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Disease-gene discovery & repairing of a gene causing human cytochrome-c oxidase deficiency by Docking method

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ABSTRACT

An especial gene is responsible for cytochrome c diseases which need exact information about that gene's position in bio-systems. Obviously, the docking availability of genome map of RNA and consequently protein expression prepare important sources of data for applied insight. In this work, we investigate how such data sets can predicate problem-gene discovery, by applying them for identifying the gene causing a human cytochrome *c* oxidase defect in related chromosome. Through RNA expression information, we define all genes and their similarity in RNA-expression profiles for knowing mitochondrial genes via docking and ΔG estimation (free energies). Using docking, the human genes have been classified with a probability of those proteins product which is associated with the mitochondrion. Via analyzing the calculated data with the relevant genomic region, we identified some candidate genes in the first step. In the second step, the exact details have been analyzed again and a mutation has been identified and an additional mechanism of mitochondrial processors has been suggested. In this work, it has been exhibited that the halogenated of Cardiolipin increase the efficiency of its behavior as the catalyst for stabilizing enzymes. It has been shown that with substitution three fluorine, Chlorine, bromine, and iodine the yields of catalysts are F_3- Cardiolipin> Cl_3- Cardiolipin> Br_3- Cardiolipin> I_3- Cardiolipin, respectively

Keywords: *gene discovery, cytochrome-c, Docking Method.*

1. INTRODUCTION

The c-types (Cyt-c) cytochromes are defined as a proteins having one or more proto-Heme covalently bound to the polypeptide chain through thio-ether linkages. Firstly the cytochrome has been identified by spectroscopic properties [1-20]. Cytochrome c contains a heme group with Fe^{+2} inside which easily accepts and releases an electron at any time. Cytochrome c is a suitable protein for electron-transport and is a segment of the respiratory replaced to mitochondrial inter-membrane spaces and released from mitochondria through procaspase-9[2-30]. Cyt-c plays a significant role in a wide range of basic biological systems and many other processes such as drug delivery, bio-sensors, fuel cells and bio-electronic section [3, 8 and 9]. High resolution crystallographic investigation has been exhibited the subclasses of segments which are generally defined as: (1) consisting of a polypeptide section (85 to135 residues), including a heme group with a covalent bond to the close amino function, (2) the Histidine and methionine amino acids which are the axial heme-iron ligands and (3) having approximately high oxidation or reduction potentials between of + 150 to +380 mV. High potential cytochromes c include mitochondrial cytochrome c, cytochrome c2 , cytochrome c 550, cytochromes f, Pseudo-monas cytochromes (c551), and various others of prokaryotic cells [4,12,15]. Cytochrome c shuttles electrons during the cellular metabolism and electrons are transported one by one, jumping from one protein to another protein (Scheme 1). Cytochrome c oxidase is an enzyme that is a huge trans-membrane protein and found both in prokaryotes and in the mitochondrion of eukaryote cells. It grabs an electron from each part of 4 cytochrome c sections and pushes it to one oxygen atom. In the mechanism, it takes eight protons from the inner phase for making two molecules water and dislocates four protons amidst the membrane and helps to charge a Transmembrane electrochemical potential for synthesizing and using ATP. The reaction is as follows:

$$4Fe^{2+}\text{cytochrome } c + 8H^{+}_{in} + O_2 \rightarrow 4Fe^{3+} + \text{cytochrome } c + 2H_2O + 4H^{+}_{out} \quad (1)$$

In this mechanism, mitochondrial membrane-bound protein has a complicated subunit structure and H^+ to water pumps protons against gradient into the cytosol. The Cyt-c oxidase counterpart to the oxygen evolving in photosynthesis and here the electron for the reduction of oxygen is obtained from the cytochrome c (Fig.1). Simulation of disease genes remains a challenging phenomenon. Although the availability of the sequenced genome has been investigated widely, many difficulties are remaining because genetic maps provide only recombination which is not sufficient for any further research. Currently sifting is a strong tool for detecting the poor genes in genetic studies [5, 6, 9]. Fortunately, genomics has wide databases of genetic information including exact sequences, RNA expression, genetic position, protein-protein interaction and so on. Such these important experimental information and data can be applied for detecting precise correlations among the gene properties and disease independent of patient samples and might provide a worth of re results. In this work via the integration of database information about DNA chains, mRNA, and protein-membrane interaction, the disease-genes problems have been investigated theoretically. We report the successful method of this approach for human cytochrome c oxidase (COX) problems through molecular mechanic simulation and docking calculations. Various COXs

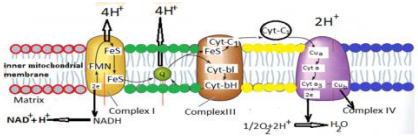
which consists of 20 structural conserved subunits (Table.1) and consists of 14 structural Assembly subunits (Table.2) are responsible for electron-transport mechanism and serves to transfer decreasing equivalent from cytochrome *c* to oxygen. It is notable that three of subunits are encoded by mitochondrial DNA and several secondary proteins are needed for appropriate assembling with Cu cofactor and heme section. As an instance, this assembly in yeast is not understandable due to the fast and irreversible aggregation of hydrophobic subunits (as well as aggregation of mutant segments) [6]. Subunits of various COXs are encoded in mitochondrial (3 subunits of the COX catalytic core) and also nuclear genomes. The two heme structure and copper atoms aid with the continued transfer of electrons between subunits I to II. Various subunits make intermediates complexes which are ready to bind with other units for providing larger COX complexes [6, 13-18].

In an advanced-assembly modification, COXs will produce a homo-dimer which is required for any further activities and these dimers are connected via 1, 3-bis (*sn*-3'-phosphatidyl)-*sn*-glycerol molecule (Cardiolipin) [6, 13, 14], which plays as a catalyst for stabilizing the halo-enzyme. Cardiolipin is a necessary molecule in the inner mitochondrial membrane, which can also be found in the membranes of most bacteria and is essential for the optimal function of several enzymes that are involved in mitochondrial energies metabolisms. Several accessories proteins are necessary for suitable subunits assembling to coordinate with copper cofactor and also heme groups. In some of the clinically distinct autosomal recessive human's COXs, the related genes for a few of them have been cloned. Several subunits encoded of the genomes nuclear play important role in protein dimerization and stabilities and mutations of those subunits remove COXs functions [6]. Assembly has three rate-determining sections and the compounds of each section have been found, via specific subunits structures which are unknown yet [6, 10, 14-17]. Synthesis and assembling of first three COX_m (m=1, 2 and3) subunits are simplified through translation actuator, which has interaction with the un-translated region of mitochondrial m-RNA transcription and it is noted that translation actuator are encoded in the nucleus. A pair electron from the equation (1) is transferred from two cytochromes, via the copper and to makes Fe^{2+} and Cu^{+} ions. The oxygen atom is quickly reduced, due to two electrons from the Fe^{2+} [30, 31 and 32]. The oxygen atom close to copper picks up one electron from Cu^{+}, and the second electron and the proton from the OH groups of Tyr (244) consequently Tyrosyl radical appears[33-35]. The 3'rd electron from another cytochrome is transfer via Cu- binuclear center and caused to convert the Tyrosyl radical back to Tyr[. The 4^{th} electron from another cytochrome transfers through Cu and causes to produce the $Fe3^{+}$ [36, 37, 38].

2. EXPERIMENTAL SECTION

2.1. Genetic defecting and disordering. Defecting due to genetic mutations changes the cytochrome *c* oxidase function and causes dangerous metabolic irregularity which mostly appears in early childhood and destroys the tissues of the brain, heart, muscle and so on. In wide ranges of mitochondrial diseases, the compounds contain insufficient COXs assembling are the main disordering is due to mutations into nuclear-encoded proteins assembly factors. These assembling factors chip into COXs functionalities are contain several important processes such as transcription, translation of mitochondrion-encoded subunits, processing of pre-proteins, membrane insertion, and finally cofactor biosynthesis and interpolation [15, 39, and 40]. Up to now, mutations have been characterized in eight COXs assembling cofactors including COX15, COX20, COxA5, COX6c, SURF1, SCO1,

SCO2, LRPPRC, COX10. Mutations in those complexes are consequent in alternative functionalities of several COXs assembling, copper crossing and translation regulations [40, 41]. Each mutation is an associating with the etiologies of the specifics disease within some symbolization in several disorders, including anemia, sensor neural, Leigh syndromes and cardiomyopathies. [42-44].



Scheme 1: The mitochondrial electron transfer diagram

2.2. Docking analysis. The complex structures of 1hrc, 1oco, 2y69, 3s8f and 3zcf (Fig.2) predicted by the dockings simulation were computationally calculated and accredited by the experimental data of Cyt-*C* in a mutation to the C*c*O [45, 46]. The interaction energy analysis using O- Cyt-*c* structures indicated the hydrophobic and hydrophilic contributions of related amino acid to the Gibbs free energies required for the complex formations. Some of the charged residues exhibited a large unfavorable depends on non-solvation interactions that were cancelled out by large favorable columbic interaction, but resulting in the destabilization of the structures [46, 47]. The free energies of destabilizations are compensated by the van der Waals interactions contemplated by hydrophobic amino acids for giving the stabilizing complexes. Thus, a hydrophobic interaction is the basic agents that boost complexes formation among various Cyt *c* under efficiencies conditions; meanwhile, the changing in the destabilization free energies provides the difference of the binding free energies in a mutant [48, 49]. Cooperative on the reduction of oxygen, C*c*-O agents as a proton's pumping along the membrane, and the proton's gradients are the preliminary driving forces for producing ATP [46-49]. In the respiratory mechanism of mitochondria, an electron for reducing atom of oxygen is given from hemo-protein, Cyt *c* and Cyt *c* reacted from the iron in Cyt *c* to the CuA site [50]. The amino acid sequences and isoelectric points of Cyt *c* suggest many positively charged which are replaced on the protein surfaces [51]. In a part of this work, we calculated the complexes between Cyt *c* via accomplishing docking simulation. We also through a mutation of some amino acids interaction with Cyt-*c*, attempt to estimate the Michaelis constant, *K*m, for those reactions.

2.3. Computational methods. In this work, the iGEMDOCK has been applied. Through this software, the acceptable receptor can

be defined for the binding site in whole protein structures. The protein composition is worked with a ligand, and iGEMDOCK can helps to quickly define the suitable binding site. Following steps have been done in docking simulation :(a), Prepare Binding Site on the Protein Ligand. (b) Browsing and selecting the protein file. (c) Defining the binding site type as a bounded ligand. (d) Defining the center of the binding site by selected ligand. (e) Setting the size of the binding site through the extended radius from the selected ligand. IGEMDOCK yields an analysis surrounding with visualized tools and post-analysis tools for users which can be visualize the docked states, and categories through the protein-ligand interactions. Consequently, the prediction and scores of ligands can be saved in the output path. The minimum energies poses of each ligand will be outputted into the location of "best: Pose". These analysis tools are premeditated based on the analysis of those poses. Via looking for the bounded structures of some ligands, they can be select via the check box of ligand. If the co-crystallized ligands are retained on the binding site structures, it will be predicted poses. Cluster analysis is the partitioning of a data set into subsets. The data in each ideally subset will share some common trait. IGEMDOCK clusters the ligands based on interaction and atomic composition features. Interaction feature is extracted from the protein-ligand interactions and atomic composition is accounted atomic types in different functional groups. You are able to specify the number of cluster for your data or adjust the number by the preliminary clustered result. Cluster estimation is the analyzing of a data ranges into subsets. The information in each subset will share some general properties. These are based on interaction and atomic combination aspects. Interaction aspects are extracted from the protein-ligand couples and atomic combinations are calculated atomic types in various functional groups [52-55].

2.4. Gene mutation. Based on Mootha *et al* works [65], Genotyping of the exon 35 mutation has been simulated for clearing the mechanism of mutation in Cyt *c*, Fig.3. Mootha *et al* exhibited a mutation which was performed by primer extension of PCR and then detected by matrix assisted laser desorption ionization. PCR 5-AGCGGATAACTCAGAAACCT TCACTTACTG-3 and 5-AGCGGATAACGGAACA ACAACAAAATCGGG-3 and homogeneous Mass Extend (5-AATAATGTTTTAATTTTTAGAGAT3 primers were designed by using Spect- Designer. PCR products were purified by using the shrimp alkaline phosphatase method and extended by the addition of a homogeneous Mass-Extend primer as per the Sequencer- Mass-Array protocol. Each coordinate of genes are defined by its expression vector in an mRNA microarray experiment. Genes are close to one another if they have similar expression profiles. We investigated our model with a wide range of megabase region of that genome containing several definite genes and some other unknown genes through translation and expression data of m- RNA and the results is confirmed with experimental data. As improvement genes with higher-density m-RNA expression and more comprehensive protein-membrane interaction become available, it should be able for applying such analysis widely.

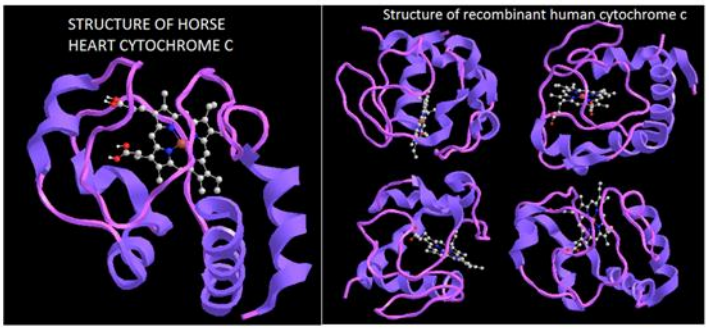


Fig. 1: Optimized structure of horse heart and recombinant human cytochrome C

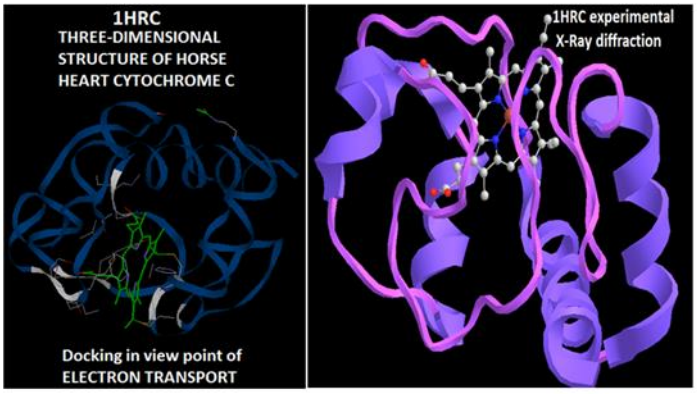


Fig. 2: Three dimensional structures of horse heart ctC and X-ray diffraction

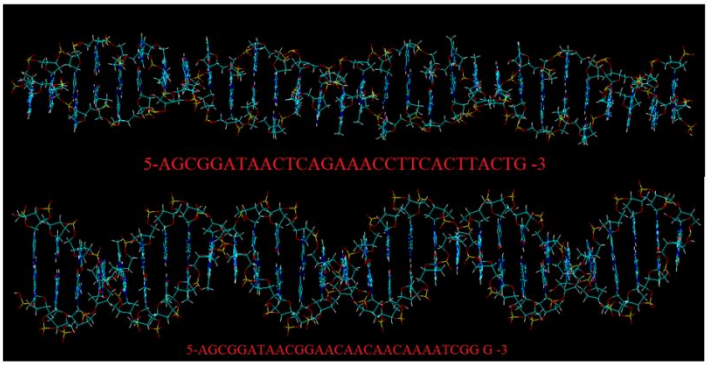


Fig. 3: The 5-AGCGGATAACTCAGAAACCT TCACTTACTG-3 and 5-AGCGGATAACGGAACA ACAACAAAATCGGG-3 sequences optimized for investigation a condition of mutant gene

3. RESULTS SECTION

In this study the advanced-assembly modification, COXs has been produced a homo-dimer which is required for any further activities. These dimers are connected via 1, 3-bis (*sn*-3'-phosphatidyl)-*sn*-glycerol molecule as the name Cardiolipin, [6, 13, 14], which plays as a catalyst for stabilizing the halo-enzymes. Cardiolipin groups are an important molecule in the inner mitochondrial membrane, which can also be found in the membranes of most bacteria and is essential for the optimal function of several enzymes that are involved in mitochondrial energies metabolisms Fig. 4. The NMR Calculation for this molecule indicates the behavior of this molecule as a catalyst. It has also been shown that the halogenated of this molecule

increases the efficiency of its behavior as the catalyst for stabilizing enzymes. It has been shown that with substitution three fluorine, Chlorine, bromine and iodine the yields of catalysts are F_3- Cardiolipin> Cl_3- Cardiolipin> Br_3- Cardiolipin> I_3- Cardiolipin, respectively (Fig. 4).

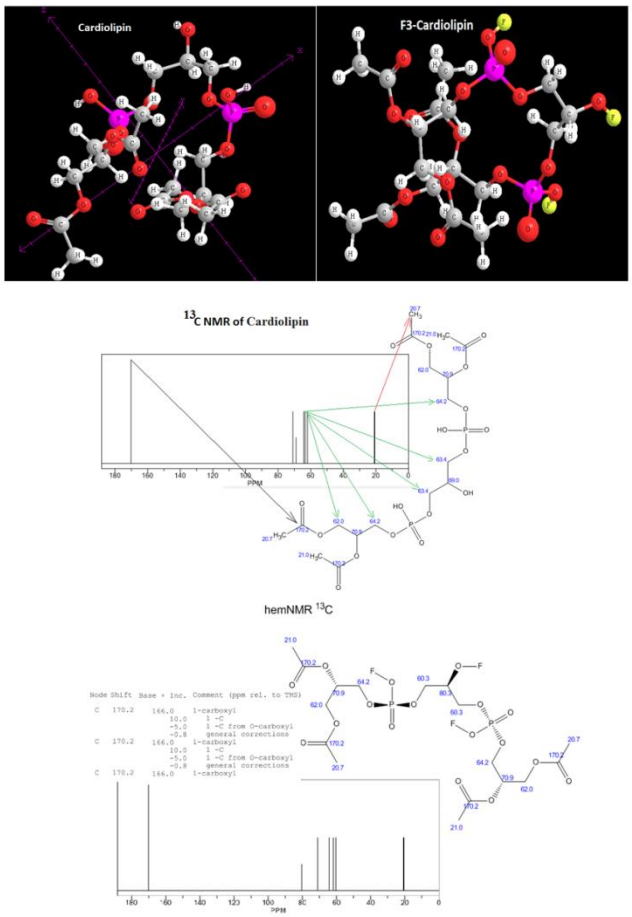


Fig. 4: Cardiolipin and F3-Cardiolipin, optimized and NMR shielding data as important

Table 1: conserved subunits of cytochrome c oxidase complex [7, 8]

Subunit (Human Protein)	Protein description	Family protein(p-fam)
Cox3, subunit 3	Cytochrome c oxidase	*P-fam PF00510*
Cox2, subunit 2	Cytochrome c oxidase	*P-fam PF02790, P-amPF00116*
Cox1, subunit 1	Cytochrome c oxidase	*P-fam PF00115*
Cox5b, subunit 5B	Cytochrome c oxidase, mitochondrial	*P-fam PF01215*
Cox4a2 subunit 4	Cytochrome c oxidase ,isoform 2, mitochondrial	*P-fam PF02936*
Cox4i1, subunit 4	Cytochrome c oxidase, isoform 1, mitochondrial	*P-fam PF02936*
Cox5a, subunit 5A	Cytochrome c oxidase, mitochondrial	*P-fam PF02284*
Cox6a1, subunit 6A1	Cytochrome c oxidase, mitochondrial	*P-fam PF02046*
Cox6b1, subunit 6B1	Cytochrome c oxidase	*P-fam PF02297*
Cox6c, subunit 6C	Cytochrome c oxidase	*P-fam PF02937*
Cox6a2, subunit 6A2	Cytochrome c oxidase, mitochondrial	*P-fam PF02046*
Cox6b2, subunit 6B2	Cytochrome c oxidase	*P-fam PF02297*
Cox7a1, subunit 7A1	Cytochrome c oxidase, mitochondrial	*P-fam PF02238*
Cox7a2, subunit 7A2	Cytochrome c oxidase, mitochondrial	*P-fam PF02238*
Cox7a3, subunit 7A3	Putative cytochrome c oxidase, mitochondrial	*P-fam PF02238*
Cox7b, subunit 7B	Cytochrome c oxidase, mitochondrial	*P-fam PF05392*
Cox7c, subunit 7C	Cytochrome c oxidase, mitochondrial	*P-fam PF02935*
Cox7r, subunit7A	Cytochrome c oxidase, related protein, mitochondrial	*P-fam PF02238*
Cox8c, subunit 8C	Cytochrome c oxidase, mitochondrial	*P-fam PF02285*
Cox8a, subunit 8A	Cytochrome c oxidase, mitochondrial P	*P-fam PF02285*

In this work the Simulation of protein cytochrome C with interacting inside the lipid bilayers membrane has been done. Although, precise structures of the bilayers which are in biological pertaining fluid phases are not possible for getting experimental data, fluctuations of those kinds of bilayers indicate correct structures. Molecular mechanics & Molecular dynamic modeling are strong tools for clearing and guiding the interpretation of those experimental sections. The credit of simulation, in other words, might be measured against existing experimental results. The absence of experimental data and results are reversed in molecular modeling of lipid membranes, due to several force fields parameterization. Tight level AB-initio estimation is needed for definition and parameterization of those force fields and presently allows evaluation of the heavy atoms for gaining accurate results. Moreover, there are some limitations in weak QM calculations due to London's dispersion of non-bonded interactions for such molecules. We simulated our model based on our previous works [56-71]. The anisotropy parameter of the standard parameters, for the shielding and non-shielding space of the hetero rings in all antibiotics, (σ_{11}, σ_{22}, σ_{33}), are labeled according to the IUPAC instruction. Therefore, σ_{33} indicates the direction of minimum shielding, with the highest frequency, while σ_{11} indicates to the direction of maximum shielding, with the lowest frequency.

In addition, the orientations of the asymmetry tensors are given by $(\kappa = \frac{3a}{\Omega})$ *and the skew is* $\kappa = \frac{3(\sigma_{1so}-\sigma_{22})}{\Omega}$; (-1 ≤ κ ≤+1).

Conserved subunits of cytochrome c oxidase complex and Assembly subunits of cytochrome c oxidase complex are listed in tables 1 and 2 which are categorized in a suitable form for each of mechanism reaction. Docking method is suitable for sorting out various numbers of proper complexes through their energies grade. Therefore, docking must be refined by extra criterion due to single structure near the native structures and among different complexes, in tables 1 and 2 we have choose those complexes with the highest energy grads for any further calculations and analysis. The best complexes are included of the protein-membrane interaction consist of hydrophobic segments this information confirms the experimental data that those compounds play a main role in the reaction and produce of the complexes (Fig. 5). We simulated the lipid bilayers with the interaction of ba3 cytochrome c oxidase from thermos thermophiles in DPPC and DMPC phosphor lipids (Fig.6 & Fig. 7). Although, precise structure of a bilayer that is in the biological pertaining fluid phase is not able for obtaining experimental data, fluctuation of this kind of bilayer indicates correct structure. Molecular modeling is a strong tool for guiding the interpretation of the experimental section.

Table 2: Assembly subunits of cytochrome c oxidase complex [9-12]

Subunit (Human Protein)	Protein description	Family, protein(p-fam)
Coa1, factor 1 homolog	Cytochrome c oxidase assembly	*P-fam: PF08695*
Coa3, factor 3 homolog	Cytochrome c oxidase assembly, mitochondrial	*P-fam: PF09813*
Coa4, factor 4 homolog	Cytochrome c oxidase assembly, mitochondrial	*P-fam: PF06747*
Coa5, factor 5	Cytochrome c oxidase assembly	*P-fam: PF10203*
Coa6, factor 6 homolog	Cytochrome c oxidase assembly	*P-fam: PF02297*
Coa7, factor 7	Cytochrome c oxidase assembly	*P-fam: PF08238*
Cox11, protein COX11	Cytochrome c oxidase assembly, mitochondrial	*P-fam: PF04442*
Cox14, protein COX14	Cytochrome c oxidase assembly, protein	*P-fam: PF14880*
Cox15, COX15 homolog	Cytochrome c oxidase assembly, protein	*P-fam: PF02628*
Cox16, COX16 homolog	Cytochrome c oxidase assembly, protein, mitochondrial	*P-fam: PF14138*
Cox17, protein COX17	Cytochrome c oxidase copper chaperone	*P-fam: PF05051*
Cox18[12], protein COX18	Mitochondrial inner membrane protein, Cytochrome c oxidase assembly	*P-fam: PF02096*
Cox19, protein COX19	Cytochrome c oxidase assembly	*P-fam: PF06747*
Cox20, protein 20 homolog	Cytochrome c oxidase	*P-fam: PF12597*

The credit of simulation, in other words, might be measured against existing experimental results. There are various techniques such as docking that can give certain results of physical properties such as membrane electrostatics area per lipid, membrane thickness and acyl parameters. The absence of experimental data is reversed in molecular modeling of lipid membranes, due to force field parameterization.

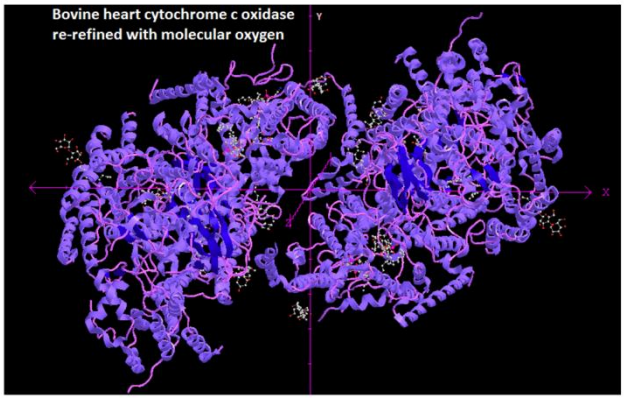


Fig. 5: Docking of single structure near the native structures and among different complexes

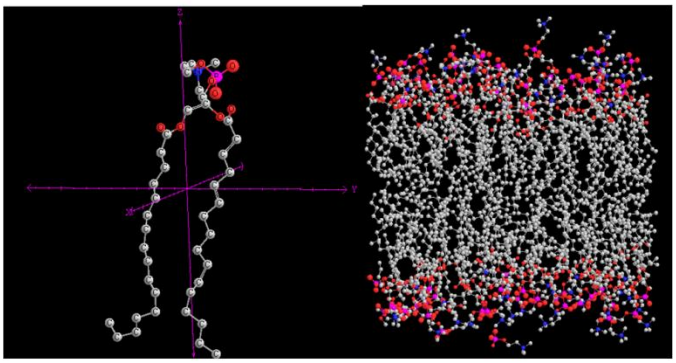


Fig. 6: Optimized of DPPC and membrane simulation including 120 molecules of DPPC phospholipids

Tight level ab-initio estimation which is needed for definition and parameterization of force fields, presently allows evaluation of those heavy atoms for gaining accurate results. Moreover, there is a limitation in weak QM calculation due to London's dispersion of non-bonded interaction for molecules.

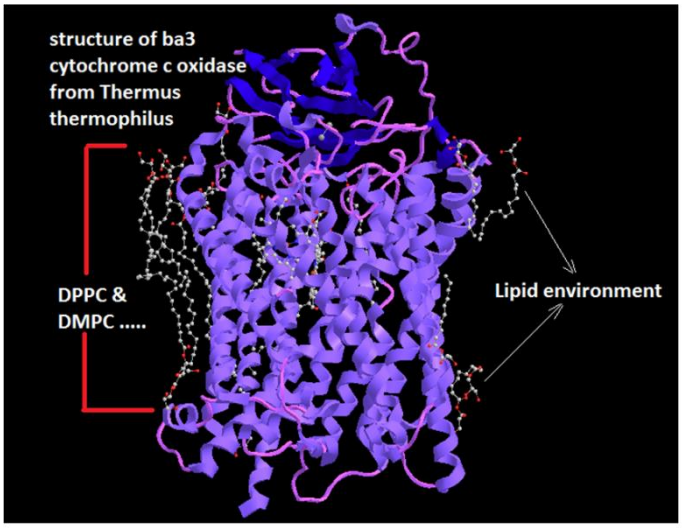


Fig. 7: Structure of ba3 cytochrome c oxidase from thermos thermophiles in DPPC and DMPC

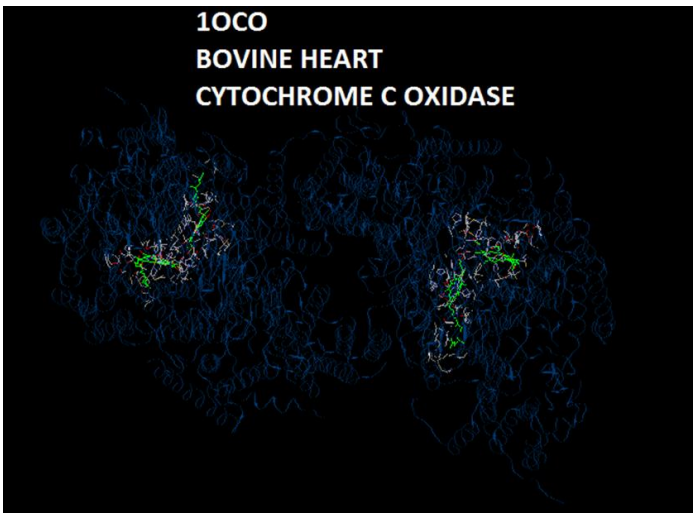


Fig. 8: Simulated form of bovine heart cytochrome c oxidase

4. CONCLUSIONS

The Docking methods have allowed researchers to draw out a suitable complex between various cytochrome C oxidase whose transient character makes difficult an experimental investigation. In this work, it has been exhibited that the halogenated of cardiolipin increase the efficiency of its behavior as the catalyst for stabilizing enzymes. It has been shown that with substitution three fluorine, Chlorine, bromine and iodine the yields of catalysts are F_3- Cardiolipin> Cl_3- Cardiolipin> Br_3- Cardiolipin> I_3- Cardiolipin, respectively.

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