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(SD2022-270) Algorithm for de novo drug discovery

Tech ID: 32916 / UC Case 2021-Z08-1

ABSTRACT

Generation of drug-like molecules with high binding affinity to target proteins remains a difficult and resource-intensive task in drug discovery. Existing approaches primarily employ reinforcement learning, Markov sampling, or deep generative models guided by Gaussian processes, which can be prohibitively slow when generating molecules with high binding affinity calculated by computationally-expensive physicsbased methods.

Researchers a UC San Diego have developed a new approach, named Latent Inceptionism on Molecules (LIMO), which significantly accelerates molecule generation with an inceptionism-like technique. LIMO employs a variational autoencoder-generated latent space and property prediction by two neural networks in sequence to enable faster gradient-based reverse-optimization of molecular properties.

TECHNOLOGY DESCRIPTION

In drug discovery, a common paradigm today involves performing an initial high-throughput experimental screening of available compounds to identify hit compounds, which is both resource-intensive and can only identify which existing compounds are promising, relying on the further work of medicinal chemists to optimize these hit compounds into lead compounds. As an alternative, many computational methods have been proposed for de novo drug design, including genetic algorithms and other deep learning-based approaches. Methods outside of deep learning are generally not flexible enough to be entirely useful in drug discovery, while current state-of-the-art deep learning methods are either prohibitively slow or cannot generate molecules with an adequate level of desirability.

Researchers a UC San Diego have developed a new approach, named Latent Inceptionism on Molecules (LIMO), which significantly accelerates molecule generation with an inceptionismlike technique. LIMO employs a variational autoencoder-generated latent space and property prediction by two neural networks in sequence to enable faster gradient-based reverse-optimization of molecular properties. Comprehensive experiments show that LIMO performs competitively on benchmark tasks and markedly outperforms stateof-

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OTHER INFORMATION

KEYWORDS

de novo drug discovery, machine learning, protein-ligand binding

CATEGORIZED AS

▶ **Medical**
  ▶ New Chemical Entities, Drug Leads
  ▶ Research Tools
  ▶ Software
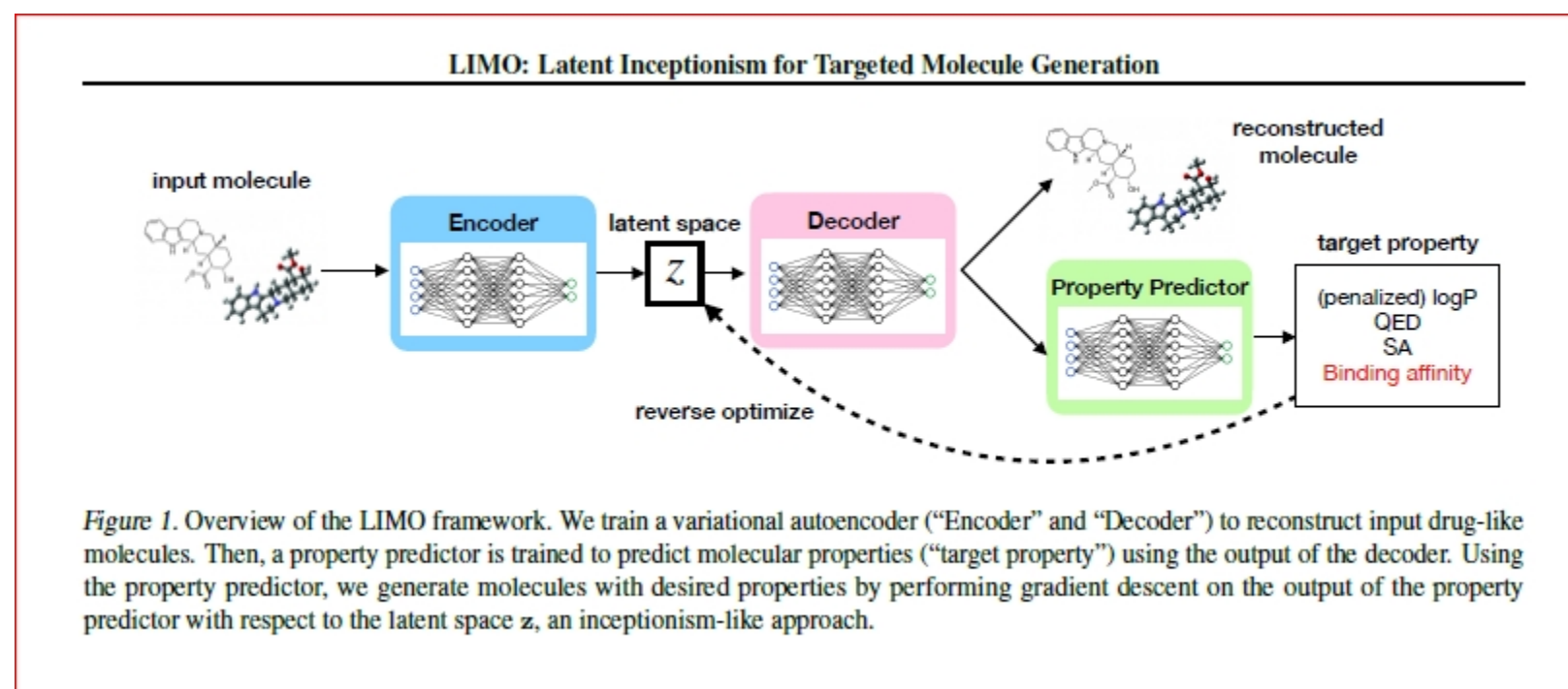 ▶ Therapeutics

RELATED CASES

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the-art techniques on the novel task of generating drug-like compounds with high binding affinity, reaching nanomolar range against two protein targets. We corroborate these docking-based results with more accurate molecular dynamicsbased calculations of absolute binding free energy and show that one of our generated drug-like compounds has a predicted KD (a measure of binding affinity) against the human estrogen receptor, well beyond the affinities of typical early-stage drug candidates and most FDA-approved drugs to their respective targets.

ADVANTAGES

▸ builds on the variational autoencoder (VAE) framework, combined with a novel property predictor network architecture;

▸ employs an inceptionism-like reverse optimization technique on a latent space to generate drug-like molecules with desirable properties;

▸ is much faster than existing reinforcement learningbased methods (6 - 8X faster) and sampling-based approaches (12X faster), while maintaining or exceeding baseline performances on the generation of molecules with desired properties;

▸ allows for the generation of molecules with desired properties while keeping a molecular substructure fixed, an important task in lead optimization;

▸ markedly outperforms state-of-the-art methods in the novel task of generating drug-like molecules with high binding affinities to target proteins.

STATE OF DEVELOPMENT

Figure 1. Overview of the LIMO framework. We train a variational autoencoder ("Encoder" and "Decoder") to reconstruct input drug-like molecules. Then, a property predictor is trained to predict molecular properties ("target property") using the output of the decoder. Using the property predictor, we generate molecules with desired properties by performing gradient descent on the output of the property predictor with respect to the latent space z, an inceptionism-like approach.

INTELLECTUAL PROPERTY INFO

UC San Diego is seeking companies interested in commercializing this patent-pending technology.

RELATED MATERIALS

▸ Eckmann, Peter and Sun, Kunyang and Zhao, Bo and Feng, Mudong and Gilson, Michael K. and Yu, Rose. LIMO: Latent Inceptionism for Targeted Molecule Generation. - 06/17/2022