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Editorial

Computation to Fight SARS-CoV-2 (COVID-19)

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1. Introduction

In April 2020, during the last pandemic health emergency, we launched a Special Issue hosted by Computation—section Computational Biology, entitled "Computation to Fight SARS-CoV-2 (COVID-19)". The COVID-19 infective condition is caused by the etiological agent SARS-CoV-2 (2019-nCoV), a novel, highly virulent betacoronavirus. Therefore, SARS-CoV-2 is an important worldwide health hazard with high mortality and high contagiousness. Despite the introduction of vaccines and therapeutic options, the occurrence of resistant phenomena in SARS-CoV-2 keeps the public attentive to health concerns with a relevant interest in developing effective antiviral agents, vaccines, and social measures to mitigate the transmission of the virus and its variants. Accordingly, to advance our knowledge of the pathogenic mechanism of viruses and to identify novel drug candidates, computer science may play a significant role in the search for effective therapeutics to cure this infection. In addition, because of this global health alert, such computational methodologies could hasten the development of creative and focused solutions to the coronavirus emergency. This Special Issue showcases advancements in epidemiology, virus biology, and medication discovery to provide researchers with cutting-edge computational strategies for combating SARS-CoV-2. Based on this consideration, the Special Issue has attracted the attention of scientists in the field, and 27 research articles have been published on this topic. We divided this editorial article into two sections, one dedicated to the progress in the development of computer-based tools, mathematical models, and algorithms related to the socioeconomic impact, epidemiology, diffusion, and dynamics of SARS-CoV-2. The second section is devoted to computational approaches for understanding virus behavior, selecting possible vaccine candidates, and identifying promising antiviral agents.

1.1. Socioeconomic Impact, Epidemiology, Diffusion, and Dynamics of SARS-CoV-2

In this section, we analyze the articles published in the Special Issue that focused on the development of computational models related to the impact on society, with a particular focus on social, epidemiological, and management issues raised from the inception of SARS-CoV-2 diffusion. The first article, authored by Chowdhury and coworkers, explored the social media impact on awareness of COVID-19 related to the global health emergency, considering scholars at Bangladeshi University. To assess actual shifts in student isolation, psychological numbness, and trust and belief in social media coverage data, the authors used a cross-sectional design with a quantitative method. The authors presented to the students an online survey to determine the connection between knowledge of the pandemic health emergency and the activity on social media. Data were extracted from 189 completed surveys. Using exploratory factor analysis (EFA) and path analysis, the authors indicated that social media are changing the perspective of health problems, affording information and advice on undesired effects of SARS-CoV-2 infections, favoring psychological wellness, and having a beneficial effect on quarantine or lockdown. This interesting work indicated

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that social media are pivotal in improving knowledge about current and future pandemic conditions [1]. Examining the media's contribution to the COVID-19 pandemic in more detail, Yakunin and colleagues investigated the mass media influence in relation to the COVID-19 global health emergency, considering that this situation is an excellent example of a time when the media are crucial for educating the public about essential information. The purpose of this study was to undertake a comparative examination of the depiction of pandemic-related issues in Kazakhstani and Russian Federation internet media. The major objective of this study is to suggest a technique that would enable the analysis of the relationship between COVID-19 data from the World Health Organization and dynamic indicators from mainstream media. Three methods for numerically representing mass media dynamics were devised and used to complete this challenge, each of which was used in accordance with a manually chosen set of search terms. The result analysis indicated both parallel and divergent representations of the epidemiological situation in Russian and Kazakhstan periodicals. In particular, there was a correlation between publication activity in the two categories and absolute measures, e.g., the daily death rate and the daily rate of novel infections. However, the media typically fails to include viral reproduction and positive rates of confirmed cases. When the rigorousness of quarantine measures is considered, mainstream media in Russia and Kazakhstan exhibit very different correlations. According to an analysis of search terms, the issue of fake news and misinformation in Kazakhstan is worse during times when the epidemiological condition is deteriorating and crime and poverty are rising. The originality of this study lies in the formulation and application of a methodological approach that enables a comparison between media indices and objective COVID-19 statistical parameters [2]. Another important study was conducted by González-Parra and Arenas. To model the COVID-19 pandemic, the authors used a highly nonlinear mathematical model to investigate the Omicron wave, considering the effects of the vaccine. The developed model comprises asymptomatic and immunized individuals, which affects SARS-CoV-2 dynamics. In addition, the developed computational tool considered the decrease in vaccination immunity and efficacy against the Omicron strain. The results of the simulation suggested that even if the Omicron strain is less lethal, it may still result in more deaths, infections, and hospitalizations. Interestingly, the authors presented some scenarios that aid in understanding the Omicron wave and its repercussions. Overall, the described mathematical modeling approach, along with the simulation of the selected biological systems, explained the enormous Omicron wave under varied vaccination and transmissibility circumstances. These findings raise awareness that even though SARS-CoV-2 genotypes have a reduced mortality rate, they can nevertheless result in more deaths. Accordingly, the developed model can be useful for understanding the Omicron wave and the impact of novel highly transmissible strains [3]. In a different study authored by Afiahayati and colleagues, a computer-based technique was described for precisely estimating the number of cases of COVID-19 in the coming days, which could be extremely valuable in decision-making for providing proper advice to mitigate pandemic health emergencies. The researchers forecasted the total number of verified cases of COVID-19 in Indonesia using the flower pollination algorithm (FPA), a metaheuristic optimization algorithm. FPA is a robust and adaptive computational technique for optimizing the curve fitting of COVID-19 cases. A machine learning (ML) technique known as the recurrent neural network (RNN), which is popular for prediction, was used for analyzing and comparing the FPA performance. The best hyperparameters for the RNN and FPA were found after a thorough experiment (For the FPA and RNN, there are 24 and 72 different hyperparameter combinations, respectively) to be used for developing the COVID-19 predictive model. According to the outcomes, the FPA method outperformed the RNN in both long- and short-term predictions of the COVID-19 cases. Notably, in the last iteration for long-term forecasting, the FPA model (0.38%) had a substantially lower mean absolute percentage error (MAPE) than the RNN model (5.31%). In the last iteration for short-term forecasting of the cumulative COVID-19 instances in Indonesia, the MAPE for the FPA model (0.74%) was also lower than that for the RNN model (4.8%). The cutting-

edge findings from this study could aid efforts to combat the global COVID-19 health emergency [4]. Intriguingly, a multivariate analysis using COVID-19 vaccine infodemic data in Brazil was described by da Penha Harb and colleagues. This study deals with the exposure of people to an enormous volume of data considering diverse media channels. Notably, this information and these data are not always official and true, and often, when false, they can affect data readability and disease control; incorrect information might worsen the pandemic's harmful impacts. Using the multivariate analytic technique, the research uncovered similar patterns of behavior in the selected population throughout 2021 in two analyses by including information on immunizations from all age groups and with people aged 64 years or older (13% of the population). The authors employed dendrograms as a cluster visualization method. To validate the formed clusters, two techniques were used: the cophenetic correlation coefficient, which produced good findings over 0.7, and the elbow technique, which confirmed the quantity of identified clusters. As a consequence of examining Brazilian states across all age categories, more homogeneous divisions were detected, according to the findings. In contrast, the second analysis produced more heterogeneous clusters, indicating that at the time of vaccinations, there may have been fear, skepticism, and a strong belief in the infodemic [5]. In another paper related to the social impact of vaccination campaigns, Shahzad and collaborators used an ML approach to categorize COVID-19 vaccine-related user responses. In fact, in the pandemic global health emergency, the availability of COVID-19 immunization offered hope for humanity. Unfortunately, people still believe that vaccinations have risks, and they express their beliefs and experiences on social media platforms despite determined vaccination efforts and recommendations from medical professionals and governments. Such opinions may be analyzed to identify societal trends and develop strategies for boosting vaccination acceptance. Accordingly, the authors described a method for sentiment analysis of worldwide opinions and impressions of COVID-19 immunization. The study was conducted using data from Twitter and considered five vaccines, including Moderna, AstraZeneca, Sinovac, Pfizer, and Sinopharm. For sentiment classification, the tweet datasets were divided into three categories (e.g., positive, negative, and natural) using different ML classifiers such as Random Forest (RF), Support Vector Machine (SVM), Logistic Regression (LR), Decision Tree (DT), and Naive Bayes (NB). Interestingly, compared with the other ML methods, the DT classifier has the best classification performance among all the selected datasets. The highest accuracy for COVID-19 vaccine tweets with sentiment annotation was 93.0%. This accuracy was also achieved for the vaccine dataset of AstraZeneca (90.94%), Pfizer (91.07%), Moderna (88.01%), Sinovac (92.8%), and Sinopharm (93.87%). The quantitative comparisons indicated that the proposed study was extremely accurate. Therefore, starting from this type of work, it will be possible to apply deep learning (DL) methods to achieve better accuracy [6]. De La Hoz-M and colleagues conducted a different type of study. They examined the published research on COVID-19 from its beginning and monitored the development of research over two years (February 2020–January 2022). Accordingly, using text mining, latent Dirichlet allocation modeling, trend analysis, and other techniques, the authors searched the PubMed database to extract topics and examine the time-based variations in research for each subject. Furthermore, the authors examined how these themes are covered in different nations (e.g., United States of America, United Kingdom, Italy, India, and China), and journals (7040 sources such as Sci. Rep., PLoS ONE, and Int. J. Environ. Res. Public Health, which represented the leading publishing journals on the COVID-19 outbreak), and 16 research topics and 126,334 peer-reviewed publications were found. The authors found eight topics (vaccine immunity, telemedicine, prevention, morbidity and mortality, mental health, ML, risk factors, academic parameters, and information synthesis methods) showing a rising trend, five (COVID-19 pathology complications, etiopathogenesis, epidemiology, diagnostic test, and political and health factors) showing a falling trend, and the remaining three (pharmacological factors, therapeutics, and others) varied over time with no clear patterns. In conclusion, the findings can offer new study guidelines and be helpful to academics and politicians in understanding research trends in the context

of global events. The outcomes demonstrated that topic modeling is a rapid and effective technique for assessing the development of a sizable and rapidly evolving research topic, such as COVID-19 [7]. Another type of work was focused on the development of a computational method for classifying time-series data related to the number of cases of COVID-19 infection per day. Pangestu and collaborators assessed the effectiveness of community activity limitations in reducing the number of novel COVID-19 cases in West Java (WJ). For this investigation, the researchers used time-series clustering on daily positive case data for COVID-19 across 27 cities and regencies in WJ. Clustering was accomplished using the k-medoids clustering method with shape-based lock step metrics, notably the cross-correlation-based distance. During the worst outbreak, the researchers utilized daily new COVID-19 infection cases in the mentioned cities and regions, considering different periods. The findings indicated that four was the optimal number of clusters that could be generated from the data used considering the first period, whereas two was the optimal number of clusters considering the second period, with silhouette values of 0.2633 and 0.6363, respectively. Results showed that, except for Bogor and Depok, the activity restriction period was successful in reducing COVID-19 infection during the initial time frame and during the second period throughout the whole city and region of WJ. Interestingly, the authors discovered that geography, in addition to the activity restriction period effectiveness, had an impact on the cluster that was formed. A city's likelihood of experiencing an increase in COVID-19 instances depends on the distance from a COVID-19 hotspot area [8]. Curiously, Alinizzi and colleagues investigated traffic congestion during the COVID-19 pandemic period as a rising issue in addition to several socioeconomic problems. Accordingly, the period of traffic congestion hazard (HTC) in metropolitan areas depends on commuters' decisions regarding home-to-shopping center departure times. The decision to leave early or stay late to go shopping depended on both internal (related to commuters) and external (related to shopping centers) considerations. A useful method to evaluate the HTC time following curfew timings was developed in the selected study. The commuters' perception of time spent shopping was evaluated, along with the effects of eight internal (family size, nature of the job, involvement in extracurricular activities, education level, number of cars, number of children, age, and availability of a private driver) and three external (dimensions of the city, distance to shopping center, and approachability of favored shopping center in proximity) factors on their choice. Chi-square and Cramer's V tests, with an acceptable 20% response rate, identified family size and participation in other activities as the most important internal factors and accessibility to the preferred shopping area as the key external factor. The commuters' choices of leaving early or later depended in part on their age, the number of children they had, and the dimensions of the city. Except for educational level and the presence of household drivers, most of the characteristics showed significant relationships. The commuters' responses were divided into four categories using fuzzy synthetic evaluation (FSE): no delay, short delay, moderate delay, and long delay. The peak period of traffic congestion was successfully identified by hierarchical bottom-up aggregation. According to the survey findings, most commuters (approximately 65%) go shopping within 15 min of the curfew lifting; hence, HTC within the first hour of the no curfew time deserved consideration. Traffic regulation agencies can use the described method to determine the HTC period and conduct practical traffic management methods in accordance with the basic sociodemographic information of residents of an urban neighborhood. By implementing the proposed strategy in various locations and conducting traffic monitoring studies when the curfew is lifted for the duration of the pandemic, future research can confirm the results of the current study [9]. Sukandar and coworkers conducted an important study. They used the cumulative case function to generate dynamic operators that recover all state dynamics of a susceptible exposed infectious recovered (EIRs) model for the transmission of COVID-19. In particular, to accommodate immeasurable control and intervention mechanisms, this analysis considered known and unrecorded EIRs and a time-dependent infection rate. Cumulative cases were used to build and implement the dynamic operators. By implementing the generating operators,

all infection processes hidden in this cumulative function can be completely recovered. All recorded state dynamics were obtained by directly implementing the operators on the cumulative function. Furthermore, the unrecorded infection rate per day was calculated using the ratio of the infection mortality ratio (IFR) to the case mortality ratio (CFR). The generating operators were used to obtain the residual dynamics of the unrecorded states. The simulations were run using infection data from ten different countries provided by Worldometers. The increased amount of daily PCR testing was demonstrated to have a direct influence on lowering the effective reproduction ratio. Simulations of all state dynamics, infection rates, and effective reproduction ratios were performed for a number of countries during the first and second waves of transmission. With this method, daily transmission indicators are directly measured and can be utilized to successfully control the epidemic on a daily basis [10]. Aslam published a further article of interest. In this paper, artificial intelligence was used to predict death and ventilator support early in COVID-19 patients to reduce mortality and increase the chance for more effective and prompt therapies. COVID-19 hospitalized patients from King Abdulaziz Medical City in Riyadh were included in this study. To determine the influence of specific qualities on the prediction of death and ventilator support in patients affected by COVID-19, this work coupled a DL model with explainable artificial intelligence (EAI). Despite producing important results, the DL model is difficult to interpret. Data were collected from patient demographics, laboratory tests, and chest X-ray (CXR) results. Due to the unbalanced nature of the dataset, specificity, sensitivity, balanced accuracy, AUC metrics, and the Youden index were applied to assess the efficiency of the developed computational tool. In addition, the SMOTE (over- and under-sampled) datasets and the original datasets were used in the studies. With a balanced accuracy of 0.98 and an AUC of 0.998 to predict mortality employing the entire feature set, the developed model performs better than the baseline study. A maximum adjusted accuracy of 0.979 and an AUC of 0.981 were obtained to predict ventilator support. The described predictive computer-based tool could help physicians identify patients with COVID-19 who may need ventilator assistance or die early on, which would improve the use of hospital resources [11]. Demongeot and coworkers investigated other attractive aspects related to the pandemic scenario. In fact, it is infrequently investigated how to estimate daily reproduction counts during the contagiousness phase, and only their aggregate R0 is usually estimated to define an infectious disease contagiousness level. Using a deconvolution method on a set of novel COVID-19 infections, the researchers derived an equation for the discrete dynamics of epidemic propagation and determined the number of daily reproductions. Considering various nations and waves of the COVID-19 outbreak, results and estimations were obtained to determine how noise can affect the stability of the epidemic dynamics. Accordingly, it will be possible to enhance estimates of the distribution of daily reproduction numbers during the infectious period by accounting for heterogeneity owing to different host age classes [12]. Moreover, Bertrand and Pirch developed a susceptibility-exposed-infected-quarantined-recovered-deceased (SEIQRD) model for the propagation of COVID-19 using a flux-based finite element method. The model was largely based on susceptible-exposed-infected-recovered-deceased (SEIRD) models recently established, with the addition of a quarantined compartment of the living population. A least-squares mesoscale method is then used to solve the resulting first-order system of coupled PDEs. To establish an indicator that affects the predictions generated by the approach, a variety of data on governmental actions taken to control the spread throughout 2020 was used. When compared with actual disease-spreading data, the results of numerical tests showed that predictions of the virus's space-time behavior were remarkably accurate [13]. In an interesting paper, Zeng and coworkers investigated the possibility of understanding the relationship among components crucial to patient disease progression to decrease the effects of the epidemic. For this purpose, the authors developed an improved COVID-19 structured dataset from many sources, incorporating local weather information and study sentiment relevant to a particular nation using natural language processing. The researcher used both ML and DL methods on the 301,363 samples and 43 attributes in

the expanded structured dataset to predict the likelihood that a patient will survive. To enhance the model performance, the authors imported alignment sequence data. When used on the expanded structured dataset, Extreme Gradient Boosting (XGBoost) predicted patient survival with 97% accuracy, with climatic conditions and age exhibiting the greatest significance. Similarly, a multilayer perceptron (MLP) application achieved 98% accuracy. Accordingly, it would be beneficial to add more potentially significant variables to the patient data that are already available, such as the current weather, to improve the prediction of the likelihood that the patient will survive [14]. Sarv Ahrabi and colleagues investigated the patient monitoring issue. They highlighted the importance of careful patient monitoring in keeping the condition entirely under control, in addition to extensive medical research. It is well established that the study of X-rays is useful because of its accessibility; however, viral testing is most commonly used to discover COVID-19. Many studies have used DL paradigms with the goal of enhancing COVID-19 radiography-based identification of lung infection. In this context, the authors compared notable methods for binary classification of infected photos using DL techniques, deriving a convolutional neural network (CNN) variation with optimized parameters that showed satisfactory performance on a recent dataset of images obtained from COVID-19 patients. Contrary to the other models provided, the effectiveness of the generated model is of great importance. In this method, a random selection of a few images from the dataset was used as a holdout set. The developed tool successfully identified the majority of COVID-19 X-rays, showing an outstanding general accuracy of 99.8%. Additionally, the relevance of the findings from evaluating other datasets with various features (which, notably, are not utilized in the training process) showed that the suggested approach is beneficial in terms of accuracy up to 93% [15]. Moreover, Gencoglu and collaborators reported an analysis of effective crisis management during unfavorable health occurrences. During this period, it is fundamental to comprehend the traits of public attention and sentiment. This is extremely relevant during a pandemic like COVID-19 because the primary role of risk management is disseminated across society rather than being centered on a single entity. While many studies have used Twitter data to describe or anticipate the COVID-19 outbreak, causal modeling of public attention has not been studied. In the mentioned work, a causal inference approach was utilized to pinpoint and measure causal links among Twitter activity, public opinion, and pandemic features such as infection and mortality rates. The outcomes showed that the suggested strategy may effectively capture epidemiological domain knowledge and recognize factors that influence public opinion. Notably, by separating events that correlate with public attention from those that cause public attention, this work could advance the discipline of infodemiology [16]. Finally, an interesting aspect that correlated SARS-CoV-2 diffusion and transmission with air pollution and related pollutants was investigated in two papers published in the Special Issue. In particular, Delnevo and collaborators explored the correlation between air pollution and the fatal effects of COVID-19. To this end, the authors considered a series of daily values of $PM_{2.5}$, PM_{10}, and NO_2 over time, and the Granger causality statistical hypothesis test was used to determine the presumption of causation. Surely, numerous additional investigations at a level commensurate with the size of this phenomenon (e.g., physical, chemical, and biological) would be required to fully comprehend the relationship between the spread of this lethal virus and air pollutants. However, as strictly viewed from a Granger causality standpoint, the outcomes acquired both during and after the government lockdown decisions demonstrate a definite association [17]. Subsequently, the same research team focused further attention on the correlation between the propagation of the virus and the presence of airborne particle pollutants ($PM_{2.5}$, PM_{10}, and NO_2). In this study, the authors have described a new metric for forecasting COVID-19 diffusion. An ML model was developed and trained using the following data: (i) all COVID-19 illnesses that occurred between February and July 2020 in Emilia Romagna (Italy), a region in Europe that is among the most polluted; (ii) the region-specific daily values of all particulates. The traditional ten-fold cross-validation approach was then utilized on the ML model, and the results showed an accuracy rate of

90%. Finally, the model was applied to forecast the potential reappearance of the virus in Emilia-Romagna between September and December 2020. The authors were unable to verify the accuracy of the forecasts at the time of writing this article. However, this COVID-19 prediction model is the only one of its kind in the world because the authors speculated on a scenario based on a novel premise [18].

1.2. Structural Modeling, Vaccines, and Antiviral Drug Discovery

The second section is dedicated to the development and applications of computer-aided procedures for antiviral drug discovery, vaccine candidate selection, and understanding the behavior of the virus, simulating the dynamics of drug targets. In this context, Liang and collaborators investigated SARS-CoV-2 spike glycoprotein (S-protein) dynamics by employing a coarse-grained approach using physic-informed ML. Coarse-grained methods are useful for modeling systems that are not possible to model utilizing classical all-atom molecular dynamics (MD). Accordingly, by employing learned interaction parameters, coarse-grained MD simulations attained the microsecond time scale with stability (simulation speed 40,000 times faster than the conventional MD). When compared with the usual iterative approach, the proposed framework more accurately matches all-atom reference structures. The increased efficiency improves the timeliness in developing long-time simulations of SARS-CoV-2 drug targets and creates opportunities for revealing protein processes and anticipating environmental changes [19]. Regarding the selection of vaccine candidate, Oluwagbemi and coworkers developed a computational protocol using bioinformatics and immunoinformatic techniques to generate a multi-epitope mRNA vaccine that protects against the SARS-CoV-2 S-protein variants that were present in African nations at the time of the study. In particular, predictions of T- and B-lymphocyte epitopes were performed using various immunoinformatic methods. To select epitopes that could trigger a long-lasting immune response, they were subjected to additional tests. Seven epitopes, a highly immunogenic adjuvant, an MHC I-targeting domain (MITD), a signal peptide, and linkers comprise the proposed vaccine. The proposed vaccine was also antigenic, nonallergenic, nontoxic, thermostable, and hydrophilic, according to the results. In 100 randomly chosen SARS-CoV-2 S-proteins, none of the seven epitopes showed alterations. The vaccine construction secondary structure was stabilized by 36.44% α-helices, 20.45% drawn filaments, and 33.38% random helices. The simulated vaccine exhibited a strong affinity for TLR-4, as revealed by molecular docking, indicating its capacity to activate both innate and adaptive immunity. Further in vitro and in vivo studies should be conducted after the results and performance of this computational research [20]. In an interesting paper, Singh and colleagues described a computational approach to find chemicals potentially able to recover the activity of interferon-stimulated genes (ISGs). ISGylation is a critical step in the process by which ISGs induce an antiviral response in host cells. In fact, numerous viruses, such as SARS-CoV-2, decrease host immune responses by negatively influencing the ISGylation process (de-ISGylation). SARS-CoV-2 papain-like protease (PLpro) interacts with host ISG15, resulting in de-ISGylation. Thus, blocking de-ISGylation to recover ISG activity may be an appealing method for enhancing the host immunological response to SARS-CoV-2. For this purpose, the authors evaluated in silico several phytochemicals derived from well-known immunomodulatory herbs, including *Andrographis paniculata*, *Tinospora cordifolia*, and *Ocimum sanctum*, for their influence on de-ISGylation induced by SARS-CoV2 PLpro. The authors used a crystallographic complex that reflects the SARS-CoV-2 PLpro and ISG15 protein interacting model (PDB ID: 6XA9). The ability of these phytochemicals to bind to the interface region between PLpro and ISG15 was evaluated. Molecular docking calculations revealed that 14-deoxy-15-isopropylidene-11,12-didehydroandrographolide (AG1), isocolumbin (GU1), and orientin (TU1) have satisfactory binding energies. According to MD parameters and MM/PBSA calculations, TU1, GU1, and AG1 may bind to the interface, targeting pivotal residues in the PLpro-ISG15 complex [21]. In the field of antiviral drug discovery, Brogi and collaborators published two papers within the Special Issue considering two different SARS-CoV-2 drug targets, the RNA-dependent RNA polymerase

(RdRp) and the main protease (Mpro or 3CLpro). The first paper described a computational approach aimed at optimizing the alkaloid Quinadoline B (Q3) as a possible SARS-CoV-2 RdRp inhibitor. For this purpose, starting from a previously identified anti-viral fungal metabolite Q3 as a SARS-CoV-2 RdRp inhibitor, a computational combinatorial methodology was used to generate a chemical library based on the Q3 compound. The resulting chemical library (>900,000 different Q3 derivatives) was screened against RdRp to identify RdRp binders with higher affinity than the Q3-derived starting molecule. Using this method, along with the evaluation of the physchem profile, 26 derivatives were identified as potential RdRp inhibitors. In addition, the most promising derivatives were subjected to MD simulation to thoroughly examine the binding mechanism. Five compounds showed improved binding affinity for the RdRp enzyme and are therefore worth further study as potential antivirals. The described in silico strategy offers a practical computational method for hit-to-lead optimization, with implications for the search for anti-SARS-CoV-2 drugs and the overall drug optimization process [22]. Later, the same research group analyzed in silico the potential of peptide-based derivatives containing bifunctional warheads that could interact with prime and non-prime residues to covalently bind the Mpro of SARS-CoV-2 to develop novel antiviral agents. As a result, the authors proposed a computer-based protocol for discovering potential SARS-CoV-2 Mpro covalent inhibitors. They examined the possibility of a peptide-based scaffold with diverse warheads as a substantial alternative to aldehyde and nitrile electrophilic groups using multiple in silico methodologies. As warheads, we rationally generated four possible inhibitors, including difluorostatone and a Michael acceptor. Based on molecular and covalent docking, MD simulation, and free energy perturbation (FEP), the in silico investigation showed that the generated compounds might function as covalent inhibitors of Mpro and that the examined warheads could be employed to develop inhibitors that can covalently bind cysteine or serine proteases, including the Mpro of SARS-CoV-2. Notably, the abovementioned research provided a rigorous computational protocol for identifying and developing powerful antiviral agents [23]. Further considering Mpro and other possible drug targets, Muhammad and colleagues examined the interactions of eight natural eucalyptus compounds with SARS-CoV-2 Mpro to determine whether they could be used as herbal treatments for the emerging SARS-CoV-2 virus. Atomistic interactions were inspected using various in silico techniques, such as molecular docking, MD simulations, and MM/PBSA calculations. On the basis of the outcomes of molecular docking, all drugs examined showed significant binding energy for Mpro. Three computational hits, α-gurjunene, aromadendrene, and alloaromadendrene, with satisfactorily predicted affinity, were simulated using GROMACS to analyze the interactions between Mpro and inhibitor molecules at the molecular level. According to the results of our MD simulation, aromadendrene and α-gurjunene were found to be the most promising compounds, with binding energies of −18.99 kcal/mol and −17.91 kcal/mol, respectively. The outcomes indicated that eucalyptus could be a hypothetical therapeutic opportunity to inhibit the Mpro enzyme. Remarkably, this work is one of the first in which has been investigated the role of structural flexibility in Mpro interactions with herbal drugs [24]. Culletta and coworkers used different computational techniques to identify drugs against different established drug targets (3CLpro, PLpro, and different non-structural viral proteins). Homology modeling (for targets with no available experimental structures) and a structure-based pharmacophore modeling study were conducted for each drug target. Next, using the developed pharmacophore models, a virtual screening was conducted employing the chemical library provided by DrugBank. Each target's potential inhibitors were identified using XP docking, induced fit docking, and MM/GBSA calculations. After the docking study, 34 hits for the explored targets were selected (26 experimental drugs, 5 investigational drugs, and 3 approved drugs). The best binding energy for each molecule, as determined by MM/GBSA calculations, was used to make the final selection of candidate inhibitors. These chemicals were found able to interact with crucial residues of each target according to the molecular recognition analysis. The effectiveness of these drug candidates in successfully inhibiting COVID-19 can be

further assessed. The findings of this study provide crucial information for anti-COVID-19 drug discovery efforts, identify the primary binding sites for the most significant SARS-CoV-2 proteins, and present a crucial path for the development of novel antivirals [25]. Finally, Qiao and coworkers developed two computational protocols to identify SARS-CoV-2 S-protein and 3CLpro inhibitors for possible COVID-19 treatment. Among the screened compounds showing a significant inhibitory profile in preventing the recognition of the S-protein of SARS-CoV-2 and ACE-2 in host cells, vancomycin, amphotericin B, and ergotamine were identified as the most promising compounds. On the other hand, the researchers also identified possible inhibitors of SARS-CoV-2 3CLpro. Among them, the most interesting drugs identified were dasatinib, rivaroxaban, montelukast, sildenafil, saquinavir, tadalafil, and vardenafil, which showed docking scores lower than −8.5 kcal/mol [26]. Aminpour and colleagues authored the last paper analyzed here. They used in silico methods to explore the possible mechanism of action of ivermectin and its derivatives as possible multitarget antivirals. The authors conducted computational work to estimate the binding affinity of possible antivirals for the S-protein of SARS-CoV-2, the CD147 receptor (secondary attachment point for the virus), and the α-7 nicotinic acetylcholine receptor (α-7nAChr) (important for viral penetration of neuronal tissue as well as an activation site for the cholinergic anti-inflammatory pathway controlled by the vagus nerve). For each compound's various docking locations and binding mechanisms, binding affinities were computed. Our findings show that ivermectin has a strong affinity for all three of these molecular targets, with some other drugs having even greater affinities. Interestingly, these findings point to potential molecular processes through which ivermectin could reduce the infectiousness and morbidity of the SARS-CoV-2 virus and activate an anti-inflammatory pathway controlled by α-7nAChR, which might reduce the production of cytokines by immune cells [27].

Finally, as Guest Editors, we express our gratitude to the Computation Editorial team for their generous support, all the authors and co-authors for their pertinent contributions to this Special Issue, and all the reviewers for their work in assessing the submissions. All of these combined efforts contributed to the research topic's outstanding success. In addition to being a significant source of knowledge and inspiration for researchers and students, we anticipate that this topic will boost the understanding of SARS-CoV-2 behavior, helping to find effective treatments and measures for reducing viral transmission. You can freely obtain this Special Issue by clicking on the following link: https://www.mdpi.com/journal/computation/special_issues/computation_COVID_19, (accessed on 13 September 2023).

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