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Bridging artificial intelligence and physics-based docking for better modelling of biomolecular complexes

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Proteins and other biomolecules, such as DNA and RNA, are the minimal functional entities that realize life. Understanding how they execute their functions through their 3D structures and interaction dynamics provides a fundamental view of what defines life. This knowledge also allows us to exploit or modify these elegant molecules for a wide variety of purposes, such as gene therapy, drug design, immunotherapy, novel enzymes and others.

Since it is still challenging to experimentally study protein interactions at high-resolution, we combine the computational power of data-driven machine learning with physics-based molecular docking to better model 3D protein complexes (static) and their binding affinity (thermodynamic). Specifically, we exploit deep learning and graph theory to tackle the major challenge in docking, namely scoring, the identification of correct conformations from a large pool of docked conformations, which still suffers from a low success rate. Another challenge in the field of biomolecular interaction is to quantitatively characterize the impact of a mutation on the binding affinity of a complex. For this purpose, we developed iSEE, a fast and reliable predictor for binding affinity changes upon single point mutation. iSEE is trained and cross-validated over a diverse dataset consisting of 1102 mutations in 57 protein-protein complexes, and it outperforms state-of-the-art methods on two independent test datasets. Reliably predicting binding affinity changes upon mutations has wide applications in, for example, the study of the relation between coding variants and phenotype, design of antigen-binding CDR loops of antibodies, and engineering binding specificity.

Our projects integrate statistical models learned from the huge wealth of heterogeneous experimental data with fundamental physics rules governing protein interactions at atomic level. By combining machine learning with physics-based modelling we aim to markedly enhance our capability to reliably model biomolecular complexes. This will help molecular biologists formulate testable hypotheses to answer important questions about cells' molecular machinery and aid the development of new therapeutics.

Primary author: Dr XUE, Li (Utrecht University)

Co-author: Dr BONVIN, Alexandre M.J.J. (Utrecht University)

Presenter: Dr XUE, Li (Utrecht University)

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