Intrinsically Disordered Proteins

Extending the Model of Proteins to Account for Disorder

Maeve Andersen

Autumn Semester, 2023

Preface

- This is a trans, gender queer, and disabled presentation
- My pronouns are she/her
- While I am feminine, I am non-binary so please refrain from refferring to me as a woman

Thank You!

Introduction

History

- In 1894, Fischer developed a protein model to describe the biological function of proteins.
- In this model, the protein acts as a key of sorts, where the protein's unique shape determines its unique biological function (the lock) [3].
- This is the so called "lock and key model" which depends on proteins having rigid 3D structure [3].

Disorder in Proteins: A lack of rigid structure

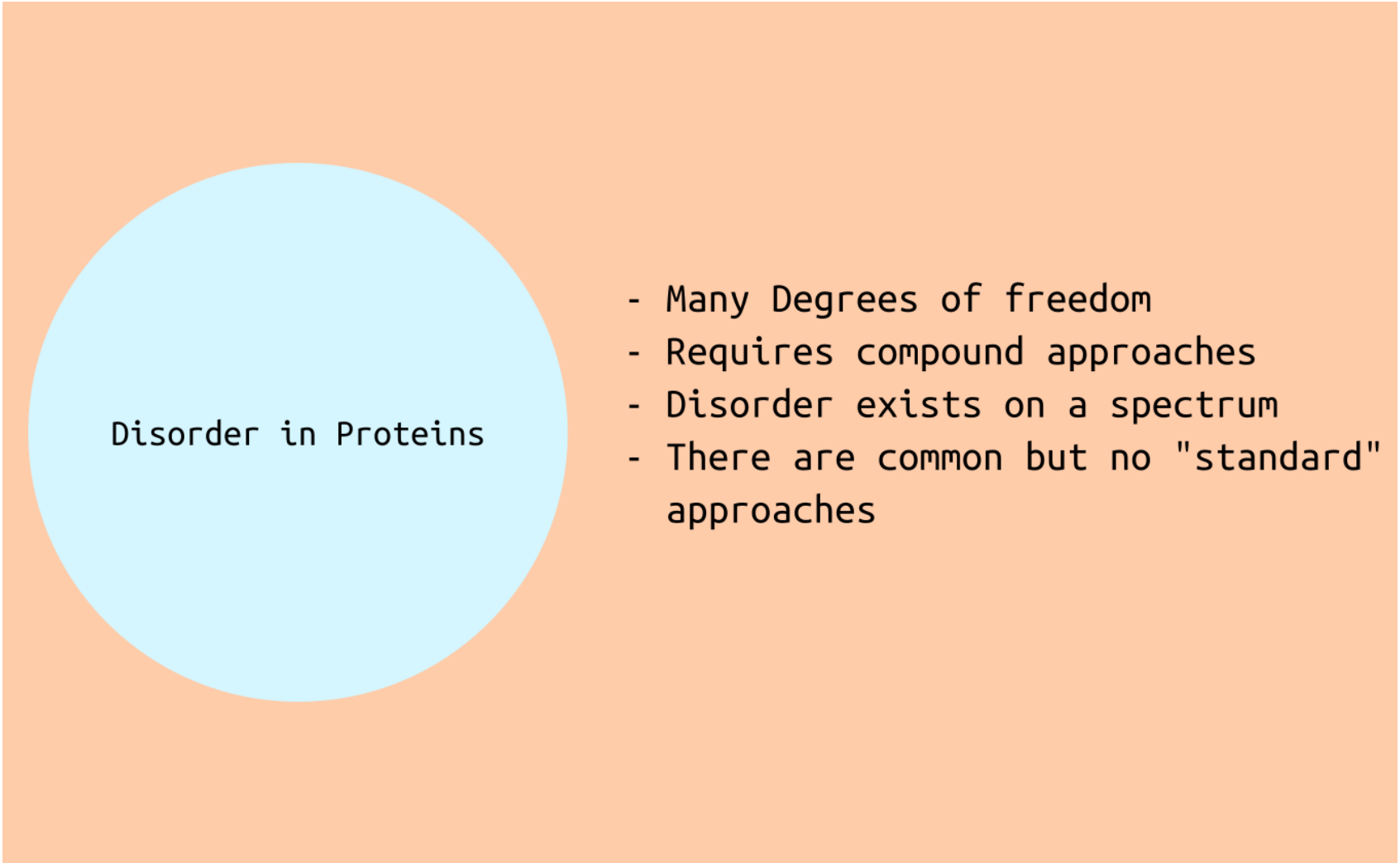

Figure: Proteins with disorder lack a rigid structure and require specialized approaches.

Motivation

Characterization of disorder in proteins is important as disordered proteins are involved in cellular signaling and regulation,[8] and are associated with human diseases, such as neurodegenerative disease, cardiovascular disease, amyloidoses, cancer, and diabetes.[7] Although challenging, modern methods of characterizing proteins can provide new insights to crucial protein function human biological mechanisms. [1].

Characterization Requires a Combination of Theory and Experiment

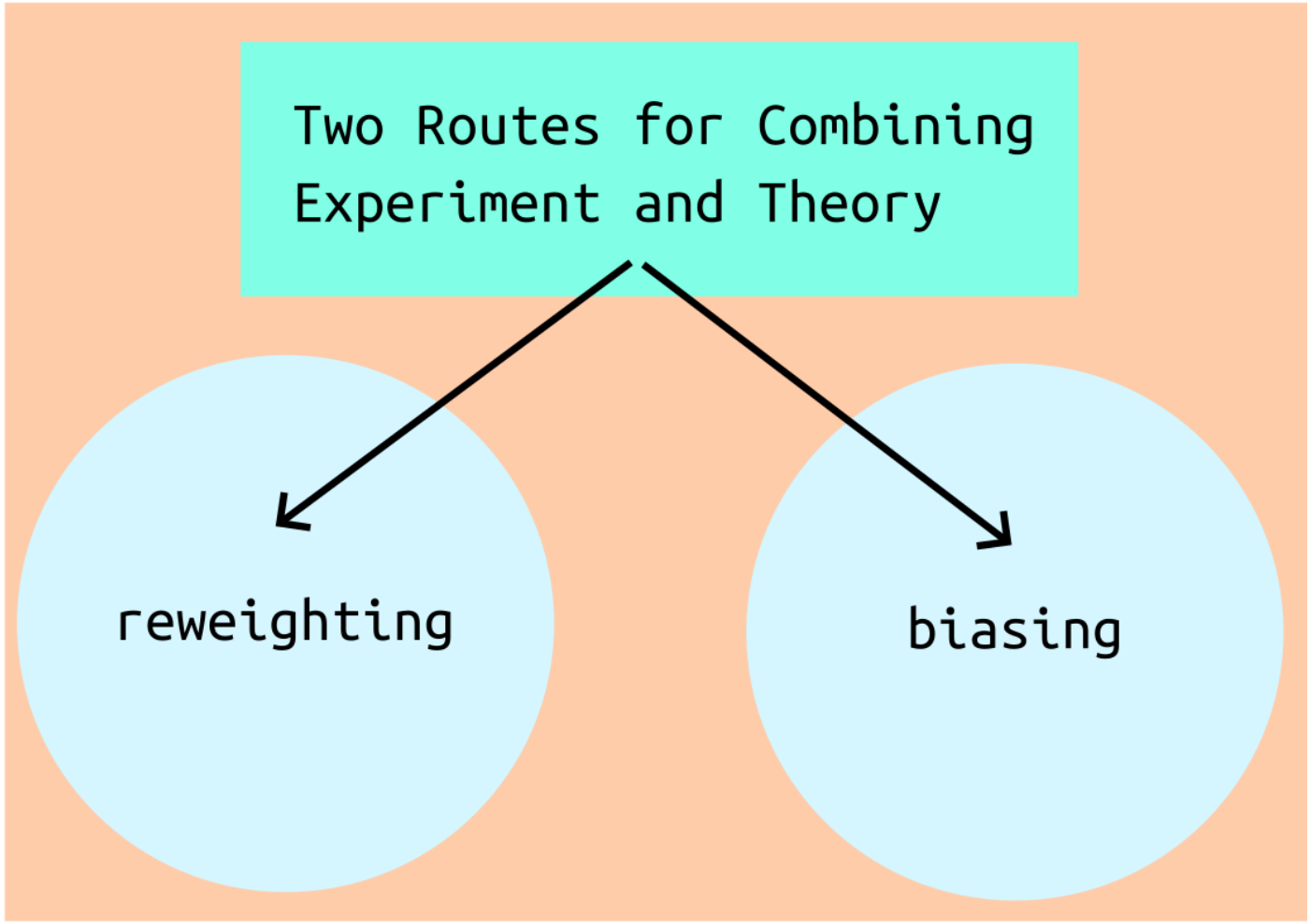

Figure: Two main ways of integrating theory and experiment [6].

Roadmap

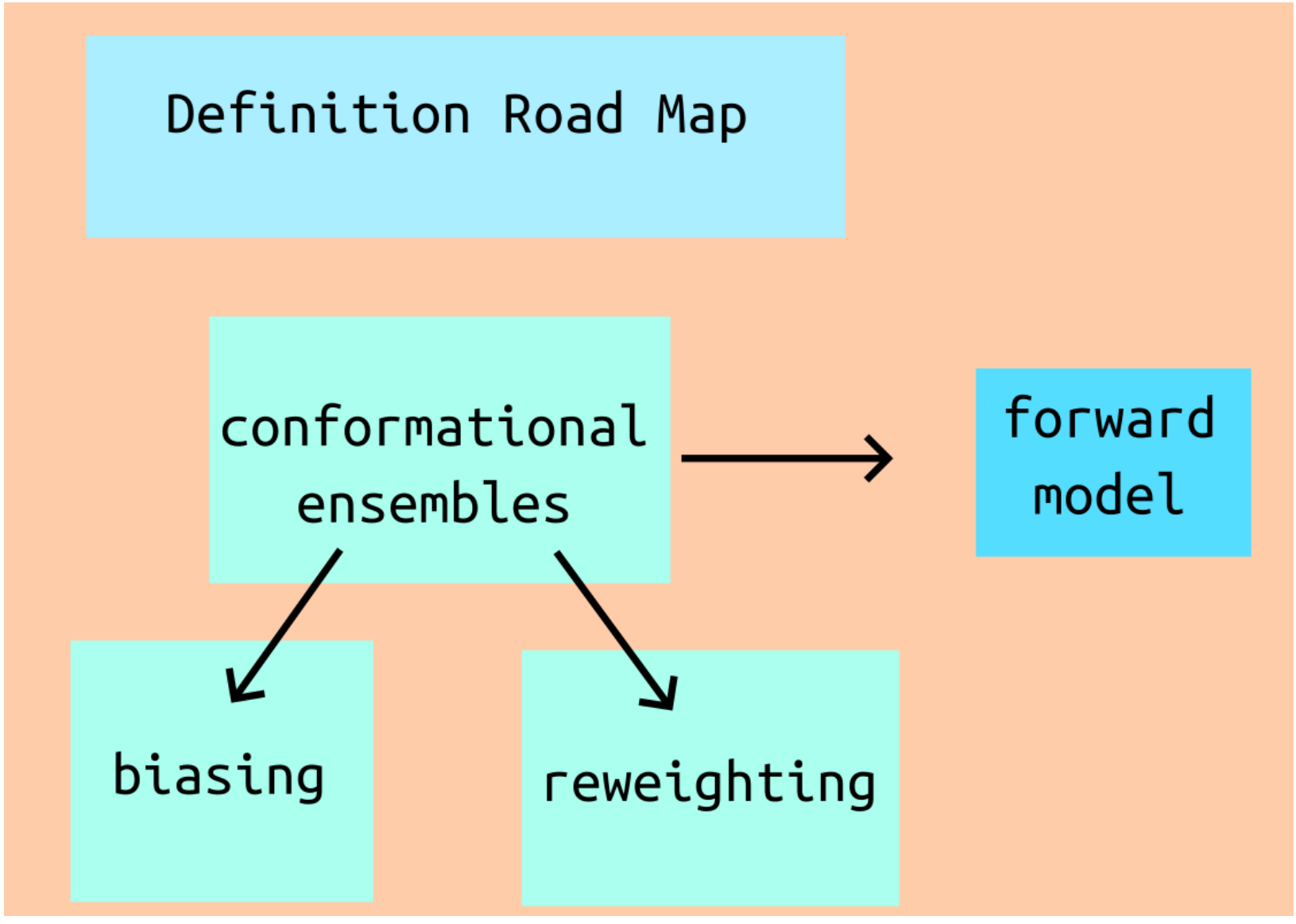

Figure: Definition roadmap

Conformational Ensembles

A Concrete Construction of a Conformational Ensemble

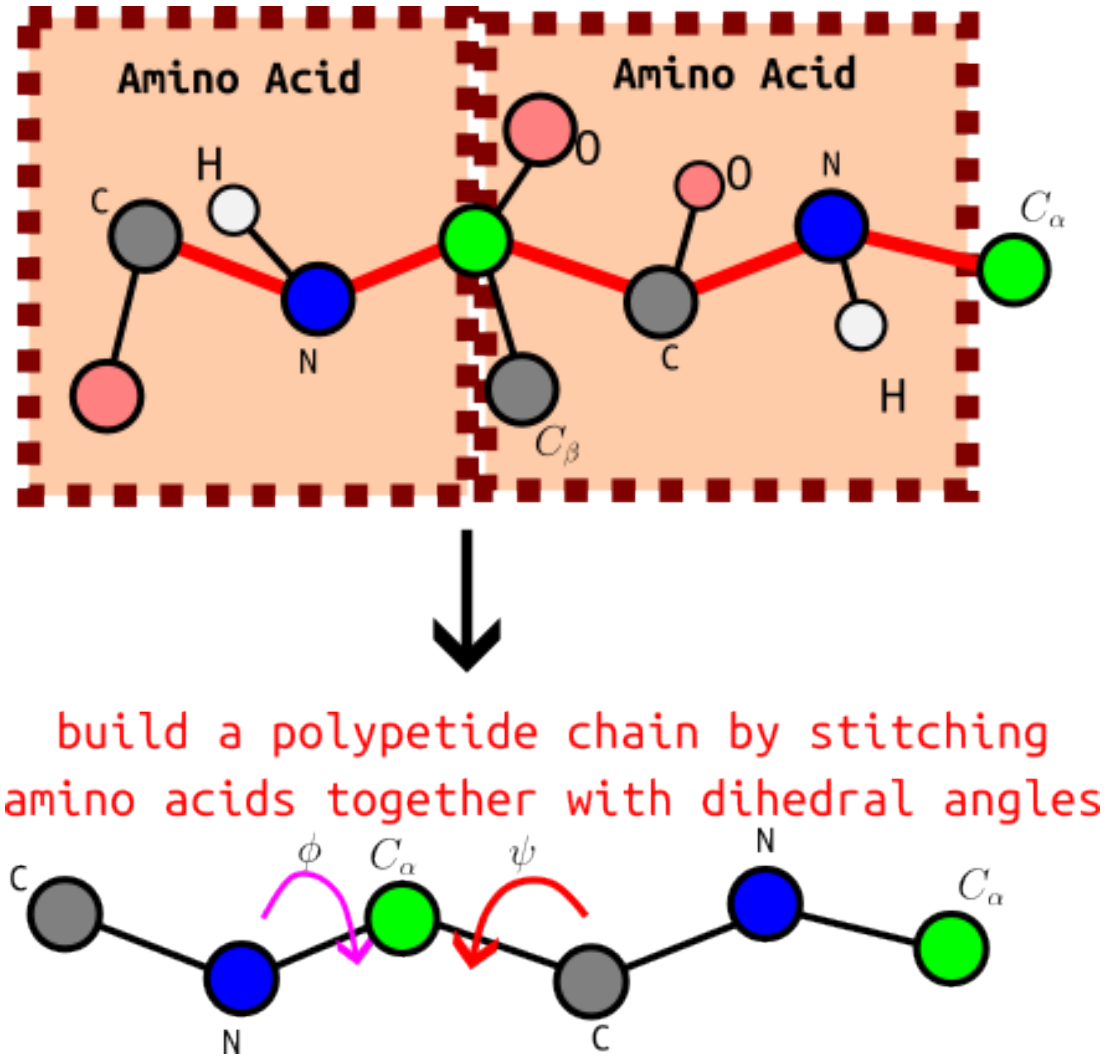

Figure: A simple method of constructing a polypetide is to chain together amino acids. In this case, the only parameter would be the dihedral angles between amino acids [5].

A Concrete Construction of a Conformational Ensemble

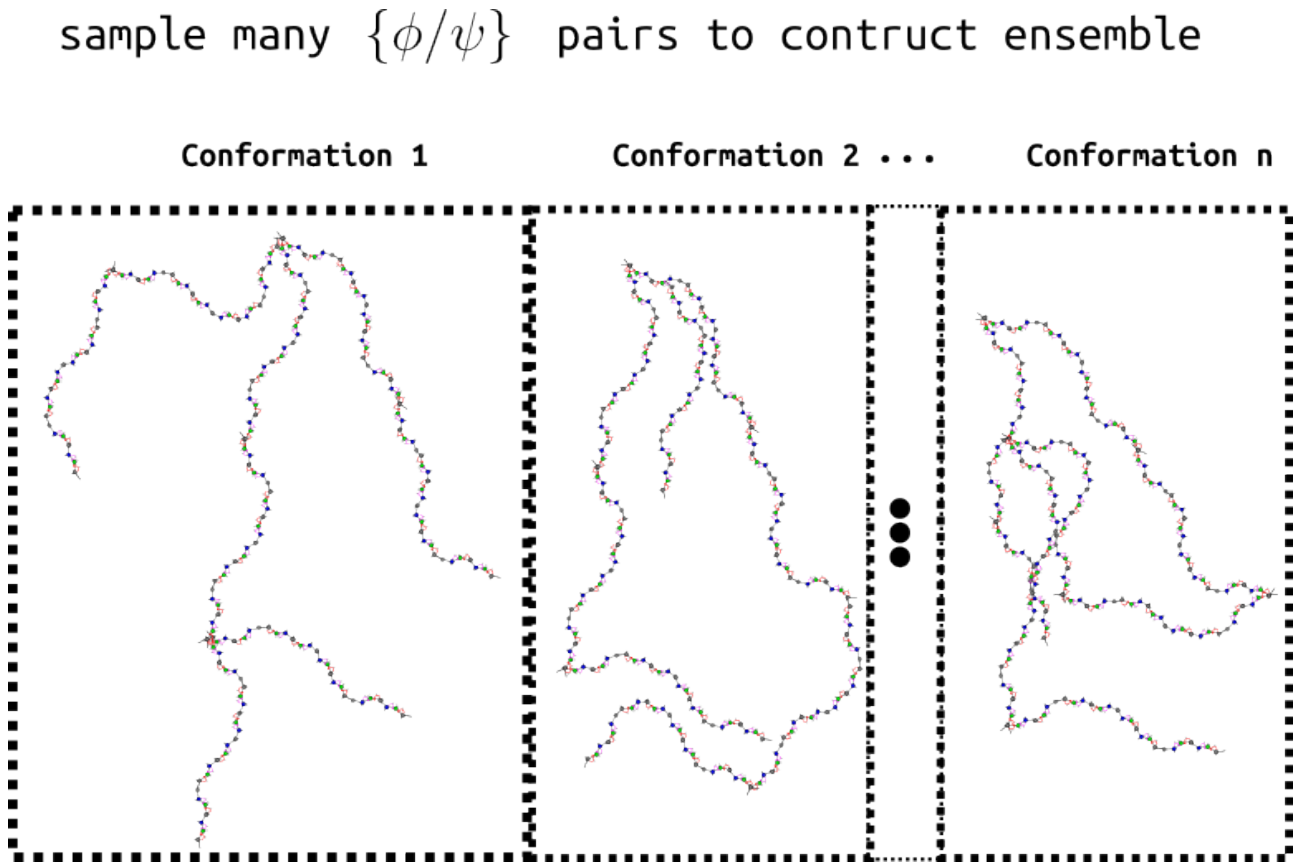

Figure: One can sample many dihedral pairs to construct an ensemble, such as in Flexible-Meccano [5].

Define Biasing

Biasing

- In the previous slides we sampled ϕ/ψ to construct an ensemble of polypeptides.
- The practice of biasing is where experimental data is used to alter the way in which the sampling occurs to match the experimental data.

Define Weighting

Weighting and Reweighting

- Another approach to conformational ensembles is to assign a weight to each conformation after sampling.
- Forward models are used to compute ensemble obeservables.
- The weights assigned to the conformations can be reweighted to better match experimental data.

Forward Models

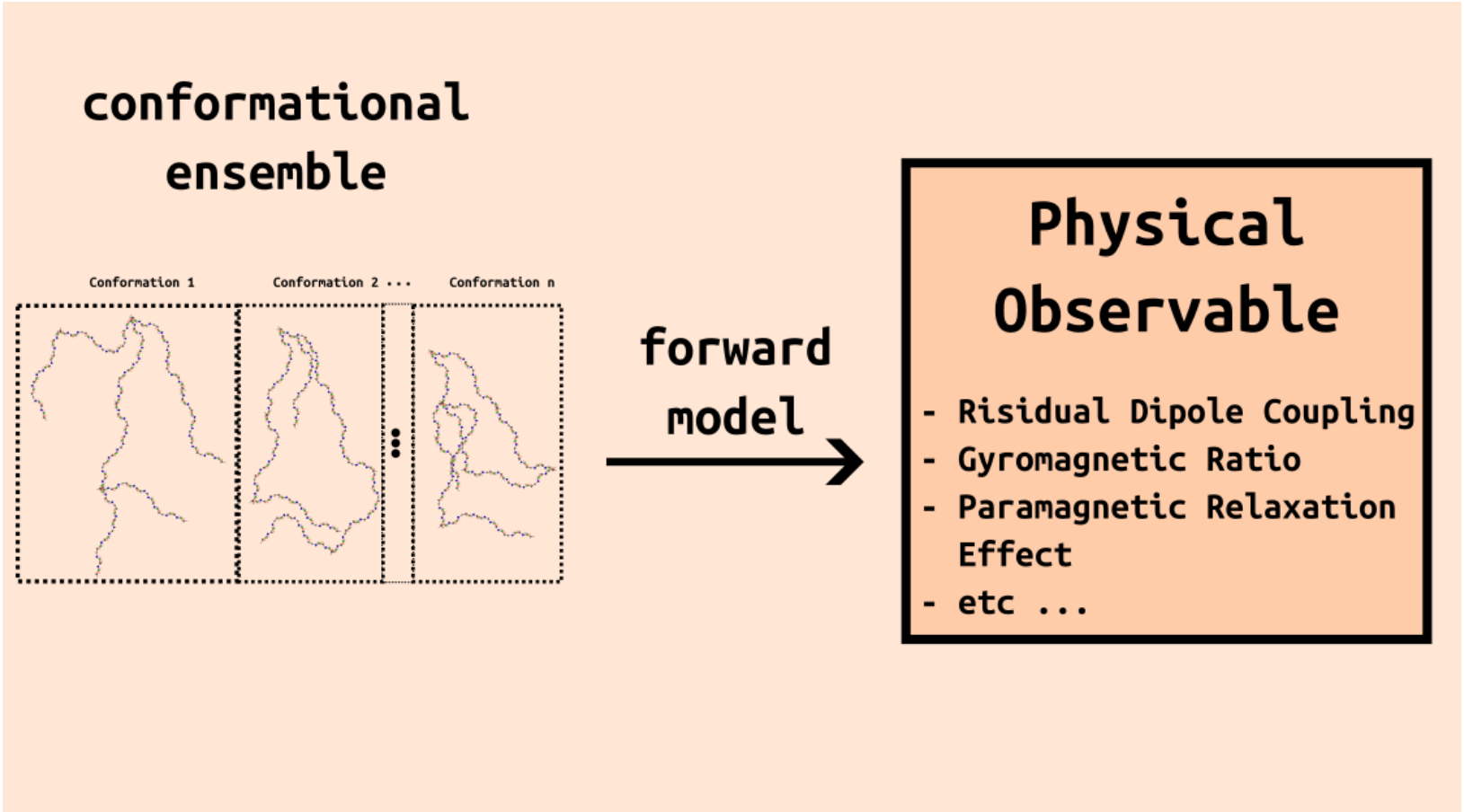

Figure: Forward models take a computed conformational ensemble and "forward" it to a physical obeservable. This is often used as a verification or as a biasing tool [6], [5].

Example of Forward Model

Residual Dipole Coupling

- An example of an experimental measurment is residual dipole coupling (RDC).
- RDC is an ensemble averaged and time averaged measurement from nuclear magnetic resonance experiments [4].
- That being said, the time averaging is often ignored unless specialized methods are used [6].

Example of Forward Model

For example, in the algorithm Flexible-Meccano, the RDCs for each conformer, (indexed by j) with axial and rhombic components A_a, A_r of an alignment tensor A are [5]:

$$D_{IS}^{j} = -\frac{\gamma_I \gamma_S \hbar \mu_0}{8\pi^2 r_{IS}^3} \left[A_a(3\cos^2\theta - 1) + \frac{3}{2} A_r \sin^2\theta \cos(2\phi) \right] \quad (1)$$

Example of Forward Model

The total RDC is calculated by averaging over the conformations in the ensemble [5].

$$D_{IS} = \left\langle D_I IS^j \right\rangle \tag{2}$$

Reweighting

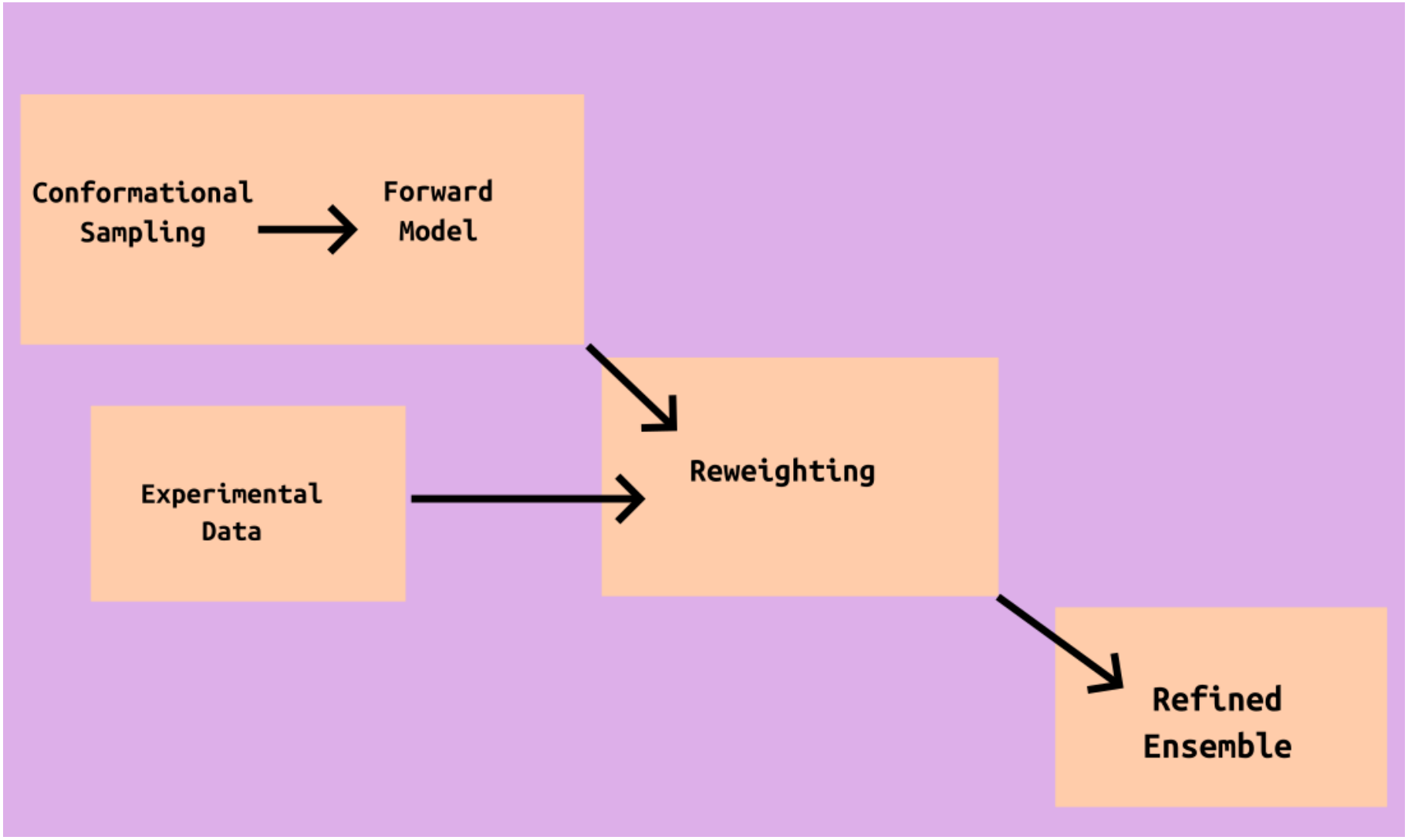

Figure: Diagram of reweighting method [6].

Biasing

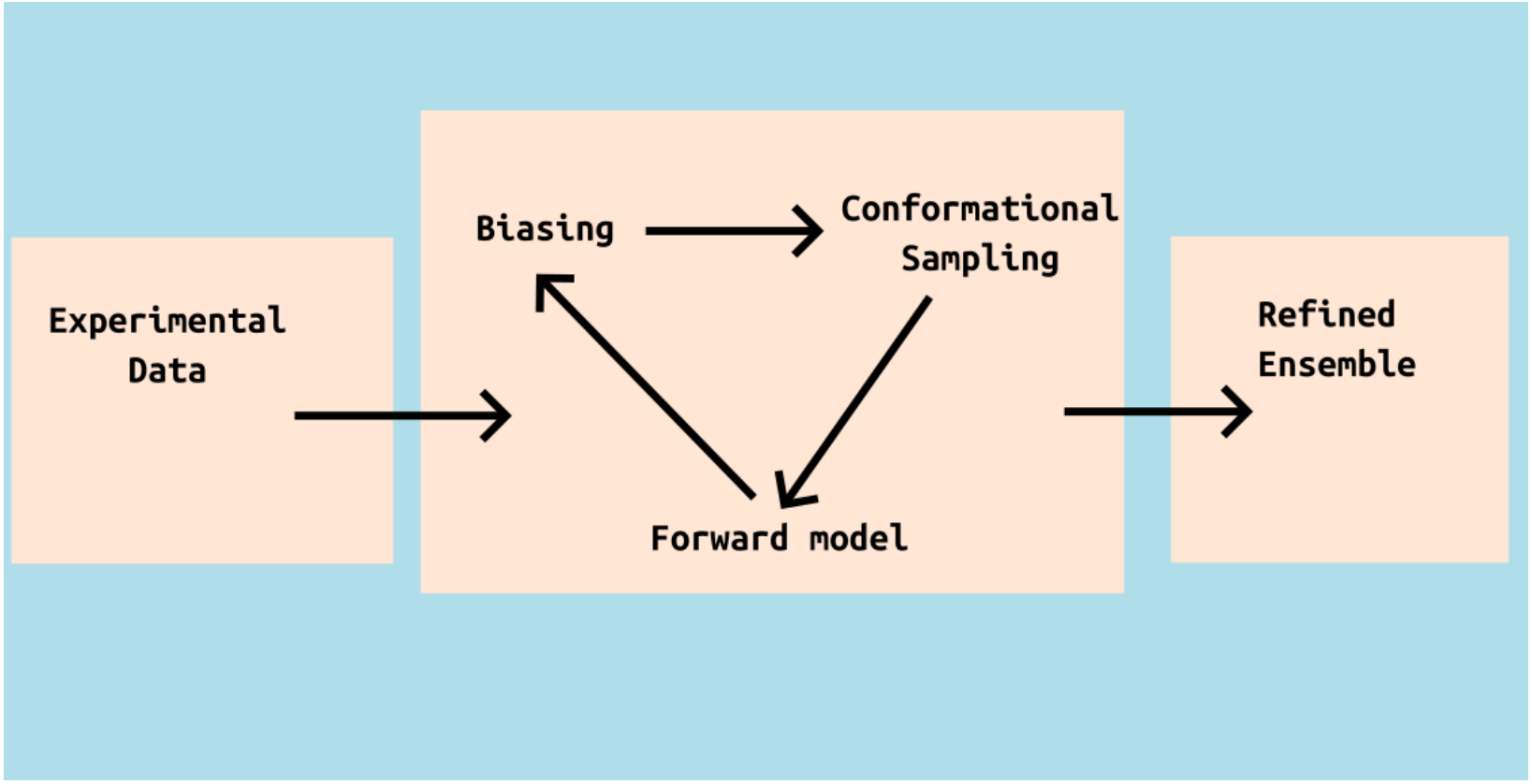

Figure: Diagram of biasing method [6].

A Note on Dynamics and Kinematics of Disordered Proteins

Energy Landscapes

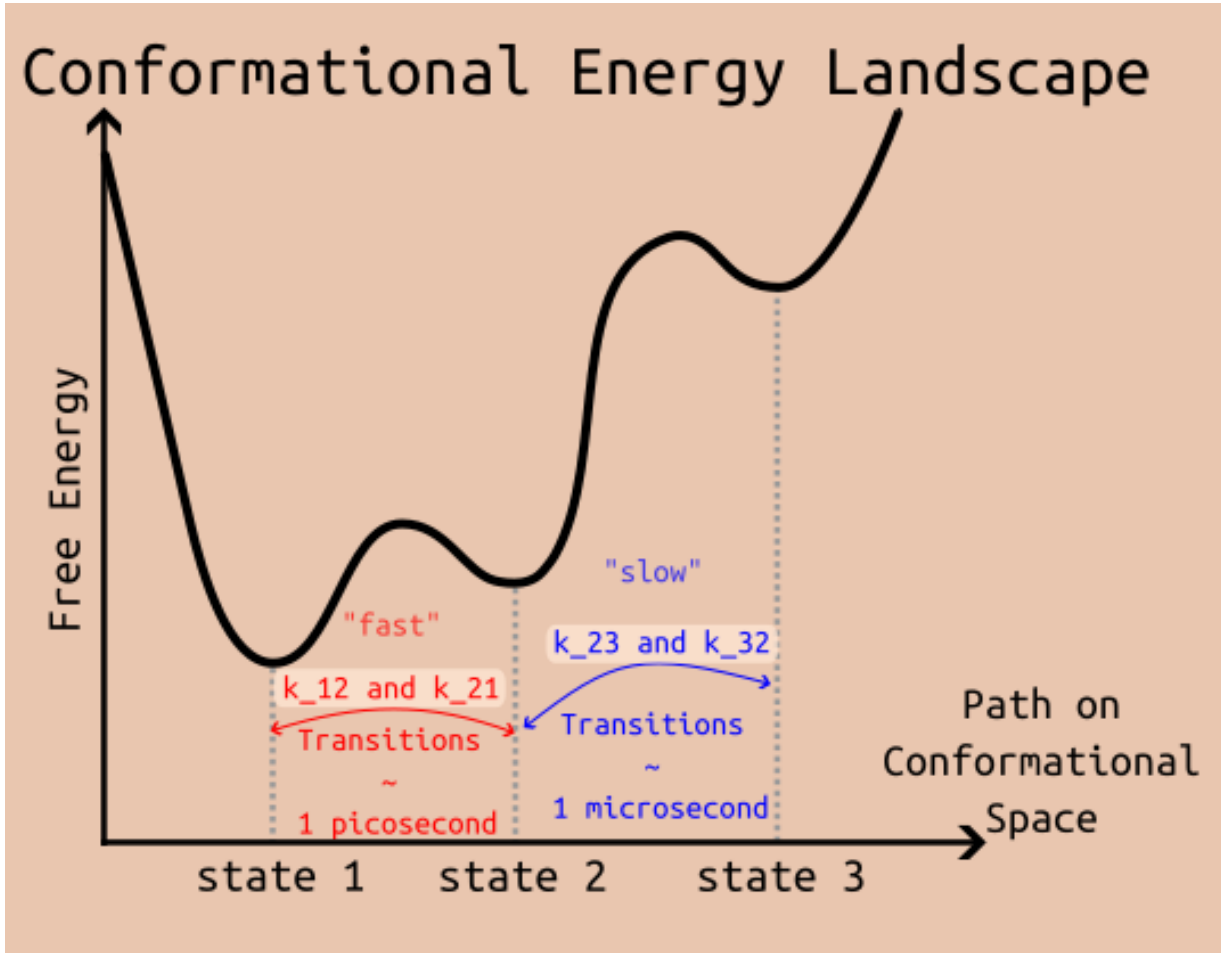

Figure: Transition rates and the protein's energy landscape. Low populated states often switch "slow" on a time scale of millisecons. Highly populated states often switch "fast" on the time scale of picoseconds [2].

Wrapping Up

Perspectives on Protein Science

Below are perspectives on disordered proteins taken from various review papers:

- More robust/transferrable representations of structural ensembles [2]
- Well defined threshold of "acceptable" results/accessible ways of comparing ensembles [2]
- More transferrable and accurate force fields to help with integrative methods [6]
- Unified forward models: Developing forward models that are transferrable between proteins that do and do not have disorder [6]

Conclusion

In this talk I reviewed the current state of protein science regarding how to handle disorder in proteins. Disorder is a many dimensional problem, which has necessitated the use of rigourous methods that combine computation with experiment. This has led to many interesting sub problems such as how to handle degeneracy and how to deal with the and quantification of errors. Most importantly though, the recent work done to characterize proteins may lead to many practical applications in treating human disease.

References I

[1] Massimiliano Bonomi, Riccardo Pellarin, and Michele Vendruscolo. "Simultaneous Determination of Protein Structure and Dynamics Using Cryo-Electron Microscopy". In: *Biophysical Journal* 114.7 (Apr. 2018), pp. 1604–1613. ISSN: 00063495. DOI: 10.1016/j.bpj.2018.02.028. URL: https://linkinghub.elsevier.com/retrieve/pii/S0006349518302881 (visited on 11/28/2023).

[2] Massimiliano Bonomi and Michele Vendruscolo. "Determination of Protein Structural Ensembles Using Cryo-Electron Microscopy". In: *Current Opinion in Structural Biology* 56 (June 2019), pp. 37–45. ISSN: 0959440X. DOI: 10.1016/j.sbi.2018.10.006. URL: https://linkinghub.elsevier.com/retrieve/pii/S0959440X18301180 (visited on 11/28/2023).

References II

[3] Emil Fischer. "Einfluss der Configuration auf die Wirkung der Enzyme". In: *Berichte der deutschen chemischen Gesellschaft* 27.3 (Oct. 1894), pp. 2985–2993. ISSN: 0365-9496. DOI: 10.1002/cber.18940270364. URL: https://onlinelibrary.wiley.com/doi/10.1002/cber.18940270364 (visited on 04/15/2023).

[4] Dominique Marion. "An Introduction to Biological NMR Spectroscopy". In: *Molecular & Cellular Proteomics* 12.11 (Nov. 2013), pp. 3006–3025. ISSN: 15359476. DOI: 10.1074/mcp.O113.030239. URL: https://linkinghub.elsevier.com/retrieve/pii/S1535947620345850 (visited on 12/02/2023).

References III

[5] Valéry Ozenne et al. "*Flexible-Meccano:* A Tool for the Generation of Explicit Ensemble Descriptions of Intrinsically Disordered Proteins and Their Associated Experimental Observables". In: *Bioinformatics* 28.11 (June 1, 2012), pp. 1463–1470. ISSN: 1367-4811, 1367-4803. DOI: 10.1093/bioinformatics/bts172. URL: https://academic.oup.com/bioinformatics/article/28/11/1463/266803 (visited on 11/29/2023).

[6] F. Emil Thomasen and Kresten Lindorff-Larsen. "Conformational Ensembles of Intrinsically Disordered Proteins and Flexible Multidomain Proteins". In: *Biochemical Society Transactions* 50.1 (Feb. 28, 2022), pp. 541–554. ISSN: 0300-5127, 1470-8752. DOI: 10.1042/BST20210499. URL: https://portlandpress.com/biochemsoctrans/article/50/1/541/230748/Conformational-ensembles-of-intrinsically (visited on 11/28/2023).

References IV

[7] Vladimir N. Uversky, Christopher J. Oldfield, and A. Keith Dunker. "Intrinsically Disordered Proteins in Human Diseases: Introducing the D ^{2} Concept". In: *Annual Review of Biophysics* 37.1 (June 1, 2008), pp. 215–246. ISSN: 1936-122X, 1936-1238. DOI: 10.1146/annurev.biophys.37.032807.125924. URL: https://www.annualreviews.org/doi/10.1146/annurev.biophys.37.032807.125924 (visited on 11/28/2023).

[8] Peter E. Wright and H. Jane Dyson. "Intrinsically Disordered Proteins in Cellular Signalling and Regulation". In: *Nature Reviews Molecular Cell Biology* 16.1 (Jan. 2015), pp. 18–29. ISSN: 1471-0072, 1471-0080. DOI: 10.1038/nrm3920. URL: https://www.nature.com/articles/nrm3920 (visited on 11/28/2023).

Thank you to:

- CU Prime: for funding me this semester
- Kevin Stenson: for supporting me over the summer and during this semester
- My girlfriends: Beth, Rae, June, and Maya: for emotionally supporting me through this time of rapid change
- My parents, Sherry and Rob: for making this "try" financially possible
- The queer and disabled community: for giving me a foundation of understanding for who I am and for creating spaces for me to feel safe

Questions?