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the ABO system and the severity of covid-19: In silico study

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Dedication

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I wanna thank me,

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Abstract:

Considering the ABO blood system as a risk factor in many infectious diseases is widely accepted and several hypothesis was proposed to explain this association. In COVID19 infection this association remain unclear.

In this study we suggest that the A and B blood antigens could bind the structural proteins of the Sars-cov2 virus which has a potential to modulate the susceptibility and the severity of the infection.

The objective of this study was to process an In silico, protein-protein molecular docking, and repurpose the ABO proteins antigen A and antigen B as ligand for the corona virus structural proteins in the purpose to find out a computational explanation for the epidemiological and clinical studies showing that the blood phenotype, mostly the A one, is risk factor for severe symptoms of the COVID19

This study primarily relied on molecular docking methods using free website such as Cluspro and HDOCK. Additionally, we utilized the software Discovery Studio 2021 to evaluate the result.

The result illustrates that the despite that the B antigen has the highest affinity with the corona virus the three structural proteins (spike, N and E) compared to the A protein, the latest exhibit a stronger affinity M protein of the virus. Known that this structural protein a main role in the virus life cycle is essential for help in the production and release of virus-like particles. This high affinity interaction between the A antigen and M protein could be feasible in experimental tries and explain the severity of this infection in the host with A blood type. Interestingly, the ABO system protein shows more affinity with corona protein then their natural protein ligand except for N protein. This data gives a further argument that the red blood cell might play a crucial role in the spread of the virus whole over the body.

In conclusion, this data gives a computational explanation for the link between the severity of the symptoms of the disease and the A blood phenotype of the patients.

Keywords: ABO blood antigens, COVID-19 structural Proteins, severity, susceptibility, protein-protein Molecular docking.

Résumé :

Considérer le système sanguin ABO comme un facteur de risque dans de nombreuses maladies infectieuses est largement accepté et plusieurs hypothèses ont été proposées pour expliquer cette association. Dans l'infection par le COVID19 cette association demeure peu claire.
Dans cette étude, nous suggérons que les antigènes sanguins A et B pourraient se lier aux protéines structurelles du virus Sars-cov2 qui a le potentiel de moduler la susceptibilité et la gravité de l'infection.

L'objectif de cette étude était de procéder à un encadrement moléculaire In silico, protéine-protéine, et de réutiliser les protéines ABO antigène A et antigène B comme ligand pour les proteines structurelles du virus du coronavirus dans le but de trouver une explication computationnelle pour les études épidémiologiques et cliniques montrant que le phénotype sanguin, principalement celui A, est un facteur de risque pour les symptômes graves du COVID19.

Cette étude s'appuyait principalement sur des méthodes de docking moléculaire à l'aide de sites Web gratuits tels que Cluspro et HDOCK. En outre, nous avons utilisé le logiciel Discovery Studio 2021 pour évaluer le résultat.

Le résultat montre que, bien que l'antigène B ait la plus grande affinité avec le coronavirus, les trois protéines structurelles (spike, N et E) par rapport à la protéine A, les plus récentes présentent une affinite plus forte avec la prothèse M du virus. On sait que cette protéine structurelle joue un rôle majeur dans le cycle de vie du virus est essentielle pour aider à la production et à la libération de particules semblables aux virus. Cette interaction d'affinité élevée entre l'antigène A et la protéine M pourrait être réalisable dans les essais expérimentaux et expliquer la gravité de cette infection chez l'hôte avec le groupe sanguin A. Il est intéressant de noter que les protéines du système ABO montrent plus d'affinité avec la protéine corona que leur ligand naturel à l'exception de la Protéine N. Ces données donnent un autre argument que les globules rouges pourraient jouer un rôle crucial dans la propagation du virus tout au long du corps.

En conclusion, ces données fournissent une explication computationnelle du lien entre la gravité des symptômes de la maladie et le phénotype sanguin A des patients.

Mots clés: Antigènes sanguins ABO, COVID-19 structurelle Protéines, sévérité, sensibilité, protéine-protéine Docking moléculaire.

الملخص:

يعتبر نظام الدم ABO كعامل خطر في العديد من الامراض المعدية مقبول على نطاق واسع واقترح عدة فرضيات لتفسيرهذه الرابطة. وفي حالة الاصابة بفيروس COVID-19.لا تزال هذه الرابطة غير واضحة.

في هذه الدراسة تقترح ان مضادات الدم A و B يمكن ان تربط البروتينات الهيكلية للفيروس SARS-Cov2 الذي لديه القدرة على تعديل قابلية التعرض لشدة العدوى .

وكان الهدف من هذه الدراسة هو معالجة رسو جزئيي للبروتين و البروتين البروتين ,و اعادة توجيه البروتينات ABO المضاد A و المضاد B على انها Ligand للبروتينات الهيكلة لفيروس الكورونا بغرض العثور على تفسير حسابي للدرسات الوبائية و الاكلينيكية التي تبين ان نمط الظاهري للدم .و معظمه A هو عامل خطر للاعراض الحادة من COVID-19.

وتعتمد هذه الدراسة اساسا الرسو الجزيئي موقع مجاني مثل ClusPro و HDOOk بالاضافة الى ذلك استخدمنا البرنامج Discovery studio 2021 لتقييم النتيجة.

وتبين النتيجة انه على الرغم من ان المستضدات B لها اعلى صلة مع فيروس الكورونا فان البروتينات الهيكلية الثلاثة N; spikeوE مقارنة بالبروتين A فان اخر البروتينات تظهر تشابها اقوى في البروتينات المتكونة من الفيروس .من المعرف ان هذا البروتين الهيكلي دور رئيسي في دورة حياة الفيروسات ضروري للمساعدة في انتاج و اطلاق الجسيمات الشبيهة بالفيروسات .وهذا التفاعل العالي القرابة بين البروتين المضاد A و البروتين M يمكن ان يكون ممكنا في التجارب التجريبية وشرح شدة هذه العدوى في العائل مع فصيلة دم A ومن المثير للاهتمام ان بروتين نظام ABO يظهر المزيد من التشابه مع بروتين مع بروتين الكورونا ثم البروتين الطبيعي الخاص بها Ligand باستثناء البروتين N وتعطي هذه البيانات حجة اخرى بان خلية الدم الحمراء قد تلعب دورا حاسما في انتشار الفيروس باكمله على الجسم .

في الختام تقدم هذه البيانات تفسيرا حسابيا للعلاقة بين شدة اعراض المرض و النموذج الظاهري لدم المرضى A

الكلمات الدالة: الأنسجة الدموية ABO ، COVID-19الهيكلية البروتينات، صعوبة، حساسية، البروتين-البروتين docking .

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List of abbreviations:

Symbol

Nomenclature

3D**:**Three dimensensional.

ACE 2: Angiotension Converting Enzyme-2.

AGD: Argyrophilic grain disease.

COV**:** Corona Virus.

COVID-19**:** Corona virus disease-19.

CNS: Central Nervous.

CPUs: Central processing unit.

DNA: Seoxyribonucleic Acid.

FiO2: Fraction of inspired Oxygen.

IL6 : Interleukin-6.

IgM : Immunoglobulin M.

IgA: Immunoglobulin A.

IgG: Immunoglobulin G.

ITScorePP: Information technology score for Public Policy.

ITScorePR: Information Technology Score for Puerto Rico.

ID: Identification or Identity.

NSP: Non-structural proteins.

NIH: National Institutes of health.

ORFs: Open Reading Frames.

PDB: Protein Data Bank.

PaO2: Partial Pressure of Oxygen in arterial blood .

POTS: Postural orthostatic tachycardia syndrome.

RNA: Ribonucleic Acid.

ROS: Reaction Oxygne species.

RT-PCR: Reverse transcription-polymerase chain reaction.

RH : Rhesus.

RAI: Radioactive Iodine.

RMSD: Root Mean Square Deviation.

RHD: Rhesus Factor D.

RHCE: Rhesus Factor C/E.

SARS-COV-2: Severe Acute Respiratory Syndrme Coronavirus 2.

SPO2 : Saturation pulséé en oxygéne.

TYK2: Tyrosine kinase two.

UCSF: University of California, San Francisco.

WHO: world health organization

INTRODUCTION:

The COVID-19 (coronavirus disease 2019) infection, caused by the severe acute respiratory syndrome coronavirus-2 (Sars-cov2), which has caused two deadly epidemics in humans, SARS-CoV in 2003 and MERS-CoV in 2012, and a remerged in China at the end of 2019 then rapidly and globally spread to became a pandemic. As declared by the World Health Organization (WHO) in 6th of May, 2022, (*Coronavirus*, n.d.).[1]

The progression and the evolution of this disease remain unclear, depending on several parameters: physiological factors, genetics, age… This multifactorial aspect of the COVID19 prognostic makes difficult the management and prediction of the disease evolution. Emerging evidence suggests that blood type may influence an individual's risk of contracting COVID-19 and the severity of the disease. Nonetheless, the current data still could not explain the real role of the ABO phenotype of the patients on the personnel disease story because of the heterogenicity of the results and lack in the genetics and environmental parameters. Understanding the underlying mechanisms of this relationship could provide valuable insights into the pathogenesis of COVID-19.(Kim et al., 2021)

In this work, we proceed by a protein-protein molecular docking which is an in silico tool using a free platform. This method provides a potent way to investigate the computational simulations to explore global datasets of molecular interactions to dissect biological patterns and mechanisms that are not readily detectable in the laboratory.

In this work we propose that the ABO blood phenotype might have an impact on the severity of the sars-cov2 infection. We suggest the existence of a physical contact between the blood antigen A and B with the structural proteins of the virus. Also we try to find out a computational explanation of the link between the A phenotype and the severity of the disease previously mentioned in many epidemiological and clinical studies.

We present this study as an in silico study to elucidate the possible association of ABO blood types and COVID-19 severity by proceeding the protein-protein molecular docking. For these, we operate HDOCK and Cluspro docking web sites to analyse the possible association between

[1] https://www.who.int/health-topics/coronavirus#tab=tab_1

the A and B blood antigens and the four structural proteins of the virus spike, M, N end E on the other side. By using this approach, we generate a graphical pose of the association of those protein and calculate multiple coefficient that lead to find a possible and the best association between the ABO blood system and COVID19 virus.

The results may deepen our understanding of the effects of blood types on COVID-19 status and further validate or contradict the hypothesis that individuals with blood phenotype could have an impact on the personnel predisposition to the infection, and provide evidence for devising precise and individualized therapeutic strategies.

CHAPTER I: GENERAL REVIEW

I-1. SARS-cov2:

Coronavirus disease 2019 (COVID-19) is a zoonotic pathogen, with its origin likely linked to bats and the potential for transmission through an intermediate animal host, such as pangolins**(Haider et al., 2020).** SARS-CoV-2, the virus responsible for COVID-19, The virus interacts differently with the angiotensin-converting enzyme 2 (ACE 2) receptor, allowing for stronger binding and greater efficiency at invading host cells. The exact origin of SARS-CoV-2 has not been definitively identified, but research suggests it likely resulted from viral evolution in nature and jumped to humans or through an unidentified animal host **(*Origins of Coronaviruses | NIAID*, 2022),(Rat et al., 2020)**

I-1-1. Genomic:

The genomic organization of SARS-CoV-2, the virus responsible for COVID-19, consists of a single-stranded positive-sense RNA genome that is approximately 27–32 kilobases in length. The genome contains six open reading frames (ORFs):

1. ORF1a/b, which encodes non-structural proteins (nsp) 1 to 16.
2. ORFs located on the 3’ end, which encode structural proteins: spike (S), envelope I, membrane (M), and nucleocapsid (N) proteins.
3. Accessory proteins, encoded by ORF3a, ORF3d, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF14, and ORF10.

The genome also contains leader and untranslated regions (UTRs) that are essential for replication and transcription of the viral genome. Each structural and accessory gene is preceded by transcriptional regulatory sequences (TRSs), which are required for their functional expression.**(Ravi et al., 2022)**

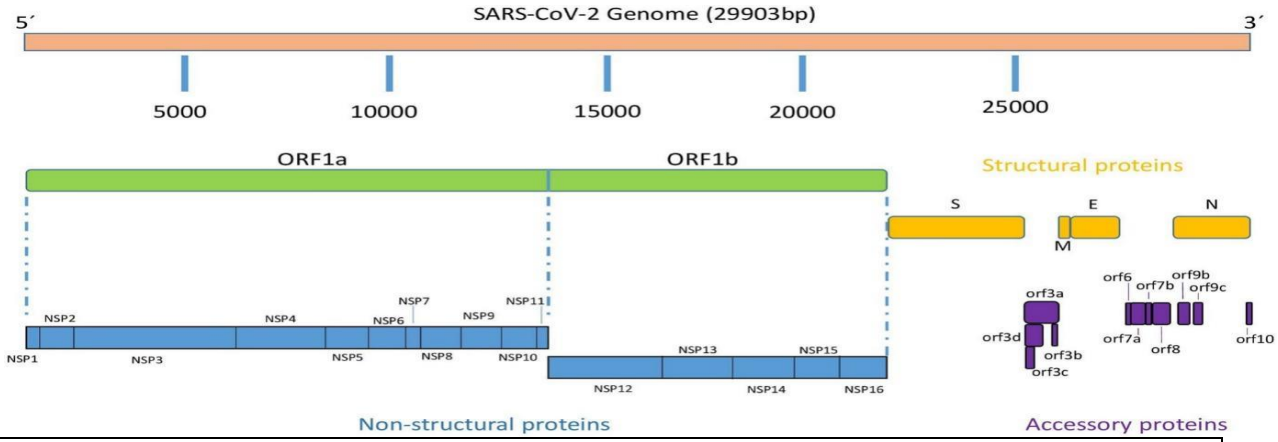


Figure 1 : SARS-CoV-2 genomic organization with edition **(Redondo et al., 2021)**

I-1-2. Structure:

Covid19 virus are spherical virus with club-shaped spikes projecting from the surface, giving a solar corona appearance**(Fehr & Perlman, 2015).**

The COVID-19 virus has several major proteins that play critical roles in its life cycle and pathogenesis.

- The S protein is a highly conserved protein that mediates attachment, fusion, and entry of the virus into host cells**(Ravi et al., 2022).**

The structure of coronaviruses involves a spike (S) protein composed of two subunits, S1 and S2. The S1 subunit contains a receptor-binding domain that recognizes and binds to host receptors, while the S2 subunit mediates viral cell membrane fusion. The S protein 2 rotein2 form a crown-like halo around the viral particle, with the S1 and S2 subunits forming the head and stalk regions. During infection, the S protein is cleaved into S1 and S2 subunits by cellular proteases, activating membrane fusion after viral entry into target cells. The genome of coronaviruses consists of single-stranded RNA enclosed in a protective capsid, with spike proteins on the outer envelope facilitating cell infection**(Huang et al., 2020)**

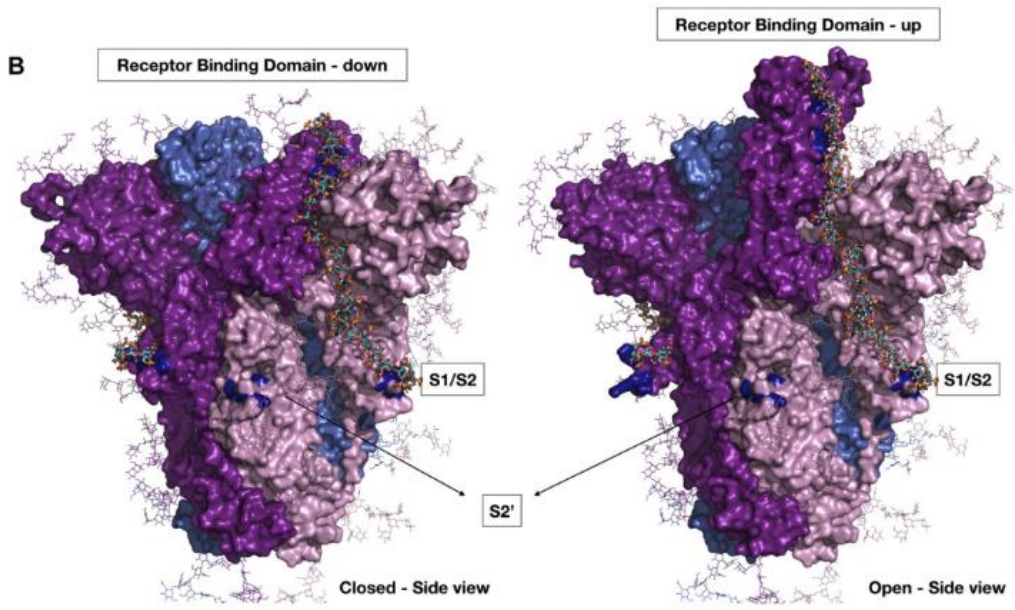


Figure 2: side views of the models of the spike head homotrimer

before the MD simulations in closed (left) andopen (right) conformations with three heparin chains bound. Only one complete heparin chain can be seen from this view. The SA, SB, and SC subunits are shown as surfaces in blue, pink, and magenta, respectively. The dark blue surface patches correspond to the putative HBDs. N-glycans covalently attached to the spike are shown in line representation, colored according to the subunit to which they are attached. The 31mer heparin chains that span from the S1/S2-HBD to the RBD-HBD are shown in stick representation, colored by element with cyan carbons. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. With edit **(Paiardi et al., 2022)**

- The M protein is the most abundant protein and has three transmembrane domains. It has 222 residues and participates mostly in the assembly of virions thanks to the different interactions it has with the other structural proteins of the virus, that define the shape of the viral envelope**(Catherine, 2023)**
- The E protein is the smallest of all and is abundantly expressed inside the infected cell. This protein is the least abundant and smallest of structural proteins with only 75 amino acids in its component. It is incorporated into the virus envelope and participates in viral assembly and budding. It plays a major role in the maturation and production of new virions through its ion channel activity**.(Catherine, 2023)**
- The N protein is ribonucleoprotein of 422 amino acids binds in its N-terminal part to the nucleotide, while its C- terminal part allows its dimerization. This complex stabilizes the genome RNA of the virus by forming the heliocoidal nucleocapside.

This protein involved in viral assembly, budding, and complete virion formation**.(Catherine, 2023)**

The interaction between the S and M proteins is essential for the retention of S in the ER-Golgi intermediate compartment and its incorporation into new virions. **(De Haan & Rottier, 2005)**

The M and E proteins making the viral envelope help in the production and release of virus-like particles. The SARS-CoV-2 S protein is highly conserved among all human coronaviruses and is involved in receptor recognition, viral attachment, and entry into host cells. Due to its indispensable functions, it represents one of the most important targets for COVID-19 vaccine and therapeutic research . **(Ravi et al., 2022)**

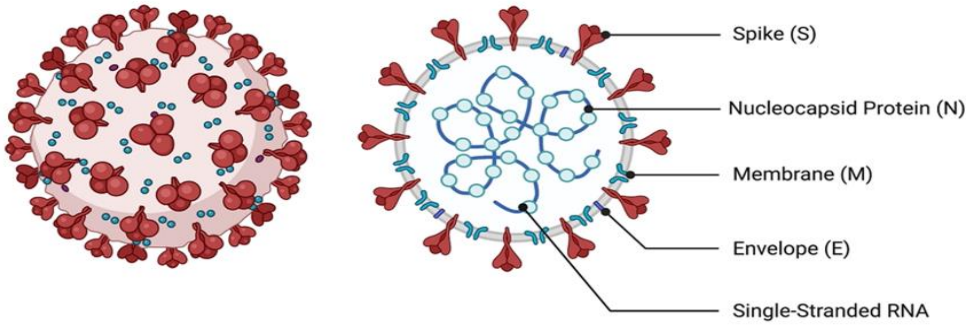


Figure 3: humen SARS-CoV-2 structure**. (Jamison et al., 2022)**

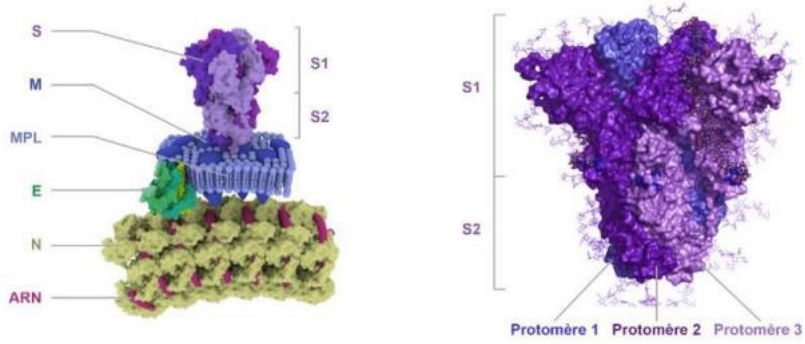


Figure 4: Concentrated view of the different structural proteins of SARS-CoV-2.

Spike protein trimester, each promoter being divided into two subunits: S1, which will interact with the target cell ACE2 receptor, and S2, which plays a role in the anchoring of the spike protein to the phospholipid membrane**.(Catherine, 2023)**

I-1-3. Risk factors:

The COVID-19 disease does not impact all populations in the same way, from many factors such as age, gender, health status, or the presence of certain genes play a leading role in the ability of individuals to fight the disease.

I-1-3-1. Age:

According to a cohort study on people hospitalized for COVID-19 during the first epidemic wave in France, compared to the general population, regrouping 87809 patients (113 per 100,000) including 15,661 deaths (24 per 100,000), age appeared as being the main risk factor leading to hospitalization, and even more so the death **(Semenzato et al., 2021)**. For example, people aged between 60 and 64 were twice more likely to be hospitalized for COVID-19 than the age category 40-44 years, taken for reference.

The risk of a death in these same people was 12 times higher. These figures become more pronounced with the higher age categories, reaching a probability 6 times higher hospitalization rate among 80-84-year-olds and with a 100 times higher risk of to pass away. This is mainly explained by the phenomenon of immunosenescence inducing less effective control of viral replication and an accentuated inflammatory response, as well as by the presence of comorbidities that become more frequent with age. **(Semenzato et al., 2021)**

I-1-3-2. Sex:

In this same study, it would also seem that men are more at risk of being hospitalized from COVID-19 and dying from it. One of the reasons mentioned would be the protective role of the X chromosome and female sex hormones inducing a better response innate and adaptive immunity. A more recent study, always carried out by Laura Semenzato and covering more than 28 million vaccinated adults in France, compared the characteristics of people who were hospitalized and died in the hospital **(Semenzato et al., 2022).** It has thus been observed that men were 1.6 times more likely to be hospitalized and death occurred 2 times more often than in women.

Pregnant women are five times more likely to be admitted to intensive care units, leading to serious complications for both mother and fetus, potentially leading to death**(Anselem, 2021)**.

I-1-3-3. Genetic factors:

Although genetic factors in humans do not represent the major point in the inequalities in the face of COVID-19, several elements deserve to be mentioned. “The COVID-19 Host Genetics Initiative" is a collaboration whose goal is to map the genetic determinants of the COVID-19 host. This meta-analysis of 46 studies extended out of 19 countries, 13 loci involved in the disease have been identified. Four of them are associated with the infection, while the other nine relate to the severity of the disease (COVID-19 Host Genetics Initiative et al., 2021).

By way of example, the rs74956615T>A mutation of the TYK2 gene (Tyrosine kinase 2, a protein involved in the activation of the immune system) is correlated with a risk hospitalization rate increased by 27% in COVID-19 **(Zabihi Rizi et al., 2023)**

I-1-4. Symptoms:

The symptoms of COVID-19 vary between people, ranging from asymptomatic cases to cases of serious illness. The guidelines of the American Institutes of Health NIH (National Institutes of Health), classify the clinical aspects of people who have tested positive for SARS-CoV-2 into 5 categories: asymptomatic, mild illness, moderate illness, severe illness and disease critical. It is important to provide a particular follow-up of the evolution of the symptom , all the more so when it comes to people with risk factors such as those mentioned above **(Wynberg et al., 2022).**

I-1-4-1. Asymptomatic or presymptomatic infection:

It happens that some people do not develop any symptoms of the disease, despite a proven infection by a positive test. This percentage of asymptomatic cases is hardly evaluable, on the one hand because the symptoms and their appearance can evolve in intensity and in time, and on the other hand because people with no clinical signs do not systematically perform a diagnostic test to confirm an infection. **(Gao et al., 2021)**

I-1-4-2. Mild illness:

Most people infected with SARS-Cov-2 develop mild signs. not requiring treatment to recover apart from symptomatic treatments. A hospitalization is generally preventable, otherwise, a management outpatient is sufficient.

These symptoms can be related to those of an influenza-like illness: fever, cough, aches throat, asthenia, headache, myalgia and rhinorrhea. Can also be added other symptoms such as loss of taste (ageusia), loss of smell (anosmia), a skin rash, or gastrointestinal signs (nausea, vomiting, diarrhea, pain abdominal pain) **(Wynberg et al., 2022; J. Zhang et al., 2022).**

The distinction between mild and moderate cases of illness is the appearance of disorders respiratory symptoms such as shortness of breath and dyspnea, which may be accompanied by abnormalities at the level of chest imaging.

I-1-4-3. Moderate illness

The decrease in respiratory capacity observed during the clinical examination or imaging performed by the patient is a criterion for defining these moderate cases. They keep however, an oxygen saturation (SpO2) ≥ 94%**.(McCarron et al., 2024)**

I-1-4-4. Severe illness:

A SpO2 <94%, a hypoxemia (ratio between the partial pressure of the oxygen in the arterial blood PaO2 and the inspired oxygen fraction FiO2) < 300 mmHg, a rhythm respiratory rate greater than 30 breaths/min, or a pulmonary infiltrate greater than 50% allow to consider a case of COVID-19 as being severe.[2]

I-1-4-5. Critical illness:

Finally, the last stage of the disease can lead to SARS, respiratory failure, septic shock, cardiogenic shock, an exaggerated inflammatory response, disorders thrombotic, and/or dysfunction of several organs.[2]

I-1-4-6. Long COVID:

Long covid is a severe condition resulting from SARS-CoV-2 infection, affecting 65 million people worldwide. It is associated with all ages and acute phase disease severity, with the highest percentage of diagnoses between 36 and 50 years. Most cases are in non-hospitalized patients with mild acute illness, representing the majority of overall COVID-19 cases.**(Koc et al., 2022)**

Are estimated to be experienced by 31%-69% of COVID-19 survivors after initial recovery from SARS-CoV-2 infection. Initial symptoms include fatigue, muscle pain, palpitations, cognitive impairment, dyspnea, anxiety, chest pain, and arthralgia. Fatigue is most prevalent among long COVID patients (51%), followed by dyspnea (35%), arthralgia (25%), and concentration difficulties (25%). Cognitive-related symptoms develop at later long COVID stages.

SARS-CoV-2 infection leads to respiratory system dysfunction in long COVID, leading to chronic inflammation responses that trigger sustained production of inflammatory cytokines and reactive oxygen species (ROS). In the long term, viral-induced complement activation and disruption of coagulant pathways favor the development of prolonged inflammation and hypercoagulable state, predisposing the patient to the risk of thrombosis.

Long COVID patients also experience cardiac complications, with chronic inflammation of cardiomyocytes leading to myositis and cell death. Chronic inflammation and cellular damage prompt fibrotic changes and reduce cell adhesion, all of which could lead to arrhythmia and the development of coagulopathy. Inflammation of the autonomic nervous system might progress

[2] https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19

to postural orthostatic tachycardia syndrome (POTS)**(Davis et al., 2023).**

Long COVID can affect the central nervous system (CNS) through chronic neuro-inflammation, leading to neurodegenerative disorders. SARS-CoV-2 induces both direct and indirect pathology, contributing to multi-organ dysfunction. Hyperinflammation of kidney tissues may activate the complement system, contributing to focal segmental glomerulosclerosis and glomerular involution. Pancreatic damage observed in long COVID may be consequences from a combination of direct viral attack and indirect effect of systemic inflammation.

Altered gastrointestinal system functions were reported in both acute and subacute COVID. Understanding the full clinical spectrum of symptoms experienced by these patients over time is crucial for developing effective treatment options and identifying the risk factors associated with long COVID**.(Koc et al., 2022)**

I-1-5. Comorbidities:

According to Semenzato et al. However, the prognosis for hospitalization and death is poor for nearly all chronic diseases**(Semenzato et al., 2021).** People with trisomy 21, dialysis patients with mental disorders, and end-stage kidney disease are among those most at risk of hospitalization (the 13 risk for these people ranges from 3.5 to 7 times, depending on the disease). Than those without comorbidities) and death (risk 4 to 23 times higher). Other comorbidities increase the risk of hospitalization and death, such as diabetes, obesity, hypertension and heart disease, chronic respiratory disease and even cancer (risk up to 2-fold).

Immunocompromised patients who have received organ transplants such as lungs or kidneys, cancer chemotherapy or even long-term corticosteroid treatment are more likely to develop severe COVID-19 **(Semenzato et al., 2021).**

I-1-6. Diagnosis:

I-1-6-1. RT-PCR:

RT-PCR (reverse transcription-polymerase chain reaction) is the test of choice for diagnosis, is the direct research of viral RNA. This research is done on a nasopharyngeal or oropharynx patch. In some cases, this may be done on samples by broncho-alveolar washing reserved for certain specific clinical situations **(Dutta et al., 2022).**

The sensitivity of RT-PCR varies according to the studies. A first negative result does not therefore completely rule out the diagnosis. Similarly, given the evolution of the viral load over time, if RT-PCR is performed too early or beyond a week of symptoms the result may also be negative.

I-1-6-2. The scan:

The chest scanner quickly established itself. Indeed, the abnormalities observed in confirmed cases have enabled the establishment of diagnostic criteria classifying patients in different categories: from unlikely to suspicious and through possible, with a sensitivity of up to 98%. However, the scanner image is not easily distinguishable from some other viral or atypical pneumonia **(Long et al., 2020).**

I-1-6-3. Serology:

Serology is also used as a method of diagnosis of COVID-19. IgM and IgA antibodies begin to appear from the fifth day of infection, and IgGs from the tenth day. For patients with chronic symptoms (> one week). In the diagnosis of COVID-19, serology is mainly used to determine the seroprevalence of the disease among populations **(Rong et al., 2023).**

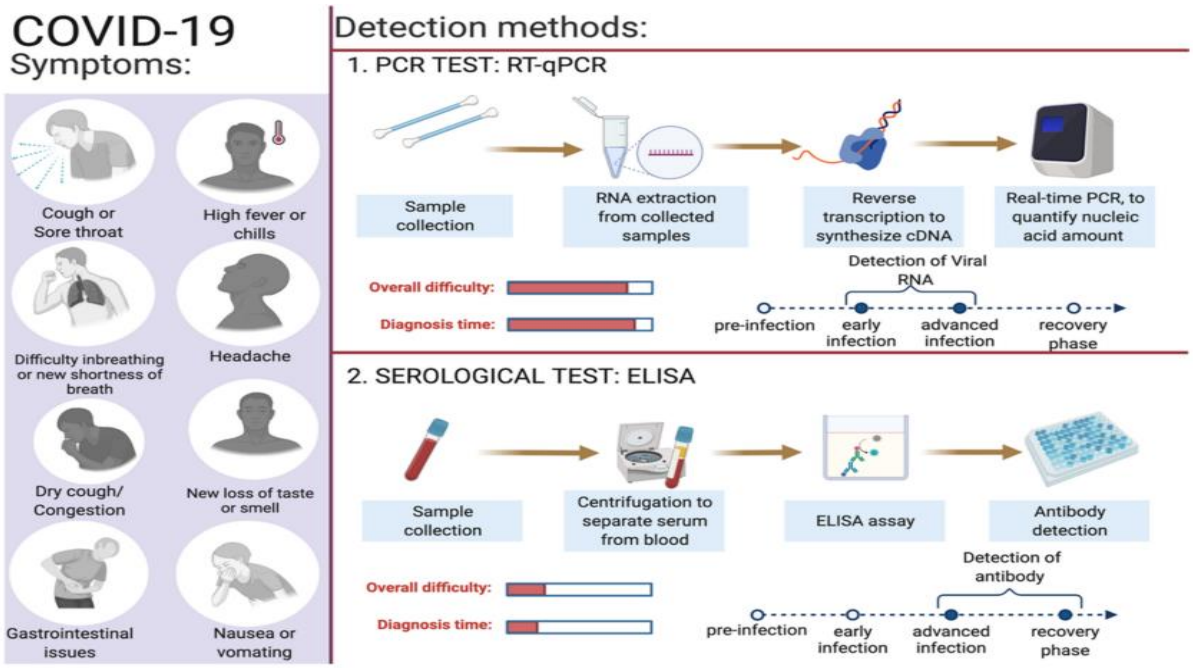


Figure 5 : Overview of COVID-19 symptoms and SARS-CoV-2 detection methods for COVID-19 diagnosis. **(Dutta et al., 2022)**

I-1-7. Treatment of the disease:

I-1-7-1. Oxygen therapy

Serious cases of COVID-19 can rapidly evolve into acute respiratory distress syndrome (AGD), leading to decreased organ functions and even death. Therefore, respiratory symptoms must be treated urgently.

Rapid and effective application of oxygen therapy to patients is recommended. If possible, patients should be treated by mixed inhalation with a ratio of hydrogen to oxygen =66.6/33.3% **(Singh & Kumar, 2021).**

I-1-7-2. Hydroxychloroquine:

Hydroxychloroquine is characterized by antiviral properties. Depending on the model, the treatment can be extended to 4 days and includes a dose of 400 mg of hydroxychloroquine orally twice daily followed byining a maintenance dose of 200 mg twice a day (18) **(Jankelson et al., 2020; White et al., 2020).**

I-1-7-3. Tocilizumab:

Tocilizumab is a humanized monoclonal antibody that blocks the action of interleukin-6 receptors. Interleukin-6 is involved in COVID-19 inflammation, it is produced by macrophages. Treatment with tocilizumab leads to a decrease in mortality **(Rubin et al., 2021)**.

I-2. ABO system:

Erythrocyte blood groups are antigens that are expressed on the surface of the red blood cell, genetically transmitted, and recognized by specific antibodies.

The immunogenic nature of their polymorphism explains their involvement in transfusion, in the context of pregnancy monitoring, in grafts and transplantations.

Currently, nearly 380 different blood group antigens belonging to around forty different systems are described.

I-2-1. The nature of each abo antigen:

It is possible to classify blood group antigens into two major categories based on their biochemical nature:

I-2-1-1. The blood groups of carbohydrate nature:

the leader of which is the ABO system. This system has 2 main antigens, A and B, coded by two alleles which are respectively the A allele and the B allele. Alongside these active alleles, there is a third inactive allele, the O allele. Depending on the genotype, we can have 4 different phenotypes: group A expressing antigen A (Genotype: A/A or A/O), group B expressing antigen B (Genotype: B/B or B/O), group AB expressing both antigens A and B (Genotype A/B), and group O expressing none of the antigens (Genotype: O/O)

Table 1 : Antigen and corresponding antibodies for each blood group

Antigen and corresponding antibodies for each blood group.(Shibeeb & Khan, 2022)		
ABO blood group	Antigen	Antibody
A	A	Anti-B
B	B	Anti-A
O	None	Anti-A and Anti-B
AB	A and B	None

This system shares several characteristics with other carbohydrate systems (H, P1PK, Lewis, I, GLOB).

- The first characteristic is related to their biochemical nature. Indeed, given their carbohydrate nature, the antigens of the ABO system are considered as "secondary products" of genes. Indeed, a gene that can only synthesize proteins must go through a protein intermediary to produce the antigen. This intermediary is an enzyme that can bind the antigen to the red blood cell. We do not go directly from the gene to the antigen but through the gene sequence to enzyme to antigen. Thus, the A allele codes for the enzyme A which binds antigen A to the surface of the red blood cell and so on.
- The second characteristic is related to their ubiquitous distribution both in the body (the ABO system antigens, present on endothelial cells, are true tissue groups involved in graft rejections in case of incompatibility) and in nature. Indeed, they are not unique to humans and are shared by many species including viruses and bacteria. The presence of antigens A and B in the environment, especially on microbiota bacteria, explains the synthesis of so-called natural antibodies outside of any interhuman stimulation such as transfusion or pregnancy. Thus, a group A subject, expressing antigen A on their cells, will synthesize an anti-B present in their plasma. A group B subject will have an anti-A, a group AB subject will have neither anti-A nor anti-B, and a group O subject will have an anti-A and an anti-B (table 1). These antibodies, present constantly (regularly) with major hemolytic power, impose transfusion compatibility rules for red blood cells, avoiding bringing the antigen corresponding to the recipient's antibody, for plasma avoiding bringing the

antibodies corresponding to the recipient's antigens. Thus, in the context of red blood cell concentrate transfusion, it can be understood that the universal recipient is O and for plasma transfusion, it is AB.

I-2-1-2. The blood groups of protein nature:

Whose leader is the RH (formerly "Rhesus"). These antigens are direct products of genes, and tend (with more or less important exceptions) to be localized on the red blood cell. Since these antigens are specific to humans, the occurrence of immunization can only happen through interhuman stimulation such as transfusion or pregnancy. These antibodies are called "immune" and "irregular" because their occurrence, following immunization, is not constant. The detection of these antibodies directed against blood group antigens other than ABO is carried out by the search for anti-erythrocyte antibodies (RAI). Among the 40 blood group systems described, 5 (Rh, Kell, Duffy, Kidd, MNS) are routinely explored due to their clinical significance (risk of transfusion reaction in case of administration of the corresponding antigen and risk of hemolytic disease of the fetus and/or newborn) of their antibodies and their frequency. They ensure 95% of routine transfusion compatibilities. **(Abdollahi et al., 2020)**

I-2-2. The Rh system:

The Rh blood group system, first described over six decades ago, is a complex and polymorphic system involving multiple antigens. Intense research has revealed the molecular basis of this system, revealing the genes responsible for Rh proteins and their interactions within the erythrocyte membrane.

The Rh blood group system includes nearly 50 antigens, with the most immunogenic being the RhD antigen (Rh1) **(Avent & Reid, 2000).**

The Rh system consists of two genes, RHD and RHCE, located on chromosome 1. The presence of the RhD antigen is determined by the combination of two alleles—the active RHD allele and the inactive d allele. An RhD+ individual can have genotypes RHD/RHD or RHD/d (RH:1=85% of the European population) , while an RhD- individual only has the genotype d/d (RH:-1=15% of the population) . also The genes encoding Rh proteins carrying two pairs of "antithetical" antigens: C (RH2)or c (RH4)with E(RH3) or e(RH5) antigens, along with the D antigen, have been cloned. The Rh glycoprotein is crucial for assembling the Rh protein complex on erythrocyte membranes**.(Avent & Reid, 2000)** Encoded by the RHCE gene, with allelic forms determining four possible antigenic combinations:

- The RH*Ce allele codes for the RhC and Rhe antigens

- The RH*ce allele codes for the Rhc and Rhe antigens
- The RH*Ce allele codes for the Rhc and RhE antigens
- The RH*CE allele codes for the RhC and RhE antigens **(Abdollahi et al., 2020)**

I-2-2. Characteristic of each blood group ABO (the surface antigens)

The ABO blood group antigens are oligosaccharides present on glycoproteins and glycolipids at the cell surface. These antigens are part of the ABO blood group system, which classifies blood into four main types: A, B, AB, and O. The A and B antigens are attached to glycoproteins and glycolipids on the surface of red blood cells. The main glycoproteins carrying the ABO antigens include Band 3, Band 4.5 proteins, and glycophorin. Specific sugar additions to an oligosaccharide precursor chain determine the antigenic determinants of the ABO blood group system**(*Blood Group Antigen - an Overview | ScienceDirect Topics*, n.d.)** .

The structure of the ABO blood group antigens involves specific sugar additions to precursor chains on glycoproteins and glycolipids. The A antigen is created by the addition of N-acetylgalactosamine to the precursor chain, while the B antigen is formed by adding galactose. The O antigen, on the other hand, lacks these additional sugars, resulting in an unmodified precursor chain.**(*Blood Group Antigen - an Overview | ScienceDirect Topics*, n.d.)**

The A and B antigens are formed by the addition of specific sugars to an oligosaccharide precursor chain, which can be bound through sphingosine to fatty acids (glycolipid) or through serine or threonine to a peptide chain (glycoproteins). The glycosyltransferase enzymes encoded by the ABO gene catalyze the addition of these specific sugars, determining an individual's blood group activity **(Green, 1989)**

I-3. susceptibility between group ABO and infectious diseases:

Since the time of its discovery, attempts have been made to study the potential linkage of the ABO blood group system with various disorders and infections. The polymorphism of the ABO blood group was reported to be associated with the susceptibility to, and outcomes of, several diseases and infections, including tumors, coronary heart disease, hepatitis B virus, SARS-CoV and Helicobacter pylori.(Jing et al., 2020; Liu et al., 2021) 13,14 In addition, growing evidence suggests a potential role of the ABO blood group in the SARS-CoV-2 infection susceptibility and severity**.(Miotto et al., 2021)**

I-4. Docking molecular:

I-4-1. Definition:

Molecular docking is a crucial technique used in the field of structural molecular biology and computational drug design. The primary objective of ligand-protein docking is to estimate and predict the most likely binding mode(s) of a ligand to a protein with a known three-dimensional structure. In addition, the process of docking protein-protein involves predicting the preferred orientation of one protein relative to another, aiming to understand the interactions between proteins and gain insights into biological mechanisms. Protein-protein docking is crucial for modelling protein complexes, especially when experimental determination of complex structures is challenging. **(Morris & Lim-Wilby, 2008)**

I-4-2. Docking objective:

The objective of protein-protein docking is to predict the binding mode and affinity of two proteins or a protein and a small molecule ligand. This is an important task in drug discovery and design, as it allows researchers to understand the interactions between proteins and their potential therapeutic agents, and to design new drugs that can modulate these interactions. Protein-protein docking algorithms use various scoring functions and optimization techniques to search the conformational space of the proteins and find the most favourable binding mode. The aim is to accurately predict the binding mode and affinity, which can be used to guide experimental studies and drug design efforts**.(Krüger et al., 2014)**

The aim of DOKING protein-protein is to enhance the immune system, specifically in the context of COVID-19. DOKING protein-protein is a fusion protein developed by researchers at the University of California, San Francisco (UCSF) and the University of California, Berkeley. It is designed to bind to the spike protein of SARS-CoV-2, the virus that causes COVID-19, and neutralize the virus.

I-4-3. Docking types:

The two types of protein-protein docking are:

I-4-3-1. Template-based docking:

This method involves manually docking the structures of individual proteins using the template structure of a dimer in the same protein family. This method is fast and simple, as it does not require automatic docking and scoring algorithms. The generated structure of the complex based on a template is minimized to obtain the docked conformation.**(Sable & Jois, 2015)**

I-4-3-2. Template-free docking:

This method involves docking the structures of monomers using docking algorithms with or without the support of experimental data. The structures of monomers are docked using docking algorithms, and several protein-protein docking methods are available. The calculated configurations are given a score based on energy functions used. One of the drawbacks of these methods is that it is almost impossible to search every possible rotation and translation for the complex geometry, making the calculation very time-consuming and seldom resulting in a unique solution method of computational in silico in the study of 15 protein-protein.**(Sable & Jois, 2015)**

I-4-4. Molecular docking methods and their use:

Protein-protein interactions play a fundamental role in a variety of biological processes, and the three-dimensional (3D) structures of the protein-protein complexes thus formed are a crucial resource for reasoning about their molecular functions. It is useful to determine the intricate architectures of these interactions, and molecular docking has been a key tool in this process.**(Christoffer et al., 2021)**

Numerous protein-protein docking techniques are available to automatically utilize the binding information from the PDB in docking. These include s LzerD (Venkatraman et al., 2009), Multi-LzerD (Esquivel-Rodríguez et al., 2012), ZDOCK(Mintseris et al., 2007), HADDOCK (Dominguez et al., 2003), ClusPro (Kozakov et al., 2017),RosettaDock (Lyskov and Gray, 2008), HEX (Ritchie and Venkatraman, 2010), SwarmDock(Torchala et al., 2013), ATTRACT (de Vries and Zacharias, 2013), and SymmDock (SchneidmanDuhovny et al., 2005) . unique web servers of our hybrid docking algorithm of template-based modeling and free docking, which can save cases with misleading templates. The server takes both sequence and structural inputs for proteins and supports protein-protein**.(Yan et al., 2017)**

I-5 Conception

Protein-protein docking is a computational method used to predict the interaction between two proteins, which is essential for understanding the molecular mechanism of various biological processes, including viral infection and it spread on the body by the blood thus to understand this mechanism we use the docking protein-protein between the corona virus proteins-protain of the ABO system .

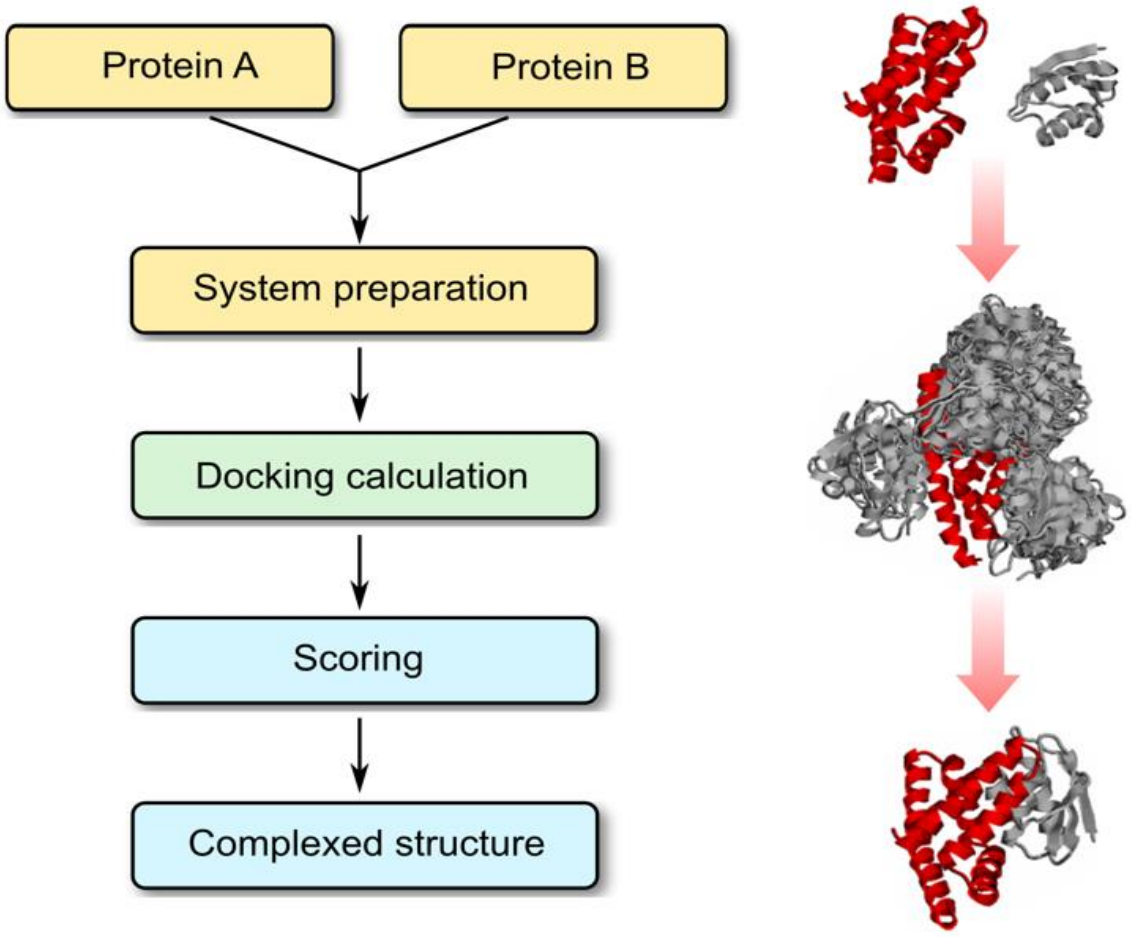


Figure 6: Protein–protein docking process **(Protein–Protein Docking - Profacgen, n.d.)**

I-6. Study design

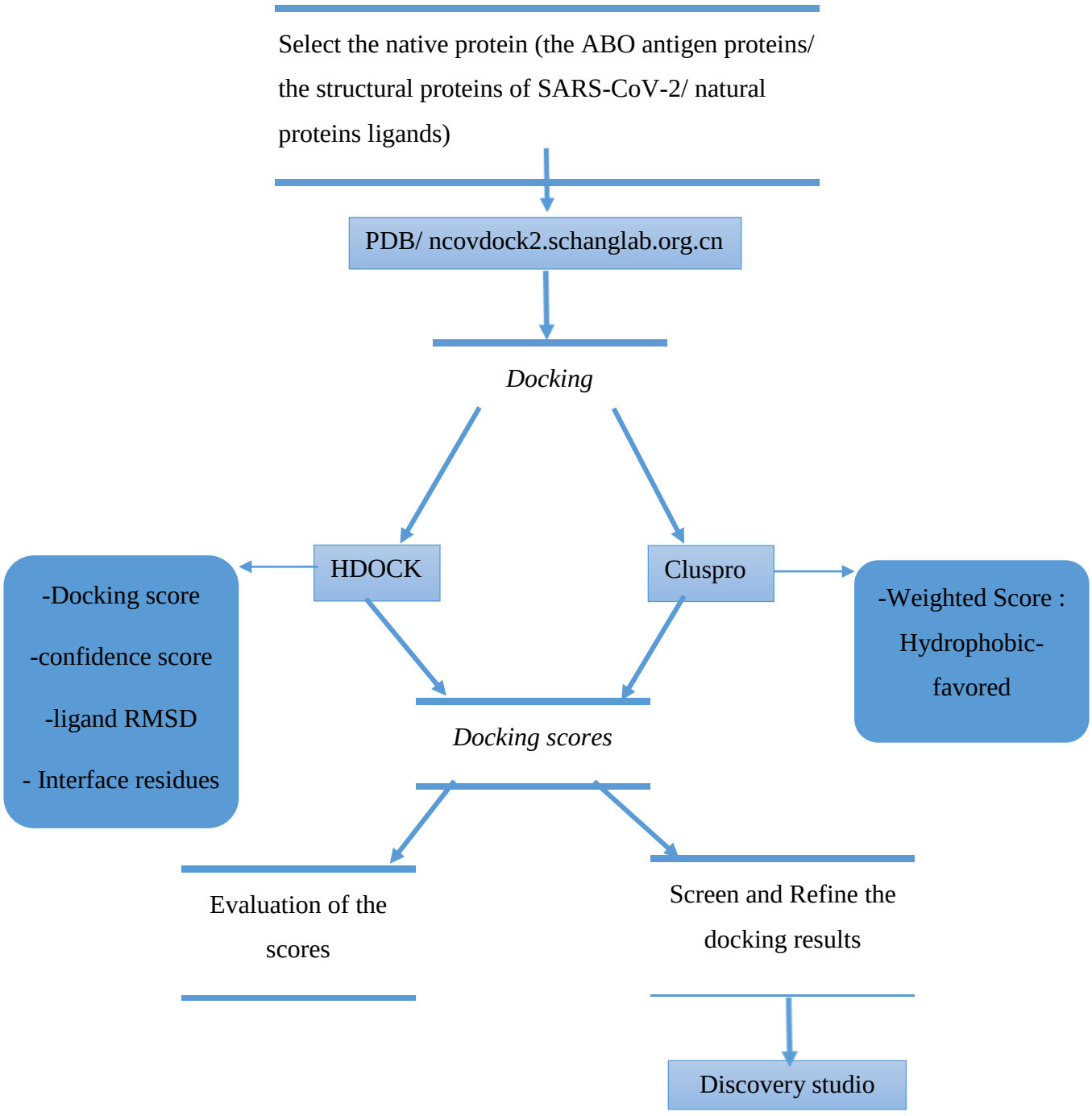


Figure 7: Docking Protocol

CHAPTER II: MATERIALS AND METHODS

II-1. Materials

II-1-1. Microcomputer:

Two Micro-computer was used for the execution, analysis, and interpretation of the results.

Table 2: The characteristics of the Laptop

	Micro-computers 1	Micro-computers 2
Processor	INTEL(R) Core (TM)i5	INTEL (R) Core (TM) i5
Graphic card	INTEL(R)HD graphics 520	INTEL(R)HD Graphics 520
RAM memory	64 Bits	64 Bits
Type of system	Operating system 64 bits	Operating 64 bits
Operating system	*windows* 10 *professionnel*	Windows 10 professionnel
System manufacturer	Hp	Lenovo

II-1-2. PDB:

The Protein Data Bank (PDB) is known as the International Virtual Data Core, Sources of basic information on atomic structure, crystallography, and related the three-dimensional (3D) structure of biomolecules, including nucleic acids and proteins (e.g.enzymes, immune glycoproteins, adhesins) for education and research. In this context, biotechnology, biopharmaceuticals, bioengineering, biomedicine, biology disciplines are directly dependent on the use of PDBs. In fact, data and information on biomolecule crystallography and 3D structures published by PDB have been enables us to use biochemical, biophysical and physicochemical

properties, including affinities and bonds of related macromolecules and small biomolecules.**(Behzadi & Gajdács, 2022)**[3]

The protein we used are encoded in the following table:

Table 3 : les Code PDB:

Code	protein	Molecule	chains
5TJK	Protein A.	Histo-blood group ABO system transferase.	A
5TJN	Protein B.	Histo-blood group ABO system transferase.	A
8H15	Protein Spike Closed status.	Spike glycoprotein.	A,B,C
8H16	Protein Spike Open status.	Spike glycoprotein.	A,B,C
8CTK	Protein Membrane.	Membrane protein.	A,B
8FD5	Protein Nucleocapsid.	Nucleoprotein.	A
MODEL	Protein Envelope.	**.**	ALL
1R42	ACE-2	Angiotensin I converting enzyme 2.	A
4FCG	G3BP1 Protein.	uncharacterized protein.	A
4NYA	14-3-3 Protein.	ThiM TPP riboswitch.	A,B
7NTK	PALS1	MAGUK p55 subfamily member 5.	A

[3] https://www.rcsb.org/

II-1-3. HDOCK

HDOCK is a web server designed for predicting protein-protein and protein-DNA/RNA interactions using a hybrid strategy. It supports both sequence and structure inputs for proteins, allowing users to input amino acid sequences or Protein Data Bank structures for the molecules they want to dock. The server runs on a Linux server with high-performance CPUs and memory, enabling fast docking calculations with an average running time of 10-20 minutes. Users can submit jobs without registration, track job status in real-time, and access results through a unique job ID link. The server can handle up to 20 concurrent jobs and queue hundreds more. Additionally, it provides options for specifying binding site residues and distance restraints to enhance docking accuracy. **(Yan et al., 2017)**

This step is for advanced users if they want to obtain more than 100 predicted complex models or filter the docked complex models with their own experimental information. The downloaded package contains an HDOCK output file, named like hdock_5c984053e4b83.out, that includes all 4392 docking solutions.[4]

II-1-4. Cluspro:

The ClusPro server, a prominent tool for protein-protein docking available, offers a user-friendly interface for basic usage, necessitating only two files in Protein Data Bank format. Beyond its fundamental features, ClusPro presents various advanced functionalities to enhance the docking process. These advanced options encompass capabilities such as eliminating unstructured protein regions, implementing attraction or repulsion forces, incorporating pairwise distance restraints, generating homo-multimers, analyzing small angle X-ray scattering (SAXS) data, and identifying heparin binding sites.[5]

II-1-5. BIOVIA Discovery studio:

BIOVIA Discovery Studio 2021: Bringing together over thirty years of research in a single setting using peer-reviewed and cutting-edge in silico methods including mechanical molecular, biotherapeutics development, free energy calculations, etc. From target identification to head of series optimization, it offers researchers an extensive toolkit to investigate the subtleties of protein chemistry and drive the discovery of small and large therapeutic compounds.[6]

[4] http://hdock.phys.hust.edu.cn/
[5] https://cluspro.org/login.php
[6] https://discover.3ds.com/discovery-studio-visualizer-download

II-2. Methods

II-2-1. Choosing and preparation of the proteins (receptor and target):

In our work, we used proteins in Pdb format, they downloaded from the “Protein Data Bank” (PDB). We choose them depended on their native nature.

The model Envelop small membrane protein (E protein): It forms pentamer and functions as ion channel, also named as E channel. The modeled structure of E protein was downloaded from the Zhang’s lab and prepared for peptide or antibody docking**(C. Zhang et al., 2020)**

https://ncovdock2.schanglab.org.cn/index/annotation/index.html

We use for docking the HDOCK website and cluspro without any changing in it form just upload them.

II-2-2. Molecular docking protein-protein process

II-2-2-1. Cluspro :

II-2-2-1-1. Input :

The current version of ClusPro provides a very simple home page for the basic use of the server, and a number advanced options that modify the docking process. Some options can be requested by simply clicking on a label, whereas others require providing additional information. Figure shows the web interface of the ClusPro server.the server accepts four types of inputs for proteins as follows:

i. Job Name: Provide a name for the job (optional).

i. Enter the four-digit PDB ID in the "PDB ID" field.

ii. Click on "Upload PDB" and select a file containing the structure in PDB format from your computer

iii. Click on the "DOCK" button to initiate the docking calculation.

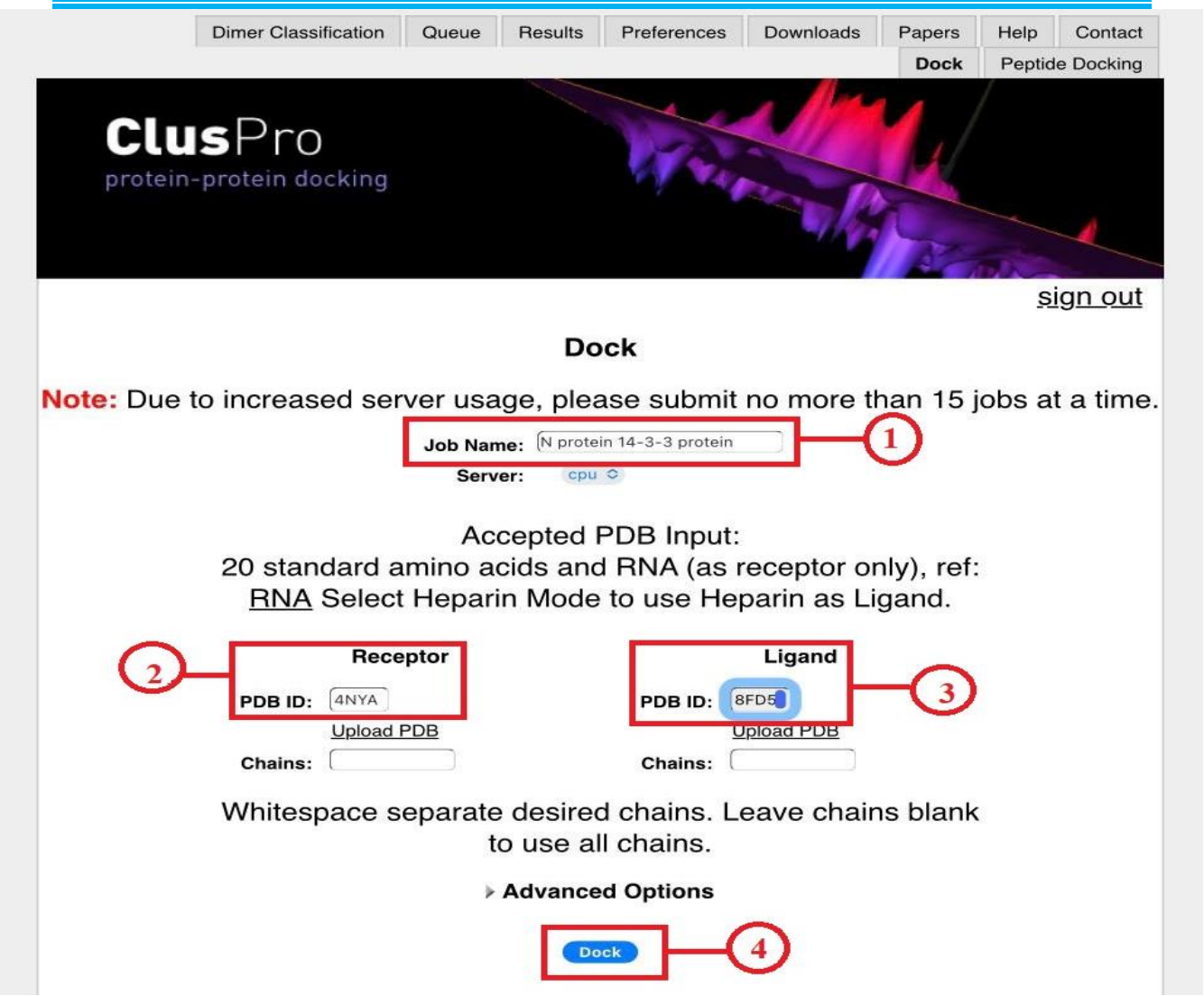


Figure 8 : Home screen of the ClusPro server.

The example shows submission of the job to dock Natural ligand of n protein (ligand, PDB ID 8FD5) to the Nucleoprotein (receptor, PDB ID 4NYA). Job Name (1), Receptor (PDB ID)(2),ligand (PDB ID)(3), Dock(4).

II-2-2-1-1. Output:

1.

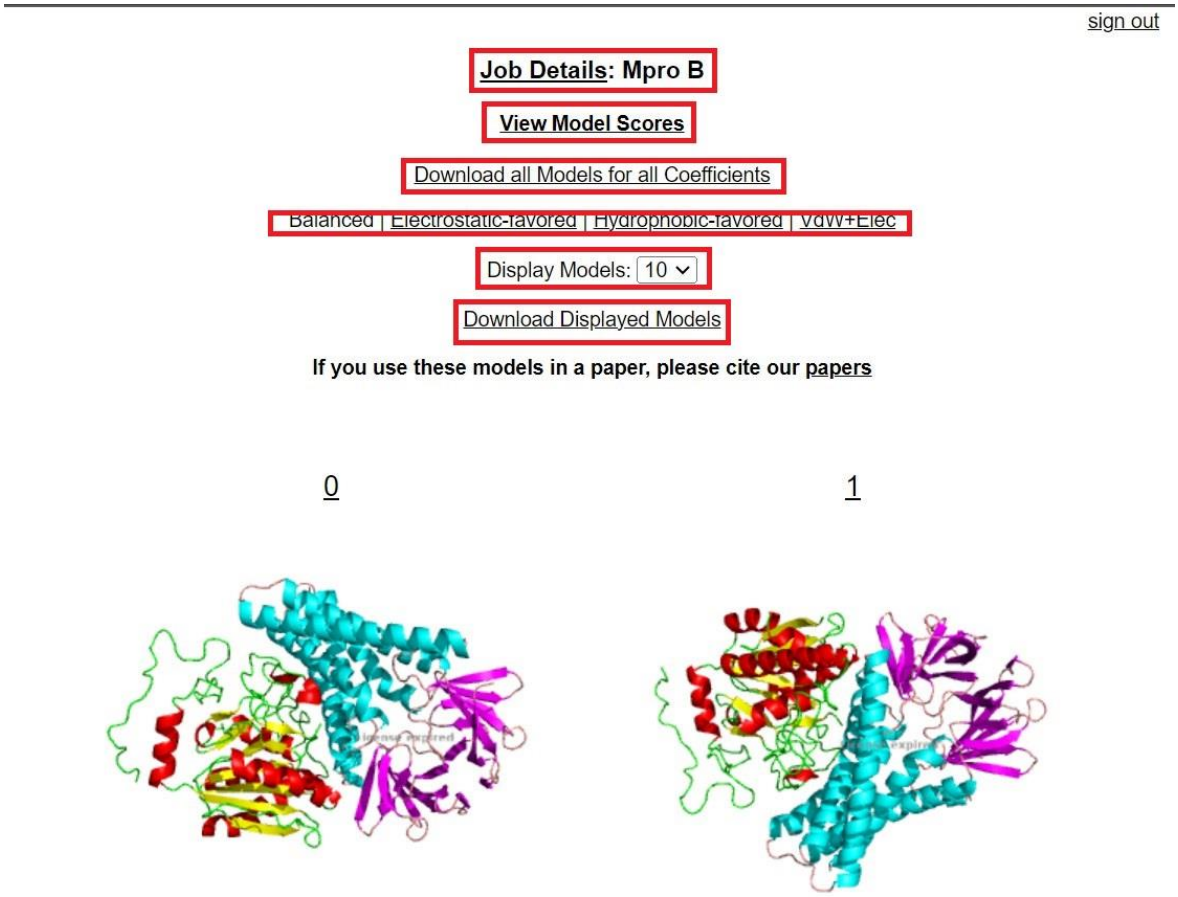


Figure 9: Screen capture of the ClusPro Results page for docking (ligand) to (receptor).

The page shows the job name and, by default, results for the balanced set of scoring function coefficients. Results for electrostatic-favored, hydrophobic-favored, or

van der Waals + electrostatics (VdW+Elec) sets can be viewed by clicking the corresponding labels. For each parameter set the result page shows small

pictures representing the top 10 models, but we can display more models (up to 30 (or less if fewer than 30 clusters have been created)). Clicking on

the number above a picture will download that model as a PDB file for your viewing. The page also provides the label to download models for all coefficients

sign out

Job Details: Mpro B

View Models

Balanced | Electrostatic-favored | Hydrophobic-favored | VdW+Elec

Download Model Scores for this Coefficient

Coefficient Weights

See *Kozakov et. al.* in Papers for a description of these terms

$$E = 0.40E_{rep} + -0.40E_{att} + 600E_{elec} + 1.00E_{DARS}$$

Cluster Scores

We strongly encourage you to read the FAQ related to these scores before using them.

Cluster	Members	Representative	Weighted Score
0	69	Center	-1532.8
		Lowest Energy	-1662.0
1	62	Center	-1556.3
		Lowest Energy	-1618.2
2	52	Center	-1277.4
		Lowest Energy	-1481.5

Figure 10 : Screen capture of the ClusPro Results page showing model scores.

for the balanced coefficient set when docking . The page shows the actual weighting coefficients of the energy terms, and a table that lists the clusters of docked structures in the order of cluster size. For each cluster, the table shows the size (i.e., the number of docked structures), the energy of the cluster center (i.e., the structure that has the highest number of neighbor structures in the cluster), and the energy of the structure in the cluster with the lowest energy.

II-2-2-2. HDOCK:

II-2-2-2-1. Input:

To best facilitate the use of the HDOCK server by normal users, especially for non-expert users, the server is designed to accept both sequence and structure inputs for proteins. **Figure 11** shows the web interface of the HDOCK server. For each molecule, the server accepts four types of inputs for proteins, two for structures and two for sequences, as follows:

i) Upload your pdb file in PDB format.

ii) Provide your pdb file in PDB ID:ChainID (e.g. 8H16:E).

iii) Copy and paste your protein sequence below in FASTA format.

iv) Upload your protein sequence file in FASTA format. **(Yan et al., 2017)**

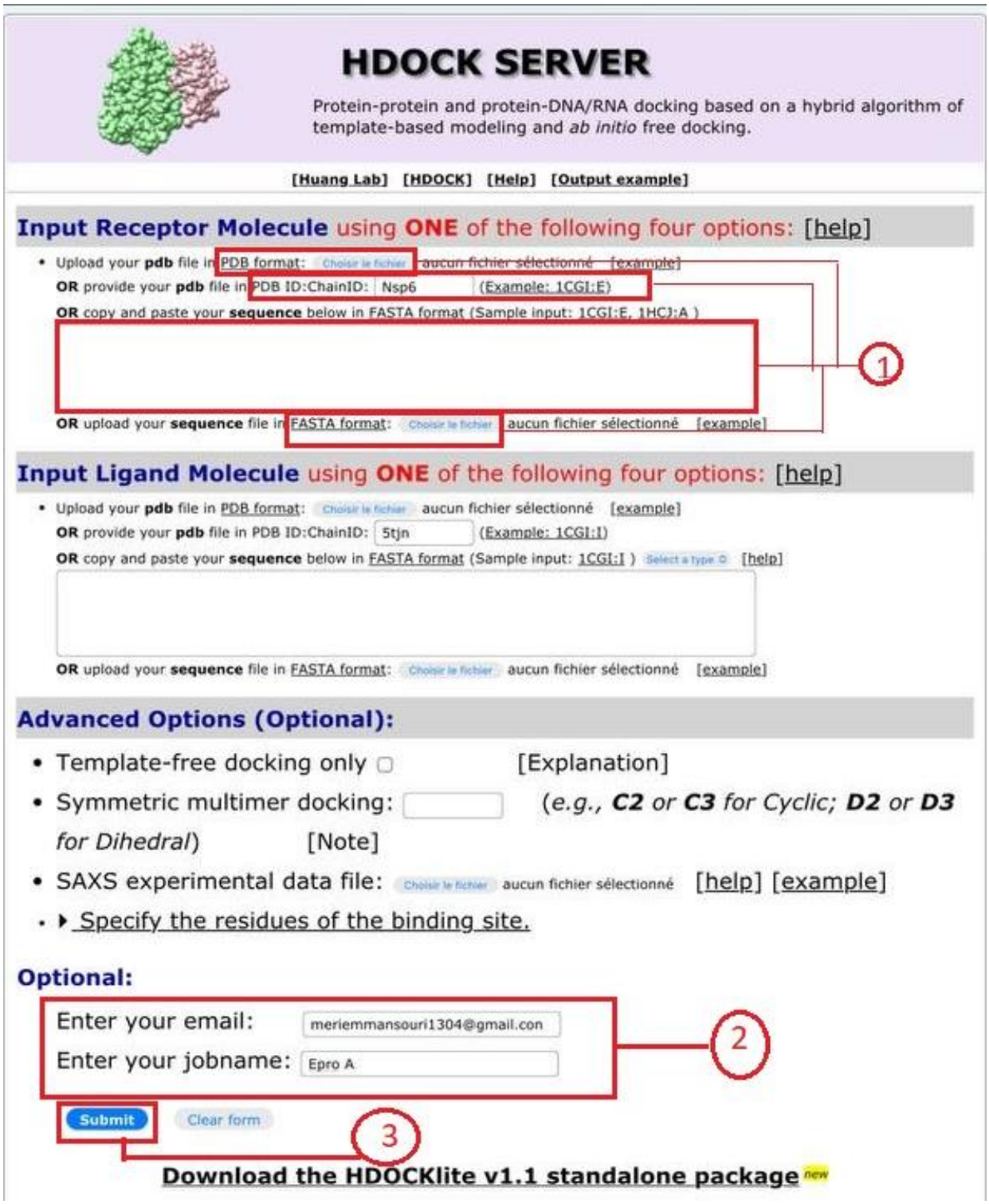


Figure 11: HDOCK server job submission.

that includes: PDB file/sequence input fields (1), optional user email address and job name (2) and the 'submit' button (3).

II-2-2-2-2. Output:

Once a job is finished, the job status page will be automatically redirected to the result page, as shown in **Figure II.12**. The docking results include three basic files:

i) Receptor PDB file uploaded by users or constructed by the server from the FASTA sequence provided by users.

ii) Ligand PDB file uploaded by users or constructed by the server from the FASTA sequence provided by users.

iii) HDOCK Output that include 4392 ligand binding modes represented by their transformations.**(Yan et al., 2017).**

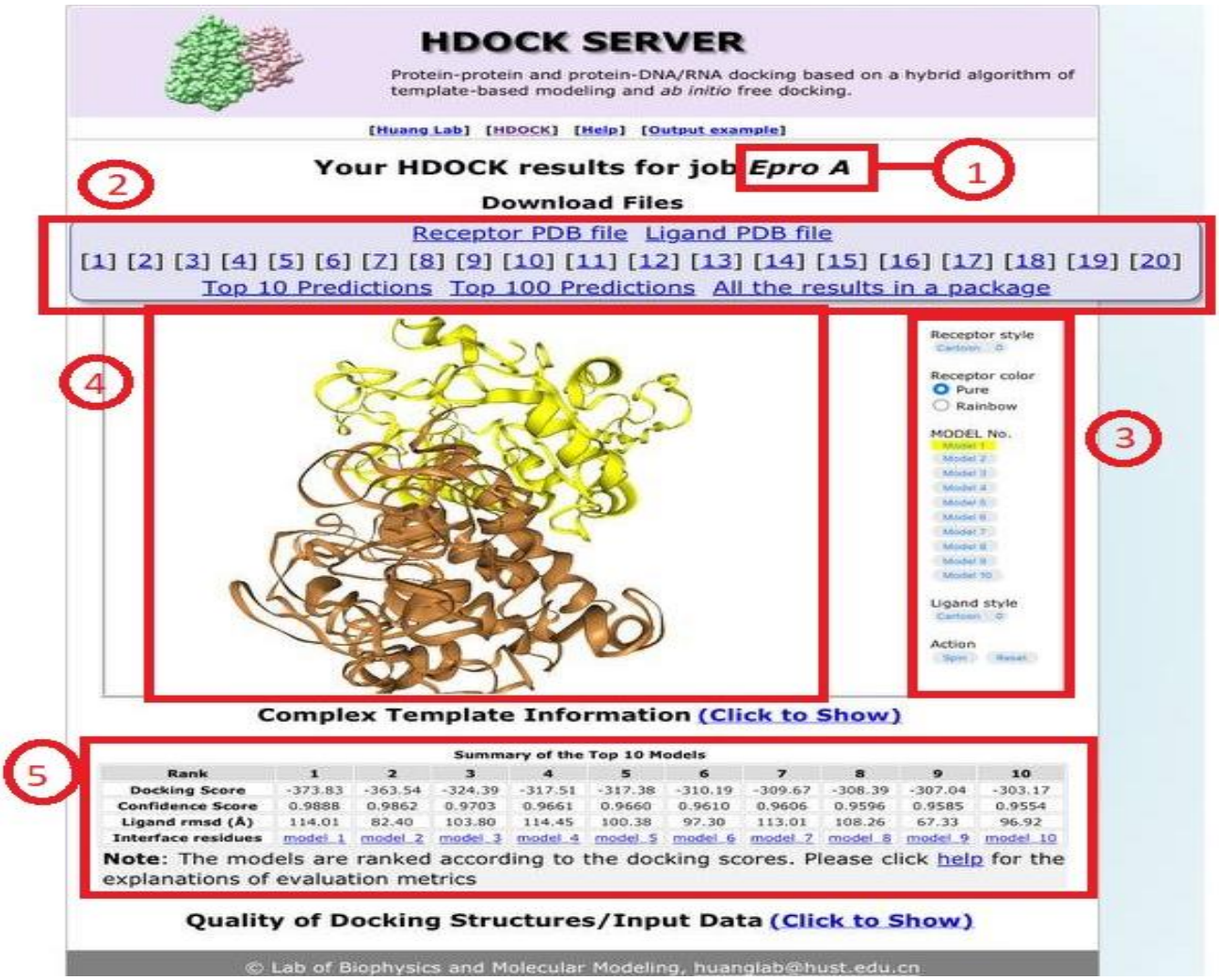


Figure 12: HDOCK server output page.

At the top of the page is the unique job ID (1), and the files for download (2). Optional buttons on the right can control Jmol to choose which model to view and how to view (3) on the left (4). A docking summary of the top 10 models is shown on the bottom (5).

II-2-2-3. Data analysis

- **Docking Score**: The docking scores are calculated by our knowledge-based iterative scoring function ITScorePP or ITScorePR. A more negative docking score means a more possible binding model, but the score should not be treated as the true binding affinity of two molecules because it has not been calibrated to the experimental data.**(*HDOCK Help*, n.d.)**
- **ITScorePR:** (Interaction Transformation Score for Protein-Protein Recognition) is a scoring function used in protein-protein docking algorithms like HDOCK.

ITScorePP is a knowledge-based scoring function used in protein-protein docking to evaluate the quality of interactions between proteins and assess the likelihood of a predicted protein complex being biologically relevant. It is an iterative scoring function that considers various factors, such as atomic interactions, surface complementarity, and statistical potentials derived from known protein complex structures

- **Confidence Score:** Given that the protein-protein/RNA/DNA complexes in the PDB normally have a docking score of around -200 or better, we have empirically defined a docking score-dependent confidence score to indicate the binding likeliness of two molecules as follows,

$$\text{Confidence_score} = 1.0/[1.0+e^{0.02*(\text{Docking_Score}+150)}]$$

Roughly, when the confidence score is above 0.7, the two molecules would be very likely to bind; when the confidence score is between 0.5 and 0.7, the two molecules would be possible to bind; when the confidence score is below 0.5, the two molecules would be unlikely to bind. Nevertheless, the confidence score here should be used carefully due to its empirical nature.**(*HDOCK Help*, n.d.)**

- **Ligand RMSD:** The ligand RMSDs are calculated by comparing the ligands in the docking models with the input or modeled structures. Therefore, the ligand RMSD is not necessarily a metric of the accuracy for the corresponding model.**(*HDOCK Help*, n.d.)**
- **Root Mean Square Deviation (RMSD):** is a measure used in various fields, including computational chemistry and structural biology, to quantify the difference between two sets of coordinates. It's often used to assess the similarity between molecular structures or to evaluate the accuracy of protein structure predictions compared to experimental data.

In simple terms, RMSD calculates the average distance between corresponding atoms in two structures after they are optimally aligned. Lower RMSD values indicate greater similarity between the structures.**(Sapundzhi et al., 2023)**

- **Interface residues:** The interface information for each model includes all the residue pairs within 5.0 A between the receptor and the ligand for the corresponding model. Users can click to check/download the files for different models**(*HDOCK Help*, n.d.)**
- **Coefficient Weights:** In the realm of protein-protein docking, the Weighted Score, often identified as the "cluspro score" within the framework of the ClusPro protein-protein docking server, serves as a pivotal metric for gauging the fidelity of predicted protein-protein complex conformations. It amalgamates diverse energy terms, encompassing electrostatic, van der Waals, and desolation energies, among others, into a comprehensive scoring scheme. This composite score elucidates the extent to which the predicted complex adheres to established tenets of protein-protein interactions, thus facilitating the appraisal of the putative biological relevance of the predicted structure. Lower scores typically correlate with a superior fit between the interacting proteins, indicative of a more plausible and potentially biologically significant protein complex arrangement.**(Kozakov et al., 2017)**
- Calculation of Weighted Score:

See Kozakov et. al. in Papers for a description of these terms, for example the balanced:

$\mathbf{E}=0.40E_{rep}+-0.40E_{att}+600E_{elec}+2.0E_{DARS}$

Table 4Weighting coefficients of PIPER energy terms in various docking modes (Kozakov et al., 2017)

Coefficient set	Energy term weight coefficients			
	Erep	Eattr	Eelec	EDARS
Balanced	0.40	−0.40	600.0	1.0
Electrostatic-favored	0.40	−0.40	1200.0	1.0
Hydrophobic-favored	0.40	−0.40	600.0	2.0
Van der Waals + electrostatics	0.40	−0.40	600.0	0.0
Others Mode, Set 1	0.30	−0.30	300.0	1.25

Others Mode, Set 2	0.50	−0.20	300.0	0.50
Others Mode, Set 3	0.50	−0.20	300.0	0.0

Choosing Among Docking Result Options: Balanced, Electrostatic-favored, Hydrophobic-favored, Van der Waals + electrostatics and more...

The website Cluspro provide many different options for docking because they believe good results go hand-in-hand with experimental knowledge of the complex. If you don't have any prior knowledge of what forces dominate in your complex, the website recommend using the balanced coefficients. If the complex is antibody-antigen, we recommend using our antibody mode.**(*ClusPro 2.0: Protein-Protein Docking*, n.d.)**

Choosing the "Hydrophobic-favored" docking option in ClusPro is suitable when the association between the two proteins is primarily driven by hydrophobic interactions. This option doubles the weight of the hydrophobic term in the energy function, which can help in cases where hydrophobic interactions are the dominant force in binding.**(Kozakov et al., 2017)**

Hydrophobic interactions: are a key driving force in protein-ligand binding and docking. The hydrophobic effect, where nonpolar groups in an aqueous environment exclude water molecules, generates a significant amount of free energy that stabilizes the folded protein structure and protein-ligand complexes **(Li et al., 2020).**

II-2-3. Screen and refine the docking results:

For screening and refining the score form we used the discovery studio to :

1- Delete the ligands associated with the target if they exist.

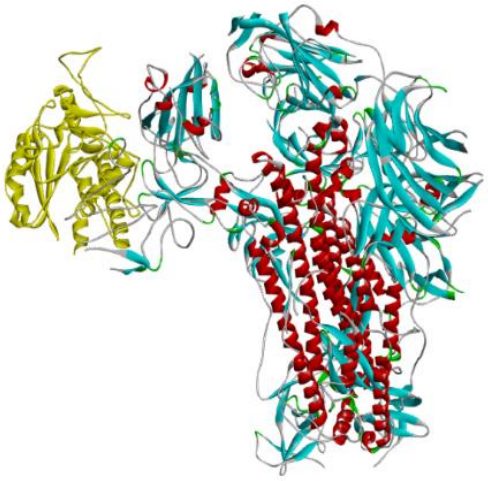
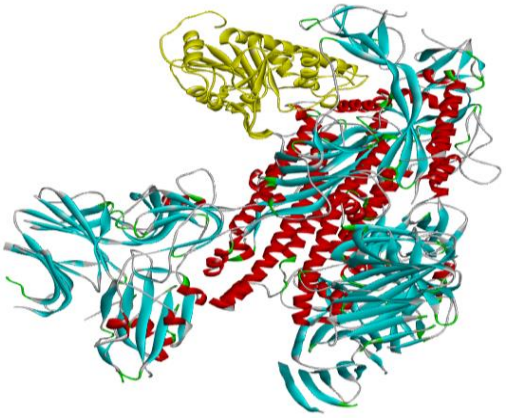
2- Remove water molecules and the hetatm.

CHAPTER III: RESULTS

III-1. ABO antigen A analysis:

The following table summarize the best score result for every molecular docking between the A antigen, encoded as 5TJK on PDB, and all structural proteins of the COVID 19 virus: spike protein, close and open status, the protein M, N and E. with the Graphic results: pose 3D representation.

Table 5: Results of molecular docking of ABO "A" proteins with corona virus structural proteins.

The COVID virus protein Code PDB	**Docking Score ITscorePP**	**Confidence Score**	**Ligand RMSD**	**Weighted Score "cluspro score"**	**The best pose score**
Protein Spike "closed Status" **8H15**	-319.09	0.9671	349.77	-1610.4	 A
Protein Spike "open Status" **8H16**	-285.53	0.9376	245.65	-1338.2	 B

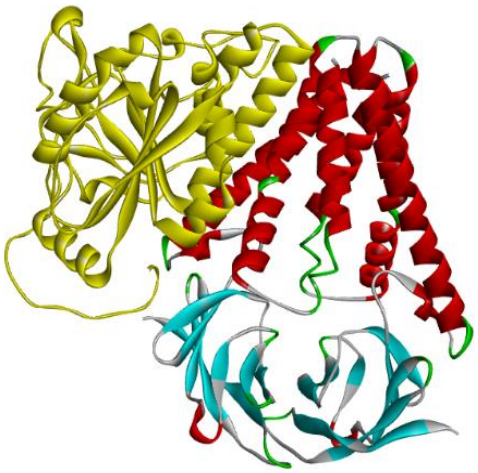
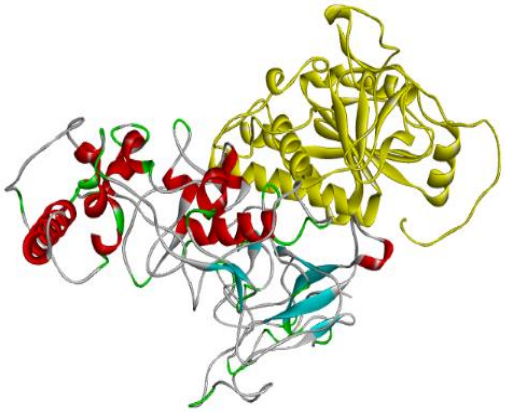
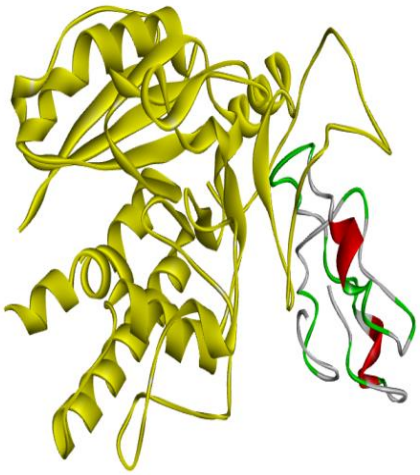
Protein M Protein Membrane **8CTK**	-370.42	0.9880	166.58	-2636.3	 C
Protein N Protein Nucleocapsid **8FD5**	-273.16	0.9215	62.47	-1191.5	 D
Protein E Protein Envelope **MODEL**	-299.02	0.9517	57.22	-2109.1	 E

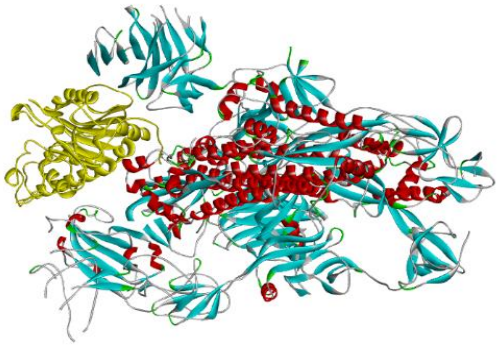
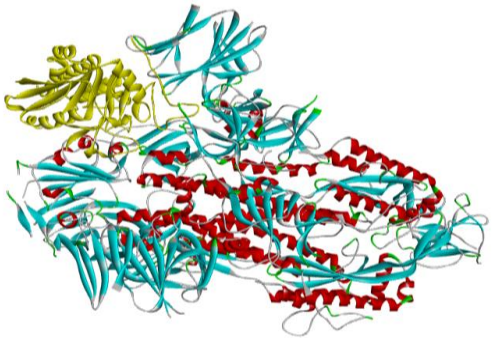
Figure 13: result of docking protein "A" with corona virus structural proteins. **A :**Protein spike "close status". **B:** with Protein spike "open status". **C:** with Protein Membrane "M". **D:** with Protein Nucleocapsid "N". **E:** Protein Envelope "E".

According to this data, we notice the that the antigen A could effectively bind all the structural proteins of the COVID19 virus. The best confidence score was obtained between the antigen A and viral M protein. The same observation was highlighted concerning the docking score ITscorePP evaluation. Interestingly, the best RMSD was obtained for the N protein which indicates a good overlap between the ligand in the reference structure and in the docking prediction. Systematically the best Weighted Score was sourced for M protein which indicates the high level of energy.

III-2. ABO antigen B analysis

The following table summarize the best score result for every molecular docking between the B antigen, encoded as 5TJN on PDB and all structural proteins of the COVID 19 virus: spike protein, close and open status, the protein M, N and E. with the Graphic results: pose 3D representation.

Table 6: Results of molecular docking of ABO "B" proteins with corona virus structural proteins.

The COVID virus protein **Code PDB**	**Docking Score** **ITscorePP**	**Confidence Score**	**Ligand RMSD**	**Weighted Score** **"cluspro score"**	**The best pose score**
Protein Spike "closed status" **8H15**	-338.77	0.9776	343.57	-1540.8	 F
Protein Spike "open status" **8H16**	-315.76	0.9649	365.78	-1507.5	 G

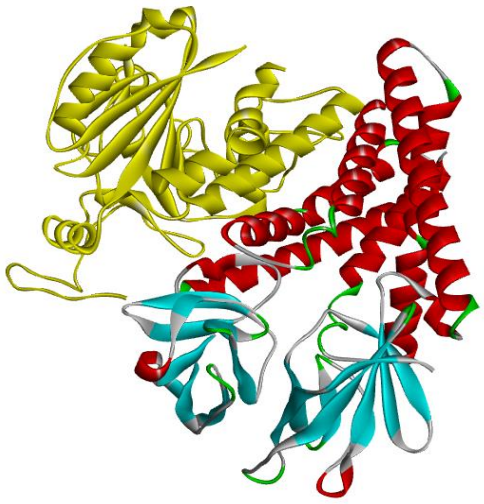
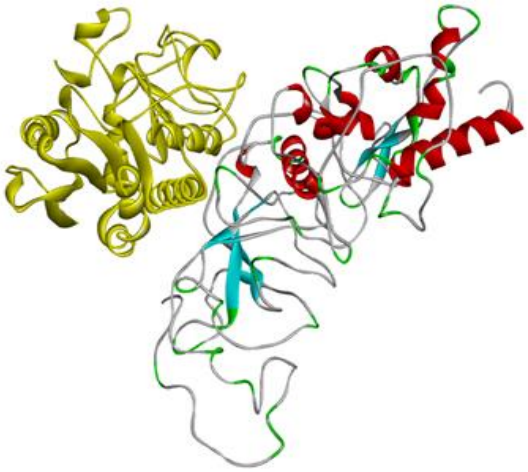
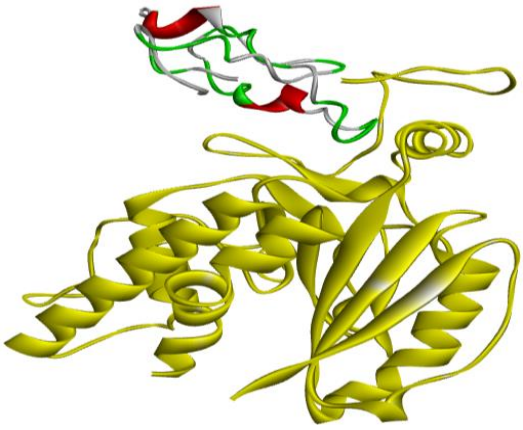
Protein M Protein Membrane **8CTK**	-343.84	0.9797	202.94	-2388.0	 H
Protein N Protein Nucleocapsid **8FD5**	-273.10	0.9214	93.01	-1312.4	 I
Protein E Protein Envelope **MODEL**	-304.67	0.9566	83.56	-1945.5	 J

Figure 14 :result of docking protein "A" with corona virus structural proteins. **F**:Protein spike "close status". **G**: with Protein spike "open status". **H**: with Protein Membrane "M". **I**: with Protein Nucleocapsid "N". **J**: Protein Envelope "E".

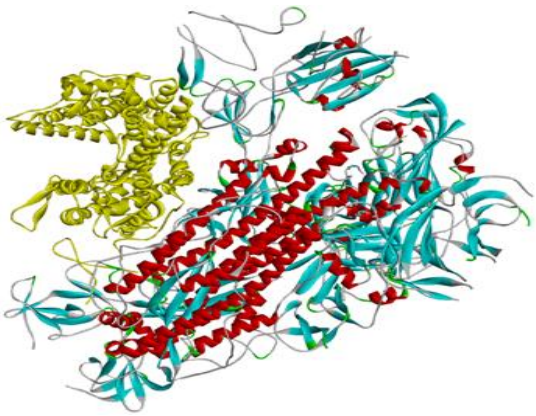
According to this data, we can see that the antigen B could effectively bind all the structural proteins of the COVID19 virus. The best confidence score was obtained between the antigen B and viral E proteins. The same observation was highlighted concerning the docking score evaluation. Interestingly, the best RMSD was obtained for the N protein which indicates a good overlap between the ligand in the reference structure and in the docking prediction. Objectively the best Weighted Score "cluspro score" was accessed for M protein which indicates the high level of energy.

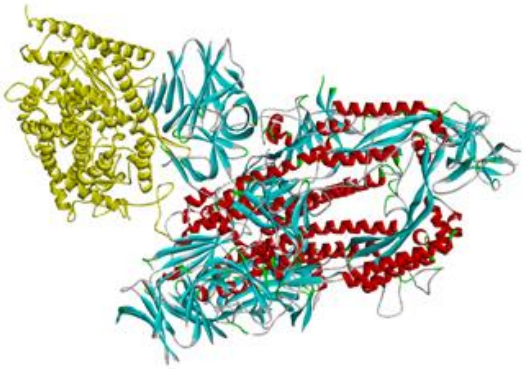
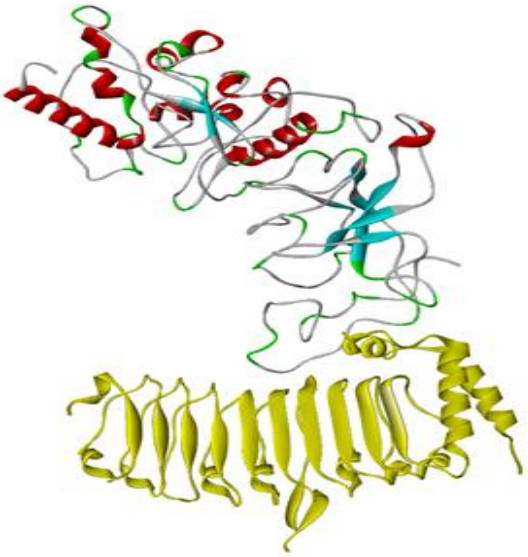
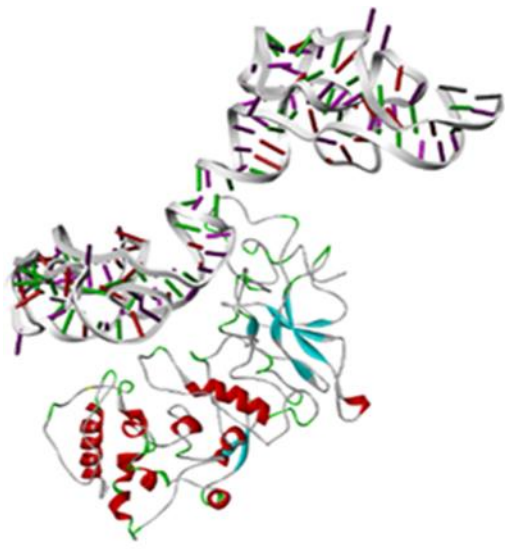
III-3. COVID-19 virus proteins analysis

III-3-1. Score calculation:

The following table summarize the best score result for every molecular docking between all structural proteins of the COVID 19 virus: spike protein, close and open status with ACE-2 encoded as 1R42 on PDB. and the protein N with his both ligand the G3BP1 encoded as 4FCG on PDB and the protein 14-3-3 encoded 4NYA on PDB and E with PALS1 protein, encoded as 7NTK natural proteins ligand. with the Graphic results: pose 3D representation.

Table 7: Results of molecular docking of between all structural proteins of the COVID 19 virus with their natural proteins ligand.

The COVID virus protein Code PDB	**Docking Score ITscorePP**	**Confidence Score**	**Ligand RMSD**	**Weighted Score "cluspro score"**	**The best pose score**
Protein Spike "closed status" **8H15**	-291.74	0.9445	236.68	-945.8	 K

Protein Spike “open status” **8H16**	-253.14	0.8872	287.46	-952.2	 L
Protein N Protein Nucleocapsid **8FD5**	-271.76	0.9195	52.62	-1332.0	 M
	-306.34	0.9580	132.49	-3001.0	 N

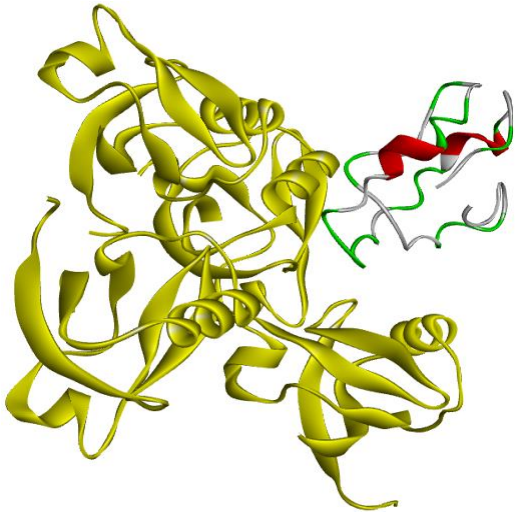
Protein E Protein Envelope **MODEL**	-221.43	0.8067	69.43	-1491.5	 O

Figure 15: Results of molecular docking of between all structural proteins of the COVID 19 virus with their natural proteins ligand. **K** result of docking protein "ACE-2" with spike "closed status".**L** result of docking protein "ACE-2" with spike "open status".**M:** result of docking protein Nucleocapsid "N" with his natural ligand G3BP.**N:** result of docking protein Nucleocapsid "N" with his natural ligand14-3-3 protein.**O:** result of docking protein Envelope "E" with his natural ligand PALS1

From this data we see the interaction between all the structural proteins of the COVID19 virus but the M with their natural ligand, we can see that the N protein has the highest confidence Score with his ligand 14-3-3 protein and same with the docking scores but the best RMSD result between the N protein and his ligand G3PB1. And noticeably the best weighted score was obtained for E protein with the protein PALS1.

III-4. Comparing the obtained score of the different proceeded molecular docking (Antigen A-viral proteins, Antigen B-viral proteins and viral proteins- natural ligand)

The following table summarizing all the previous result of the calculated scores in the aim to establish a general comparison between the blood antigen and natural ligand association with the structural proteins of the COVID19 virus.

Table 8 : Comparing the obtained score of the different proceeded molecular docking (Antigen A-viral proteins, Antigen B-viral proteins and viral proteins- natural ligand)

Ligand	SCORE	SPIKE CLOSE	SPIKE OPEN	M PROTEIN	N PROTEIN	E PROTEIN
A PDB CODE 5TJK	Docking Score	-319.09	-285.53	-370.42	-273.16	-299.02
	Confidence Score	0.9671	0.9376	0.9880	0.9215	0.9517
	Ligand RMSD	349.77	245.65	166.58	62.74	57.22
	Weighted Score "cluspro score"	-1610.4	-1338.2	-2636.3	-1191.5	-2109.1
B PDB CODE 5TJN	Docking Score	-338.77	-315.76	-343.84	-273.10	-304.67
	Confidence Score	0.9776	0.9649	0.9797	0.9214	0.9566
	Ligand RMSD	343.57	365.78	202.94	93.01	83.56
	Weighted Score "cluspro	-1540.8	-1507.5	-2388.0	-1312.4	-1945.5

	score”						
Natural ligand	SCORE	ACE-2		/	G3BP1 protein	14-3-3 protein	PALS1 protein
	Docking Score	-291.74	-253.14	/	-271.76	-306.43	-221.43
	Confidence Score	0.9445	0.8872	/	0.9195	0.9580	0.8067
	Ligand RMSD	236.68	287.46	/	52.62	132.94	69.43
	Weighted Score “cluspro score”	-945.8	-952.2	/	-1332.0	3001.0	-1491.5

- **Comparison between the protein A Scores and the protein B Scores**

1. **Spike Protein (Closed Status):**

Analysis: Protein B shows a more favorable docking score and confidence score compared to Protein A, indicating a slightly better interaction and higher confidence. The ligand RMSD values are similar, suggesting comparable binding conformations. The weighted score also indicates a stronger interaction for Protein B.

2. **Spike Protein (Open Status) :**

Analysis: Protein B again shows more favorable scores and higher confidence, indicating better interaction. The ligand RMSD is lower for Protein A, suggesting greater variability in binding conformations. The weighted score is more negative for Protein B, indicating a stronger interaction.

3. **Membrane Protein :**

Analysis: the interactions with M protein shown the best score among all the interaction with both A and B proteins, but Protein A has a more favorable docking score ITscorePP and confidence score, indicating better interaction and higher confidence and same with the weighted score. The ligand RMSD is lower for Protein A, suggesting more consistent binding conformations.

4. **Nucleocapsid Protein :**

Analysis: The docking scores ITscorePP are nearly identical for both proteins, indicating similar interactions and confidence levels. Protein A has a significantly lower ligand RMSD, suggesting more consistent binding conformations. The weighted score is more negative for Protein A, indicating a stronger interaction.

5. **Envelope Protein :**

Analysis: Protein A shows a more favorable docking score and, indicating better interaction and higher confidence. The ligand RMSD is lower for Protein B, suggesting more consistent in binding conformations. The weighted scores are similar, with Protein A having a slightly stronger interaction.

- From this analysis we can conclude:

- **Overall Interaction Strength**: Protein B generally shows more favorable docking scores and higher confidence scores across most interactions, suggesting better overall binding interactions with the COVID19 virus proteins compared to Protein A. However, M protein exhibiting the highest affinity with both A and B antigens when comparing to other structural proteins, and shows a greater affinity for the A antigen.
- **Binding Conformation Consistency**: Protein A tends to have lower ligand RMSD values, indicating more consistent binding conformations.
- **Weighted Scores**: The weighted scores, which reflect the overall interaction strength, generally favor Protein B, however with the membrane proteins.

These results indicate that while both proteins interact favorably with the COVID virus proteins, Protein B shows slightly higher binding affinities across most interactions compared to Protein A, except for the nucleocapsid protein where they are almost identical.

- **Comparison b1etween the blood antigen A and B scores to natural ligands' one:**

We compered the result of the ABO protein (A and B) interaction with all covid-19 structural proteins with the result of the structural protein with their natural ligand and we notice:

- **Binding Affinity:** Both ABO protein antigen (A and B) generally show higher docking scores and weighted scores compared to the natural ligand, indicating potentially stronger binding interactions with the COVID virus proteins.

- **Natural Ligand:** The natural ligand shows less negative docking scores overall, suggesting it might have a weaker interaction compared to the ABO proteins with COVID virus proteins.

This comparative analysis highlights the potential efficacy of ABO proteins in interacting with COVID virus proteins, possibly more so than natural ligands like ACE-2.

ABO proteins, both antigen A and B, generally exhibit stronger binding affinities to COVID virus proteins compared to the natural ligand. Protein B shows slightly better performance in terms of binding affinity and confidence scores than Protein A. The natural ligand, while still showing good binding, is generally weaker compared to the ABO proteins, particularly against the spike protein in both closed and open conformations.

CHAPTER IV: Discussion:

SARS-Cov-2 is a highly contagious and deadly viral disease that has caused a global pandemic. It severity and mortality is linked to its ability in to spread into the majority of organs and affecting the sensitive organs like lungs and heart and also it cause a blood clots. **(Alberca et al., 2021) (J. Zhang et al., 2022)**

This study is the first investigation giving computational data of the link between the ABO blood system and the severity of the COVID19 infection. We proceed by a protein-protein molecular docking using two free web sites HDOCK and Cluspro. We demonstrate that both the A and B antigens could be a ligand for all the structural proteins of the Sars-cov2. In this work we demonstrate that the A antigen presents a stronger link to Covid19 structural proteins mostly the M protein.

Our finding is corroborated to the epidemiological observations, various studies has given evidence that the A blood group is associated with a high risk of severe COVID-19 infection and worse outcomes. In study included 101 hospitalized COVID-19 patients in Tehran, Iran, where they analyzed the relationship between blood group, disease severity, and patient outcomes they demonstrated that the most common blood group among the affected cases was O+ (37.6%), followed by A+ (35.6%). Patients with blood group A were more susceptible to severe and fatal cases of COVID-19. The most common underlying disease was hypertension (45.5%) **(Kouchek et al., 2024)**.The A blood group is associated with a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and worse outcomes. Studies have consistently shown that patients with the A blood group have more comorbidities, such as hypertension, and are more susceptible to infections, including COVID-19**(Tamayo-Velasco et al., 2022).**

The underlying mechanisms may involve the presence of natural anti-A antibodies, which can interfere with the virus-host cell interaction. These findings have significant implications for public health and the management of the COVID-19 pandemic. Patients with severe COVID-19 often show elevated levels of D-dimer, a marker of blood clotting, and may require anticoagulation therapy to manage these risks. COVID-19 has been associated with an increased risk of blood clots, including deep vein thrombosis, pulmonary embolism, and micro-vascular thrombosis. This is partly due to the virus's impact on the endothelium (lining of blood vessels) and the immune system's inflammatory response **(Johnson et al., 2022).** This explanation miss many other severe symptoms was noted with COVID19 patients phenotypically classed as Blood A+

These symptoms may have relation with blood cell that help the virus to spread in the whole body organs and to prove this suggestion, which are not readily detectable in the laboratory. But the question highlighted behind those observation is what the impact played by the A antigen when comparing to the B one.

Actually, the computer simulation tools present themselves as a good shortcut for the development of new views without going through experimental efforts. These in silico models are essential for understanding complex biological systems and can be used to identify new drug targets and design more effective treatments. They are particularly useful in disease modeling, where they can complement experimental research and provide insights into the mechanisms underlying disease progression.**(Barh et al., 2014)**

Thus, we use bioinformatics tools to analyze global datasets, model molecular interactions. Employing epidemiological; in silico studies to dissect biological patterns and mechanisms.

In this work, we studied the interaction between the ABO system protein antigens A and B with the SAES-CoV-2 structural proteins: SPIKE in both statuses closed/open, protein membrane M, protein nucleocapsid N and protein envelope E. We searched for the scores of the complexes formed and evaluated their affinity. The main results of the proceeded protein-protein molecular dockings are grouped in the tables (5 and 6) which represent the binding affinity, confidence scores, the ligand RMSD, and the affinity energies.

In addition, we analyzed through the same web site the protein-protein interaction between the structural proteins of the virus and their natural ligand excepting for the M protein because of the lack of the available information. The obtained results were compared to the blood antigens score. We summarize all the data on tables (7).

In light of this, we demonstrate that both blood antigens possess the ability to bind this important structural protein of the virus and we notice overall interaction strength that the natural ligand has the lower scores compared to the ABO system antigen. Which give another argument supported that the ABO system displays stronger scores that take into consideration as favorable interaction except for the N protein, such interactions may attributed serve as potential causes for various systemic manifestations of the virus.

First conclusion when analyzing the data is probably the red blood cell could be considered as a mobile vehicle of the sars-cov2 to be spread into the whole body proved by the capacity of both A and B antigens to bind effectively and significatively to all the structural proteins of the virus. By the way, even patients with the O phenotype presented a systemic manifestation of the infection which means there are other factor leading to the spread of this virus or the H

antigen is the responsible part of the link between the blood antigens and the virus structural proteins. In this study we didn't investigate or analyze the sequences of the binding sites. It's one of the major limits of the two used web site. To confirm our idea, we have collected the necessary data (annex) that could help us to make this possible through more sophisticated platform in further study.

Generally, in our work the protein B shows slightly better performance with the three structural proteins (spike, N and E) in terms of binding affinity and confidence scores than protein A across most interactions. However, both the A and B antigens exhibit stronger scores when binding to M protein comparing to the other structural proteins. Interestingly, in this case the A antigen presents the highest binding affinity, confidence scores, the weighted scores, and the best ligand RMSD that the B antigen.

According to these observations we can conduct our second conclusion, this finding allowed us to suggest that probably the blood antigens could be the natural ligand of the M protein of the sars-cov2. This idea needs to be deeply studied and examined to be proven or rejected. In the second hand, and according to this data, we propose that the link between the blood phenotype A and the severity of the COVID19 infection could be linked to the ability of the GTA to bind M protein more than the B antigen. In this case, the antigen A could interfere to reenforce the role of the M protein during the virus cycle more potentially than the B antigen.

Looking the role played by the M protein (membrane protein) of coronaviruses, and according to the literature, this structural protein is implicated in virus assembly and morphology. It is involved in turning cellular membranes into sites where virus and host factors interact to produce new virus particles. The M protein interacts with other viral components such as the transmembrane domain, endodomain, and RNA carrying the genomic packaging signal. Studies have shown that the minimum requirement for producing virus-like particles is the co-expression of M and E proteins, with the additional co-expression of N increasing efficiency in some systems **(Neuman et al., 2011).**

The M protein is essential for coronavirus assembly, as it interacts with viral ribonucleoprotein (RNP) and S glycoproteins at the budding site. It forms a network of interactions that can exclude certain host membrane proteins from the viral envelope. Additionally, the M protein captures other structural proteins at the budding site, while the N protein protects the viral RNA genome, the S glycoprotein promotes receptor binding and fusion, and the E protein enhances budding**.(Neuman et al., 2011)**

According to this, the attachment of the A antigen and the M protein might have an impact on all the crucial step in the virus cycle and the pathology progression and severity.

So, the general idea that we can close with it this study is probably the red blood cell could be the natural vehicle of the virus to be spread into whole body and linked to the di-dimer formation. Also, the blood phenotype A is linked to the severe symptoms in many epidemiological and clinical study could be explained by the fact of its ability to bind strongly to the M protein than the other blood antigen. This leads the virus to achieve many vital organs and interfere with the virus cycle favorizing its assembly and morphology.

Protein-protein molecular docking allows to analyze the interaction between proteins, demonstrates their binding affinity, energy, and suggest new hypothesis or add an argument for an existing one's but still need to be validated through experimental or observational investigations to ensure their accuracy and reliability. In silico models are only as good as the data used to create them and can be limited by the complexity and accuracy of the algorithms employed. Moreover, these models are subject to the limitations of computational power and the assumptions made in their development **(Chang et al., 2022).** Plus, one of our limit work in utilizing the websites is that we couldn't input 3 proteins at the same time to try the AB blood type or the rhesus protein with A or B proteins or both. Furthermore, this interaction cannot be as perfect in realty as they modeled in the simulation bioinformatics tools.

General conclusion

This study is driven by the need to better understand the role of the ABO blood group system in COVID-19 susceptibility and severity, with the ultimate goal of improving public health responses and treatment options.

In this context, we provide valuable insights into the interactions between ABO blood group antigens A and B and the structural proteins of the COVID-19 virus through in silico methods. Our findings indicate that both antigen A and antigen B exhibit strong binding affinities to the COVID-19 structural proteins compared to the natural ligand, suggesting potential therapeutic applications. Protein A, in particular, shows slightly better performance with M protein in terms of binding affinity and confidence scores than Protein B. The comparative analysis underscores the efficacy of ABO proteins in interacting with the virus, possibly more effectively than natural ligands such as ACE-2. This study highlights the potential for the interaction with ABO proteins to be investigated further for therapeutic agents against COVID-19, due to their strong binding interactions with key viral proteins.

This study opens up several potential avenues for future research and therapeutic development. It highlights the strong binding interactions between ABO blood group antigens and COVID-19 structural proteins, suggesting that these proteins, particularly antigen A, may serve as effective therapeutic agents. . Future work should focus on experimentally validating these in silico findings, exploring the clinical implications of using the interactions with ABO antigens for therapeutic interventions such as in inhibit its interaction with protein M , and understanding the detailed mechanisms behind the stronger binding affinities observed. Additionally, the study encourages further investigation into the broader application of blood group antigens in combating other viral infections.

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ANNEXES

the Interface residues :

1) result of docking protein “A” with Protein spike close:

```
====== Model 1 ======

# Receptor interface residue(s):

ASN    321B     2.866

LEU    322B     2.855

PRO    324B     3.960

ARG    342B     4.857

LYS    343B     3.709

LYS    344B     2.142

SER    346B     2.453

ASN    347B     2.767

ASN    381B     4.206

TYR    383B     4.413

ASN    505B     4.279

ALA    506B     4.011

PRO    507B     2.922

THR    509B     4.771

PHE    545B     3.205

GLN    546B     2.481

PRO    547B     2.236

PHE    548B     3.051

LYS    566B     2.986

THR    567B     3.305

SER    568B     2.883

ARG     38C     3.586

GLY     39C     3.661

VAL     40C     3.505
```

```
TYR     41C     3.868

TYR     42C     2.881

GLU     45C     4.312

ILE     87C     3.413

TYR     88C     3.611

PHE     89C     2.477

ALA     90C     3.778

ALA     91C     4.572

VAL     98C     4.920

ARG     99C     2.482

GLY    100C     3.628

TRP    101C     3.226

PHE    103C     2.633

GLN    112C     3.296

SER    113C     2.992


# Ligand interface residue(s):

PRO     89A     3.566

TRP     90A     2.453

LEU     91A     2.855

GLU    242A     2.992

ALA    243A     4.881

THR    245A     4.727

TYR    246A     3.641

GLU    247A     3.881

ARG    248A     3.346

ARG    249A     2.477

PRO    250A     3.912

GLN    251A     3.413
```

```
GLN    253A     3.051

LYS    258A     2.633

ASP    259A     4.857

GLU    260A     4.413

ASP    262A     2.142

GLN    275A     4.594

ARG    279A     2.883

ARG    282A     3.767

ALA    283A     2.236

CYS    284A     4.301

GLN    286A     2.442

ALA    287A     4.836

VAL    290A     2.721

ASN    294A     3.505

GLY    295A     3.586

ILE    296A     4.338

VAL    299A     3.226

TRP    300A     2.482

TYR    309A     4.723

ARG    312A     3.971

HIS    313A     2.922

LYS    314A     2.818

HSH      1B     4.817

A2G      3B     4.116


# Receptor-ligand interface residue pair(s):

321B  -  90A     4.314

321B  -  91A     2.866

322B  -  91A     2.855
```

324B	-	89A	3.960
342B	-	259A	4.857
343B	-	89A	3.709
344B	-	89A	3.687
344B	-	90A	3.601
344B	-	262A	2.142
344B	-	314A	2.818
346B	-	89A	3.566
346B	-	90A	2.453
346B	-	314A	2.928
347B	-	90A	2.767
347B	-	91A	4.740
347B	-	314A	4.441
381B	-	314A	4.206
383B	-	260A	4.413
505B	-	312A	4.279
506B	-	312A	4.011
507B	-	312A	3.971
507B	-	313A	2.922
509B	-	312A	4.890
509B	-	314A	4.771
545B	-	286A	3.205
546B	-	286A	2.481
546B	-	290A	2.721
547B	-	279A	4.774
547B	-	282A	3.767
547B	-	283A	2.236
547B	-	284A	4.301
547B	-	286A	2.442

547B - 287A 4.836

547B - 309A 4.723

547B - 313A 4.310

548B - 253A 3.051

566B - 275A 4.623

566B - 279A 2.986

567B - 275A 4.594

567B - 279A 3.305

568B - 279A 2.883

38C - 294A 4.811

38C - 295A 3.586

39C - 251A 3.661

39C - 294A 4.624

40C - 251A 4.593

40C - 294A 3.505

41C - 250A 3.912

41C - 251A 3.868

41C - 294A 4.510

42C - 253A 3.451

42C - 290A 2.881

42C - 294A 4.467

45C - 312A 4.312

87C - 250A 4.451

87C - 251A 3.413

88C - 249A 4.964

88C - 251A 3.611

88C - 294A 4.939

88C - 295A 4.116

88C - 296A 4.805

```
89C  -  249A     2.477

89C  -  251A     4.667

89C  -  296A     4.338

90C  -  249A     3.778

91C  -  249A     4.572

98C  -  299A     4.920

99C  -  299A     4.059

99C  -  300A     2.482

99C  -  1B     4.817

99C  -  3B     4.116

100C  -  245A     4.727

100C  -  299A     3.628

100C  -  300A     4.764

101C  -  246A     3.641

101C  -  247A     3.881

101C  -  248A     3.932

101C  -  249A     4.063

101C  -  258A     4.686

101C  -  299A     3.226

103C  -  248A     3.346

103C  -  258A     2.633

112C  -  242A     3.296

113C  -  242A     2.992

113C  -  243A     4.881
```

2) result of docking protein “A” with Protein spike open:

```
====== Model 1 ======
# Receptor interface residue(s):
TYR    689B     2.199
ILE    694B     4.293
ALA    695B     4.794
```

```
PRO    697B     4.814
GLY    892B     4.609
LYS   1020B     4.802
VAL   1022B     2.342
TYR   1029B     3.457
PRO   1061B     4.626
PHE   1071B     4.728
PRO   1072B     3.675
ARG   1073B     3.668
GLU   1074B     2.686
GLY   1075B     4.898
VAL   1076B     3.901
ARG   1089B     1.999
ASN   1090B     4.392
PHE   1103B     2.363
SER   1105B     1.121
GLY   1106B     3.808
ASP   1109B     3.990
VAL   1110B     2.186
VAL   1111B     3.916
ILE   1112B     3.649
GLN    769A     2.632
MET    770A     2.645
TYR    771A     2.868
LYS    772A     4.806
TRP    868A     3.215
THR    869A     3.963
GLY    871A     2.461
ALA    872A     1.497
GLY    873A     2.797
ALA    874A     3.957
ALA    875A     2.227
LEU    876A     1.013
GLN    877A     3.076
ILE    878A     2.233
MET    882A     4.420
TYR    886A     2.689
ASN    889A     4.964

# Ligand interface residue(s):
PRO     89A     3.299
TRP     90A     3.120
LYS    124A     2.227
```

```
LYS    125A     2.645
TYR    126A     2.632
ARG    180A     3.664
TRP    181A     2.233
GLN    182A     4.401
VAL    184A     1.013
SER    185A     3.542
ARG    187A     4.563
GLU    242A     3.457
PRO    250A     2.686
GLN    251A     3.406
SER    252A     4.855
GLN    253A     2.363
TYR    255A     2.933
ILE    256A     4.933
PRO    257A     1.999
LYS    258A     2.342
ASP    259A     4.794
GLU    260A     2.528
ASP    262A     4.426
GLU    276A     3.655
ARG    279A     2.186
ARG    282A     3.207
GLN    286A     1.121
VAL    290A     3.191
ASN    294A     4.939
GLY    295A     4.674
ILE    296A     4.441
GLU    297A     2.689
TRP    300A     4.161
HIS    301A     3.471
LYS    308A     4.063
TYR    309A     4.961
ARG    312A     2.035
HIS    313A     3.649
LYS    314A     2.199
HSH      1B     4.365
A2G      3B     1.497

# Receptor-ligand interface residue pair(s):
689B  -  89A     3.299
689B  -  90A     3.120
689B  -  262A     4.426
```

689B - 314A 2.199
694B - 260A 4.293
695B - 259A 4.794
697B - 259A 4.814
892B - 250A 4.609
1020B - 258A 4.802
1022B - 242A 3.457
1022B - 258A 2.342
1029B - 258A 3.457
1029B - 259A 4.890
1061B - 312A 4.626
1071B - 253A 4.728
1071B - 286A 4.909
1072B - 253A 3.675
1073B - 250A 3.668
1073B - 252A 4.855
1073B - 253A 3.910
1073B - 294A 4.939
1074B - 250A 2.686
1074B - 251A 3.406
1075B - 312A 4.898
1076B - 260A 4.689
1076B - 312A 3.901
1089B - 255A 2.933
1089B - 256A 4.933
1089B - 257A 1.999
1089B - 259A 4.899
1089B - 260A 2.528
1089B - 308A 4.063
1089B - 312A 2.035
1090B - 255A 4.392
1090B - 259A 4.991
1103B - 253A 2.363
1103B - 290A 3.191
1105B - 286A 1.121
1106B - 286A 3.808
1109B - 279A 3.990
1110B - 279A 2.186
1110B - 282A 3.207
1111B - 313A 3.916
1112B - 276A 3.655
1112B - 309A 4.961
1112B - 312A 4.729

```
1112B  -  313A     3.649
769A  -  125A     2.676
769A  -  126A     2.632
770A  -  125A     2.645
771A  -  125A     2.868
772A  -  125A     4.806
868A  -  181A     3.215
868A  -  301A     4.494
869A  -  181A     3.963
871A  -  3B     2.461
872A  -  300A     4.161
872A  -  301A     3.471
872A  -  1B     4.365
872A  -  3B     1.497
873A  -  126A     3.662
873A  -  3B     2.797
874A  -  126A     3.957
874A  -  184A     4.995
874A  -  3B     4.958
875A  -  124A     2.227
875A  -  184A     4.906
876A  -  124A     3.953
876A  -  181A     3.133
876A  -  184A     1.013
876A  -  185A     3.542
876A  -  187A     4.563
877A  -  124A     4.512
877A  -  180A     3.664
877A  -  181A     3.076
878A  -  181A     2.233
878A  -  182A     4.401
882A  -  182A     4.420
886A  -  181A     4.230
886A  -  295A     4.674
886A  -  296A     4.441
886A  -  297A     2.689
889A  -  295A     4.964
```

3) result of docking protein “A” with Protein Membrane “M

```
====== Model 1 ======
# Receptor interface residue(s):
```

```
LEU     17B     2.228
GLU     18B     4.475
GLN     19B     2.900
TRP     20B     3.433
VAL     23B     3.395
LEU     27B     4.480
ARG     44B     3.865
PHE     45B     3.085
ILE     48B     2.690
ILE     49B     4.565
LEU     51B     3.604
ILE     52B     1.510
PHE     53B     4.234
TRP     55B     1.819
LEU     56B     2.086
PRO     59B     4.234
VAL     60B     2.185
LEU     62B     4.517
ALA     63B     3.189
VAL     66B     2.946
LEU     67B     4.084
VAL     70B     3.346
TYR     71B     2.369
TRP     92B     1.931
LEU     93B     3.127
PHE     96B     2.150
PHE    100B     2.742
PHE    103B     3.401
ARG    107B     4.781
SER    108B     4.998
MET    109B     1.958
PHE    112B     2.420
ASN    113B     3.924
PRO    114B     3.557
GLY    126B     3.320
THR    127B     3.044
ILE    128B     2.462
THR    130B     3.974

# Ligand interface residue(s):
ILE     59A     3.960
GLY     60A     3.610
GLU     61A     3.044
```

```
PHE     62A     2.462
MET     63A     4.907
TRP     90A     3.362
GLU    197A     4.096
ARG    198A     4.755
LEU    201A     3.643
SER    202A     3.085
PRO    227A     3.401
PRO    250A     3.346
GLN    251A     3.634
SER    252A     4.888
GLN    253A     2.946
SER    273A     4.349
GLN    275A     1.958
GLU    276A     3.569
GLN    278A     4.414
ARG    279A     1.510
LEU    280A     4.533
ARG    282A     2.018
ALA    283A     4.234
GLN    286A     2.185
MET    289A     2.900
VAL    290A     3.433
ALA    293A     2.951
ASN    294A     2.228
TYR    309A     1.819
LEU    311A     4.822
ARG    312A     3.127
HIS    313A     1.931
LYS    314A     2.742
PRO    315A     4.077
THR    316A     3.311

# Receptor-ligand interface residue pair(s):
17B  -  290A     4.355
17B  -  293A     2.951
17B  -  294A     2.228
18B  -  293A     4.475
19B  -  289A     2.900
19B  -  290A     4.658
19B  -  293A     4.369
20B  -  286A     4.366
20B  -  289A     4.991
```

20B	-	290A	3.433
20B	-	293A	4.211
23B	-	286A	4.767
23B	-	289A	3.395
27B	-	286A	4.480
44B	-	201A	3.865
45B	-	198A	4.755
45B	-	201A	4.278
45B	-	202A	3.085
48B	-	201A	3.643
48B	-	275A	2.690
49B	-	197A	4.601
49B	-	201A	4.565
51B	-	275A	4.143
51B	-	279A	3.604
52B	-	197A	4.096
52B	-	275A	3.948
52B	-	278A	4.414
52B	-	279A	1.510
52B	-	282A	2.018
53B	-	282A	4.234
55B	-	276A	4.863
55B	-	279A	3.162
55B	-	280A	4.533
55B	-	283A	4.688
55B	-	309A	1.819
55B	-	313A	2.755
56B	-	282A	2.086
56B	-	286A	2.804
59B	-	283A	4.234
60B	-	286A	2.185
62B	-	253A	4.673
62B	-	312A	4.517
63B	-	253A	3.189
63B	-	290A	4.627
66B	-	250A	4.767
66B	-	252A	4.888
66B	-	253A	2.946
67B	-	253A	4.343
67B	-	290A	4.084
67B	-	294A	4.369
70B	-	250A	3.346
70B	-	251A	3.634

```
71B  -  294A     2.369
92B  -  312A     4.326
92B  -  313A     1.931
93B  -  311A     4.822
93B  -  312A     3.127
96B  -  312A     3.149
96B  -  313A     2.150
96B  -  314A     4.473
100B  -  90A     3.362
100B  -  314A     2.742
100B  -  315A     4.077
100B  -  316A     3.311
103B  -  227A     3.401
103B  -  316A     4.698
107B  -  60A     4.781
108B  -  60A     4.998
109B  -  59A     3.960
109B  -  273A     4.349
109B  -  275A     1.958
112B  -  227A     3.755
112B  -  276A     3.569
112B  -  279A     2.420
112B  -  316A     3.833
113B  -  279A     3.924
114B  -  279A     3.557
126B  -  62A     3.320
127B  -  61A     3.044
127B  -  62A     3.986
128B  -  60A     3.610
128B  -  61A     3.611
128B  -  62A     2.462
128B  -  63A     4.907
130B  -  60A     3.974
```

4) result of docking protein “A” with Protein Nucleocapsid “N”

```
====== Model 1 ======

# Receptor interface residue(s):
TRP     52A     2.730
ARG     92A     3.052
ARG     93A     2.004
ARG     95A     2.560
ARG    107A     3.592
```

TYR	109A	2.342
ARG	149A	1.182
ALA	155A	2.792
ALA	156A	2.825
ARG	177A	2.054
GLY	178A	4.047
GLY	179A	2.918
SER	180A	3.264
GLN	181A	4.553
ALA	182A	2.921
SER	183A	3.391
ALA	208A	3.203
ARG	209A	2.519
MET	210A	3.222
ALA	211A	4.108
ASN	213A	3.002
LYS	249A	2.324
SER	250A	4.061
ALA	251A	2.946
ALA	252A	4.231
GLU	253A	3.009

Ligand interface residue(s):

TRP	90A	3.002
PRO	227A	4.483
LEU	228A	2.560
PRO	250A	4.223
SER	252A	4.080
GLN	253A	2.921
TYR	255A	2.324
ILE	256A	4.897
PRO	257A	4.061
ASP	259A	2.946
GLU	260A	2.626
SER	273A	4.078
GLN	275A	2.004
GLU	276A	2.790
GLN	278A	4.703
ARG	279A	2.342
LEU	280A	4.886
ARG	282A	2.730
ALA	283A	3.456
GLN	286A	1.182

```
ALA    287A     3.922
MET    289A     4.218
VAL    290A     3.391
LYS    308A     3.718
TYR    309A     2.918
LEU    311A     4.154
ARG    312A     2.054
HIS    313A     3.264
LYS    314A     2.717
PRO    315A     4.227
THR    316A     4.700

# Receptor-ligand interface residue pair(s):
52A  -  278A     4.703
52A  -  279A     2.934
52A  -  280A     4.886
52A  -  282A     2.730
52A  -  283A     3.901
52A  -  286A     3.768
52A  -  309A     4.917
92A  -  275A     3.052
92A  -  279A     4.294
93A  -  227A     4.483
93A  -  273A     4.078
93A  -  275A     2.004
93A  -  276A     2.790
93A  -  279A     2.563
95A  -  228A     2.560
95A  -  276A     2.843
95A  -  309A     4.327
95A  -  313A     3.395
95A  -  314A     2.717
95A  -  315A     4.227
95A  -  316A     4.700
107A  -  279A     3.592
107A  -  313A     4.483
109A  -  279A     2.342
149A  -  282A     2.835
149A  -  286A     1.182
155A  -  286A     2.792
155A  -  289A     4.218
156A  -  286A     2.825
177A  -  312A     2.054
```

177A - 313A 3.452
178A - 253A 4.047
178A - 287A 4.840
178A - 308A 4.216
178A - 312A 4.509
179A - 253A 4.940
179A - 283A 3.456
179A - 308A 3.893
179A - 309A 2.918
179A - 312A 4.408
179A - 313A 3.737
180A - 283A 3.532
180A - 309A 4.713
180A - 313A 3.264
181A - 286A 4.553
182A - 253A 2.921
182A - 286A 4.812
182A - 287A 3.922
182A - 290A 3.487
183A - 286A 3.582
183A - 290A 3.391
208A - 311A 4.939
208A - 314A 3.203
209A - 260A 2.626
209A - 311A 4.154
209A - 312A 2.519
209A - 313A 4.648
209A - 314A 4.968
210A - 312A 3.290
210A - 313A 3.434
210A - 314A 3.222
211A - 312A 4.108
213A - 90A 3.002
213A - 314A 4.437
249A - 250A 4.223
249A - 252A 4.080
249A - 255A 2.324
249A - 256A 4.897
249A - 308A 3.718
249A - 312A 4.994
250A - 255A 4.554
250A - 257A 4.061
251A - 255A 4.216

```
251A  -  257A     4.484
251A  -  259A     2.946
252A  -  259A     4.231
253A  -  259A     3.009
```

5) result of docking protein “A” with Protein Envelope “E”

```
====== Model 1 ======

# Receptor interface residue(s):
MET       1     3.441
TYR       2     2.496
PHE      23     4.456
VAL      25     4.016
PHE      26     2.338
LEU      27     3.183
LEU      28     2.931
VAL      29     3.156
THR      30     3.036
LEU      31     3.026
ALA      32     3.269
ILE      33     3.784
LEU      34     3.331
THR      35     2.108
ALA      36     3.341
LEU      37     4.147
ARG      38     3.740
LEU      39     2.879
CYS      40     3.317
VAL      52     3.668
PRO      54     3.362
SER      55     4.878
TYR      59     3.446
VAL      75     3.302

# Ligand interface residue(s):
GLY     60A     3.446
GLU     61A     3.713
MET     63A     4.456
LEU     66A     2.955
PRO     74A     3.331
VAL     76A     3.362
THR     78A     4.908
PRO     79A     3.740
```

```
CYS     80A     3.026
ARG     81A     4.520
VAL     86A     2.108
VAL     87A     3.348
THR     88A     2.879
PRO     89A     2.555
TRP     90A     3.177
LEU     91A     2.496
PRO     93A     3.269
THR     99A     3.036
PHE    100A     3.156
ASN    101A     4.625
ILE    104A     3.959
LEU    105A     3.246
GLN    108A     2.338
PHE    109A     3.721
GLU    223A     4.083
LEU    225A     2.931
THR    226A     3.276
PRO    227A     4.123
THR    316A     4.817
LYS    317A     3.324

# Receptor-ligand interface residue pair(s):
1  -  91A     3.441
2  -  89A     2.555
2  -  90A     3.177
2  -  91A     2.496
23  -  63A     4.456
25  -  93A     4.016
26  -  66A     2.955
26  -  104A     4.478
26  -  105A     4.353
26  -  108A     2.338
27  -  63A     4.462
27  -  105A     3.601
27  -  108A     3.183
27  -  109A     3.721
27  -  317A     4.491
28  -  93A     3.447
28  -  105A     4.891
28  -  108A     4.901
28  -  109A     4.689
```

28 - 225A 2.931
28 - 226A 3.276
28 - 227A 4.123
28 - 316A 4.817
28 - 317A 3.324
29 - 99A 3.527
29 - 100A 3.156
29 - 105A 3.246
29 - 223A 4.083
29 - 317A 3.817
30 - 99A 3.036
30 - 100A 4.148
30 - 101A 4.696
30 - 104A 3.959
30 - 105A 4.929
31 - 74A 3.723
31 - 80A 3.026
31 - 99A 3.136
31 - 100A 4.990
31 - 101A 4.625
32 - 86A 4.074
32 - 87A 4.171
32 - 93A 3.269
32 - 99A 3.762
33 - 87A 4.979
33 - 91A 3.784
34 - 74A 3.331
35 - 86A 2.108
35 - 87A 3.596
36 - 87A 3.348
36 - 91A 3.341
37 - 76A 4.147
38 - 76A 4.517
38 - 78A 4.908
38 - 79A 3.740
38 - 80A 4.696
38 - 81A 4.520
38 - 86A 4.268
39 - 87A 3.596
39 - 88A 2.879
39 - 89A 3.811
39 - 90A 4.885
39 - 91A 3.126

```
40  -  91A     3.317
52  -  91A     3.668
54  -  76A     3.362
55  -  74A     4.878
59  -  60A     3.446
59  -  61A     3.713
75  -  90A     4.049
75  -  91A     3.302
```

6) result of docking protein “B” with Protein spike closed

```
====== Model 1 ======

# Receptor interface residue(s):
ASP     44A     4.537
GLU     45A     1.565
ILE     46A     1.439
PHE     47A     3.382
SER     49A     4.437
THR    160A     3.909
PHE    161A     3.157
GLU    162A     2.922
TYR    163A     1.780
PHE    193A     3.762
TYR    195A     4.175
TYR    197A     4.630
PRO    218A     3.701
ILE    219A     2.952
PHE    220A     3.390
LYS    221A     2.686
LEU    222A     3.105
PRO    223A     3.982
MET    722A     4.077
TYR    723A     3.743
CYS    725A     4.485
GLN    818A     2.320
GLN    835A     4.812
LYS    836A     2.807
PHE    837A     2.278
ASN    838A     3.238
LEU    948A     2.507
SER    957A     4.720
VAL    958A     2.795
LEU    959A     3.428
```

ASN	960A	4.547
ASP	961A	3.061
LEU	963A	3.668
SER	964A	2.652
ARG	965A	1.999
LEU	966A	2.729
ASP	967A	3.071
LYS	968A	2.908
ARG	982A	3.380
GLN	396B	4.192
THR	402B	3.874
GLY	403B	2.798
VAL	404B	3.695
TYR	408B	4.857
TYR	440B	4.932
TYR	442B	1.696
LEU	443B	3.604
ARG	444B	3.610
HIS	445B	2.563
GLY	446B	2.910
LYS	447B	4.841

Ligand interface residue(s):

PHE	62A	2.507
MET	63A	2.278
VAL	64A	2.997
SER	65A	2.320
LEU	66A	4.381
PRO	67A	4.437
GLU	107A	3.382
ARG	110A	1.439
GLN	112A	2.795
ASN	113A	3.838
THR	114A	4.656
THR	115A	4.277
GLU	135A	4.870
GLY	144A	3.193
ARG	161A	2.922
VAL	162A	3.982
THR	163A	1.780
LEU	164A	2.686
GLY	165A	3.064
THR	166A	1.565

```
GLY    167A     3.288
ARG    168A     2.735
GLN    169A     3.762
LEU    170A     4.654
GLU    197A     3.639
PHE    200A     4.565
LEU    201A     2.154
SER    202A     4.063
GLU    203A     3.993
VAL    204A     2.615
ASP    205A     1.999
TYR    206A     4.338
PRO    250A     4.227
GLN    251A     2.251
SER    252A     3.314
GLN    253A     1.696
TYR    255A     3.604
PRO    257A     4.305
GLU    260A     3.029
SER    273A     2.652
VAL    274A     2.678
GLN    275A     2.908
GLN    278A     4.044
ARG    279A     4.684
ARG    282A     4.113
GLN    286A     2.798
VAL    290A     2.557
ASP    291A     1.900
ASN    294A     2.911
ILE    296A     4.049
LYS    308A     3.867
ARG    312A     2.563
HIS    313A     4.841
MPD    402A     2.952

# Receptor-ligand interface residue pair(s):
44A  -  110A     4.537
45A  -  110A     2.721
45A  -  144A     3.193
45A  -  166A     1.565
45A  -  167A     3.940
46A  -  110A     1.439
46A  -  113A     3.838
```

47A - 107A 3.382
49A - 67A 4.437
160A - 161A 3.909
161A - 161A 3.157
161A - 162A 4.249
161A - 163A 3.884
162A - 161A 2.922
162A - 162A 4.988
163A - 135A 4.870
163A - 161A 4.680
163A - 162A 4.429
163A - 163A 1.780
193A - 164A 4.857
193A - 168A 4.099
193A - 169A 3.762
193A - 170A 4.654
195A - 166A 4.175
197A - 166A 4.630
218A - 166A 3.701
219A - 165A 4.814
219A - 402A 2.952
220A - 163A 3.390
220A - 164A 3.766
220A - 165A 4.817
221A - 163A 4.236
221A - 164A 2.686
221A - 165A 3.064
221A - 166A 3.159
221A - 167A 3.288
221A - 168A 2.735
221A - 169A 4.477
222A - 163A 3.105
222A - 164A 4.783
223A - 162A 3.982
223A - 164A 4.926
722A - 62A 4.077
723A - 62A 3.743
725A - 62A 4.485
818A - 64A 3.689
818A - 65A 2.320
835A - 65A 4.812
836A - 65A 2.807
837A - 62A 3.162

837A - 63A 2.278
837A - 64A 2.997
837A - 65A 3.378
837A - 66A 4.381
838A - 62A 3.238
838A - 63A 4.549
838A - 65A 4.979
948A - 62A 2.507
957A - 62A 4.720
958A - 62A 4.252
958A - 112A 2.795
959A - 62A 3.428
960A - 62A 4.749
960A - 63A 4.725
960A - 112A 4.547
961A - 112A 3.106
961A - 113A 3.860
961A - 114A 4.656
961A - 205A 3.061
963A - 273A 4.913
963A - 275A 3.668
964A - 205A 3.096
964A - 206A 4.338
964A - 273A 2.652
964A - 274A 2.678
964A - 275A 3.402
965A - 113A 4.711
965A - 115A 4.277
965A - 200A 4.565
965A - 201A 2.154
965A - 202A 4.063
965A - 203A 3.993
965A - 204A 2.615
965A - 205A 1.999
965A - 273A 4.752
965A - 274A 3.560
965A - 275A 4.409
966A - 201A 2.729
966A - 274A 4.787
966A - 275A 3.208
967A - 197A 3.639
967A - 201A 3.454
967A - 275A 3.071

```
967A  -  278A     4.044
967A  -  282A     4.160
968A  -  275A     2.908
968A  -  279A     4.684
982A  -  62A     3.380
396B  -  286A     4.192
402B  -  282A     4.113
402B  -  286A     3.874
403B  -  286A     2.798
404B  -  286A     4.330
404B  -  290A     3.695
408B  -  253A     4.857
440B  -  290A     4.932
442B  -  250A     4.232
442B  -  251A     2.251
442B  -  252A     3.314
442B  -  253A     1.696
442B  -  290A     2.557
442B  -  291A     1.900
442B  -  294A     2.911
442B  -  296A     4.049
443B  -  250A     4.227
443B  -  253A     4.573
443B  -  255A     3.604
443B  -  308A     3.867
444B  -  312A     3.610
445B  -  257A     4.305
445B  -  260A     3.029
445B  -  312A     2.563
446B  -  312A     2.910
447B  -  313A     4.841
```

7) result of docking protein “B” with Protein spike open

```
====== Model 1 ======

# Receptor interface residue(s):
PRO     43B     2.933
ASP     44B     3.787
GLU     45B     2.306
ILE     46B     4.361
TYR     53B     4.556
```

```
THR     55B     3.234
GLN     56B     3.769
ASP     57B     2.605
PHE     83B     3.367
LYS     84B     3.154
ASP     85B     4.464
LYS    110B     3.144
GLN    112B     3.082
ARG    126B     3.947
ALA    127B     3.239
CYS    128B     2.966
TYR    163B     2.128
ILE    164B     1.752
SER    165B     3.772
LYS    188B     2.971
LYS    190B     3.945
ASP    191B     3.271
PHE    193B     3.640
TYR    195B     3.481
TYR    197B     3.699
LYS    221B     1.695
PRO    223B     2.996
LEU    224B     3.363
GLY    225B     4.547
ILE    226B     4.808
ASN    227B     2.440
ILE    228B     3.103
THR    229B     3.869
SER    353B     4.806
LEU    355B     4.611
TYR    356B     1.738
ASN    357B     2.439
SER    358B     3.004
THR    359B     2.443
PHE    361B     3.947
THR    372B     3.345
LYS    373B     4.496
PRO    317A     3.742
ASN    530A     4.760
PHE    551A     3.747

# Ligand interface residue(s):
PHE     62A     2.966
```

```
MET     63A     2.128
VAL     64A     3.168
SER     65A     1.752
LEU     66A     3.761
ARG     68A     3.742
VAL     70A     3.918
TYR     71A     3.869
GLN     73A     2.747
PRO     74A     1.695
LYS     75A     2.306
VAL     76A     2.687
LEU     77A     2.605
THR     78A     4.732
CYS     80A     3.271
TRP     90A     3.103
LEU     91A     2.440
ALA     92A     4.001
GLY     98A     4.853
THR     99A     3.746
ILE    104A     3.640
GLN    108A     2.996
THR    226A     4.679
PRO    227A     3.082
SER    235A     4.569
PHE    236A     3.287
GLY    238A     4.496
SER    239A     3.345
THR    245A     2.439
GLN    275A     3.396
GLU    276A     3.144
ARG    279A     3.367
TRP    300A     3.227
THR    316A     4.689
HSH      1B     1.738
FUC      2B     2.443
GLA      3B     3.147

# Receptor-ligand interface residue pair(s):
43B  -  76A     3.613
43B  -  77A     2.933
44B  -  75A     4.431
44B  -  77A     3.787
45B  -  73A     2.747
```

45B - 75A 2.306
46B - 75A 4.361
53B - 77A 4.556
55B - 77A 3.234
56B - 77A 3.769
57B - 76A 2.687
57B - 77A 2.605
83B - 91A 3.367
84B - 91A 3.154
85B - 91A 4.464
110B - 275A 3.396
110B - 276A 3.144
110B - 279A 3.367
112B - 226A 4.679
112B - 227A 3.082
126B - 62A 3.947
126B - 63A 4.814
127B - 63A 3.239
128B - 62A 2.966
128B - 63A 4.169
163B - 63A 2.128
163B - 64A 3.168
163B - 65A 4.105
163B - 66A 3.761
164B - 62A 3.043
164B - 63A 2.472
164B - 64A 3.364
164B - 65A 1.752
164B - 66A 4.756
165B - 65A 3.772
188B - 76A 2.971
190B - 76A 3.945
191B - 74A 4.011
191B - 78A 4.732
191B - 80A 3.271
191B - 98A 4.853
191B - 99A 3.746
193B - 71A 3.869
193B - 74A 3.643
193B - 104A 3.640
195B - 74A 3.677
195B - 75A 4.596
195B - 76A 3.481

197B - 76A 3.699
221B - 73A 4.424
221B - 74A 1.695
223B - 66A 3.937
223B - 71A 3.988
223B - 104A 3.741
223B - 108A 2.996
224B - 108A 3.363
225B - 108A 4.547
226B - 91A 4.808
227B - 90A 3.103
227B - 91A 2.440
227B - 92A 4.001
227B - 316A 4.689
228B - 91A 3.103
229B - 90A 3.869
229B - 91A 4.186
353B - 245A 4.806
355B - 1B 4.611
356B - 236A 4.525
356B - 1B 1.738
357B - 236A 3.287
357B - 245A 2.439
357B - 300A 3.227
357B - 1B 3.135
357B - 3B 3.840
358B - 300A 4.248
358B - 1B 3.004
358B - 3B 4.216
359B - 1B 4.074
359B - 2B 2.443
359B - 3B 3.147
361B - 1B 3.947
372B - 235A 4.569
372B - 239A 3.345
373B - 238A 4.496
317A - 68A 3.742
317A - 70A 3.918
530A - 70A 4.760
551A - 75A 3.747

8) result of docking protein “B” with Protein Membrane “M

```
 ====== Model 1 ======


# Receptor interface residue(s):
LEU     17B     2.081
GLU     18B     4.520
GLN     19B     3.125
TRP     20B     3.495
VAL     23B     3.477
LEU     27B     4.529
ARG     44B     4.081
PHE     45B     4.163
LEU     46B     4.207
ILE     48B     2.692
ILE     49B     4.193
LEU     51B     3.826
ILE     52B     1.725
PHE     53B     4.276
TRP     55B     1.952
LEU     56B     2.123
PRO     59B     4.296
VAL     60B     2.117
LEU     62B     3.878
ALA     63B     3.158
VAL     66B     2.875
LEU     67B     4.112
VAL     70B     3.466
TYR     71B     2.651
GLY     89B     4.612
TRP     92B     2.094
LEU     93B     3.080
PHE     96B     1.859
PHE    100B     2.666
PHE    103B     3.328
MET    109B     1.760
PHE    112B     2.290
ASN    113B     3.906
PRO    114B     3.729
GLY    126B     3.563
THR    127B     4.019
ILE    128B     2.452


# Ligand interface residue(s):
```

```
PHE     62A     2.452
TRP     90A     3.639
GLU    197A     4.065
ARG    198A     4.193
LEU    201A     3.974
SER    202A     4.163
PRO    227A     3.328
PRO    250A     3.466
GLN    251A     3.473
SER    252A     4.827
GLN    253A     2.875
SER    273A     4.475
GLN    275A     1.760
GLU    276A     3.563
GLN    278A     4.484
ARG    279A     1.725
LEU    280A     4.598
ARG    282A     1.874
ALA    283A     4.296
GLN    286A     2.117
MET    289A     3.125
VAL    290A     3.495
GLN    292A     4.307
ALA    293A     2.992
ASN    294A     2.081
TYR    309A     1.952
LEU    311A     4.922
ARG    312A     3.080
HIS    313A     1.859
LYS    314A     2.666
PRO    315A     4.317
THR    316A     3.472

# Receptor-ligand interface residue pair(s):
17B  -  290A     4.477
17B  -  293A     2.992
17B  -  294A     2.081
18B  -  293A     4.520
19B  -  289A     3.125
19B  -  290A     4.824
19B  -  292A     4.307
19B  -  293A     4.316
20B  -  286A     4.468
```

20B	-	290A	3.495
20B	-	293A	4.017
23B	-	286A	4.981
23B	-	289A	3.477
27B	-	286A	4.529
44B	-	201A	4.081
45B	-	198A	4.923
45B	-	201A	4.509
45B	-	202A	4.163
46B	-	198A	4.207
48B	-	201A	3.974
48B	-	275A	2.692
49B	-	197A	4.448
49B	-	198A	4.193
49B	-	201A	4.804
51B	-	275A	4.338
51B	-	279A	3.826
52B	-	197A	4.065
52B	-	275A	4.236
52B	-	278A	4.484
52B	-	279A	1.725
52B	-	282A	1.874
53B	-	282A	4.276
55B	-	279A	3.288
55B	-	280A	4.598
55B	-	283A	4.520
55B	-	309A	1.952
55B	-	313A	2.928
56B	-	282A	2.123
56B	-	286A	2.558
59B	-	283A	4.296
60B	-	286A	2.117
62B	-	253A	4.541
62B	-	312A	3.878
63B	-	253A	3.158
63B	-	290A	4.349
66B	-	250A	4.647
66B	-	252A	4.827
66B	-	253A	2.875
67B	-	253A	4.307
67B	-	290A	4.112
67B	-	294A	4.194
70B	-	250A	3.466

```
70B  -  251A     3.473
71B  -  294A     2.651
89B  -  312A     4.612
92B  -  312A     4.518
92B  -  313A     2.094
93B  -  311A     4.922
93B  -  312A     3.080
96B  -  309A     4.925
96B  -  312A     3.154
96B  -  313A     1.859
96B  -  314A     4.662
100B  -  90A     3.639
100B  -  314A     2.666
100B  -  315A     4.317
100B  -  316A     3.472
103B  -  227A     3.328
103B  -  316A     4.684
109B  -  273A     4.475
109B  -  275A     1.760
112B  -  227A     3.912
112B  -  276A     3.563
112B  -  279A     2.290
112B  -  316A     4.056
113B  -  279A     3.906
114B  -  279A     3.729
126B  -  62A     3.563
127B  -  62A     4.019
128B  -  62A     2.452
```

9) result of docking protein “B” with Protein Nucleocapsid “N”

```
====== Model 1 ======

# Receptor interface residue(s):
THR     49A     2.606
ALA     50A     4.759
TRP     52A     2.359
PHE     53A     3.777
ALA     55A     4.189
THR     91A     4.325
ARG     92A     4.587
ARG     93A     2.574
```

```
ILE     94A     4.497
ARG     95A     1.661
GLY     96A     3.263
GLY     97A     3.550
ASP     98A     4.344
GLY     99A     4.189
MET    101A     4.203
ARG    107A     2.688
TYR    109A     3.020
LYS    127A     2.813
ARG    149A     2.545
ASN    150A     3.549
PRO    151A     3.854
ARG    177A     2.181
GLY    178A     3.750
GLY    179A     2.308
SER    180A     2.945
GLN    181A     4.398
ALA    182A     2.205
SER    183A     4.904
PRO    207A     4.470
ALA    208A     3.411
ARG    209A     2.637
MET    210A     3.151
ASN    213A     2.742
LYS    249A     3.541
GLU    253A     4.859

# Ligand interface residue(s):
PHE     62A     2.813
TRP     90A     2.742
LEU     91A     4.189
GLN    112A     4.587
GLU    197A     2.545
ARG    198A     2.547
LEU    201A     4.255
TYR    206A     4.341
THR    226A     4.259
PRO    227A     2.574
LEU    228A     1.661
GLN    253A     3.541
GLU    260A     4.859
SER    273A     3.225
```

```
GLN    275A     2.874
GLU    276A     2.099
GLN    278A     4.118
ARG    279A     2.308
LEU    280A     4.109
ARG    282A     2.945
ALA    283A     2.696
GLN    286A     2.205
TYR    309A     3.883
LEU    311A     3.656
ARG    312A     2.637
HIS    313A     2.181
LYS    314A     3.211
PRO    315A     4.483
THR    316A     2.426

# Receptor-ligand interface residue pair(s):
49A  -  198A     2.606
50A  -  201A     4.759
52A  -  197A     4.310
52A  -  275A     2.874
52A  -  276A     4.935
52A  -  278A     4.118
52A  -  279A     2.359
52A  -  282A     3.514
53A  -  279A     3.777
55A  -  279A     4.189
91A  -  62A     4.325
92A  -  112A     4.587
93A  -  206A     4.341
93A  -  226A     4.259
93A  -  227A     2.574
93A  -  273A     3.225
94A  -  227A     4.497
95A  -  227A     3.008
95A  -  228A     1.661
95A  -  276A     2.099
95A  -  314A     4.156
95A  -  315A     4.483
95A  -  316A     2.426
96A  -  90A     4.389
96A  -  316A     3.263
97A  -  90A     3.550
```

97A - 91A 4.205
98A - 91A 4.344
99A - 91A 4.189
101A - 91A 4.203
107A - 275A 3.477
107A - 276A 2.688
107A - 279A 2.969
109A - 275A 3.020
109A - 279A 4.810
127A - 62A 2.813
149A - 197A 2.545
149A - 198A 2.547
149A - 201A 4.255
149A - 282A 4.107
150A - 198A 3.549
151A - 198A 3.854
177A - 312A 4.969
177A - 313A 2.181
178A - 283A 4.476
178A - 286A 3.750
179A - 279A 2.308
179A - 280A 4.109
179A - 282A 4.742
179A - 283A 2.696
179A - 309A 3.883
180A - 279A 3.100
180A - 282A 2.945
180A - 283A 4.900
180A - 309A 4.760
181A - 282A 4.398
182A - 282A 4.289
182A - 286A 2.205
183A - 286A 4.904
207A - 314A 4.470
208A - 311A 3.656
208A - 312A 3.411
208A - 313A 4.657
208A - 314A 3.884
209A - 312A 2.637
209A - 313A 2.857
210A - 312A 3.151
210A - 313A 3.801
210A - 314A 3.386

```
210A  -  316A     4.575
213A  -  90A     2.742
213A  -  91A     4.975
213A  -  314A     3.211
249A  -  253A     3.541
253A  -  260A     4.859
```

10) result of docking protein “B” with Protein Envelope “E”

```
====== Model 1 ======

# Receptor interface residue(s):
MET       1     3.368
TYR       2     2.445
PHE      23     4.073
VAL      25     3.969
PHE      26     2.078
LEU      27     3.410
LEU      28     2.887
VAL      29     3.121
THR      30     2.974
LEU      31     2.781
ALA      32     3.125
ILE      33     3.696
LEU      34     3.326
THR      35     1.871
ALA      36     3.183
LEU      37     4.027
ARG      38     3.636
LEU      39     2.923
CYS      40     3.322
VAL      52     3.698
PRO      54     3.281
SER      55     4.679
VAL      75     3.224

# Ligand interface residue(s):
MET     63A     4.073
LEU     66A     2.863
PRO     74A     3.326
VAL     76A     3.281
THR     78A     4.722
PRO     79A     3.636
CYS     80A     3.770
ARG     81A     4.325
```

```
VAL     86A     1.871
VAL     87A     3.183
THR     88A     2.923
PRO     89A     2.446
TRP     90A     3.304
LEU     91A     2.445
PRO     93A     3.125
THR     99A     2.781
PHE    100A     3.121
ASN    101A     4.104
ILE    104A     3.892
LEU    105A     3.273
GLN    108A     2.078
PHE    109A     3.643
GLU    223A     3.711
LEU    225A     2.887
THR    226A     3.094
PRO    227A     3.814
THR    316A     4.617
LYS    317A     3.381

# Receptor-ligand interface residue pair(s):
1  -  90A     4.975
1  -  91A     3.368
2  -  89A     2.446
2  -  90A     3.304
2  -  91A     2.445
23  -  63A     4.073
25  -  93A     3.969
26  -  66A     2.863
26  -  104A     4.371
26  -  105A     4.149
26  -  108A     2.078
27  -  63A     4.661
27  -  105A     3.909
27  -  108A     3.410
27  -  109A     3.643
27  -  225A     4.848
27  -  317A     4.291
28  -  93A     3.347
28  -  105A     4.971
28  -  109A     4.914
28  -  225A     2.887
```

28 - 226A 3.094
28 - 227A 3.814
28 - 316A 4.617
28 - 317A 3.456
29 - 93A 4.969
29 - 99A 3.776
29 - 100A 3.121
29 - 105A 3.273
29 - 223A 3.711
29 - 317A 3.381
30 - 99A 2.974
30 - 100A 3.884
30 - 101A 4.507
30 - 104A 3.892
30 - 105A 4.551
31 - 74A 3.988
31 - 80A 3.918
31 - 99A 2.781
31 - 100A 4.487
31 - 101A 4.104
32 - 86A 4.014
32 - 87A 4.195
32 - 93A 3.125
32 - 99A 3.613
33 - 87A 4.898
33 - 91A 3.696
33 - 93A 4.954
34 - 74A 3.326
35 - 80A 3.770
35 - 86A 1.871
35 - 87A 3.480
36 - 87A 3.183
36 - 91A 3.470
37 - 76A 4.027
38 - 76A 4.652
38 - 78A 4.722
38 - 79A 3.636
38 - 80A 4.408
38 - 81A 4.325
38 - 86A 4.125
39 - 87A 3.495
39 - 88A 2.923
39 - 89A 3.943

```
39  -  91A     3.151
40  -  91A     3.322
52  -  91A     3.698
54  -  76A     3.281
55  -  74A     4.679
75  -  90A     4.014
75  -  91A     3.224
```

11) result of docking Protein spike close status with his natural protein ligand ACE2

```
====== Model 1 ======

# Receptor interface residue(s):
SER    750A     3.054
ALA    754A     2.043
GLU    755A     4.655
ASP    757A     3.979
ARG    758A     3.075
ARG    761A     2.427
LYS    768A     2.394
LEU    846A     3.110
ALA    872A     4.931
ASN    522B     3.201
THR    539B     4.110
PRO    540B     2.831
SER    541B     3.417
SER    542B     2.471
LYS    543B     2.537
ARG    544B     1.330
GLN    546B     4.793
VAL    555B     4.250
ASP    572B     3.066
ASP    600B     4.777
GLN    632B     3.331
ALA    654B     4.546
GLY    655B     4.956
LEU    681B     2.980
ASP    684B     4.538
ILE    687B     2.554
ALA    688B     3.145
TYR    689B     3.121
SER    690B     2.913
ASN    691B     4.228
THR    693B     1.821
ILE    694B     2.419
```

```
ALA    695B     3.683
VAL   1022B     3.899
GLY   1028B     4.217
TYR   1029B     3.322
THR   1059B     4.105
PRO   1061B     3.216
PHE   1071B     3.070
PRO   1072B     4.557
GLY   1075B     4.516
VAL   1076B     3.700
ARG   1089B     2.727
PHE   1103B     2.485
SER   1105B     3.536
VAL   1110B     3.288
VAL   1111B     4.730
ILE   1112B     4.623
MET     37C     2.454
ARG     38C     4.105
VAL     40C     3.769
TYR     41C     4.436
TYR     42C     2.843
PHE     47C     4.549
ARG     48C     3.761
SER     49C     2.602
ASP     50C     2.214
THR     51C     1.695
LEU     52C     2.835
PHE     62C     2.998

# Ligand interface residue(s):
ASP    213A     3.201
GLY    214A     4.343
TYR    215A     2.831
GLY    220A     3.931
ILE    223A     4.479
GLU    224A     3.331
SER    254A     2.394
PRO    258A     4.738
ILE    259A     4.588
LYS    416A     4.311
GLU    467A     2.980
ILE    468A     4.788
PRO    469A     3.983
```

ASP	471A	4.538
GLN	472A	4.888
PHE	523A	4.402
GLN	524A	2.427
PHE	525A	4.573
GLU	527A	2.214
ALA	528A	3.004
GLN	531A	1.695
ALA	532A	4.938
LYS	534A	2.843
HIS	535A	4.513
GLU	536A	2.454
GLY	537A	4.287
GLU	549A	4.793
GLN	552A	4.875
LYS	553A	2.833
ASN	556A	1.924
MET	557A	4.066
LEU	568A	3.113
GLU	571A	2.488
ASN	572A	1.330
VAL	573A	3.574
VAL	574A	2.300
GLY	575A	2.537
ALA	576A	4.285
LYS	577A	3.297
ASN	580A	4.918
ARG	582A	4.250
PRO	583A	4.093
ASN	586A	2.835
ASN	599A	4.682
LYS	600A	2.043
ASN	601A	2.427
SER	602A	3.729
PHE	603A	3.075
ASP	615A	4.931
UNK	903B	4.646
UNK	904B	3.914
UNK	905B	3.848
UNK	906B	3.322
UNK	907C	4.035
UNK	927D	2.554
UNK	928D	1.821

```
UNK    929D     3.528
UNK    931D     2.913
UNK    932D     2.419
UNK    933D     3.505
UNK    935D     3.656
UNK    936D     2.727
UNK    937D     4.012
UNK    939D     3.070
UNK    940D     4.630
UNK    942D     3.536
UNK    943D     2.485
UNK    944D     3.887
UNK    945E     3.797
UNK    947E     3.288
UNK    949E     4.623

# Receptor-ligand interface residue pair(s):
750A  -  600A     3.054
754A  -  599A     4.682
754A  -  600A     2.043
754A  -  601A     4.119
755A  -  600A     4.655
757A  -  601A     3.979
758A  -  259A     4.588
758A  -  601A     3.807
758A  -  602A     4.380
758A  -  603A     3.075
761A  -  258A     4.738
761A  -  601A     2.427
761A  -  602A     3.729
761A  -  603A     3.567
768A  -  254A     2.394
846A  -  601A     3.110
872A  -  615A     4.931
522B  -  213A     3.201
522B  -  214A     4.670
539B  -  213A     4.686
539B  -  214A     4.343
539B  -  577A     4.110
540B  -  215A     2.831
540B  -  571A     4.843
541B  -  215A     3.417
541B  -  571A     3.430
```

542B	-	215A	3.600
542B	-	568A	3.113
542B	-	571A	2.488
542B	-	572A	2.471
543B	-	571A	4.231
543B	-	575A	2.537
543B	-	576A	4.285
544B	-	552A	4.875
544B	-	553A	2.833
544B	-	556A	1.924
544B	-	557A	4.066
544B	-	571A	4.480
544B	-	572A	1.330
544B	-	573A	3.574
546B	-	549A	4.793
555B	-	582A	4.250
572B	-	215A	4.736
572B	-	571A	3.066
572B	-	577A	3.297
600B	-	224A	4.777
632B	-	220A	3.931
632B	-	223A	4.479
632B	-	224A	3.331
654B	-	467A	4.546
655B	-	467A	4.956
681B	-	467A	2.980
681B	-	468A	4.788
681B	-	469A	3.983
681B	-	472A	4.888
684B	-	471A	4.538
687B	-	927D	2.554
688B	-	927D	3.336
688B	-	928D	3.145
689B	-	927D	3.121
689B	-	928D	4.028
689B	-	931D	3.718
690B	-	927D	4.572
690B	-	928D	3.847
690B	-	931D	2.913
691B	-	931D	4.228
693B	-	928D	1.821
693B	-	929D	3.816
693B	-	931D	4.401

693B - 932D 4.039
694B - 928D 3.261
694B - 929D 3.528
694B - 932D 2.419
694B - 933D 4.052
695B - 928D 4.727
695B - 929D 3.683
1022B - 903B 4.646
1022B - 904B 3.914
1022B - 905B 3.899
1022B - 907C 4.035
1028B - 905B 4.217
1029B - 905B 3.848
1029B - 906B 3.322
1059B - 932D 4.105
1061B - 935D 3.656
1061B - 939D 3.216
1071B - 939D 3.070
1071B - 940D 4.630
1071B - 942D 3.730
1071B - 943D 3.382
1072B - 939D 4.557
1075B - 936D 4.516
1076B - 932D 4.932
1076B - 936D 3.700
1089B - 932D 4.231
1089B - 933D 3.505
1089B - 936D 2.727
1089B - 937D 4.012
1103B - 940D 4.810
1103B - 943D 2.485
1103B - 944D 4.861
1105B - 942D 3.536
1105B - 943D 4.134
1105B - 944D 3.887
1110B - 945E 3.797
1110B - 947E 3.288
1111B - 942D 4.730
1112B - 949E 4.623
37C - 416A 4.311
37C - 535A 4.513
37C - 536A 2.454
37C - 537A 4.287

```
38C  -  536A     4.105
40C  -  534A     3.835
40C  -  536A     3.769
41C  -  534A     4.436
42C  -  531A     4.469
42C  -  532A     4.938
42C  -  534A     2.843
47C  -  575A     4.549
48C  -  531A     3.761
49C  -  531A     3.761
49C  -  574A     2.602
49C  -  575A     3.255
49C  -  576A     4.575
50C  -  523A     4.402
50C  -  524A     2.427
50C  -  525A     4.573
50C  -  527A     2.214
50C  -  528A     3.004
50C  -  531A     3.561
50C  -  574A     2.300
50C  -  580A     4.918
50C  -  583A     4.093
50C  -  586A     4.970
51C  -  527A     2.935
51C  -  531A     1.695
51C  -  586A     4.670
52C  -  527A     3.781
52C  -  531A     3.915
52C  -  586A     2.835
62C  -  536A     2.998
62C  -  537A     4.499
```

12) result of docking Protein spike open status with his natural protein ligand ACE2

```
====== Model 1 ======

# Receptor interface residue(s):
GLU     45B     2.929
ARG     99B     2.951
VAL    102B     4.606
MET    107B     4.016
ASN    109B     2.986
ILE    115B     2.739
```

```
ILE    116B     4.832
ILE    117B     1.626
ASN    118B     2.974
VAL    123B     4.586
VAL    124B     3.121
ARG    126B     2.917
CYS    128B     4.519
ASN    129B     1.984
TYR    163B     3.313
ILE    164B     4.078
ASP    166B     4.496
ASP    191B     3.915
PHE    193B     2.552
LYS    221B     3.183
PRO    223B     2.966
ARG    232B     2.408
ILE    234B     4.814
ASP    727B     4.447
SER    728B     2.643
THR    729B     2.421
GLU    730B     2.909
LEU    959B     4.494
ASN    960B     3.183
LEU    963B     2.740
GLY    311A     4.786
ASP    312A     2.541
VAL    313A     4.780
VAL    314A     2.219
PHE    316A     3.621
PRO    317A     3.004
SER    516A     4.231
THR    517A     2.918
ASN    526A     4.522
ASN    528A     3.738
ASN    530A     4.991
THR    533A     2.281
GLY    534A     4.359
PHE    551A     4.952

# Ligand interface residue(s):
TYR     50A     4.076
ILE     54A     3.121
THR     55A     4.494
```

```
GLU     56A     2.974
GLU     57A     2.951
LYS    131A     3.680
ASN    137A     3.915
GLN    139A     2.929
GLU    140A     3.885
CYS    141A     2.552
LEU    142A     4.630
LEU    143A     2.966
GLU    145A     3.651
PRO    146A     3.664
SER    170A     3.854
GLU    171A     3.004
LYS    174A     4.276
GLN    175A     3.460
ASP    335A     1.984
GLY    337A     4.357
ASN    338A     2.662
VAL    339A     2.408
GLN    340A     4.690
LYS    341A     1.626
ALA    342A     2.917
VAL    343A     4.973
CYS    344A     4.429
HIS    345A     4.078
LYS    363A     3.329
UNK    915C     3.738
UNK    931D     3.819
UNK    935D     3.637
UNK    938D     3.152
UNK    942D     4.806
UNK    944D     2.421
UNK    945E     2.643
UNK    946E     4.479
UNK    947E     2.281
UNK    948E     3.398
UNK    949E     2.541
UNK    950E     2.918
UNK    951E     2.219
UNK    952E     4.711

# Receptor-ligand interface residue pair(s):
45B  -  139A     2.929
```

99B - 56A 4.505
99B - 57A 2.951
102B - 339A 4.606
107B - 338A 4.016
109B - 335A 2.986
109B - 337A 4.357
115B - 337A 4.433
115B - 341A 2.739
116B - 341A 4.832
117B - 54A 3.199
117B - 55A 4.779
117B - 341A 1.626
118B - 55A 4.494
118B - 56A 2.974
123B - 56A 4.586
124B - 50A 4.076
124B - 54A 3.121
124B - 341A 3.735
126B - 335A 4.200
126B - 337A 4.765
126B - 340A 4.690
126B - 341A 3.479
126B - 342A 2.917
126B - 343A 4.973
126B - 344A 4.927
128B - 344A 4.519
129B - 335A 1.984
129B - 344A 4.429
129B - 363A 3.329
163B - 143A 3.313
163B - 145A 3.651
163B - 146A 4.453
164B - 345A 4.078
166B - 50A 4.496
191B - 137A 3.915
193B - 139A 4.564
193B - 140A 3.885
193B - 141A 2.552
193B - 142A 4.630
221B - 131A 3.680
221B - 139A 3.183
221B - 141A 4.596
223B - 131A 4.802

223B - 141A 4.071
223B - 142A 4.786
223B - 143A 2.966
223B - 146A 3.664
232B - 338A 2.662
232B - 339A 2.408
234B - 339A 4.814
727B - 945E 4.447
728B - 945E 2.643
729B - 942D 4.806
729B - 944D 2.421
729B - 945E 3.837
730B - 944D 3.899
730B - 945E 2.909
730B - 946E 4.891
959B - 945E 4.494
960B - 945E 3.183
960B - 946E 4.848
963B - 945E 2.740
963B - 946E 4.479
311A - 935D 4.786
312A - 935D 3.637
312A - 938D 3.152
312A - 948E 3.398
312A - 949E 2.541
312A - 950E 2.993
313A - 949E 4.780
314A - 949E 2.849
314A - 950E 3.333
314A - 951E 2.219
314A - 952E 4.711
316A - 171A 4.103
316A - 951E 3.621
317A - 170A 3.854
317A - 171A 3.004
317A - 174A 4.563
317A - 175A 3.460
516A - 174A 4.276
516A - 951E 4.231
517A - 931D 3.819
517A - 950E 2.918
517A - 951E 4.418
526A - 942D 4.958

```
526A  -  948E     4.522
528A  -  915C     3.738
528A  -  947E     4.850
528A  -  949E     3.924
530A  -  171A     4.991
533A  -  947E     2.281
534A  -  947E     4.359
551A  -  139A     4.952
```

13) result of docking Protein Nucleocapsid “N” with his natural protein ligand G3PB1

```
====== Model 1 ======
# Receptor interface residue(s):
GLN      7A     2.502
GLN      9A     4.501
ALA     12A     4.616
PRO     13A     2.456
ARG     14A     2.182
THR     16A     3.678
PHE     17A     2.795
GLY     18A     4.734
GLY     19A     2.194
PRO     20A     3.173
SER     21A     4.498
ASN     29A     3.572
GLU     31A     3.294
ARG     32A     2.718
SER     33A     2.772
GLY     34A     2.967
ALA     35A     4.592
ARG     36A     3.866
SER     37A     2.561
LYS     38A     3.846
GLN     39A     2.162
PRO     42A     2.925
GLN     43A     1.944
GLU    118A     1.594
ALA    119A     2.621
GLY    120A     3.641

# Ligand interface residue(s):
ARG    165A     2.502
ASN    166A     2.925
```

```
ARG    167A     2.682
TRP    168A     4.527
HIS    169A     2.945
SER    170A     1.944
ALA    171A     4.624
ARG    173A     2.621
GLN    174A     2.182
ALA    175A     4.424
SER    177A     2.194
ASN    178A     3.033
THR    184A     4.048
ARG    185A     4.786
ARG    258A     3.770
ARG    262A     2.561
ALA    281A     2.795
CYS    282A     3.766
PRO    283A     2.895
GLU    284A     3.976
LEU    285A     4.862
THR    286A     2.772
TRP    314A     2.974
THR    315A     2.798
GLY    316A     2.718
ILE    317A     4.894
ARG    318A     3.407
ASN    337A     4.572
SER    338A     4.299
PRO    339A     3.294
PO4    505A     1.594
PO4    507A     4.749

# Receptor-ligand interface residue pair(s):
7A  -  165A     2.502
7A  -  169A     2.945
7A  -  173A     4.969
7A  -  505A     4.416
9A  -  177A     4.501
12A  -  170A     4.616
12A  -  174A     4.918
13A  -  174A     2.456
14A  -  170A     4.638
14A  -  173A     3.149
14A  -  174A     2.182
```

```
14A  -  175A     4.424
14A  -  177A     3.479
16A  -  174A     3.678
17A  -  174A     4.427
17A  -  258A     3.770
17A  -  281A     2.795
18A  -  174A     4.920
18A  -  177A     4.734
19A  -  177A     2.194
19A  -  178A     3.033
20A  -  177A     4.325
20A  -  178A     3.173
21A  -  178A     4.498
29A  -  314A     3.572
31A  -  315A     4.620
31A  -  337A     4.840
31A  -  338A     4.299
31A  -  339A     3.294
32A  -  281A     2.999
32A  -  282A     3.766
32A  -  283A     2.895
32A  -  314A     2.974
32A  -  315A     2.798
32A  -  316A     2.718
32A  -  317A     4.894
32A  -  337A     4.572
32A  -  339A     3.739
33A  -  283A     3.796
33A  -  285A     4.862
33A  -  286A     2.772
33A  -  315A     4.835
33A  -  316A     3.213
33A  -  317A     4.989
33A  -  318A     3.407
33A  -  339A     3.682
34A  -  283A     2.967
34A  -  284A     3.978
34A  -  286A     4.032
34A  -  316A     4.488
35A  -  286A     4.592
36A  -  262A     3.866
36A  -  284A     3.976
37A  -  262A     2.561
```

```
38A  -  262A     3.846
39A  -  166A     3.899
39A  -  167A     2.682
39A  -  170A     2.162
42A  -  166A     2.925
43A  -  165A     3.065
43A  -  166A     3.679
43A  -  167A     3.018
43A  -  168A     4.527
43A  -  169A     3.453
43A  -  170A     1.944
43A  -  171A     4.624
118A  -  165A     2.623
118A  -  173A     4.749
118A  -  505A     1.594
118A  -  507A     4.749
119A  -  173A     2.621
119A  -  184A     4.048
119A  -  185A     4.786
119A  -  505A     3.265
120A  -  173A     3.641
```

14) result of docking Protein Nucleocapsid "N" with his natural protein ligand 14-3-3 protein

```
====== Model 1 ======

# Receptor interface residue(s):
ASN     11A     4.484
PRO     13A     3.508
ILE     15A     3.742
THR     16A     2.521
SER     26A     2.695
GLN     28A     1.969
GLY     30A     3.407
GLU     31A     3.307
SER     33A     3.975
GLY     34A     2.779
ALA     35A     3.660
ARG     36A     1.854
SER     37A     1.630
LYS     38A     2.869
GLN     39A     3.144
ARG     40A     2.586
PRO     80A     4.036
ASP     81A     4.379
```

```
LEU    139A     3.944
THR    141A     4.393
PRO    142A     2.481
LYS    143A     2.338
ASP    144A     4.462
HIS    145A     4.529
ARG    189A     2.953
LYS    237A     2.902
GLN    239A     4.521
GLN    240A     2.877
GLN    241A     3.070
LEU    394A     3.611

# Ligand interface residue(s):
C      27A     4.542
U      28A     2.779
G      29A     3.660
C      30A     1.630
G      31A     1.909
U      32A     3.646
C      24B     4.459
U      25B     2.338
U      26B     2.481
C      27B     2.521
U      28B     1.854
G      29B     2.464
C      30B     4.026
G      31B     4.720
G      33B     4.102
A      34B     1.969
A      35B     2.695
G      36B     3.944
G      37B     4.379
C      38B     2.902
U      39B     4.515
G      65B     3.611
G      66B     2.877
A      67B     2.878
U      68B     4.458
A      69B     2.953
A      70B     3.881
C      74B     3.933
```

```
# Receptor-ligand interface residue pair(s):
11A  -  27B     4.484
13A  -  27B     3.530
13A  -  28B     3.508
15A  -  26B     3.742
15A  -  27B     4.593
16A  -  27B     2.521
26A  -  35B     2.695
26A  -  36B     4.688
28A  -  26B     2.762
28A  -  27B     3.260
28A  -  33B     4.699
28A  -  34B     1.969
28A  -  35B     2.874
30A  -  34B     3.407
31A  -  33B     4.102
31A  -  34B     3.307
33A  -  28A     3.975
34A  -  27A     4.542
34A  -  28A     2.779
35A  -  28A     4.254
35A  -  29A     3.660
35A  -  31B     4.850
36A  -  28A     4.110
36A  -  29A     4.739
36A  -  31A     4.893
36A  -  27B     3.847
36A  -  28B     1.854
36A  -  29B     4.750
36A  -  31B     4.720
37A  -  28A     3.261
37A  -  29A     3.878
37A  -  30A     1.630
37A  -  31A     1.909
37A  -  32A     3.646
37A  -  29B     2.464
37A  -  30B     4.026
38A  -  31A     2.869
38A  -  32A     3.888
38A  -  28B     3.421
38A  -  29B     3.901
39A  -  28B     3.144
39A  -  29B     3.740
```

```
40A  -  26B     3.879
40A  -  27B     2.971
40A  -  28B     3.522
40A  -  29B     2.586
80A  -  25B     4.036
81A  -  37B     4.379
139A  -  36B     3.944
141A  -  25B     4.393
141A  -  26B     4.396
142A  -  25B     4.570
142A  -  26B     2.481
142A  -  27B     4.080
143A  -  24B     4.459
143A  -  25B     2.338
143A  -  26B     3.293
144A  -  26B     4.462
145A  -  25B     4.660
145A  -  26B     4.529
189A  -  68B     4.458
189A  -  69B     2.953
237A  -  38B     2.902
237A  -  39B     4.515
237A  -  70B     3.881
239A  -  67B     4.521
240A  -  65B     4.454
240A  -  66B     2.877
240A  -  67B     2.878
240A  -  74B     3.933
241A  -  66B     3.070
241A  -  67B     3.160
394A  -  65B     3.611
394A  -  66B     3.79
```

15) result of docking protein “E” Envelope with his natural Protein ligand PALS1

```
====== Model 1 ======
# Receptor interface residue(s):
LEU      18     4.225
LEU      19     3.552
ALA      22     2.448
PHE      23     2.196
VAL      24     3.190
PHE      26     2.916
LEU      27     1.929
LEU      28     1.698
```

```
VAL      29     4.723
THR      30     2.735
LEU      31     3.551
LEU      34     4.693
PRO      54     2.745
SER      55     2.342
PHE      56     3.022
TYR      57     2.930
TYR      59     2.317
SER      60     2.691
ARG      61     4.892

# Ligand interface residue(s):
GLY    311A     3.719
GLU    316A     4.693
LYS    261B     4.033
ARG    263B     4.420
ASP    264B     2.735
ILE    265B     4.070
PRO    266B     3.173
ASN    315B     3.022
GLU    316B     4.595
PHE    318B     2.448
ASP    319B     2.342
LEU    321B     4.736
SER    322B     2.916
ASP    323B     2.806
ASP    264D     2.317
PRO    266D     1.929
ASN    315D     4.621
PHE    318D     2.318
SER    322D     3.591
LEU    209E     1.698
LEU    210E     2.855
VAL    211E     4.865
PRO    207G     4.934
LEU    209G     3.984
LEU    210G     2.196
VAL    211G     4.805
EDO    401D     3.211

# Receptor-ligand interface residue pair(s):
18  -  315B     4.225
```

19 - 315B 3.552
19 - 207G 4.934
19 - 209G 3.984
22 - 315B 4.791
22 - 318B 2.448
22 - 209G 4.088
23 - 266B 3.173
23 - 318B 3.177
23 - 264D 3.680
23 - 210G 2.196
23 - 211G 4.805
24 - 318D 3.190
26 - 261B 4.033
26 - 264B 3.070
26 - 265B 4.070
26 - 266B 3.263
26 - 318B 4.061
26 - 321B 4.736
26 - 322B 2.916
26 - 323B 4.916
26 - 210E 4.772
27 - 264B 4.424
27 - 266D 1.929
27 - 318D 2.318
27 - 210E 2.855
27 - 211E 4.865
27 - 401D 3.211
28 - 315D 4.621
28 - 318D 4.260
28 - 209E 1.698
28 - 210E 3.799
29 - 264B 4.723
30 - 264B 2.735
30 - 322B 3.736
30 - 323B 2.806
31 - 311A 3.719
31 - 263B 4.420
31 - 323B 3.551
34 - 316A 4.693
54 - 319B 2.745
55 - 318B 3.135
55 - 319B 2.342
55 - 322B 4.133

56	-	315B	3.022
56	-	316B	4.595
56	-	318B	4.403
56	-	319B	3.304
57	-	318B	3.468
57	-	322B	2.930
57	-	323B	4.995
59	-	264D	2.317
59	-	318D	4.420
59	-	322D	3.591
59	-	401D	4.347
60	-	264D	2.691
61	-	209G	4.892