to know the physical structure of the molecules regarding their experiments. In this way they can better understand the function that is played by the molecules due to the fact that the physical structure of the molecules is in direct link with their functionalities. Many techniques for predicting the functions of the proteins also use the structure homology in companion with sequence homology for reaching the optimum results[110].

Table 1: Useful programs for comparative protein structure modeling

PROGRAMS	
Comparative modeling	Modeller
	ICM
	FAMS
	Composer
	3D-JIGSAW
	CPH-models
	SWISS-model
Model evaluation	Prosall
	BIOTECH
	AQUM
	PROVE
Template	PDB-BLAST
	BLAST
	FastA
	PROFIT
	3D-PSSM
	Super family
	123D
Alignment	Blast
	PDB-BLAST
	ClustalW
	T-Coffee
Databases	NCBI
	TrEMBL
	Pfam
	PDB
	Target DB
	Gene bank

The modeling itself is also intricate to the concept of proteomics, the study of the proteins, their functions and structures since proteins are the important components of the metabolic pathways of the cells. It has to be explained in this way that the so called field "Proteomics" will use the structure of the proteins as important molecules to understand the function of the protein besides their functional experiments being conducted every day[111].

One more thing that should be taken in to consideration is the contribution of this field to our knowledge of system biology. There also another consideration that many useful computational algorithms are the discovery of the computational specially proteins in this context. It means a bi-relational nature of the proteomics and structural biology [Table 1].

Protein structure prediction

Protein structure prediction is defined of prognosis of protein's three-dimensional structures based on sequence of its amino acids. Since protein structure prediction is highly valuable in medicine and biotechnology, it is one of the main aims followed by bioinformatics expertise. It is expected that the intense research effort focused on these approaches will produce significant contributions to overcome some known bottlenecks in proteomics. The follow list is brief description of some helpful softwares in prediction of protein structure with their links [Table 2a,b].

Category	Software	Description
Protein Sorting	SignalP	Prediction of presence and location of signal peptide cleavage sites in amino acid sequences from different organisms
	TargetP	Prediction of location of eukaryotic proteins. Based on the predicted presence of any of the N-terminal presequences: chloroplast transit peptide (cTP), mitochondrial targeting peptide (mTP) or secretory pathway signal peptide (SP)
	NetNES	With help of combination of neural networks and hidden Markov models to Predict leucine-rich nuclear export signals
Post-Translational Modifications of Proteins	*NetPhos*	For prediction of serine, threonine and tyrosine phosphorylation sites in eukaryotes based on Neural network predictions

studies on the target of the molecular components

Table 2: Protein Structure Prediction softwares and their brief Description

	NetPhosK	Neural network predictions of kinase specific eukaryotic protein phosphoylation sites
	NetOGlyc	Neural network predictions of mammalian mucin type GalNAc O-glycosylation sites
	NetNGlyc	Prediction of N-Glycosylation sites in human proteins using artificial neural networks
Prediction of Transmembrane Helices	TMHMM	Prediction Based on Hidden Markov Model method
	DAS	With an advanced use of hydrophobicity patterns Predict location of transmembrane helices
Secondary Structure Prediction	JPred	A webserver Neural network assignment prediction
	PredictProtein	A webserver Profile-based neural network that When you submit any protein sequence PredictProtein retrieves similar sequences in the database and predicts aspects of protein structure and function Tutorial

Category	**Groups**	**Software**	**Description**
Tertiary Structure Prediction	Homology Modeling	Swiss-Model	An Automated webserver (based on ProModII) that predicts the three-dimensional structure of sequence based on the similarity of sequence to a protein of experimentally determined structure
	Treading/Fold	GenTHREADER	Fold recognition method employed to complete translated genomic sequences or to distinctive protein sequences
	Ab initio	ROBETTA	Rosetta homology modeling and ab initio fragment assembly with Ginzu domain prediction
		HMMSTR/ROSETTA	Protein structure Prediction from sequence

CONCLUSION

With the advancements of the biotechnology today and the huge amount of data being published every day we come to this certain conclusion that there is no border between sciences any more. The advent of the interdisciplinary majors like computational biology is the result of this concept.

Recent advancements in the computational biology have opened doors to our knowledge and understanding of the concept of life. It is not false if one say "All the sciences will be ended to mathematics in their process of development".

Therefore more and more computational advancements are needed to handle such projects of modeling. Many techniques should be invented to better model the molecules. In this sense many computer scientists are attracted every day to work in the interdisciplinary fields of research like structural biology and computational biophysics. However there are so many limitations regarding issues like modeling of molecular components and analyzing the built structures.

It seems that it is an open door that would never be closed and every step that we make toward the improvement of our methodologies and techniques, we will be closer to the understanding of the concept of life.

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