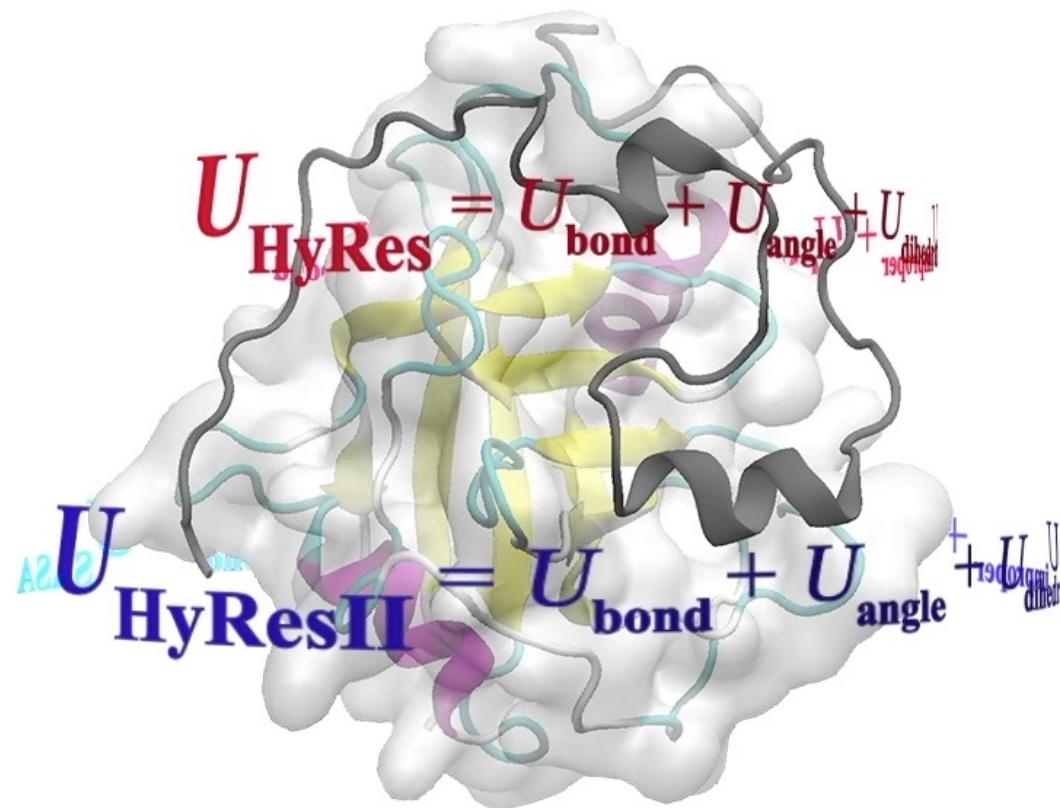
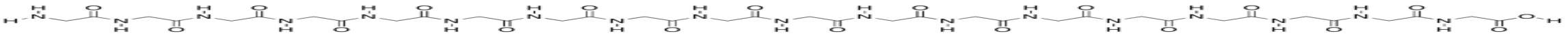


Towards accurate coarse-grained simulations of disordered proteins and dynamic protein interactions

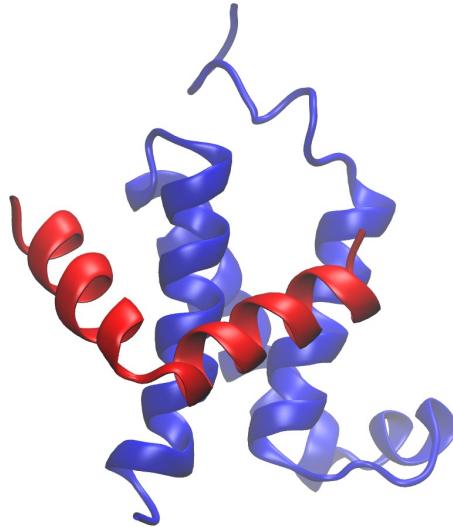


Chen Lab
Yumeng Zhang

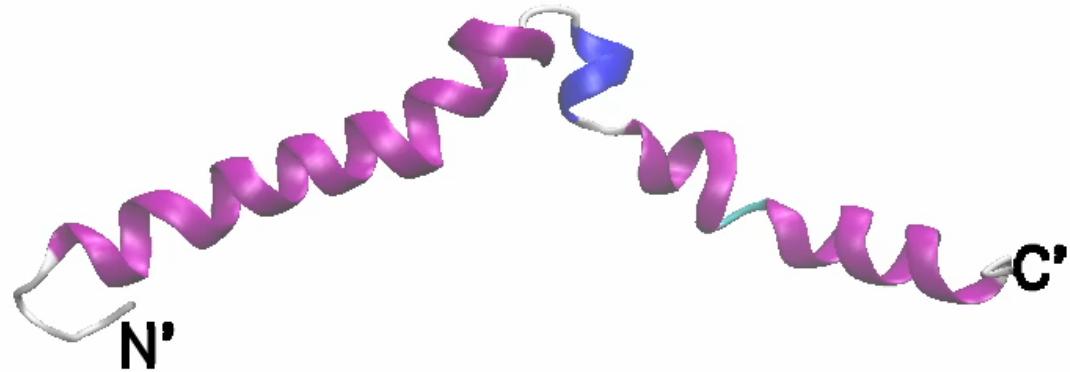
Orderly Chaos of Intrinsically Disordered Proteins



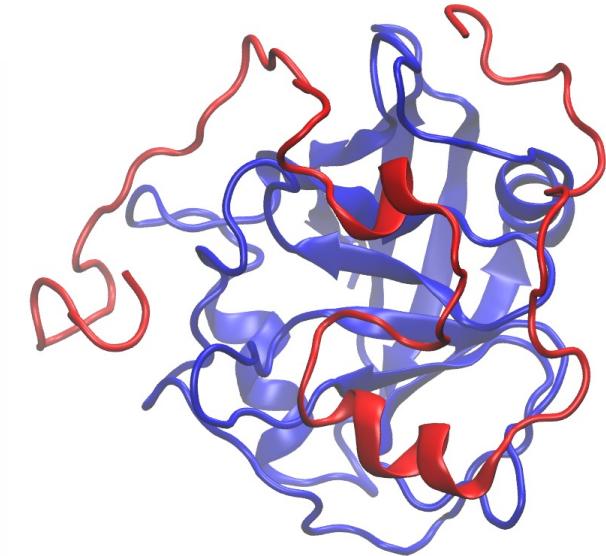
- Rely on structural disorder for function
- Crucial in cellular regulation and signaling
- Can fold or remain dynamic upon binding



KID/CREB Complex



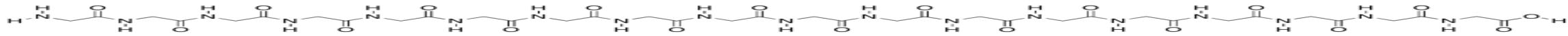
N-terminal Domain of p53 (p53-TAD)



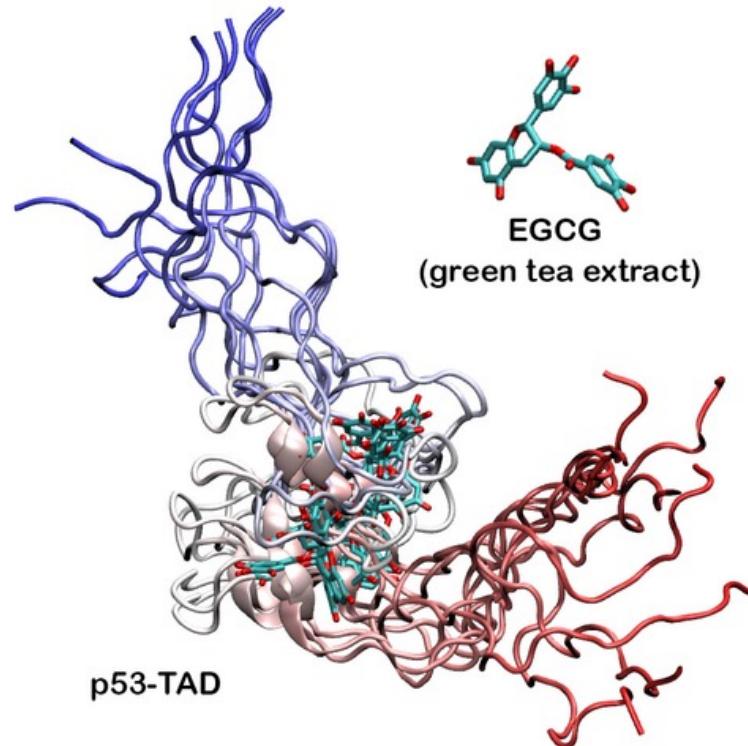
p53-TAD/CypD Complex

- Not amendable to traditional ensemble-based experiments
- Structural prediction tools, including AlphaFold, are not applicable to disordered proteins

Molecular Dynamic Simulations: The ‘Net’ to Capture IDPs

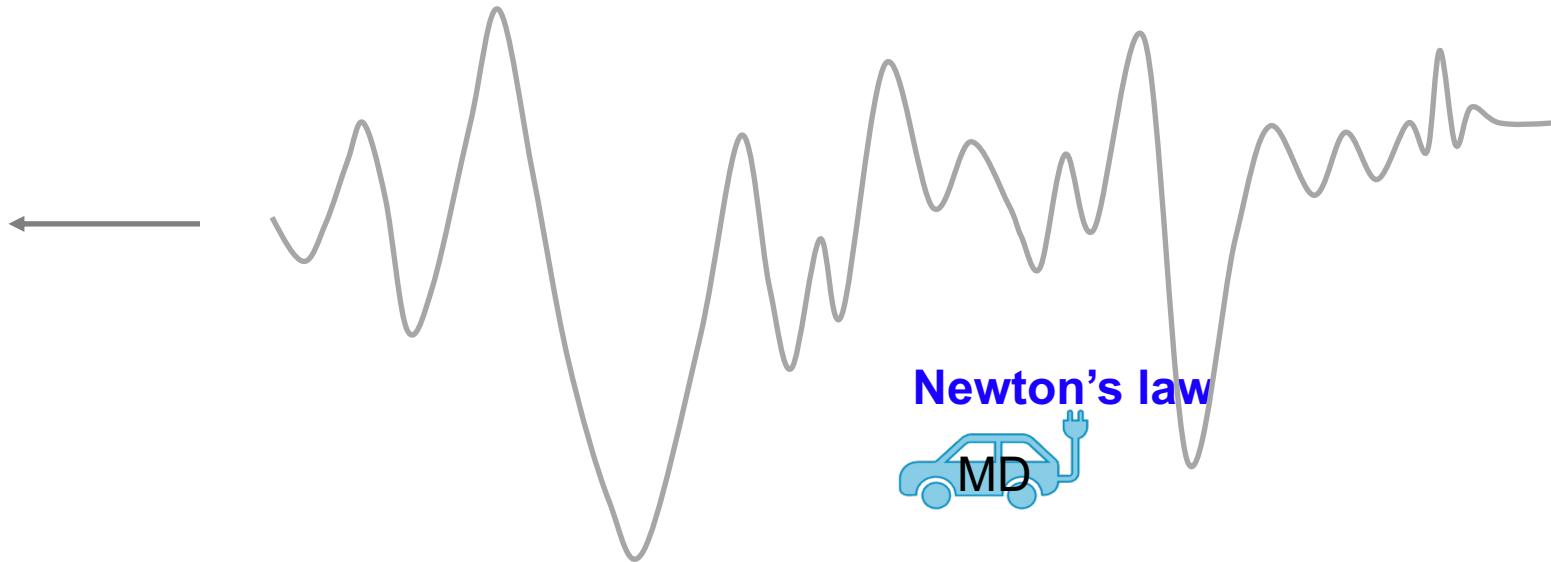


- Ensembles for p53-TAD/EGCG complex
- MD simulation for protein dynamics.



Atomistic Simulations

Protein Energy Landscape

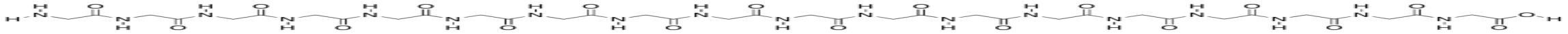


- MD provides the heterogeneous structural ensemble to analyze IDP functions.

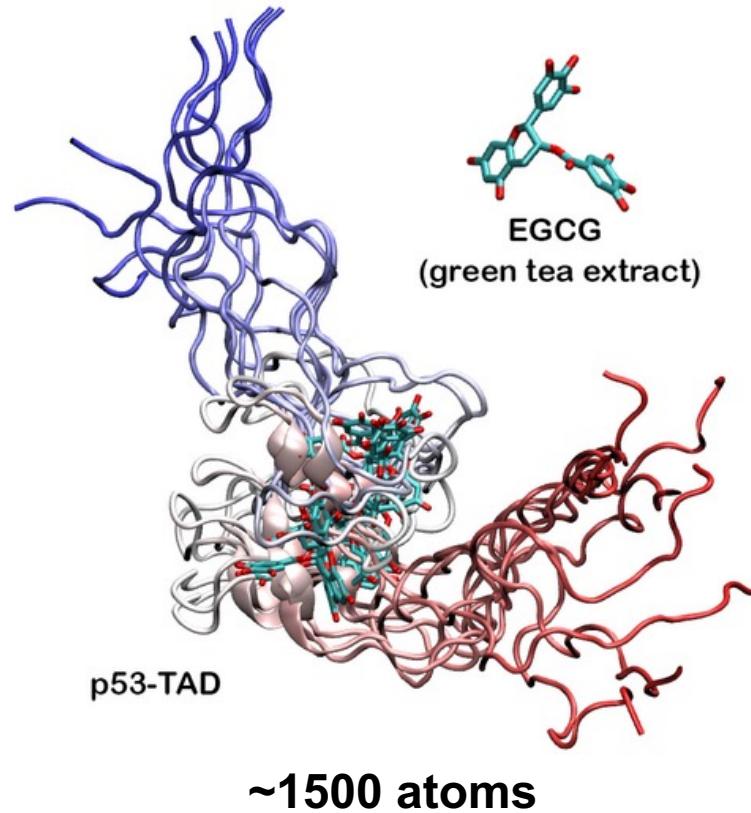
Nature Communications (2020)

<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

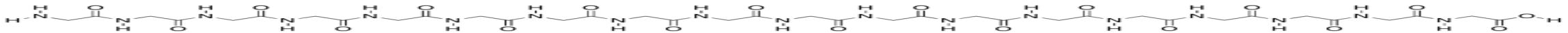


p53-TAD/EGCG

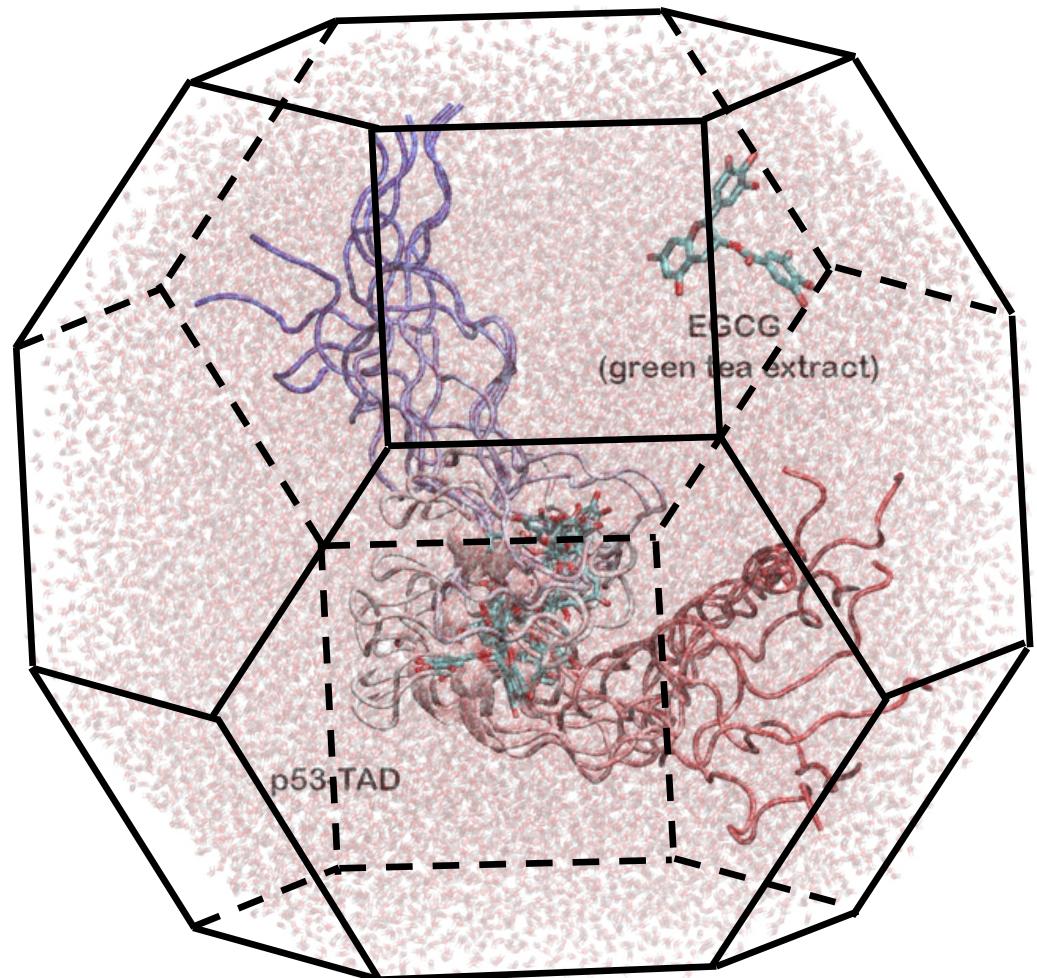


Nature Communications (2020)
<https://www.umass.edu/news/article/2-million-nih-mira-grant-will-support-trailblazing-research-umass-amherst-lab>

Computational Cost of Atomistic MD Can Be Prohibitive



Explicit Solvent Box

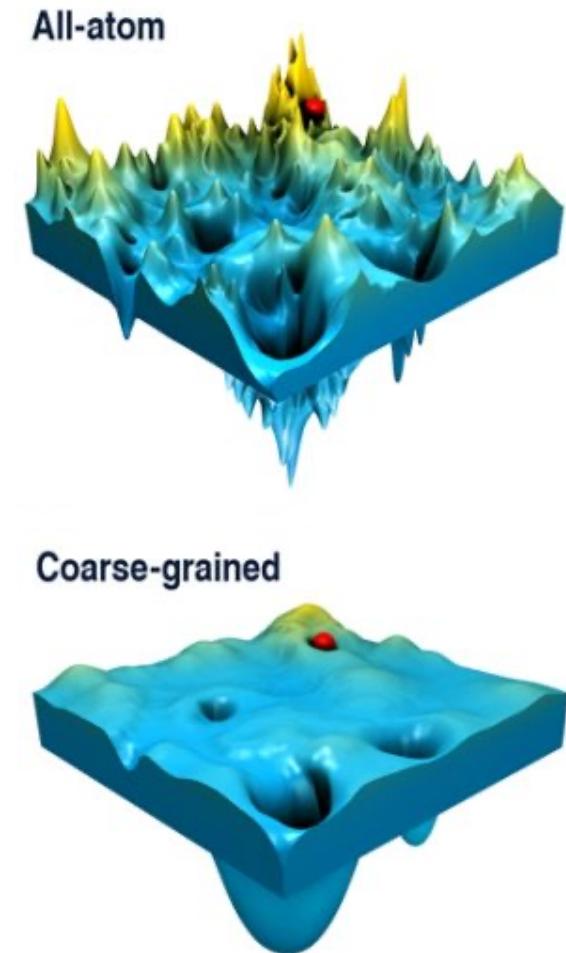
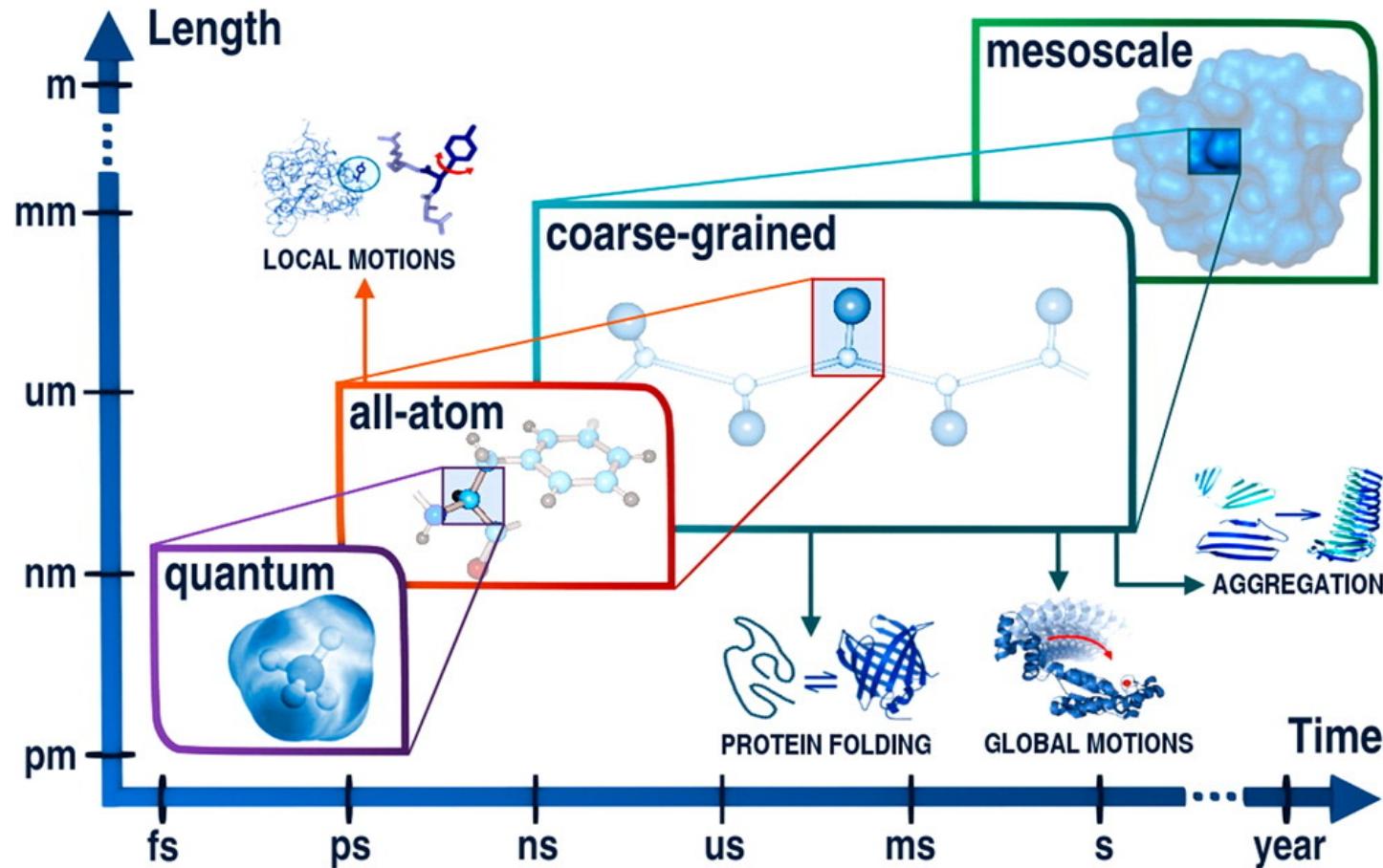
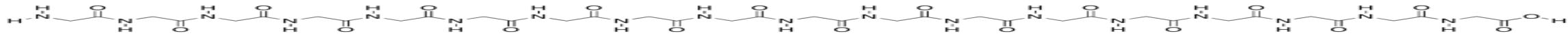


~100,000 atoms in the actual box!

1 μ s simulation time (GPU)
≈ 30 days real time!

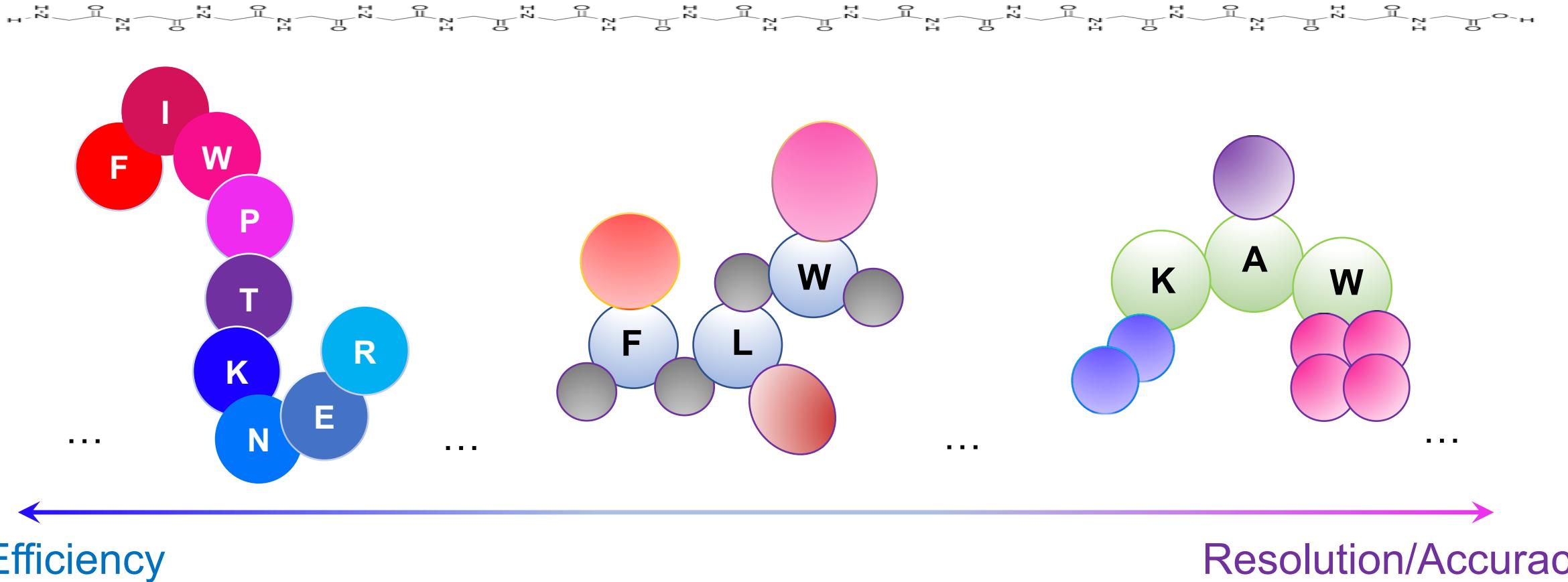
Actual cost: 16 replicas x 3 μ s (GPU)
≈ 48 Months!!

Coarse-Grained Modeling of Protein Dynamics



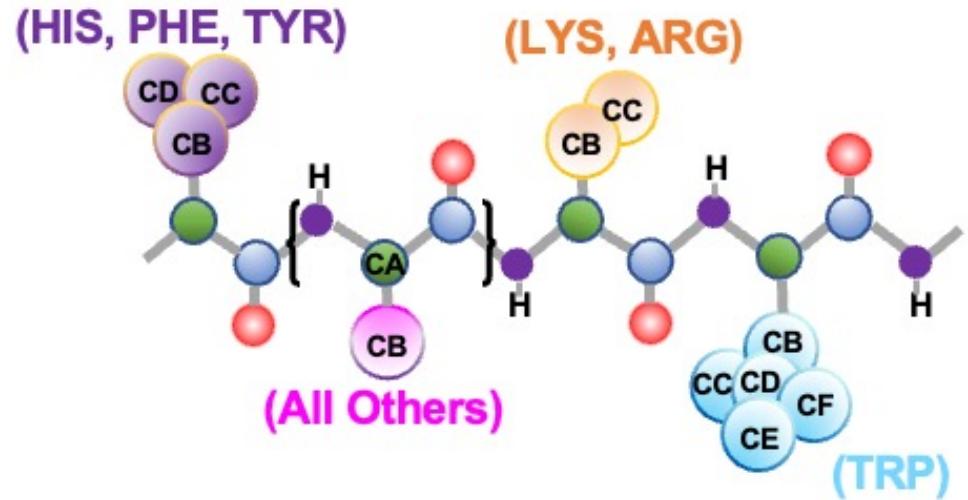
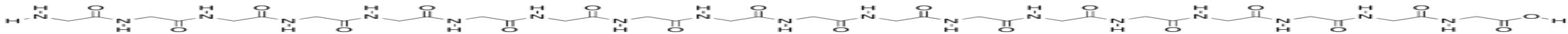
- CG models can more efficiently explore the energy landscape.

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

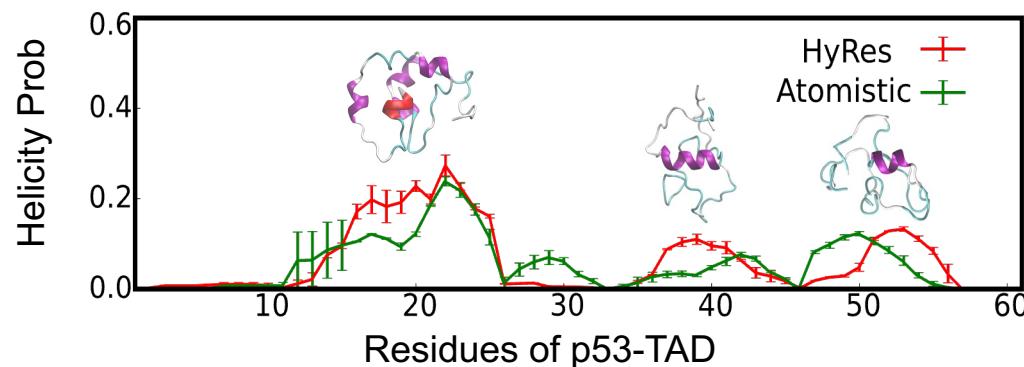


Hybrid-Resolution (HyRes) Model:

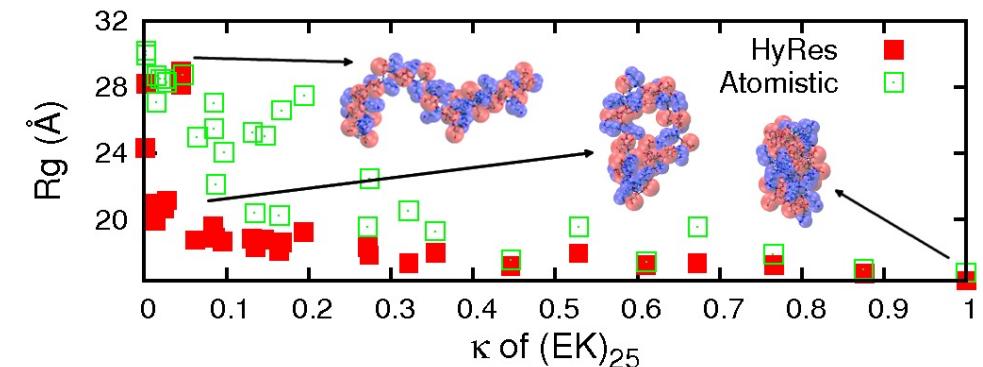
- Atomistic representation for backbone atoms.
- Coarse-grained sidechains up to five beads resolution.
- Physics-based energy terms.

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

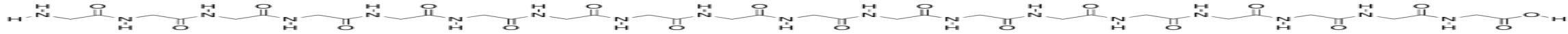
➤ Semi-quantitatively 2nd structural profile descriptions.



➤ Qualitatively long-range interaction characterizations.

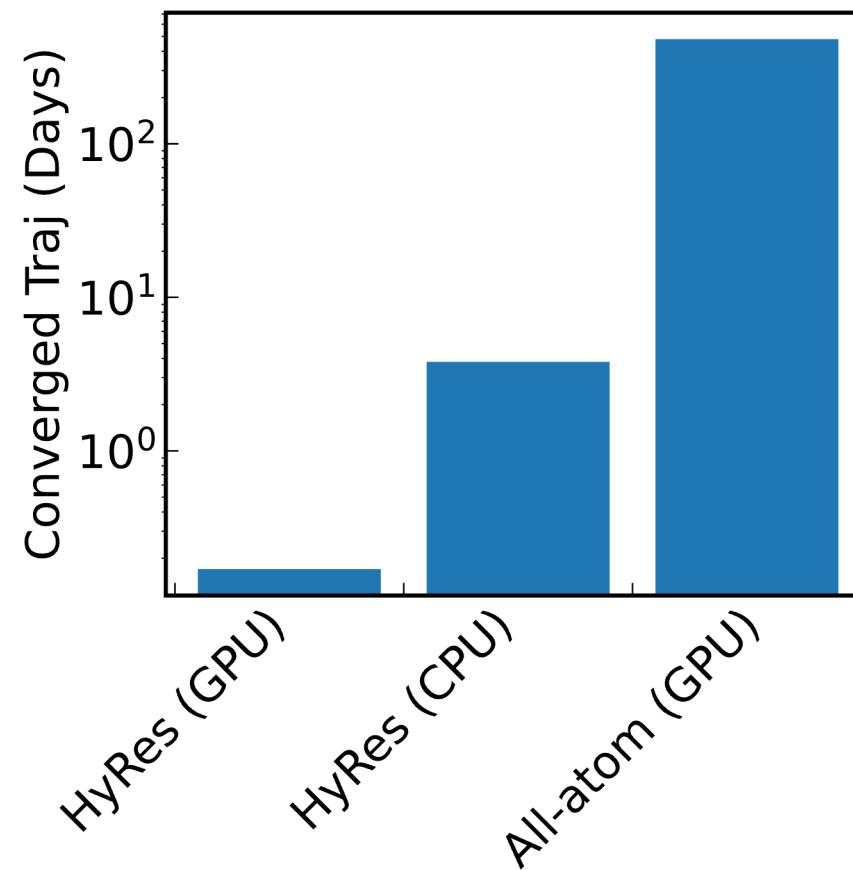
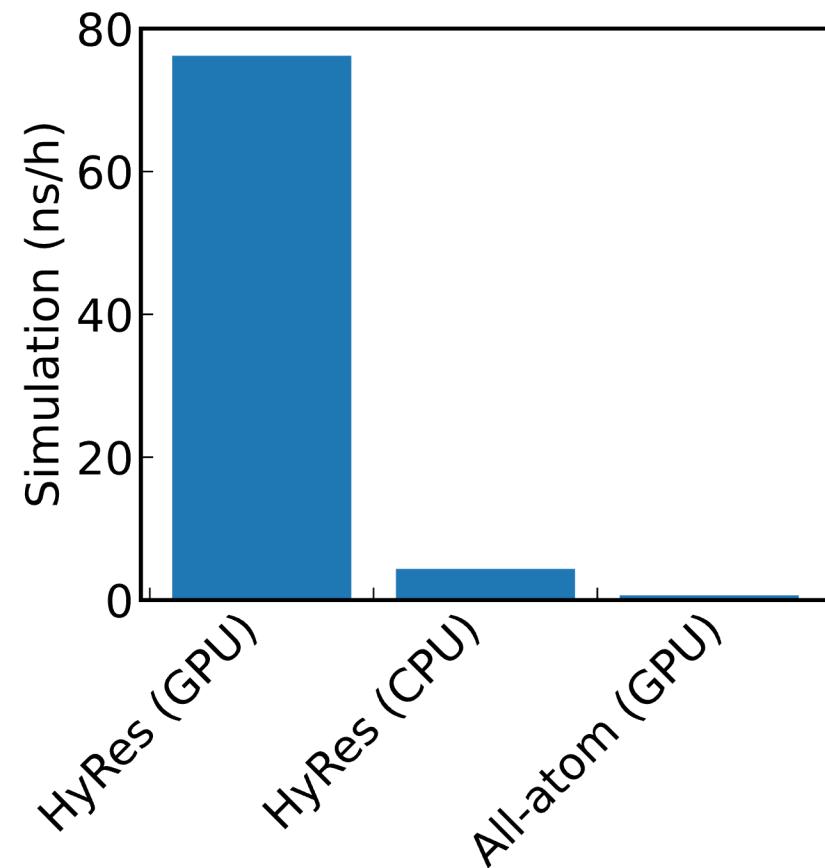


HyRes is ~ 3,000 Faster Than Atomistic Models

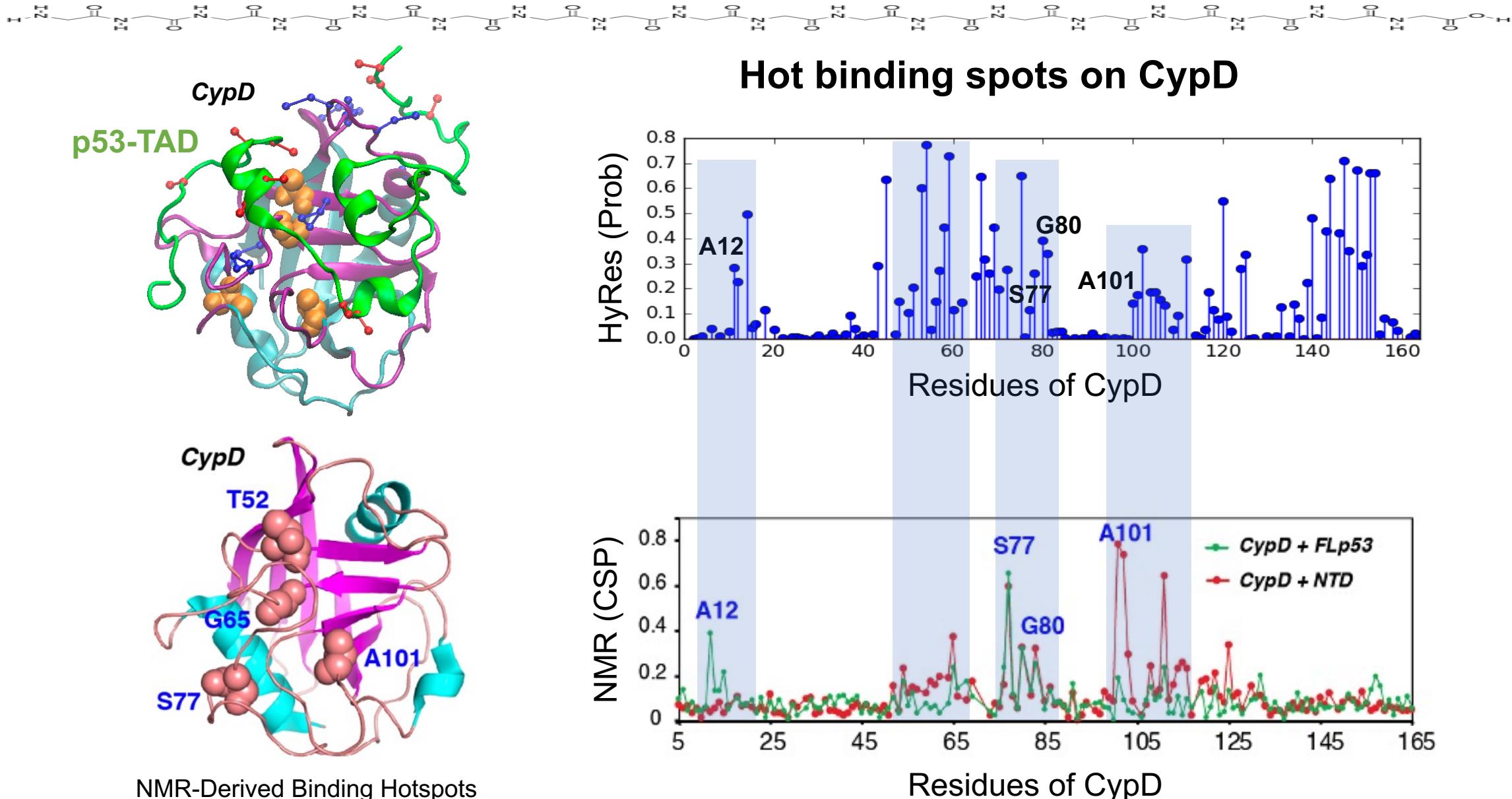


HyRes:

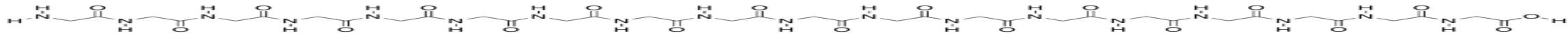
- Achieves **~ 100 times** faster than all-atom GPU in per nanosecond simulations.
- Achieves **~ 3000 times** faster in generating converged trajectories for analysis.



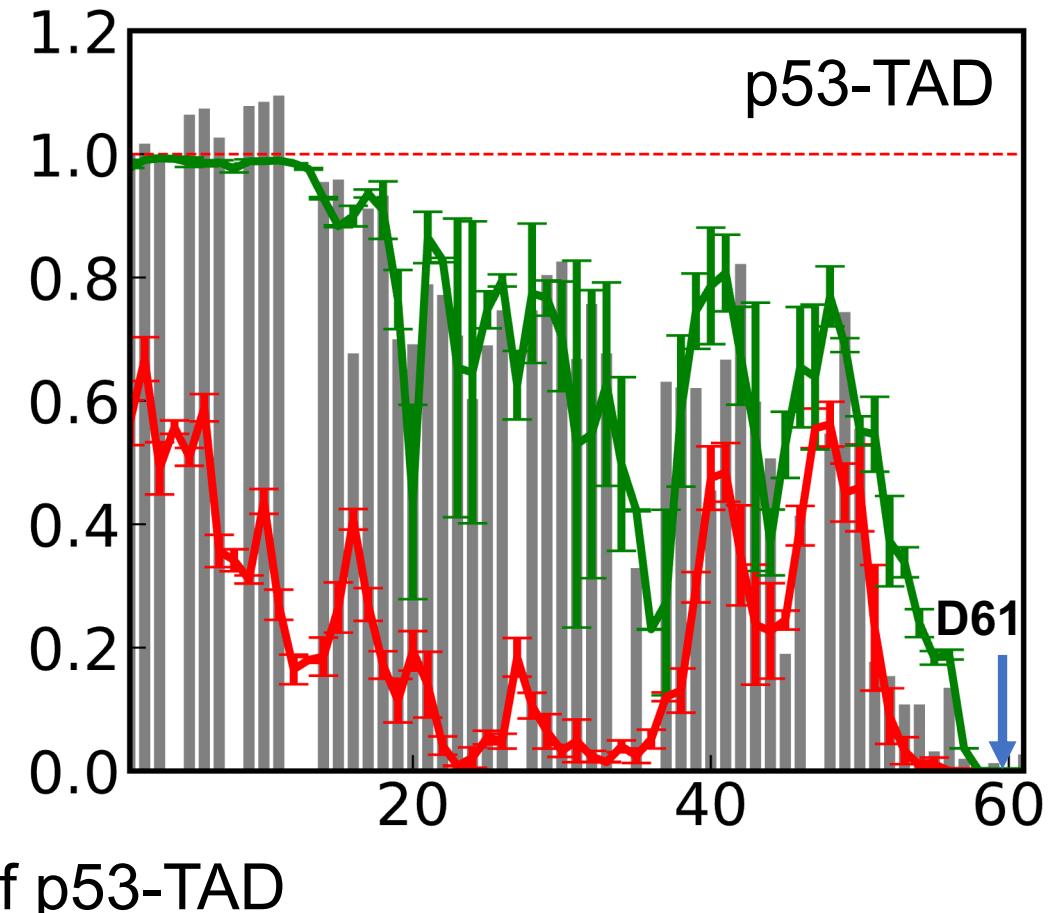
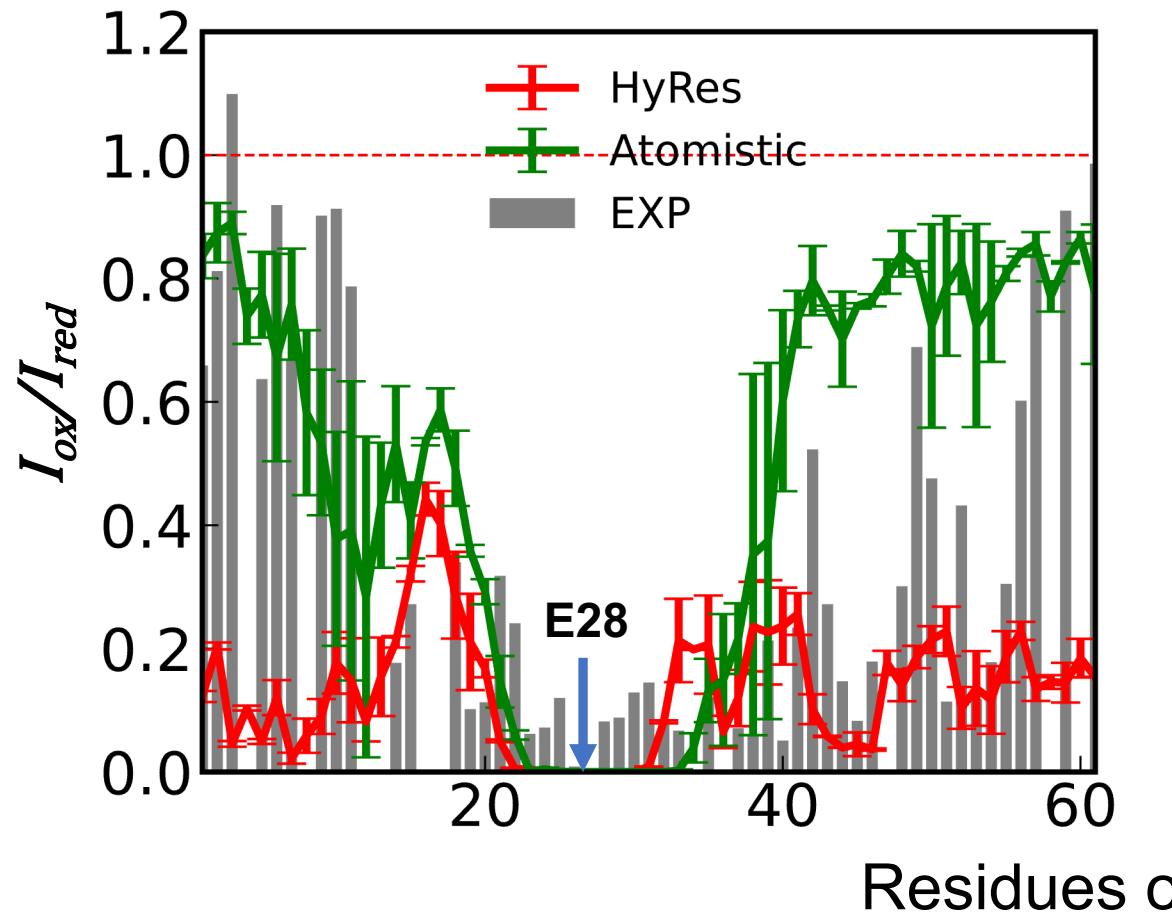
HyRes Can Capture Dynamic p53-TAD/CypD Interactions



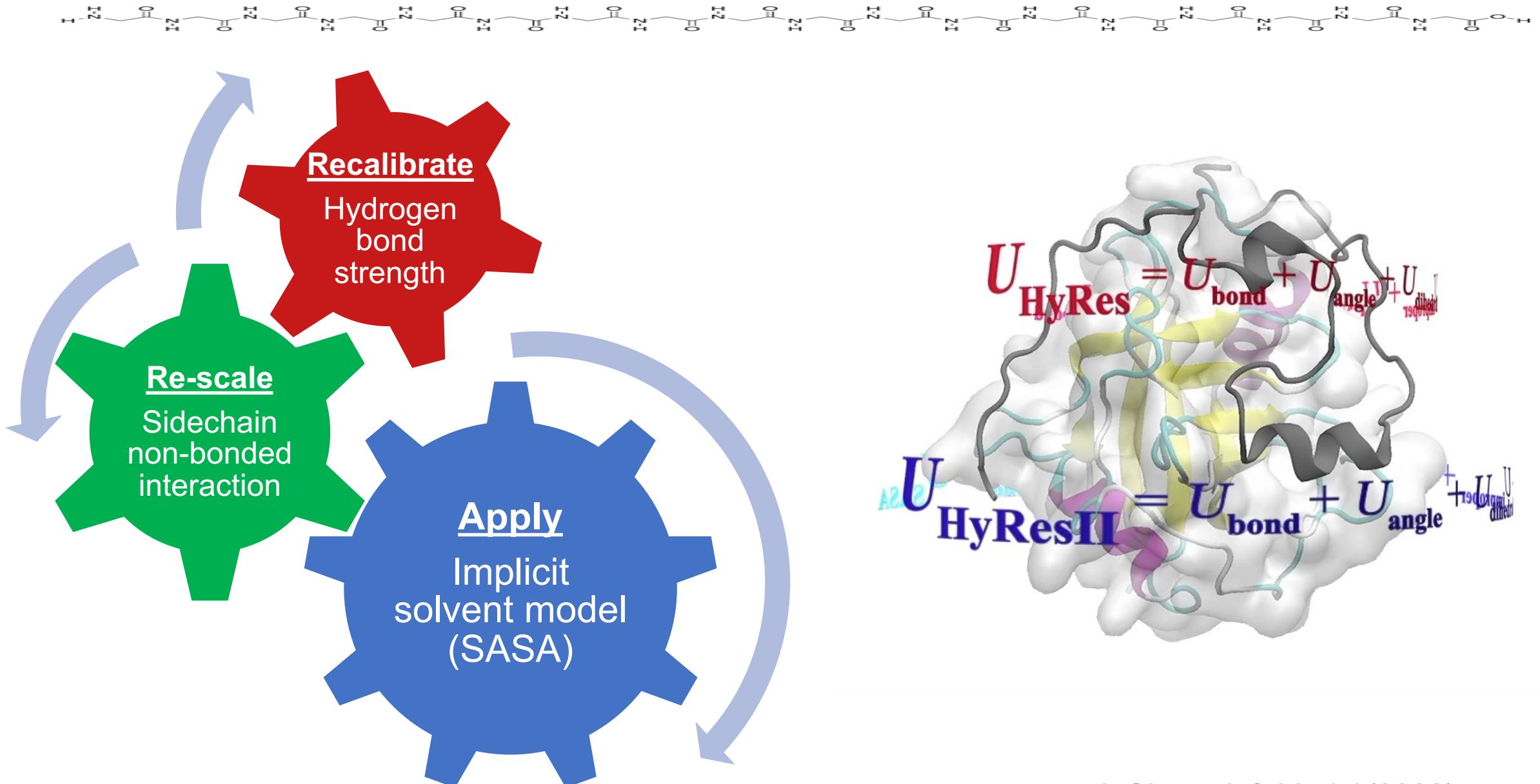
Over Compaction of IDPs in HyRes



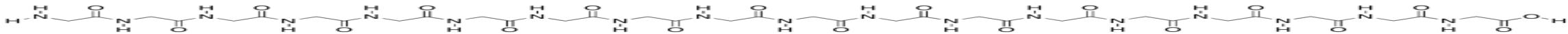
$$U_{\text{HyRes}} = U_{\text{bond}} + U_{\text{angle}} + U_{\text{dihedral}} + U_{\text{improper}} + U_{\text{CMAP}} + U_{\text{LJ}} + U_{\text{Hbond}} + U_{\text{elec}}$$



HyRes II: Design and Optimization

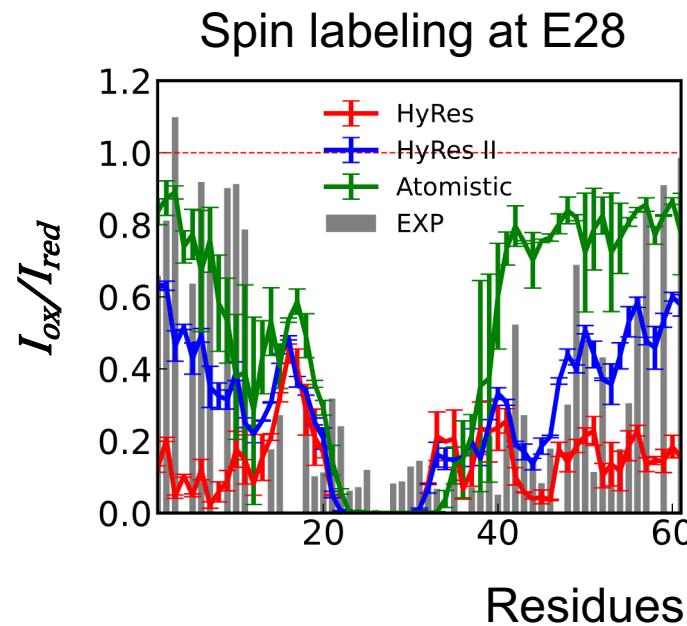


Disordered Ensembles of p53-TAD in HyRes II

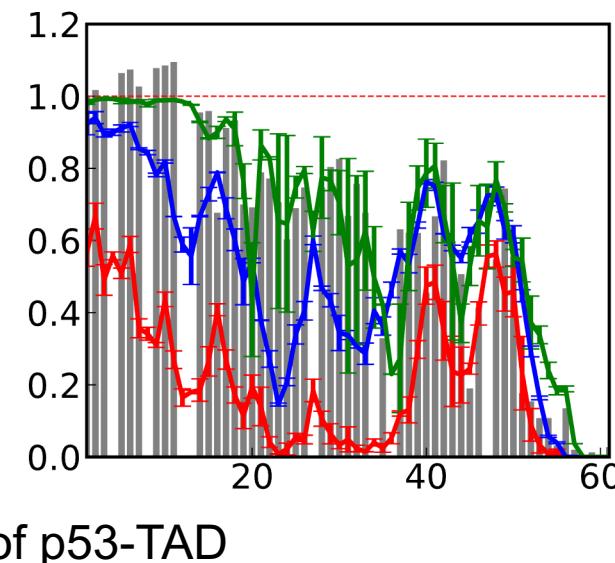


- HyRes II generated disordered ensembles are highly consistent with various experimental data from NMR, SAXS etc
- It quantitatively captures key local and global structural properties of IDPs

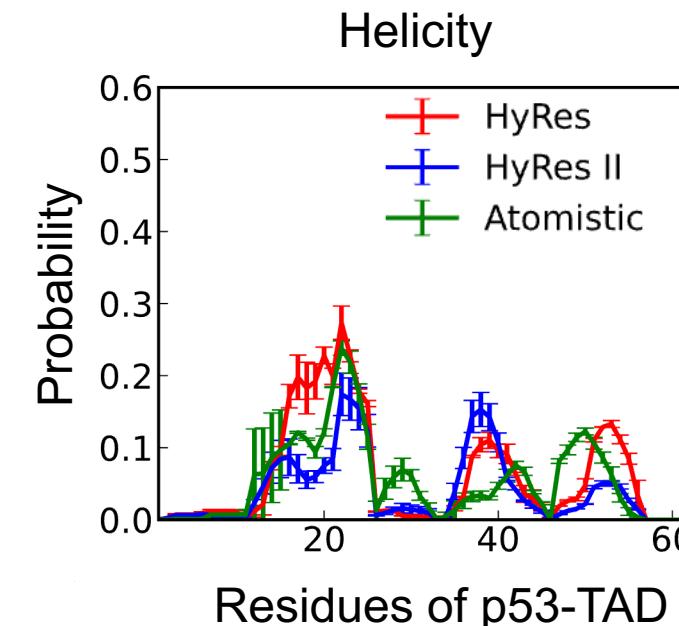
➤ Long-range transient contacts: PRE NMR



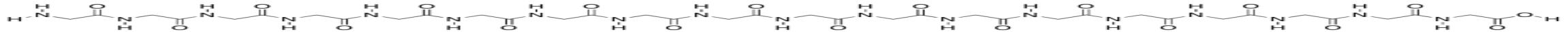
Spin labeling at D61



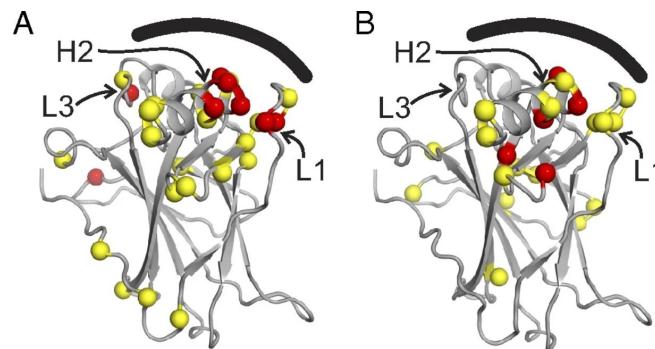
➤ 2nd Structures



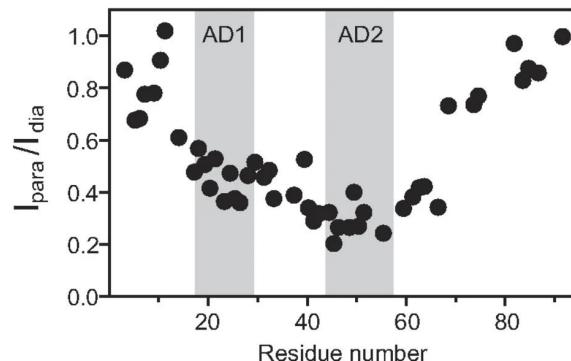
HyRes II Simulation of Dynamic p53-TAD/DBD Interactions



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

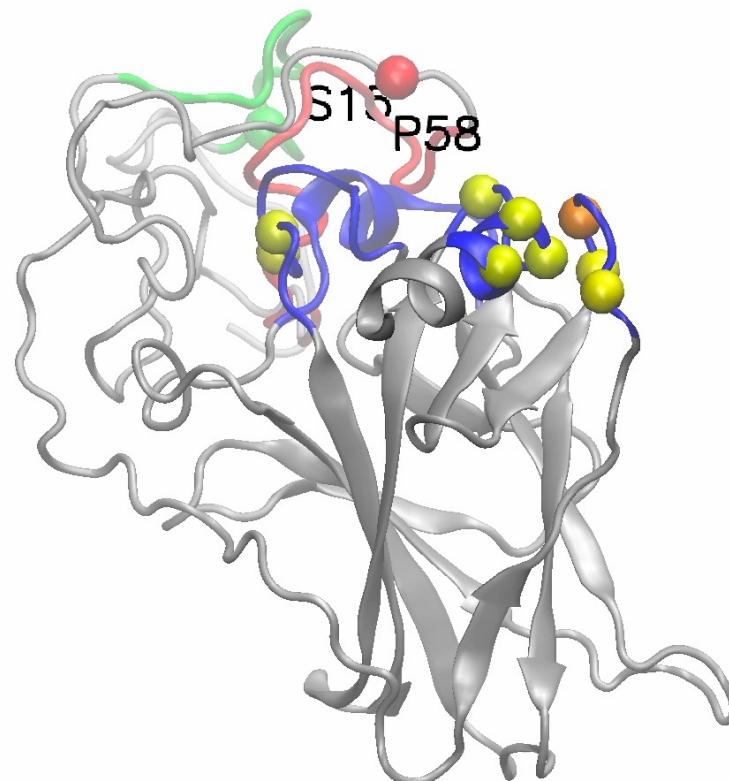


- Two subdomains on TAD: AD1 and AD2, can dynamically interact with DBD.

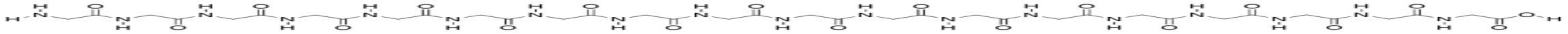


AD1 —

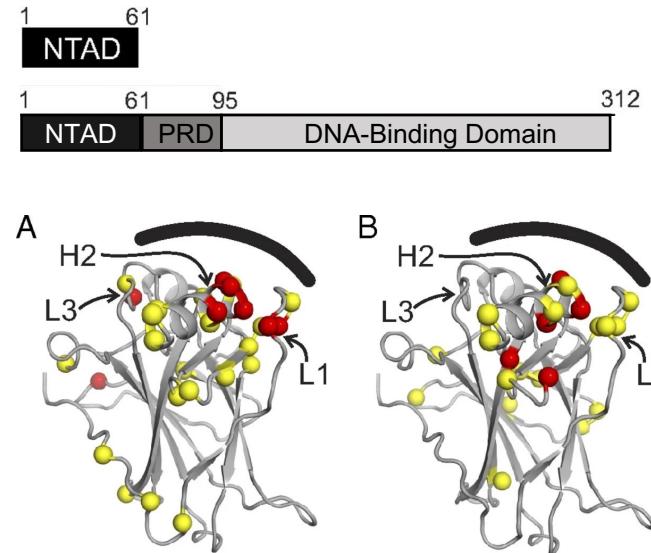
AD2 —



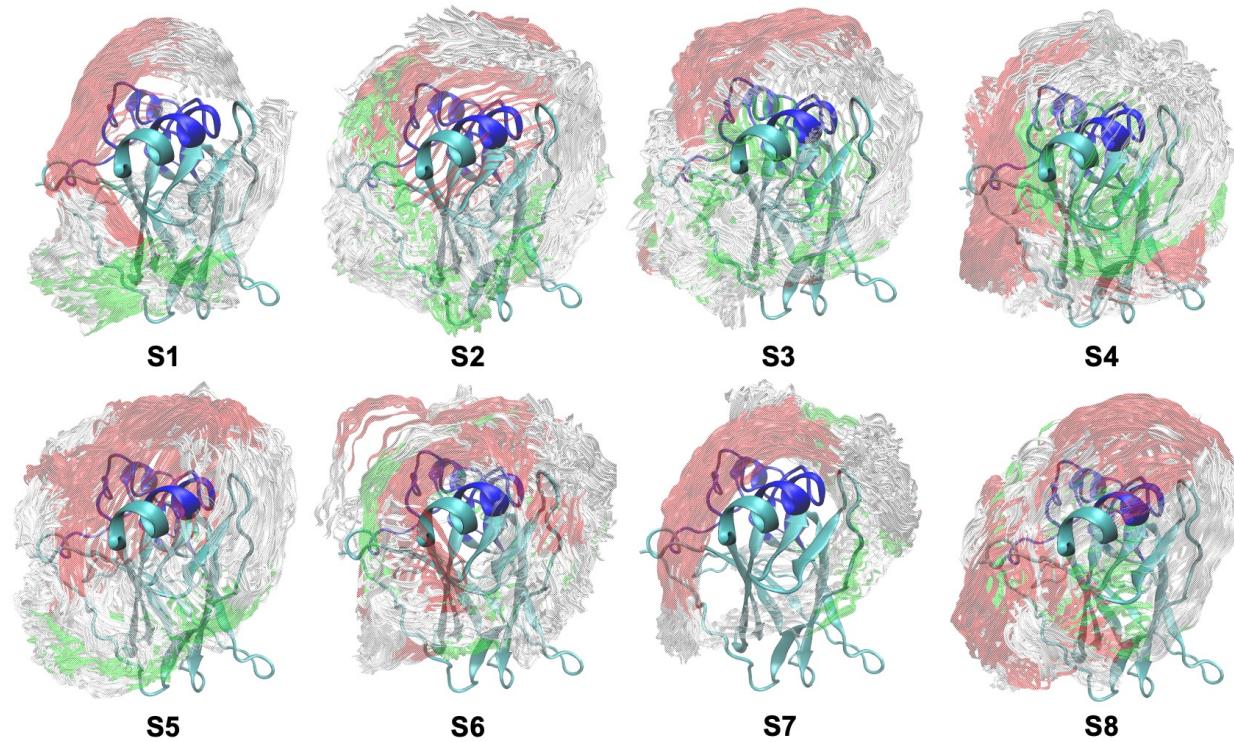
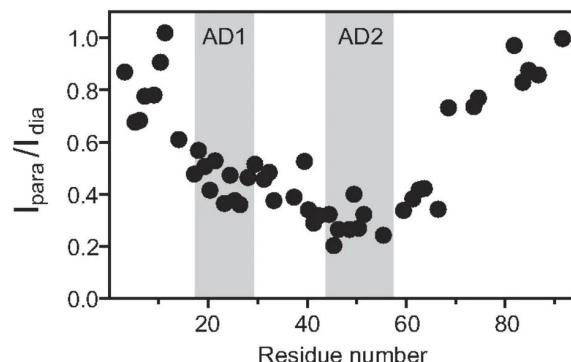
The Main Binding Subdomain: AD2



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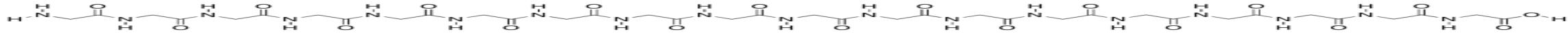
- Two subdomains on TAD: AD1 and AD2, can dynamically interact with DBD.



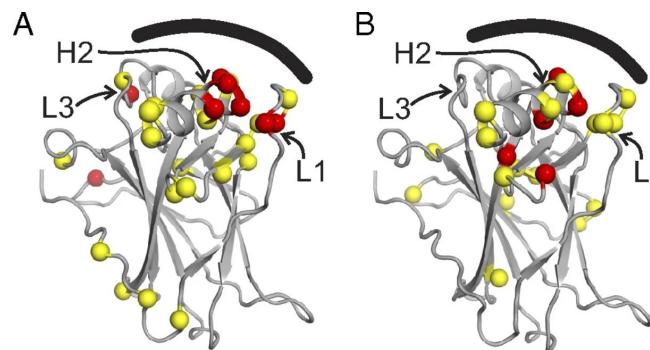
S1~S4: TAD randomly bind to DBD at initial.

S5~S8: TAD is fully extended at initial.

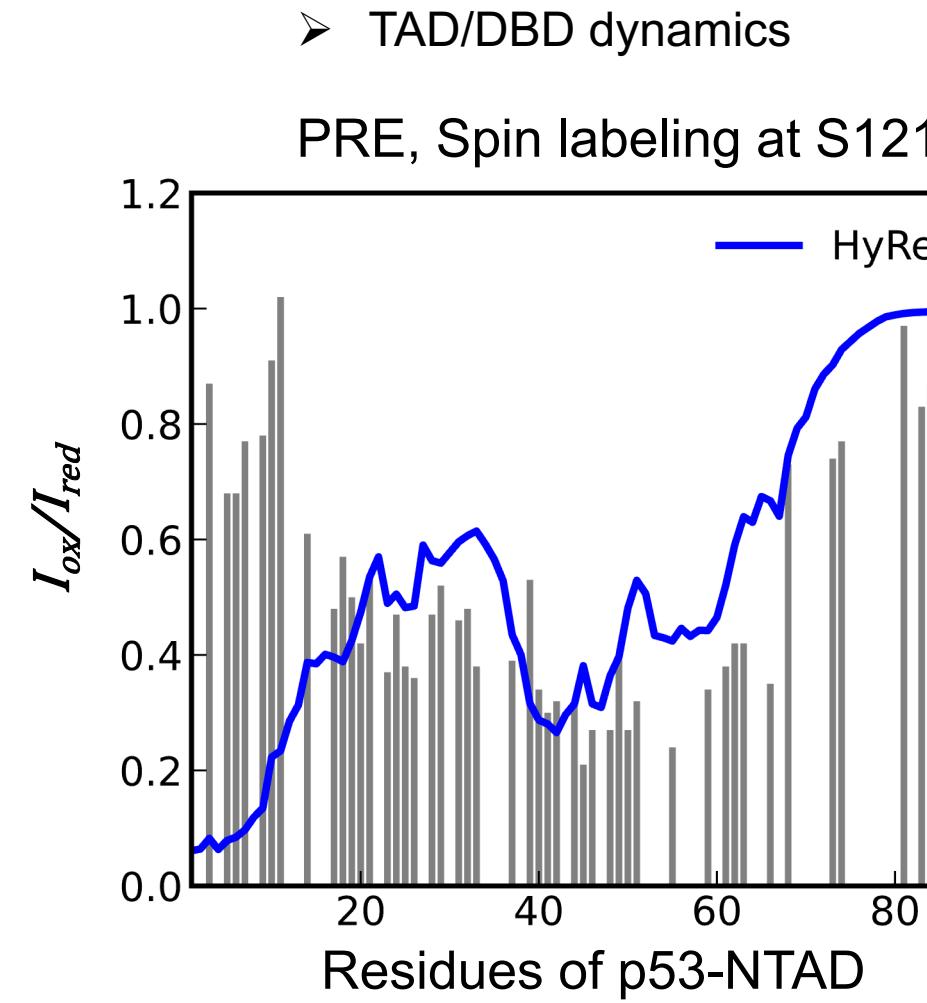
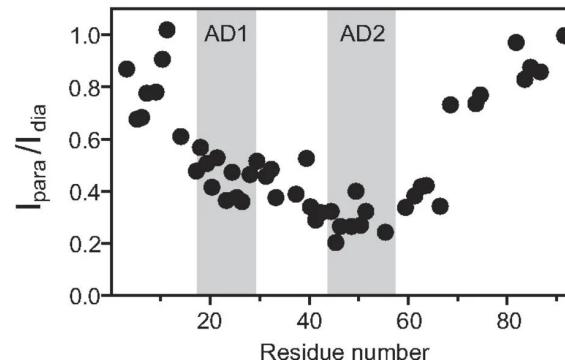
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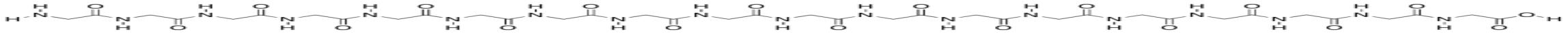
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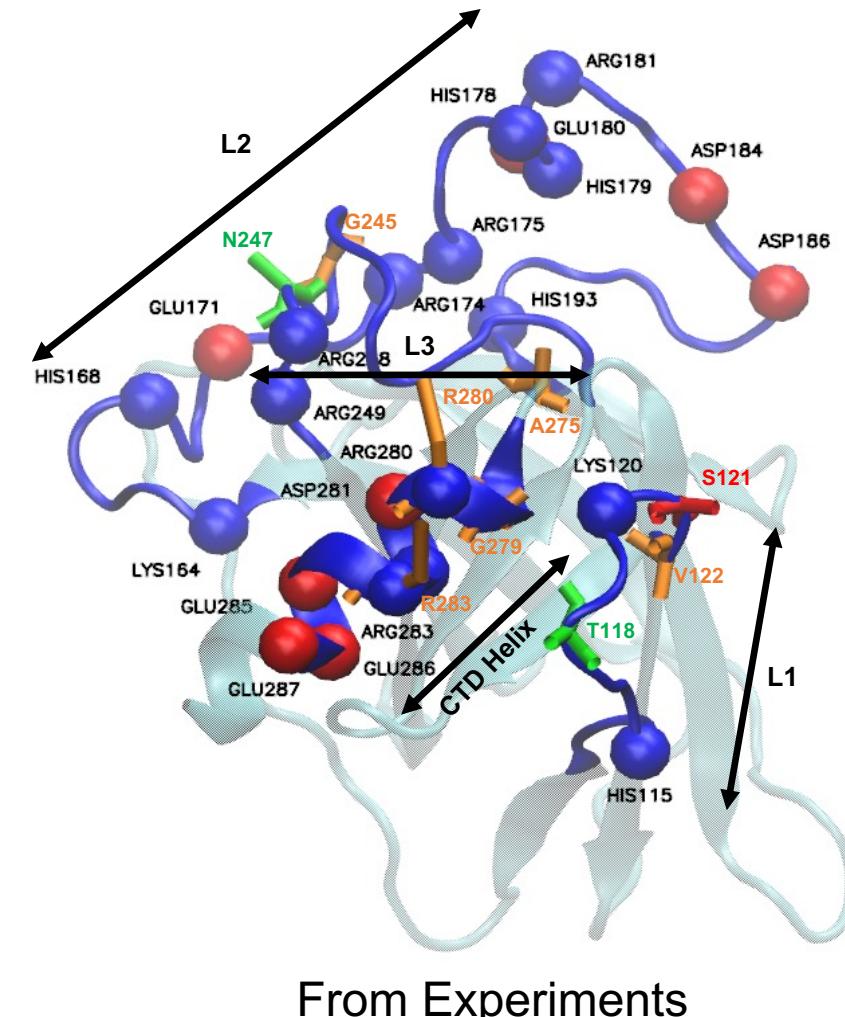
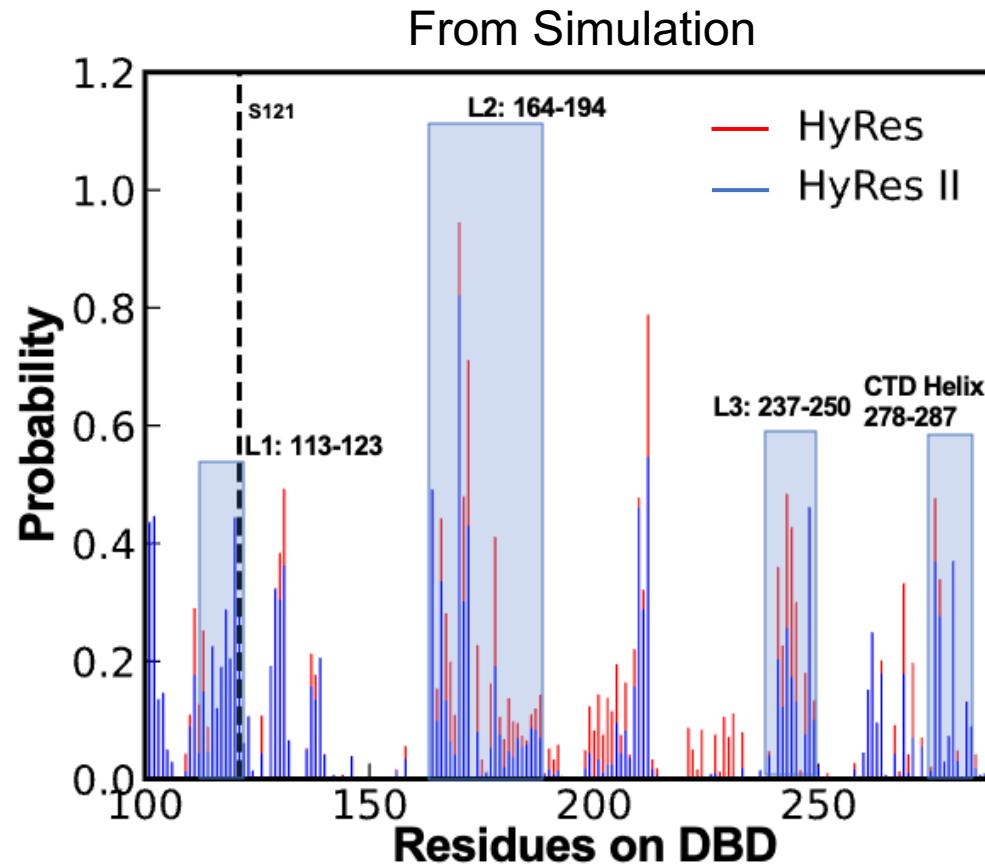
- Two subdomains on TAD: AD1 and AD2, can dynamically interact with DBD.



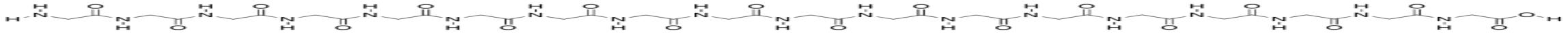
TAD Binds to DNA-binding Surface on DBD



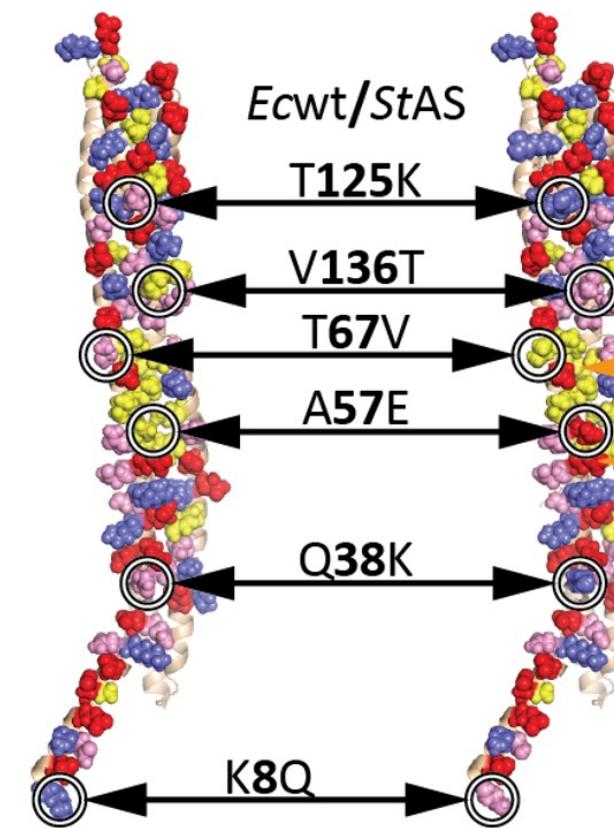
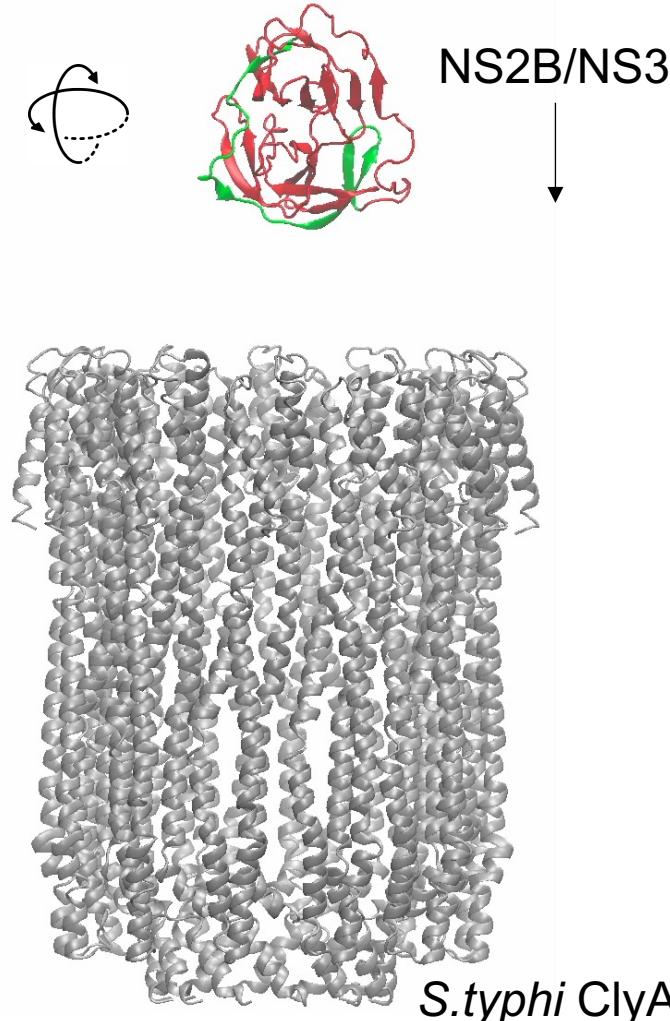
- Hot binding spots on DBD



HyRes II for Studying Protein Nanopore Tweezers

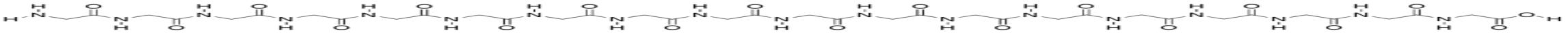


- Exploring Proteases Dynamics in ClyA Nanopore.
- Engineering ClyA pore to stably capture proteases functional dynamics.



(By: Spencer Shorkey)

Summary & Future Plan

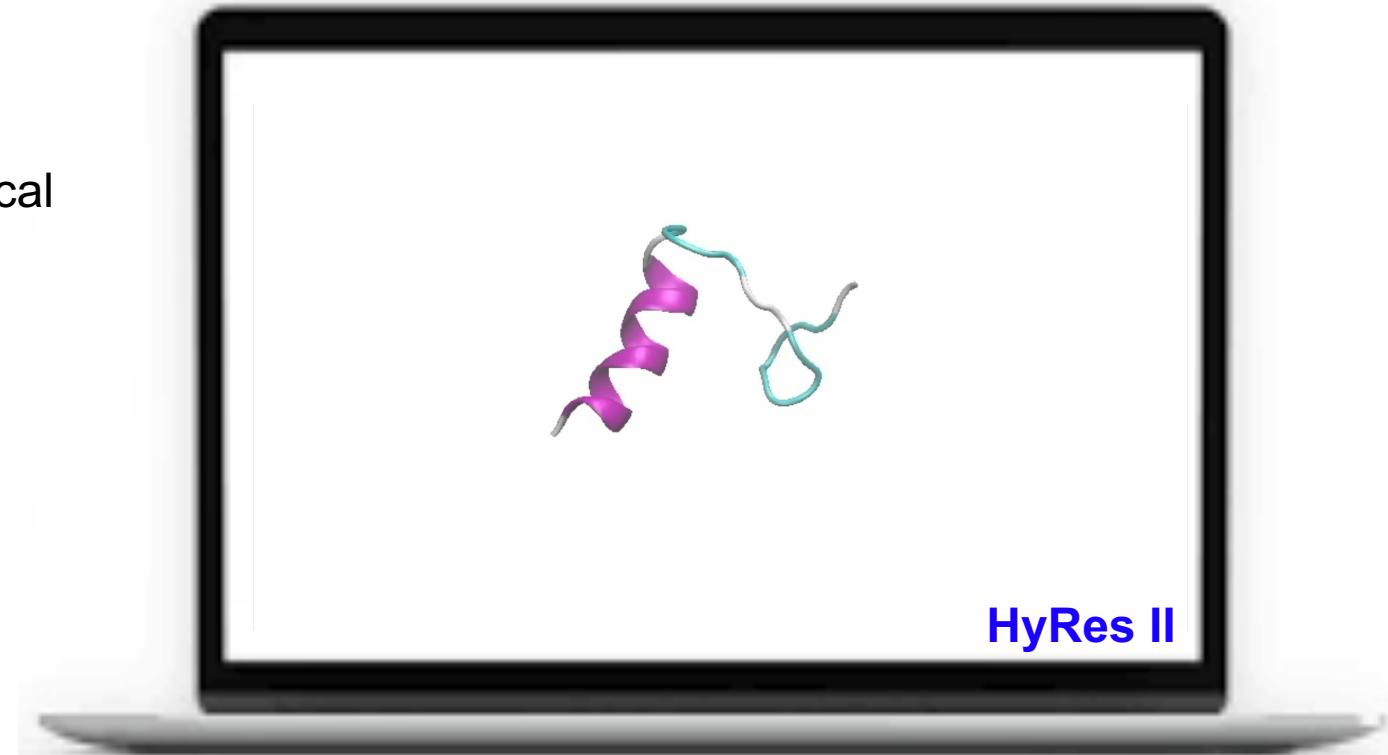


HyRes II is

- 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:

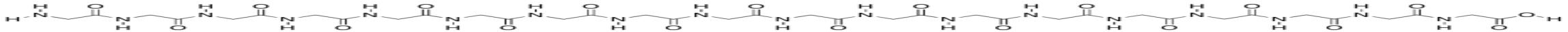
Dr. Xiaorong Liu
Xiping Gong

Committee members:

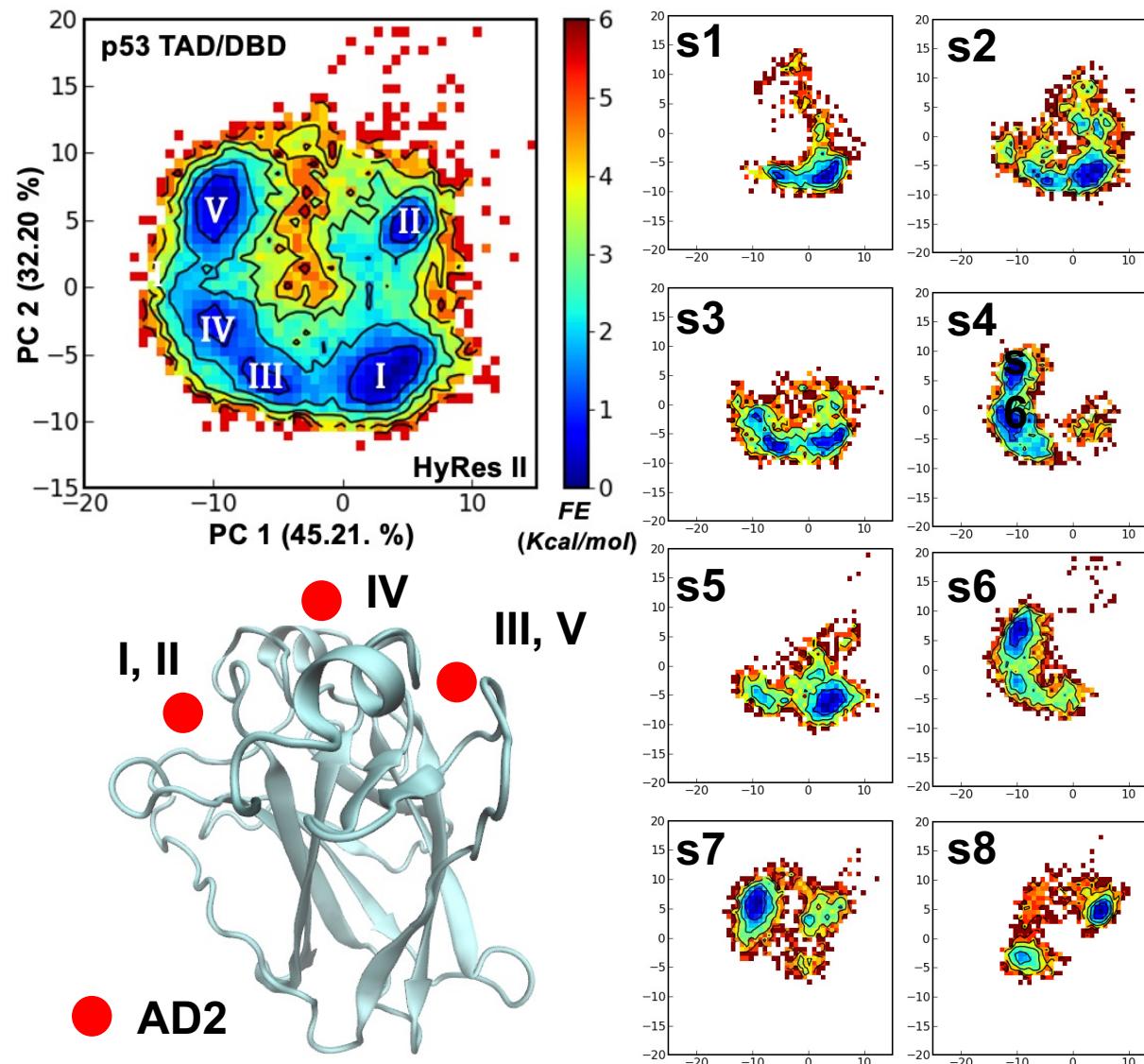
Prof. Jianhan Chen
Prof. Min Chen
Prof. Scott Auerbach
Prof. Greg Grason



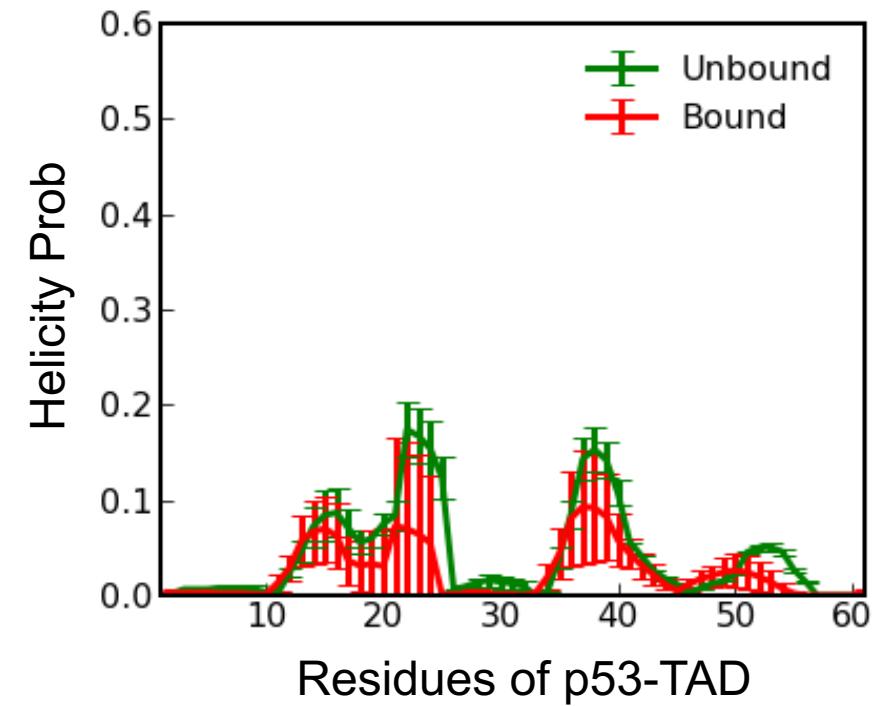
TAD Remains Highly Dynamic



- 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.