Thesis proposal

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Introduction & Background

Drug discovery—the process by which a potential new medicine is identified—is a complex process that encompasses the intersection of several fields (such as biology, statistics, chemistry or pharmacology). The entire process is a long and costly endeavor, with a typical time-frame of 10 to 20 years till market release and an estimated cost between 2 and 3 billion USD [Schneider, 2019, Scannell et al., 2012], with only 1 out of 10000 synthesized molecules obtaining market approval. Many of these dropouts happening at the early stages of the entire process. Subsequently, there is a need for tools that enable us to identify better drug candidates.

One of the most promising directions is to improve the *in-silico* methods; which are relatively cheap and quick, making them an interesting solution. *In-silico* simulations then cover two main aspects: **predictive modelling**, meaning modeling the dynamics of the human body—such that any effect relevant to the drug or the disease will be captured by it—and **generative modelling**, i.e. methods to generate good candidates by being effective at exploring the vast space of possible compounds, estimated to be on the order of 10^{60} [Reymond et al., 2012]. Several computational approaches have been used over the years, from molecular dynamics simulations to data-driven statistical methods [Hung and Chen, 2014, Kuhn et al., 2016]. Among the possible approaches, deep learning (DL) has shown signs to be a potential game-changer in drug-discovery [Dargan et al., 2019].

DL has been able to capitalize on the exponential growth of data and the higher availability of computational resources. DL has had remarkable success in computer vision (CV) [Guo et al., 2016] and natural language processing (NLP) [Young et al., 2018], and has become the go-to solution for any problem in these two fields. For instance, in the case of CV, where we deal with images, a key element of any architecture's success is the use of convolutional layers—one will mainly observe convolutional neural networks (CNNs) when analyzing the state of the art in CV—which introduces a structural a prior based on the structure of the data [Fukushima, 1980, LeCun, 1989, Ulyanov D., Vedaldi A., 2018]. A similar approach can be proposed to we deal with biological and molecular data by leveraging their graph representations. Efforts in generalizing the convolution operator on non-euclidian structures have given rise to graph convolutional neural networks (GCNNs) [Wu et al., 2019]. GCNNs, then, pose an opportunity to drug discovery due to their capacity to deal natively with graph data [Sun et al., 2019].

Nevertheless, there is a set of shared challenges for *in-silico* models. One of them is unifying the different aspects of drug-discovery by incorporating all the relevant biological and chemical information when designing possible candidate molecules. An initial success story on that line is a recent paper [Zhavoronkov et al., 2019] where the authors describe a deep learning method by which they are able to discover, synthesize, and test in an animal model, inhibitors of discoidin domain receptor 1 (DDR1)—a kinase implicated in fibrosis—in less than two months.

Those promising results, albeit encouraging, are just the tip of the iceberg. There is still a long way until a model can satisfactorily capture the biological complexity of an arbitrary target and produce promising candidates. On top of that, there is an added dimension, as such model should account for the variability from patient to patient and be able to generate a molecule that accommodates for all the genotypic and phenotypic variants, or otherwise generate different candidates for each of the populations of interest. That is especially important for hypercomplex diseases, such as cancer, where a genotypically heterogeneous tumoral population

may appear within a single patient [Boland and Yurgelun, 2017]. These diverse tumor subpopulations may, in turn, react distinctly to a drug, leading to an evolutionary pressure that can complicate the treatment prognosis [Enriquez-Navas et al., 2015].

The aforementioned example illustrates the need for the development of models that can be conditioned based on a large set of biological factors, and meaningfully account for these when generating a compound or evaluating a compound's effect. In other words, there is a need to adopt precision medicine methods.

Finally, from a more holistic perspective, it is of interest to develop multi-scale models that integrate a system's complexity at all different levels. For instance, a model that can learn protein-compound interactions—commonly known as the docking problem—while at the same time use this information to predict effects of the introduction of the compound on the larger protein-protein interaction (PPI) network [Sun et al., 2019].

Aim & Methods

The aim of this thesis has two distinct though interconnected objectives. One the one hand, analyze how the explicit use of GCNNs may open new opportunities when dealing with biological and chemical data. On the other hand, explore how modeling the biology at different scales (e.g. molecular structure v.s. molecular interaction network) may help create better models and, additionally, evaluate how these different scales may be integrated.

The project would be based on the ideas about GCNNs for drug discovery in presented literature [Sun et al., 2019], which will be expanded and tested in a wider framework for drug design recently proposed in an article [Born et al., 2019]. In that context, two main areas of application appear. One of them is to re-design the generative model, for instance by reframing the variational autoencoders used for molecule generation to architectures that operate over graphs [Simonovsky and Komodakis, 2018, Li et al., 2018a, Li et al., 2018b]. The second area is to improve the predictive model, by finding better ways to asses the activity of these molecules and assess their relevance as drug candidates. In the specific case of the mentioned drug discovery framework, it is done by using a critic network [Manica et al., 2019], which can be expanded on a set of different fronts. Those would be: using structural data instead of SMILES[1] [Li et al., 2017, Do et al., 2019], by using GCNNs on the PPI networks in a manner that allows for a more effective way to extract the information from them [Oskooei et al., 2019, Wang et al., 2019], or by introducing particular scores (rewards) based in the interaction of the compound to certain targets [Yingkai Gao et al., 2018, Zhavoronkov et al., 2019] or the combination of the compound with other drugs [Zitnik et al., 2018]. All these possible changes to the critic model would apply at different abstraction levels, that opens the door to integrating the representations learnt at those different levels in a single model [Ying et al., 2018, Ma and Zhang, 2019, Huang et al., 2019]. Furthermore, this integration could be then leveraged on the drug generation part of the framework.

The proposed ideas will be done in the context of designing anticancer compounds. The work will be done in collaboration with the Computational Systems Biology group at IBM Research (Zurich), currently part of the iPC consortium[2]. As part of such, an end goal of this project is for its results to help in the consortium efforts on pediatric cancer. For instance in contributing to the ongoing research in neuroblastoma, the most common type of cancer diagnosed on the first year of life [Maris, 2010].

Data & Baselines

The data from this project will be obtained from multiple sources including, but not limited to, the Genomics of Drug Sensitivity in Cancer (GDSC) databse [Yang et al., 2013], STRING and STICH, [Szklarczyk et al., 2019, Szklarczyk et al., 2016], DrugBank [Wishart, 2006], ChEMBL [Gaulton et al., 2017], PubChem [Kim et al., 2019] and ZINC 15 [Sterling and Irwin, 2015]. For the development of the models PyTorch [Paszke et al., 2019] will be used as the main framework, most likely alongside DeepChem[3].

The novel predictive model will be evaluated against empirically measured properties of drugs in the mentioned data sources. Furthermore, the model's performance will be compared to that of other models in the literature. For example, by comparing IC50 prediction values for cell-drug pairs (unseen during training) to the empirically

[1] http://opensmiles.org/
[2] https://ipc-project.eu/
[3] https://deepchem.io/

measured values from the data sources, as done in [Oskooei et al., 2019, Joo et al., 2019, Oskooei et al., 2018]. Another prospective set of benchmarks to be used are those proposed by MoleculeNet [Wu et al., 2018].

Previous work [Theis et al., 2016] has discussed how different metrics measure different conceptions of performance for the evaluation of generative models. In order to deal with different considerations, such as diversity, novelty, molecular activity, or stability, metrics like the Fréchet ChemNet Distance (FCD) [Preuer et al., 2018] have been proposed. In this project one of the metrics for the generative model will come from the predictive model, which will be used to evaluate the effectiveness of the generated compounds. Simultaneously, another metric for the generative model will be the similarity of the generated compounds to already existing drugs. An approach that has already been used in the literature [Born et al., 2019]. Moreover, a wider benchmarking framework for generative models, GucaMol, was proposed recently [Brown et al., 2019], incorporating elements like the mentioned FCD score, so it will be explored as a benchmark for this project.

Lastly, a natural final step for the entire evaluation of the system would be the actual in-vitro synthesis of the generated compounds, as done in [Zhavoronkov et al., 2019]. However, the complexity of carrying out that evaluation will likely make it far too ambitious for what the scope of this project is.

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