International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 11 Issue: 12 | Dec 2024 www.irjet.net p-ISSN: 2395-0072

Deep Learning in Drug Discovery and Pharmaceutical Research

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Abstract - Deep learning has revolutionized the field of drug discovery and pharmaceutical research. This paper provides a comprehensive review of the applications of deep learning in drug discovery and pharmaceutical research. We discuss the various deep learning architectures and techniques used in drug discovery, including convolutional neural networks (CNNs), recurrent neural networks (RNNs), and generative adversarial networks (GANs). We also highlight the challenges and limitations of using deep learning in drug discovery and pharmaceutical research.

Key Words: bioinformatics · cheminformatics · drug design · machine-learning · neural network · virtual screening

1.INTRODUCTION

Machine-learning provides a theoretical framework for the discovery and prioritization of bioactive compounds with desired pharmacological effects and their optimization as drug-like leads. Biological target identification and protein design are emerging areas of application. Among the many machine-learning approaches in molecular informatics, chemocentric methods have found widespread application. Their underlying logic typically follows three steps. First, there is the selection of a problem-specific set of descriptors that are believed to capture the essential properties of the molecules involved. At present, there are over 5000 diverse molecular representations ("descriptors") that address the various properties of chemical entities.[1] Second, a metric or scoring scheme is used to compare the encoded molecules to one another.[2] Finally, a machine-learning algorithm is employed to identify the features that may serve to qualitatively or quantitatively distinguish the active from the inactive compounds.[3] Artificial neural networks (ANNs) were among the first methods borrowed from the computer sciences for this purpose.

In 2013, public attention was drawn to a multi-problem QSAR machine-learningchallengein drug discovery posted by Merck. This competition on drug property and activity prediction was won by a deep learning network with a relative accuracy improvement of approximately 14% over Merck's in-house systems and resulted in an article in The New York Times. [5] Here, we present state-of-the-art of advanced chemocentric machine-learning methods with a focus on emerging "deep learning" concepts. We highlight recent advances in the field and point to prospective applications and developments of this potentially game changing technology for drug discovery. Ageneral task for machine-learning is to uncover the relationship between the molecular descriptors used and the measured activity of the compounds to obtain qualitative classifiers or quantitative structure-activity relationship (QSAR) models. Feature extraction from the descriptor patterns is the decisive step in the model development process.[6,7] In current cheminformatics applications, the prevalent machine-learning architectures are "shallow" and contain a single layer of feature transformation. These architectures include linear and nonlinear principle component analysis, k-means clustering methods, partial least square projection to latent structures, decision trees, multivariate linear regression, linear discriminant analysis, support vector machines (SVMs), logistic and kernel regression, multi-layer Perceptrons and related neural network approaches.[8] Although all of these methods have proven to be useful for (Q)SAR modeling and molecular design,[9] the single feature transformation step into a suitable space for the subsequent application of a linear pattern separation model might limit their modeling and representational power when applied to more complex data and setups. A reason for their success in pharmacological applications may stem from the fact that a major part of the complexity inherent to molecular interactions has been engineered into the descriptors employed as patterns for model training, thereby allowing single layer machinelearning architectures to tackle the problem.[10] One challenging question is whether the underlying data complexity and hidden features can be more efficiently dealt with by shifting attention from descriptor engineering to the architecture of the machine-learning system and the training of the algorithms involved. This is the domain of "deep learning".

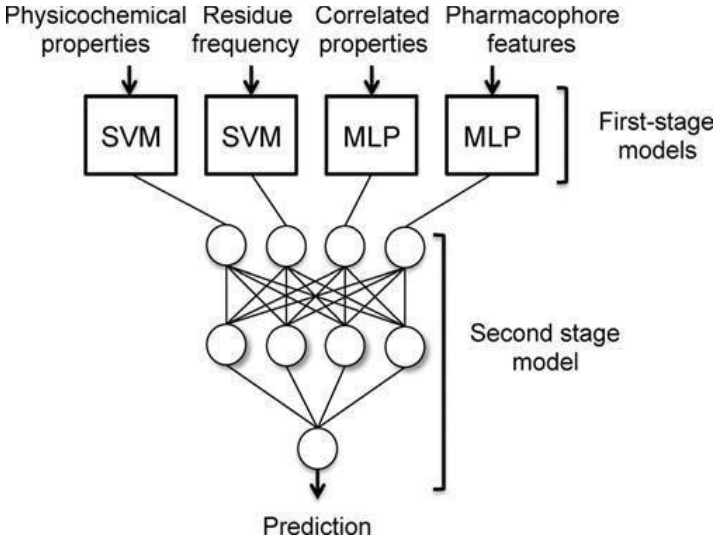

Figure 1. Schematic of a jury network (adapted from ref. 31). In this particular architecture, feature extraction is performed in two stages. The second- stage model is a feed-forward network that weighs the relevance of the first-stage model and improves the overall prediction performance. Note that each first- stage model receives a different set of molecular descriptors as input. SVM, support vector machine; MLP, multi-layer Perceptron.

2 Properties of Deep Learning Architectures

There are several advantages of deep learning neural net- works that suggest that they should replace shallow ANNs:

- A deep, hierarchical architecture enables ANNs to per-form many nonlinear transformations, which leads to the learning of more abstract features compared to shallow networks.[53] This development allows for a more sophisticated combination of low-level features (i.e., nonlinear descriptor combinations) to achieve a better molecular representation and thus classification of compounds. This approach reduces the need for the a priori engineering of more sophisticated descriptors. More abstract nonlinear features tend to be invariant to local changes in the input, leading to inherent noise reduction and increased network robustness.

Therefore, deep learning architectures capture certain families of functions exponentially more efficiently than shallow architectures.

- Deep architectures promote the reuse of features. This ensemble view of the same data corresponds to an improvement on the principle of cascading networks that share the intelligence of different algorithms. How well- regularized deep learning networks can actually exploit commonalities between different tasks to transfer knowledge as inductive bias remains a matter of debate. This aspect is relevant for missing classes within the training set, which is typical for large QSAR data sets. Aside from enabling "educated guesses" on missing information, multitask learning also has the benefits of presenting a shared, learned feature extraction pipeline for multiple tasks. Dahl suggested that this concept might have a regularization effect because weights tend to develop in a way that is useful for many targets instead of overfitting one target in particular.[54] All of these findings promise the simultaneous testing of bioactivities against many related targets at a realistic computational cost. Such applications may be driven even further by the field of polypharmacology.[55] In this case, deep learning might accompany current kernel methods to find additional applications for drugs ("re-purposing") and to assist in the identification of undesired off-target activities.

- As highlighted by the Merck QSAR contest,[5] deep multitask neural networks can be successfully applied to QSAR modeling.[57] Generative deep architectures complement evolutionary algorithms in computational drug discovery that are often used to find new compounds with specific features identified by some previously trained machine-learning architecture.[58] A trained deep generative neural network has learned to separate compound activity classes within its architecture while being able to generate output according to the learned representation; thus, this network contains both functions in one algorithm. Therefore, deep learning might provide a fresh approach to solving the "inverse QSAR problem".

However, simply trading network width for depth alone does not automatically lead to better models. In the following sections, we highlight two deep learning architectures that we think deserve special attention and consideration for drug design and discovery: the Restricted Boltzmann Machine (RBM) and Convolutional Neural Networks (CNN). Many more deep learning approaches have been conceived, and the interested reader is referred to the respective literature.

3 Restricted Boltzmann Machine

Boltzmann machines are undirected, generative, stochastic neural networks that rose to prominence when Hinton and coworkers proposed contrastive divergence[60] as a fast unsupervised learning algorithm.[61] Restricted Boltzmann Machines (RBM) are instances of Boltzmann machines without intra- layer interactions (Figure 3). Boltzmann machines are

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