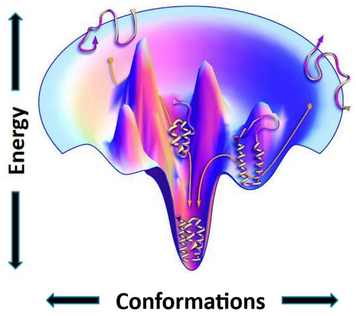
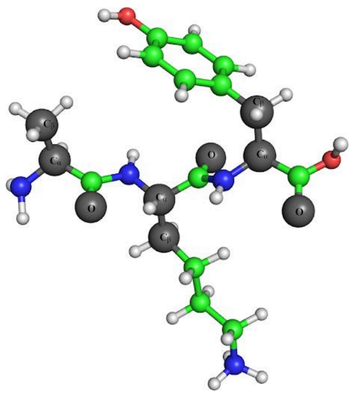
AWSEM Model



Associative Memory, Water Mediated, Structure and Energy Model was derived based on Energy Landscape Theory[1].

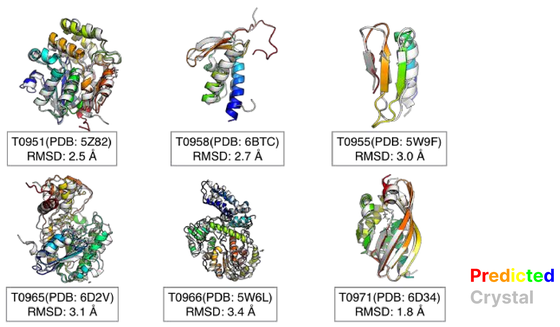
- Beads placed at the positions of Cα, Cβ, O describe each amino acid
- Energy function that balances physical terms and bioinformatics provide interactions between beads
- Simple yet effective representations allows for description of complex behavior of polypeptide chain



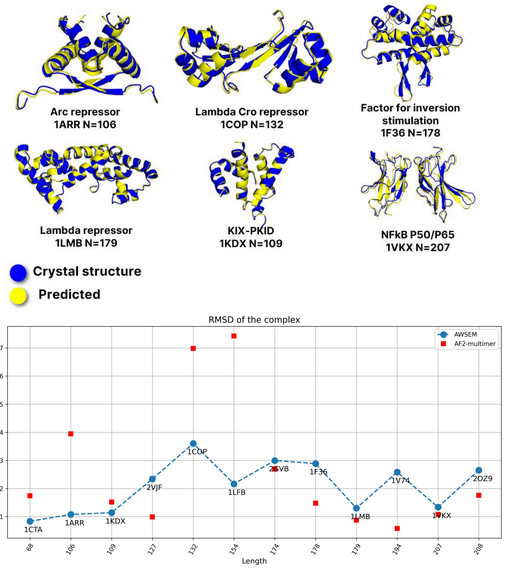
Model performance on protein folding and binding

The model can predict structures of proteins with complex folds

Performance of in CASP13[2]



AWSEM demonstrated exceptional performance in predicting binding of homo- and hetero-dimers[3]



Implications of Protein Dynamics for Design of PROTACs and Molecular Glues

Aram Davtyan, Artur Hakobyan, Aleksandr Kaminskii, Garik Petrosyan, Jason Sunardi, Natalie Ma, Garegin Papoian, Macromolecular Modeling Group, Deep Origin

Having an accurate protein structure is a necessary condition for modern drug design and discovery because it provides a mechanistic picture of drug-target interactions and guides the path for the rational optimization of efficacy and therapeutic characteristics. However, in many cases, especially for newer modalities such as biologics and proximity inducers (i.e., PROTACs and molecular glues) which often extend beyond the single-protein paradigm, structural information is lacking and is hard to obtain using existing computational methods. In addition, static structural information is often not sufficient in those cases. Thus, modeling protein dynamics and the formation of multiprotein complexes is recognized as an important but extremely challenging next frontier for computational chemistry as a whole, and for drug design in particular. Here, we would like to present our most recent results in the development of computational methods for modeling protein dynamics and protein-protein interactions, as well as their applications to complex therapeutic problems such as the design of PROTACs and molecular glues. Our results demonstrate the usefulness of our approach for solving challenging problems in biology and therapeutic design.

Our Macromolecular modeling group

Developing tools for modeling proteins and nucleic acids for

- Studying protein dynamics and complex formation
- Modeling of protein interactions with DNA and RNA
- Examining mechanism of complex biological processes
- Applications such as prediction of protein stability, design of biologics and development of proximity-based therapeutics

Aims of this work

- Enable rational design of proximity-based therapeutics through integrated pipeline
- Expand effector and target space by alleviating limitations imposed by lack of experimental structural data
- Enhance predictability and efficacy of proximity-based therapies

Progress

- The effector/target docking and complex selection methods were validated against known experimental structures
- Implementation of ternary complex prediction and scoring is underway

We are interested in partnering for validation and applications of our methods

About Deep Origin

We help scientists solve disease and extend health-span by building tools that simplify R&D, simulate biology, and untangle the complexity of life. We provide our tools as software and work in partnership with others to design better therapeutics faster.

References

[1] Davtyan, Schafer, Zheng, Clementi, Wolynes, Papoian, J. Chem Phys B, 116, (2012), 1709–1715
[2] Jin, Chen, Chen, Bueno, Lu, Schaefer, Lin, Onuchic, Wolynes, J Chem Theory Comput, 16, (2020), 3977-3988
[3] Zheng, Schafer, Davtyan, Papoian, Wolynes, PNAS, 109, (2012), 19244-19249

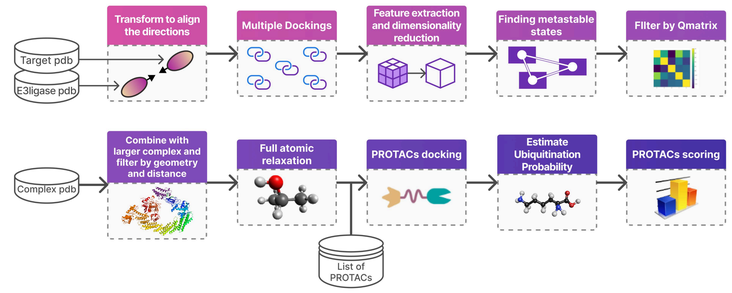
Applying AWSEM for design of PROTACs and molecular glues

Current challenges for computational methods:

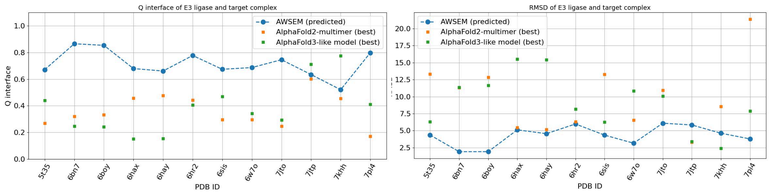
- Limited structural data for binary and ternary complexes
- Challenges in sampling non-native protein-protein interactions
- Lack of robust scoring and evaluation methods

DO PROTAC and molecular glue design pipeline

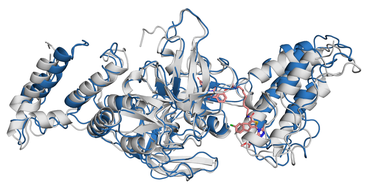
PROTAC scoring pipeline



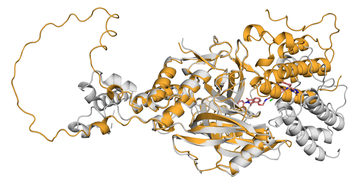
The DO PROTAC pipeline allows for sampling and selection of metastable E3 ligase/target complexes closely related to known structures



Examples



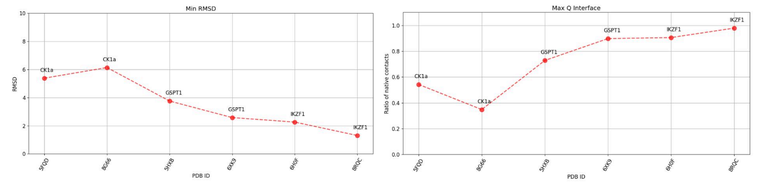
Deep Origin Results
6BN7 (CRBN/Brd4BD1/dBET23)



AF2-multimer Results
6BN7 (CRBN/Brd4BD1/dBET23)

- The missing E3 subunits and E2 ligase can be added to obtain E2-E3 ubiquitin ligase assembly bound to target
- The side-chain reconstruction and equilibration allows for PROTAC docking and estimation of ubiquitination probability and complex stability scores for given list of PROTACs
- Our method works well across different E3 ligase and target pairs

Preliminary molecular glue mediated complexe prediction results



Interested in Collaborating?

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