Beyond Validity and Novelty: Scaffold-based Metrics for Evaluating Chemical Structure Generators

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Chemical structure generators systematically explore chemical space to identify novel compounds with desirable properties. However, assessing the quality of these generators is challenging due to the vast number and variety of chemical structures they produce. The existing evaluation metrics are based on simple concepts such as chemical validity or novelty [1]. These metrics do not, however, align with the primary objective of de novo chemical structure generation: the creation of new biologically active compounds. Therefore, we propose new metrics for evaluating chemical structure generators that better reflect the biological activity of the generated compounds. These proposed metrics are based on the analysis of molecular scaffolds, aiming to identify known (i.e., experimentally verified) biologically active scaffolds in a virtual library that were not used as inputs to the molecular generation process. Employing this approach, we compared the performance of the molecular generators Molpher[2] and DrugEx[3],[4]. DrugEx surpassed Molpher by generating a larger number of active scaffolds and a more diverse virtual library. Proposed metrics serve a dual purpose: they enable the comparison of different molecular generators and facilitate the optimization of their parameters to improve the quality of the generated virtual libraries.

Bibliography :

[1] N. Brown, M. Fiscato, M. H. S. Segler, and A. C. Vaucher, “GuacaMol: Benchmarking Models for de Novo Molecular Design,” *J. Chem. Inf. Model.*, vol. 59, no. 3, pp. 1096–1108, Mar. 2019, doi: 10.1021/acs.jcim.8b00839.
[2] D. Hoksza, P. Škoda, M. Voršilák, and D. Svozil, “Molpher: a software framework for systematic chemical space exploration,” *J. Cheminformatics*, vol. 6, no. 1, p. 7, Mar. 2014, doi: 10.1186/1758-2946-6-7.
[3] X. Liu, K. Ye, H. W. T. van Vlijmen, M. T. M. Emmerich, A. P. IJzerman, and G. J. P. van Westen, “DrugEx v2: de novo design of drug molecules by Pareto-based multi-objective reinforcement learning in polypharmacology,” *J. Cheminformatics*, vol. 13, no. 1, p. 85, Nov. 2021, doi: 10.1186/s13321-021-00561-9.
[4] X. Liu, K. Ye, H. W. T. van Vlijmen, A. P. IJzerman, and G. J. P. van Westen, “DrugEx v3: scaffold-constrained drug design with graph transformer-based reinforcement learning,” *J. Cheminformatics*, vol. 15, no. 1, p. 24, Feb. 2023, doi: 10.1186/s13321-023-00694-z.