POSTER SESSIONS

Poster Session 1:

01 The New Age of Protein Structure, Prediction and Design

P-1.1

Out of Distribution Predictions by Alphafold

Joerg Anton Gsponer [1]

[1] UBC, Vancouver, Canada

Sophisticated protein structure prediction models, such as AlphaFold and RosettaFold, have demonstrated remarkable accuracy, often approaching that of experimental methods. However, these models are primarily trained on data derived from independently folding protein domains with limited structural heterogeneity. This raises an important question: can these models reliably predict the structures of proteins that have multiple functional states accessed via allosteric changes or those that only conditionally fold? To address these questions, we evaluated AlphaFold's performance on both categories of proteins Our analysis reveals that while AlphaFold2 and AlphaFold3 can surprisingly predict structures of intrinsically disordered regions (IDRs) upon binding—even when they fold differently with various partners—they struggle with heterogeneous interactions. The greatest limitations emerge in proteins that undergo allosteric structural changes to sample different functional states, where even state-of-the-art MSA subsampling fails to capture functionally relevant conformational diversity.