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# Understanding Protein Interaction – A Review

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**ABSTRACT:** Protein interactions, also known as protein-protein interactions, abbreviated as PPIs, are crucial in all organisms' cellular and biological procedures. This review on understanding protein interactions is necessary to understand the importance of molecular interaction and protein, techniques and approaches associated with it as they apply to identify PPIs, also to know PPI networks and proteomics and suitable examples to support the review. Nevertheless, computational techniques can be expensive, particularly time-consuming, and until now have covered a tiny share of the entire PPI networks only. Consequently, the requirement for techniques has increased to uphold experimental outcomes and anticipate PPIs that have not been found yet.

**KEYWORDS:** Protein interactions, protein-protein interactions (PPI), PPI techniques, computational techniques, PPI networks, and proteomics.

## I. INTRODUCTION

Protein stimulates numerous biological functions in a cell, comprising of:

- Cell development
- Nutrition absorption
- Gene expression
- Proliferation
- Motility
- Morphology
- Intercellular communication
- Apoptosis

However, cells react to a host of stimuli. Thus, protein manifestation is a vigorous process. The proteins that finish distinct tasks might not always be defined or activated. Further, even cells are unequal, and most proteins are represented in a cell type-dependent form. These primary features of proteins indicate an intricacy that can be hard to examine, especially when trying to comprehend the role of protein in an accurate biological framework.

Following are the essential elements needed to learn (Chen, Tan, Wang, Zhong, Liu, Yang, & Zheng, 2020) the role of protein:

- **Protein structure and sequence** - utilized to uncover motifs predicting process of protein.
- **Revolutionary account and conserved sequence** - recognizes critical regulatory remnants.
- **Expression profile**- explicitly indicates cell type and regulation of expression.
- **Post-translational changes**- glycosylation, acylation, phosphorylation, also ubiquitination suggest localization, activation and/or process
- **Interactions with other proteins** - anticipating function by learning the role of binding partners.
- **Intracellular localization**- might infer the role of the protein.

On the other hand, protein interactions (Du, Zhang, Yang, Yong, Awan, & Yang, 2017) are essential to nearly every cell process, so it is vital in drug development since drugs can affect them. Protein interaction networks or PPIN (Hussain, Lee, Abba, Chen, Aldaz, 2018) are arithmetical expressions of the physical contact between proteins found in the cell. This contact:

- is specific
- happens among definite binding areas in protein



- hasaspecificbiologicalinterpretation(thatis,theyhaveaspecificrole)

Information on PPI can signify transient as well as stable interactions. PPI data can represent both transient and stable interactions. Transient interactions (Alvarez, Schinke, Brooks, Pasquino, Leonelli, Varala, & Coruzzi, 2020) are short-lived interactions modifying or carrying a protein, causing it to change further (for example, protein kinases). They are the most dynamic component of the interactome (sum of all PPIs that occur in an organism, a cell, a life form, or a specific biological connotation). Stable interactions are a part of protein complexes (Shen, Yi, Jiang, He, Yang, Xie, & Hu, 2017) (for example, hemoglobin, ribosome). Interaction of the protein with another protein can:

- Alter enzymes' kinetic properties
- Serve as a broad process for substrate channeling
- Create one unique binding site for tiny effector molecules
- Stifle a protein
- Modify the particularity of protein for its substrate by interacting with a plethora of binding partners
- Function as a regulatory role in the downstream or upstream level

Until the late 20th century, protein function analyses focused mainly on a single protein. However, for proper functioning, as most of the proteins interact with other proteins, their exploration shall be in the substance of their interacting partners to know their function fully.

With the studies on the human genome and the development of proteomics, understanding how a protein interacts with another protein and determining biological networks is vital for understanding how protein functions in the cell. Thus, that is the aim of our research paper.

## II. SIGNIFICANCE OF MOLECULAR INTERACTION AND PROTEIN

Molecular biologists consider molecular interactions (Qin, Cho, Cavanagh, & Ting, 2021) significant as they help:

- Understand the function and behavior of protein
- Make predictions of the biological functions that proteins of unspecified function are a part of:
  - a. We might guess "Guilt by association," a protein of incognito function links with one known process.
  - b. The protein part of the identical process shall bunch concurrently under network maps.
- Characterize protein pathways and complexes; interaction channels could be used as a rough map to incorporate detail to biological pathways and functions and aid in the discovery of new complexes, pathways, and functional segments in the cell.

## III. EXPERIMENTAL APPROACHES TO DETECT PPI

Protein interactions (Mabonga, Kappo, 2019) are the basis of many critical cellular processes such as signal transduction, molecular transport, and various metabolism pathways, while aberrant PPIs are the basis of multiple aggregation-related diseases, like Alzheimer's disease, and might cause cancer. Hence, we review the main recent approaches used in detecting and analyzing protein interaction.

### ● Co-immunoprecipitation

Co-immunoprecipitation or Co-IP (Lin & Lai, 2017) determines and confirms physiologically related PPIs. Target protein-specific antibodies indirectly collect proteins secured to a particular target protein. This method is put into screening new PPIs or proving the presence of PPIs.

In this method, PPI is performed in a refined, almost physiological state. Regardless, transient interaction or



Low affinity betwixt proteins might not be noticed. However, on the contrary, the Co-IP result cannot determine the type of interaction - direct or indirect - as the likelihood of the presence of supplementary proteins cannot be nullified.

- **Pull-down assays**

The in vitro method is utilized to assess the physical interaction betwixt multiple proteins (Louche, Salcedo, Bigot, 2017). In addition, it is used to confirm present protein interactions found by initial screening or any other technique to determine new PPIs.

It works on the principle of utilizing a tag fused protein (for example, GST-tag, biotin-tag, and His-tag) inactivated to affinity resin - bait protein or prey protein. Proteins securing the prey protein can be seized and "pulled down" when the target protein flows. Then, following elution and examination, employing Mass Spectrometry or Western Blot can be used to uncover foreseen or previously unknown contact.

- **Yeast two-hybrid (Y2H)**

This method screens or confirms PPIs using two protein domains which have two distinct functions (Velásquez-Zapata, Elmore, Banerjee, Dorman, & Wise, 2020):

1. ADNA binding domain (DBD) that allows securing to DNA
2. The activation domain (AD) that activates DNA transcription

Both domains are needed for the reporter gene transcription. In addition, Y2H allows the recognition of PPI betwixt protein tandems directly. Nonetheless, this method might incur many wrong positive interactions. At the same time, the Y2H assay might not trace many genuine interactions causing incorrect negative results.

- **Far-Western Blotting**

It is a molecular biological approach based on the western blotting technique to recognize PPI (Deshoux, Monsion, & Uzest, 2018) in vitro. Typical western blotting employs an antibody to recognize a protein of interest. On the other hand, this approach uses a non-antibody protein to secure the protein of interest. Therefore, while the formed is utilized to detect specific proteins, the latter is used to detect PPIs.

- **Tandem affinity purification-mass spectroscopy (TAP-MS)**

This approach was designed to explore PPIs in the inherent cell conditions. It is as per the double tagging of the protein of interest on its chromosomal locus, pursued by a purification procedure of two steps. First, proteins that stay linked with the protein of interest can afterward be studied and recognized via SDS-PAGE headed by mass spectrometry analysis. Thus, determining the PPI co-partner of the actual target protein.

- **Protein microarrays**

This method gains a reputation as a solid medium to recognize proteins, scan protein's expression levels (Zhang, Song, Tang, Xu, & Guo, 2018), and quest PPIs and processes. This method uses a glass piece upon which different protein molecules have been fastened at different places in an orderly manner. Protein microarrays (Chen, Dodig-Crnković, Schwenk, Tao, 2018) have seen tremendous progress and interest at the moment. They have become one of the active areas emerging in biotechnology. The intent is to achieve efficient and sensitive high-throughput protein analysis, carrying out large numbers of determinations in parallel by an automated process.

#### IV. COMPUTATIONAL APPROACHES TO DETECT PPI

PPIs' experimental detection and depiction require much labor, plus it is time-consuming. However, prediction of many PPIs can also be done computationally, generally employing experimental information as the first step.

However, methods have been designed that permit PPI de novo prediction, i.e., without any previous proof for this interaction.

1. **Genomic Context Methods**

- **The Domain Fusion method** hypothesizes the interacting proteins merged to a protein in some other genome from time to time. Therefore, determining whether two proteins may interact or not can be done by clinching, they have non-overlapping order resemblance to an area, of one protein arrangement in any other genome.
- **The Conserved Neighborhood method** is based on the theory that if two genes encoding two proteins are located on the same chromosome in many genomes, they are likely functionally related (might also interact physically).
- **The Phylogenetic Profile method** relies on the theory - if multiple proteins exist or do not exist in multiple genomes at a time, they are probably functionally rel. As a result, presumably, protein



interaction can be recognized by identifying the genes availability across multiple genomes and choosing genes availability together always.

## 2. Text Mining

The internet makes public data from biomedical records readily available, and it is quickly becoming a valuable resource for gathering known PPIs, PPI assessment, and protein docking. It is significantly less expensive and time-consuming than other efficient techniques. This methodology currently employs rule or pattern-based data extraction and machine learning methods (Sarkar & Saha, 2019) to diagnose binary relationships between proteins interacting from single sentences. Many text mining apps for PPI mining and forecasting are openly available, like repositories storing manually tested and computationally anticipated PPIs. This process can be done in two phases:

- **Data retrieval** - Texts comprising the names of one or both PPIs are retrieved.
- **Data extraction** - Extraction of information of interest (PPIs, involved by-products, type of interaction, etc.)

## 3. Machine Learning

Numerous methodologies for PPI forecasting have been proposed and evaluated. However, they require developing a positive set (PPI pairs) and a negative set (antagonistic PPI pairs).

Relying on labeling input variables as per intended results, predicting using machine learning (Liu, Liu, Deng, 2018) can be divided into supervised and unsupervised.

A mating-based ubiquitin system (mbSUS) was used to study the integral membrane proteins of *Saccharomyces cerevisiae* more than a decade ago. It identifies extracellular signaling proteins membrane proteins. There were less than 2,000 interactions involving 536 proteins among the 705 integral membrane proteins. A support vector machine was used to define high, low, and medium confidence interactions for sorting and classifying them. The split-ubiquitin membrane Y2H system identifies yeast transformants that define PPI pairs using transcriptional reporters.

Near that time only, the supervised technique was discovered to be the most effective machine learning method (Sun, Zhou, Lai, & Pei, 2017) for predicting PPIs. Furthermore, such approaches have been used to discover PPIs on the interactome of the human being, specifically Schizophrenia-associated proteins, and Membrane proteins interactome.

A year back, a method employing residue cluster classes or RCCs correctly classified around 98 percent of PPIs. RCCs contain all concurrently contacted residue pairs that can help study the evolution and relationships of protein structure-function.

## V. EXAMPLES OF PROTEIN INTERACTION

### ● Electron transfer proteins

In numerous metabolic reactions, protein acting as an electron carrier secures enzyme acting as its reductase. After receiving an electron, it detaches and binds to the subsequent enzyme acting as its oxidase (an electron acceptor). These protein interactions are binding and based between proteins to ensure electron transfer. For instance: microsomal (Stefanutti, 2020).

### ● Signal transduction

Extracellular signals control cell activity. Signal propagation within and across the cell interior is based on protein interactions between the different signaling molecules (Liu, & Wellen, 2020). The appointment of signaling routes through protein interaction is called signal transduction and has a primary part in various biological functions and diseases – cancer and Parkinson's.

### ● Membrane transport

The protein might carry other proteins, such as cytoplasm and nucleus (Vermaas, Dixon, Chen, Mansfield, Boerjan, Ralph, & Beckham, 2019).

### ● Cellular metabolism

In numerous biosynthetic functions, the interaction of enzymes (Baig, 2020) gives rise to tiny compounds or some other types of molecules.

### ● Muscle contraction

Muscle contraction (Caruel & Truskinovsky, 2018) physiology includes a few interactions. Muscle contraction physiology involves several interactions. Myosin filaments serve like molecular motors and actin allows them to slide. Additionally, members of the lipid droplet proteins family link with different proteins, as adipose triglyceride lipase activators and coactivator relative gene identification-58 controls lipolysis present in skeletal muscle.



## VI. PPI NETWORKS AND PROTEOMICS

One of the primary protein interaction network (Rudolph & Cox, 2019) goals is to anticipate the protein's functionality. Given the current extensive research on yeast, the yeast dataset contains several biologically uncategorized proteins, indicating the eventual requirement to categorize the proteins. The characterization of human proteins can lay the basis for a detailed understanding of cell processes, useful for drug development and discovery (Andrei, Sijbesma, Hann, Davis, O'Mahony, Perry, & Ottmann, 2017). Because of the broader accessibility of PPI networks, different approaches for predicting the function of proteins have been devised. The access of reliable data on PPIs, as well as their existence in physiological as well as pathological procedures, is critical to developing PPI-based therapeutics.

Modularization techniques can be used to anticipate (Chen, Ju, Zhou, Chen, Zhang, Chang, & Wang, 2019) the functions of the protein. However, assumptions obtained using this manner might be inaccurate as the accuracy of the modularization technique itself is minimal.

Other techniques for predicting protein functions include Prodistin, Chi-square, neighbor counting, Markov random field, and weighted-interactions-based methods. Protein functions should indeed be projected explicitly from the topology for greater precision. Several topology-based methods for predicting protein functions depending on PPI networks have been proposed. At its most basic, the "neighbor counting method" anticipates the unexplored protein function based on the frequency of known characteristics of the nearest neighbor of protein. Most outcomes of the nearest neighbors can be evaluated statistically. Lately, the number of related neighbors shared by the specific protein and the foreign protein has been used to indicate their role. A new approach in the field is weighted-graph-mining-based protein function (Zaharia, Labedan, Froidevaux, & Denise, 2019) prediction.

Identifying protein-protein complexes is a critical step in determining signal transduction pathways. Protease-inhibitor antibody-antigen complexes are the most prevalent protein complexes. The primary method for identifying protein complexes at atomic resolution is crystallography.

A thorough examination of PPIs can better understand cellular processes, organization, and functions.

Other PPI Network applications incorporate:

- Evaluating the drug-ability of molecular point of interest dependent on network topology
- Biological in dispensability analysis
- Estimating reliability of interaction
- Identifying domain-domain interactions
- Predicting protein interaction
- Detecting proteins that are a part of disease paths
- Outlining regular interaction network motifs
- Comparing humans and organisms
- Identifying protein complex

## VII. CONCLUSION

We have reviewed protein interactions with cellular and biological procedures, diseases, and drug development, as drugs influence protein interactions. The interactome is the PPIs' sum occurring in cells, organisms, or a biological framework. Plus, experimental and computational methods to detect PPIs. The experimental detection and features of PPIs are an immense requirement of labor and time. Therefore, experimental data is also used as a first step for computationally detecting PPIs. Also, molecular interactions affect the function and behavior of proteins. Moreover, we learned that the primary objective of PPIN is anticipating the functionality of the protein.

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