EUROPEAN ACADEMIC RESEARCH
Vol. X, Issue 4/ July 2022

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Molecular docking interactions of macrostructural complexes of infectious agents with the transmembrane angiotensin-converting enzyme 2 (ACE2)

SIMONE LOPES DE MATOS
Federal University of Pará (UFPA)
Post-Graduate Program in Engineering of Natural Resources of the Amazon, ITEC, UFPA, Belem, PA, Brazil
TIAGO DA SILVA AROUCHE
Federal University of Pará, Belém, PA, Brazil
WILSON LUNA MACHADO ALENCAR
Federal Institute of Pará (IFPA), Castanhal, PA, Brazil
RUBENS DE OLIVEIRA MEIRELES
Federal Institute of Pará (IFPA), Castanhal, PA, Brazil
CARMEN GILDA BARROSO TAVARES DIAS
Federal University of Pará, Department of Mechanical Engineering
Graduate Program in Mechanical Engineering
Belém, PA, Brazil

Abstract

Protein binding sites undergo minor conformational changes when an interaction occurs. In protein-binding pockets, this is a common occurrence. Most conformal changes occur at the interface between the two binding proteins. Therefore, many methods attempt to predict the side-chain conformational changes for a given structure in the interaction area. There are several possibilities for molecular protein-protein interactions.Molecular analysis studies are relevant to unravel studies on the transmembrane Angiotensin 2 Converting Enzyme, an enzymatic agent with pharmacological perspectives that indicates the mechanisms of action of viruses and bacteria. The goal of this work was to use the three-dimensional coordinates of two independent crystallized proteins that are known to interact and derive a model for the bound structure. The resulting output of these coupling algorithms is typically some quasi-native structures nested in a multitude of false-positive structures that also have favorable surface complementarity. Using the ClusPro server, we quickly filter the output results and perform analysis on your electrostatic, balancing, and van der Waals energy values. This approach resulted in several structures from which we could draw results to predict interactions, and we used a docking approach of different conformations that were active to avoid searching the entire or flexible conformational space of two proteins during the docking process.

Keywords: Interaction, Protein-Protein, Docking, Energy, Protein.

1. INTRODUCTION

Decades of research in cell biology, molecular biology, biochemistry, structural biology, and biophysics have resulted in a vast repository of information about the function and molecular characteristics of individual proteins. Large protein databases such as the Protein Data Bank [1] have this knowledge carefully recorded. A mechanism of action [2] usually includes mention of a specific molecular target to which the drug binds, such as an enzyme or receptor. However, proteins infrequently function alone, often forming molecular devices [3] with complex dynamic physicochemical bonds to perform biological functions at the cellular and systemic levels. Mapping physical protein-protein interactions is a crucial step in deciphering the complex molecular bonds in biological systems.

Viruses show enormous diversity in genetic makeup, evolutionary patterns as a function of proteins and in comparison, with the processes found in cellular organisms. When studying protein-protein interactions (PPI's) [4-5] in virus-host systems, these variations on the pathogen side must be considered. Protein recognition events can occur as stable or transient interactions, and some proteins can establish multiple interactions [6].

PPIs are necessary for cells of all living species and larger biological systems to function properly. X-ray crystallography is the gold standard for validating and understanding such structures. [7] However, protein complexes can be difficult to crystallize, and the number of PPIs discovered considerably exceeds the number of complex structures. Protein-protein interaction is a computational method that can fill this gap by revealing atomic-level details of the interactions of two proteins. Molecular docking (MD) can produce models that can be verified using basic procedures such as cross-linking or site-directed mutations. The adoption of a fast Fourier transform (FFT) [8] for energy assessment is widely recognized as one of the most important advances in protein-protein coupling.

This manuscript aims to study protein interactions between external proteins of infectious agents such as influenza (PDB ID: 2VIR) [9], parainfluenza (PDB ID: 4WEF) [10], Spike protein from the Omicron variant of Sars-Cov-2 (PDB ID: 7QO7) [11] and Mycobacterium tuberculosis (PDB ID: 7NAA) [12] complex human nasal receptor protein to transmembrane angiotensin converting enzyme 2 (ACE2) (PDB ID: 7U0N) [13]as can be seen in figure 1. Protein domains are basic units that define protein interactions, and the uniqueness of viral domain repertoires, their mode of evolution and their roles during viral infection make viruses interesting models to study. Mutations at protein interfaces can reduce or increase their binding affinities, altering the protein's electrostatic and structural properties during an infection [14].

The scoring procedures of most MD software incorporate structure-based energy expressions to account for energy contributions. In the present manuscript, the ClusPro server [15] was used, which uses the DARS potential [16] based on decoys as the reference state. The conformational change in complex formation and the type of proteins in the target (antibody, enzyme or "other") are the two aspects in which we assess performance. As expected, more rigid complexes produce better results than complexes with considerable conformational changes between unbound and bound

states. We explain the results provided by the ClusPro server, which makes rigid-body MD, also derive broad generalizations.

2. MATERIALS AND METHODS

2.1 Ligand Structures

2.1.1 Influenza Virus Hemagglutinin (HVI)

The structure of the hemagglutinin (HA) [17] of a mutant influenza virus that escapes neutralization by a monoclonal antibody reveals that the mutation induces changes in the structure of HA that prevent a less energetically advantageous conformation. Hemagglutinin (HA) is a glycoprotein found in the envelope, the outermost covering of the virus. It identifies sialic acid [18], a sugar found in our cell membrane, and is crucial for identifying and binding the virus to our respiratory cells. One of the first tests created to diagnose the virus was its ability to recognize and attach to cells, as well as agglutinate red blood cells (red blood cells). More than 15 types of HA have been identified, with H1, H2 and H3 being the most frequent among the viruses that infect people [19].

The basic mechanism of the pathophysiology of influenza is lung inflammation and the impairment produced by direct viral infection of the respiratory epithelium [20], mixed with the impact of lung inflammation generated by immune responses mobilized to combat the spread of the virus.

2.1.2 Structure of human parainfluenza virus hemagglutinin-neuraminidase III (HNPH)

Hemagglutinin is the protein responsible for the adhesion of the virus and its first contact with the cell, while neuraminidase causes the virus to penetrate and replicate in the cell [21]. Human viruses belong to the Paramyxoviridae viral family, hPIV1-3 [22], as well as avian Newcastle disease virus, cause acute respiratory infections in young children, the elderly and, the immunocompromised [23]. Hemagglutinin neuraminidase (HN) [24] and the fusion protein are two membrane glycoproteins found in these viruses. HN has a variety of activities, including receptor binding, cleavage of sialic acid, accelerating the release and propagation of the virus, and interacting with the protein to promote membrane fusion. NA inhibitors such as zanamivir, which targets influenza virus NA, and 2-deoxy-2,3-dehdihydroacetyl neuraminic acid (DANA) [25] may not only disrupt the function catalytic activity of HN, bt also interfere with receptor binding.

HN catalysis involves the creation of a covalently connected sialosyl-enzyme intermediate that has been trapped together with an oxocarbene ion-like transition state analog, [26] according to the crystal structure of hPIV3 HN complexed with the acidic substrate analogdifluoro sialic acid (DFSA). The crystal structure of influenza N9 neuraminidase complexed with DFSA confirmed this mechanism of enzymatic catalysis [27]. In addition, new secondary receptor binding sites in the hPIV3 HN-DFSA complex [28] were discovered, including one near the catalytic cavity that imposes minor modifications on DFSA binding and may help HN balance opposing activities. Multiple receptor binding sites can increase avidity, facilitating cell binding and fusion.

2.1.3 SARS-CoV-2 S Omicron Spike (SCv2-OS)

The Spike(S) protein of SARS-CoV-2 is vital for mediating entry into host cells and is the main target of neutralizing antibodies [29], the structure of the S protein is an essential feature of any variety, and understanding this structure helps us to better understand the Omicron variant [29]. The SARS-CoV-2 S protein is vital for mediating entry into host cells and is the main target of neutralizing antibodies The structure of the S protein is an essential feature.

Due to the huge number of changes contained in its genome and the lack of knowledge about how these mutations will affect current SARS-CoV-2 vaccines and therapies, the emergence of the latest variant of SARS-CoV-2, Omicron, is of particular concern. [30-31]. We found that the Omicron S protein has the greatest evolutionary distance from the other SARS-CoV-2 variants. Many amino acids in the RBD have indeed been altered, which may affect RBD-ACE2 interactions [32], as well as proving that the S309 antibody can still neutralize this RBD variant. The Omicron S1 NTD structures differ significantly from the original strain, [33] which may contribute to lower antibody recognition, immune escape, and decreased vaccine efficacy. However, this investigation of the Omicron variant was mainly focused on structural predictions, which should be further investigated and verified in future tests. This research provided essential data on the structures of this protein, laying the groundwork for future research on the SARS-CoV-2 Omicron variant.

2.1.4 Crystal structure of Mycobacterium Tuberculosis (MT)

Effector proteins are returned to their initial state by the reverse reaction, ready to trigger a new signaling event [34-35]. Kinases and phosphatases function as molecular switches that modulate certain signal transduction pathways in this way. As a result, serine/threonine protein kinases (STPKs) [36-37] are an essential environmental sensing mechanism in bacteria as they can alter the biological activity of proteins as well as improve their ability to bind to other proteins via of phosphorylation-dependent interactions. There are eleven STPKs in MT [38], the causative agent of tuberculosis, which play a vital role in physiology and pathogenesis, operating on hundreds of substrates involved in all biological activities of the bacterium [39]. The fact that these genes have survived evolution and that at least eight members of this family are upregulated after MT infection demonstrates their importance in pathogenesis. MT has the ability to evade a variety of cellular defense systems, including responses to oxidative stress, suppression of phagosome-lysosome fusion, and alterations in host macrophage cell death mechanisms, all of which are critical for its infectivity and spread [40], and antibiotic extrusion. Four MT proteins with FHA domains are involved in processes linked to cell wall synthesis or remodeling.

Tuberculosis drugs target several aspects of TM biology, including inhibition of cell wall synthesis, protein synthesis, or nucleic acid synthesis. For some drugs, the mechanisms of action have not been fully identified [41]. Tuberculosis drugs target several aspects of TM biology, including inhibition of cell wall synthesis, protein synthesis, or nucleic acid synthesis. For some drugs, the mechanisms of action have not been fully identified.In figures 2 and 3 one can see the proteins used in the docking study, their 3D structures minimized using UCSF Chimera and then subjected to docking studies.

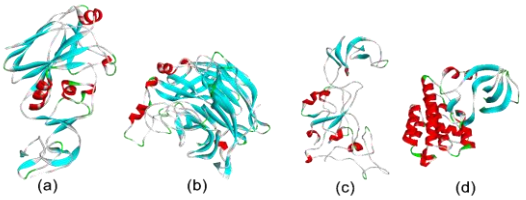


Figure 1: Structures used as ligands (a) HVI, (b) HNPH, (c) SCv2-OS, and (d) MT

2.2 ACE2 human respiratory tract receptor structure (ACE2H)

The receptor for SARS-CoV-2 attachment and entry, transmembrane angiotensin-converting enzyme 2 (ACE2), [42-43] has been identified as a prospective research pathway. As a result, several researchers began to investigate the involvement of ACE2 in the etiology of COVID-19[44-45]. Human angiotensin-converting enzyme 2 (ACE2) and its receptor play a critical role in SARS-CoV-2 tissue tropism. The increased binding of ACE2 can facilitate the infection of the human body by viruses that attack the respiratory tract, where the level of ACE2 expression is high, the shape of the enzyme can be seen in figure 2.

The entry of the new coronavirus (SARS-CoV-2) into cells occurs through the binding of the S protein to angiotensin-converting enzyme 2 (ACE2) receptors [46-47], which are on their surface. Olfactory neurons do not have these receptors, which is not the case for support cells, which have many [48-49]. These cells maintain a delicate ionic balance in the mucus that neurons depend on to send signals to the brain. If this balance is disrupted, neuronal signaling can be disrupted, and consequently, the sense of smell. Support cells also provide necessary physical and metabolic support to the cilia of olfactory neurons, where the receptors that detect odors are concentrated. Damage to these cilia leads to loss of smell [50-51].

There are several pharmacological possibilities in the testing phases. There is relevance in unveiling studiesAngiotensin-Converting Enzyme 2 (ACE2) and Transmembrane Protease, serine 2 (TMPRSS2) [52-53] in SARS-CoV-2, enzymatic targets with pharmacological perspectives for the treatment of COVID-19.

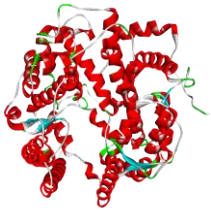


Figure 2: ACE2 Human Structure

The PDB (https://www.rcsb.org) was used to retrieve the 3D macrostructures. All simulations were based on the protein + protein model [54-55], in which five structures were chosen and optimized using the Chimera 1.15.6 (CHM) software [56-57] to find the ideal conditions that satisfied several predefined targets; tasks that require experimentation or computational calculations add to the complexity. We employ CHM

as a multi-target scalar realization function [58-59-60], where evaluations are the limiting factor, and its performance has been thoroughly established using various single-purpose optimization algorithms. The findings show that CHM can swiftly locate a wide range of optimization strategies. In this case, we employ the AMBERFF14SB force field [61-62] to find the structure with the optimum conformation under ideal conditions.

2.3 ClusPro Interaction Protocol

All necessary parameters were specified using the ClusPro platform (https://cluspro.org) [63-64-65-66]. The ClusPro server is a widely used tool for protein-protein MD. It also offers several advanced options to modify the search; these include removing unstructured protein regions, applying attraction or repulsion, accounting for pairwise distance constraints, constructing homomultimers [67], considering small-angle X-ray scattering data, and locating binding sites. Four different energy functions can be used, depending on the type of protein. Coupling with each set of energy parameters results in ten models defined by centers of highly populated clusters of low-energy anchored structures. This protocol describes the use of the various options, the construction of auxiliary constraint files, the selection of energy parameters and the analysis of the results, the equations for the calculations of Energy Balancing eq.1[68], Energies, favorable electrostatics eq .2[69], favorable hydrophobic eq.3[70] and Van der Waals + Electrostatic eq.4[71].

$$E = 0.40E_{rep} + -0.40E_{att} + 600E_{elec} + 1.00E_{DARS} \quad (1)$$

$$E = 0.40E_{rep} + -0.40E_{att} + 1200E_{elec} + 1.00E_{DARS} \quad (2)$$

$$E = 0.40E_{rep} + -0.40E_{att} + 600E_{elec} + 2.00E_{DARS} \quad (3)$$

$$E = 0.40E_{rep} + -0.10E_{att} + 600E_{elec} + 0.00E_{DARS} \quad (4)$$

The goal is to use the three-dimensional coordinates of two independent crystallized proteins that are known to interact and derive a model for the bound structure. The resulting output from these coupling algorithms is typical to some quasi-native structures nested in a multitude of false-positive structures that also have favorable surface complementarity. In ClusPro, we quickly filter the output of the Fourier correlation algorithm using a combination of desolation and electrostatic energies (calculated using a Coulomb potential). This approach results in several quasi-native structures passing through the filter, eliminating many of the false positives.

We used the ClusPro algorithm, and with it we had the option of selecting DOT or ZDOCK [73-74] to perform the rigid body coupling, both based on fast Fourier transform (FFT) correlation techniques [75]. Although the DOT allows the use of electrostatic potential in the scoring function, we based the scoring only on the superficial complementarity between the two structures. DOT runs on a grid of 113 Å × 109 Å × 101 Å, using a grid spacing of 0.1 Å. Using the predefined list of 13,000 rotations, more than 2.7 × 1010 structures are evaluated, keeping 20,000 structures with the best results for comparison in terms of surface interaction [76-77]. Fragment-

to-frame coupling: Each of the fragments is docked to the receiving frame using an FFT-based sampling protocol. The top 250 [78] results from each simulation are combined into a group. In the output of results, there is the selection of models, which aims at the set of models grouped using a cluster radius of 3.5 Å, which was chosen because it represents the best resolution of attraction, and then a file in pdb format is generated, and the resulting final results are sorted according to the lowest energy worked, thus generating the output in PDB format and tables.

3. RESULTS AND DISCUSSIONS

3.1 Docking protein-protein

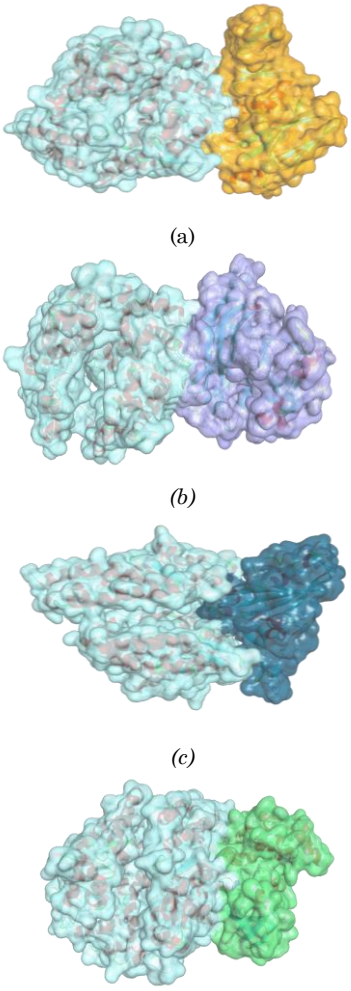
The problem of protein-protein coupling differs substantially from the coupling of small protein ligands. In protein-ligand interactions, the binding pocket of the target is generally known and, due to the restricted nature of the problem and the small size of the ligand, the flexibility of the latter can usually be considered. In contrast, the protein-protein coupling site at the interaction site is rarely available and, in most cases, it is necessary to explore all possible interactions, generating and evaluating billions of putative conformations of the complex. Because of this huge search space, protein-protein coupling often starts with the hard-body search, using simplified protein models and simplified energy functions.

The use of rigid protein models requires tolerance of some levels of overlap and, as the energy functions are approximate, structures close to the native conformation do not necessarily have the lowest energies. Thus, to avoid the loss of potentially useful conformations, it is necessary to retain a large number (generally 2000 to 20,000) [79-80] of low-energy anchored structures for further processing. Thus, the initial coupling produces a long list of candidate structures rather than a small number of models, and obtaining meaningful results requires some form of post-processing, which includes refinement of the anchored conformations, usually representing some level of flexibility.

In the docking methodology is the notion of steric complementarity at the protein-protein interface [81]. These interfaces are compacted, as seen in co-crystallized complexes in the Protein Data Bank. Complementarity has been the main driving force in the development of docking approaches, as can be seen in Figure 3, often with the addition of physicochemical, hydrophobic, and electrostatic complementarity. Structural complementarity has been observed at different resolutions, from atomic to ultra-low. The structure of protein-protein complexes using docking approaches has challenges that include identifying correct solutions and adequately dealing with molecular flexibility and conformational changes.

Rigid-body docking involves six degrees of freedom of the two rigid-body systems (three translations and three rotations in Cartesian coordinates). Flexible fitting [82] involves a much larger number of coordinates, given the conformational search in the internal coordinates of proteins. However, this research typically does not involve solving the protein folding problem but may be restricted to a much more tractable binding-to-binding conformational transition. In protein-protein docking, the similarity between proteins in complexes can be assessed by comparing/aligning sequences, sequences, and structures, or just the structures, as the structures of the

protein to be nested are considered known by the nesting definition itself.The MD is an effective and competent tool for in silico screening. It is playing an important and growing role in rational drug design. Docking is a computational procedure to search for an appropriate ligand that fits energetically and geometrically to the binding site of the protein. In other words, it is a study of how two or more molecules,ligand and protein fit together. Protein-protein docking refers to the search for the precise conformations within a target protein when the structure of the proteins is known, the active site of ACE2H, has linked with the structures in its side chain as shown in Figure 3, where there may be greater interaction affinity.



(a)

(b)

(c)

(d)

Figure 3: Blue structure of the complex with ACE2 coupled a) HVI, b) HNPH, c) SCv2-OS, d) MT

Molecular coupling done in ClusPro created model structures for analysis, even when faced with challenges such as side chain movement and uncertain monomer structures. The ClusPro algorithm was able to well define interactions that aimed to fit large and flexible proteins, classify models consistently, and produce models accurate enough to allow computational design of higher affinities or specificities.The form of contact indicated by the positions may imply that it has a great capacity for interaction, based on the average of the distances of interatomic interactions and the data provided in Table 1. The reliability of the predicted complex was evaluated using HVI and SCv2-OS, which had the lowest relative distance from the estimated ACE2 affinity, and the fit was able to establish a promising shape. The sites that proteins take allow them to interact with the amino acids that are present. Each position can lead to connections with different amino acids in the area. The stronger the connections between protein molecules and amino acids, the better the binding energies.

Table 1: Average of interaction distances in MD

Macrostructure	Distance (Å)
HI	2.9291
HNPH	3.0005
SCv2-OS	2.9264
MT	3.1351

Tables 2 and 3 show that in the molecular docking of ACE2 with the four proteins, the interactions were restricted to amino acids. In table 3 we can see the formation of hydrophobic bonds in proteins which arise as a consequence of the interaction of their hydrophobic amino acids (ie "they don't like water") with the polar solvent, water. Ionic or electrostatic bonds are formed when amino acid atoms with opposite electrical charges are juxtaposed. Ionic bonds can be important for protein structure because they are potent electrostatic attractions. In the hydrophobic interior of proteins, ionic bonds can approximate the strength of covalent bonds. Hydrophobic Amino Acids Conventional Hydrogen Bond which is a hydrogen bond (or H bond) is a primarily electrostatic force of attraction between a hydrogen (H) atom that is covalently bonded to a more electronegative atom or group, and another electronegative atom that charges a lone pair of electrons – the acceptor of the hydrogen bond (Ac), Salt Bridge; Attractive Charge defined as Salt bridges in proteins are bonds between oppositely charged residues that are sufficiently close together to experience electrostatic attraction, Carbon Hydrogen Bond, the carbon-hydrogen bond is a chemical bond between carbon and hydrogen atoms that can be found in organic compounds.

This bond is a single covalent bond, which means that carbon shares its outer valence electrons with up to four hydrogens. Sulfur-X, Sulfur-X Interactions Sulfur-X interactions are found between divalent sulfur and N, O, or S atoms, Pi-Cation, Pi-Anion, the presence of the cation and anion on opposite sides of the cloud of π electrons of benzene leads to a strongly polarized reorganization of the π electron density. This brings the anion closer to the π system and therefore leads to an improved binding energy gain. Pi-Donor Hydrogen Bond, the negatively charged hydrogen atom may also play a role in the proton acceptor. In this case, the so-called dihydrogen bond is formed, Pi-Pi Stacked, Alkyl, Pi-Alkyl. These Pi-Alkyl, Pi-Pi T, and Pi-Sulfur interactions come

under the broad category of non-covalent interactions. In pi-alkyl interactions there in the s interaction ofpi-electron cloud over an aromatic group and an electron group of any alkyl group. In the pi-pi T-shaped interaction, there is an interaction of T-pi-electron cloud between two aromatic groups, but in the form of a T, i.e., side electron cloud of 1 ring and head in the electron cloud of the other ring.

The aromatic ring's pi-electron cloud interacts with the sulfur atom's lone pair electron cloud in the pi-sulfur interaction. The binding energies are substantial in the non-covalent molecular interaction between the face of an electron-rich system, with the solution phase values falling in the same order of magnitude as the bonds. Cation-interactions, like these other non-covalent connections, are crucial in nature, especially in protein structure, molecular recognition, and enzymatic catalysis. The center portion of this ligand, like the preceding ones, obtained intramolecular interactions with higher favorable energy values. This is since these groups adapt better to the protein's active site, making interaction with the amino acids easier.

Table 2: Types of interaction in MD

Interaction Type	Number of Interactions			
	HVI	HNPH	SCv2-OS	MT
Conventional Hydrogen Bond	306	482	244	279
Salt Bridge;Attractive Charge	16	29	22	25
Carbon Hydrogen Bond	44	65	26	38
Sulfur-X	1	2	0	1
Pi-Cation	1	3	2	3
Pi-Anion	0	5	1	3
Pi-Donor Hydrogen Bond	2	6	0	3
Pi-Sigma	11	15	7	4
Pi-Sulfur	4	1	1	3
Pi-Pi Stacked	1	3	4	3
Pi-Pi T-shaped	5	4	3	6
Amide-Pi Stacked	5	4	2	7
Alkyl	59	125	43	82
Pi-Alkyl	35	69	49	57

Table 3: MD Bond Categories

Bond Category	Number of Interactions			
	HVI	HNPH	SCv2-OS	MT
Hydrogen Bond	352	553	268	318
Hydrogen Bond;Electrostatic	16	29	23	25
Other	5	3	1	5
Hydrophobic	116	220	107	157
Electrostatic	15	29	18	34

3.2 Energy Analyze

To analyze the docking results in table 4, the interaction of ACE2 with HNPH and SCv2-OS acquired the optimal states with lower energy and will possibly occur with a greater probability than those with higher energy. on a system. We believe that taking the standard average of binding scores or selecting the best binding score is a more sensible approach. The one with the biggest volume, which contains the binder's conformation, was chosen for consideration out of the four predicted lateral cavities.

The best poses were chosen for each snap utilizing ClusPro functions based on their re-rating ratings.

The goal of protein-protein docking was to anticipate the structure of a protein-protein complex based on its unbound components. Because of the critical role of S-pro in the infection process following viral contact, this structural component could be a target for antibody or small chemical neutralization, and the analysis of the pre-fusion S structure provided significant information. to influence the design and development of inhibitory agents at the atomic level.

The HNPH active site required amino acids were compared to those previously reported before the MD investigation to ensure that the correct binding pocket was chosen. The MD results suggested interactions with the so-called active site Glycoprotein, which has a better possibility of binding related to the molecular targets in question, considering the linkages that this protein facilitated.According to the distances of interatomic connections and the docking data, the way of contact indicated by the positions may infer that it has a great capacity for interaction. MD was able to find a promising conformation after HVI obtained a significant number of bonds, such as hydrogen, the primary molecular bond interactions, and the computed affinity energy were used to assess the dependability of the projected complex.

Another thing to keep in mind is that the SCv2-OS catalytic site possesses hydrophobic properties, as seen in table 3. A full description of the and hydrogen bonds agrees with the coupling study, and it was discovered that there is bond affinity, which could indicate that this form of interaction has some influence on the affinity energy. The creation of hydrogen bonds has been observed in practically all interactions. They can therefore relate that such interactions with macromolecular structures contributed to the establishment of better associations, examining the electronegativity differences between atoms, because the bonds are relatively close and have appealing and hydrophobic qualities. The ligands' locations in the active site allow them to interact with the amino acids present.Each position taken can lead to associations with different local amino acids. The better the binding energies, the stronger the interactions that occur between protein molecules and amino acids.

After processing the coupled structures, the dynamic behavior of selected MT compounds is examined for low energy profiles, as well as the bonding dependability of the compound within the flexible binding pocket. Using surface area energy, solvation energy, and energy minimization of the ligand and receptor complexes, the ClusPro technique produced the most feasible structures. As the ACE2 side-chain interaction reaches bigger surfaces in comparison to others, the binding energy value can be decomposed per residue, as shown in Table 4.

The goal of examining the fluctuation in van der Waals energy (vdW) for these interactions was to learn more about the complexes' structural features. As a result, vdW interactions are crucial in the characteristics of systems with substantially stronger dipole-dipole interactions. in the interaction's potential energy Including both bound and unbound terms, such as angle and torsional energy, as well as vdW and electrostatic interactions. The second term oversees the extinction of several species. Using an implicit solvation model, it is quantified by the sum of two energy factors, namely the polar and non-polar solvation energies. HNPH had a -262.8 kcal/mol value,

SCv2-OS had a -254.2 kcal/mol value, HVI had a -242.8 kcal/mol value, and MT had a -206.9 kcal/mol value.

The electrostatic and hydrophobic energy analysis of the protein interaction significantly increased as structures with just a greater range of coupling to the ACE2 surface were tested; the lack of changes in binding affinities suggests that domain movements are largely responsible for the observed balancing energy landscape sample size; in all cases, the values present in the electrostatic terms compensate for each other, resulting in minimal structural changes. Electrostatic attraction is seen as a universal feature of all ionic systems using both modeling approaches.

Table 4: Energy values obtained from the protein-protein interaction

	Energy Coefficients (kcal/mol)			
ACE2H with Structure	**Balanced**	**Electrostatic**	**Hydrophobic**	**Van der Wals**
HVI	-751.2	-792.9	-917.6	-242.8
HNPH	-970.5	-930.2	-1197.2	-262.8
SCv2-OS	-906.1	-907.3	-1052.3	-254.2
MT	-758.9	-792.0	-927.2	-206.9

4. CONCLUSION

We demonstrate remarkable performance in the deterministic global coupling of peptides to protein domains using an approach that capitalizes on the relationship between sequential and structural motifs and employs accurate FFT-based sampling. Results are shown for a set of protein-protein interactions. It is important to note that this set was derived from the generic reference set, which was designed with no motive information in mind, which demonstrates that motive information is generally available for a wide class protein-protein interaction. In this work, we explore the energetic coupling landscapes of known protein complexes using sets of anchored structures generated by a rigid-body global energy optimization procedure. Earlier we described a two-step coupling procedure that allowed sampling of approximately the surface of the receptor around the known binding site. We extend the search to the entire surface of the receiver.

The electrostatic and vdW terms contributed to the ligand coupling, according to the data. Among the several forms of computed energy, these found inhibitors agree with essentially two factors: surface area (molecule geometry) and electronic polarizability (molecular size). To understand the binding properties and mechanism of action of interactions, the coupling mode of ligands was known. The ACE2 active site residues strongly coupled with the proteins, particularly the HNPH, according to the pooled results of the coupling calculations. While the results of such simulations can surely help with better understanding and streamlining of experimental data, there are certain limitations and drawbacks to this technique.

Two proteins are only considered to be interacting if they form stable, isolable complexes, and even non-specific interactions are still considered to involve a substantial degree of contact between the partner proteins. One aspect that will become clear in this work is that within the area of atomically detailed models there will likely be different levels of approximation that are acceptable depending on the specific application of interest. For example, it is a safe bet that a general solution to the protein anchoring problem, assuming it does not require any new physics to be

discovered, will certainly require the inclusion of conformational flexibility in proteins. At a minimum, this will involve allowing the sidechains some freedom of movement, but more generally, it will also require sidechain flexibility. The question of how to efficiently incorporate these features into existing protein fitting algorithms remains unresolved at present. On the other hand, conformational flexibility may be a less urgent requirement for a general description of weak protein-protein interactions.

REFERENCES

1- Berman, H. M., Narayanan, B. C., Di Costanzo, L., Dutta, S., Ghosh, S., Hudson, B. P., Catherine L.Lawson., Ezra P., Andreas P., Peter W.Rose., Chenghu S., Huanwang Y., Jasmine, Y&Zardecki, C. (2013). Trendspotting in the protein data bank. FEBS Letters, 587(8), 1036-1045.

2- Paeshuyse, J., Dallmeier, K., &Neyts, J. (2011). Ribavirin for the treatment of chronic hepatitis C virus infection: a review of the proposed mechanisms of action. Current opinion in virology, 1(6), 590-598.

3- Shen, C., Ding, J., Wang, Z., Cao, D., Ding, X., & Hou, T. (2020). From machine learning to deep learning: Advances in scoring functions for protein-ligand docking. Wiley Interdisciplinary Reviews: Computational Molecular Science, 10(1), e1429.

4- AcunerOzbabacan, S. E., Engin, H. B., Gursoy, A., & Keskin, O. (2011). Transient protein-protein interactions. Protein engineering, design, and selection, 24(9), 635-648.

5- Rao, V. S., Srinivas, K., Sujini, G. N., & Kumar, G. N. (2014). Protein-protein interaction detection: methods and analysis. International Journal of proteomics, 2014.

6- Reddy Chichili, V. P., Kumar, V., & Sivaraman, J. (2013). Linkers in the structural biology of protein-protein interactions. Protein Science, 22(2), 153-167.

7- Shi, Y. (2014). A glimpse of structural biology through X-ray crystallography. Cell, 159(5), 995-1014.

8- Jung, J., Kobayashi, C., Imamura, T., & Sugita, Y. (2016). Parallel implementation of 3D FFT with volumetric decomposition schemes for efficient molecular dynamics simulations. Computer Physics Communications, 200, 57-65.

9- Fleury, D., Wharton, S., Skehel, J. et al. Antigen distortion allows influenza virus to escape neutralization. Nat Struct Mol Biol 5, 119–123 (1998). https://doi.org/10.1038/nsb0298-119

10- Streltsov, V. A., Pilling, P., Barrett, S., &McKimm-Breschkin, J. L. (2015). Catalytic mechanism and novel receptor binding sites of human parainfluenza virus type 3 hemagglutinin-neuraminidase (hPIV3 HN). Antiviral Research, 123, 216-223.

11- Saxena, S. K., Kumar, S., Ansari, S., Paweska, J. T., Maurya, V. K., Tripathi, A. K., & Abdel-Moneim, A. S. (2022). Characterization of the novel SARS-CoV-2 Omicron (B. 1.1. 529) variant of concern and its global perspective. Journal of medical virology, 94(4), 1738-1744.

12- Prisic, S., Dankwa, S., Schwartz, D., Chou, M. F., Locasale, J. W., Kang, C. M., Husson, R. N. (2010). Extensive phosphorylation with overlapping specificity by Mycobacterium tuberculosis serine/threonine protein kinases. Proceedings of the National Academy of Sciences, 107(16), 7521-7526.

13- Geng, Q., Shi, K., Ye, G., Zhang, W., Aihara, H., & Li, F. (2022). Structural Basis for Human Receptor Recognition by SARS-CoV-2 Omicron Variant BA. 1. Journal of Virology, 96(8), e00249-22.

14- Held, M., Metzner, P., Prinz, J. H., & Noé, F. (2011). Mechanisms of protein-ligand association and its modulation by protein mutations. Biophysical Journal, 100(3), 701-710.

15- Kozakov D, Hall DR, Xia B, Porter KA, Padhorny D, Yueh C, Beglov D, Vajda S. (2017). The ClusPro web server for protein-protein docking. Nature protocols, 12(2), 255-278.

16- Vajda S, Yueh C, Beglov D, Bohnuud T, Mottarella SE, Xia B, Hall DR, Kozakov D. New additions to the ClusPro server motivated by CAPRI. Proteins: Structure, Function, and Bioinformatics. 2017 Mar; 85(3):435-444.

17- Welch, B. D., Yuan, P., Bose, S., Kors, C. A., Lamb, R. A., &Jardetzky, T. S. (2013). Structure of the parainfluenza virus 5 (PIV5) hemagglutinin-neuraminidase (HN) ectodomain. PLoS pathogens, 9(8), e1003534.

18- Li, Y., & Chen, X. (2012). Sialic acid metabolism and sialyltransferases: natural functions and applications. Applied microbiology and biotechnology, 94(4), 887-905.

19- Zhang, W., Qi, J., Shi, Y., Li, Q., Gao, F., Sun., Gao, G. F. (2010). Crystal structure of the swine-origin A (H1N1)-2009 influenza A virus hemagglutinin (HA) reveals similar antigenicity to that of the 1918 pandemic virus. Protein & cell, 1(5), 459-467.

20- Carlson, L. A., & Hurley, J. H. (2012). In vitro reconstitution of the ordered assembly of the endosomal sorting complex required for transport at membrane-bound HIV-1 Gag clusters. Proceedings of the National Academy of Sciences, 109(42), 16928-16933.

21- Ghrici, M., El Zowalaty, M., Omar, A. R., & Ideris, A. (2013). Induction of apoptosis in MCF-7 cells by the hemagglutinin-neuraminidase glycoprotein of Newcastle disease virus Malaysian strain AF2240. Oncology reports, 30(3), 1035-1044.

22- Mizuta, K., Abiko, C., Aoki, Y., Ikeda, T., Itagaki, T., Katsushima, F., Ahiko, T. (2012). Epidemiology of parainfluenza virus types 1, 2, and 3 infections based on virus isolation between 2002 and 2011 in Yamagata, Japan. Microbiology and immunology, 56(12), 855-858.

23- Low, C. Y., & Rotstein, C. (2011). Emerging fungal infections in immunocompromised patients. F1000 medicine reports, 3.

24- Metreveli, G., Zohari, S., Ejdersund, A., & Berg, M. (2010). Phylogenetic analysis of the hemagglutinin gene of low pathogenic avian influenza virus H7N7 strains in mallards in Northern Europe. Avian diseases, 54(s1), 453-456.

25- Itzstein, M. V., & Thomson, R. (2009). Anti-influenza drugs: the development of sialidase inhibitors. Antiviral strategies, 111-154.

26- Sannikov, O. (2019). Synthesis of conformationally constrained inhibitors for glycoside hydrolases (Doctoral dissertation, Science: Department of Chemistry).

27- Meiser, J., Weindl, D., & Hiller, K. (2013). The complexity of dopamine metabolism. Cell Communication and Signaling, 11(1), 1-18.

28- Streltsov, V. A., Pilling, P., Barrett, S., &McKimm-Breschkin, J. L. (2015). Catalytic mechanism and novel receptor binding sites of human parainfluenza virus type 3 hemagglutinin-neuraminidase (hPIV3 HN). Antiviral Research, 123, 216-223.

29- Jiang, S., Hillyer, C., & Du, L. (2020). Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends in immunology, 41(5), 355-359.

30- Jiang, S., Zhang, X., & Du, L. (2021). Therapeutic antibodies and fusion inhibitors target the spike protein of SARS-CoV-2. Expert Opinion on Therapeutic Targets, 25(6), 415-421.

31- Cerutti, G., Guo, Y., Liu, L., Liu, L., Zhang, Z., Luo, Y.Yiming H., Harris H W., David D H.,& Shapiro, L. (2022). Cryo-EM structure of the SARS-CoV-2 Omicron spike. Cell reports, 38(9), 110428.

32- Ye, G., Liu, B., & Li, F. (2022). Cryo-EM structure of a SARS-CoV-2 omicron spike protein ectodomain. Nature communications, 13(1), 1-7.

33- Yang, Q., Syed, A. A. S., Fahira, A., & Shi, Y. (2021). Structural analysis of the SARS-CoV-2 Omicron variant proteins. Research, 2021.

34- Cheval, C., & Faulkner, C. (2018). Plasmodesmal regulation during plant-pathogen interactions. New Phytologist, 217(1), 62-67.

35- Bugaj, L. J., Choksi, A. T., Mesuda, C. K., Kane, R. S., & Schaffer, D. V. (2013). Optogenetic protein clustering and signaling activation in mammalian cells. Nature methods, 10(3), 249-252.

36- Canova, M. J., &Molle, V. (2014). Bacterial serine/threonine protein kinases in host-pathogen interactions. Journal of Biological Chemistry, 289(14), 9473-9479.

37- Molle, V., & Kremer, L. (2010). Division and cell envelope regulation by Ser/Thr phosphorylation: Mycobacterium shows the way. Molecular Microbiology, 75(5), 1064-1077.

38- Chao, J., Wong, D., Zheng, X., Poirier, V., Bach, H., Hmama, Z., & Av-Gay, Y. (2010). Protein kinase and phosphatase signaling in Mycobacterium tuberculosis physiology and pathogenesis. Biochimica et Biophysica ACTA (BBA)-ProteinsandProteomics, 1804(3), 620-627.

39- Jilani, T. N., Avula, A., Gondal, Z., &Siddiqui, A. H. (2018). Active tuberculosis.
40- Sancho-Vaello, E., Albesa-Jové, D., Rodrigo-Unzueta, A., & Guerin, M. E. (2017). Structural basis of phosphatidyl-myo-inositol mannosides biosynthesis in mycobacteria. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1862(11), 1355-1367.
41- Doenhoff, M. J., Cioli, D., & Utzinger, J. (2008). Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. Current opinion in infectious diseases, 21(6), 659-667.
42- Vieira, C., Nery, L., Martins, L., Jabour, L., Dias, R., & Simões e Silva, A. C. (2021). Downregulation of membrane-bound angiotensin-converting enzyme 2 (ACE2) receptor has a pivotal role in COVID-19 immunopathology. Current Drug Targets, 22(3), 254-281.
43- Wu, C., Ye, D., Mullick, A. E., Li, Z., Danser, A. J., Daugherty, A., & Lu, H. S. (2020). Effects of renin-angiotensin inhibition on ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) expression: insights into COVID-19. Hypertension, 76(4), e29-e30.
44- Noe, C. R., & Noe-Letschnig, M. (2021). The role of ACE2 in the renin-angiotensin-system: Etiology and therapy of COVID-19 from a pharmaceutical perspective. Die Pharmazie-An International Journal of Pharmaceutical Sciences, 76(8), 342-350.
45- Stein, R. A., & Young, L. M. (2020). From ACE2 to COVID-19: A multiorgan endothelial disease. International Journal of Infectious Diseases, 100, 425-430.
46- Tan, C. W., Chia, W. N., Qin, X., Liu, P., Chen, M. I. C., Tiu, C., Wang, L. F. (2020). A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein-protein interaction. Nature Biotechnology, 38(9), 1073-1078.
47- Yin, W., Xu, Y., Xu, P., Cao, X., Wu, C., Gu, C., Xu, H. E. (2022). Structures of the Omicron Spike trimer with ACE2 and an anti-Omicron antibody. Science, 375(6584), 1048-1053.
48- Su, C. Y., Menuz, K., & Carlson, J. R. (2009). Olfactory perception: receptors, cells, and circuits. Cell, 139(1), 45-59.
49- Wilson, R. I. (2013). Early olfactory processing in Drosophila: mechanisms and principles. Annual review of neuroscience, 36, 217.
50- Glezer, I., Bruni-Cardoso, A., Schechtman, D., &Malnic, B. (2021). Viral infection and smell loss: The case of COVID-19. Journal of neurochemistry, 157(4), 930-943.
51- McEwen, D. P., Jenkins, P. M., & Martens, J. R. (2008). Olfactory cilia: our direct neuronal connection to the external world. Current topics in developmental biology, 85, 333-370.
52- Wu, C., Ye, D., Mullick, A. E., Li, Z., Danser, A. J., Daugherty, A., & Lu, H. S. (2020). Effects of renin-angiotensin inhibition on ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) expression: insights into COVID-19. Hypertension, 76(4), e29-e30.
53- Wang, H., Sun, X., L VonCannon, J., Kon, N. D., Ferrario, C. M., & Groban, L. (2021). Estrogen receptors are linked to angiotensin-converting enzyme 2 (ACE2), ADAM metallopeptidase domain 17 (ADAM-17), and transmembrane protease serine 2 (TMPRSS2) expression in the human atrium: insights into COVID-19. Hypertension Research, 44(7), 882-884.
54- Sterpone, F., Melchionna, S., Tuffery, P., Pasquali, S., Mousseau, N., Cragnolini, T., Derreumaux, P. (2014). The OPEP protein model: from single molecules, amyloid formation, crowding, and hydrodynamics to DNA/RNA systems. Chemical Society reviews, 43(13), 4871-4893.
55- Tompa, P., &Fuxreiter, M. (2008). Fuzzy complexes: polymorphism and structural disorder in protein-protein interactions. Trends in biochemical sciences, 33(1), 2-8.
56- Liao, C., Sitzmann, M., Pugliese, A., & Nicklaus, M. C. (2011). Software and resources for computational medicinal chemistry. Future medicinal chemistry, 3(8), 1057-1085.
57- Huang, C. C., Meng, E. C., Morris, J. H., Pettersen, E. F., & Ferrin, T. E. (2014). Enhancing UCSF Chimera through web services. Nucleic acids research, 42(W1), W478-W484.
58- Ameen, F., Mamidala, E., Davella, R., &Vallala, S. (2021). Rilpivirine inhibits SARS-CoV-2 protein targets: A potential multi-target drug. Journal of Infection and Public Health, 14(10), 1454-1460.
59- Pontiki, E., &Hadjipavlou-Litina, D. (2018). Multi-target cinnamic acids for oxidative stress and inflammation: Design, synthesis, biological evaluation, and modeling studies. Molecules, 24(1), 12.

60- Chainoglou, E., Siskos, A., Pontiki, E., &Hadjipavlou-Litina, D. (2020). Hybridization of curcumin analogues with cinnamic acid derivatives as multi-target agents against Alzheimer's disease targets. Molecules, 25(21), 4958.
61- Majumder, R., & Mandal, M. (2022). Screening of plant-based natural compounds as a potential COVID-19 main protease inhibitor: an in silico docking and molecular dynamics simulation approach. Journal of Biomolecular Structure and Dynamics, 40(2), 696-711.
62- D'Souza, S., Du Plessis, S. M., Egieyeh, S., Bekale, R. B., Maphasa, R. E., Irabin, A. F., Dube, A. (2022). Physicochemical and biological evaluation of curdlan-poly (lactic-co-glycolic acid) nanoparticles as a host-directed therapy against Mycobacterium tuberculosis. Journal of pharmaceutical sciences, 111(2), 469-478.
63- Kozakov, D., Hall, D. R., Xia, B., Porter, K. A., Padhorny, D., Yueh, C., Vajda, S. (2017). The ClusPro web server for protein-protein docking. Nature protocols, 12(2), 255-278.
64- Yueh, C., Hall, D. R., Xia, B., Padhorny, D., Kozakov, D., & Vajda, S. (2017). ClusPro-DC: Dimer classification by the CLUSPRO server for protein-protein docking. Journal of molecular biology, 429(3), 372-381.
65- Xia, B., Vajda, S., & Kozakov, D. (2016). Accounting for pairwise distance restraints in FFT-based protein-protein docking. Bioinformatics, 32(21), 3342-3344.
66- Porter, K. A., Xia, B., Beglov, D., Bohnuud, T., Alam, N., Schueler-Furman, O., & Kozakov, D. (2017). ClusProPeptiDock: efficient global docking of peptide recognition motifs using FFT. Bioinformatics, 33(20), 3299-3301.
67- Pierce, B. G., Wiehe, K., Hwang, H., Kim, B. H., Vreven, T., & Weng, Z. (2014). ZDOCK server: interactive docking prediction of protein-protein complexes and symmetric multimers. Bioinformatics, 30(12), 1771-1773.
68- Ignatov, M., Kazennov, A., & Kozakov, D. (2018). ClusPro FMFT-SAXS: ultra-fast filtering using small-angle X-ray scattering data in protein docking. Journal of molecular biology, 430(15), 2249-2255.
69- Verma, R., Yadav, M., Pradhan, D., Bhuyan, R., Aggarwal, S., Nayek, A., & Jain, A. K. (2016). Probing the binding mechanism of interleukin-6 and olokizumab: in silico design of potential lead antibodies for autoimmune and inflammatory diseases. Journal of Receptors and Signal Transduction, 36(6), 601-616.
70- Brenke, R., Hall, D. R., Chuang, G. Y., Comeau, S. R., Bohnuud, T., Beglov, D., Schueler-Furman O, Vajda S& Kozakov, D. (2012). Application of asymmetric statistical potentials to antibody-protein docking. Bioinformatics, 28(20), 2608-2614.
71-Akbal-Delibas, B., Pomplun, M., & Haspel, N. (2014, September). AccuRMSD: A machine learning approach to predicting structure similarity of docked protein complexes. In Proceedings of the 5th ACM Conference on Bioinformatics, Computational Biology, and Health Informatics (pp. 289-296).
72- Krawczyk, K., Liu, X., Baker, T., Shi, J., & Deane, C. M. (2014). Improving B-cell epitope prediction and its application to global antibody-antigen docking. Bioinformatics, 30(16), 2288-2294.
73- Jia, Y., Kowalski, P., & Lopez, I. (2021). Using yeast two-hybrid system and molecular dynamics simulation to detect venom protein-protein interactions. Current Research in Toxicology, 2, 93-98.
74- Ambrosetti, F., Jiménez-García, B., Roel-Touris, J., &Bonvin, A. M. (2020). Modeling antibody-antigen complexes by information-driven docking. Structure, 28(1), 119-129.
75- Kozakov, D., Hall, D. R., Beglov, D., Brenke, R., Comeau, S. R., Shen, Y., Vajda, S. (2010). Achieving reliability and high accuracy in automated protein docking: ClusPro, PIPER, SDU, and stability analysis in CAPRI rounds 13–19. Proteins: Structure, Function, and Bioinformatics, 78(15), 3124-3130.
76- Alekseenko, A., Ignatov, M., Jones, G., Sabitova, M., & Kozakov, D. (2020). Protein-Protein and Protein–Peptide Docking with ClusPro Server. In Protein Structure Prediction (pp. 157-174). Humana, New York, NY.
77- Chaves, B., Sartori, G. R., Vasconcelos, D. C. A., Savino, W., Caffarena, E. R., Cotta-de-Almeida, V., & da Silva, J. H. M. (2020). Guidelines To Predict Binding Poses of Antibody–Integrin Complexes. ACS Omega, 5(27), 16379–16385. doi:10.1021/acsomega.0c00226.

78- Porter, K. A., Xia, B., Beglov, D., Bohnuud, T., Alam, N., Schueler-Furman, O., & Kozakov, D. (2017). ClusProPeptiDock: efficient global docking of peptide recognition motifs using FFT. Bioinformatics, 33(20), 3299-3301.

79- Nwogu, N., Ortiz, L. E., & Kwun, H. J. (2020). The surface charge of Merkel cell polyomavirus small T antigen determines cell transformation through allosteric FBW7 WD40 domain targeting. Oncogenesis, 9(5), 1-12.

80- Bartholow, T. G., Sztain, T., Patel, A., Lee, D. J., Young, M. A., Abagyan, R., & Burkart, M. D. (2021). Elucidation of transient protein-protein interactions within carrier protein-dependent biosynthesis. Communications Biology, 4(1), 1-10.

81- Vajda, S., Yueh, C., Beglov, D., Bohnuud, T., Mottarella, S. E., Xia, B., Kozakov, D. (2017). New additions to the C lus P or server motivated by CAPRI. Proteins: Structure, Function, and Bioinformatics, 85(3), 435-444.

82- Fan, J., Fu, A., & Zhang, L. (2019). Progress in molecular docking. Quantitative Biology, 7(2), 83-89.