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CHAPTER

21

Present and future challenges in therapeutic designing using computational approaches

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21.1 Introduction

Recent development in the field of computer hardware, software, and algorithms eases the drug design and development effort. The drug discovery process is extremely complicated and necessitates an interdisciplinary effort to produce effective and commercially sustainable therapeutics. The time and expenditure of drug development can be considerably reduced using computational methods. Bioinformatics can assist in uncovering the pathophysiological functions of drug-able genes from a large amount of genomic data in general (Bakheet & Doig, 2009; Yamanishi et al., 2008) and hence offer possible target proteins for drug screening and design. Protein structure prediction methods can assist in elucidating the protein structures with high precision (Moult et al., 2018). Biomolecular simulations with multidisciplinary approaches can provide structural and thermodynamic capabilities of target proteins (Ayton et al., 2007) which might be beneficial for figuring out drug binding sites and elucidating drug action mechanisms.

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Random screening of natural compounds or laboratory-synthesized compounds is one of the traditional drug design strategies. The disadvantages of this strategy are the lengthy design cycle and high expense. A few critical questions must be addressed in this context, such as "which areas of the chemical environment should be examined to uncover possible therapeutic candidates. Searching on the traditional, drug-like medicinally relevant chemical space has not led to the identification of many new chemical entities."

Although many computational strategies are being utilized in therapeutics design however numerous demanding situations have additionally been seen. Identification and confirming molecular targets with therapeutic applicability is a critical step in drug development. One of the most critical issues is determining the physiologically relevant chemical space. Further, it is also of significant importance to study polypharmacology and try to predict the interactions of a drug candidate with all its putative target partners. Computer-aided drug design (CADD) methods face challenges such as improving multitarget drug design and multitarget property prediction, identifying better ways to address protein−protein interactions, and continuing to explore molecular targets associated with neglected diseases. Computational approaches can also aid in the discovery of druggable binding pockets, allosteric sites, and transient binding sites that can be used in drug development.

21.2 Therapeutic designing using computational approaches

21.2.1 Drug discovery using computational approaches

CADD contributes to the generation of clinically useful molecules. Such methods are generally categorized into two types, that is, structure-based and ligand-based methods (Fig. 21.1). Today, in the fast-moving world with technological advancement, CADD has become an inevitable, highly effective, and cost-effective approach. CADD is one of the crucial approaches that have paved a way for the development of new therapeutic drugs. Though several steps have been taken care of in CADD, the relevance of high-throughput screening (HTS) has found a vital position in finding new therapeutic applications.

The main advantage of this method is that the compounds that are considered inactive are overlooked while those considered as the most active are given prominence. Such methods serve as a robust tool for identifying the drug target (Drie, 2007).

This technique is useful in getting minimal information on the design of compounds due to which screenings of large libraries have become more feasible. Though the HTS used traditionally lead to developing several hit compounds, out of which some compounds could be modified to develop into a better drug healer. This leads to a low hit rate for HTS compounds, which limits its use in research programs so that the large compound libraries can be screened easily (Macalino et al., 2015). Presently, it has been observed that the enormous databases of the compounds are easily and commercially accessible, and investigating the ligand chemical space gives the scientists control a huge amount of data. Many novel techniques established on the already available information on the biotic system under investigation helps in modifying, manipulating, and controlling the data (Sliwoski et al., 2013).

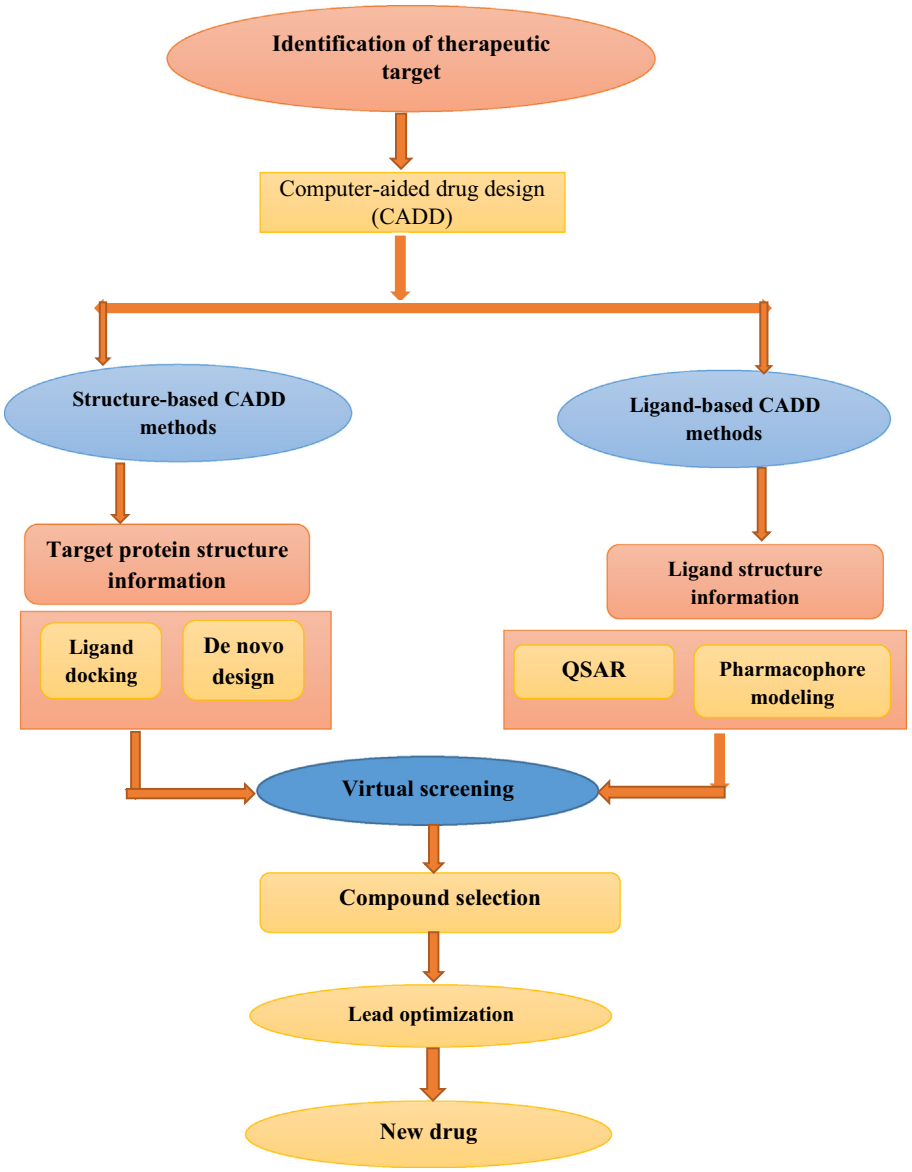

FIGURE 21.1 Illustration of methodology in computer-aided drug discovery.

Apart from these applications, the inclusion of "-omics" technologies and databases may also help in identifying the new drug targets and the development of network-related targeted drugs. Structure and ligand-based processes are more commonly used techniques in the discovery of the drug, but new approaches such as proteo-chemometrics modeling are also upcoming tools.

CADD is a cost-effective approach, which requires less preparation time. It has the ability to accelerate the hit rate of new evolved drug compounds as it applies the most targeted search rather than traditional HTS. Based on the information of the structure, either a structure-based approach or a ligand-based approach is used. After the virtual screening, multiple lead compounds are identified, which is followed by lead optimization (Fig. 21.1) resulting in the development of new drugs (Sliwoski et al., 2013).

21.2.1.1 Classification of computer-aided drug design

21.2.1.1.1 Structure-based methods

Structure-based methods basically analyze the three-dimensional structure of proteins to target those relevant areas from the perspective of biological nature. The details from the structure-based methods can be used to develop essential drugs such as antibiotics that can engage with the target interactions, thus blocking the metabolic pathways necessary for the survival of microorganisms. It actually seeks the information related to the structure of the target protein so that the interlinkage of all the compounds can be tested and is generally prioritized where the hierarchical data with high resolution of the target protein such as soluble proteins are easily accessible, and which can be crystallized. Structure-based CADD basically designs those compounds that bind firmly with the target, like reducing free energy, improving properties of DMPK/ADMET, and becoming target specific (Jorgensen, 2010). It mainly focuses on ligand docking, pharmacophore, and ligand design methods.

In CADD methods, de novo drug design is considered to be an important tool that is better known for designing and developing new compounds (Basak, 2012). Thus, it is significant to put in computational tools to enfold the chemical space mitigating the number of compounds that need to be examined in the in vitro testing methods. The reasonable price of CADD in comparison to chemical synthesis and characterization of compounds results in more focused and attractive methods which explore the chemical space (Enyedy & Egan, 2008; Sawyer et al., 2003).

21.2.1.1.2 Ligand-based computer-aided drug design

Ligand-based CADD is usually used when either no or limited information regarding the known active and inactive molecules is available. Generally, it uses the information of the studied and investigated active and inactive molecules by looking into their chemical similarity or establishing the quantitative structure–activity relation (QSAR) models (Kalyaanamoorthy & Chen, 2011). A combined application of both structure and ligand-based methods helps in developing a compound that can be tested and authenticated both in vitro and in vivo, confirming the location of its binding sites. When the structural information of the target is not known, then QSAR techniques can be employed for de novo drug design techniques. Instead of structure-based CADD methods like docking, descriptor along with model generation is conducted, which is used to score the de novo-generated molecules. The compound generation process has iterative algorithms where modifications and alterations are conducted continuously in the structures, and their physiological and biological actions are assessed through QSAR models. In comparison to the structure-based de novo design, ligand-based de novo drug design is not performed

always on a continuous basis due to the challenges faced while assessing a novel molecule without the receptor structure.

21.2.1.2 Evolution of artificial intelligence and machine learning

21.2.1.2.1 Artificial intelligence

Artificial intelligence (AI) is a vast range of scientific disciplines which is supposed to innovate new systems aiming at displaying properties of intelligence.

21.2.1.2.2 Machine learning

It is a subsystem of AI which goes for analyzing data that works automatically in building the analytical model. It is a part of AI where the systems use data, specify patterns and take decisions with nominal human intercession. This method significantly applies the data of statistical analysis with the help of computers. Machine learning (ML) employs a significant range of statistical methods which are widely used in medicines.

21.2.1.2.3 Deep learning

Deep learning (DL) methods help in feeding a substantial amount of raw data in the machine to come up with the representations required for identification or categorization. DL methods depend mainly on varied layers of data representation with repeated alterations in a sequential manner which boost up the input features necessary for making differences and which put down the immaterial variations. DL could be guided or unguided. DL methods are known better for the latest fundamental approaches in ML.

21.2.1.2.4 Supervised learning

In supervised learning, computer programs are trained in such a manner that when the input data is fed into the machine, the output is generated. It is one of the most appreciable forms of ML with various instances in the healthcare industry.

21.2.1.2.5 Unsupervised learning

Unsupervised learning is a kind of ML in which AI algorithms are applied where it analyzes and clusters unlabeled datasets. Specifically, it is applied for data clustering, data association, and dimensional curtailment. It recognizes the unseen and concealed patterns within the datasets alone on its own ability without the help of human arbitration.

21.2.1.2.6 Reinforcement learning

It is one of the most important aspects of ML apart from supervised learning and unsupervised learning. Reinforcement learning (RL) algorithms have gained a prominent position in medicinal and therapeutic applications. In comparison to other techniques of AI, it has many advantages in the context of medicinal applications like improving novel methods for the benefit of patients which can lead to long-term benefits instead of immediate benefits. RL uses a combined form of both supervised and unsupervised learning, where functions of both supervised and unsupervised learning can be used for varied sets of data (Botvinick et al., 2019; Sutton & Barto, 1998).

21.2.1.3 Combating diseases with computational strategies

CADD tools have paved the way in innovating novel drugs have accelerated the process of developing new drugs and cost-effectively conducting the research and development. Due to the advanced technology in chem-informatics, bioinformatics, proteomics, genomics, and structural information, considerable progress has been made in identifying proteins as drug targets. At all phases of the designing and development of novel drugs, including target identification and authentication; lead discovery and optimization, pharmacokinetics, and toxicity profile prediction, computational approaches play a very significant role. All the mentioned stages need a great inclusion of computational methods.

The CADD tools are highly effective in the healthcare industry (Doman et al., 2002). CADD methods had been used earlier for the development of unique molecules; that have successfully shown their therapeutic potential conducted in the clinical trials effectively in treating various disorders. Some of the best illustrations of the applications of CADD tools in the innovation of approved drugs are captopril, the angiotensin-converting enzyme (ACE) inhibitor used in the treatment and prevention of cardiovascular diseases, was approved in 1981 (Talele et al., 2010); dorzolamide, the carbonic anhydrase inhibitor used in treating glaucoma was approved in 1995 (Vijayakrishnan, 2009). Similarly, three compounds as medications, namely saquinavir (approved in 1995), ritonavir, and indinavir (both approved in 1996) were given approval for the treatment of human immunodeficiency virus in compliance with the safety regulations (Drie, 2007).

21.2.1.4 Machine learning methods accelerate drug development

ML models have been used in several promising technologies. For example, modern speech recognition, deep learning (DL)-assisted self-driving cars, etc. The emergence of these computer-based computational approaches embarked in the 1950s has already shown its efficacy in the area of bioinformatics, drug discovery, chem-informatics, etc. (Afouras et al., 2018; Deng & Li, 2013; Fayyad et al., 2020; Joachims & Radlinski, 2007).

ML computational algorithms are used extensively in drug discovery such as "Random Forest (RF), Naive Bayesian (NB), and support vector machine (SVM), forecasting drug–protein interactions, exploring the effectiveness of the drug," ensuring biomarker safety improving the activity of bioactive components (Khamis et al., 2015; Leelananda & Lindert, 2016; Maia et al., 2020; Réda et al., 2020; Usha et al., 2017). For the design and construction of novel drug targets and innovation of new drugs, combined methods of both ML and DL algorithms increase the ability, strength, effectiveness, and standard of the evolved products. The production and establishment of huge data have increased the efficacy and dependability of both ML and DL integrated methods by way of HTS and computational analysis of databases in drug (Fig. 21.1) development. With the extraordinary development in data assemblage and DL methods, AI and ML techniques have shown a key role in medicinal and therapeutic applications.

In the case of orthopedics, the huge amount of data with the inclusion of ML has helped orthopedic surgeons in many aspects of orthopedic-related applications to evaluate the current and latest advances in this field to assess its impact on the musculoskeletal system of humans beings. Also, it is assessed as the value-based healthcare in treating and serving the patients in a better manner.

21.3 Design of nucleic acid-based therapeutics and related issues

Conventional therapeutic heavily rely on targeting a protein instead of the underlying cause. They often tend to bind with nontarget proteins while binding with the target protein and are known for generating transient therapeutic effects. The inefficiency and lack of specificity of these conventional therapeutic led to the development of nucleic acid-based therapeutics. Nucleic acid-based therapeutics work by targeting the mRNA encoding for the target protein, instead of the protein product itself. The basic principle behind this therapeutic is the synthesis of complementary sequences that are responsible for recognizing single-stranded nucleotide sequences and then binding with them through complementary bases and thus interrupting their function (Zhang & Salaita, 2021). This principle, along with its variations is widely prominent in different types of nucleic acid inhibitors such as antisense oligonucleotides, RNAi, ribozymes, aptamers, etc. The key discoveries and evolution of nucleic acid-based therapeutics have been identified (Kulkarni et al., 2021).

21.3.1 Antisense oligonucleotides

Antisense oligonucleotides consist of 15−20 nucleotides (approximately), and they were recognized as a successful viral inhibitor by Zamecnik and Stephenson. This technology follows two mechanisms. The first mechanism involves cleaving of the RNA moiety of DNA by activating RNAase, leading to degradation of the target. The second mechanism involves inhibition of the translation process instead of inducing RNAase H cleavage. The inhibition is carried out by interrupting the binding of either the polymerase or the ribosome to the 5′-end of Fig. 21.2 specific sequence, which in turn prevents the assembly of the target machinery. Fig. 21.2 indicates the steps required in the generation of antisense oligonucleotides as a potential therapeutic.

21.3.2 RNA interference

RNA interference (RNAi) utilizes a specific sequence of double-stranded RNA (dsRNA) to knock down the expression level of target genes. This dsRNA molecule (short hairpin RNA, shRNA) is complementary to the target mRNA. The mechanism of this technology involves the uptake of dsRNA by the cells followed by its cleavage into segments ($\sim$ 21−22 nucleotides in length) which is commonly known as short interfering RNA (siRNA). After base-pairing the complex of siRNA and target mRNA is formed, which binds to the multiprotein complex known as RNA induced silencing complex (RISC). The RISC contains the Argonaute-2 (splicing proteins), which help in the cleaving of the target mRNA molecules at specific positions (between bases 10 and 11 relatives to 5′ end of antisense siRNA strand) followed by its degradation by cellular RNase (Fig. 21.3). This further leads to efficient and specific knockdown of the specific gene expression (Fig. 21.3) (Silva & Jemc, 2015).

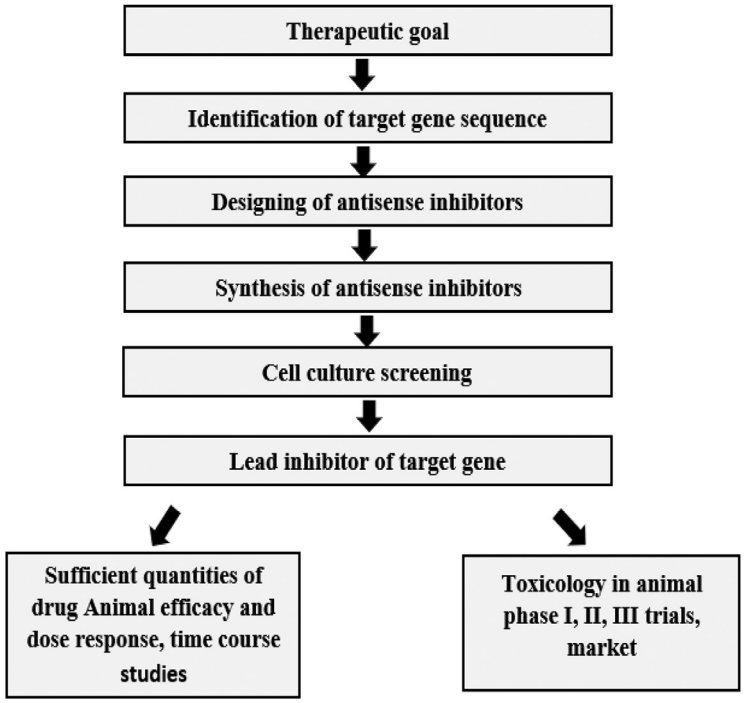

FIGURE 21.2 Steps required in the generation of antisense oligonucleotides as a potential therapeutic.

21.3.3 Ribozymes

Ribozymes were first discovered in *Tetrahymena thermophila* (algae). They are nucleic acid enzymes that focus on targeting (cleaving) substrate mRNA in a highly sequence-specific manner leading to selective inhibition of the expression of deleterious genes. Their mechanism involves binding of ribozyme or Deoxyribozyme specifically to their intracellular substrate mRNA strand in a specific pattern and then cleaving it, thus hindering the translation. This enzyme is further released after cleavage so that it can destroy another mRNA molecule. This, in turn, leads to a highly specific knockdown of the encoded protein.

21.3.4 Aptamers

Aptamers were first described in HIV-1 in 1980. They comprise of short, single-stranded oligonucleotides (RNA or DNA) that recognize their targets based on shape complementarity. Aptamers bind to the target in a highly specific manner, and their affinity for the target is the same as that of monoclonal antibodies. The mechanism of aptamers requires for them to bind with target proteins present on the surface and outside of the cell (directly) to alter their function, unlike the oligonucleotide therapeutics that destroy the mRNA so that it can target the translational machinery of the cell. The high-affinity binding and specificity along with negligible immunogenicity (nucleic acid are not

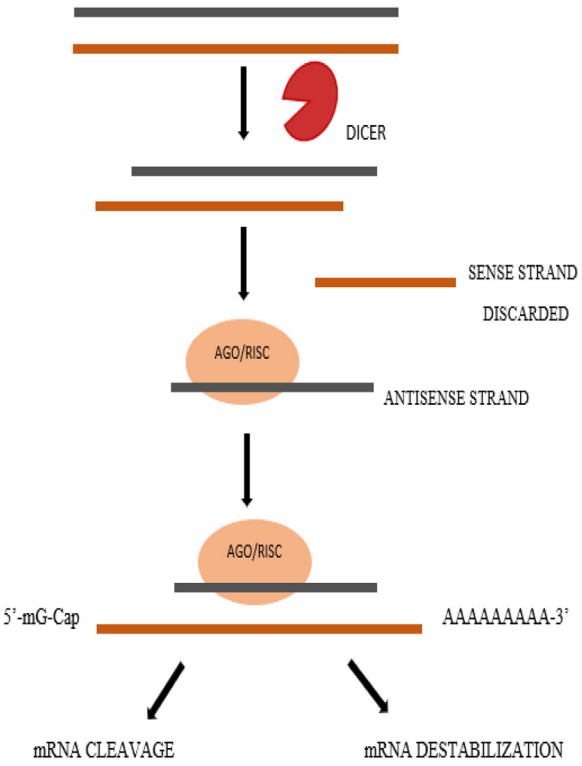

FIGURE 21.3 Mechanism of RNA interference technology.

recognized as a foreign particle by the immune system; hence no immunogenic response is triggered) and versatility (they can be used for proteins, carbohydrates, nucleic acids, small molecules, whole cells and even organisms due to their dependency of a shape complementary for interaction) have made aptamers more effective.

21.3.5 Related issues

1. In biological systems, one protein influences the function of more than one protein which serves as a requirement in different pathways. The oligonucleotides block the protein synthesis, which in turn has more adverse effects (Hammond et al., 2021). This issue can be solved by using aptamer technology which focuses on blocking a single domain of protein without degrading its structure.
2. The delivery of oligonucleotides into cells is influenced by a certain biological barrier such as a vascular endothelial wall. They also get degraded by nucleases that are present in serum and tissues (Bhandari et al., 2014). Apart from this, the phagocytes present in the reticuloendothelial system engulf these oligonucleotides. The slow diffusion through and binding in the extracellular matrix and inefficient release from the endosome has still been an area of concern (Zhou et al., 2020).

3. The RNAi generates TLR-mediated inflammation (during the treatment of Age-related Macular Degeneration and Diabetic Macular Edema) and has also been proved insufficient during in vivo drug efficacy. This raises a serious concern about the efficiency and specificity of delivery, stability, minimization of immune stimulation, and the prolonged duration of the drug. Several chemical modifications need to be employed to minimize the inflammation and the use of natural and synthetic carriers to ensure efficient and tissue-specific delivery.
4. The clinical translation of GalNAc − siRNA conjugate requires an appropriate diagnostic biomarker other than liver biopsies. To overcome this, developing a biomarker-based on mRNA concentration in serum and urine can be beneficial as it can easily provide a pharmacodynamic biomarker that can be used to monitor therapeutic endpoint without the involvement of invasive procedures (Kulkarni et al., 2021).
5. The use of vectors leads to immunotoxicity and genotoxicity. This can be improved by using adeno associated virus (AAV) vectors as they require a helper virus for their replication (this makes them nonpathogenic), and their genomic integration occurs at low frequency (this reduces genotoxicity).
6. AAV vectors have low packaging capacity (less than 5 kb), so they can only be used in case of diseases whose transgene can be packed in a single vector. Apart from that, they are naturally found in multiple species. Due to this, the neutralizing antibodies present in humans reduce the AAV-mediated gene therapy in case of intravenous administration.

21.4 Computational therapeutic design and Coronavirus disease-2019

The pandemic that occurred due to the novel COVID-19 has created the worst scenario all over the world. To address these issues, there is an urgent need to explore effective treatment options against this COVID-19. Computational techniques have played a significant role in the exploration of compounds and drug targets in severe acute respiratory syndrome-Coronavirus-2 (SARC-CoV-2). Ligand-receptor binding modeling has played a greater role in carrying out the screening of FDA-approved drugs against three SARS-CoV-2 proteins namely main protease (Mpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase (RdRp). Computational studies have detected some novel ligands in inhibiting SARS-CoV-2, such as antiemetics, rolapitant, and ondansetron for Mpro. Molecular docking studies are highly effective in the identification of compounds for the treatment of COVID-19. Some of the antiviral agents have been highly effective against various viral diseases such as Hepatitis, HIV, Influenza, Herpes, Cytomegalovirus, Small Pox, and the Ebola virus. Molecular dynamics simulation has shown the stability and firmness of the ligand-protein complexes. SARS-CoV-2 inhibitors were identified by a computational molecular docking approach and virtual screening. Remdesivir, an FDA-approved SARS-CoV-2 drug has exhibited effectiveness in targeting both RdRp and Mpro with low binding energies. Ondansetron, the most potent Mpro inhibitors, have slightly higher binding energy in comparison to remdesivir/Mpro (Nguyen et al., 2020; Rochwerg et al., 2020; Yin et al., 2020).

In silico drugs, the repurposing technique has gained popularity as a precise computational tool for achieving quick and trustworthy outcomes. Drug repurposing is a new technology that allows an approved or investigational drug to be used for a disease other than the one for which it was developed. Drug repurposing is a less expensive and faster technique because commercialized drugs have already passed clinical trials and safety checks. Although regulatory and phase III expenses for a repurposed drug may be similar to those for a new drug in the same indication, there may be significant savings in preclinical and phase I and II costs.

The study looked at a drug repurposing technique that screened FDA-approved drugs against viral entry receptors (ACE2 and CD147) and integral enzymes of the viral polymerase (RdRp). The suppression of CD147 and ACE2 can stop the virus from infecting the host cells. Furthermore, inhibiting RdRp, the key enzyme involved in viral replication, is useful in combating the virus (Mahdian et al., 2021).

The study investigated a drug repurposing strategy aiming to screen compatible inhibitors of FDA-approved drugs against viral entry receptors (ACE2 and CD147) and integral enzymes of the viral polymerase (RdRp). The inhibition of CD147 and ACE2 can prevent the entering of the virus into the host cells. Besides, the inhibition of RdRp, as the main enzyme for viral replication, is effective in fighting the COVID-19 (Mahdian et al., 2021). It has been identified five drugs with ACE2, four drugs with RdRp, and seven drugs with CD147 achieved the most favorable free binding energy

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21.5 Present and future challenges in the design of therapeutic strategies

The cutting edge in recognition of speech, visual object, and detection of an object is currently being explored in the biomedical and genomic area has dramatically improved by DL-based approaches.

Network-based tools have been widely used in computational biology for discovering specific targets and interactions of the new drug molecules (Schadt, 2009). In these models, nodes in the networks are used to represent drug, disease, or gene products, the edges are used to represent the interactions or relationships between them. These networks are either knowledge-based or pharmaceuticals computationally construed utilizing numerous data resources and have multiple representations. These include drug−drug, drug−target, drug−disease, disease−disease, disease−gene, disease−drug, protein−protein interactions, and transcriptional networks. Cheng and Liu enumerated likenesses—drug-related, target-related, and network-related to identify drug−target interaction in a bi-partite network and reported this technique executed best with a normal ROC AUC of 0.96 (Chen et al., 2015). Analogous homogenous or bi-partite network models have been included using phenotype data such as side-effect (Campillos et al., 2008; Mizutani et al., 2012;

Ye et al., 2014), transcriptional (Brown et al., 2016; Chang et al., 2011; Setoain et al., 2015), drug–disease (Chen et al., 2015; Wu et al., 2013), and signaling pathway data (Jadamba & Shin, 2016).

Integrating heterogeneous data provides a ton of information and can possibly divulge hidden or unknown drug–disease relationships based on the guilt-by-association rule. A large portion of similitude-based approaches could be drug-based or disease-based networks, with relatively few methods that fabricated a drug–disease heterogeneous network using compendia of gene notations and network clustering to predict drug repositioning candidates (Wu et al., 2013; Zhao & So, 2017).

Interestingly, to predict psychiatric drug indications based on the expression profiles of drugs deep neural networks (DNNs) approach was compared with the SVM-based approach and reported by Zhao et al. (2017). While more studies are needed to understand if DNN-based approaches indeed have the claimed benefits, there have been previous literature suggested that DL-based methods execute better than traditional ML algorithms in toxicity identification by allowing multitask learning (Himmelstein et al., 2017; Luo et al., 2017a, 2017b).

Luo et al. (2017a, 2017b) built an identical network-related framework using heterogeneous data through a network diffusion method and used the diffusion distributions to acquire the identification scores of drug–target relationships (Ashburn & Thor, 2004). Recently, Himmelstein et al. included data from 29 public resources to predict drug repositioning candidates and identify the possibility of repositioning for 209,168 drug–disease pairs (Himmelstein et al., 2017).

CADD still faces various difficulties, which comprises, but are not limited to: (1) expanding the efficiency of virtual screening; (2) enlarging the number and quality of online computational resources; (3) further developing the field of computational chemogenomics; (4) strengthening the design of drugs aimed at numerous molecular targets; (5) improving the predictive capacity of toxicity models and side effects, and (6) strengthening the interaction with other disciplines to optimize the search for bioactive compounds for the treatment and/or prevention of diseases.

The missing drug–disease indication data is a major principal issue. The predictive power of the computational biology for drug repurposing candidate discovery can potentially compromise the missing indications as true negatives or ignore them from training. The lack of a truly high standard dataset for drug repositioning makes it challenging for in silico approaches to evaluate results. As a result, to assess the utility of computational drug repurposing algorithms, common performance metrics such as sensitivity, specificity, and precision are used. Lastly, existing computational approaches tend to be predominantly/potent one-sided (e.g., drug-centric or disease-centric).

Growing scientific evidence suggests that a bioactive compound found to be safe and effective in humans is likely to have various therapeutic uses. Given that this "simple" approach for repositioning is filling in prevalence, there is a dire requirement for more proficient and orderly computational ways to deal with and first organize the accessible genomic and pharmacological information bases for portrayal and information revelation and afterward utilize these datasets and example disclosure instruments to predict the possible new uses for pre-existing medications. What is required; obviously is a change in outlook in the methodologies of genomic, bio pharmacological, and computational-based

approaches for a more educated efficient medication rediscovery ("orderly good fortune") keeping in mind the entirety of the information assets.

Given the increasing number of cancer patients, environmental and ecosystem safety must be included in the list of topmost issues for finding effective anticancer therapeutics. While finding effective treatments for so far incurable diseases remains a key goal, prevention, including a healthy diet, reduced stress, and exercise (Chang et al., 2018; Purushotham et al., 2018) from early childhood should be of top importance. Representative and predictive phenotypes should be identified, taking into consideration not only the cancer cells as selected genetic entities of a particular patient but also their evolving epigenetic status and influence of tumor microenvironment, the immune system, the microbiota, and hormonal and neural systems. A major challenge is thus not only to speed up the repurposing of known drugs but to develop personalized phenotypic validation schemes.

Despite the reported successes of artificial intelligence within cancer imaging, several limitations and hurdles must be overcome before widespread clinical adoption. With the constant increase in demand for CT and MRI, care providers are constantly generating large amounts of data.

Data-hungry methods, including DNNs, aggravate these issues. The research community has yet to reach a consensus on specific datasets that can be utilized for comparing and contrasting efforts in terms of performance, generalizability, and reproducibility, although the volume of medical data is being made public is an encouraging move forward (Barrett et al., 2015). Furthermore, access to available datasets should be improved to promote intellectual collaboration with government groups, professionals, and institutes. It should be encouraged to share validated data to support the development of AI algorithms, which requires overcoming certain fundamental technical, legal, and perhaps ethical concerns (Char et al., 2018).

Another limitation includes the interpretability of AI and the ability to interrogate such methods for reasons behind a specific outcome, as well as the anticipation of failures. Although the present state of research has focused on performance gains over clarifying ability and transparency, the interpretability of AI is an active and functioning area of research. Algorithms can be unethical by design (Wu et al., 2017) and might worsen the already existing tension between providing care and turning profits. What's more, a defend against "learned defenselessness" should be utilized as a way to check high dependence on robotization and a definitive relinquishment of the presence of mind. Finally, automated systems also might challenge the dynamics of responsibility within the doctor-patient relationship, as well as the expectation of confidentiality (Wu et al., 2016).

It is likely that AI application software will need to meet meticulous testing that is a decree for new submissions for regulatory approval, including quality control and risk assessment.

Although AI can detect incidental findings which is clinically not relevant, these findings also may be clinically impertinent and, if not carefully framed in the right clinical context, may increase patient stress, healthcare costs, and undesired side effects from treatment.

Although several recently proposed network-based methods can be used to discover potential drug–target interaction for both approved drugs and new chemical entities

(Cheng, Liu, et al., 2012; Cheng, Zhou, et al., 2012), they cannot predict potential DTIs for those targets without known ligands. Second, network-based methods are still not quantitative. They only give a predictive score for each potential DTI, where a higher score means a higher probability of occurrence. The binding affinities of the predicted DTIs are unknown. Moreover, the interaction type is not considered yet.

Given the highly complicated and regulated nature of drug development, a long-term vision is required when developing AI applications in drug repurposing that could increase efficiency and effectiveness in the various processes involved and decrease the barriers between many research components in the ecosystem to create new therapy options. Drug discovery is a tedious process that included multilevel interactions between the biological system and chemical compounds. Therefore, a newer way of building an effective and interpretable model of drug identification is to enrich the biologically inspired visible neural network model with drug-related entities such as chemical compounds and diseases. The model parameters can be optimized in an end-to-end way as in other DL models.

21.6 Conclusion

The drug discovery and development process are long and requires a lot of money. The development of computational methods makes easier the exploration of drugs. Computer-aided drug design, nucleic acid-based therapeutics, and the use of AI are being contributed a lot in the prediction of potential compounds/drugs against life-threatening diseases including COVID-19. But simultaneously some challenges have been associated with them. The complicated and regulated nature of drug development needs a long-term vision when developing AI applications in drug repurposing that could increase efficiency. We have to address the issues related to therapeutics; it would be helpful in therapeutics against life-threatening diseases like COVID-19.

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