De novo design of small molecules against drug targets of central nervous system using multi-property optimization

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Abstract

Drug design and development is a time- and cost-intensive process with a low success rate. The process is more complex in case of drugs targeting diseases of the central nervous system (CNS) where blood-brain barrier (BBB) acts as an additional challenge for drug delivery. Recent applications of deep learning in ligand-based drug discovery are promising, although these methods can suffer from lack of target-specific ligand data to train the models. To address these issues, we have developed a *de novo* drug design method which can design novel molecules by optimizing target specificity as well as multiple properties that make them suitable to cross the BBB. A target-specific ligand dataset is curated by collecting known inhibitors of proteins structurally similar to the target protein. The generative model which learns and designs new molecules is systematically optimized using transfer and reinforcement learning. The reward function is designed to optimize multiple properties simultaneously with state-of-the-art predictive models. The proposed method was validated against the human 5-hydroxy tryptamine receptor 1B (5-HT1B), a G protein-coupled receptor responsible for several psycho-physiological functions and disorders. All existing 5-HT1B inhibitors were collected but used only for validation. We were able to design inhibitors with better binding affinity when compared to the existing inhibitors, with optimized property to cross the BBB. Results from the study show the capability of the proposed method to learn the molecular features required to produce novel small molecules with multiple desired physico-chemical properties against the target protein rapidly.

1 Introduction

Drug design is one of the crucial steps of the drug discovery and development process [1]. The success rate of the complete process can be maximized by efficiently designing the small molecules with suitable drug-like properties. Multiple properties need to be considered while designing drug-like small molecules. For example, designing drugs for neurological diseases is challenging due to the protective barrier of the central nervous system (CNS). Apart from target specificity, these drugs additionally require effective BBB permeability [2]. Multiple properties such as octanol-water partition coefficient (logP), molecular weight (MW), polar surface area and hydrogen bonding [3] are important factors for successful design of drugs against the proteins responsible for CNS disorders. Another major issue of ligand-based drug design is the presence of insufficient target-specific ligand data to train the deep learning models. In this work, we have proposed a method which can overcome the issue of target-specific ligand dataset and design small molecules specific to novel target proteins, while also being able to control multiple desirable physico-chemical properties simultaneously.

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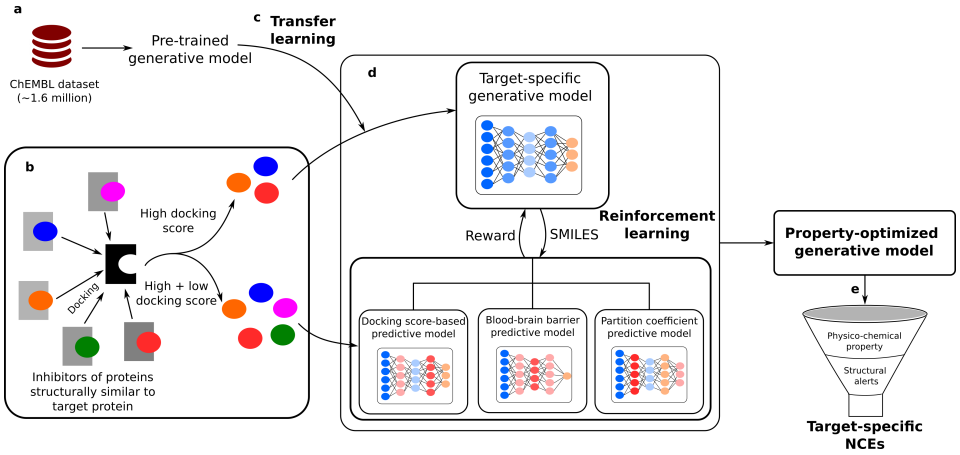

Figure 1: Ligand-based *de novo* small molecule design method. **a** Pre-trained generative model on the ChEMBL database; **b** A dataset curated from small molecules that modulate the activity of structurally related proteins; **c** Transfer learning with the curated dataset; **d** Multi-property optimization using reinforcement learning; **e** Physico-chemical properties and structural alerts (rule-based filters) were used to filter drug-like molecules specific to the target protein of interest.

2 Background

2.1 Related work

Recent developments in the field of artificial intelligence (AI) and big data have shown the potential to radically transform the accuracy and reliability of computational models in several fields of healthcare [4–6], including drug discovery [7]. While earlier studies were focused on generation of libraries for virtual screening [8], the introduction of reinforcement learning for property optimization has helped in biasing the models to generate compounds with the properties of interest [9–12]. Further, the efficiency of the models to generate chemically valid molecules can be significantly improved by using memory-augmented neural networks [10, 11, 13].

2.2 This work

In this study, we have developed a *de novo* ligand-based drug design method that addresses three major problems: a) Data availability to train the deep learning models, b) Efficient sampling of chemical space and c) Simultaneous optimization of multiple properties. As a proof of concept, the method was used to design novel small molecules against the human 5-hydroxy tryptamine receptor 1B (5-HT1B) protein, which acts as a major target protein for therapeutics in the CNS. We have optimized the binding affinity, logP and the probability of crossing the BBB of the designed molecules.

3 Materials and Methods

3.1 Dataset curation and preprocessing

The dataset for pre-training the generative model was obtained from the ChEMBL database [14]. The molecules were represented in the SMILES format [15] to leverage the effectiveness of recurrent neural networks (RNNs) in handling sequential data through existing natural language processing algorithms. The RDKit library in Python was used for dataset pre-processing.

3.2 Pre-training the generative model and predictive models

The generative model was pre-trained on a dataset of ~1.6 million SMILES strings from the ChEMBL database [14] (step a, Fig. 1). The use of stack-augmented memory [13] enabled the generation of chemically valid SMILES with high accuracy. The trained generative model was used to sample

100,000 compounds in 10 batches of 10,000 compounds each. The model was found to have a high accuracy of 96.6% defined as the mean percentage of chemically valid molecules present in all the sampling batches. The predictive model learns a mapping between the small molecules and their corresponding property values [9, 10]. In this study, three predictive models were trained to predict the blood-brain barrier (BBB) permeability (classification), logP and docking score (regression) against the 5-HT1B protein, for any given small molecule. The corresponding datasets for training were obtained from MoleculeNet [16], an earlier work [10] and Ex-CAPE DB [17], respectively. After extensive hyperparameter tuning, we attained the state-of-the-art ROC-AUC score of 0.90 for the BBB permeability model. The docking score prediction model had a root mean square error (RMSE) of 0.28 and a R2 score of 0.82. The logP prediction model had a RMSE of 0.43 and a R2 score of 0.91. The models were trained using mini-batch gradient descent with the Adam optimizer [18].

3.3 Ligand-based drug design via transfer learning and multi-property optimization with reinforcement learning

The drug design pipeline aims to discover novel small molecules against a specific target protein. In most cases, there is limited or no knowledge about the small molecules that can bind to the target protein. In this study, an initial target-specific small molecule dataset was curated considering known small molecules targeting active sites similar to that of the target protein (step b, Fig. 1). The suitability of this dataset was further enhanced by docking these molecules in the active site of the protein of interest. The molecules with high docking scores (<= -7.0) were used to re-train the generative model to capture the molecular features specific to a target protein of interest through transfer learning (step c, Fig. 1). During transfer learning, the weights of all the layers of the pre-trained generative model (prior network) were frozen except for the last dense layer [19]. The model was trained until the inferred molecules showed an observable shift in similarity with respect to the training dataset, quantified using the Tanimoto coefficient [20].

The generative model obtained after transfer learning was combined with the predictive model to bias the generative model towards the property space of interest using reinforcement learning (step d, Fig. 1) [9]. The method was modified to support simultaneous multi-property optimization. The reward function for training the agent (generative model) was,

$$r(MPO) = \begin{cases} 11, & \text{if } x = 1 \\ 1, & \text{if } x = 0 \end{cases} + e^{(-y/3)} + \begin{cases} 11, & \text{if } 0 < z \leq 4 \\ 1, & \text{otherwise} \end{cases} \tag{1}$$

where *x* is the predicted BBB permeability class, *y* is the predicted docking score specific to the active site of the target protein and *z* is the predicted logP value. The reward function (1) helps in optimizing all the three properties of the generated molecules in the desired range. To avoid catastrophic forgetting of the canonical policy gradient algorithm, the regularization was required to keep the new policy anchored to the learned prior policy of the agent [9, 21]. The regularized policy gradient method was trained using mini-batch gradient descent with AMSGrad optimizer [22].

3.4 Identification of potential molecules through property filters and rule-based filters

The 10,000 molecules sampled from the trained model after transfer learning and reinforcement learning, were subjected to several stringent drug-like physico-chemical property filters. The molecules obtained after applying drug-like property filters (logP, MW, synthetic accessibility score (SAS) [23]) were further subjected to four empirical rule-based filters – PAINS, BRENK, NIH and ZINC, to remove molecules with potentially unwanted subgroups (step e, Fig. 1).

4 Results and Discussion

In the following sections, the results of the case study based on our method is discussed.

4.1 Designing small molecules against the human 5-hydroxy tryptamine receptor 1B (5-HT1B) protein

5-HT1B belongs to the G protein-coupled receptor family and is the target of serotonin (5-HT). It has been implicated in cancer proliferation [24] and several CNS disorders including obsessive-compulsive disorder (OCD) [25], depression [26], migraine and Parkinson's disease [27].

The known inhibitors of 5-HT1B were collected from Ex-CAPE DB (Sun et al., 2017) but used only for validation. Small molecules specific to the proteins of the 5-HT1 receptor family (A, D, E and F, which are similar to 5-HT1B) were collected. Docking calculation was performed with these molecules to identify molecules specific to 5-HT1B. This produced a dataset of 2,807 small molecules, which was utilized for training the pre-trained generative model using transfer learning. A multi-property optimization (MPO) was performed using reinforcement learning so that the designed small molecules can cross the blood brain barrier (BBB). After reinforcement learning, 10,000 molecules were sampled from the trained generative model. We have also observed that by optimizing the logP, the model could generate molecules with low MW (data not shown). Upon pre-processing, application of property filters (200 Da < MW < 450 Da, 0 < logP <= 4.0, SAS <= 4.0 and TPSA < 70 $Å^2$) and rule-based filters, a final dataset of 3,476 molecules were obtained.

This final set of molecules was compared against the validation dataset of 5-HT1B-specific molecules. It was observed that, 49 molecules from the generated set of molecules have Tanimoto coefficient above 0.75 [20] to the molecules from the validation dataset, indicating high similarity. Based on the virtual screening scores, we also observed that the new molecules are better inhibitors of 5-HT1B compared to the best known inhibitor molecules. The embedding provided below (Fig. 2A) highlights the molecule with the highest docking score and molecules which show high similarity to the training and validation dataset. To validate the docking score predictive model, the final set of molecules were subjected to virtual screening within the binding site of the 5-HT1B protein using AutoDock Vina [28]. A R2 score of 0.80 was observed between the values obtained from the docking software and predicted values (Fig. 2B) A sub-structural fragment analysis was performed to understand whether newly designed molecules captured the features of the validation dataset. The generated molecules showed the presence of tertiary amines and secondary amines in accordance with the natural ligand of 5-HT1B receptor (serotonin, which is an amine) [29]. Also, bicyclic and tricyclic groups containing aromatic heterocyclics (anilines, piperazines, piperidines and indoles) were more frequently observed, which is also in alignment with their well-known capability to act as selective 5-HT1B inhibitors [29, 30]. These results indicate that the generative model was able to capture and generate molecules with features specific to inhibit the 5-HT1B protein and also enhance the binding affinity using transfer learning and reinforcement learning.

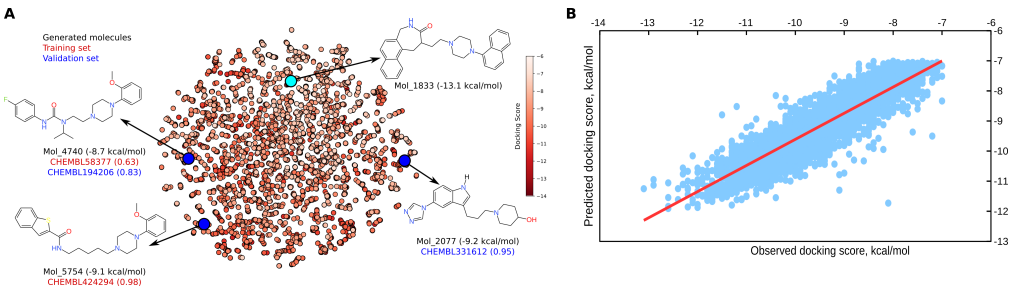

Figure 2: **A**. Embedding of the final set of generated small molecules colored based on their docking score. The generated molecules with their corresponding docking score are colored in black. The most similar molecules (in terms of Tanimoto coefficient) from the training set (red font) and the validation set (blue font) are indicated with their ChEMBL ID followed by Tanimoto coefficient in bracket. **B**. Comparison between the predicted and observed docking scores.

5 Conclusion

We have proposed a ligand-based *de novo* drug design method for generating small molecules against any novel target of interest. The fundamental problem of data availability for a given target protein could be overcome using the concept of active site similarity in closely related proteins. Transfer

learning, followed by reinforcement learning, is used for generation of a focused library of molecules against the 5-HT1B protein responsible for central nervous system disorders with multiple desired properties.

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