

Quantum-Mechanics Based Multiscale Modeling and Rational Design of Insulin Analogs with Improved Binding Affinities

Accurate modeling of electronic effects in protein–protein interactions (PPIs) remains a significant challenge in computational biophysics. Classical force fields fail to describe polarization and charge transfer, while full quantum mechanical (QM) methods are often computationally prohibitive. To address this, we developed a multiscale protocol that integrates molecular dynamics, system fragmentation, semiempirical quantum mechanics (PM6-D3H4S/COSMO2), and virtual glycine scanning (VGS) to dissect residue-level contributions to protein interface energetics [1]. Using the insulin–insulin receptor complex as a model, we applied this approach to evaluate the impact of point mutations at seven key positions within the receptor-binding region. The calculated changes in binding free energy ($\Delta\Delta G$) show strong correlation with experimental binding data and clearly outperform classical Molecular Mechanics/Generalized Born (MM/GB) approaches. Notably, our scoring protocol is conceptually linked to the recently published SQM2.20 scoring function for protein–ligand systems, which yields DFT-quality predictions with practical speed [2]. Building on these insights, we designed a series of novel insulin analogs predicted to exhibit enhanced receptor binding. Several promising candidates—such as A19Phe, B16Arg, and B26Lys— are being synthesized and are currently undergoing experimental evaluation. These analogs were selected based on favorable QM-predicted interaction profiles, taking into account both individual residue contributions and the overall binding energetics. Preliminary experimental results confirm improved receptor binding for several variants, supporting the predictive power of our quantum-informed design strategy.

[1] Yurenko, Y et al. ChemRxiv 2024, DOI:10.26434/chemrxiv-2024-4jjrc

[2] Pecina, AY.; Fanfrlík, J; Lepšík, M.; Řezáč, J. Nat. Commun. 2024, 15, 1127

Primary author(s) : YURENKO, Yevgen (IOCB Prague)

Presenter(s) : YURENKO, Yevgen (IOCB Prague)