What is computer aided drug design pdf

DIFACQUIM Research Group, Department of Pharmacy, School of Chemistry, National Autonomous University of Mexico, Mexico City, MexicoComputer-aided drug discovery (CADD) has become an essential part of several projects in different settings and research environments. CADD has largely contributed to identifying and optimizing hit compounds leading them to advanced stages of the drug discovery pipeline or the market (Prieto-Martínez et al., 2019). CADD includes several theoretical disciplines, including chemoinformatics, bioinformatics, molecular modeling, and data mining, among others (López-López et al., 2021). Artificial intelligence (AI) that has been used since the 60 s (Gasteiger, 2020) in drug discovery is regaining momentum, in particular with machine learning (ML) and deep learning (DL) (Bajorath, 2021; Bender and Cortés-Ciriano, 2021). In parallel to the continued contribution of CADD, several methodologies used in CADD have entered the hype cycle with waives of hope, inflated expectations, disappointments, and productive applications. The disillusionments are frequently driven by fashion, exacerbated misuse, and a lack of proper training to interpret the results (Medina-Franco et al., 2021). Examples are quantitative structure-activity relationship studies (QSAR). A few decades ago, there was a hype for QSAR studies; but uneducated use, bad practices, and poor reporting led to inflated expectations and disappointment (Johnson, 2008). As part of the hype, scientific journals containing the word “QSAR” in the title emerged, and years later, some journals were re-named. Molecular docking is another example of a method that is often misused, leading to false expectations and disappointments, not because the technique is not useful but because it is tried to be used for purposes that was not initially designed (e.g., correlation of docking cores with experimental binding affinities). At the time of writing this manuscript, there is a hype for AI, ML, DL; quoting Bajorath, an “AI ecstasy” (Bajorath, 2021).Despite the contributions of CADD in different stages of the drug discovery pipelines and technological advances, there are challenges that need to be addressed. Table 1 outlines the grand challenges that face drug discovery using in silico methods and AI and are further commented on in this manuscript. The list of topics is not exhaustive; the selected challenges are based on the author’s opinion, and it is intended to be a reference for a continued update. Here, the challenges are organized into six sections. The first two are related to the chemical and biological relevant chemical spaces, respectively; that is, what spaces are being explored? Another section covers methodological challenges: how is being conducted the search for new and better drugs at the intersection of the relevant chemical and biological spaces? The next three sections present hurdles associated with communication and Human interaction in research teams, scientific dissemination, data sharing, and education, respectively. The last section contains the Conclusions.TABLE 1. Grand challenges that face drug discovery and design using in silico methods and AI.Chemical SpaceThe chemical space itself, including its visualization, has been fundamental in decision making and analyzing the advances in the drug discovery process (Reymond, 2015). The searchable chemical space offers a vast number of possibilities to find hit compounds, in particular with the advent of approaches to increase its size rapidly. In this context, the grand challenge question could be framed as follow: which regions of the chemical scape should be investigated to identify potential drug candidates? Searching on the traditional, drug-like medicinally relevant chemical space has not led to the identification of many new chemical entities (Mullard, 2021). As such exploring novel regions might help to identify novel starting points. Challenges in this direction include but are not limited to expand the searchable drug-like chemical space (e.g., take advantage of the ultra-large chemical libraries); revisit and repurpose existing chemical libraries, including revisiting large corporate collections and the SAR of in-house data: rescue missing hits; search traditional chemical spaces with novel techniques; revisit “neglected chemical spaces,” e.g., type of molecules poorly explored: peptides, peptidomimetics, macrocycles, biologics, metallodrugs (Anthony et al., 2020; Pandya and Patravale, 2021). These types of molecules could lead to promising starting points to develop drug candidates for the novel or difficult targets. To this end, novel computational approaches will have to be developed.Biological SpaceA crucial quest in drug discovery is identifying and validating molecular targets with clinical applications. The grand challenge is in what regions of the biologically relevant chemical space look for? Identification of the therapeutically relevant targets has been the subject of recent comprehensive analysis (Oprea et al., 2018). Further, it is also of major importance to study polypharmacology and try to predict the interactions of a drug candidate with all its putative target partners (Méndez-Lucio et al., 2017). Challenges of CADD methods in this area include but are not limited to improving multi-target drug design and multi-target property prediction (Zhang et al., 2017); identifying better ways to address protein-protein interactions (Lu et al., 2020); and continue exploring molecular targets associated with neglected diseases. Computational methods can also help to identify druggable binding pockets and allosteric sites, and transient binding sites that can be exploited for drug discovery.MethodsIn parallel to defining the chemical and biological spaces to be addressed for drug discovery comes the grand challenge: which computational methods could be used to help designing and optimizing drug candidates? General avenues are continually developing and improving computational chemogenomics (Jacoby and Brown, 2018). On this regard, it is also crucial to keep refining the selection of descriptors to delineate the chemical and biological spaces.There are ongoing challenges in CADD, such as improving the hit rate of virtual screening; improve molecular docking, including docking of flexible compounds and macrocycles; covalent and protein-protein docking; molecular modeling of large and complex systems; prediction of druggable pockets, binding sites, including allosteric binding sites; and accurate prediction of ADMETox-related properties, among others. Another major and continued grand challenge is data curation; ensure data quality, including that stored in public databases. Such data is a key to develop reliable models and information.There are also newer or emerging challenges, a number of which are driven by AI (Schneider et al., 2020), such as (fully) automated de novo design (Schneider and Clark, 2019); improve the performance and demonstrate experimentally the practical applications of predictive models including models generated with ML and DL. A challenge is to continue enforcing proper model validation: one of the key aspects that have been discussed since the emergence of traditional QSAR modeling (Muratov et al., 2020). Another current challenge is expanding the searchable chemical space through ML-based compound and library enumeration, the rational design, and mining of large and ultra-large chemical libraries (Irwin et al., 2020; Coley, 2021).In the author’s opinion, one should avoid pursuing the single “best” or “universal CADD approach” that performs well in all cases. Likely, such a method does not exist. Instead, consider combining different and complementary approaches so as to try to solve the scientific questions more fully and efficiently (Schneider, 2018). All in all, a grand challenge involves also the selection and rational use of the best AI, ML, DL, and related trendy methods (Medina-Franco et al., 2021).Communication and Human InteractionLack of communication between research individuals and teams hampers drug discovery progress and might become one of the most significant drivers of project failures. Poor communication between principal investigators, postgraduate and undergraduate students, etc., has been a constant challenge that warrants improvement. The efforts of computational teams or individuals might be futile if there is no open dialog and credibility among research teams. It is desirable to work synergistically with experts across different research disciplines, each contributing to the projects goals from different perspectives and complementary areas of expertise. Close collaboration and effective communication will help to reduce the chances of duplicating efforts and waste valuable resources.Dissemination and Data SharingProper documentation and peer-review have been critical components in science to disseminate information and knowledge. A current challenge that is being addressed is proper data and method sharing in favor of transparency and reproducibility. Peer-reviewed journals are enforcing these practices, including the FAIR principles (Wilkinson et al., 2016). A sensitive point is when the information, data, and methods can be openly shared partially only when intellectual property is at stake. Good editorial practices, proper peer-review, and the author's ethics and responsibility should work synergistically to disseminate high-quality data essential for several CADD approaches, those that are data-driven.Education and TrainingProper education and formal training are necessary for students, young and established investigators from different disciplines moving to CADD or collaborating with computational teams. This is key to help to improve multidisciplinary work and maximize the CADD’s benefits. There are efforts towards this endeavor (Guha and Willighagen, 2020; López-López et al., 2021). A challenge is continuing the formal training of theoretical disciplines. In particular, because there are now several easy-to-use and freely available applications, their misapplication and flawed interpretation of the results can lead to false expectations and perceived CADD’s disappointments (Medina-Franco et al., 2021).ConclusionCADD has been successful but must improve by addressing old challenges and facing new ones. Technological advances are promising to revisit and expand the medicinally relevant chemical space, help to guide the repurposing of approved drugs and existent chemical libraries, and rescuing missing hits hidden as “treasures to be discovered” in the existing SAR of corporate or public data. CADD methods are promising to explore novel chemical and biological spaces relevant to drug discovery. Data-driven approaches such as ML and DL require high-quality data, which generation and dissemination is another major challenge. Researchers working directly with CADD methods or collaborators with computational teams should recognize and pursue realistic expectations to keep the rationale over fashion and hype (Medina-Franco et al., 2021). Another challenge is to continue improving traditional approaches in drug discovery; synergize and mutually improve and benefit from other traditional and successful techniques in drug discovery (for example, natural products, combinatorial chemistry, and traditional medicinal chemistry). Enhancing communication in research teams is critical to achieve and maximize the potential of the computational approaches. Proper scientific dissemination, data sharing, and education are other challenges that need to be addressed to avoid false expectations but maximize the productivity of CADD.Author ContributionsThe author confirms being the sole contributor of this work and has approved it for publication.FundingJM-F research is currently supported in part by CONACyT (Mexico) project 282785, UNAM, DGAPA projects IN201321, IV200121; and Miztly project LANCAD-UNAM-DGTIC-335.Conflict of InterestThe author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.AcknowledgmentsThe valuable feedback and suggestions of Fernanda I. Saldívar-González are greatly acknowledged.ReferencesAnthony, E. J., Bolitho, E. M., Bridgewater, H. E., Carter, O. W. L., Donnelly, J. M., Imberti, C., et al. (2020). Metallodrugs Are Unique: Opportunities and Challenges of Discovery and Development. Chem. 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