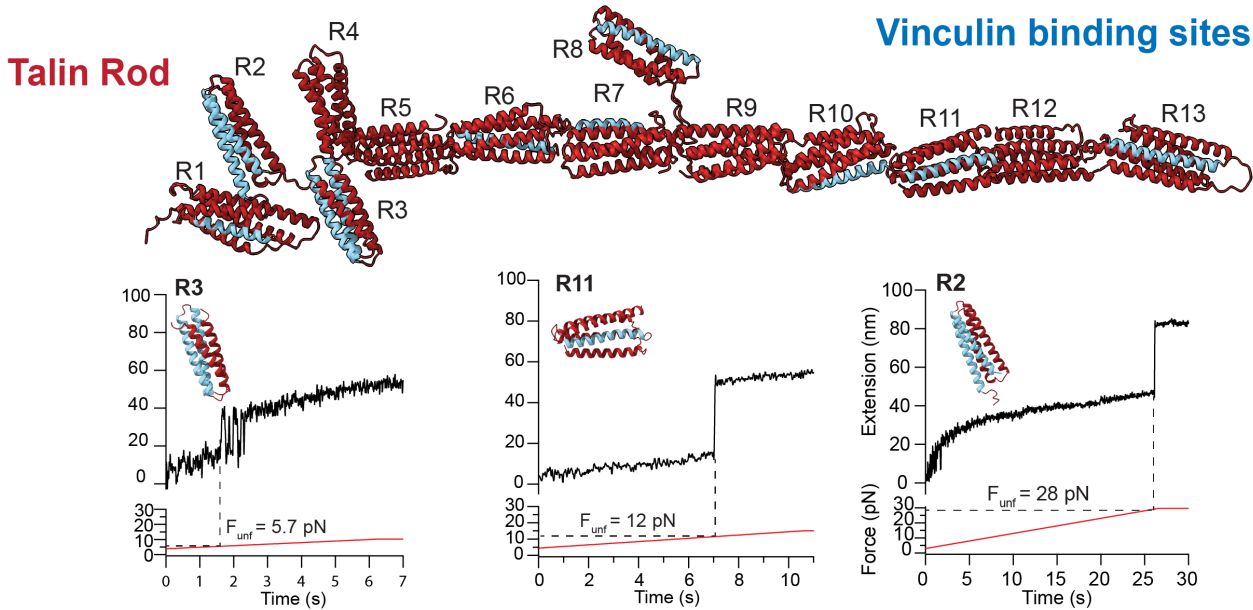


The Entropy of the Folded State Determines the Mechanical Response of Force-Sensing Proteins

Rahul Chowbey¹, Inés Martínez-Martín¹, Rafael Tapia-Rojo¹

Physics Department, King's College London, London, WC2R 2LS, United Kingdom

What Dictates the Mechanical Response of a Protein ?



Theories and Models

Unfolding Rate using the Bell-Evans model,

$$K^u(F) = K_0^u * \exp\left[\frac{F * X_\beta^u}{KT}\right]$$

Rolding Rate using the Dudko-Hummer-Szabo model,

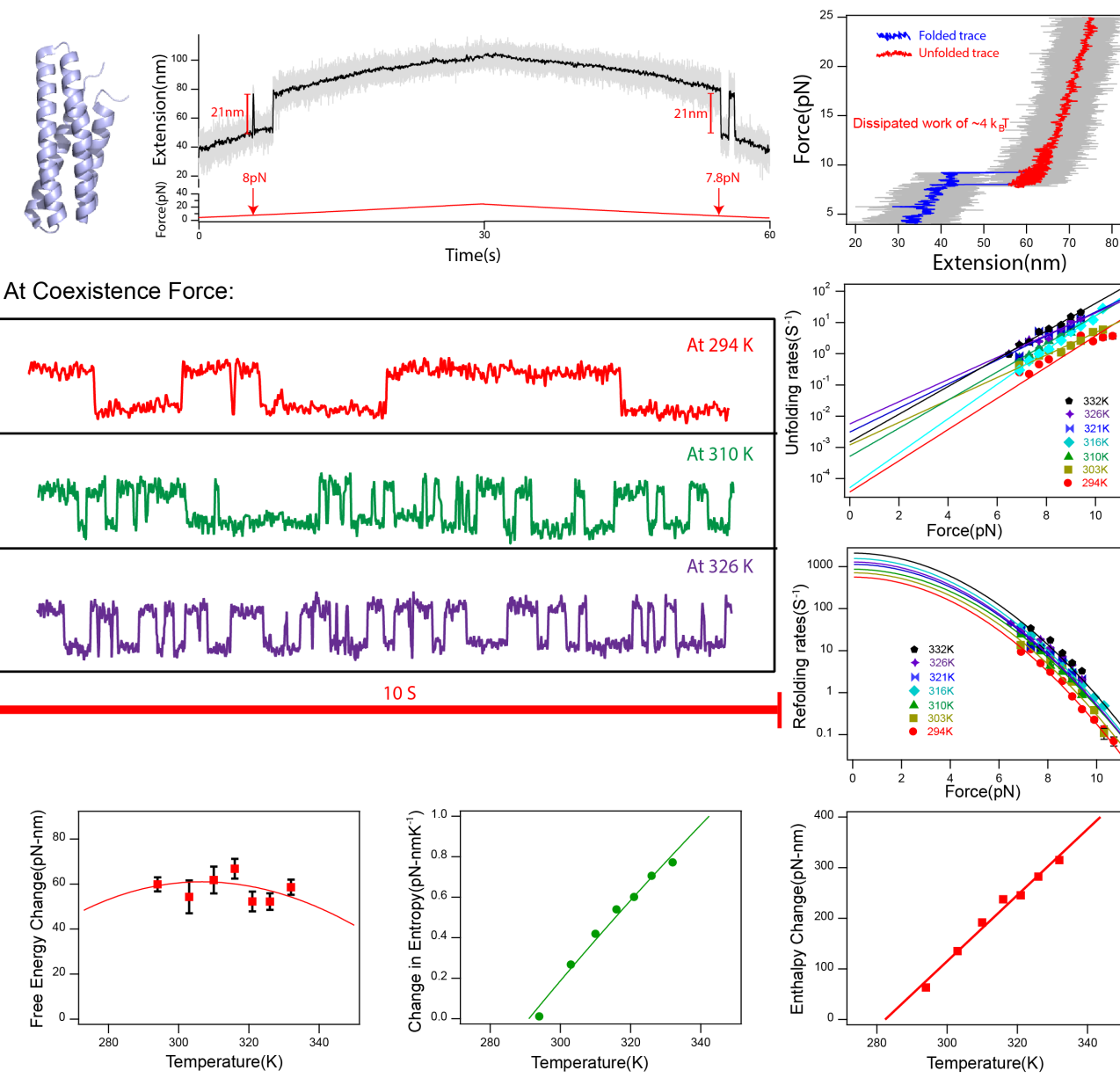
$$K^f(F) = K_0^f \exp\left[\left(-\frac{L_c}{L_k}\right) \left\{ \ln \sinh\left(\frac{FL_k}{KT}\right) - \ln\left(\frac{FL_k}{KT}\right) \right\}\right]$$

Entropy Change associated to the Protein Folding at zero force,

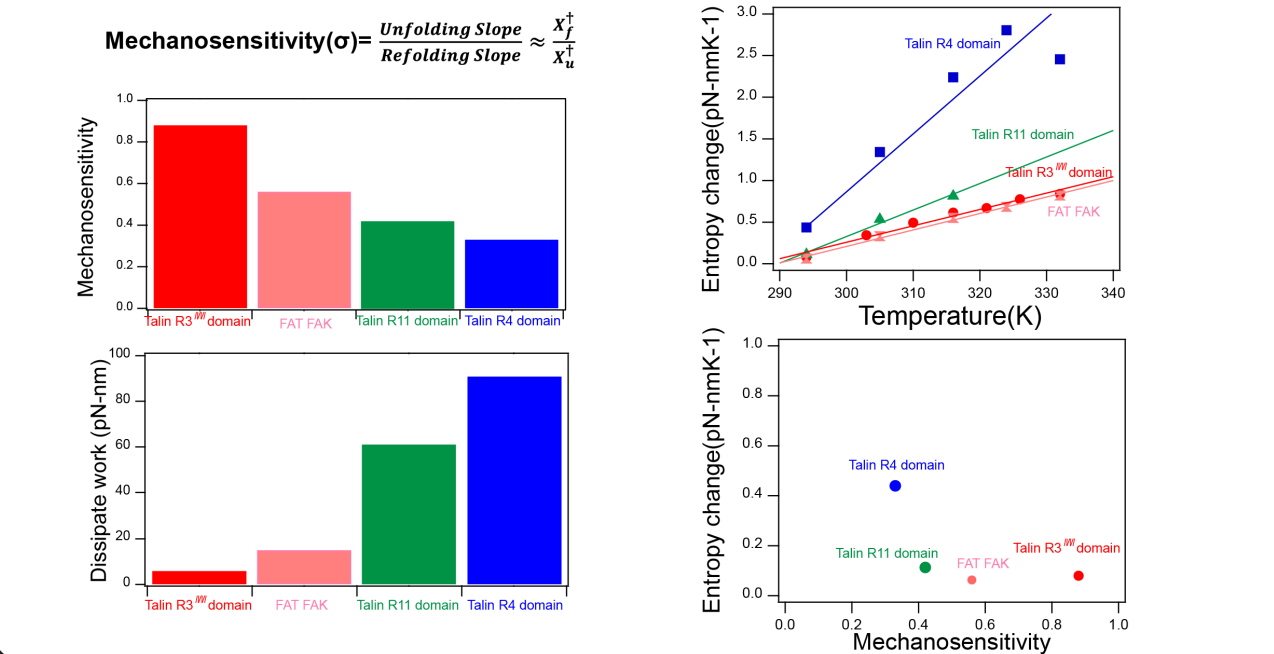
$$\Delta S_o(T) = -\frac{\partial f_c(T)}{\partial T} \Delta \lambda(f_c(T))$$

$$-\Delta Lc \left[\frac{-2f_c \coth\left(\frac{f_c L_k}{KT}\right)}{T} - \frac{2KL_n\left(\frac{f_c}{\sinh\left(\frac{f_c L_k}{KT}\right)}\right)}{Lk} + \frac{2K}{Lk} + \frac{2K}{Lk} \ln\left(\frac{KT}{Lk}\right) \right]$$

Talin R3^{III} Domain



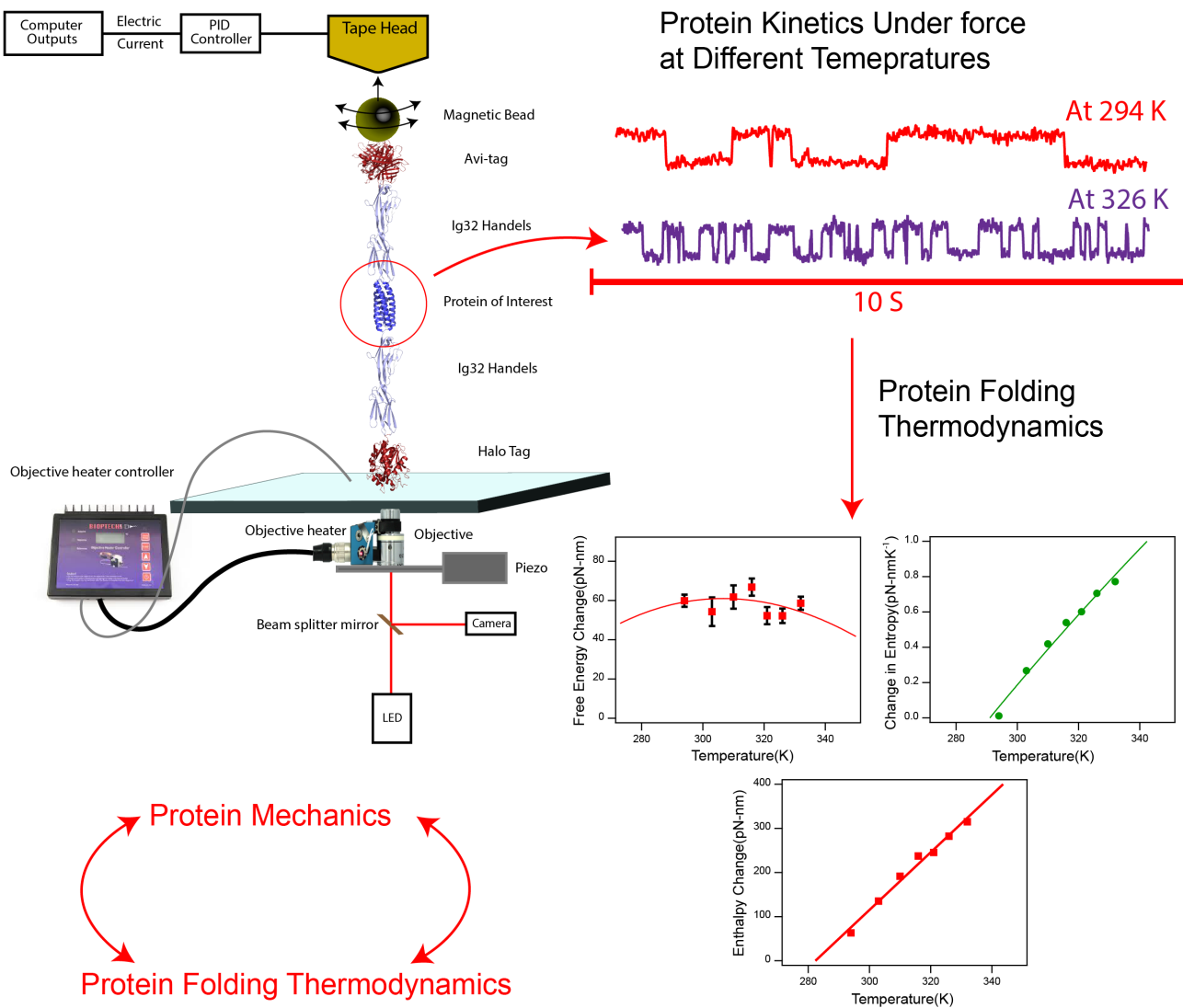
Bridging Protein's Mechanical Response with Thermodynamics



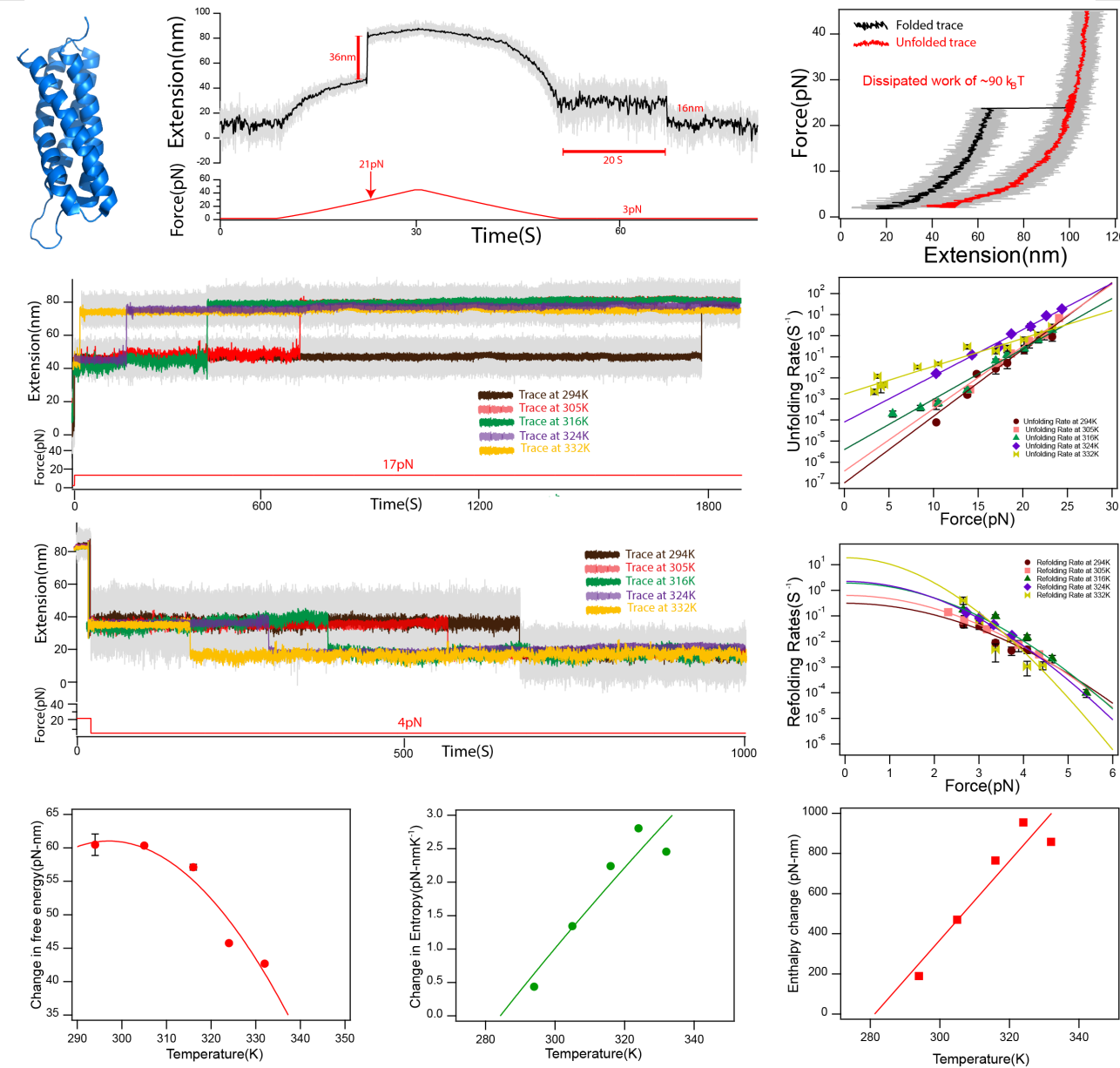
References

- Rico-Pasto, M., Zaltron, A., Davis, S. J., Frutos, S., & Ritort, F. (2022). Molten globule-like transition state of protein barnase measured with calorimetric force spectroscopy. *Proceedings of the National Academy of Sciences*, 119(11), e2112382119.
- Tapia-Rojo, R., Mora, M., & Garcia-Manyes, S. (2024). Single-molecule magnetic tweezers to probe the equilibrium dynamics of individual proteins at physiologically relevant forces and timescales. *Nature protocols*, 19(6), 1779-1806.
- Dudko, O. K., Hummer, G., & Szabo, A. (2008). Theory, analysis, and interpretation of single-molecule force spectroscopy experiments. *Proceedings of the National Academy of Sciences*, 105(41), 15755-15760.

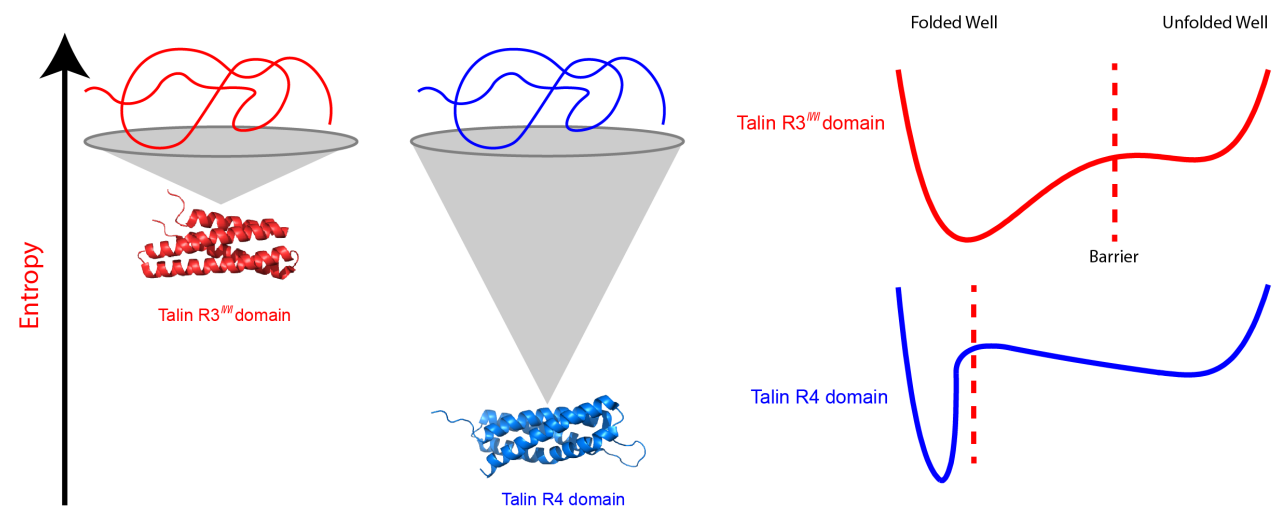
Methodology



Talin R4 Domain



Folded State Entropy Governs Protein Mechanics



Future Goals

- We will run some Molecular Dynamics Simulations to quantify folded state entropy and test if the proteins showing low entropy change have highly entropic folded state.
- We will alter the thermodynamics of the protein by introducing different chemical denaturants, stabilizers and molecular crowders to see how does that effect the protein mechanics.