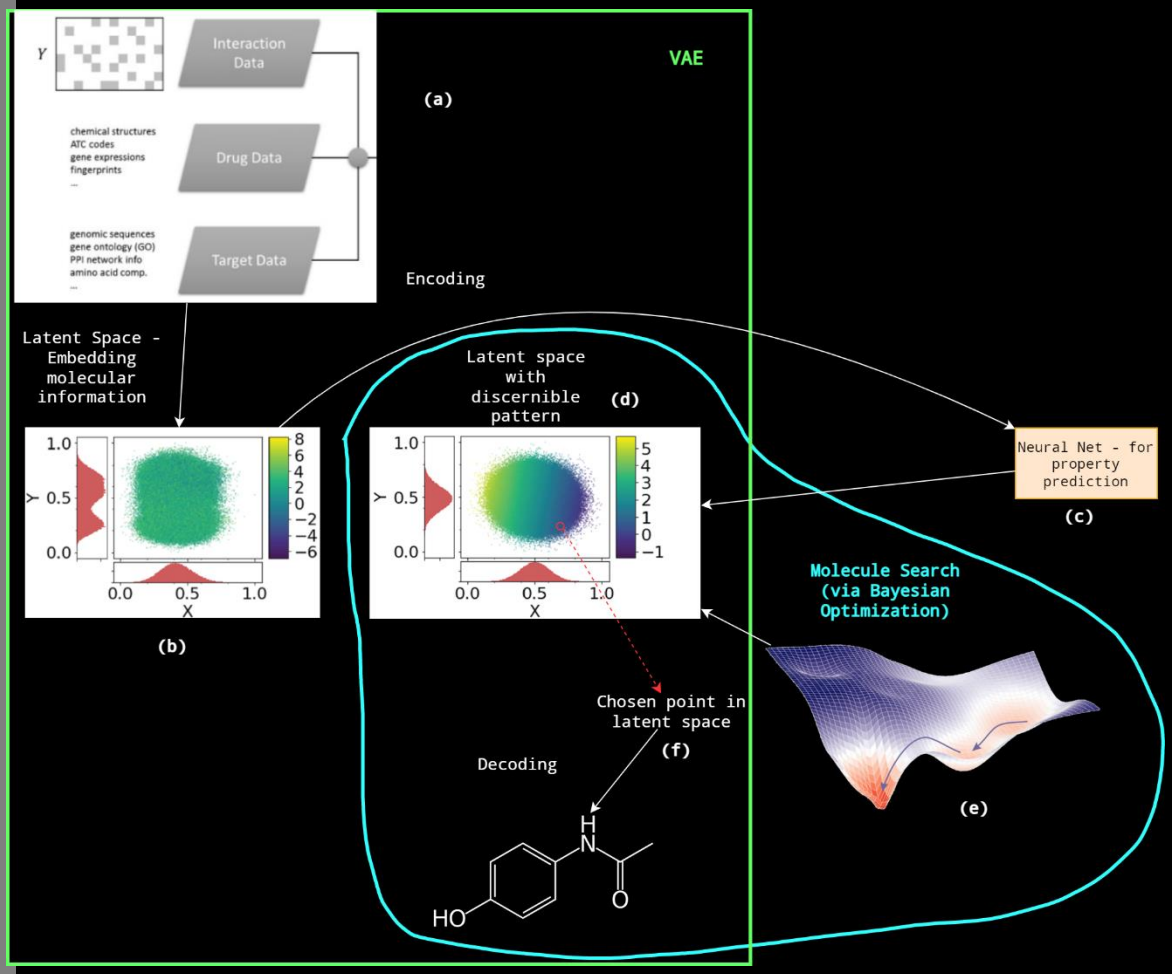

Machine Learning in Drug Development

A review of state-of-the-art machine learning methods employed in drug discovery, with proposed solutions addressing certain limitations currently present in in-silico drug discovery

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1. Introduction

Drugs are a usual form of treatment for various illnesses and diseases, and hence proper selection and development processes of said drugs are of utmost importance in the medical field. Drug discovery and testing are two critical processes in drug development, the former being credited for being very technically challenging whilst the latter being extremely tedious and ethically penumbrous. Although breakthroughs in machine learning have helped spearhead the application of machine learning methods in numerous aspects of drug discovery, the presence of reliable automated methods to aid in drug testing, primarily bottlenecked by reliable data sources, has been lacklustre. In this text, we critique some of the state of art in drug discovery and clinical outcome prediction methods in machine learning and propose a solution that addresses the limitations of the methods currently being employed today.

2. Challenges

Drug discovery is exceptionally tedious since the chemical space is vast. There are estimated to be between 10^{23} and 10^{60} possible compounds, and a typical pharmaceutical compound collection contains 10,000+ compounds before a certain number (usually 100s) of candidate molecules are selected. Pharmaceutical companies must go through various regulatory hoops, as the FDA in the US (which is responsible for most pharmaceutical exports (Center for Drug Evaluation and Research, 2019)) requires companies to undergo 4 stages of extensive clinical testing. Late-stage clinical trials take many years and millions of dollars to conduct until a single candidate drug compound is identified and approved for deployment in the market.

3. Reviewed Literature – State of the Art

3.1 Automatic Chemical Design Using a Data-Driven Continuous Representation of Molecules (Gómez-Bombarelli et al., 2019)

Aids in Drug Discovery

Gómez-Bombarelli et al describe an implementation of a variational autoencoder (VAE) architecture in this paper (Gómez-Bombarelli et al., 2019) for drug discovery. A variational autoencoder consists of two key sub-models, an encoder, and a decoder. The encoder is responsible for compressing molecular information down into a latent space (high dimensional space, Gómez-Bombarelli et al 156 and 196 dimensions for different datasets), and a decoder decodes a point in the latent space to a compound. The model is trained on existing compound representations (in SMILES - Simplified molecular-input line-entry system) and encodes it into a latent space. This encoding is then decoded with a neural network. Both the encoder and decoder are trained to get better at their jobs by comparing their outputs to each other. The latent space can be used as an optimisation landscape for obtaining molecules based on desired properties. When an optimum point in the latent space is found according to the users' objectives, it is fed to the decoder to output a candidate compound for testing.

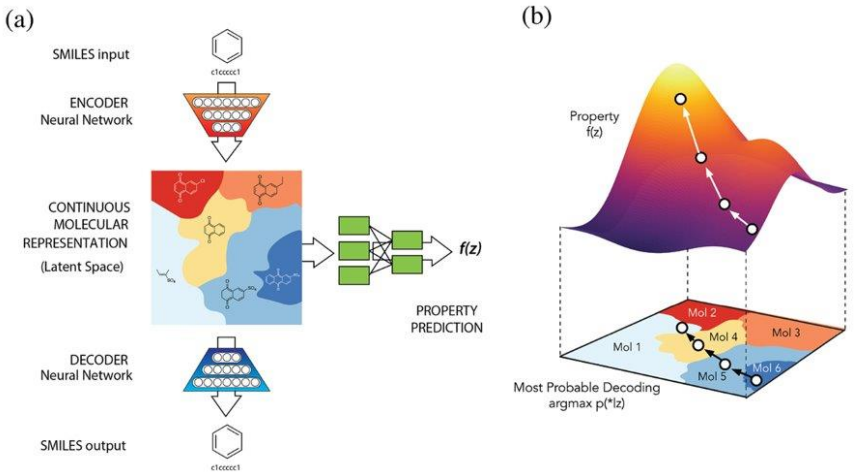

Figure 1 – (a) A visual representation of the VAE network. The encoder is responsible for encoding a string-based molecular representation into a high dimensional space, while the decoder is responsible for taking any point in that space and translating it into a molecule. (b) Example visualisation of drug search on the high dimensional space based on a chosen objective (i.e., most soluble drug).

Critique

The method requires pre-existing collection of compounds, although this will not be too much of a problem if more and data becomes available. Furthermore, the metrics used for finding candidates do not consider molecular dynamics and pharmacokinetics, and this information is critical in helping speed up clinical testing procedures. The chosen input representation format (SMILES) does not capture fully the complexities of compounds (a similar problem to the point above).

3.2 druGAN: An Advanced Generative Adversarial Autoencoder Model for de Novo Generation of New Molecules with Desired Molecular Properties in Silico (Kadurin et al., 2018)

Aids in Drug Discovery

The solution presented by this paper is remarkably like that which was displayed in Section 3.1. Uses a different loss function due to the added components taken from a GAN (Generative Adversarial Network) architecture (Goodfellow et al., 2014). It contains a 'discriminator' component that 'judges' the authenticity of molecules the autoencoder generates. The component itself can be used as a proxy for the validity of novel compound arrangements if enough data becomes available (Kadurin et al., 2018).

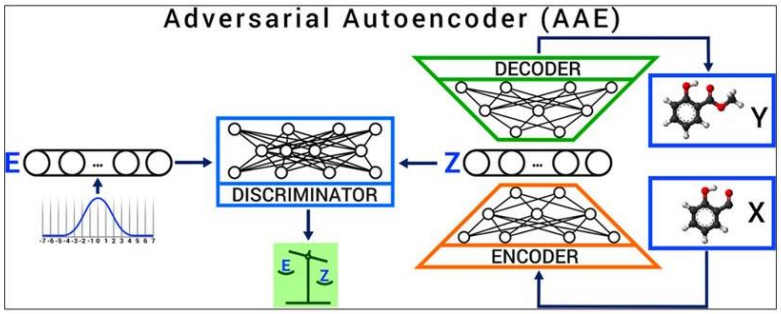

Figure 2 – A diagram of the model proposed by Kadurin et al. Similar to the VAE method displayed in 3.1, but with an added discriminator – taking inspiration from the GAN model proposed by Goodfellow et al. for synthetic data generatio.

Critique

Although the solution cleverly implements components of a GAN, it does not really address the limitations of 3.1. Furthermore, the model presented in this solution is a notable example of the "better" model vs. better data problem in machine learning. Although there is a GAN present, the VAE is the core component of this machine learning model, and all the GAN really does is modify the loss function and does not end up having much of an effect on the performance of the model overall. It is possible to get a better representation of molecules instead of SMILES to learn a richer latent space (in terms of capturing more information about molecules) instead of adding more complexity to the ML model.

3.3 Integrated deep learned transcriptomic and structure-based predictor of clinical trials outcomes (Artemov et al., 2018)

Used for Clinical Trial Outcome Prediction

Neural networks are widely utilized as a part of this method to predict side effects of drugs. It takes in drug-induced perturbation data (which represent changes in cell cultures after exposing them to drugs) and chemical formulae of the drug(s) to test as input. A random forest is used for predicting outcome of clinical trial based on changes displayed in the drug-induced perturbation. As a bonus, it also estimates the risk of using drug in clinical trial depending on the financial health of the organization designing the drug.

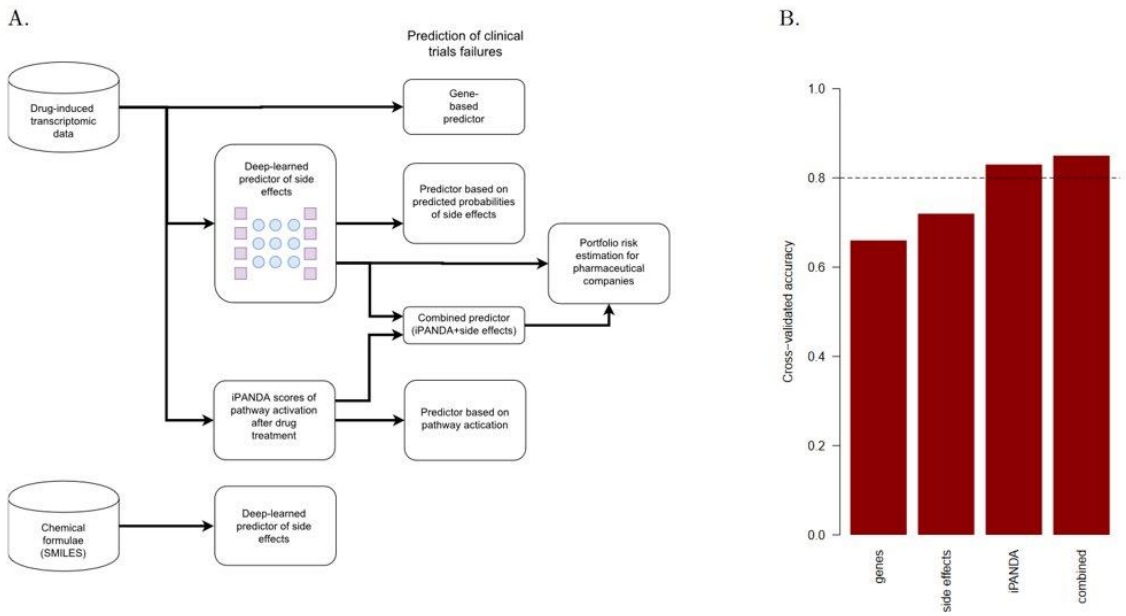

Figure 3 – (A) Diagram displaying the system proposed by Artemov et al. (B) Notice the system did not perform well when relying solely on gene expression data for side-effect prediction.

Critique

Gene expression change data is gathered after experimentation for input by inserting drugs into cell cultures. This type data is not always available for compounds. Clinical trial outcome prediction was poor when using gene expressions (see 'genes' on the x-axis on **(B)** in the picture above)**.** Also, each side effect requires a totally separate neural network, this is inefficient as it requires training a neural network every single time one wants to predict the probability of a side effect emerging when a drug is taken by a human.

4. Potential Solution – Better Representation Learning of Molecules and Pharmacokinetics

After extensive review of state-of-the-art solutions, it has become clear that although novel and highly performant models have become applicable in aiding drug development, much has been left to be desired with respect to learning better representations of molecules. Line-notation based molecular representations such as SMILES used as input for machine learning models only encode the topological representation of the drug compound they represent. This results in pharmacokinetical information surrounding drugs being left out of the table, and hence limiting the information machine learning models intrinsically retain during drug search.

Being able to encode representations of arbitrary data into a high dimensional space to be used as an exploration canvas for drug search has already been proven to be very applicable as described in Section 3.1. We further the methods described by Gómez-Bombarelli et al by introducing more input data to their VAE model, as well as further tweaks to its latent space generation and drug search methods. The inputs include a SMILES representation of a molecule, along its interaction data with the human cell signalling system (signalling pathway activations), and target data (which enzymes, proteins, etc. the drug targets on the human body), all of which are publicly available (Schubert et al., 2016). The encoder is jointly trained with a neural network for predicting the properties of a molecule given the inputs (i.e., solubility level of drug, QED for drug likeness, etc. (Bickerton et al., 2012)), helping produce more discernible patterns than the noisy plots produced by encoders alone. This form of manipulation generates an optimization landscape much more convenient to traverse, making it much more practical to run optimization and/or search algorithms on it to perform drug search.

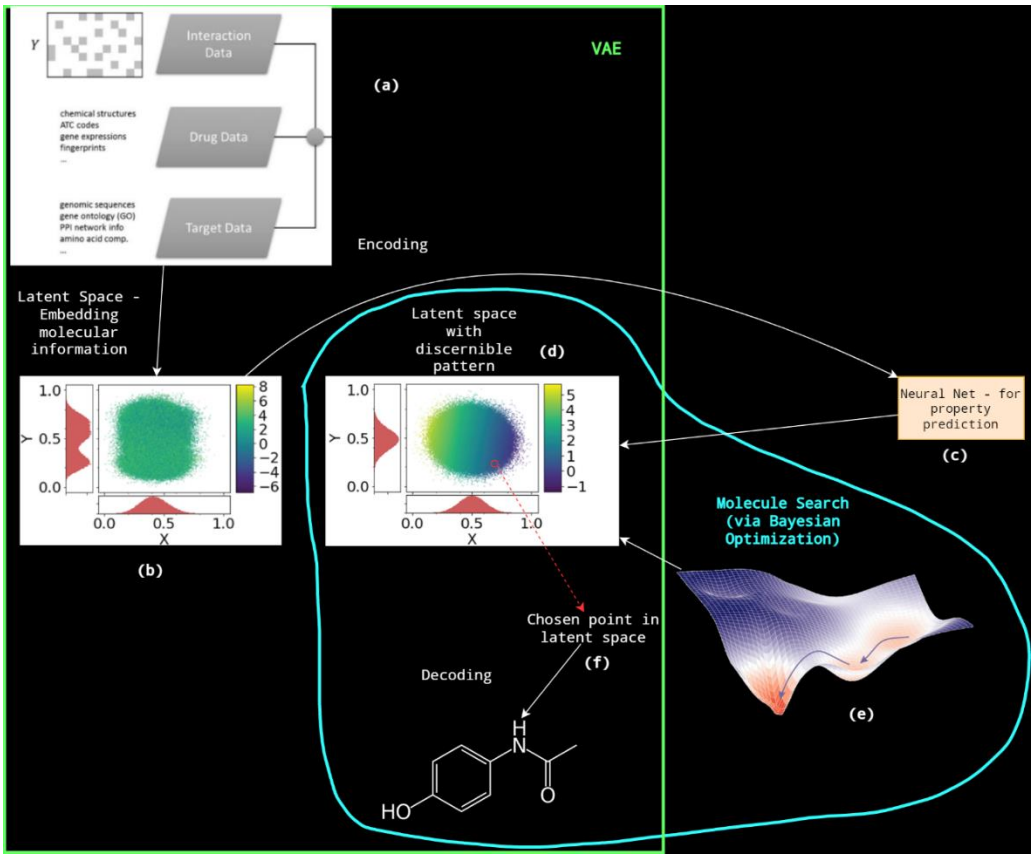

Figure 4 – Proposed Solution - (a) Input data – SMILES, drug-human interaction data and drug target data (b) Example latent space representation of thousands of molecules after using PCA for performing dimension reduction on the high-dimensional latent space for visualisation – only produced with encoder, very noisy. (d) A latent space generated by an encoder jointly trained with (d) a property-predicting neural network – has a much more discernible pattern as the values of a property (i.e., logP – drug solubility) shifts from green (values of ~5) to blue (~-1) when scanning from left to right on the X-axis. (e) An optimization algorithm can be run to find (f) a point in latent space and passed through the VAE's decoder to output a candidate molecule.

5. Discussion – Benefits and Limitations of Proposed Solution

The solution presented has two key benefits. Firstly, adding pharmacokinetical data described previously for input into a VAE with joint property prediction for encoding molecular representations produces a much richer chemical search space for drug discovery, rather than limiting it to process molecular topology via SMILES. Obtaining a richer chemical search space also presents a synthetic data generation opportunity. A version(s) of the latent space can be periodically updated and uploaded into a database for the public to use, and as it improves it can be utilized to generate more reliable synthetic data for drug interactions. By feeding points into the latent space into a Generative Adversarial Network (GAN)(Goodfellow et al., 2014), one can train a model which can generate information on how certain drugs may interact with certain targets – a modernised version of that which was described in Section 3.3. This will help alleviate the lack of clinical data available for more drug interactions with novel treatment targets, such as those targeted in cancer treatments. The main drawback with the solution proposed in Section 4, is that it is slightly more resource-intensive to train than state-of-the-art, as it requires more datapoints to train a larger and more complicated model. However, such a drawback is outweighed by the potential upside of the solution.

6. Conclusion

Drug discovery and testing are two extremely critical and challenging processes in drug development. Although breakthroughs in machine learning have helped spearhead the application of such computerized methods in numerous aspects of drug development, the presence of reliable automated methods to aid in drug testing, primarily bottlenecked by reliable data sources, has been lacklustre. Pharmaceutical companies need to go through various regulatory hoops. Clinical trials take many years and an impressive array of resources to conduct until a

single candidate drug compound has been identified and approved for deployment in the market. Various state-of-the-art methods proposed in literature were reviewed in pursuit of seeking solutions to the limitations which stifled their applicability for in-silico drug discovery and helping accelerate clinical testing. Current methods do not utilize low-level pharmacokinetical data, only considering limited topological representations of drugs for drug discovery. The solution presented in this text aimed to rectify this problem by describing data points which represent drug-human responses to their respective drugs for input into a network architecture much alike that of which was described in 3.1. We also described a joint property prediction component alongside the VAE used in the solution to generate a richer latent space for drug discovery, and further suggesting that the generated space be utilized for synthetic data generation to help alleviate the lack of clinical data for novel drug compounds.

7. Addressing Feedback from Proposal Presentation

7.1 Proposed Solution – Initial lack of technical depth and feasibility

The initially proposed architecture was slightly different from the final one proposed in this report. It relied on a reinforcement-learning-based, policy-centric algorithm to search the latent space described in 4. The technical description of such a method lacked substance, hindering the audience's ability to consider the plausibility of the proposed solution. This was rectified by presenting a more complete, technical description (along with a great visualisation) of the solution and) of the solution, but also completely swapping out the reinforcement learning component for a more traditional neural network to reduce the compute required to deploy such a solution. This is because reinforcement learning algorithms are notoriously tedious and resource-intensive to train compared to other methods present in the field (Pardo et al., 2022).

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