Advancing Drug Design with Quantum Mechanical Scoring: Bridging Accuracy and Efficiency

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Computational approaches play a central role in modern drug discovery, aiding in the identification and optimization of lead compounds. However, the accuracy of structure-based drug design (SBDD) methods remains a critical challenge, particularly in predicting binding affinities and ligand poses.[1] In this talk, I will present recent advancements in semiempirical quantum-mechanical (SQM) scoring functions, focusing on our physics-based scoring function SQM2.20 and its potential to rival expensive free energy methods while significantly reducing computational costs.[2]

We systematically evaluated SQM2.20 against both standard scoring functions and molecular dynamics-based free energy calculations across diverse protein-ligand datasets.[2,3] On the PL-REX benchmark, which consists of high-quality co-crystal structures, SQM2.20 faithfully reproduced experimental affinities and showed consistent accuracy comparable to Density Functional Theory (DFT), the state-of-the-art quantum-mechanical method applicable to systems of about a thousand atoms.[2] On the Wang dataset, which consists of docking poses, SQM2.20 rivaled or even outperformed MD-based approaches, especially when high-quality input structures were available.[3] We also systematically investigated the sensitivity of SQM2.20 to docking accuracy, addressing the need for efficient pose generation strategies.

The exceptional and consistent performance of SQM2.20 in affinity predictions across diverse protein-ligand systems positions it as an efficient and reliable approach for hit identification and lead optimization in computer-aided drug design. We believe that our scoring function represents a long-awaited breakthrough in this field, with implications extending beyond theoretical and computational chemistry.

[1] Christian Kramer, John Chodera, Kelly L. Damm-Ganamet, Michael K. Gilson, Judith Günther, Uta Lessel, Richard A. Lewis, David Mobley, Eva Nittinger, Adam Pecina, Matthieu Schapira, and W. Patrick Walters: The Need for Continuing Blinded Pose- and Activity Prediction Benchmarks. *Journal of Chemical Information and Modeling* **2025**, Article ASAP (doi: 10.1021/acs.jcim.4c02296)

[2] Adam Pecina, Jindřich Fanfrlík, Martin Lepšík, and Jan Řezáč*":* SQM2.20: Semiempirical quantum-mechanical scoring function yields DFT-quality protein–ligand binding affinity predictions in minutes. *Nature Communications* **2024**, *15*, 1127. (doi: 10.1038/s41467-024-45431-8)

[3] Mehran Jalaie, Jindřich Fanfrlík, Adam Pecina, Martin Lepšík, and Jan Řezáč: Comparative Analysis of Quantum-Mechanical and Standard Single-Structure Protein-Ligand Scoring Functions with MD-Based Free Energy Calculations; ChemRxiv **2025**.