Modeling for CADD with Small Molecules

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COVID-19 has claimed around 7 million lives (from December 2019–November 2023) worldwide and continues to impact global health. SARS-CoV-2, the virus causing COVID-19 disease, is characterized by a high rate of mutations, which contributes to its rapid spread, virulence, and vaccine escape. While several vaccines have been produced to minimize the severity of the coronavirus, and diverse treatment regimens have been approved by the US FDA under Emergency Use Authorization (EUA), SARS-CoV-2 viral mutations continue to derail the efforts of scientists as the emerging variants evade the recommended therapies. Nonetheless, diverse computational models exist that offer an opportunity for the swift development of new drugs or the repurposing of old drugs.

Keywords: drug discovery ; drug repurposing ; SARS-CoV-2 ; COVID ; molecular docking ; QSAR ; molecular dynamics

1. Computational Peptide Inhibition Studies

Peptides, although often limited by systemic bioavailability, offer promise for combating SARS-CoV-2 as the oral, nasal, and pulmonary delivery of peptides directly to the site of infection, namely the upper and lower airways. The optimization of peptides for bioavailability, potency, stability, safety, and size is crucial for large-scale manufacturing and successful clinical translation. The prophylactic and therapeutic potential of peptide-based interventions, especially in short-term applications, could significantly contribute to controlling the COVID-19 pandemic, even alongside vaccination efforts. Initially, the peptide design strategies against SARS-CoV-2 were primarily focused on extracting candidates from the ligand-binding motif of the ACE2 receptor and optimizing their sequences to create potent inhibitors targeting the RBD. The computational workflow employed in these designs typically includes established techniques such as homology modeling, computational mutagenesis, docking protocols, re-scoring methods, and MD simulations. Han and Kral designed inhibitors in silico, composed of two consecutive, self-supporting α-helices (a bundle) derived from the protease domain ACE2. MD simulations demonstrated that the α-helical peptides maintain their secondary structure and exhibit highly specific and stable binding, effectively blocking the interaction with SARS-CoV-2. Ling et al. also designed HR1- and HR2-based antiviral peptides, indicating a stronger interaction compared to the natural stage of the fusion core and having the capability to competitively bind with HR1, preventing the formation of the fusion core. In another study, antimicrobial peptides caerin 1.6 and caerin 1.10 from amphibians were identified as having an affinity for the spike protein residue Arg995, situated in the S2 subunit [1]. Another study reported conjugated TAT-peptide docked with drugs (lopinavir, ritonavir, favipiravir, and hydroxychloroquine) repurposed against M^{pro} of SARS-CoV-2 by using PatchDock. The study offered crucial information for the development of cost-effective and biocompatible TP-conjugated anti-SARS-CoV-2 therapeutics [2]. In another study, docking revealed RdRp, 3CL, spike, and nucleocapsid, demonstrated high affinities for binding glycocin F from *Lactococcus lactis* and lactococcine G from *Lactobacillus plantarum* [3]. Marine polypeptides from the Pacific oyster also showed good docking with M^{pro} [4]. Fusion inhibitors based on EK1 pan-CoV inhibitors against variants of the SARS-CoV-2 HR1 domain have also been reported [5]. Fruit bromelain-derived peptide DYGAVNEVK has also shown inhibition of RBD (spike protein) [6].

Rajpoot et al. [7] designed peptide inhibitor Mod13AApi (YADKYQKQYKDAY) with wild-type spike and Alpha, beta, gamma, and delta lineages to hinder ACE2 and spike binding. Physicochemical and computational ADMET analyses indicated favorable properties for the inhibitory peptide. Singh et al. [8] identified five antiviral peptides, AVP1056, AVP1059, AVP1225, AVP1801, and HIP755, targeting RBD of spike protein to hinder its binding with ACE2.

2. Quantitative Structure–Activity Relationships (QSAR) Mapping

QSAR is used to predict and interpret the biological activity of molecules based on their structural features. This method involves the mathematical modeling of the relationship between physicochemical properties or molecular descriptors of compounds and their biological activities. Studies have been carried out using QSAR methods to develop phosphorus-based drugs, which have good inhibitory activity against SARS-CoV-2 proteins and their non-synonymous variants [9][10]

[11]. A QSAR study based on the simplified molecular-input line-entry system (SMILES) strings of 32 bicycloproline derivatives has also been applied in the discovery of COVID-19 therapeutics, with the strings applied in calculating 0D, 1D, and 2D molecular descriptors [12]. Similar SMILES notation has been used to reveal new compounds with a potential 3C-like protease and RdRp inhibition activity in rediscovering and repurposing SARS-CoV-2 drugs. QSAR-based virtual screening of 26,467 food compounds and 360 heterocyclic variants identified promising hits against M^{pro} [13]. Apart from this, QSAR analysis on a dataset of sixty-two peptides against the M^{pro} was attempted [14]. The developed QSAR models pinpointed specific features such as the number of sp2 hybridized Oxygen atoms within seven bonds from aromatic Carbon atoms, the presence of Carbon and Nitrogen atoms at a topological distance of 3, and other atom pair interrelations as crucial pharmacophoric elements. The analysis yielded statistically robust and highly predictive models, with R2 = 0.80–0.82, Q2loo = 0.74–0.77, and Q2LMO = 0.66–0.67. These could be utilized for guiding future modifications of peptide-type compounds for anti-SARS-CoV activity. QSAR model of carbon nanoparticles and a SARS-CoV-2 RNA fragment has also been attempted [15]. Models for 17 carbon nanoparticle types revealed strong predictive capabilities, with molecular weight, surface area, and carbon atom degrees sum identified as key descriptors influencing interactions. The affinity between carbon nanoparticles and the virus RNA increased in the order of fullerenes < graphenes < carbon nanotubes.

3. Antibody Docking

SARS-CoV-2-neutralizing antibodies primarily target conformational epitopes, and, using docking simulations, researchers have inferred that the CR3022neutralizing antibody from humans and mouse antibodies F26G19 and D12 displayed high affinity for the spike protein of SARS-CoV-2 [16]. Utilizing in silico all-atom MD simulations and deep learning approaches, Zhang et al. revealed that delta variant mutations significantly diminished the binding affinity between spike protein and the LY-CoV555 antibody (also known as Bamlanivimab), which has demonstrated efficacy in neutralizing the wild-type SARS-CoV-2. Previous research has also highlighted the significant impact of a single mutation in the receptor-binding domain (RBD), with some antibodies being notably affected by individual mutations, e.g., K417N reduces the neutralizing activity of Etesevimab, and Bamlanivimab is notably weakened by E484A. Certain antibodies are influenced by multiple mutations, and the combined effect of these mutations can only be estimated based on the individual impact of each mutation. Regdanvimab may experience reduced effectiveness due to the combined presence of K417N, E484A, Q493R, and Y505H in Omicron. The neutralization effectiveness of antibodies may be variably diminished due to the extensive mutations present in the variant proteins. Antibody and nanobody interaction modeling with variant spike proteins to study the evasion of variants by comparing binding scores has also been attempted [17]. Mutations in the variants altered the conformation of the spike protein epitope, making it less recognizable to specific antibodies, including REGN10933, LYCoV555, B38, C105, or H11-H4. This shows how variants may accumulate escape mutations that confer a selective advantage by avoiding neutralization. However, Nb20 showed distinct behavior by recognizing a less variable epitope on the spike protein, enabling it to maintain neutralizing activity against the Delta variant. Antibody–variant interactions have implications for vaccine development. This information regarding interactions with neutralizing antibodies is crucial for designing vaccines that provide broad protection. Das et al. identified that tixagevimab, regdanvimab, and cilgavimab exhibit effective neutralization against a majority of SARS-CoV-2 Alpha strains, while tixagevimab, bamlanivimab, and sotrovimab form a robust complex with the Delta variants. They leveraged this information to design a chimeric antibody by combining the CDRH3 region of regdanivimab with the framework of sotrovimab. The aim was to address variants that might have the potential to evade neutralization mediated by monoclonal antibodies [18]. Tang et al. docked antibodies against the RBD portion of the protein as well.

4. Machine Learning for Inhibitor Screening

Researchers have used different AI methods for generating drug-like molecules and then screened them against SARS-CoV-2 proteins. Elend et al. [19] used an evolutionary algorithm and a neural network model coupled with MD simulations to design and assess potential drug candidates. The study illustrates this workflow by applying it to the design of drugs targeting the M^{pro}. Out of approximately 140,000 molecules generated via AI methods, MD analysis identifies 2 molecules as promising drug candidates. A Bayesian ML model identified lumefantrine, an antimalarial, as a potential candidate against spike protein from FDA-approved compounds, and its binding was confirmed via in vitro analysis [20]. Nguyen et al. [21] used algebraic topology and deep learning (MathDL) to accurately rank the binding affinities of 137 SARS-CoV-2 M^{pro} inhibitor structures. Haneckzok and Delijewski [22] employed various supervised ML models utilizing different approaches (including shallow learning methods with fixed molecular fingerprints, Graph Convolutional Neural Networks utilizing self-learned molecular representations, and a combination of fixed and Graph-CNN learned representations) to the molecular representation of FDA-approved compounds against 3CLpro. The antimicrobial drug Sulfadiazine was ranked as the top inhibitor. Qu et al. [23] employed a de novo design method, integrating a recurrent neural network,

reinforcement learning, and molecular docking to generate inhibitors for the SARS-CoV-2 main protease. Around 30,000 molecules were generated and subjected to physicochemical filters and molecular docking scores, resulting in the selection of five drug candidates. Yao et al. [24] assessed 2635 FDA-approved drugs and 1062 active ingredients from Traditional Chinese Medicine herbs using docking coupled with ML and identified Fostamatinib, Linagliptin, Lysergol, and Sophoridine as potent inhibitors after validation with experimental assays (**Figure 1**). ML has also been used to explore scaffold diversity and identify potential COVID-19 drugs, such as Tizanidine HCl and Raltegravir, against the main protease, helicase, papain-like protease, and replicase polyprotein 1ab [25]. Analyzing fragments and breaking down molecular structures revealed that pyrrolidine and indole molecular scaffolds were potent inhibitors of SARS-CoV-2. Jukic et al. [26] used virtual screening coupled with ML to maximize enrichment and incorporate structural data on known 3CLpro inhibitors into focused libraries. Decoys were used in data training, and compounds were prioritized against Alpha, beta, gamma, and delta variant proteases. Ghosh et al. [27] used a random forest approach to target spike-human protein interaction for the Alpha, Beta, Delta, Gamma, and Omicron variants. A list of 40 unique drugs, including eicosapentaenoic acid, doxercalciferol, ciclesonide, dexamethasone, methylprednisolone, among others, was prioritized based on data from DrugBank and ChEMBL.

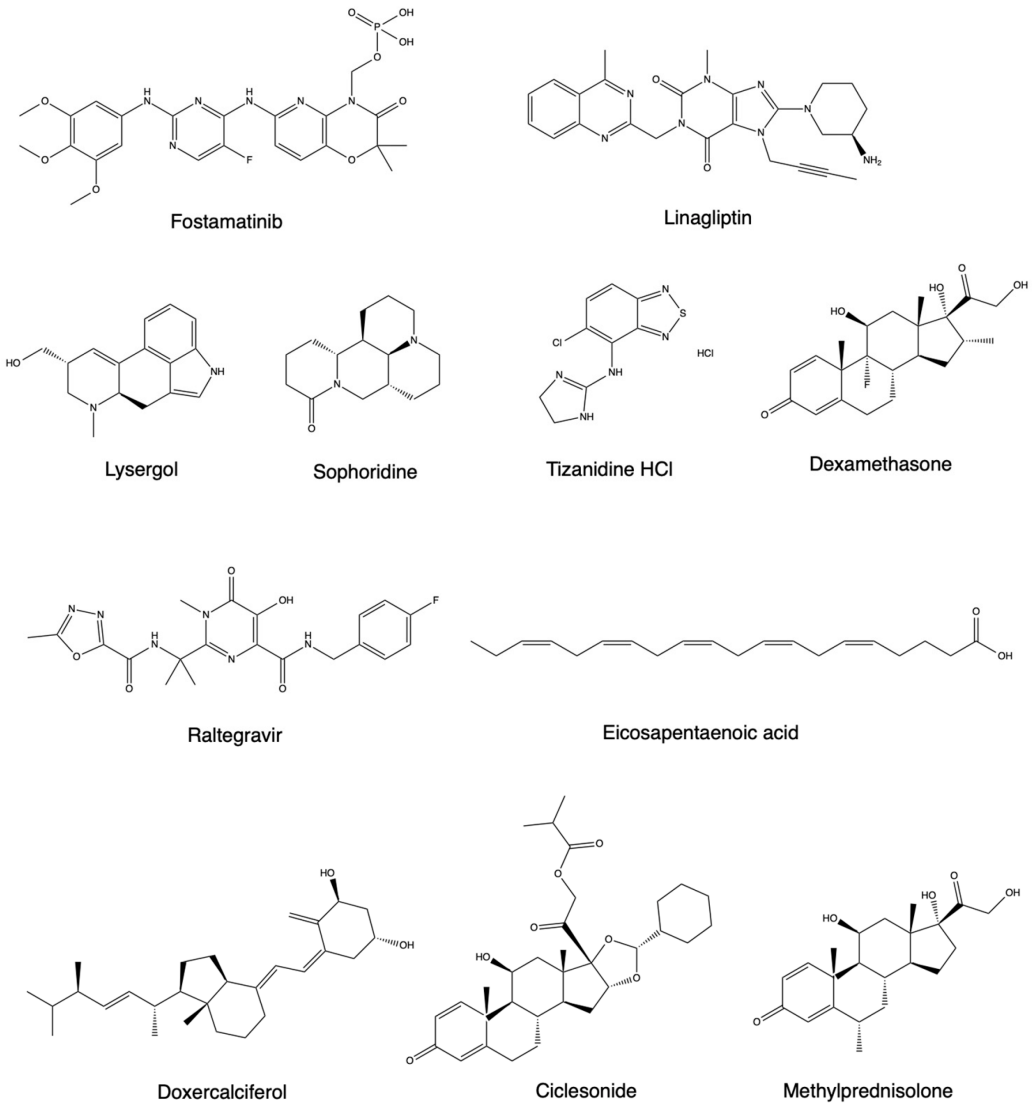

Figure 1. Structures of Fostamatinib, Linagliptin, Lysergol, Sophoridine, Tizanidine HCl, Dexamethasone, Raltegravir, Eicosapentaenoic acid, Doxercalciferol, Ciclesonide, and Methylprednisolone.

5. Machine Learning for Antibody Screening

Magar et al. [28] employed various ML models to predict potential synthetic antibodies for SARS-CoV-2 neutralization. Utilizing 1933 virus–antibody sequences with patient neutralization responses, an ML model was trained. Employing graph featurization with ML methods such as XGBoost, Random Forest, Multilayered Perceptron, Support Vector Machine, and Logistic Regression, thousands of hypothetical antibody sequences were screened. Nine stable antibodies with potential SARS-CoV-2 inhibition were identified, and their stability was verified using a combination of bioinformatics, structural biology, and MD simulations. Desautels et al. [29] generated neutralizing antibody structures for SARS-CoV-2 based on SARS-CoV-1 neutralizing antibodies using ML. These were predicted to interact with the SARS-CoV-2 RBD,

exhibiting improved interaction with free energies as low as −82.0 kcal/mol. In a study by Frei et al. [30], a deep learning-guided approach was employed to identify antibodies with enhanced resistance to SARS-CoV-2 evolution. Deep Mutational Learning, an ML-guided protein engineering method, was utilized to explore a vast sequence space of combinatorial Spike protein receptor binding domain mutations, predicting their impact on ACE2 binding and antibody escape. A high mutational distance library was constructed using the full-length RBD of Omicron BA.1 and experimentally screened for ACE2 binding or neutralizing antibodies, followed by deep sequencing. Ensemble deep learning models were trained on the resulting data, accurately predicting binding or escape for therapeutic antibody candidates targeting diverse RBD epitopes. The approach was extended to assess antibody breadth by predicting binding or escape to synthetic lineages representing millions of sequences generated via in silico evolution. This deep learning strategy holds promise for designing next-generation antibody therapies effective against future SARS-CoV-2 variants.

6. Nanoinformatics for SARS-CoV-2 Inhibition

In a docking study, Fe_2O_3 and Fe_3O_4 iron oxide nanoparticles (FDA-approved for anemia) were explored for their interaction with the domain of SARS-CoV-2 spike protein [31]. Efficient binding was observed, suggesting potential viral inactivation by inducing conformational changes. Research by Zhang et al. [15] also provided theoretical insights into the potential applications of engineered carbon nanoparticles for the adsorption, separation, and inactivation of SARS-CoV-2 RNA. Carbon nanotubes showed better binding than fullerene and graphene nanoparticles. ZnO nanoparticles docking with COVID-19 targets, including the ACE2 receptor, RdRp, and main protease, have shown favorable binding with hydrogen bond formation [32]. Skariyachan et al. [33] predicted the binding potential of carbon nanotubes and nano-fullerene to multiple targets of SARS-CoV-2, including the spike glycoprotein, RNA-dependent RNA polymerase, main protease, papain-like protease, and RNA binding domain of the nucleocapsid proteins. Docking and simulation suggested significant binding of carbon nanotubes and fullerene to the prioritized multi-targets of SARS-CoV-2, with carbon nanotubes showing better interaction. Aallaei et al. [34] used docking and MD simulation to study the cytotoxicity of various copper nanoparticle shapes and their impact on inactivating the coronavirus by binding spike and protease of the virus. The results revealed that interactions with cylindrical and conical copper NP ligands were more efficient than spherical copper NPs in controlling coronavirus replication. Al-Sanea et al. [35] also demonstrated the potential of green synthesized silver nanoparticles against SARS-CoV-2 NSP16.

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