Machine learning tools in drug design

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Traditional Methods of Drug Discovery

Zhang, Yue, et al. "Application of computational biology and artificial intelligence in drug design." *International journal of molecular sciences* 23.21 (2022): 13568.
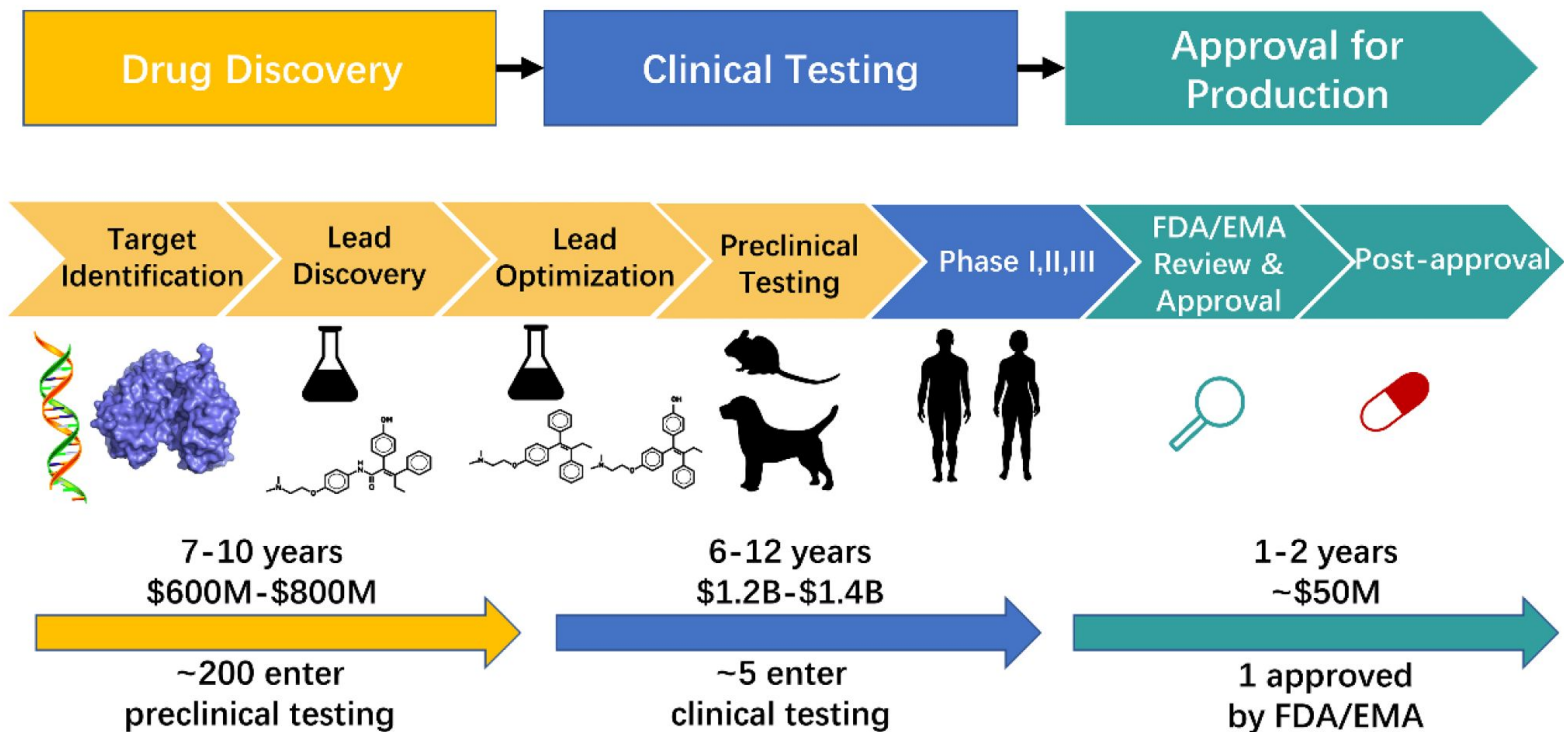
Two Big Problems

Time	Fail Rate
10+ years	85%

Computational Biology in Drug Design

- MM and QM simulations
- molecular docking
- Virtual Screening
- pharmacophore modeling
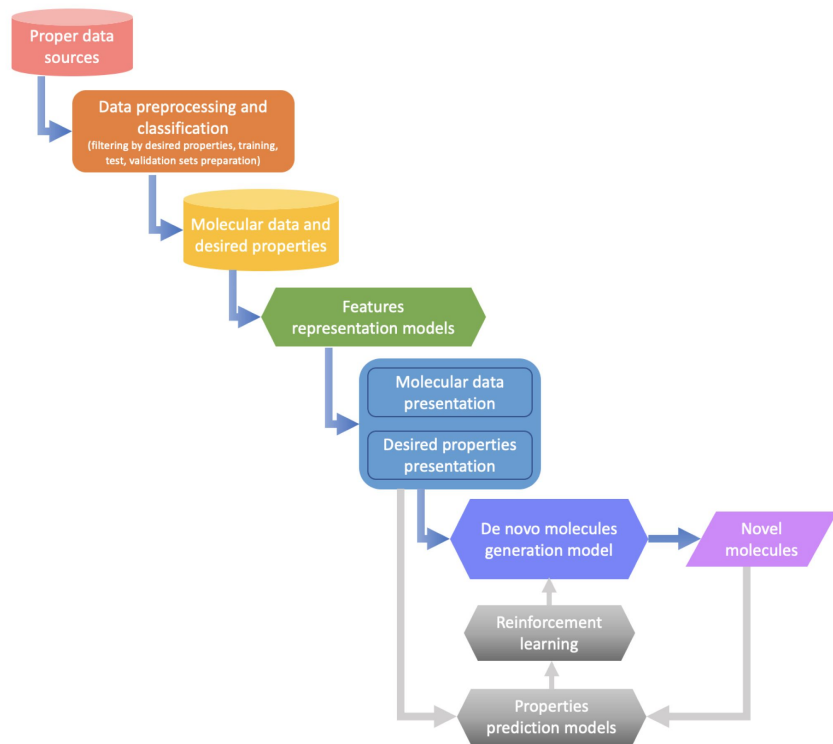- QSAR
- machine learning
- deep learning
- and many more

Today's topic: machine learning, specifically neural networks that create novel drug candidates

Goals

Create a new molecule that:

- has good pharmacokinetic properties
- is synthesizable
- is novel
- functions as a drug

De Novo Design by AI

Generative approach

Structure oriented generation

Ligand oriented generation

Important models

Structure oriented

- DeepLigBuilder
- G-SchNet
- RELATION
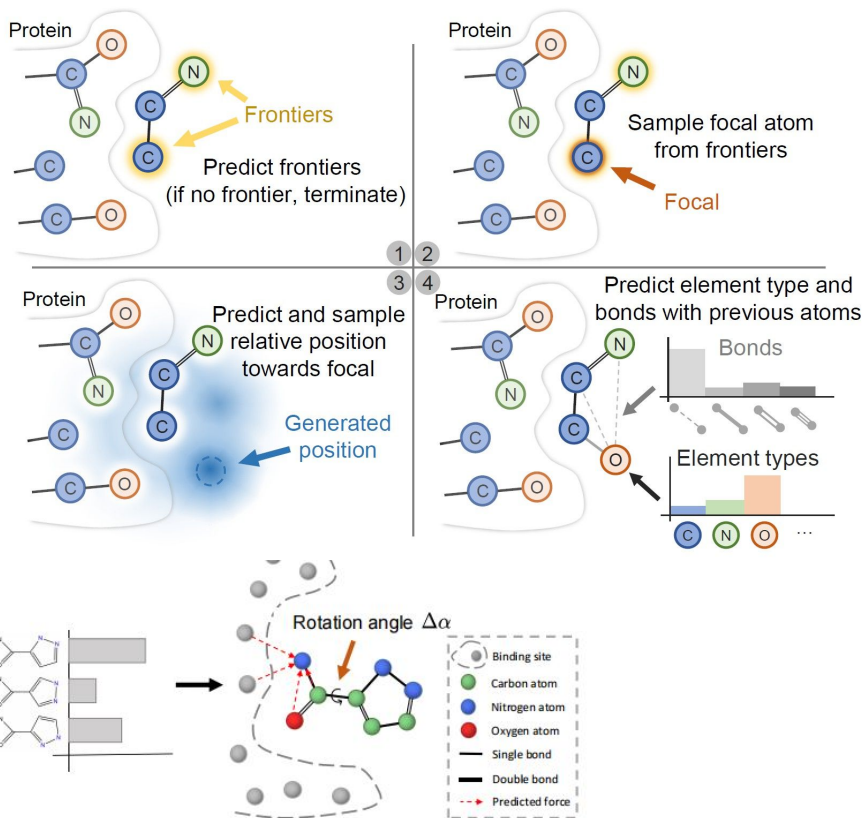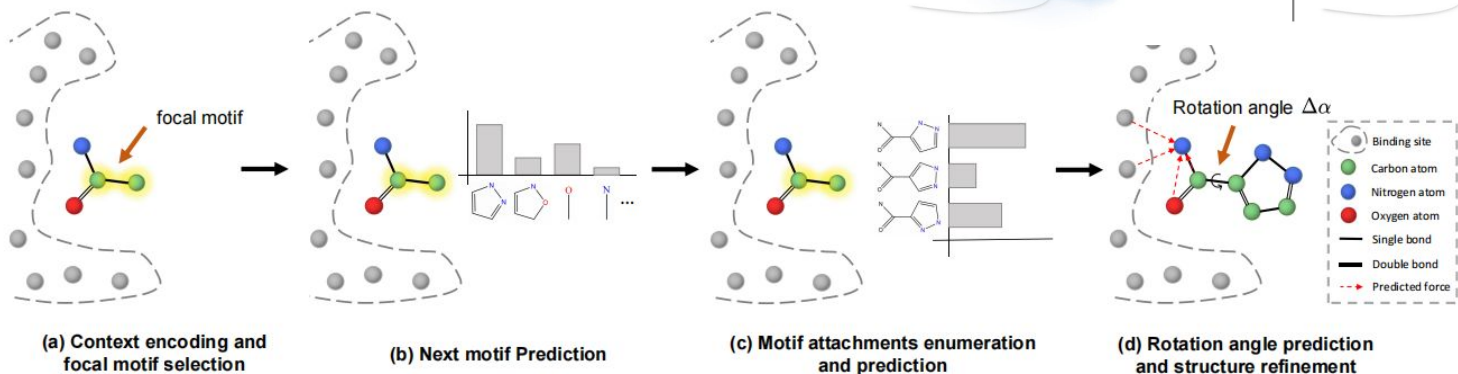- Pocket2Mol
- FLAG ICLR23

Ligand oriented

- CogMol
- MolFlow

Pocket2Mol vs FLAG

Different approaches to generation

Pocket2Mol →

FLAG ↓

(a) Context encoding and focal motif selection

(b) Next motif Prediction

(c) Motif attachments enumeration and prediction

(d) Rotation angle prediction and structure refinement

Peng, Xingang, et al. "Pocket2mol: Efficient molecular sampling based on 3d protein pockets." *International Conference on Machine Learning*. PMLR, 2022.

Zhang, Zaixi, and Qi Liu. "Learning subpocket prototypes for generalizable structure-based drug design." *International Conference on Machine Learning*. PMLR, 2023.

Problems

molecules can be unsynthesizable

molecules can lack novelty

GNN specific problems

Lack of good datasets for benchmarking

it's changing, for example: https://tdcommons.ai

Representation of molecules

Bibliography

FLAG: https://github.com/zaixizhang/FLAG

Zhang, Zaixi, and Qi Liu. "Learning subpocket prototypes for generalizable structure-based drug design." *International Conference on Machine Learning*. PMLR, 2023.

Pocket2Mol: https://github.com/pengxingang/Pocket2Mol

Peng, Xingang, et al. "Pocket2mol: Efficient molecular sampling based on 3d protein pockets." *International Conference on Machine Learning*. PMLR, 2022.

Overview of the topic:

Zhang, Y.; Luo, M.; Wu, P.; Wu, S.; Lee, T.-Y.; Bai, C. Application of Computational Biology and Artificial Intelligence in Drug Design. *Int. J. Mol. Sci*. **2022**, *23*, 13568.

Other:

Yang Zhang, Caiqi Liu, Mujiexin Liu, Tianyuan Liu, Hao Lin, Cheng-Bing Huang, Lin Ning, Attention is all you need: utilizing attention in AI-enabled drug discovery, *Briefings in Bioinformatics*, Volume 25, Issue 1, January 2024, bbad467

Hasselgren, Catrin, and Tudor I. Oprea. "Artificial intelligence for drug discovery: Are we there yet?." *Annual Review of Pharmacology and Toxicology* 64 (2024): 527-550.