Title

Protein-Protein Interaction Networks at the Residue Level

Authors

Jaime Gutierrez[1,2], Jordan C Rozum[2], Song Feng[2]

[1]Bioinformatics Program, The University of Texas at El Paso, [2]Computational Biology Group, Pacific Northwest National Laboratory (PNNL)

Abstract

The overall goal of this study was to develop and apply a multilayer network pipeline to analyze protein structures at the residue level. Protein complexes were modeled as graphs in which each amino acid was represented as a node, and edges were weighted by spatial proximity derived from experimentally resolved PDB files and AlphaFold2 docking simulations. To construct these networks, we built custom Python functions (using ProCaliper, a public package from PNNL; and NetworkX) that extracted α-carbon coordinates, mapped UniProt IDs to chain identifiers, and computed inter- and intra-protein residue distances. This approach enabled a residue-level mapping of interaction interfaces. To connect structural features with biological function, we integrated two experimental datasets: post-translational modification (PTM) data comprised of phosphorylation sites and limited proteolysis (LiP) data covering tryptic regions from an experiment done on the MRC-5 lung cell line. Residues were annotated based on binding status and modification presence. Centrality measures (degree, betweenness, eigenvector) were computed to quantify residue importance, and statistical distributions were compared using the Kolmogorov–Smirnov test. We observed that non-binding phosphorylation sites were significantly more present in low-centrality regions, consistent with localization in flexible domains. By contrast, non-binding LiP-sensitive residues were biased toward higher-degree, indicating that regions undergoing conformational changes are more structurally central. Together, these findings highlight how multilayer residue-level networks can provide a foundation for comparative proteomics and network-based exploration of key amino acids.