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Spotlight

Has Drug Design Augmented by Artificial Intelligence Become a Reality?

Hongming Chen[1,*] and Ola Engkvist[1]

The application of artificial intelligence (AI) to drug discovery has become a hot topic in recent years. Generative molecular design based on deep learning is a particular an area of attention. Zhavoronkov *et al.* recently published a novel approach in which *de novo* molecular design based on deep learning was used to discover novel potent DDR1 kinase inhibitors. It took 21 days from model building to compound design, and a total of six AI-designed compounds were synthesized and tested. The study highlights how quickly the field of AI-designed compounds is developing, and we can expect further developments in the coming years.

Drug discovery is a notorious lengthy and costly process which is often described as finding a needle in a haystack. In this case, the haystack comprises on the order of 10^{60}–10^{100} synthetically feasible molecules [1], of which we need to find a perfect compound which satisfies a plethora of criteria including bioactivity, drug metabolism and pharmacokinetic (DMPK) profile, synthetic accessibility, etc. The process from initialization of a drug discovery project to identifying a candidate drug for preclinical study usually takes 3–5 years, and hundreds to thousands of compounds need to be synthesized and tested. Developing *de novo* design algorithms to virtually design and assess compounds has potential to reduce the time and cost of finding the appropriate needle, especially if AI design is combined with automated chemistry.

Early *de novo* design algorithms [1] used structure-based approaches to grow ligands that sterically and electrostatically fit the binding pocket of the target of interest. Compounds designed via this type of method usually suffer from poor DMPK properties and synthetic intractability [2]. Another type of *de novo* design method is to first enumerate large virtual libraries and then explore the chemical space through docking and similarity/pharmacophore searches [3]. Library enumeration is based on a predefined reaction scheme and commercially available reagents. Another possibility is to use transformational rules, based on the experience of medicinal chemists [4], to make incremental modifications to a query structure. One common problem with all these methods is the inherent rigidness and scope of the predefined reaction/transformation rules. With advances in deep learning methods, generative modeling has emerged as an interesting *de novo* design method [5]. By learning the underlying probability distribution over a large set of chemical structures (hence a data-driven method), generative modeling can learn how drug-like compounds should look without introducing any rigid rules. The recurrent neural network (RNN) [6,7], variational autoencoder (VAE) [8], and generative adversary network (GAN) [9] are the most common deep learning architectures used in generative modeling methods. The first example of molecular design with experimental validation using generative modeling was reported by Merk *et al.* in which an RNN model was used to design retinoid X and peroxisome proliferator-activated receptor agonists. The designed compounds revealed nanomolar to low micromolar receptor modulatory activity in cell-based assays [10].

Recently, Zhavoronkov and colleagues [11] applied the so-called generative tensorial reinforcement learning (GENTRL) model, a deep learning approach, to design discoidin domain receptor family member 1 (DDR1) kinase inhibitors. GENTRL can be seen as a further development of the authors' earlier work on VAE [12] and GAN [9]. They first curated three sets of compounds for model training. One set is the lead-like compounds from ZINC[i] and internal compound databases that represent the general chemical space, the second set comprises kinase inhibitors and inactive compounds from the Integrity[ii] and ChEMBL[iii] databases, and the third set includes patented compounds from pharmaceutical companies. Based on these datasets, three self-organizing map (SOM) [13] models composing the scoring function for the GENTRL model were built to evaluate general kinase activity, DDR1 activity, and structural novelty, respectively. The core part of the GENTRL model is basically a variant of the VAE model, as shown in Figure 1. It employs a **gated recurrent unit** (GRU; see Glossary) RNN as the encoder to map molecule structure (in **SMILES** string format) into **latent vector**; the latent vector is then decoded to reconstruct the input structure, and the latent vector also follows a learnable **prior distribution** model at the same time. Various compound properties were also included during VAE training for creating a mapping between molecule structure, compound properties, and the latent vector. In the next step (generation strategy, Figure 1), reinforcement learning was carried out to fine-tune the model to preferentially generate DDR1 kinase inhibitors with reward functions (specific SOM,

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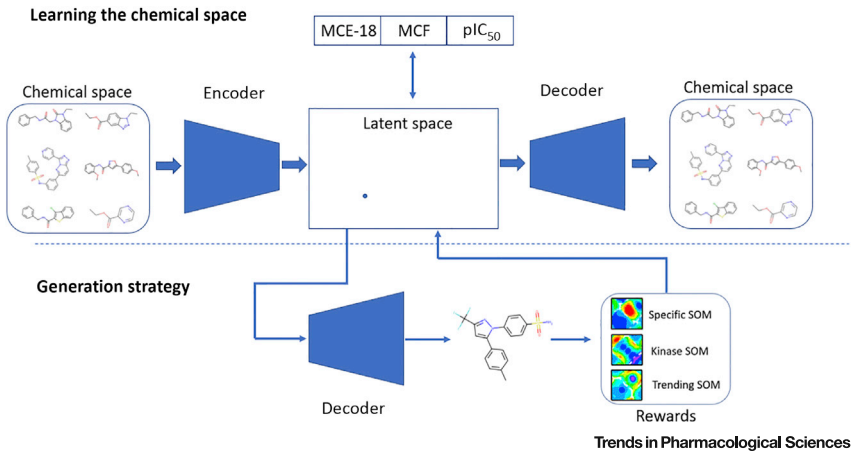

Figure 1. The GENTRL workflow for molecular design.
(Above) The VAE model, containing an encoder and a decoder component, was first trained to learn the latent vector to represent the chemical structures (learning the chemical space). (Below) Reinforcement learning was then carried out to search for chemical structures with optimal rewards (generation strategy). Abbreviations: GENTRL, generative tensorial reinforcement learning method; MCE-18, medicinal chemistry evolution 2018; MCF, medicinal chemistry filter; pIC_{50}, negative log of the IC_{50} (molarity) value; SOM, self-organizing map; VAE, variational autoencoder.

general kinase SOM, and trending SOM, as described earlier).

The authors initially generated 30 000 DDR1 inhibitor structures by running GENTRL model in a reinforcement learning setup. After going through a cascade of filters including **medicinal chemistry filters**, a **novelty filter**, **structural clustering**, DDR1 **pharmacophore models**, and **Sammon mapping**, 40 structures were selected that smoothly covered the resulting chemical space and the distribution of root-mean-square deviation (RMSD) in the pharmacophore models. Six structures were ultimately chosen for experimental validation based on synthetic accessibility. All six compounds were successfully synthesized and tested for *in vitro* inhibitory activity in an enzymatic kinase assay. Two compounds showed DDR1 inhibitory potency (IC_{50}) at 10 and 21 nM, respectively, two had moderate potency, and two were inactive. The two most potent compounds also showed strong potency in subsequent cell assays. These were also tested in various DMPK assays, and had similar DMPK profiles to the reference compounds. Finally, compound 1 was dosed in mice via intravenous and oral administration, and achieved reasonable pharmacokinetic results. Compound 1 was also tested against a small kinase panel, and DDR1 and DDR2 were the only kinases with >50% inhibition at 10 μM. Compound 1 (the most potent compound) has the same hinge-binding motif as ponatinib (a kinase inhibitor used in cancer treatment[iv]), which is not surprising because the neural network was trained on general kinase inhibitors.

From initial target nomination to obtaining the final biological evaluation results of the six compounds, the whole process took 46 days. The article has received significant attention in the press and social media[v–vii]. This is the first example of published a *de novo* design workflow that includes molecular structures and substantial experimental validation. The study highlights the need for extensive preprocessing to generate the necessary scoring models, as well as postprocessing of the *de novo* generated molecules, and emphasizes the importance of taking all available information into account in developing the models and prioritizing compounds for synthesis. Thus, AI-based *de novo* design is not merely a press-the-button exercise.

This study dispels the myth that AI-generated compounds are difficult to make: the candidate compounds in the work could be synthesized quickly. Importantly, the authors have released their source code – they should be acknowledged for supporting transparency and reproducibility in research. However, it is important to note that the selectivity panel covers only ~10% of the protein kinome and is unevenly selected with respect to kinase subfamilies. In addition, there is no benchmarking of the measured properties of the newly synthesized compounds with existing DDR1 inhibitors. Hence, although the study highlights how molecular *de novo* design can be applied to a mature target where extensive information is available, it will be interesting to see what a workflow would look like for a completely novel target outside the well-exploited target classes such as kinases and GPCRs.

Although the compounds already have good properties from the first round of design, more design cycles will certainly be necessary to further optimize potency, DMPK profile, and kinase selectivity of compound 1 to obtain a clinical candidate. Nevertheless, as a proof of concept, this example clearly highlights the potential impact on drug discovery of generative modeling based on deep learning in terms of time and cost

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savings in identifying new chemical lead series. Generative modeling is still in its infancy, and there is room to further improve *de novo* molecule generation based on deep learning. We expect that more AI-based drug design examples will be reported in the future. In particular, we look forward to how AI-designed compounds, as exemplified in this article, can be coupled with automated chemistry to speed the identification of novel lead compounds.

Resources

[i] http://zinc.docking.org/
[ii] https://integrity.clarivate.com/
[iii] www.ebi.ac.uk/chembl/
[iv] https://iclusig.com/pi
[v] https://blogs.sciencemag.org/pipeline/archives/2019/09/04/has-ai-discovered-a-drug-now-guess
[vi] https://cen.acs.org/pharmaceuticals/drug-discovery/AI-identifies-drug-candidate-weeks/97/i35
[vii] www.drugdiscovery.net/2019/09/03/so-did-ai-just-discover-its-first-drug-comment-on-deep-learning-enables-rapid-identification-of-potent-ddr1-kinase-inhibitors/

[1]Hit Discovery, Discovery Sciences, Biopharmaceutics R&D, AstraZeneca, Gothenburg, Sweden

*Correspondence:
Hongming.chen71@hotmail.com

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Glossary

Gated recurrent unit (GRU): a type of recurrent neural network for processing sequence data in deep learning research.
Latent vector: a multidimensional variable representing another multidimensional variable or matrix generated via a mapping function.
Medicinal chemistry filter: a list of functional groups in a compound that may have detrimental effects such as toxicity, compound destabilization, interference with bioassay technology, etc. These are used to filter out potentially toxic, unstable, or potential false-positive compounds.
Novelty filter: the criterion defines whether a compound generated is similar to known compounds. It was used here to remove compounds which are too similar to known compounds.
Pharmacophore model: an ensemble of steric and electronic features that are necessary for molecular recognition of a ligand by a biological macromolecule.
Prior distribution: in Bayesian statistics inference, this is the probability distribution that expresses one's beliefs about the magnitude of a variable before any evidence is taken into account.
Sammon mapping: a method to map high-dimensional data to low-dimensional space in 2D or 3D for visualization purposes.
SMILES: simplified molecular input line-entry system, a form of line notation for describing the chemical structure using short ASCII strings.
Structural clustering: a method of classification that places similar compounds in the same class. It was used here to simplify compound analysis.

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