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High-throughput free energies and water maps for drug discovery through molecular density functional theory

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The hydration or binding free energy of a drug-like molecule is a key data for early stage drug discovery. Hundreds of thousands of evaluations are necessary, which rules out the exhaustive use of full atomistic simulations and free energy methods. Instead, the current docking and screening processes are today relying on numerically e cient scoring functions that lose much of the atomic scale information and hence remain error-prone. In this article, we show how our probabilistic description of molecular liquids as implemented in the molecular density functional theory predicts hydration free energies of a state-of-art benchmark of small drug-like molecules within 0.4 kcal/mol of atomistic simulations, along with water maps, for a computation time reduced by 5 orders of magnitude.

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