Structure-based Modeling COVID-19

Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26section

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The study modelled homo-trimer structure of COVID-19 spike glycoprotein in both closed (ligand-free) and open (ligand-bound) conformation, which is involved in host-cell adhesion.

https://pubmed.ncbi.nlm.nih.gov/32178593/

Modeling

- **SwissModel:** https://swissmodel.expasy.org/

Protein-Protein docking:

- **Cluspro:** https://cluspro.bu.edu/login.php

COVID-19 spike-host cell receptor GRP78 binding site prediction

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https://pubmed.ncbi.nlm.nih.gov/32169481/

- DOI: 10.1016/j.jinf.2020.02.026COV

The study has modeled the COVID-19 spike binding site to the cell-surface receptor (Glucose Regulated Protein 78 (GRP78)) is predicted using combined molecular modeling docking and structural bioinformatics. The COVID-19 spike protein is modeled using its counterpart, the SARS spike.

A comparative analysis for SARS-CoV-2

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https://arxiv.org/pdf/2004.04281.pdf

The report provides further insights into how the SARS-CoV-2 surface glycoprotein mutated for higher binding affinity to human ACE2 receptors, compared to the SARS-CoV protein, by integrating existing 3D protein models.

2019-nCoV (Wuhan virus), a novel Coronavirus: human-to-human transmission, travel-related cases, and vaccine readiness

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https://pubmed.ncbi.nlm.nih.gov/32088679/

Protein-protein docking of Receptor Binding Domain, Phylogenetic analysis and docking

Software used:

- **Phyre2** was used for protein modeling
- **Haddock2** was used for docking

The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase.

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https://pubmed.ncbi.nlm.nih.gov/32167173

RNA-dependent RNA polymerase (RdRp) is an important protease that catalyzes the replication of RNA from RNA template and is an attractive therapeutic target. In this study, we screened these chemical structures from traditional Chinese medicinal compounds proven to show antiviral activity in severe acute respiratory syndrome coronavirus (SARS-CoV) and the similar chemical structures through a molecular docking study to target RdRp of SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV).

Simulation of the Clinical and Pathological Manifestations of Coronavirus Disease 2019 (COVID-19) in Golden Syrian Hamster Model: Implications for Disease Pathogenesis and Transmissibility section

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https://pubmed.ncbi.nlm.nih.gov/32215622/

Molecular docking on the binding between ACE2 of common laboratory mammals and the RBD of the surface spike protein of SARS-CoV-2 suggested that the golden Syrian hamster is an option.

Software Used:
I-TASSER: https://zhanglab.ccmb.med.umich.edu/I-TASSER/
Rosetta: https://www.rosettacommons.org/software

Structural modeling of 2019-novel coronavirus (nCoV) spike protein reveals a proteolyticallysensitive activation loop as a distinguishing feature compared to SARS-CoV and related SARSlike coronavirusesUntitled section

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https://arxiv.org/ftp/arxiv/papers/2002/2002.06196.pdf

Protein structure and sequence re-analysis of 2019-nCoV genome does not indicate snakes as its intermediate host or the unique similarity between its spike protein insertions and HIV-1

https://arxiv.org/ftp/arxiv/papers/2002/2002.03173.pdf

Based on our analyses and existing data of coronaviruses, we concluded that the intermediate hosts of 2019-nCoV are more likely to be mammals and birds than snakes, and that the “novel insertions” observed in the spike protein are naturally evolved from bat coronaviruses

Comparing the binding interactions in the receptor binding domains of SARS-CoV-2 and SARS-CoV

https://arxiv.org/ftp/arxiv/papers/2004/2004.02158.pdf

we used molecular dynamics simulations and Monte Carlo sampling to compare the binding affinities of the spike proteins of SARS-CoV and SARS-CoV-2 to the ACE2. We found that the SARS-CoV-2 binds to ACE2 stronger than SARS-CoV by 7 kcal/mol, due to enhanced electrostatic interactions

Genomics-guided molecular maps of coronavirus targets in human cells: a path toward the repurposing of existing drugs to mitigate the pandemic

https://arxiv.org/ftp/arxiv/papers/2003/2003.13665.pdf
(Pathway based analysis)

Gene set enrichment analyses (GSEA) of genomic features associated with the ACE2 and FURIN genes

Structural analysis of SARS-CoV-2 and prediction of the human interactome

https://arxiv.org/ftp/arxiv/papers/2003/2003.13655.pdf

In-Silico evidence for two receptors based strategy of SARS-CoV-2

https://arxiv.org/pdf/2003.11107.pdf

We propose a novel numerical method able to determine efficiently and effectively the relationship of complementarity between portions of protein surfaces

Computational Design of Peptides to Block Binding of the SARS-CoV-2 Spike Protein to Human ACE2

https://doi.org/10.1101/2020.03.28.013607

Peptide design

Structure-Based Design, Synthesis and Biological Evaluation of Peptidomimetic Aldehydes as a Novel Series of Antiviral Drug Candidates Targeting the SARS-CoV-2 Main Protease

https://doi.org/10.1101/2020.03.25.996348

Recognition of potential Covid-19 drug treatments through study of existing protein-drug structures: an analysis of thermodynamically active residues

https://arxiv.org/ftp/arxiv/papers/2004/2004.10233.pdf

We report results of our study of approved drugs as potential treatments for COVID-19 based on the application of various bioinformatics predictive methods. The drugs studied include hydroxychloroquine, ivermectin, remdesivir and α-difluoromethylornithine (DMFO). Our results indicate that these small drug molecules selectively bind to thermodynamically active residues on protein surfaces, and that some prefer hydrophobic over other active sites. Our approach is not restricted to viruses and can facilitate rational drug design, as well as improve our understanding of molecular interactions, in general.

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

https://www.cell.com/cell/pdf/S0092-8674(20)30229-4.pdf
(shows the benefit of inhibiting TMPRSS2)

Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein

https://www.cell.com/cell/fulltext/S0092-8674(20)30262-2

(provides proof of the importance of ACE2 receptor)

Decoding SARS-CoV-2 transmission, evolution and ramification on COVID-19 diagnosis, vaccine, and medicine

https://arxiv.org/pdf/2004.14114.pdf
(interesting paper that connects the mutation in the COVID-19 genome to infection)

Structural and Functional Implications of Non-synonymous Mutations in the Spike protein of 2,954 SARS-CoV-2 Genomes

https://www.biorxiv.org/content/10.1101/2020.05.02.071811v1.full.pdf

CoV-Seq: SARS-CoV-2 Genome Analysis and Visualization

https://www.biorxiv.org/content/10.1101/2020.05.01.071050v1.full.pdf

In-silico nucleotide and protein analyses of S-gene region in selected zoonotic coronaviruses reveal conserved domains and evolutionary emergence with trajectory course of viral entry from SARS-CoV2 genomic data

https://arxiv.org/ftp/arxiv/papers/2005/2005.02809.pdf

Conserved domains with antagonistic action on host innate antiviral cellular mechanisms in SARS-CoV 2 include nsp 11, nsp 13 etc. Also, multiple sequence alignments of the spike [S] gene protein of selected candidate zoonotic coronaviruses alongside the S gene protein of the SARs-CoV2 revealed closest evolutionary relationship [95.6%] with pangolin coronaviruses [S] gene

Impact of Thiol-Disulfide Balance on the Binding of Covid-19 Spike Protein with Angiotensin Converting Enzyme 2 Receptor

https://www.biorxiv.org/content/10.1101/2020.05.07.083147v1.full.pdf+html

A modified ACE2 peptide mimic to block SARS-CoV2 entry

https://www.biorxiv.org/content/10.1101/2020.05.07.082230v1.full.pdf

Table 1: **Systems simulated in this study. The last 3 systems feature mutated peptides. The points of mutation have been mentioned in red in the peptide sequence.**

S.no	Simulation Model	Peptide Sequence
1	Wild type (WT)	**IEEQAKTFLDKFNHEAEDLFYQS**
2	WT-S	**TFLDKFNHEAED**
3	E17L	**IEEQAKTFLDKFNHEAredLDLFYQS**
4	D18L	**IEEQAKTFLDKFNHEAEredLLFYQS**
5	N13E-E17L	**IEEQAKTFLDKFredEHEAredLDLFYQS**

Bulk and single-cell gene expression profiling of SARS-CoV-2 infected human cell lines identifies molecular targets for therapeutic intervention

https://www.biorxiv.org/content/10.1101/2020.05.05.079194v1

In summary, our study established in vitro cell culture models to study SARS-CoV-2 infection and identified HSP90 protein as potential drug target for therapeutic intervention of SARS-CoV-2 infection.

Coarse-grained molecular simulations of the binding of the SARS-CoV 2 spike protein RBD to the ACE2 cell receptor

https://www.biorxiv.org/content/10.1101/2020.05.07.083212v1

In silico comparison of spike protein-ACE2 binding affinities across species; significance for the possible origin of the SARS-CoV-2 virus

https://arxiv.org/ftp/arxiv/papers/2005/2005.06199.pdf

CoV3D: A database of high resolution coronavirus protein structures

https://www.biorxiv.org/content/10.1101/2020.05.12.091983v1.full.pdf

Drug targets for corona virus: A systematic review

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7074424

The 2019-novel coronavirus (nCoV) is a major source of disaster in the 21th century. However, the lack of specific drugs to prevent/treat an attack is a major need at this current point of time. In this regard, we conducted a systematic review to identify major druggable targets in coronavirus (CoV). We searched PubMed and RCSB database with keywords HCoV, NCoV, corona virus, SERS-CoV, MERS-CoV, 2019-nCoV, crystal structure, X-ray crystallography structure, NMR structure, target, and drug target till Feb 3, 2020. The search identified seven major targets (spike protein, envelop protein, membrane protein, protease, nucleocapsid protein, hemagglutinin esterase, and helicase) for which drug design can be considered. There are other 16 nonstructural proteins (NSPs), which can also be considered from the drug design perspective. The major structural proteins and NSPs may serve an important role from drug design perspectives. However, the occurrence of frequent recombination events is a major deterrent factor toward the development of CoV-specific vaccines/drugs.

Expression of ACE2, the SARS-CoV-2 receptor, and TMPRSS2 in prostate epithelial cells

https://www.biorxiv.org/content/10.1101/2020.04.24.056259v2.full.pdf

A comparison of ACE2 expression in lung tissue between males and females showed higher expression in males and a larger proportion of ACE2+ cells in male type II pneumocytes, with preliminary evidence that type II pneumocytes of all lung epithelial cell types showed the highest expression of ACE2. These results raise the possibility that sex differences in ACE2 expression and the presence of doublepositive cells in the prostate may contribute to the observed disparities of COVID-19

Mutations strengthened SARS-CoV-2 infectivity

https://arxiv.org/pdf/2005.14669.pdf

Based on a systematic evaluation of all possible 3686 future mutations on the S protein receptor-binding domain (RBD), we show that most likely future mutations will make SARS-CoV-2 more infectious. Combining sequence alignment, probability analysis, and binding affinity calculation, we predict that a few residues on the receptor-binding motif (RBM), i.e., 452, 489, 500, 501, and 505, have very high chances to mutate into significantly more infectious COVID-19 strains.

Insights on cross-species transmission of SARS-CoV-2 from structural modeling

https://www.biorxiv.org/content/10.1101/2020.06.05.136861v1

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the ongoing global pandemic that has infected more than 6 million people in more than 180 countries worldwide. Like other coronaviruses, SARS-CoV-2 is thought to have been transmitted to humans from wild animals. Given the scale and widespread geographical distribution of the current pandemic, the question emerges whether human-to-animal transmission is possible and if so, which animal species are most at risk. Here, we investigated the structural properties of several ACE2 orthologs bound to the SARS-CoV-2

spike protein. We found that species known not to be susceptible to SARS-CoV-2 infection have non-conservative mutations in several ACE2 amino acid residues that disrupt key polar and charged contacts with the viral spike protein. Our models also predict affinity-enhancing mutations that could be used to design ACE2 variants for therapeutic purposes. Finally, our study provides a blueprint for modeling viral-host protein interactions and highlights several important considerations when designing these computational studies and analyzing their results.