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Data-free Inverse Molecular Design Using Reinforcement Learning and Quantum Chemistry

The inverse design of molecules with target properties is a long-standing challenge in chemistry [1]. This fundamental paradigm shift in computational chemistry has the potential to accelerate the discovery of new functional compounds such as catalysts and drugs, moving beyond traditional rational design strategies [1]. Yet, de novo generation of molecules is challenged by the complexity of structure-property relationships and the lack of a unifying theory for inverse design. In the recent years, generative machine learning methods have emerged as powerful tools for this task, but current implementations are often limited by the need for large and high-quality datasets used for training [1,2]. In this contribution, a novel, data-free method for *de novo* molecular generation is presented. The academic-free software we developed, PROTEUS, is based on a deep reinforcement learning algorithm that generates candidate molecules, whose properties are computed on-the-fly with quantum chemistry software [3]. Thanks to the direct quantum mechanical feedback, the algorithm rapidly learns how to optimize the generation of promising candidates, effectively converging on (sub)optimal solutions. We demonstrate the capabilities of PROTEUS in the design of styrene derivatives with target isomerization energies. Despite the combinatorial complexity of the task – spanning over 2 million solutions – PROTEUS quickly finds the optimal candidates without any pre-training, outperforming a reference baseline. Thanks to its general and data-free scheme, PROTEUS opens new avenues for transferable, systematic, and broadly accessible molecular design.

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