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Sequential fragment-based ligand generation guided by geometric deep learning on protein-ligand structures

Stanford researchers have developed a geometric deep learning based novel method to aid in identification and discovery of novel drug scaffolds as well as to optimize known scaffolds, as a means to combat the major challenge in drug discovery.

A major challenge after identifying a new drug scaffold is the optimization of the molecule for medicinal use, which is usually both time and resource intensive. Moving the chemical search process from the bench top to a laptop could significantly decrease the time and physical resources that need to be devoted to creating a new drug. The novel in silico method developed by Stanford researchers does exactly that by expanding a small, fragment-like starting molecule bound to a protein pocket into a larger, more drug-like molecule. The model uses E(3) equivariant based neural networks and a 3D atomic point cloud representation, to learn how to attach new functional groups to a growing structure by recognizing realistic intermediates generated en route to a final ligand. The method also accounts for properties like binding affinity, ease of synthesis, and drug-likeness.

Stage of Development
Prototype

Applications

- Identifies new drug scaffolds
- **Optimizes known scaffolds quickly and inexpensively**

Advantages

- Faster
- Cheaper
- Learns a complex task from a relatively small number of independent training examples (4000 protein-ligand pairs)
- interpretable: the agent's actions often align with a chemist's intuition and basic physics

Publications

- Powers, A., Yu, H., et al. (2022). Fragment-based ligand generation guided by geometric deep learning on protein-ligand structures. bioRxiv.

Patents

- Published Application: 20230317212

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