Colloquium

Prediction and design of intrinsically disordered proteins and condensates

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Intrinsically disordered proteins and regions (collectively IDRs) are pervasive across proteomes in all kingdoms of life, help shape biological functions, and are involved in numerous diseases [1]. IDRs populate a diverse set of transiently formed structures yet defy commonly held sequence-structure-function relationships [1–3]. Recent developments in protein structure prediction have led to the ability to predict the three-dimensional structures of folded proteins at the proteome scale and have enabled large-scale studies of structure-function relationships. In contrast, knowledge of the conformational properties of fully disordered proteins and long disordered linkers is scarce, in part because the sequences of disordered proteins are poorly conserved and because only few have been characterized experimentally. In my talk I will describe how we can use molecular simulations with coarse-grained models and machine learning to study the relationship between sequence, conformational properties, and functions of IDRs [3].First, I will describe how we have used experimental data on ca. 100 proteins to learn a coarse-grained molecular energy function to predict conformational properties of IDRs [4,5]. By globally optimizing a transferable model, called CALVADOS, we can study the conformational ensemble of an IDR [5,6], multidomain protein [7] and IDRs interacting with disordered RNA [8]. I will describe the Bayesian formalism we developed to parameterize CALVADOS by targeting experimental data, and how this model enables us to study interactions within and between IDRs in biomolecular condensates [6–9].Second, I will describe how CALVADOS makes it possible to perform large-scale simulations to explore the relationship between sequence, structure, and function of IDRs. I will describe how we have generated conformational ensembles of all intrinsically disordered regions of the human proteome and used these to provide insight into sequence-ensemble relationships and evolutionary conservation of IDR properties [10].Third, I will briefly describe work on how we can use the information encoded in CALVADOS to design disordered proteins with desired conformational properties [11]. I will outline the basic design algorithm and experimental validation on both single-chain compaction and measurements of phase separation.Finally, I will describe how we can use CALVADOS together with active learning procedures to learn a quantitative model for the rules governing homotypic phase separation of IDRs in condensates [9].References1. Holehouse, A. S., & Kragelund, B. B. (2023). The molecular basis for cellular function of intrinsically disordered protein regions. Nature Reviews Molecular Cell Biology, 1-25.2. Lindorff-Larsen, K., & Kragelund, B. B. (2021). On the potential of machine learning to examine the

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Raiffeisen Lecture Hall

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