

Novel computational pipelines in antiviral structure-based drug design (Review)

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Abstract. Viral infections constitute a fundamental and continuous challenge for the global scientific and medical community, as highlighted by the ongoing COVID-19 pandemic. In combination with prophylactic vaccines, the development of safe and effective antiviral drugs remains a pressing need for the effective management of rare and common pathogenic viruses. The design of potent antivirals can be informed by the study of the three-dimensional structure of viral protein targets. Structure-based design of antivirals *in silico* provides a solution to the arduous and costly process of conventional drug development pipelines. Furthermore, rapid advances in high-throughput computing, along with the growth of available biomolecular and biochemical data, enable the development of novel computational pipelines in the hunt of antivirals. The incorporation of modern methods, such as deep-learning and artificial intelligence, has the potential to revolutionize the structure-based design and repurposing of antiviral compounds, with minimal side effects and high efficacy. The present review aims to provide an outline of both traditional computational drug design and emerging, high-level computing strategies.

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1. Introduction

In the last 60 years or so, the world has faced several viral pandemics, from the influenza pandemic in the late sixties, to the human immunodeficiency virus (HIV) epidemic in the eighties and lastly, to the COVID-19 pandemic that continues to challenge communities on a global scale today (1,2). By November 2021, >5 million people have lost their lives following infection by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) and many more face complications after surviving COVID-19 (3). As the pandemic unfolded, the scientific community was rapidly met with two pressing needs, that of a prophylactic vaccine, to induce immunity within the populations, and that of an effective drug against the deadly virus. The COVID-19 example effectively reaffirmed an existing challenge; the development or the repurposing of safe and effective antivirals is not an easy task.

In contrast to the development of antiviral drugs, the advancement of antibiotics was fairly quick, with the discovery of penicillin by Fleming in 1929 (4) and the effective isolation of current staples such as tetracycline and streptomycin in the 1950's (5,6). In 1963, the development of the first antiviral drug for human use, idoxuridine, marked the beginning of a revolution against infectious diseases of viral etiology (7). Within the following 50 years, however, less than a hundred antiviral drugs were approved for use against a number of viruses, such as HIV, hepatitis C virus, human influenza virus, hepatitis C virus (HBV), respiratory syncytial virus, herpes simplex virus (HSV), varicella-zoster virus and human papilloma virus (7).

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This limited number, when compared to the thousands of investigational antiviral compounds, is a testament to the strict standards that are applied to the process of antiviral drug development (8).

An inherent challenge regarding antiviral drugs stems from the very nature of the viral life cycle. Viruses, as obligate intracellular parasites, hijack the biochemical processes of the host cells in order to traverse fundamental stages of their life cycle, from the replication of their genome to the assembly of new virions within the infected cells (9). Therefore, antiviral drugs may have adverse, parallel effects on the host organism, in our case the human system, and lead to phenomenon of toxicity (10,11). As a result, during the development of anti-viral drugs, the target of choice is required to be as specific and as unrelated to the host system as possible, to ensure both increased selectivity and minimization of potential side effects (12).

The viral life cycle can be generally broken down to the following main steps: The first step involves the attachment of the viral particle to a host cell and the subsequent penetration. The second step involves the process of uncoating and replication of the viral DNA or RNA genome, which, in conjunction with the production of necessary viral proteins, leads to the assembly of new virions, which are eventually released from the infected cell in various potential manners (13). The search for candidate targets of antivirals can thus be guided by the sphere of knowledge of the multi-faceted viral life cycle and its particularities, such as in the case of HIV, an RNA virus that replicates through a cDNA intermediate (14,15). By extension, the viral enzyme that carries out the process of reverse transcription, named reverse transcriptase, constitutes an attractive and currently used target for the successful design of anti-HIV drugs, such as the nucleoside analogues didanosine, zidovudine and lamivudine (16). Generally, nucleoside analogues are an important group of antiviral agents against common viruses, such as HBV or HSV, and are believed to hinder viral replication in a variety of ways, by competitive enzyme inhibition or premature termination of the synthesis of the new DNA chain (17).

2. Structure-based drug design

Structure-based drug design has grown into a staple method in the discovery and development of drugs (18). This is largely owing to the fact that conventional drug discovery pipelines are challenged by a significant demand for labor and time, as well as by rising costs (19). Computational drug design can effectively lower these costs and accelerate the process of the development or repurposing of drugs; time is a crucial factor in the case of viral outbreaks, as evidenced by the current COVID-19 pandemic and the frantic search for therapeutic targets and effective drugs against SARS-CoV-2 (20,21).

In broad strokes, structure-based design of antivirals can be divided into three major sections: i) Identifying biomolecules of interest, such as viral enzymes or viral structural components; ii) determining the three-dimensional structure and thereby the function of the targets; and iii) designing the drug molecule that would offer a therapeutic result, through accurate estimation and evaluation of the affinity of the ligand to the target protein (20,22). Usually, the three-dimensional structure of

the biomolecular target is elucidated through nuclear magnetic resonance, cryogenic electron microscopy and X-ray crystallography experiments (23). Modern high-throughput methods have enabled the generation of ample structural data related to viral structural and non-structural proteins, which can be obtained through public databases such as the Protein Data Bank (PDB) (24). Homology modeling techniques, which exploit the fact that structure is more associated with the function of a protein in comparison to its sequence, can be employed in the case of an unsolved target-structure to carry out a structure prediction based on one or more experimentally determined template structures (25-28).

Ideally, the macromolecular target for structure-based drug design is a principal component of the viral life cycle and binds another molecule, usually a smaller substrate, to carry out a specific process (29). Viral non-structural proteins are thus an appropriate candidate since they are crucial for the replication of the viral genome and bind specific molecules in their active sites (29,30). Furthermore, certain enzymes exhibit conserved domains and motifs across viruses that belong to the same family or genus, such as in the case of RNA-dependent RNA polymerase in the Flaviviridae viral family (31,32). This high level of conservation enables the design of ‘umbrella’ antivirals, which could be effective against multiple viruses. In the case of antivirals that target viral enzymes, a standard mode of action is the inhibition of the enzymatic process (33). For example, azidothymidine, a drug used against HIV, which inhibits the process of reverse transcription, was designed to target the process of reverse transcription in avian retroviruses and was eventually repurposed towards the treatment of HIV (9).

Structure-based methods for antiviral design encompass processes like *de novo* drug design, in which the candidate antiviral molecule is designed from the start through a growing or linking method, virtual screening, which refers to the identification of active molecules out of a virtual library of candidate compounds, and ligand optimization (34). In the case of structure-based virtual screening, the computational approach of molecular docking constitutes a fundamental technique (35). In order to identify the optimal binding modes of candidate molecules in the binding cavities of the target, an assortment of available docking software programs can be employed, such as Autodock and RosettaLigand (36,37). These programs allow the ranking of binding positions on the basis of noncovalent interactions, while also enabling the visualization of the interaction between ligand and target on a structural level (36). The candidate molecules that exhibit optimal scores can then be synthesized in order to measure *in vitro* elements, such as half maximal inhibitory concentrations, and move onto subsequent optimization steps, minimizing the cost until the lead selection step with the use of *in silico* methods (18). Molecular dynamics simulations, when incorporated into a structure-based drug design methodology, allow an accurate study of the drug-target model systems, accounting for the flexibility of both the ligand and the receptor (38). During molecular dynamics, the configurations of the system can be freely explored and macroscopic properties can be evaluated (39). Overall, the *in silico* structure-based design of antiviral compounds is a dynamic and evolving process, the components of which can be modified to fit the requirements

of the viral-host system under investigation (40,41). This inherent flexibility can thus accelerate and elevate the process of antiviral drug discovery before the *in vitro* setting has been reached.

As with any approach, *in silico* structure-based drug design exhibits limitations. The quality of the data on which the computational methods are applied constitutes a decisive factor in the success of molecule design (42). Efficient use of a target biomolecule requires high-resolution data of its structure, which may not always be available. Furthermore, knowledge databases, which serve as a source of both target molecules and candidate molecules, may contain errors (42). Lastly, in structure-based virtual screening, scoring functions and other metrics employed to calculate biomolecule-ligand complexes suffer from variance in performance across different biomolecule systems (43).

3. Novel computational pipelines

In addition to the aforementioned successfully implemented methods, the rapid developments in genomics, big data and computational systems within the last decade pave the way for new opportunities in the structure-based design of antivirals. Automation has revolutionized the processes of standard experimental procedures such as whole genome and whole exome sequencing, accelerating the generation of scientific data (44). Modern databases house invaluable information related to fundamental components of the viral life cycle, such as biomolecular structures, viral genome and protein sequences, and host-pathogen interaction networks, providing the fundamental basis for the identification of novel targets of antivirals, as well as for the effective design of the antiviral compounds themselves (45,46).

The big data era in science is marked by the continuous generation of massive amounts of data, which in turn require novel computational methods for their successful utilization. High-performance computing has set the foundation for the emergence of machine learning (ML) methods, which employ algorithms for the efficient analysis of multidimensional data, such as viral genomics and proteomics, the subsequent extraction of important features, and finally, the construction of useful predictive and analytical models (47). Neural networks, which are essentially mathematical models aimed at data analysis, can provide the underlying architecture for the development of cutting-edge, deep-learning models (48).

Antiviral peptides are a promising class of molecules that may serve as a basis for the development of novel antiviral drugs (49). Thus, modern computational frameworks are required for the accurate prediction of antiviral activity exhibited by candidate therapeutic peptides. Towards that end, Timmons and Hewage (50) developed ENNAVIA, a classifier based on neural networks, which enables the screening of available peptides for their potential activity, as well as the informed design of novel antiviral peptides. Furthermore, natural compounds, such as phytochemicals, have been the subject of similar screening studies, with the aim of identifying compounds with significant antiviral action (51). In such a study, SARS-CoV-2 main protease and angiotensin-converting enzyme 2 were elected as molecular targets, against which a library of natural compounds was

screened through the structure-based method of molecular docking (52).

Deep learning, a subset of ML, stems from conventional neural network systems, and its high rates of success have cemented its status among the emerging research trends (53). Deep learning employs artificial neural networks in a multi-layered architecture, where each layer can contain different methods of extracting feature representations (54). AlphaFold2 is an innovative neural network-based model that revolutionized the field of computational structure predictions, exhibiting marked accuracy and efficacy during CASP14, the 14th Critical Assessment of Structural Prediction competition (55). The AlphaFold2-modeled human proteome, as well as proteins from 20 other organisms, have been made available in the AlphaFold Protein Structure Database (56). The next step came as ColabFold, which is described in a recent preprint as a novel framework for the prediction of protein and complex structures (57). ColabFold implements the cutting-edge neural network basis of AlphaFold2, while allowing the input of user protein sequences for the execution of the structural prediction (57). It could therefore be theorized that deep neural networks may steadily replace standard homology modeling approaches for the accurate prediction of unknown protein structures.

Moreover, during the early stages of the COVID-19 pandemic, AlphaFold2 generated models of then-unsolved SARS-CoV-2 proteins, such as its main protease, which were later found to be in close agreement with the experimentally determined structures (58). Therefore, in the context of future potential viral pandemics, deep learning models have the potential to act as a first 'barricade'. Artificial intelligence models such as AlphaFold2 could readily generate structures of viral-encoded protein sequences to be used as targets for virtual screening experiments and *de novo* drug design, potentially saving lives. Aside from the construction of novel predictive models, deep-learning methods can be implemented in stages of conventional structure-based antiviral drug design. DeepScore, a deep learning-based model, constructs target-specific scoring functions, which can generate better results in structure-based virtual screening experiments in comparison to conventional, universal scoring functions (59). Lastly, deep learning and ML approaches have been implemented in the hunt for novel antiviral drugs, acting as a driving force in the drug discovery process against notable viral pathogens such as SARS-CoV-2, Yellow Fever Virus and Ebola virus (60-62). A notable issue when implementing ML models that carry out binding affinity predictions for the discovery of antivirals is the sturdy evaluation of model performance. Francoeur *et al* (63) provided a potential solution to this problem with CrossDocked2020, a dataset of >22 million poses of ligands docked into binding pockets as they are defined in the PDB. To demonstrate the potential of the dataset as a standard tool to benchmark predictive models of target-ligand binding affinity, the study additionally described the evaluation of its own convolutional neural network models.

4. Conclusions

Traditional wet-lab studies require significant time and resources for the successful development of novel antiviral

compounds. Viral outbreaks and pandemics, on the other hand, are fast to unfold and can claim millions of lives before mechanisms of response are activated. In the face of this challenge, *in silico* methods of structure-based drug design could inform the rapid development of novel antivirals and the efficient screening of approved drugs for repurposing. The core process of structure-based antiviral design can be elevated through the use of ‘intelligent’ computational approaches, such as multi-layered neural networks. Taken together, these approaches can aid the development of highly specific, non-cytotoxic lead antivirals, and fortify public health and safety.

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