Exploring Large Chemical Spaces for Lead Optimization

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The lead optimization stage of a drug discovery program generally involves the design, synthesis, and assaying of hundreds to thousands of compounds. The design phase is usually carried out via traditional medicinal chemistry approaches and/or structure-based drug design (SBDD) when suitable structural information is available. Two of the major limitations of this approach are (1) difficulty in rapidly designing potent molecules that adhere to myriad project criteria, or the multiparameter optimization (MPO) problem, and (2) the relatively small number of molecules explored compared to the vast size of chemical space.

To address these limitations, Schrödinger has recently spearheaded the development of workflows that combine large-scale synthetically aware de novo design methods (AutoDesigner) with rigorous free energy-based scoring methods (Active Learning FEP+) for potency and selectivity optimization of small molecules. Recent developments of this technology move beyond R-group design to core exploration, enabling its expanded application to early stage hit identification efforts and the discovery of back-up series.
In this presentation, we will describe the workflows that have been developed and show how these technologies can impact and accelerate drug development programs.

Bibliography :

[1] Bos, P. H. et al., J. Chem. Inf. Model. 62 (8), (2022), 1905-1915