De Novo Molecular Design with Machine Intelligence

Gisbert SCHNEIDER

ETH Zurich, Department of Chemistry and Applied Biosciences, Zurich, Switzerland; ETH Singapore SEC Ltd, Singapore.

Molecular design may be regarded as a pattern recognition process. Chemists are skilled in visual chemical structure recognition and their association with (retro)synthesis routes and molecular properties. In this context, various “artificial intelligence” (AI) methods have emerged as potentially enabling technology for drug discovery and automation, because these systems aim to mimic the chemist’s pattern recognition process and take it to the next level by considering the available domain–specific data and associations during model development. Part of the appeal of applying AI methods in drug design lies in the potential to develop data-driven, implicit model building processes to navigate vast datasets and to prioritize alternatives. This concept represents at least a partial transfer of decision power to a machine intelligence, and could be viewed as synergistic with human intelligence; that is, a domain-specific implicit AI that would augment the capabilities of chemists in molecular design and selection. More ambitiously, the ultimate challenge for drug design with AI is to autonomously generate new chemical entities with the desired properties from scratch (de novo), without the need for the often prohibitively costly experimental compound screening.

We will review the principles of AI methods for de novo drug design, emphasizing ligand-based approaches that have proven useful and reliable in “little-data” scenarios. Selected prospective case studies will be presented, ranging from targeted molecular design to fully automated design-make-test-analyze cycles. We provide a critical assessment of the possibilities and limitations of the individual approaches and dare forecasting the future of drug design with machine intelligence.

References:

Grisoni, F., Huisman, B., Button, A., Moret, M., Atz, K., Merk, D., Schneider, G. (2021) Combining generative artificial intelligence and on-chip synthesis for de novo drug design. Science Advances 7, eabg3338.

Friedrich, L., Cingolani, G., Ko, Y.-H., Iaselli, M., Miciaccia, M., Perrone, M. G., Neukirch, K., Bobinger, V., Merk, D., Hofstetter, R. K., Werz, O., Koeberle, A., Scilimati, A., Schneider, G. (2021) Learning from nature: From a marine natural product to synthetic cyclooxygenase-1 inhibitors by automated de novo design. Advanced Science 8, 2100832.

Schneider, P., Walters, W. P., Plowright, A. T., Sieroka, N., Listgarten, J., Goodnow Jr., R. A., Fisher, J., Jansen, J. M., Duca, J. S., Rush, T. S., Zentgraf, M., Hill, J. E., Krutoholow, E., Kohler, M., Blaney, J., Funatsu, K., Luebkemann, C., Schneider, G. (2020) Rethinking drug design in the artificial intelligence era. Nature Reviews Drug Discovery 19, 353–364.

Schneider, G. (2018) Automating drug discovery. Nature Reviews Drug Discovery 17, 97–113.