Thesis Proposal: [provisional title] Retrosynthesis Development and Implementation in Molecular Generators

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Drug discovery is an unsolved puzzle, due to all the constraints that need to be satisfied for a drug to be viable. This is further exacerbated by the size of the chemical space, which is estimated to be in the order of 10^{60} to 10^{100}, making it an extreme example of finding a needle in the haystack [9]. Despite the many advances that have been made in the last decades, the complexity inherent to problems of this type (and magnitude) means that many non-trivial challenges have to be addressed concurrently to find a holistic solution. To give a high-level example, drugs can exhibit strong binding affinity to a target receptor, which in itself is usually a desirable trait. But it can turn out that because of some other properties, that same drug can be toxic to its intended user (e.g. humans). Getting all the pharmacological properties to be acceptable while still being safe for usage, has already proven to be a tough balancing act. Even after this problem is addressed appropriately, we are also faced with the task of being able to actually synthesize the accepted compound. This last task, in particular, has plagued de-novo drug design (DNDD) since its inception [1]. DNDD is, roughly, a process wherein computer algorithms are able to generate and suggest novel molecules with desired properties [11].

The value delivered by DNDD comes from the fact that these novel structures are built from building blocks without any a-priori relationships. Many of the classic approaches to DNDD algorithms are rule-based, and they attempt to implement the same manner of reasoning as experts do [11]. However, due to the nature of this problem, it becomes intractable to cover all possible

scenarios an expert chemist would go through when determining the design of a new compound. Furthermore, these rules are difficult to encode exactly into software, and chemists do not reason this rigidly either. To that end, many of the modern approaches delegate the learning of rules for proper molecular structure generation to the computers themselves. With the recent advances and the breakthroughs that came with it, machine learning has gained traction in many fields, such as image recognition and natural language processing (NLP). Some key ideas from these fields were also applicable to problems found in chemistry, and also carried over to drug discovery, such as learning the language of chemistry, representing the molecular structures in their SMILES format (a sequence of characters that denote atoms or binding properties) [4].

Deep Reinforcement Learning (DRL) has recently seen a surge of success within drug discovery. DRL has contributed to some of the biggest breakthroughs of the last decade, including highlights such as developing superhuman chess AI, a game known to be hard to solve due to the explosion of possibilities during a single match [5]. This ability to efficiently find paths in large search spaces translates well to the problem DNDD faces, as mentioned before. Due to this relation, this approach has been widely adopted, including the approach that this project will use.

DRL approaches in DNDD usually consist of a generator and a reinforcement learning (RL) agent that modifies the molecules to ensure they possess desirable pharmaceutical properties. The molecules can be represented in various ways, but in our approach we will represent them as character sequences (SMILES), as the molecular generator that we build upon (DrugEx v2 [6]) is using this approach, and has found to be effective by other independent experiments as well [9,10]. The neural networks (NNs) will be trained on tokens of known bio-active compounds for specific biological targets. These tokens will be obtained from high-quality online databases such as ChEMBL. This will let our model learn the probability distribution of pre-existing compounds, and we can use this knowledge when generating new sequences, as the model will be able to predict (with some level of confidence) which token should be next given our constraints. This stage is also the stage where are faced with the issue of generating molecules that may not be synthetically feasible, which as mentioned above, is one of the biggest hurdles for DNDD. There are several metrics that can be used, such as the synthetic accessibility (SA) score, that will give a good indication on how realistic a compound is

to synthesize.

The key idea here is that we can incorporate information of the complexity of a molecule at the structure-generation level, instead of at the end. I intend to do this using modern retrosynthetic analysis software (henceforth, retrosynthesis engines), such as AiZynthFinder [3], and Retro-star [2]. Given a target molecule, and the available building blocks, these retrosynthesis engines will attempt to find viable synthetic routes and ideally also a metric representing the confidence in the feasibility of the found route(s). This idea is not new, and has been mentioned before in a paper from 2006 [1]. In their paper, they develop an algorithm called SPROUT where they also aim to influence the molecular structure during generation, by taking into account the complexity of the intermediate structure. They had access to a rule-based expert system called CAESA that used retrosynthetic analysis to estimate synthetic accessibility of a generated compound, but this was intractable for the amount of compounds they were generating due to the long runtimes for the analysis of a single compound using this software (in the order of minutes). The goal is to be able to prune the search early on, given a structure becomes too complex at a certain stage of its generation. The authors of SPROUT noted that "many cases of synthetic complexity were caused by the presence of uncommon substitution patterns in rings and chains rather than from the presence of more obvious complex features such as stereocenters" [1]. We also partially run into this issue with the current retrosynthesis engines, as they are more flexible but still have long runtimes. To remedy this issue, we will use the Retrosynthetic Accessibility (RA) score that is produced by a model that was trained on the outcomes generated by AiZynthFinder [12]. This classifier can give an indication of synthetic feasibility without needing to compute the synthetic route each time, making it tractable for our use-case.

Given our approach, we also need to determine evaluation criteria to analyse the results obtained during our experiments. Namely, there does not seem to be a standard approach to evaluate these generated molecular compounds, so we have to establish and be transparent about what we will be looking at as our metrics that we want to optimize. Currently, we know that we should perserve the diversity of the generated compounds, and we can do this through e.g. using levenshtein distances between the generated SMILES. We must also select a suitable evaluation criteria to know if our compounds make

sense. One example of an established system is the well-established ADMET and QSAR approaches proposed by Muratov et al. to assess the relevance of the designed molecules [7, 8]. If agreed upon, however, we could determine evaluation criteria ourselves, provided it is well documented and backed up by valid reasoning. We also need benchmarks to determine if our method is worth pursuing further compared to simpler alternatives. One example hereof is by comparing the results between using RA and SA scores. The aforementioned SPROUT algorithm suggests an interesting approach where they "assign a different penalty to each fragment" during the assembly of the compounds, using a database of fragments that have known complexities as a reference [1]. This method of assigning penalties to each fragment during the structure generation will be used as a starting point for us as well. The authors also mention that a limitation at the time of writing was the low coverage given by the size of the complexity database they had access to. Given the amount of time that has passed and the explosion in data in recent years, it might be interesting to revisit this idea. However, in interest of time and the scope of this experiment, it may be desirable to defer this to a future project.

The scope of this paper will thus revolve around finding the correct implementation of RA Score within DrugEx, and the tuning thereof, i.e. when and how do we prune the structure that is being generated? Is pruning our only option, or can we steer the generation itself (e.g. manipulate the distribution of likely next SMILES tokens)?. Naturally, the fact that the RA score simply comes from a model that was trained on the predictions of another model, means that we do inject uncertainty into our approach. We can employ the retrosynthesis engines that were mentioned earlier (especially the ones that are not AiZynthFinder) to more thoroughly investigate a sample of our generated compounds to mitigate a certain amount of bias in our results. However, further manual inspection of a subset of the compounds may be desirable to truly determine how useful this approach can be to chemists in the lab.

Tools

- All code will be written to be compatible with Python ≥ 3.7
- I will be using PyTorch for the construction of any neural networks
- I will be using Jupyter notebooks for experimentation and in-code example-based explanations
- Any code that is eventually used in the main pipeline for the generation of the molecules, will be extracted as a module and added as source code
- I will be using Git and Azure DevOps for version control and planning (eventually automatically building, testing and deploying the model if time allows, but this is not a priority).

Deliverables & Timeline

- I will adhere to 2-week sprints and have a presentable demo every meeting.
- Experiments for the thesis are expected to be completed in mid December.
- The end-product (software) will be a modified version of DrugEx that can generate novel molecular structures with emphasis on synthetic feasibility, modified at the structure-generation level
- I will include several examples of generated molecules and analysis of their complexity relative to the configuration used to generate them (analysis done through e.g. Retro* or AiZynthFinder, manual inspection with Anthe etc.)
- Documentation on how to use the model and how to eventually expand on the code (for future students, or myself)
- A completed thesis (Approx. 30 pages, excluding references).
- All code & data used for the experiments, ideally tested where necessary and deployable

- A simple interface for quickly being able to reproduce and validate all experiments
- reports generated from experiments

References

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