Predicting protein-protein and protein-membrane interactions using molecular simulations and AI

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Abnormal protein-membrane attachment is involved in deregulated cellular pathways and in disease. Therefore, the possibility to modulate protein-membrane interactions represents a new promising therapeutic strategy for membrane proteins that have been considered so far undruggable. In this talk, we explore the free energy landscape of membrane protein dimerization using parallel tempering metadynamics simulations in the well-tempered ensemble and coarse-grained force fields and reproduce the structure and energetics of the dimerization process of membrane proteins and proteins in an aqueous solution in reasonable accuracy and throughput.[1] We propose that the use of enhanced sampling simulations with a refined coarse-grained force field and appropriately defined collective variables is a robust approach for studying the protein dimerization process, although one should be cautious of the energy minima ranking. Moreover, we study membrane-associated oncogenes, including the PI3Kα mutants of PI3Kα,[2] and KRAS-4B[3] using metadynamics to understand the basis of protein overactivation.
Finally, we describe an ensemble machine learning methodology to predict protein-membrane interfaces of peripheral membrane proteins.[5] and present a drug design pipeline for drugging protein-membrane interfaces using the DREAMM (Drugging pRotein mEmbrAne Machine learning Method) web-server https://dreamm.ni4os.eu.[6] We further extend this study to apply Artificial Intelligence techniques in the context of Natural Language Processing (NLP) and show that the accuracy and prediction time for protein-membrane interface analysis can be significantly improved compared to existing methods.[7]

References

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