1 Introduction

Traditionally, studies of protein function have gone hand-in-hand with studies of protein structure. Proteins such as hemoglobin exhibit complicated behavior, such as cooperativity, by modifying their structure. The cooperative transition of hemoglobin from a closed to open state is well studied with the aid of crystallography and other structure elucidation tools. (CITE)

Of more recent interest are intrinsically disordered proteins (IDPs). These proteins lack a defined structure and are capable of assuming many different conformations. Although examples of IDPs have been reported since the 1970s, it was only in the past two decades that they became a focus of major research [**?**].

As our understanding of disordered proteins develops, so too will our understanding of a variety of cellular behaviors. These studies will elucidate aspects of signaling, cytoskeleton formation, and clustered reactions. Investigations into how disordered proteins mediate each of these processes may lead to new drug targets or introduce new directions for synthetic biology.

Studies have shown that disordered proteins or disordered domains are present in at least 40% of human proteins, including those involved with signal propagation [**?**]. General functions of IDPs include as tethers between two globular domains (CITE), receptor subunits in signaling pathways (CITE), tethers to the membrane (CITE), and facilitators to actin polymerization (CITE). Given the ubiquitous nature of IDPs, many questions arise: How does their existence influence cellular functions such as biochemical reactions, signaling networks, or cytoskeletal structure? Are there any benefits to being disordered over structured? and Can IDPs exhibit the same complicated behavior as structured proteins?

One example of an intrinsically disordered protein is the CD3 ζ chain, one of six disordered chains composing the T Cell Receptor (TCR) intracellular region. This molecule facilitates signal propagation in the TCR network in the immune system. An antigen binding to the extracellular regions of the TCR creates a signal transmitted via a chain of events into the cell to the intracellular components of the TCR including the CD3ζ chain. CD3ζ undergoes multiple phosphorylation by kinase Lck before another molecule, ZAP-70 can attach and propagate the signal downstream. This pathway ultimately regulates T-cell cell fate decisions through cytokines production, e.g. interleukin-2. (CITE)

Experiments with only a reconstituted mouse CD3ζ dimer, simplified extracellular receptor, kinase, and phosphatase have shown that the number of tyrosines impacts the potency and maximum phosphorylation but not the switch-like response [**?**]. Our initial differential equation models indicate to achieve these characteristics, there would need to be a phosphorylation-dependent enhancement of more than 100-fold. That is, the sixth phosphorylation event would be at least 100-fold faster than the first phosphorylation event [**?**].

Disordered proteins are commonly represented with models from polymer physics [**?** **?**]. The distribution of end-to-end distances for disordered domains matches a worm-like chain (WLC) model with persistence length 3.04Å[**?**]. Models of disordered proteins using freely-jointed chain (FJC) and WLC converge, with the persistence length for the WLC as half the Kuhn length used for the FJC [**?**].

Alternative models for multisite phosphorylation of IDPs include molecular dynamic, ordinary differential equations, or particle based models. However, FJC or other 'mesoscale' approaches reach timescales on the order of microseconds to seconds, which are computationally out of reach for traditional atomic scale MD. This approach also allows us to capture the steric effects of a disordered chain, which are missed by coarser models.

Representations of disordered proteins as freely-jointed chains have already been used to elucidate properties of IDPs. For instance, the length of tethers between domains controls the effective concentration of one domain seen by the other, such as auto-inhibition of WASP [**?**]. In a second example, the disordered molecule, formin, captures profilin-actin monomers and delivers them to the growing end of actin, increasing the actin polymerization rate. In experimental studies of formin, exerting force on the distal end of formin

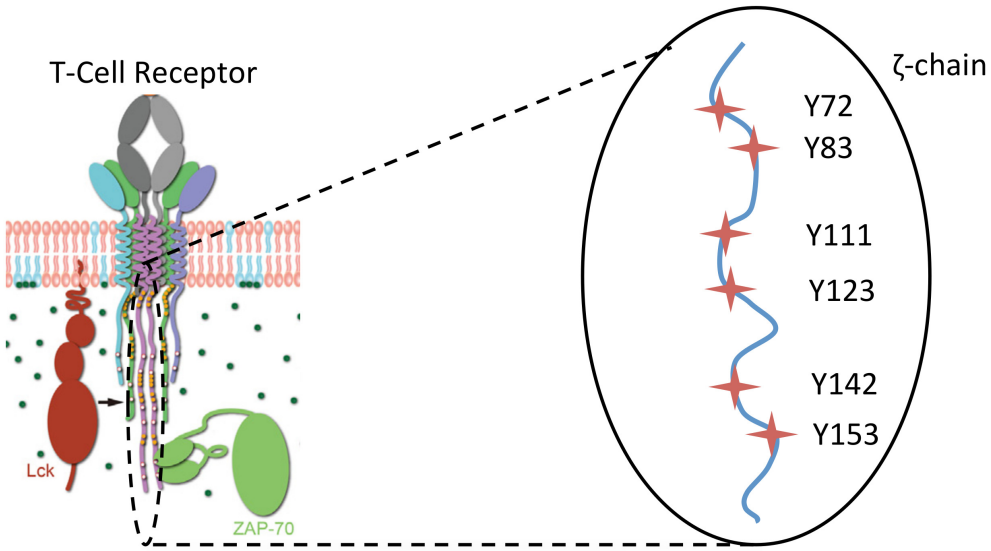

Figure 1: Cartoon of T Cell Receptor network (left) from [**?**]. Location of tyrosines in single ζ chain (right).

counterintuitively enhances the polymerization rate two-fold over relaxed formins [**?**]. From our previous work, models of formin as a freely-jointed chain offer an explanation for this phenomenon. A force exerted on a freely-jointed chain extends the polymer, increasing capture of profilin-actin by increasing the availabiltiy of binding sites. This increase of capture rate balances the reduction in delivery rate to have a net positive impact on the actin polymerization rate under some circumstances [**?**].

Given the above evidence that disordered proteins can give rise to nonlinear signaling behavior, the biological premise of the following projects is that disordered polymer properties alone can create these effects, for example through steric interactions with rigid ligands. The modeling premise is that since disordered proteins take on a wide ensemble of conformations, modeling approaches which focus on structure alone are insufficient. On the other hand, a 'mesoscale' modeling approach able to describe conformational ensembles will be able capture the nonlinear signaling properties arising from disorder.