# Collective-Variable-Enhanced Biomolecular Simulations

Cameron F. Abrams
Department of Chemical and Biological Engineering
Drexel University, Philadelphia, Pennsylvania

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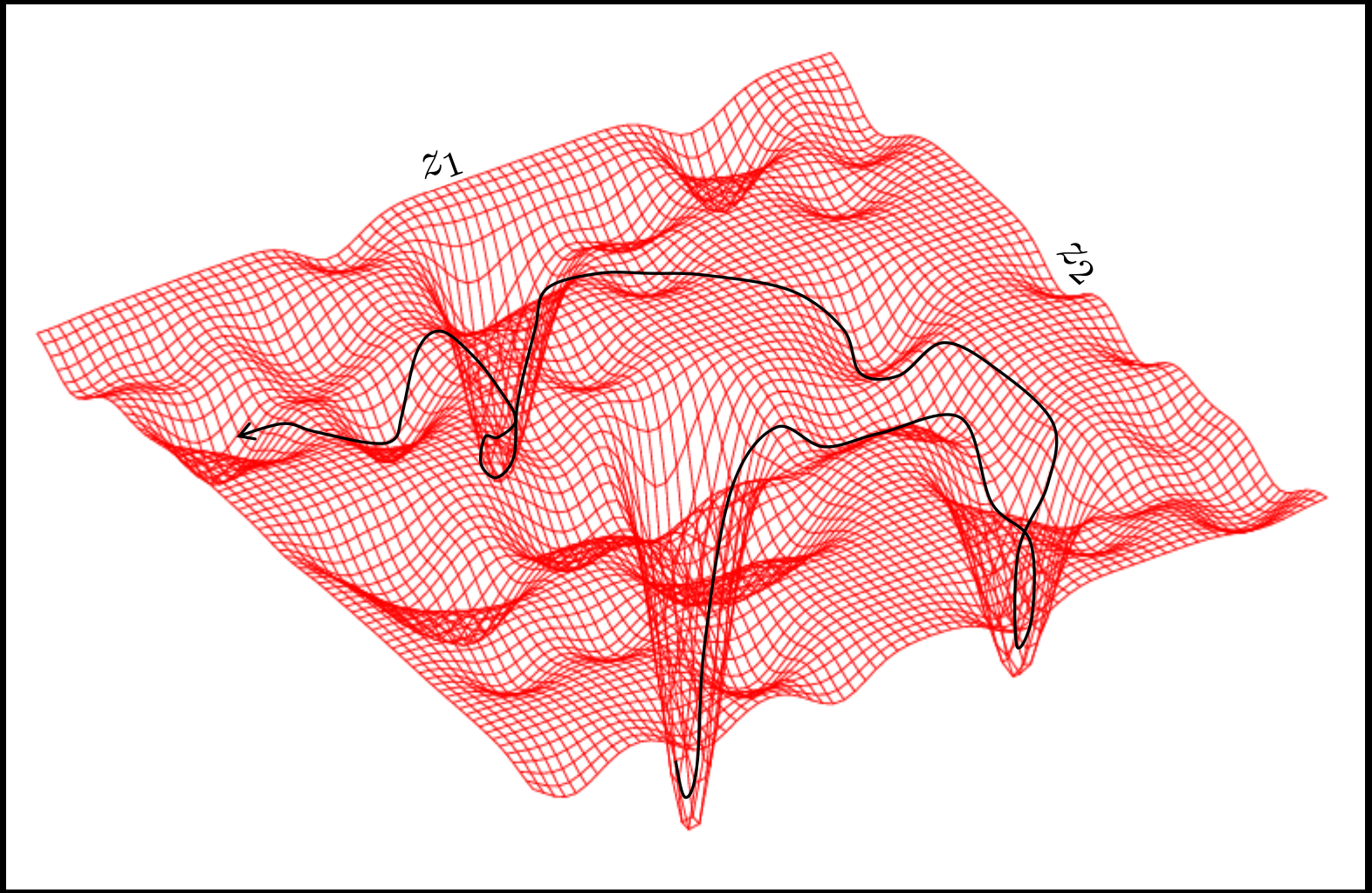


# Molecular Dynamics (MD) Simulation

*Interatomic force field*

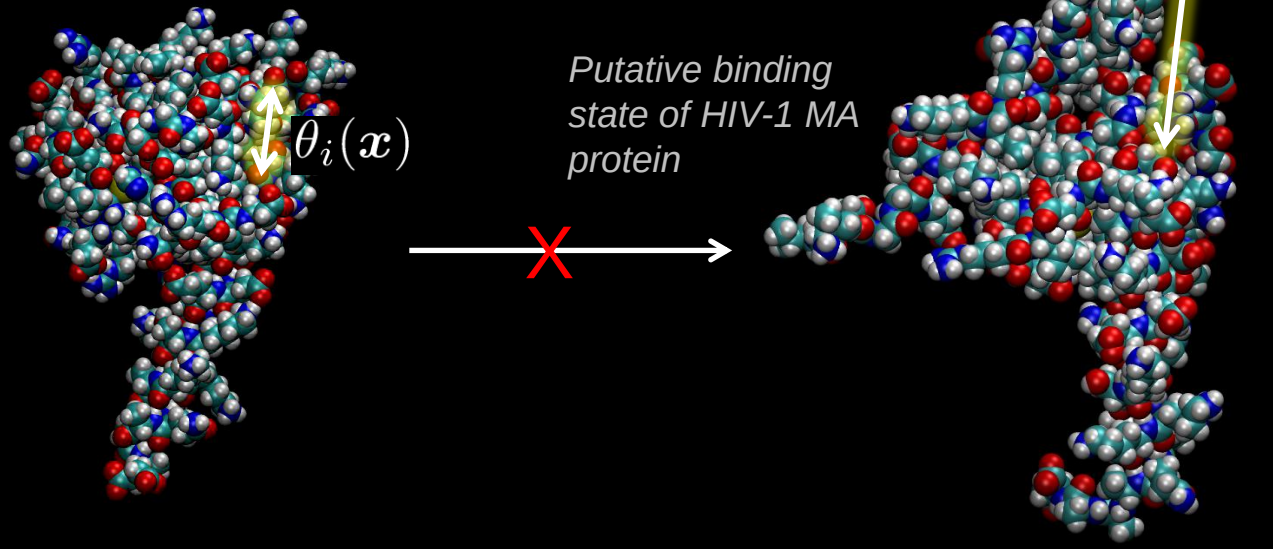
*friction*

*white noise*

*DOF's: Cartesian atom positions*

$$\underbrace{m_i\ddot{x}_i = -\frac{\partial V(\boldsymbol{x})}{\partial x_i}}_{\text{"m a = F"}} \underbrace{- \gamma m_i \dot{x}_i + \sqrt{2k_B T\gamma}\ \eta_i(t)}_{\text{thermostat}} \quad x_i \in \{r_{i\alpha} | i = 1 \ldots N;\ \alpha = x, y, z\}$$

*HIV-1 MA protein (PDB 1HIW) 1 nanosec. MD NAMD/CHARMM*




*Putative binding state of HIV-1 MA protein*

*MD alone is not good at broadly sampling interesting collective variables*

# Temperature-Accelerated MD Simulation

Maragliano and Vanden-Eijnden, *Chem Phys Lett* 426:168 (2006)

*Extended potential energy*

***Collective variables***

$$U(\boldsymbol{x}, \boldsymbol{z}) = V(\boldsymbol{x}) + \frac{1}{2} \cdot \sum_{j=1}^{M} [\theta_j(\boldsymbol{x}) - z_j]^2$$

*Auxiliary (slow) variables*

*Atomic dynamics*

$$m_i \ddot{x}_i = -\frac{\partial V(\boldsymbol{x})}{\partial x_i} - \cdot \sum_{j=1}^{M} [\theta_j(\boldsymbol{x}) - z_j] \frac{\partial \theta_j(\boldsymbol{x})}{\partial x_i} - \gamma m_i \dot{x}_i + \sqrt{2 k_B T \gamma}\, \eta_i(t)$$

*friction* *white noise*

*"harmonic restraints"*

*Aux. variable dynamics (overdamped)*

$$\bar{\gamma} \bar{m}_j \dot{z}_j = \cdot [\theta_j(\boldsymbol{x}) - z_j] + \sqrt{2 k_B \bar{T} \bar{\gamma}}\, \eta_j(t)$$

$\bar{\gamma} \gg \gamma$

*Physical free energy gradients!*

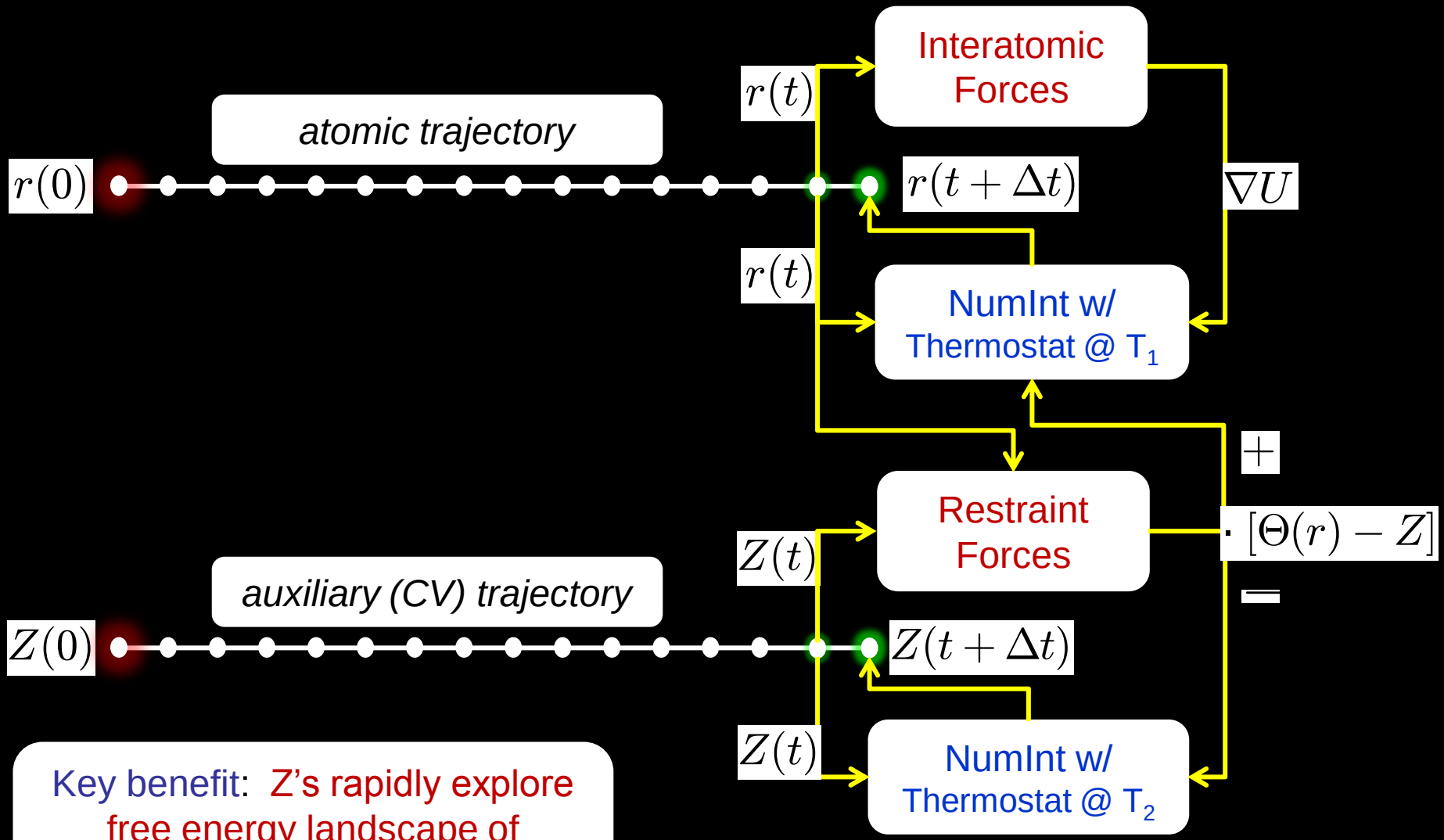
$$\bar{\gamma} \bar{m}_j \dot{z}_j = -\frac{\partial G_\kappa(\boldsymbol{z}; T)}{\partial z_j} + \sqrt{2 k_B \bar{T} \bar{\gamma}}\, \eta_j(t)$$

*Taking*

$$\bar{T} > T$$

*accelerates exploration of z!*

# TAMD generates “accelerated” trajectories

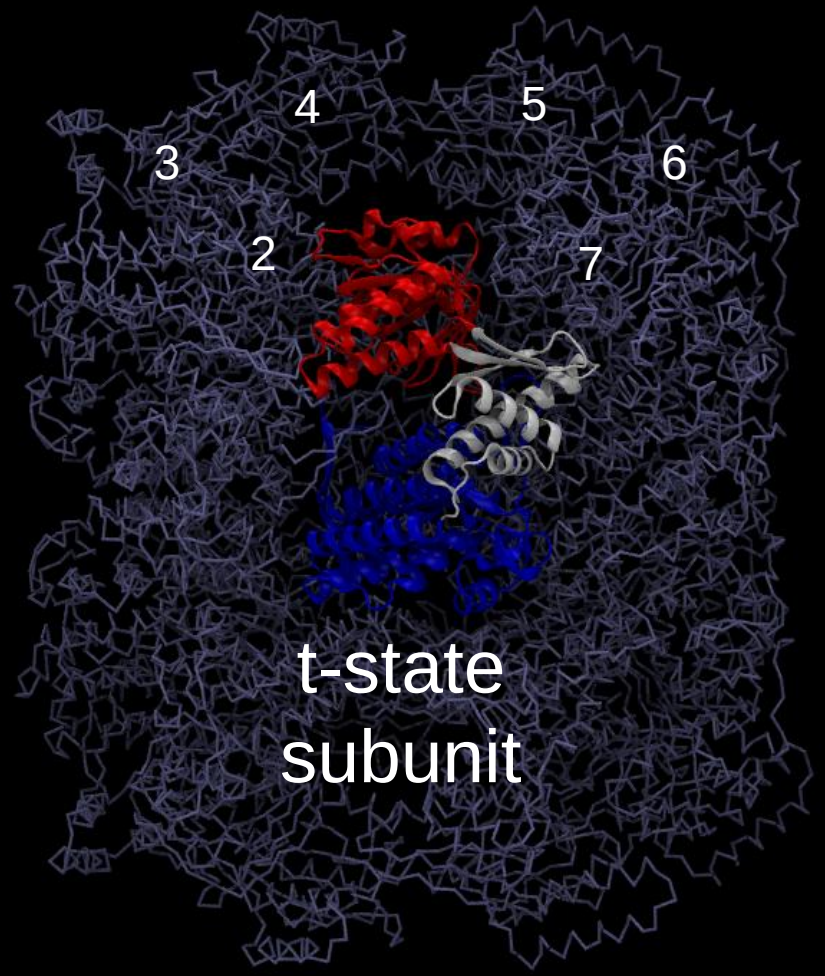



Key benefit: Z’s rapidly explore free energy landscape of specified collective variables

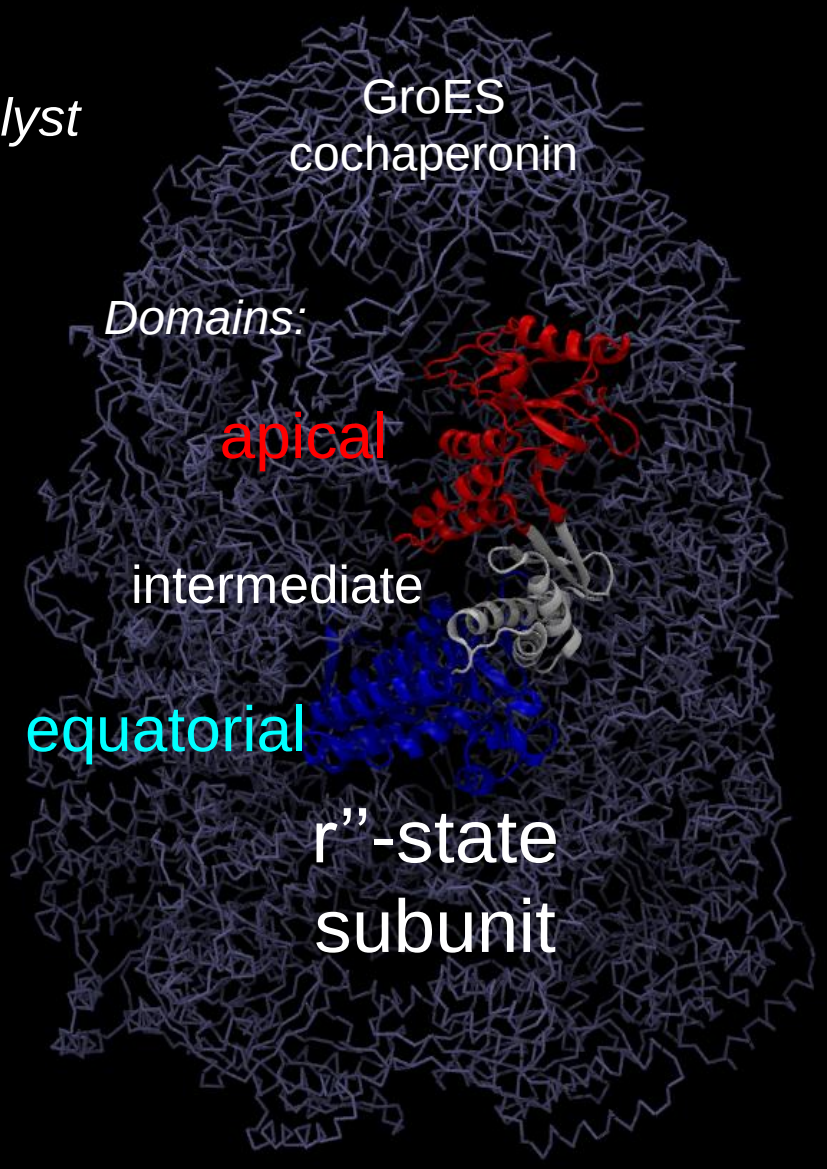
# TAMD: Large-Scale Conformational Search

*E. coli* GroEL chaperonin

*A homotetradecameric protein-folding catalyst*



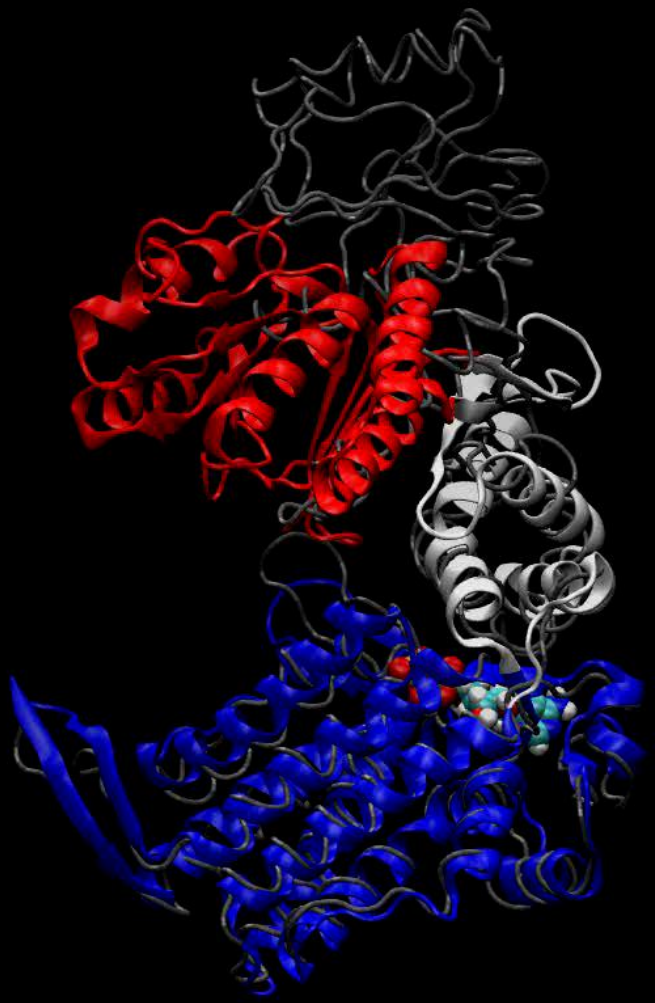

Braig, *Nat Struct Biol* **2**:1083 (1995) (1OEL)




Xu, *Nature* **388**:741 (1997) (1AON)

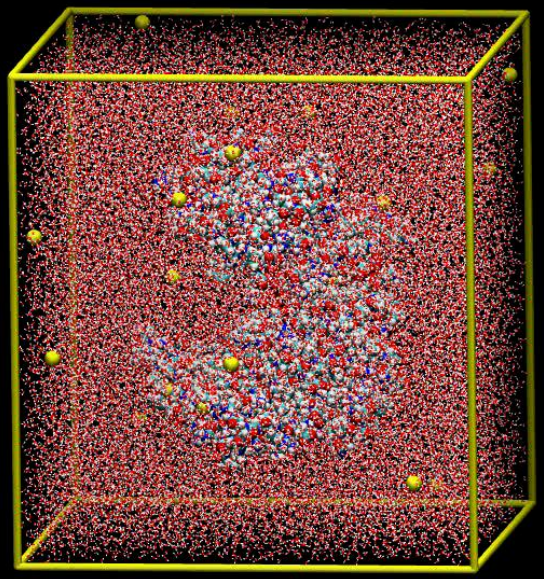
# Conformational Prediction in the GroEL Subunit using TAMD

Abrams and Vanden-Eijnden, *PNAS* 107:4961 (2010)



121,685 atoms
310 K, 1 bar
40 ns duration
$k_B T_2$ = 6 kcal/mol
Z: subdomain COM's

CHARMM/NAMD v2.7b1
Equip: TACC Lonestar



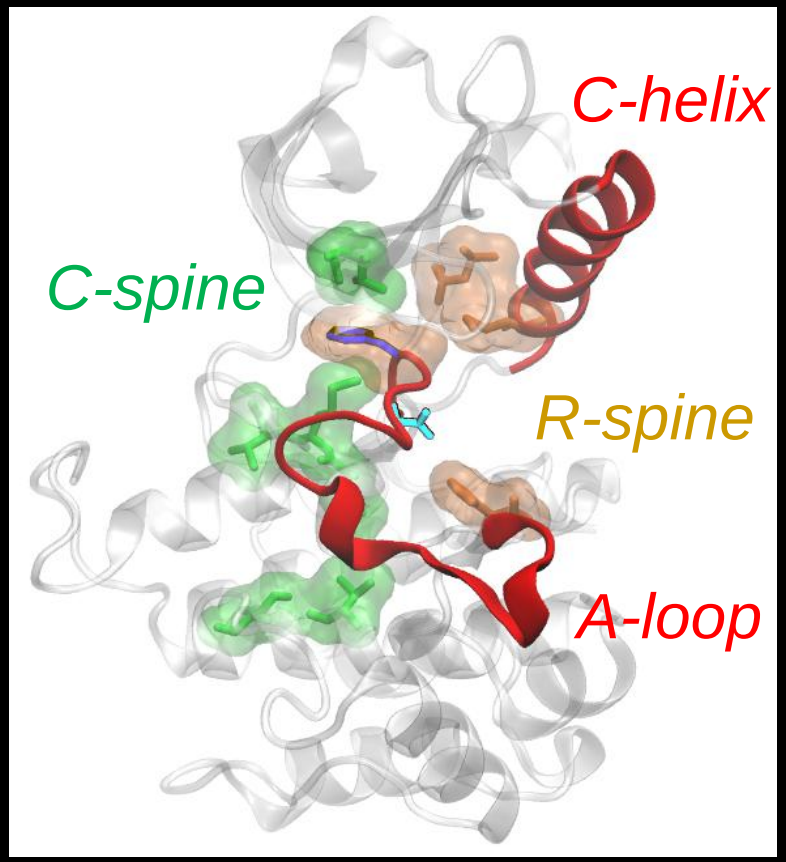
Movie:
668 frames
@ 60 ps/frame

# Conformational Sampling in the Insulin-Receptor Kinase using TAMD

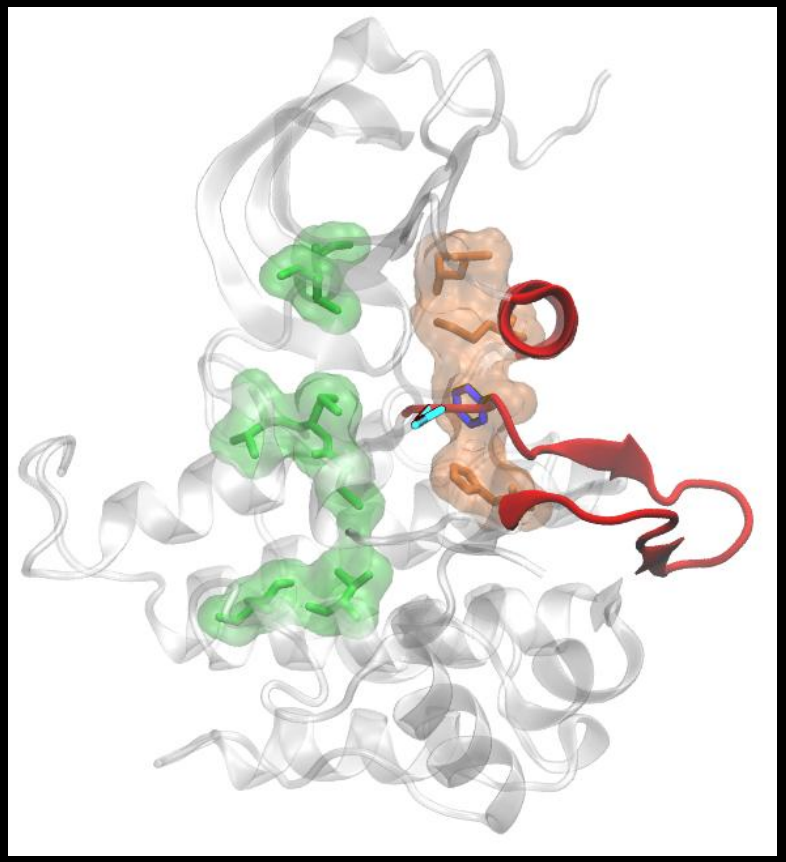
Vashisth, Maragliano, and Abrams, *Biophys J* 102:1979 (2012)

*Crystal structures*

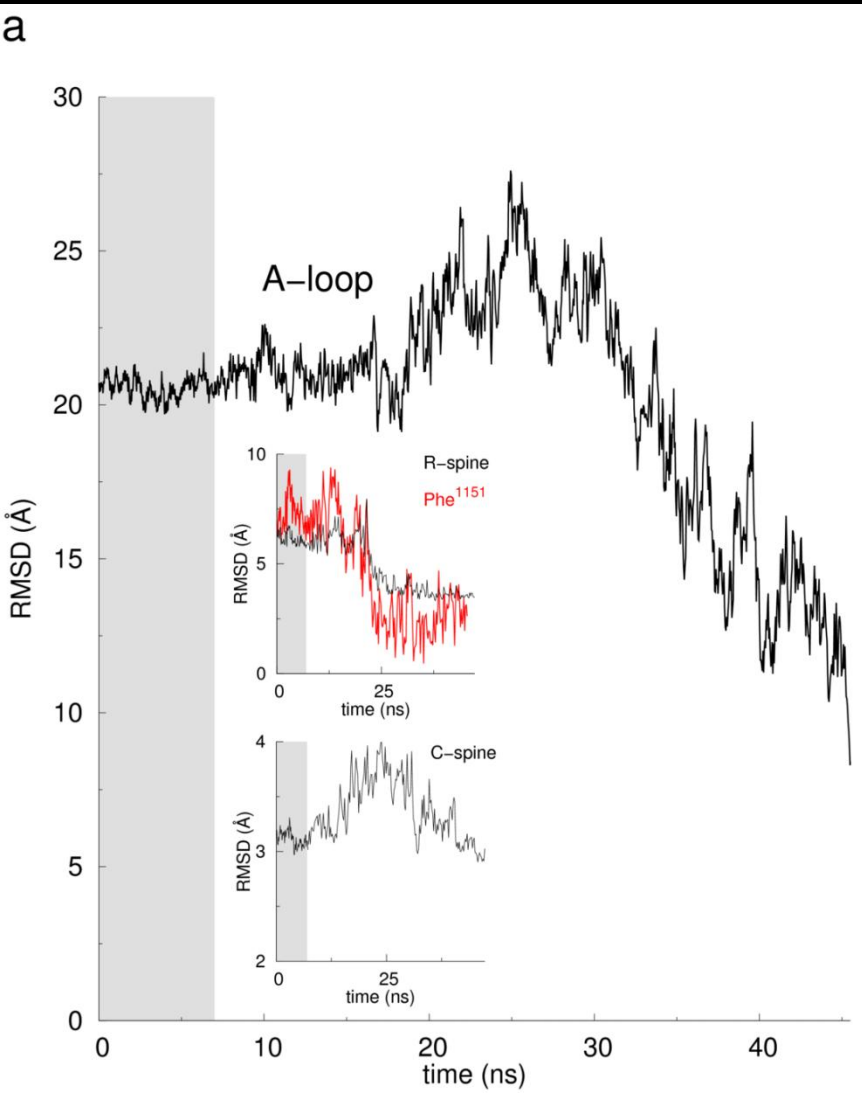
*inactive*

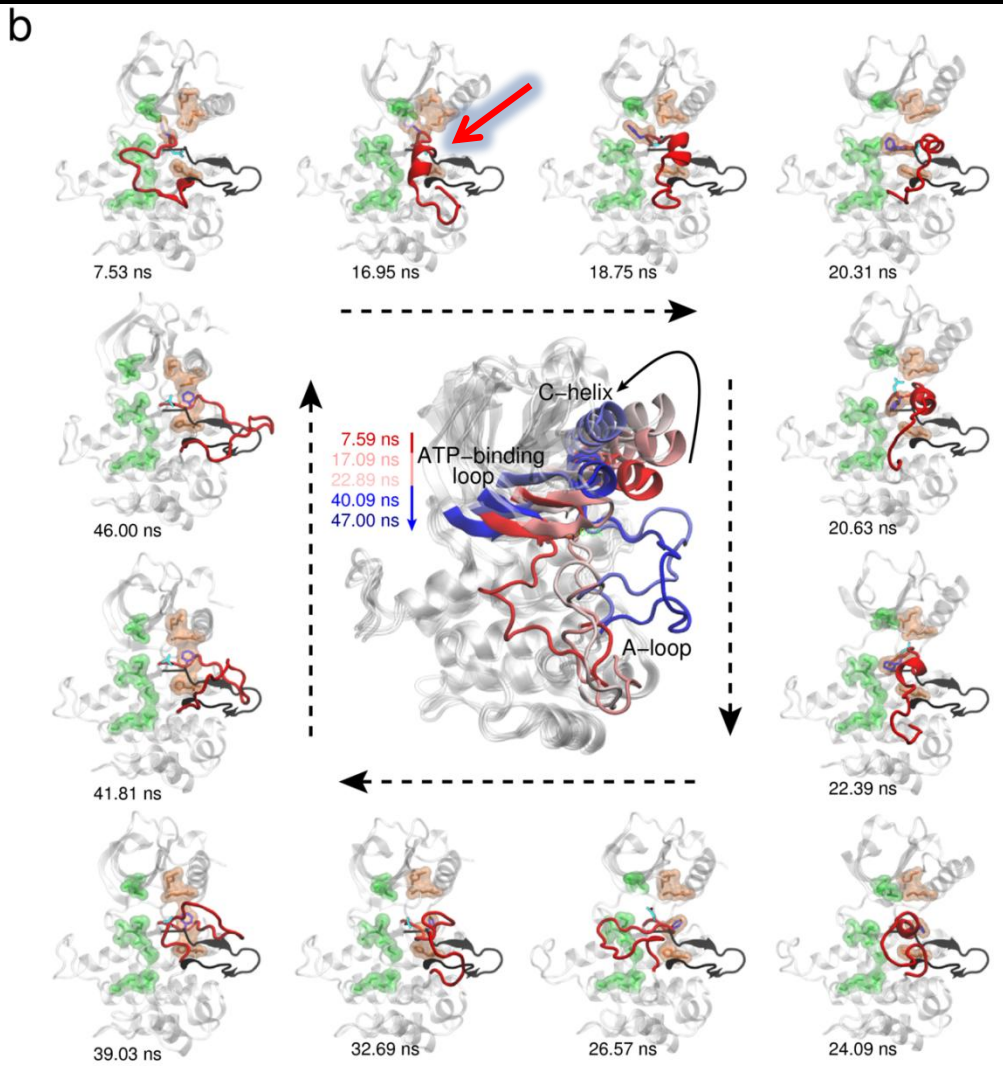



*active*



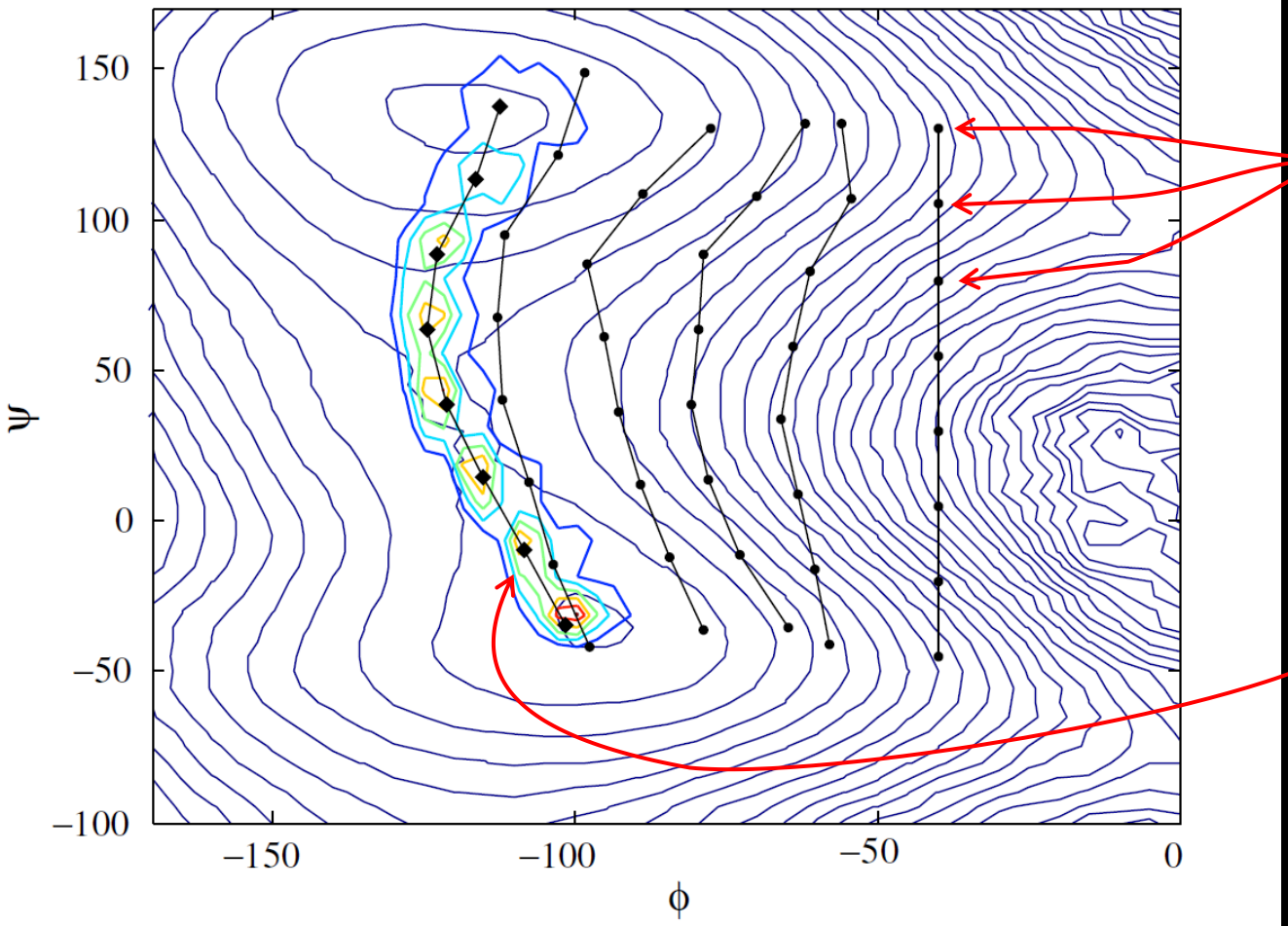
# IRK: TAMD-induced "activation" predicts an α-helical A-loop intermediate




**Is this representative of the pathway of minimal free energy?**

# String Method: Finding Pathways of Minimal Free Energy through Conformational (CV) Space

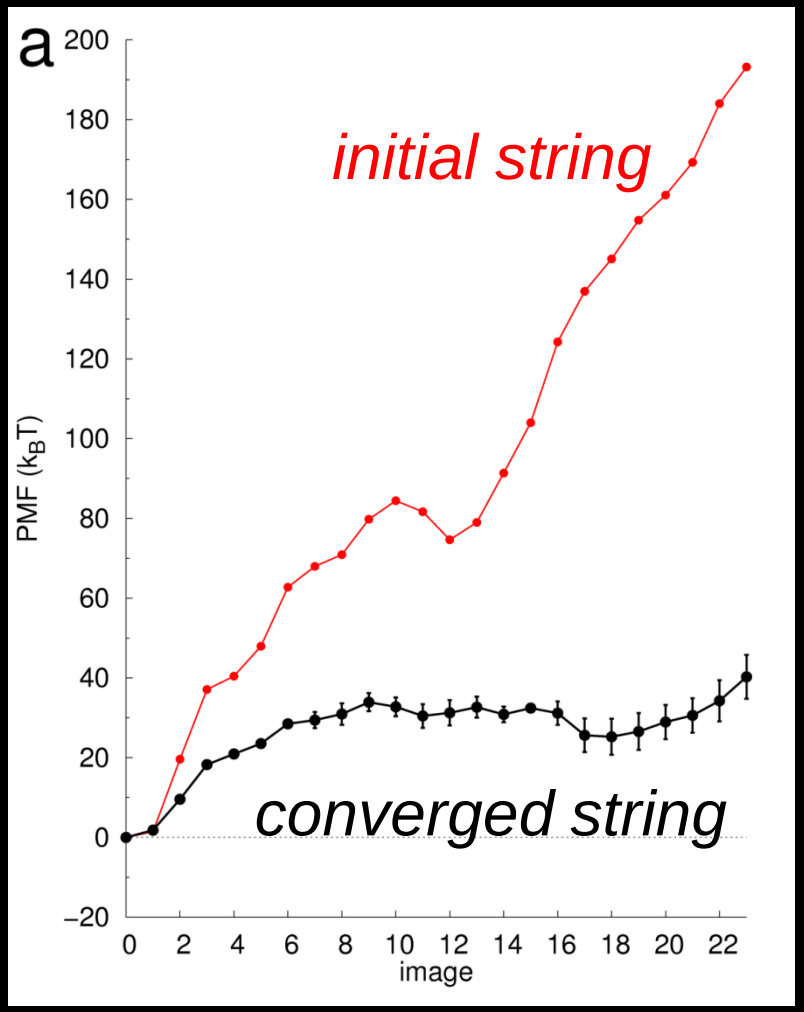


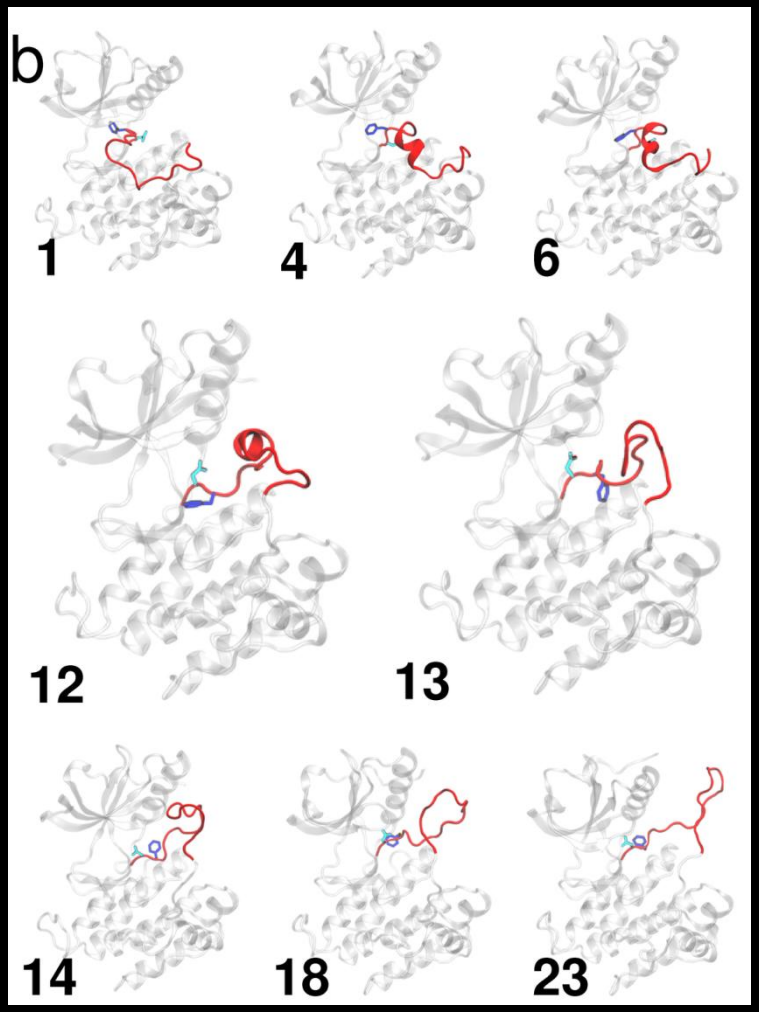

MD systems restrained at points in CV space parameterized to form a discretized string through CV space

Evolution of string converges to Minimum Free Energy Pathway (MFEP)

Maragliano, L., Fischer, A., Vanden-Eijnden, E., & Ciccotti, G. (2006). String method in collective variables: minimum free energy paths and isocommittor surfaces. The Journal of Chemical Physics, 125(2), 24106. doi:10.1063/1.2212942

# String Method: IRK A-loop α-helical intermediate is robust



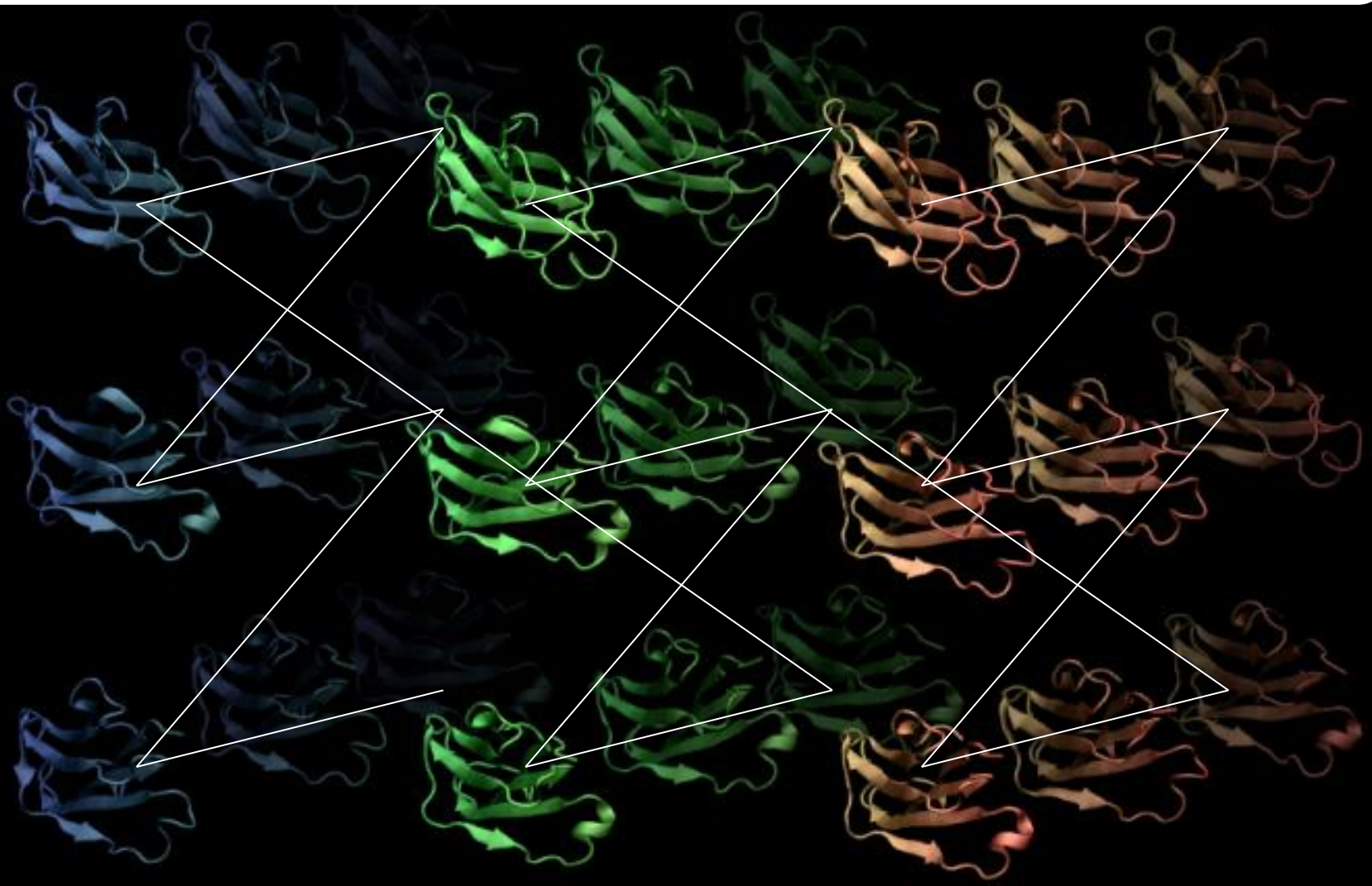
# $\beta_2$microglobulin and its amyloidogenicity


Black: Native ("H$\beta_2$m")
Red: Amyloidogenic ($\Delta$N6)
- cis-trans peptide isomerization at Pro32
- low pH; protonation of His31 + His84

Eichner, et al. 2011; Mol Cell, 41(2), 161-72

- WT amyloidogenic state "$I_T$": too transient to observe
- Model H$\beta_2$m-to-$I_T$ using $\Delta$N6 as a template
- *What are roles of protonatable histidines?*

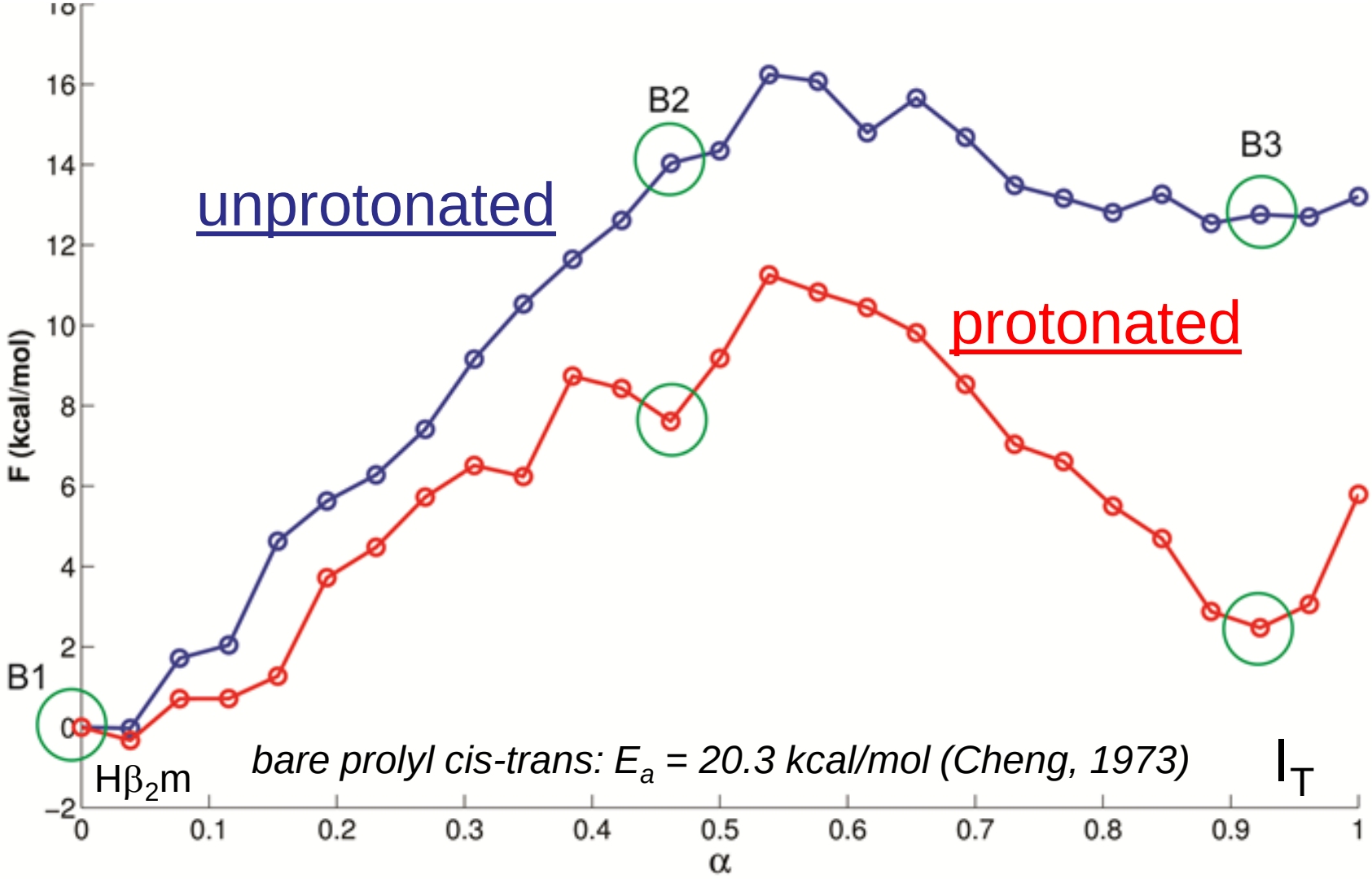
# Method: On-the-fly string with 27 concurrent replicas in one composite solvent system

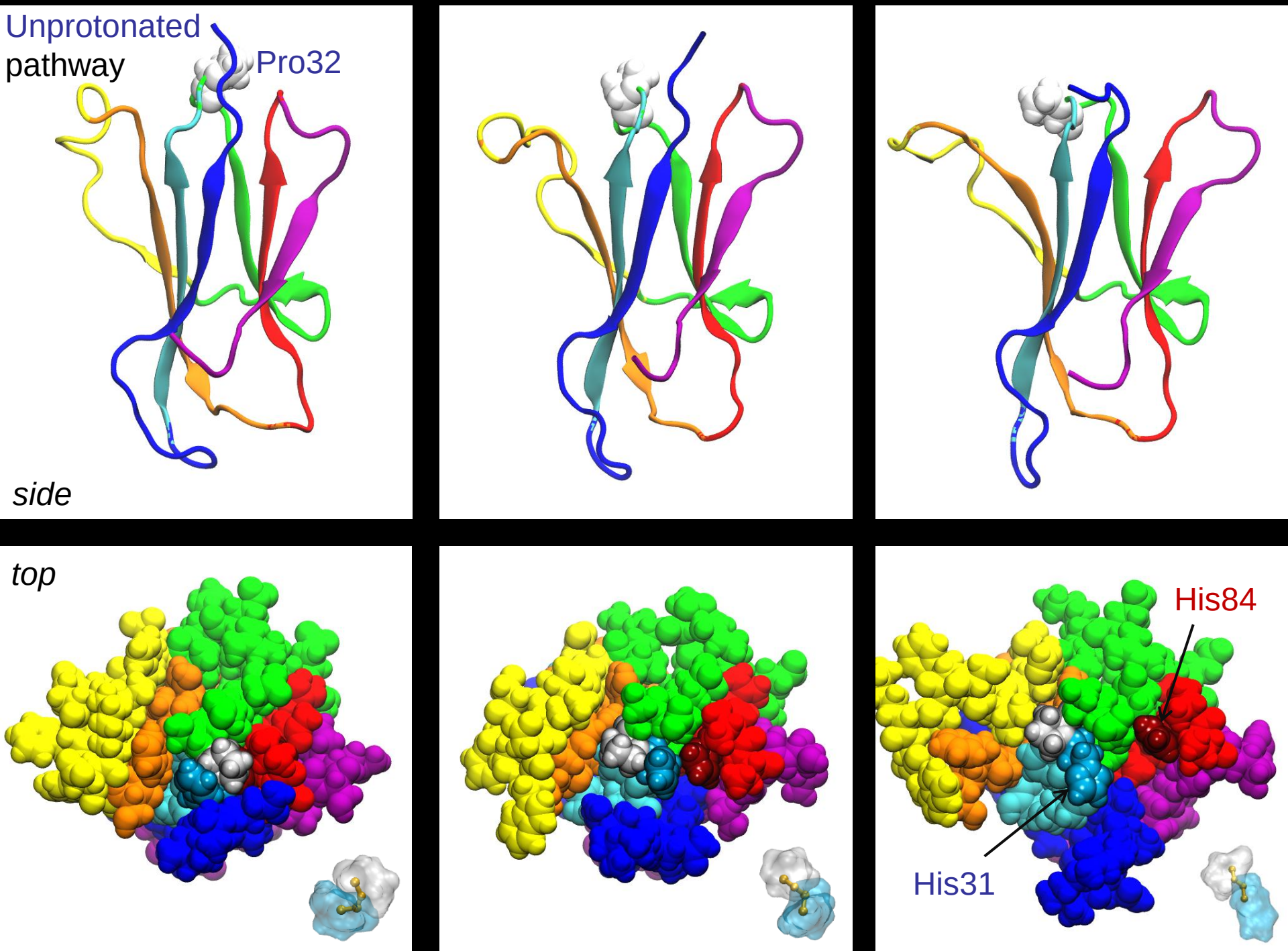


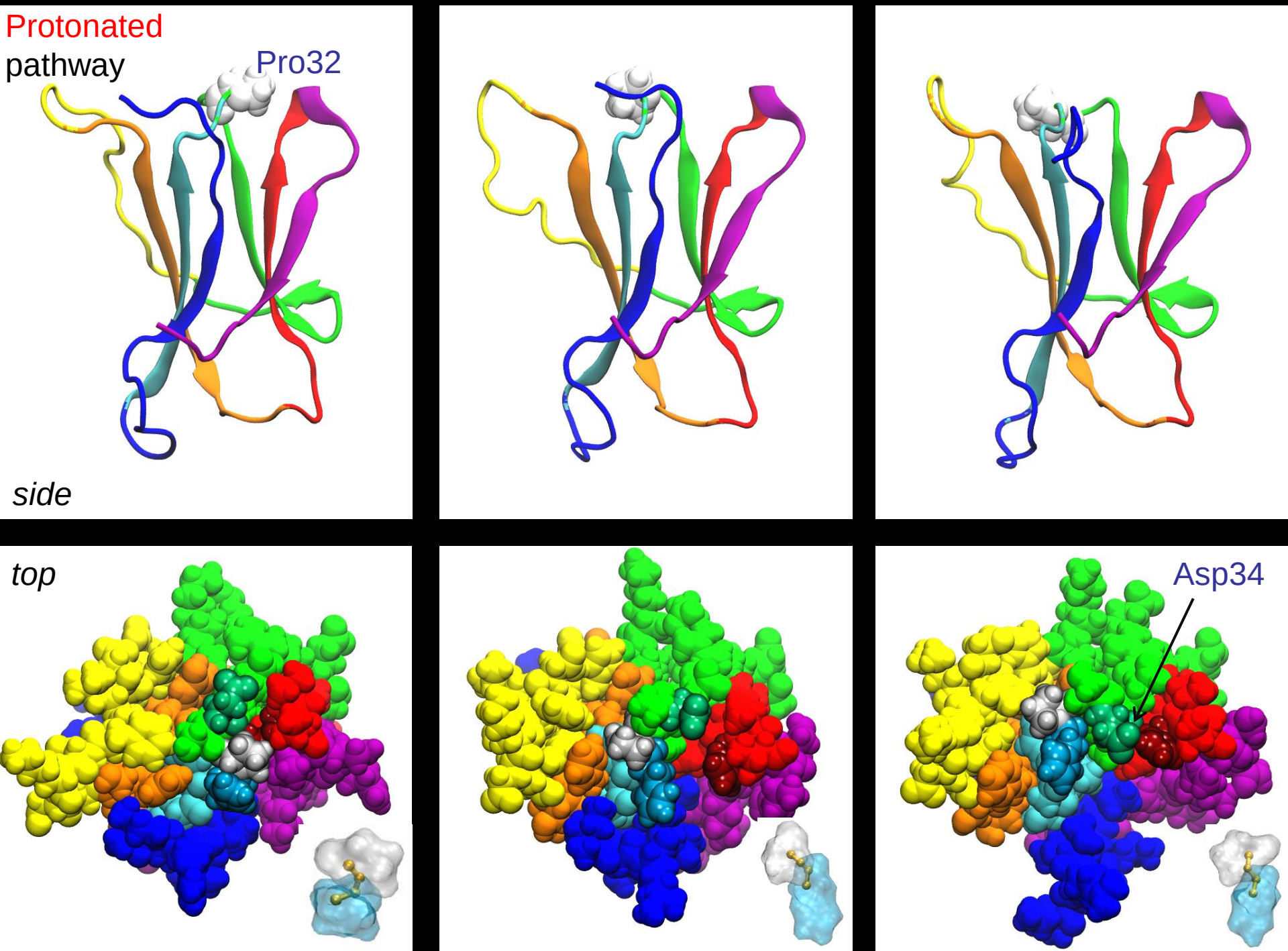
CV's: Pro32 dihedral plus 20 relevant inter-C$\alpha$ distances

# Free energy along the MFEPs: Unprotonated vs Protonated Histidines

**Stober and Abrams (JPCB submitted)**




Unprotonated
pathway
Pro32
side
top
His84
His31


Protonated
pathway
Pro32
side
top
Asp34

# Collective-variable-enhanced biomolecular simulations

- Temperature-Accelerated MD (TAMD)
  - Enhanced conformational exploration
  - Generation of initial paths
- String Method
  - Convergence of minimal free-energy paths
  - Energetics and mechanisms of conformational transitions


Acknowlegments

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