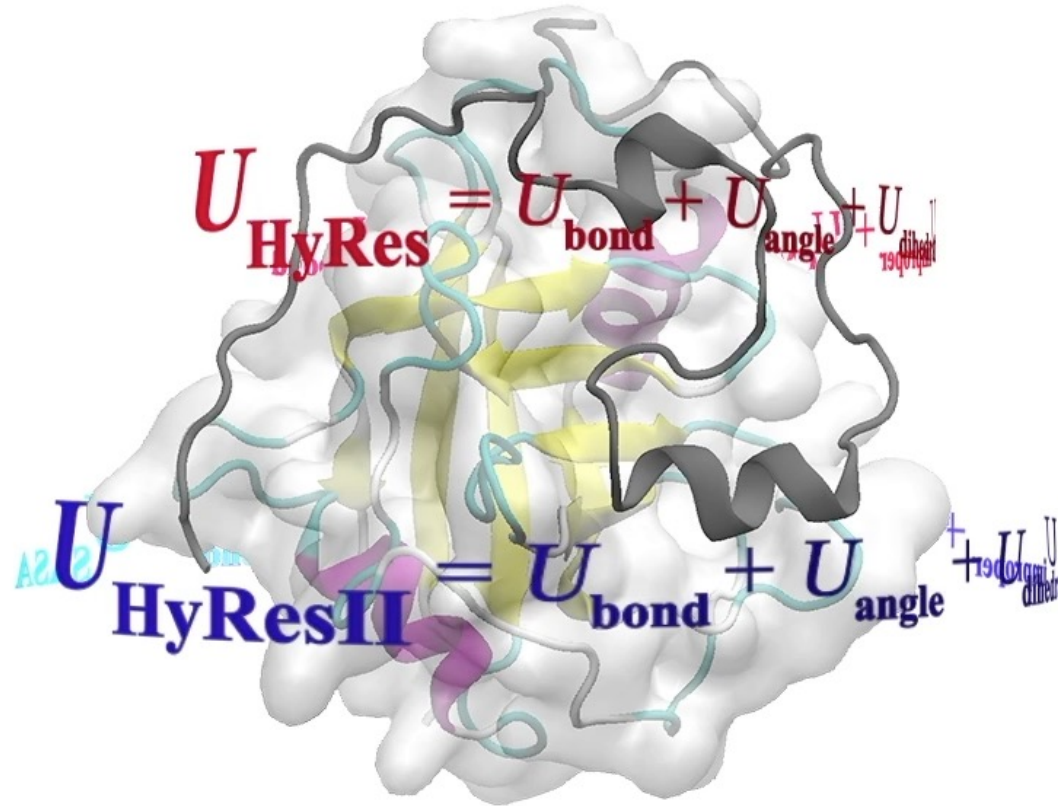
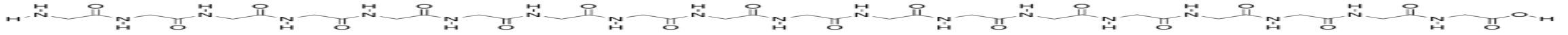


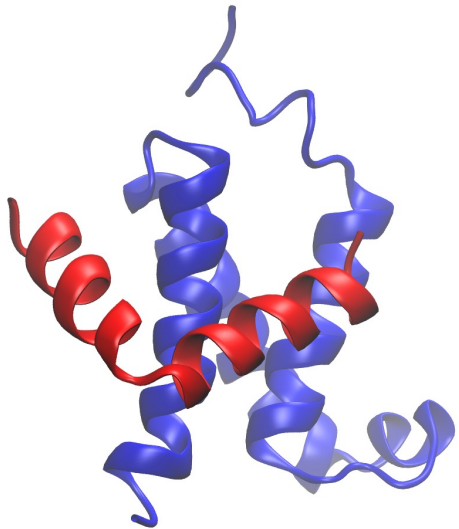
Towards accurate coarse-grained simulations of disordered proteins and dynamic protein interactions



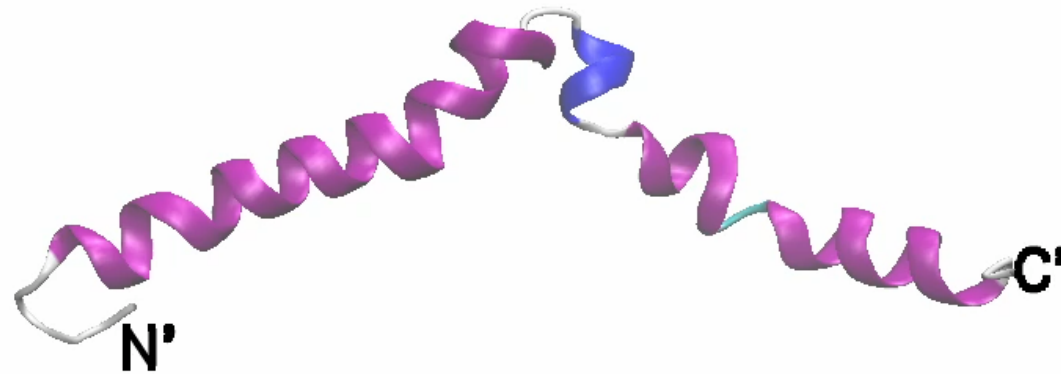
Orderly Chaos of Intrinsically Disordered Proteins



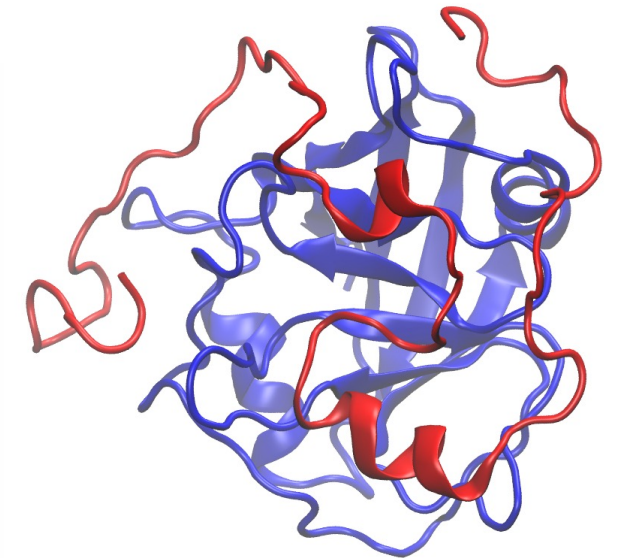
- Rely on structural disorder for function
- Crucial in cellular regulation and signaling
- Can fold or remain dynamic upon binding



KID/CREB Complex



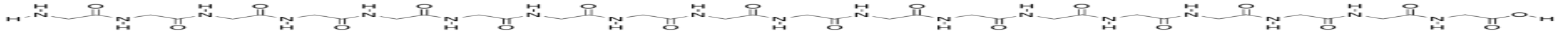
N-terminal Domain of p53 (p53-TAD)



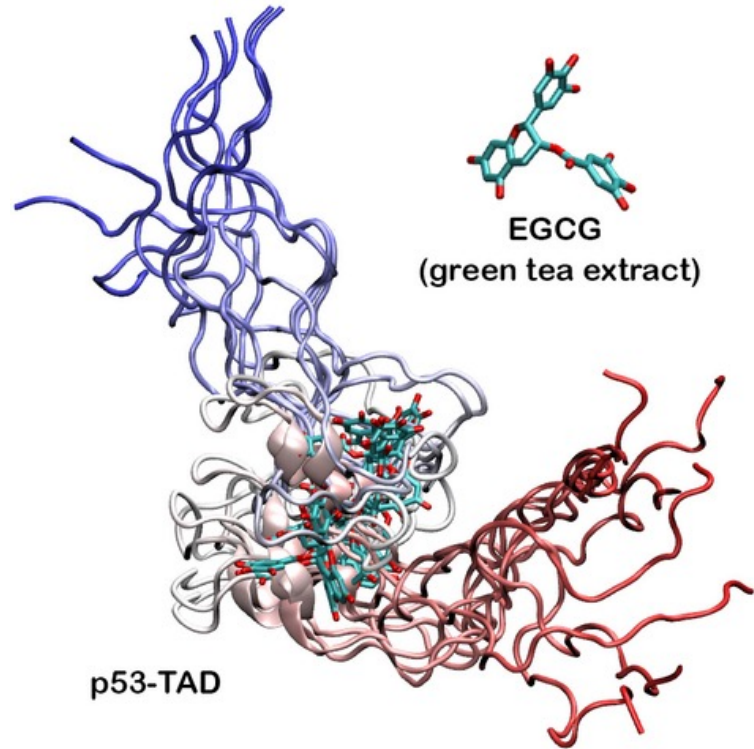
p53-TAD/CypD Complex

- Not amenable to traditional ensemble-based experiments
- Structural prediction tools, including [AlphaFold](#), are not applicable to disordered proteins

Molecular Dynamic Simulations: The 'Net' to Capture IDPs

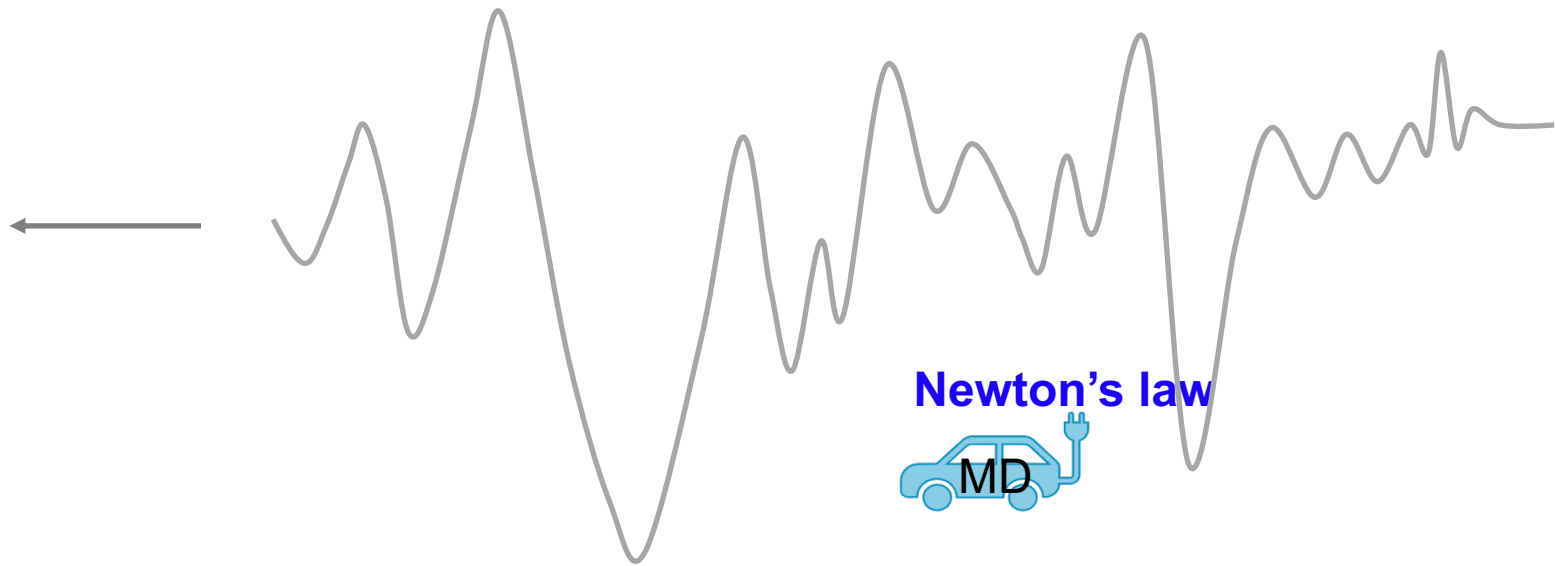


- Ensembles for p53-TAD/EGCG complex
- MD simulation for protein dynamics.



Atomistic Simulations

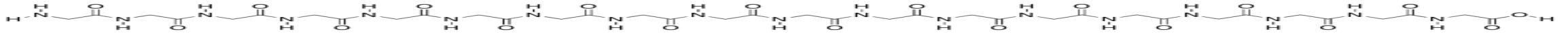
Protein Energy Landscape



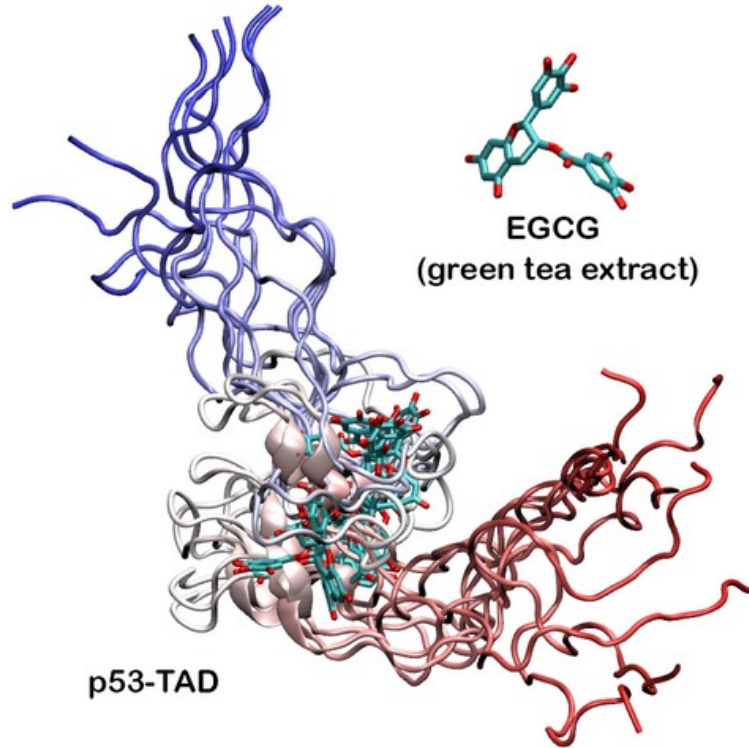
- MD provides the heterogeneous structural ensemble to analyze IDP functions.

Nature Communications (2020)
<https://www.umass.edu/news/article/2-million-nih-mira-grant-will-support-trailblazing-research-umass-amherst-lab>

Computational Cost of Atomistic MD Can Be Prohibitive



p53-TAD/EGCG

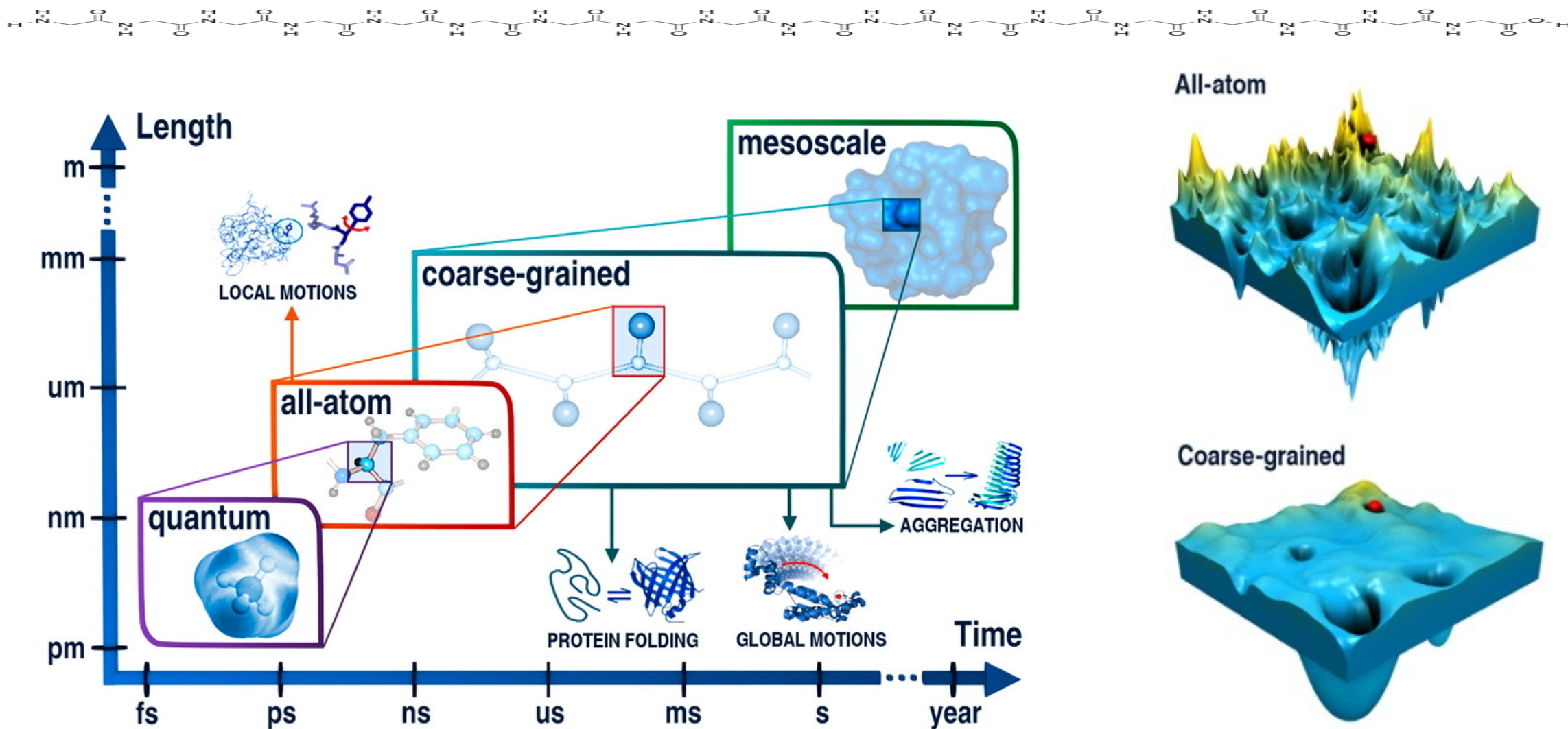


~1500 atoms

Nature Communications (2020)

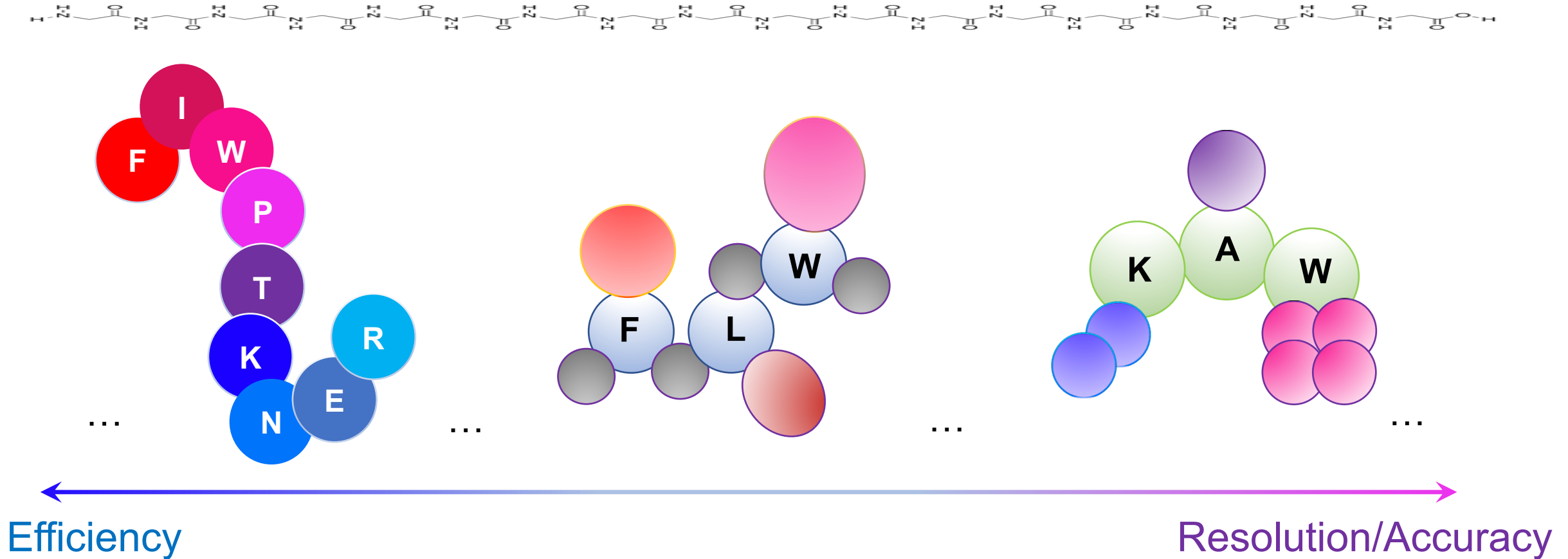
<https://www.umass.edu/news/article/2-million-nih-mira-grant-will-support-trailblazing-research-umass-amherst-lab>

Coarse-Grained Modeling of Protein Dynamics



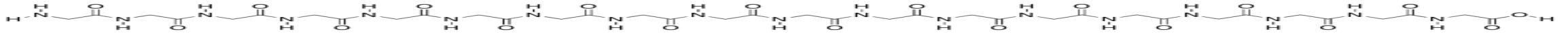
- CG models can more efficiently explore the energy landscape.

CG Models: Efficiency vs. Accuracy



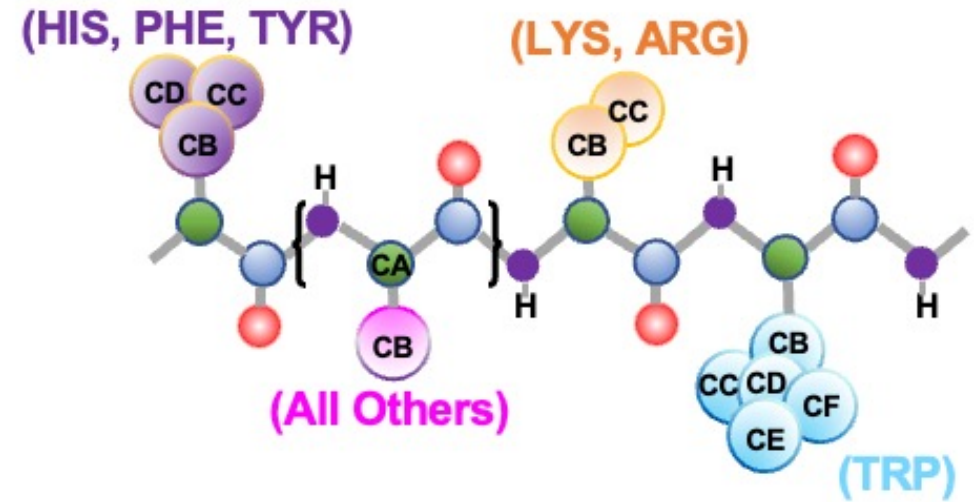
- Balance between coarse-graining and accuracy
- CG models designed for folded proteins are not appropriate for disordered proteins
- Key IDP properties: residual local structures and transient long-range interactions

HyRes: A CG Model for IDP Simulations



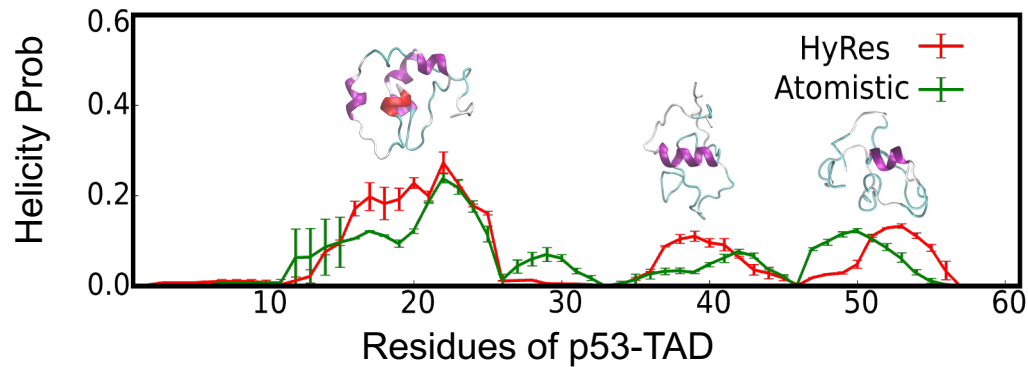
Hybrid-Resolution (HyRes) Model:

- Atomistic representation for backbone atoms.
- Coarse-grained sidechains up to five beads resolution.
- Physics-based energy terms.



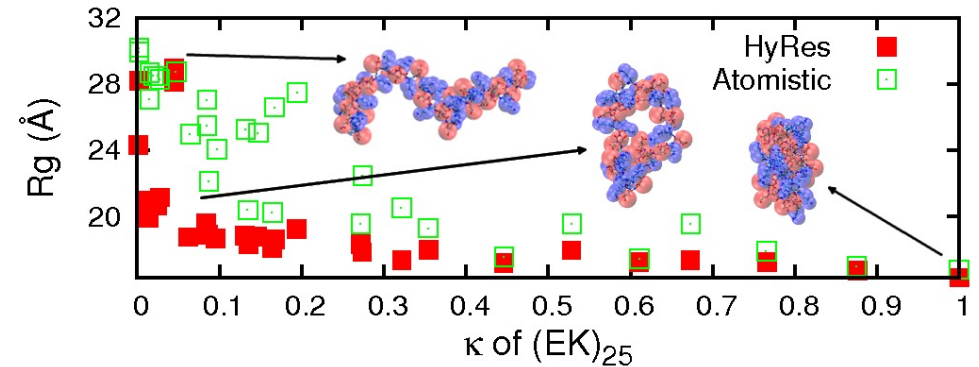
$$U_{\text{HyRes}} = U_{\text{bond}} + U_{\text{angle}} + U_{\text{dihedral}} + U_{\text{improper}} + U_{\text{CMAP}} + U_{\text{LJ}} + U_{\text{Hbond}} + U_{\text{elec}}$$

➤ Semi-quantitatively 2nd structural profile descriptions.



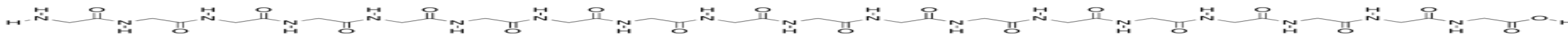
J. Mol. Biol (2022)

➤ Qualitatively long-range interaction characterizations.



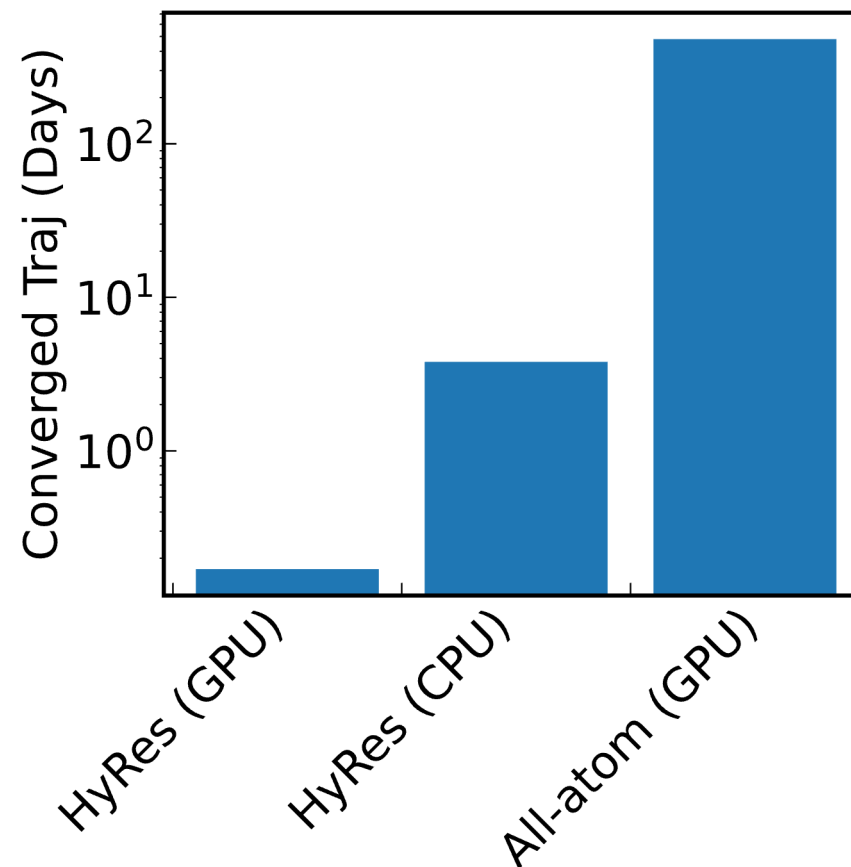
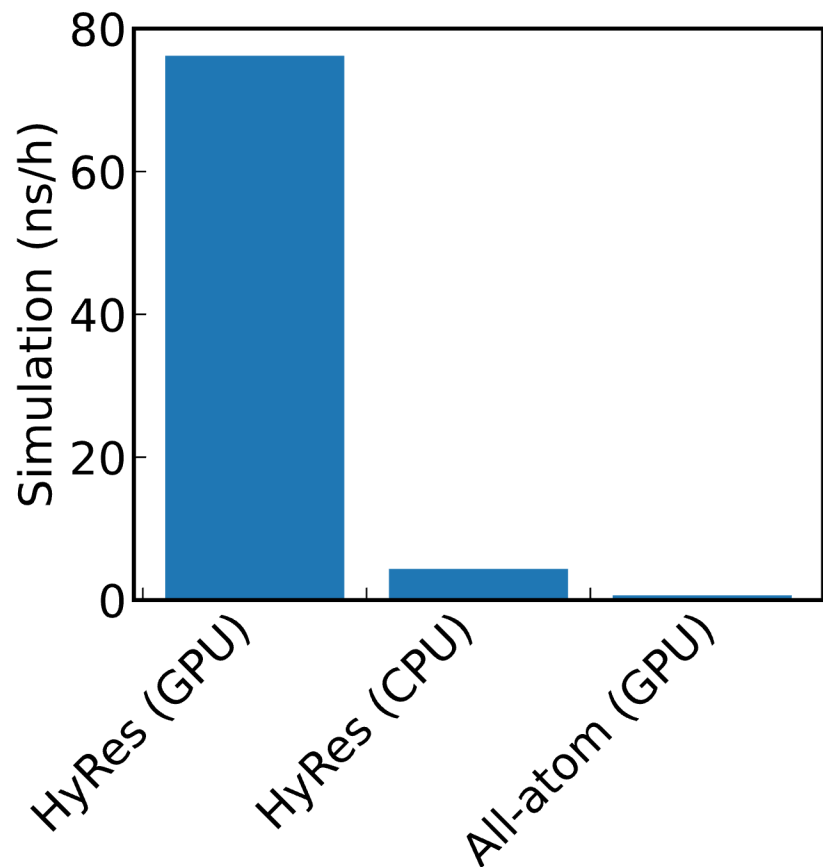
Phys. Chem. Chem. Phys (2017)

HyRes is ~ 3,000 Faster Than Atomistic Models

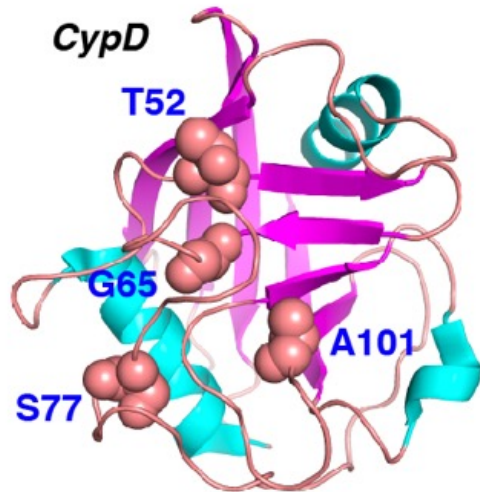
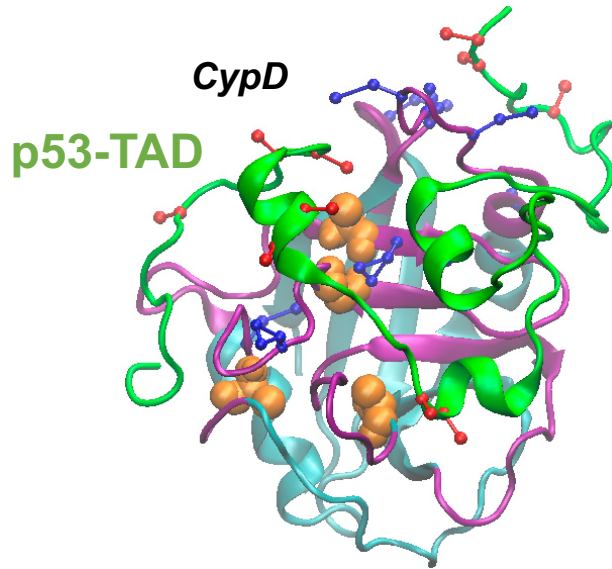
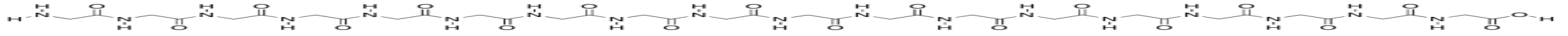


HyRes:

- Achieves ~ **100 times** faster than all-atom GPU in per nanosecond simulations.
- Achieves ~ **3000 times** faster in generating converged trajectories for analysis.

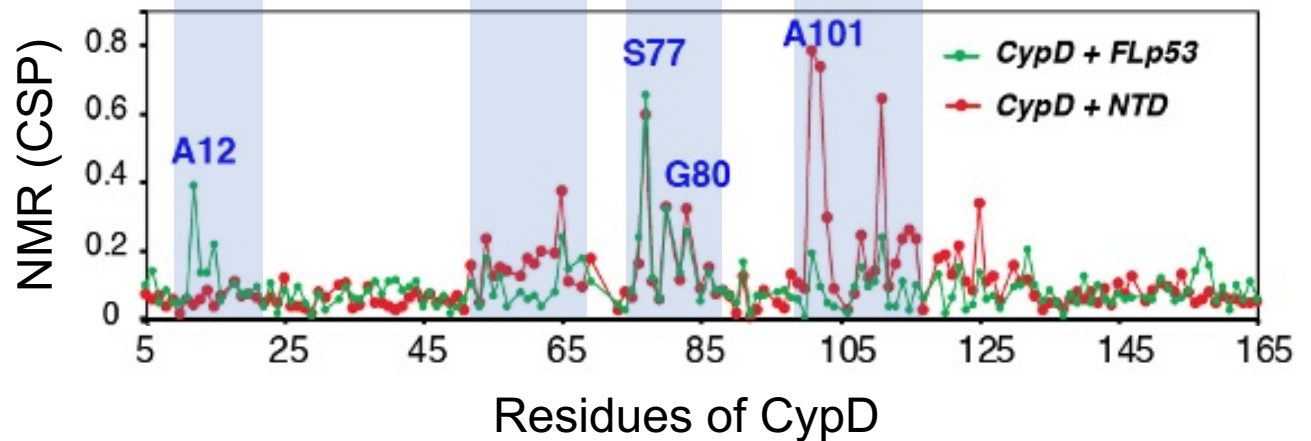
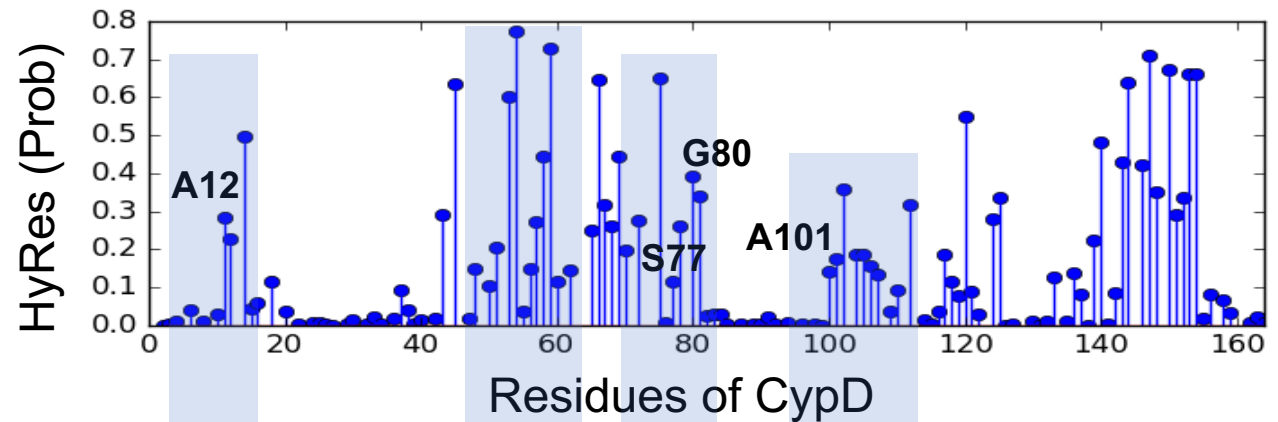


HyRes Can Capture Dynamic p53-TAD/CypD Interactions

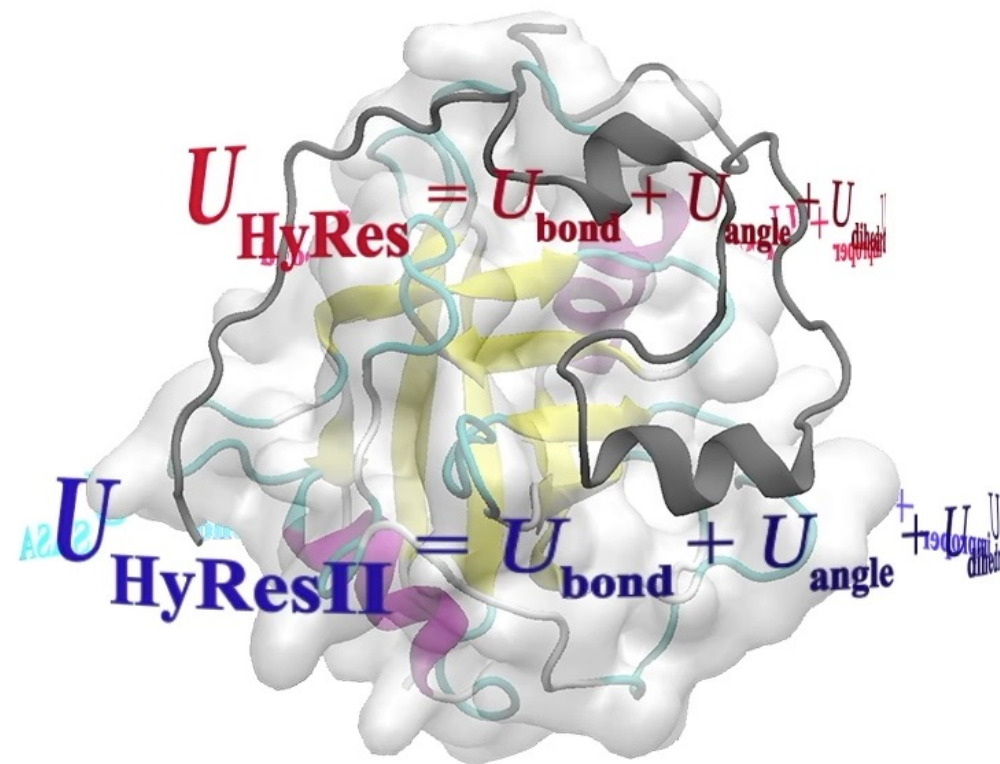
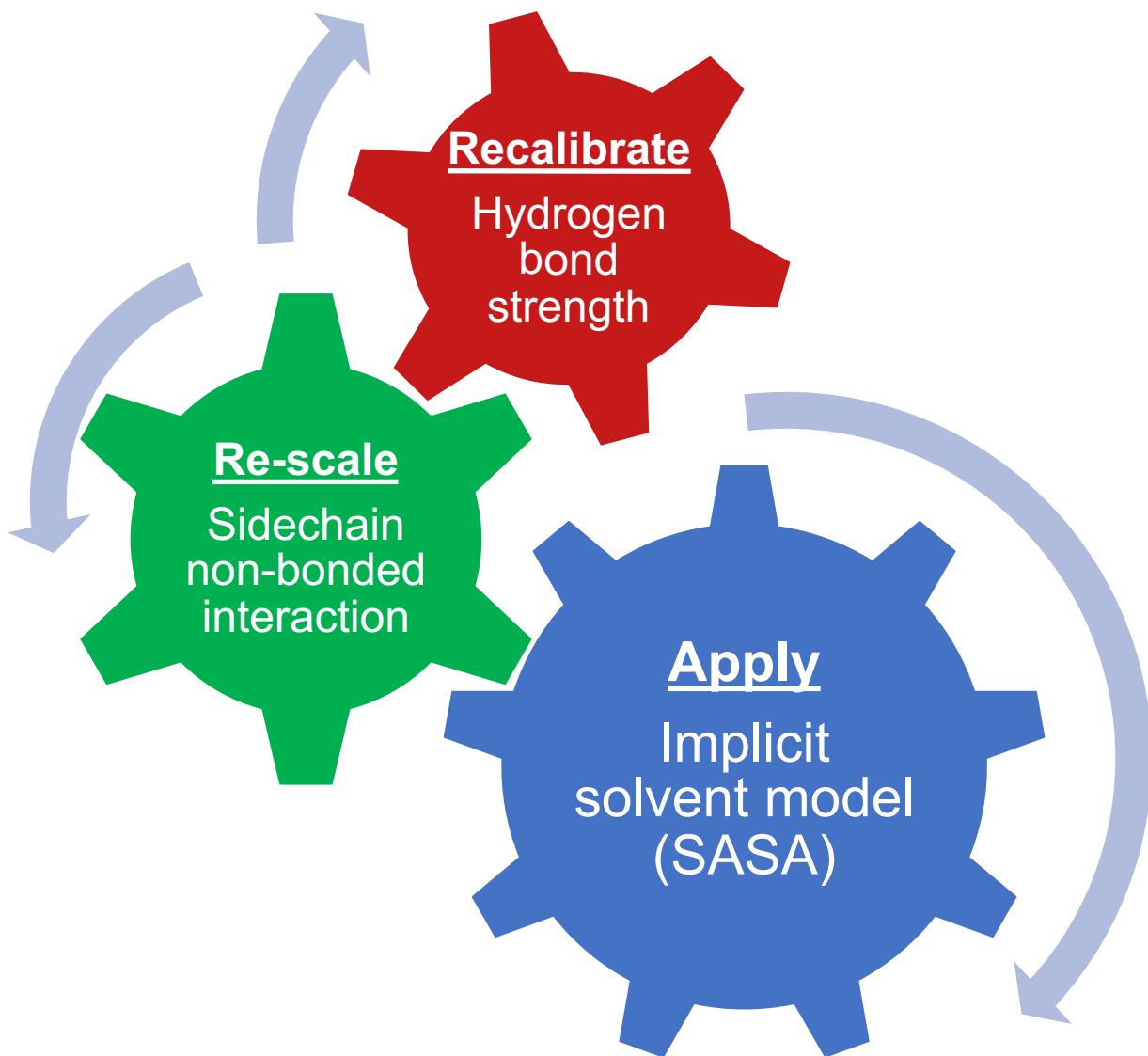
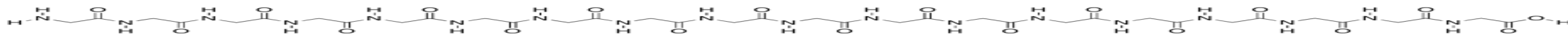


NMR-Derived Binding Hotspots

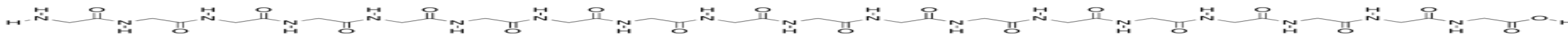
Hot binding spots on CypD



HyRes II: Design and Optimization



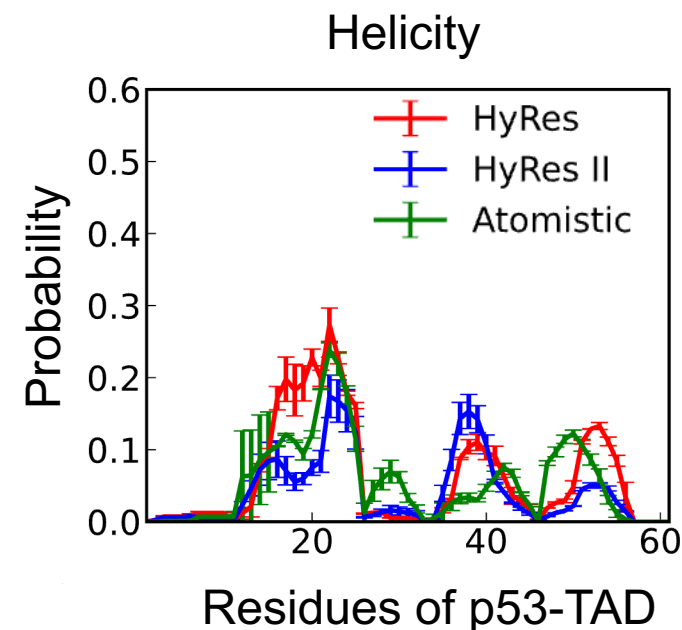
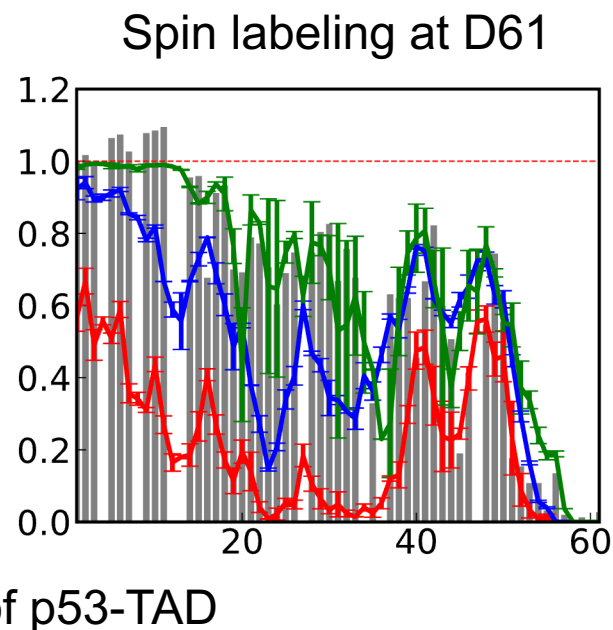
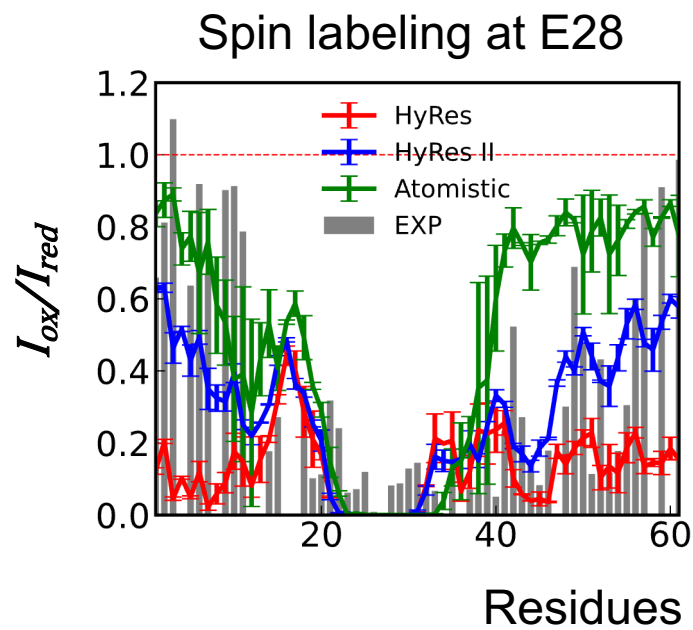
Disordered Ensembles of p53-TAD in HyRes II



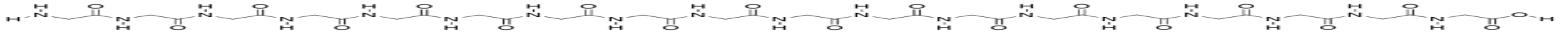
- HyRes II generated disordered ensembles are highly consistent with various experimental data from NMR, SAXS etc
- It quantitatively captures key local and global structural properties of IDPs

➤ Long-range transient contacts: PRE NMR

➤ 2nd Structures



HyRes II Simulation of Dynamic p53-TAD/DBD Interactions



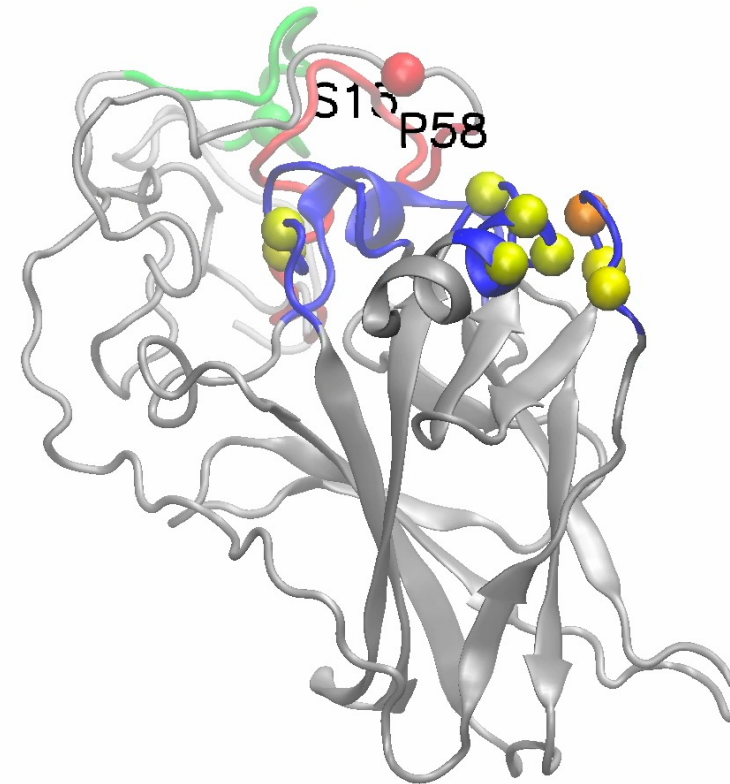
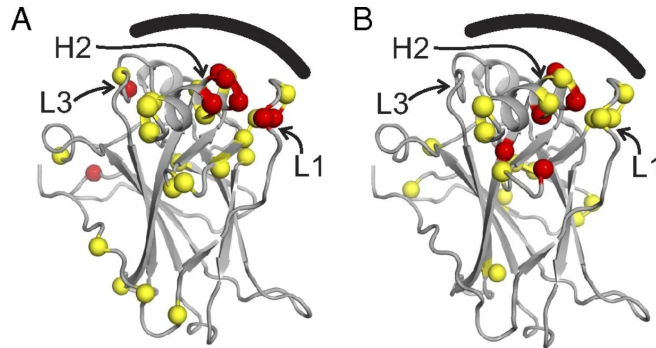
- TAD of p53 can regulate DBD signaling.

- HyRes II correctly characterized the transient interactions.

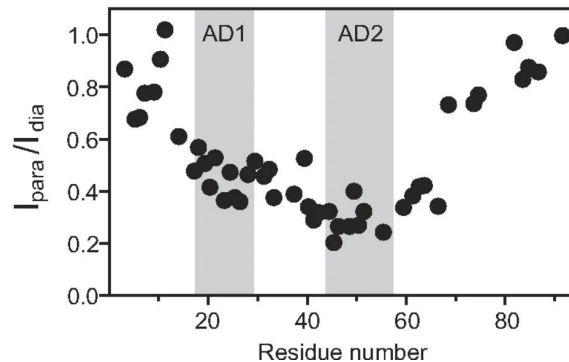


AD1 ———

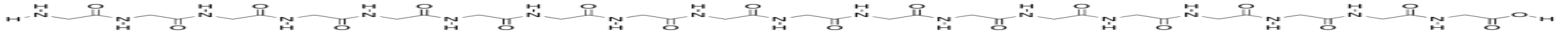
AD2 ———



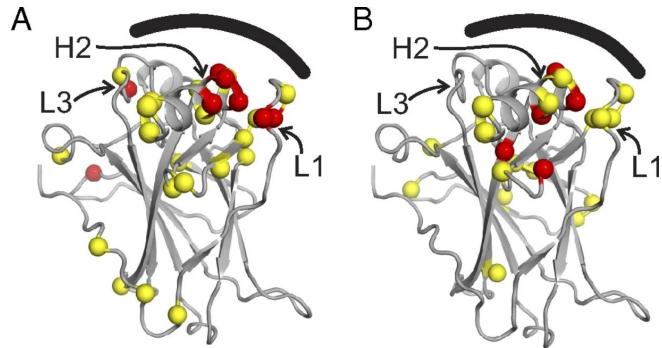
- Two subdomains on TAD: AD1 and AD2, can dynamically interact with DBD.



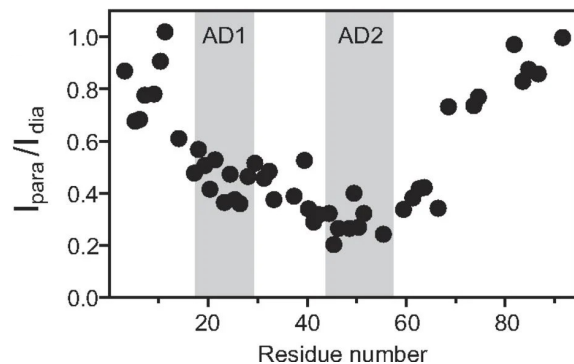
The Main Binding Subdomain: AD2



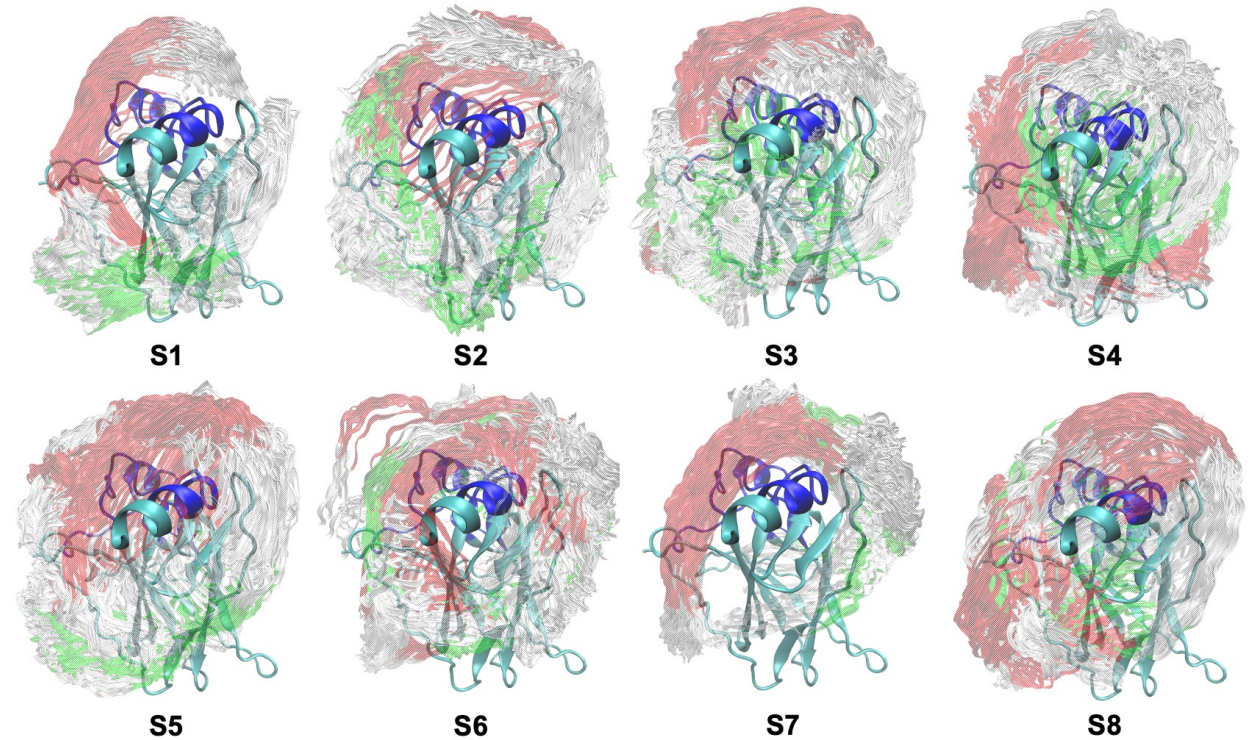
- TAD of p53 can regulate DBD signaling.
- HyRes II correctly characterized the transient interactions.



- Two subdomains on TAD: **AD1** and **AD2**, can dynamically interact with DBD.



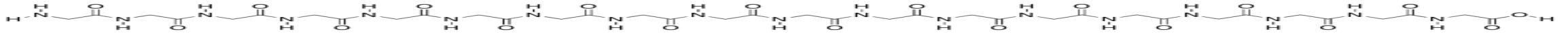
PNAS (2018)



S1~S4: TAD randomly bind to DBD at initial.

S5~S8: TAD is fully extended at initial.

The Main Binding Subdomain: AD2

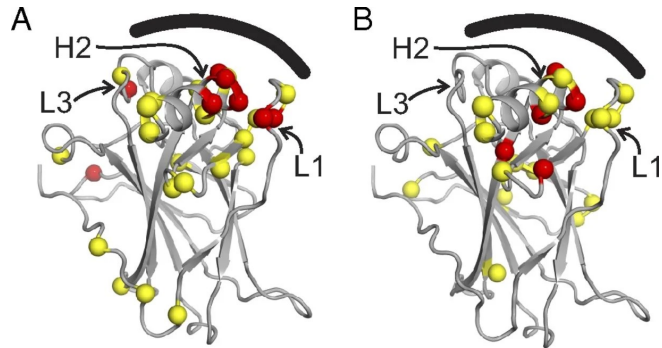


- TAD of p53 can regulate DBD signaling.
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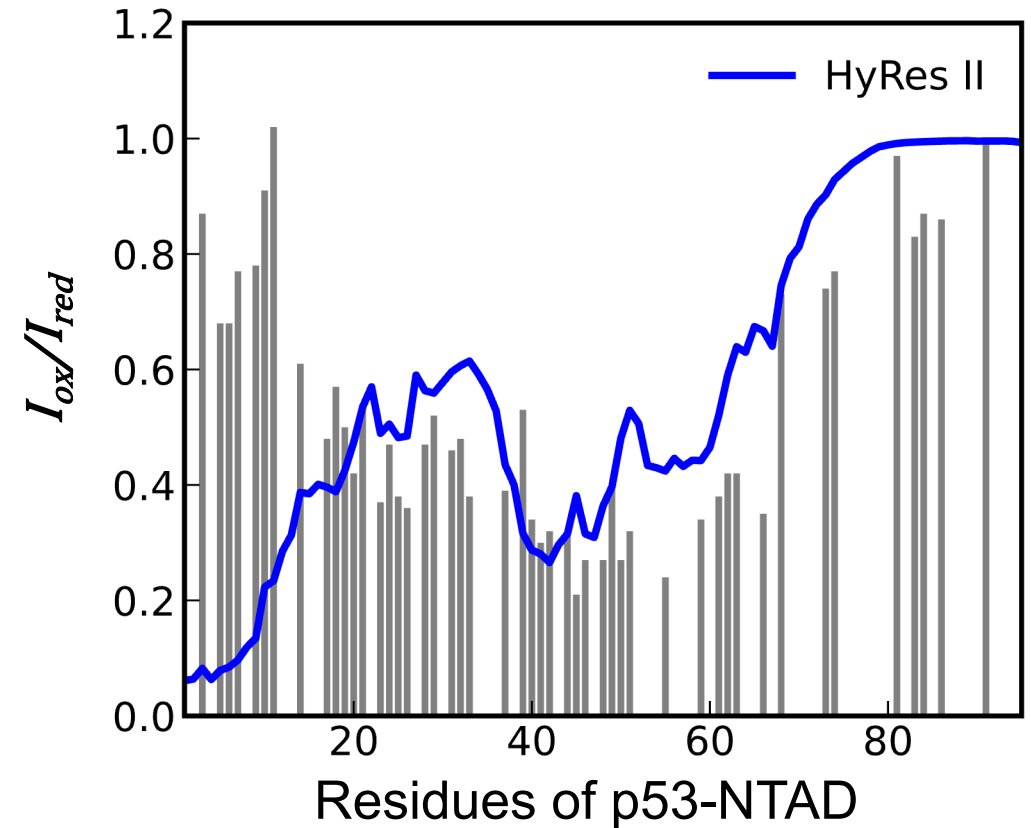
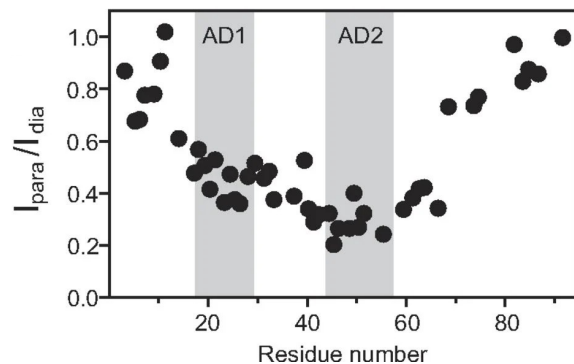


➤ TAD/DBD dynamics

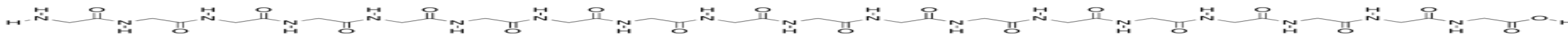
PRE, Spin labeling at S121



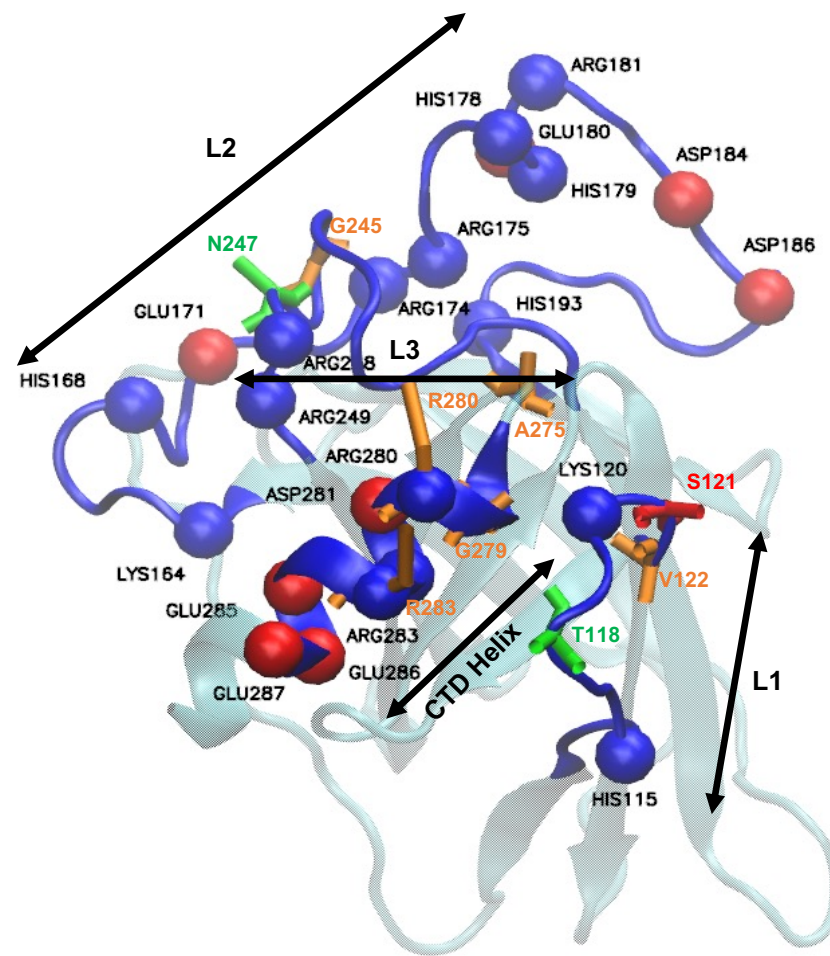
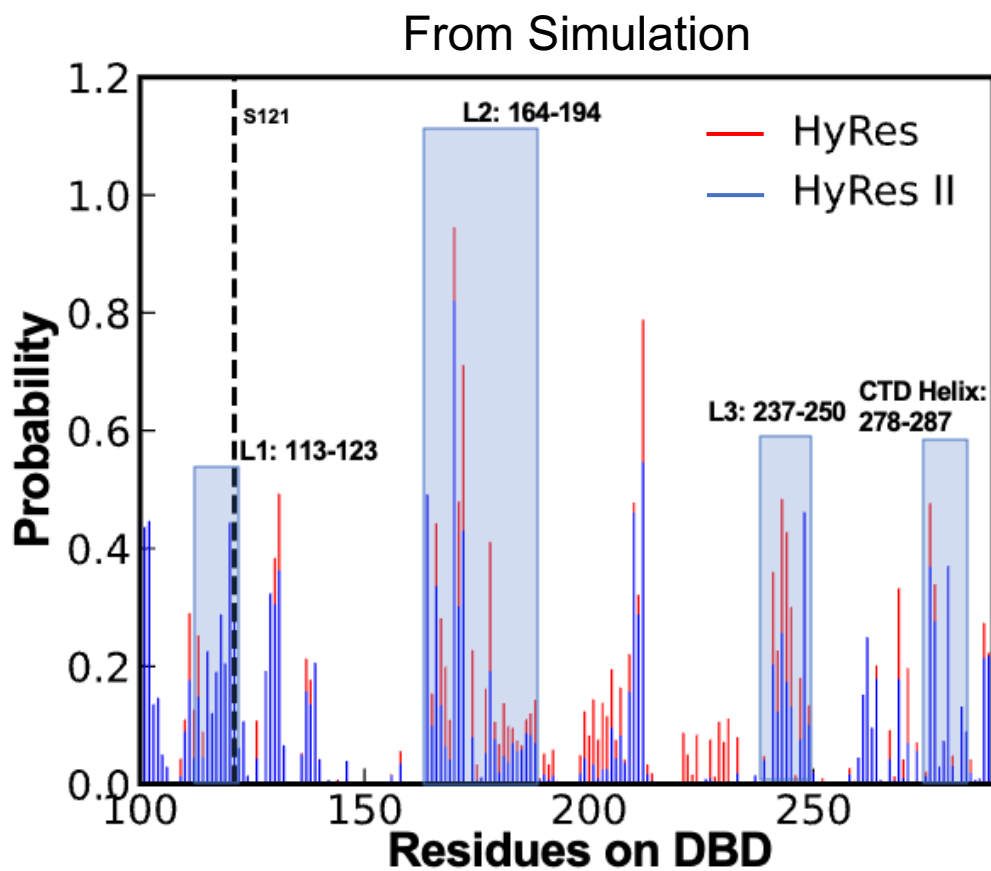
- Two subdomains on TAD: **AD1** and **AD2**, can dynamically interact with DBD.



TAD Binds to DNA-binding Surface on DBD

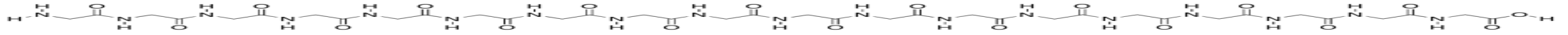


- Hot binding spots on DBD

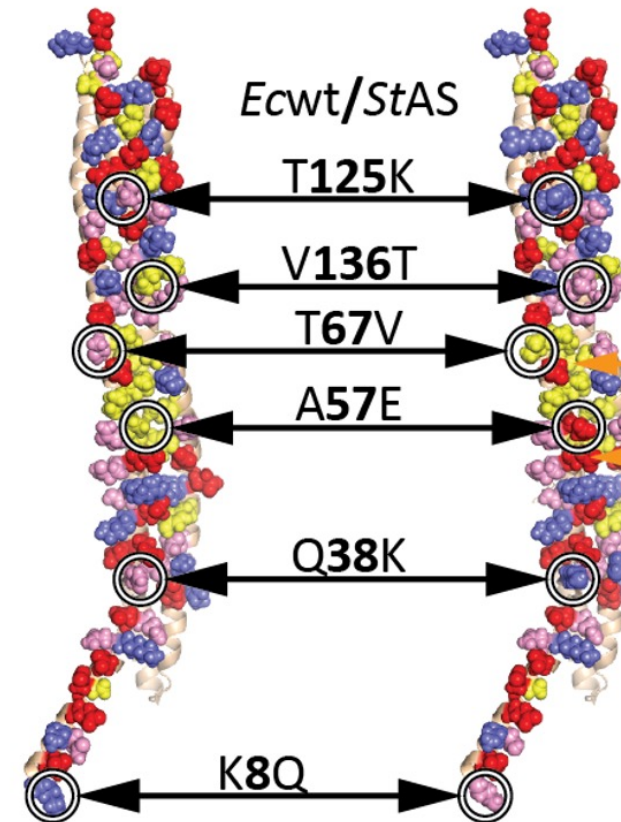
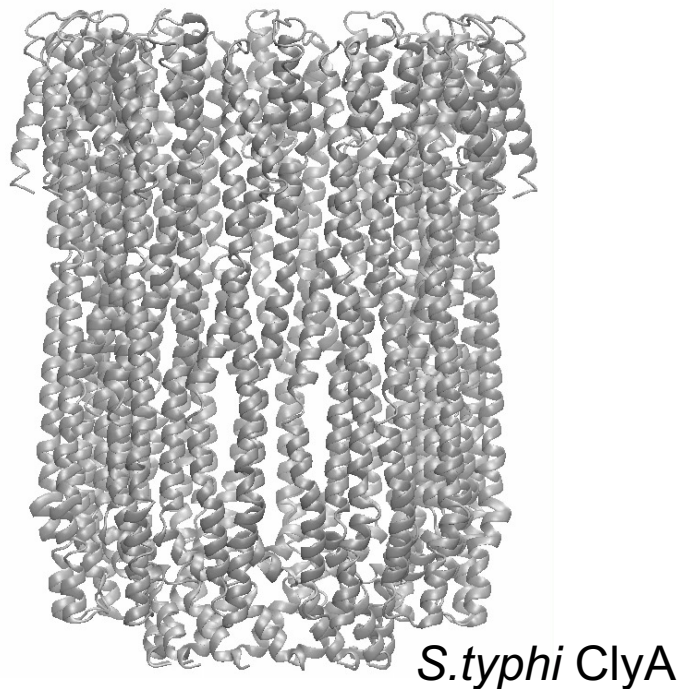
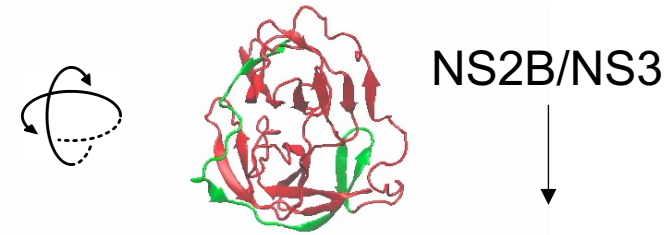


From Experiments

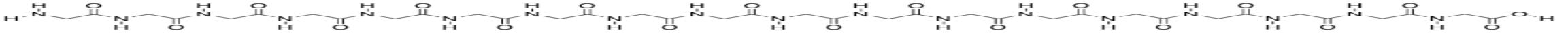
HyRes II for Studying Protein Nanopore Tweezers



- Exploring Proteases Dynamics in ClyA Nanopore.
- Engineering ClyA pore to stably capture proteases functional dynamics.



Summary & Future Plan

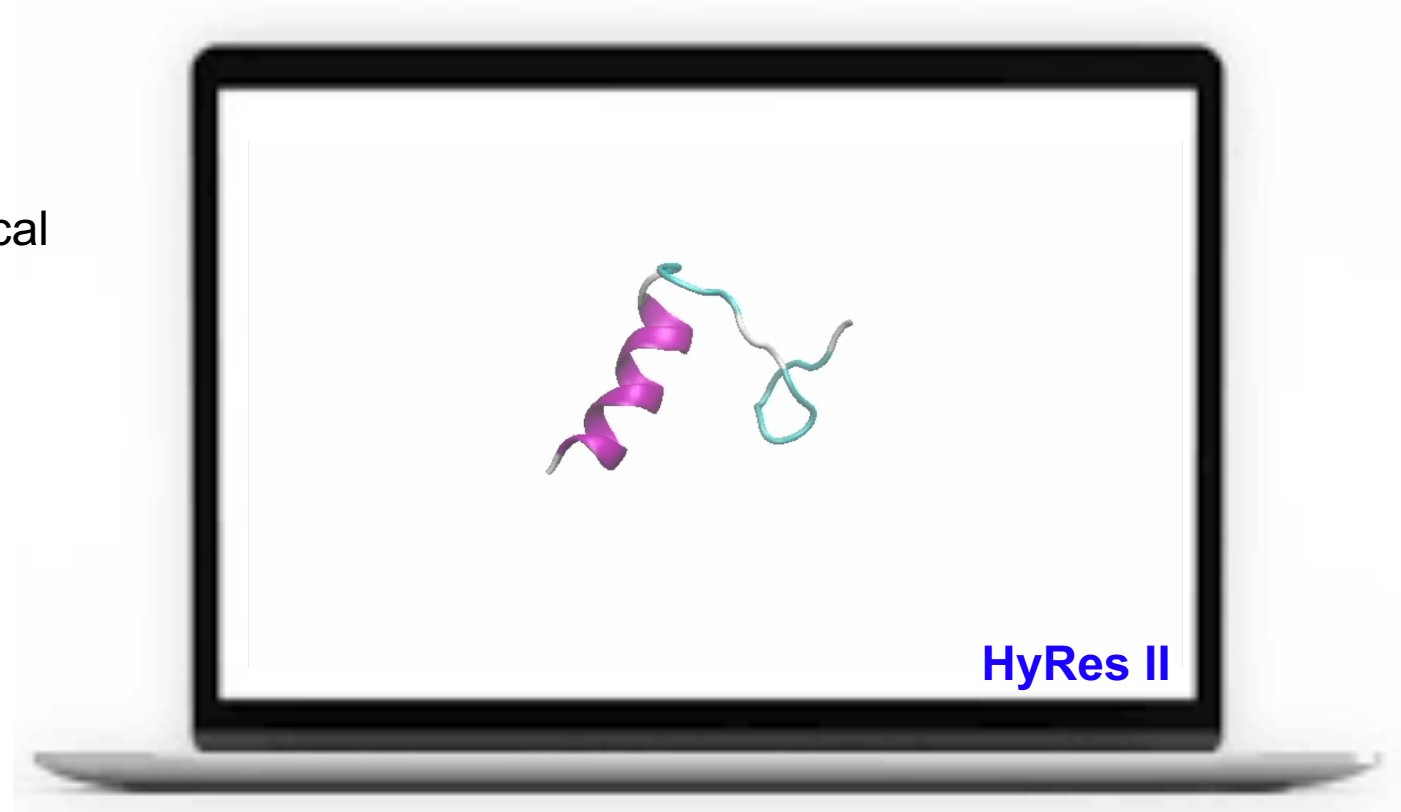


HyRes II is

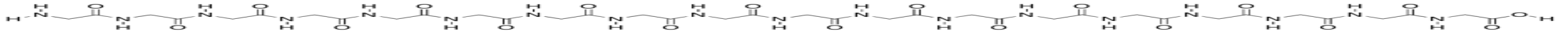
- a highly accurate coarse-grained protein model for simulation of dynamic proteins and their interactions
- highly efficient for studying larger biological systems (e.g., protein nanopores)

HyRes II will

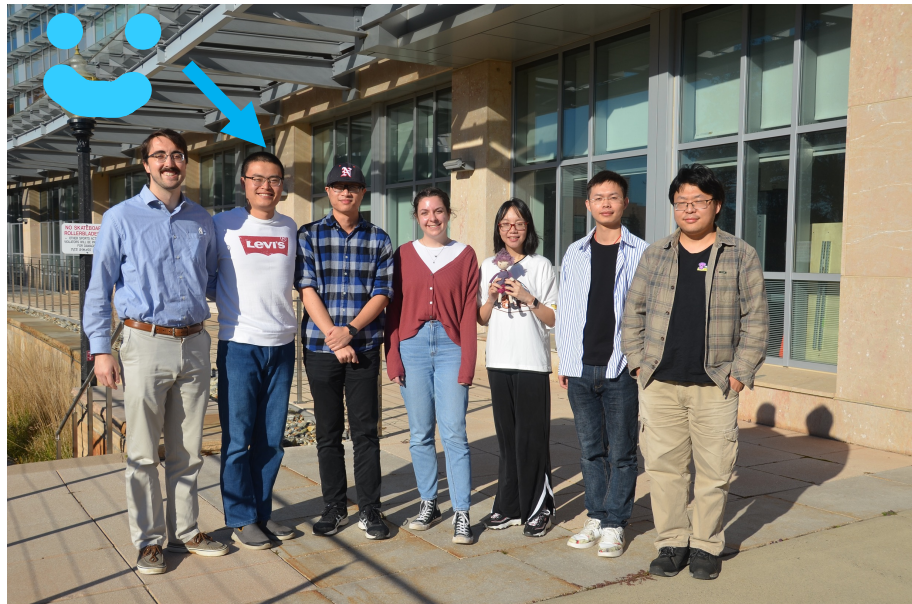
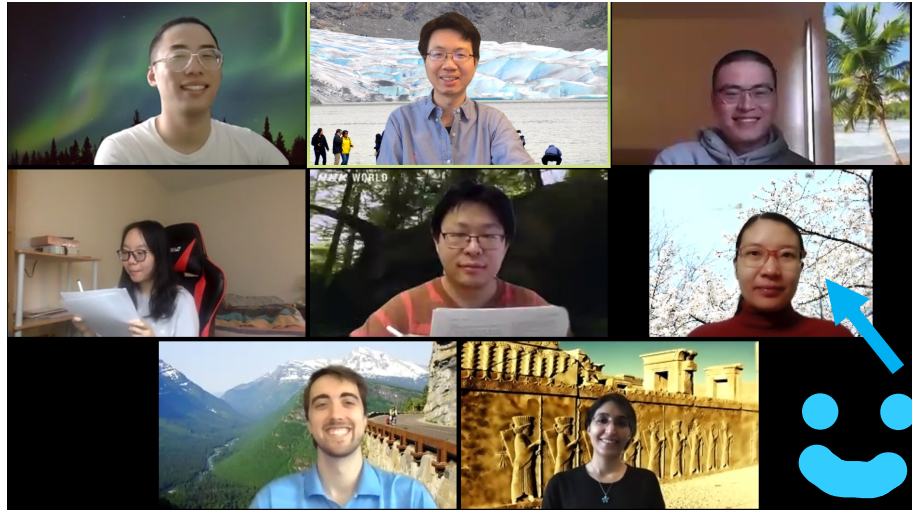
- be applied to studying flaviviral proteases in protein nanopores.
- be further optimized for more complex biological problems such as liquid-liquid phase transitions.



Acknowledgment



Chen Lab Members:



Specific Thanks to:

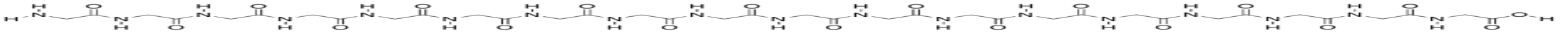
Dr. Xiaorong Liu
Xiping Gong

Committee members:

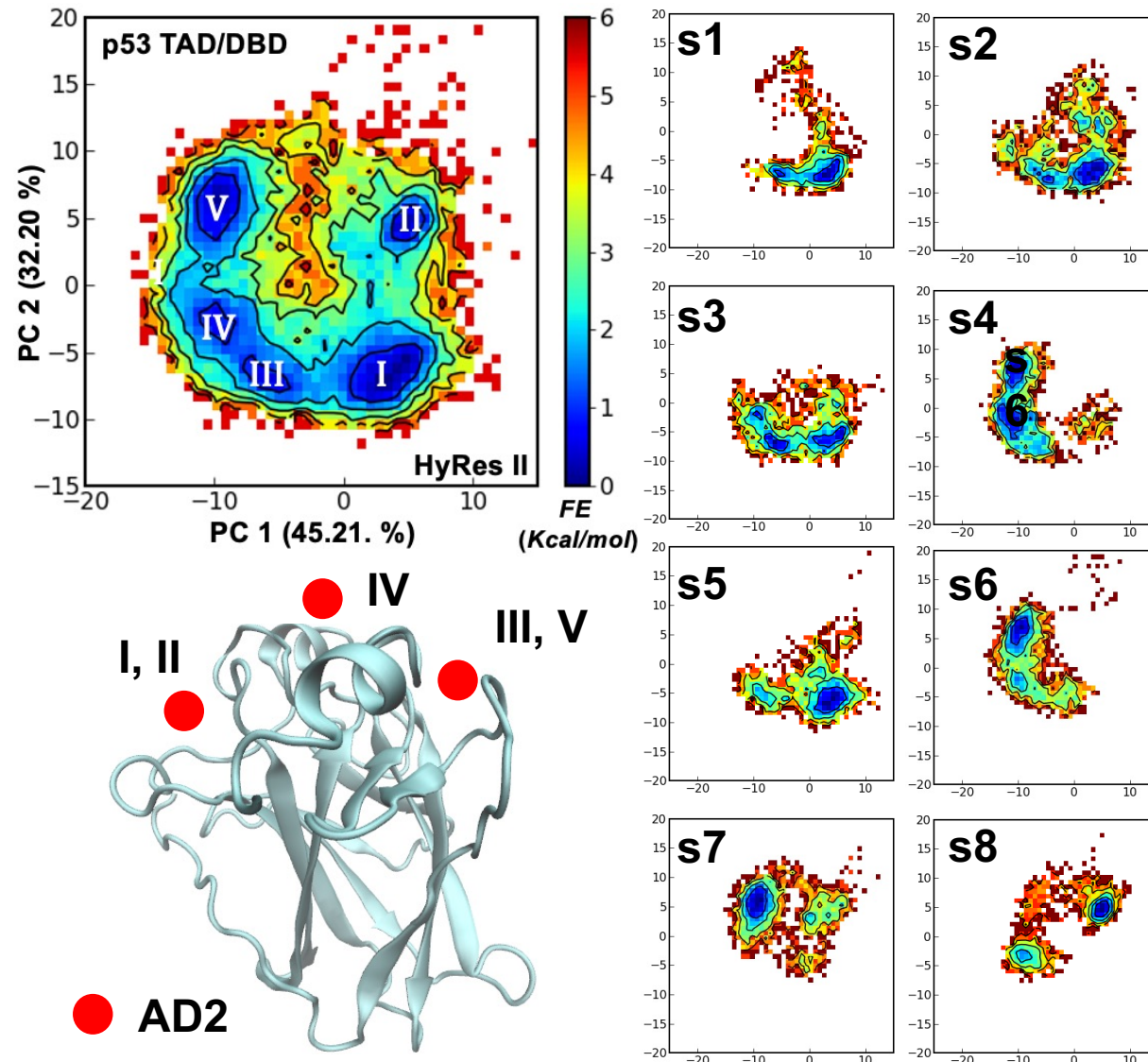
Prof. Jianhan Chen
Prof. Min Chen
Prof. Scott Auerbach
Prof. Greg Grason



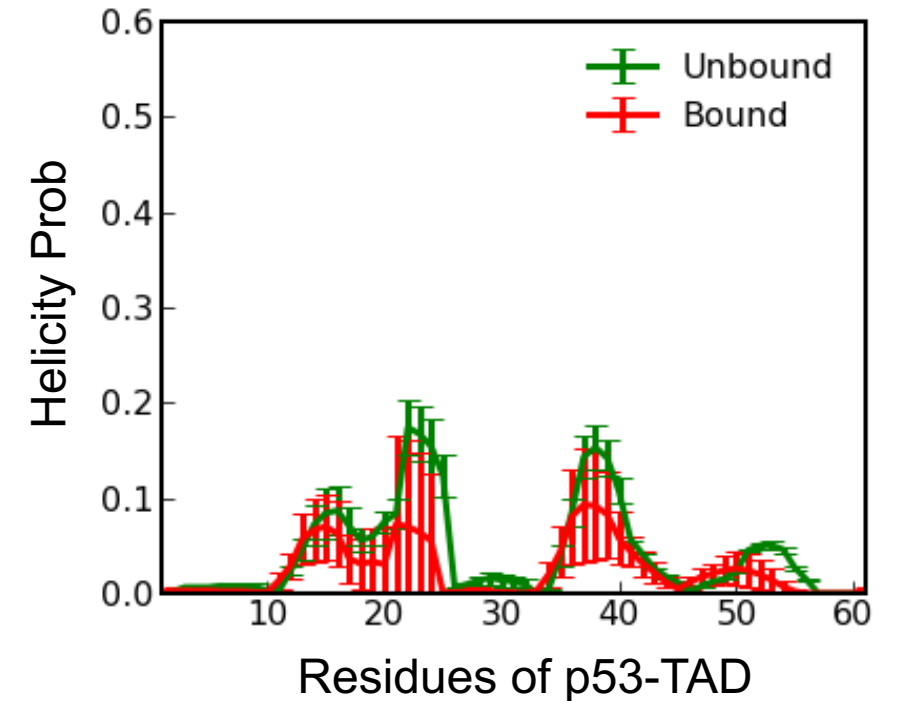
TAD Remains Highly Dynamic



- Transient intermolecular Interactions.



- Highly unfolded in bound state.



- TAD can compete over non-specific DNA bindings to DBD.
- There is no DNA-like helical conformation requirements for DBD binding.