Deciphering viral protein-protein interactions using AlphaFold.

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Abstract

In recent years, the field of structural biology has undergone significant transformations, with the advent of revolutionary technologies and methodologies. A notable milestone in this journey is the development of AlphaFold, a cutting-edge software capable of accurately predicting the three-dimensional structures of proteins based solely on their amino acid sequences. This tool has also shown remarkable proficiency in forecasting the interactions between different proteins. However, a notable omission in the vast repository of models in the AlphaFold database is the absence of viral proteins. This gap presents a unique opportunity for researchers to delve into the modelling of viral protein structures independently.

We have recently used AlphaFold to reliably study the domain decomposition and structural organization of the hepatitis E virus ORF1p protein (Fieulaine et al. 2023). Building on this success, we have extended our research to investigate the interactions between the hepatitis E virus capsid protein (ORF2i) and various cellular partners. We have employed a methodical "Top-Down" approach in our modelling. This process starts with the modelling of entire systems to pinpoint potential interactions. After identifying these interactions, we then refine our models to concentrate solely on the key areas where these interactions occur.

By applying this methodology, we were able to identify a potential novel dimerization area in the NS5A protein of the Hepatitis C virus. This discovery was further studied and validated through molecular dynamics simulations and biophysical measurements including Isothermal Titration Calorimetry (ITC), differential scanning fluorimetry (nanoDSF) and nuclear magnetic resonance (NMR).

Our work shows how versatile AlphaFold is for studying viral proteins and its potential to reveal new details about how these proteins behave and interact.