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QUANTUM GRAPH-BASED DIFFERENTIAL MODELS WITH FRACTIONAL CALCULUS AND TOPOLOGICAL DATA ANALYSIS FOR DYNAMIC CHARACTERIZATION OF PROTEIN-PROTEIN INTERACTION NETWORKS

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Abstract. Understanding the intricate dynamics of Protein-Protein Interaction Networks (PPINs) is essential to decode complex biological processes and disease mechanisms. Existing graph-theoretic approaches often fall short in capturing the temporal and spatial intricacies of dynamic PPINs. To address these limitations, this study introduces a novel framework based on Quantum Graph-Based Differential Models (QGDM) integrated with Fractional Calculus and Topological Data Analysis (FC-TDA). The quantum graph formalism models PPINs with probabilistic edge dynamics, while fractional differential equations account for memory effects and long-range dependencies in protein interactions. TDA is used to extract persistent topological features and detect critical transitions in the network structure over time. The objective is to provide a high-fidelity and mathematically robust system for dynamically characterizing PPINs, enabling better insights into protein behavior under varying cellular conditions. Results from simulations on benchmark datasets such as yeast and human interactomes demonstrate superior accuracy in detecting functional modules and predicting interaction disruptions compared to existing graph and machine learning models. This integrated mathematical approach offers a powerful tool for systems biology with potential applications in drug target identification and precision medicine.

2020 Mathematics Subject Classification. 05C90; 68Q25; 94C15.

Key words and phrases. quantum graph theory; fractional calculus; topological data analysis; protein-protein interaction networks; dynamic network modelling; persistent homology; systems biology; functional module detection; memory-dependent dynamics; precision medicine.

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1. Introduction

Over the past several decades, the study of molecular and cell biology has been shifting away from reductionist methods toward a more comprehensive understanding of molecular and cellular structures. The intricate organization of biochemical, digestive, and information-signalling processes within biological systems enables living cells to function properly [1]. These processes involve interactions among multiple proteins and genes regulate thousands of other proteins and genes to form complexes that govern cellular functions that would be impossible for any single component to carry out on its own. Thus, a cell's true activity is better defined by a collection of interdependent systems ranging from transcriptional regulation to metabolic control rather than by a single network [2]. Advances in high-throughput methods have provided researchers with reliable data on various interaction maps. For example, organism-specific PPIN networks have been identified in humans, yeast and Drosophila along with gene regulatory networks that incorporate protein–DNA interaction data. Similar high-throughput studies are also used to effectively map metabolic and signal transduction pathways [3]. Representing complex biological structures as networks encourages the study of these systems holistically rather than in isolation and aims to simplify biological processes for better understanding of their behaviour. Complex relationships are crucial across many fields, including engineering, sociology, physics, epidemiology, and the biological sciences. Graph theory is a widely used and effective approach for characterizing complex systems [4]. In this framework, a system's multiple components and their relationships are represented as graphs where nodes (or vertices) denote interacting elements and edges represent the interactions or connections between them. This abstraction allows comparison across different systems and has revealed that many such systems share key structural characteristics [5]. Numerous graph theory models have been applied to study biological systems offers valuable insights into cellular structure and development and fundamentally transforming our understanding of cell biology [6]. By leveraging graph theory, biological information organized in ways that provide new perspectives, going beyond simple mappings of a cell's physical network structures. Network biology has many applications such as the discovery and functional characterization of genes and proteins, the identification of disease-associated genes and drug targets and the development of novel therapeutic strategies all contributing to a deeper understanding of the cellular systems that underlie life [17]. Utilizing a combination of mathematical models and multiple sources of information, Physics-Informed Machine Learning (PIML) enables the simulation of physical and medical systems using artificial neural networks, graph-based models, or Gaussian process regression. PINNs solve Partial Differential Equations (PDEs) by integrating the governing equations directly into the neural network loss function, utilizing automatic differentiation to compute the required derivatives [8]. PINNs eliminate the need for mesh generation because of avoiding the substantial computational costs associated with modelling in domains involving motion or deformation. PINNs are easily adaptable to a wide range

of PDEs including stochastic PDEs, integro-differential equations and fractional PDEs. Even complex implementations of PINNs typically require fewer than 1,000 lines of code highly accessible and easy to implement [9].

In contrast to existing numerical methods, the same PINN framework can be used for both forward and inverse problems. The advantages of this approach have been demonstrated across a variety of fields such as fluid mechanics, non-destructive material evaluation, systems biology, optics, geophysics, and biomedicine. Physics-Informed Graph Networks (PIGNs) are well-suited for modelling complex physical systems where the state of an entity depends on its neighbouring states [10]. This approach allows for dynamic, relational modelling without relying on structured grids. Researchers achieved strong results in modelling the one-dimensional Burgers equation, heat transfer, and advection-diffusion processes by combining message-passing neural networks with the method of lines and neural Ordinary Differential Equations (ODEs) [11]. Extended this approach by developing a PIGN model called GrADE capable of learning system behaviours from data, including one-dimensional and two-dimensional Burgers' solutions. Proteins is organic molecules composed of twenty standard amino acids play a central role in virtually all biological and cellular processes in living organisms. PPIs are essential for numerous functions such as metabolism, hormonal regulation, DNA transcription and replication, molecular signalling and intercellular communication. Deeper understanding of PPIs has significantly contributed to the diagnosis and treatment of diseases, as well as the development of new therapeutic drugs [12].

Proteins seldom perform their functions in isolation; typically collaborate with other proteins in their environment to fulfil biological roles. One widely used high-throughput experimental technique for studying these interactions is the Yeast Two-Hybrid (Y2H) screening. Numerous studies have applied existing Machine Learning (ML) approaches to address a variety of challenges in computational biology such as enzyme classification, protein structure prediction, and PPI prediction among others [13]. These algorithms generally rely on hand-crafted features derived from fundamental protein sequences, incorporating historical data, amino acid composition, and physicochemical properties. Protein sequences were encoded using the Auto Covariance (AC) method and Support Vector Machines (SVMs) were employed for classifying and predicting PPI [14].

1.1. **Problem Statement.** The dynamic and complex nature of PPINs presents significant challenges in accurately modelling, analysing, and understanding biological processes at a systems level. Existing graph-based models often fail to capture the temporal evolution, multi-scale structural properties, and memory-dependent dynamics inherent in biological interactions. The absence of tools that effectively combine topological, algebraic, and differential mathematical perspectives limits the ability to detect functional modules and transient states critical to disease progression and therapeutic targeting. This research addresses these limitations by proposing a novel framework that integrates quantum graph

theory, fractional calculus, and topological data analysis to provide a more robust, high-resolution characterization of PPIN dynamics.

1.2. **Motivation.** The motivation behind this research stems from the pressing need to better understand the intricate and time-varying behaviours of PPINs are foundational to cellular functions and disease mechanisms. Existing models often lack the mathematical depth to capture the complexity, memory effects, and hidden topological features within these networks. Inspired by recent advancements in quantum graph theory, fractional-order dynamics, and TDA, this study seeks to develop a more accurate and interpretable framework for modelling PPINs. By integrating these advanced mathematical tools, the proposed approach aims to uncover deeper biological insights, facilitate early disease detection, and support the development of targeted therapies through enhanced dynamic characterization.

2. Related Works

A sequence-based approach for predicting self-interacting proteins was proposed. This method classifies PPIs using a weighted sparse model-based classification along with a complete encoded representation of peptide sequences. The approach begins by transforming existing protein sequences into a Position-Specific Scoring Matrix (PSSM) from which feature vectors are extracted using Low-Rank Approximation (LRA). These feature vectors are then fed into a Rotation Forest classifier to distinguish between self-interacting and non-self-interacting proteins [15]. In another method for predicting PPIs, the Gradient Boosting Decision Tree (GBDT) technique was introduced. This approach encodes protein sequences using various protein features, such as frequency, structure, composition, transition, and autocorrelation. Beyond sequence-based data, input features for PPI modelling can be derived from a variety of other biological sources, including gene fusion events, protein structure, biological function, and more [16]. Several algorithms have been developed and categorized based on these input features. Sequence-derived features remain the most commonly used source for predicting PPIs. More than 80% of proteins interact with other proteins during their essential biological functions, making them versatile macromolecules with diverse roles in living organisms [17]. PPI are highly specific physical contacts between two or more protein molecules. PPIs are critical for numerous cellular processes such as signal transduction, immune response, cell growth, DNA transcription and gene expression, and reproduction. Studying and understanding PPIs provides vital insights into the molecular structure and functional roles of proteins [18].

Although the number of identified PPIs across various species has increased rapidly due to advanced experimental techniques, the structural annotation of peptides and their interactions has not kept pace. Existing data suffer from several limitations such as incomplete coverage, high error rates, and false negatives. While high-throughput experimental methods have identified a vast number of PPI linkages, the overall volume remains relatively small compared to the enormous potential connections

present in the proteome [19]. These large-scale genome studies face challenges such as limited coverage, inherent biases, and high costs. Variability in experimental procedures, along with limitations in device resolution and environmental influences often lead to inconsistent results and testing errors. Accurately and reliably identify PPIs, there is a growing need for robust, large-scale computational approaches can complement experimental methods and support the exploration of protein functions with greater efficiency and precision [20].

A significant advancement in recent years is the emergence of deep learning and nonlinear dimensionality reduction techniques have led to a surge in methods capable of autonomously learning to represent graph structures. These methods commonly referred to as representation learning on graphs have proven highly valuable in analysing recommender systems, social networks, and molecular graph topologies [21]. To ensure that the geometric relationships in the learned feature space accurately reflect the original graph's structure, the mapping function between the two must be properly optimized. Representation learning has been successfully applied to link prediction tasks, such as predicting user–movie affinities or identifying missing friendships in social networks [22]. A major drawback of the original PINNs is the high computational cost, especially for problems involving multiscale back propagation. To address this, introduced Conservative PINNs (cPINNs)—a domain decomposition-based framework for solving conservation laws. cPINN reduces computation time by splitting the domain into subdomains and ensuring continuity of states and fluxes at the interfaces [23].

Proposed Extended PINNs (XPINNs) apply domain decomposition to both space and time. Unlike cPINNs, XPINNs are well-suited for irregular and non-convex geometries, making them more versatile for general PDEs. Introduced hp-VPINNs is a domain decomposition approach grounded in the spectral element method offering dual h-p resolution capabilities. Developed a concurrent execution framework for PINNs, enhancing computational efficiency. GNNs can be scaled to model complex structures by leveraging existing parallel architectures [24]. At the cellular level, proteins perform a wide range of functions such as molecular transport, DNA replication, catalysis of metabolic reactions, response to stimuli, and organismal development. Proteins are composed of polypeptide chains are long sequences of amino acid residues encoded by genetic information. The unique sequence of amino acids determines a protein's three-dimensional conformation, which in turn governs its biological function [25]. Proteins may undergo conformational changes to fulfill specific tasks exposing reactive regions or concealing others as needed. These conformational transitions, often termed conformational modifications, are influenced by nonlocal interactions such as hydrophobic core formation, salt bridges, hydrogen bonds, disulfide linkages, and post-translational modifications contribute to the overall structural stability of the protein [26]. Given the dynamic and flexible nature of proteins, researchers have been working to develop consistent geometric models that account for structural variability.

Several isometric-based representations have been proposed. An isometric transformation, or non-elastic deformation is defined as a shape change that preserves geodesic distances between points on the protein surface, thus maintaining the intrinsic structure despite changes in conformation [27].

The geodesic radius represents the shortest path between two points entirely confined within the shape's defined manifold. Most approaches for representing isometrically stable shapes rely on either physics-based modelling or geodesic distance metrics. In physics-based modelling, the shape is interpreted as a manifold over physical field such as heat propagates driven by associated chemical reactions [28]. By analysing the field distribution over time, it becomes possible to extract multiresolution features that, after dimensionality reduction, yield a stable, informative, and often task-specific representation, commonly referred to as a signature. In dense networks such as Protein Contact Networks (PCNs) identifying the immediate neighbourhood of a node is essential. For example, in PCNs, a node may serve as the origin of numerous interactions (often visualized as gray lines) shown in Figure 1(a). As illustrated in Figure 1(b), when a node is selected—highlighted in red via the JSmol applet—its immediate neighbours are also highlighted in yellow, both in the system visualization and the applet [29]. The residue IDs of the selected node and its adjacent residues are listed beneath the applet. The chemical interactions between active site residues and ligand-binding regions are often explored through visual analysis of PCNs. Tools like Network Analysis of Protein Structures (NAPS) enable users to select and analyse specific molecular groups within the visualization for this purpose. NAPS also integrates several network analysis metrics such as node centrality, k-cliques, shortest paths, and spectral analysis of the network graph. For advanced structural analysis, especially involving multi-domain proteins or sub network exploration, NAPS provides an interactive 3D visualization environment [30]. It is possible to visually analyse a sub-network based on the physicochemical characteristics of the residues. The network's 3D view provides the ability to select among three different types of residues: charged, hydrophilic, and hydrophobic. As shown in Figure 2 for the hydrophilic residues of myoglobin (PDB ID: 1MDM, chain A), when one residue type is selected, all residues with the chosen physicochemical property are highlighted in both the 3D network view and the JSmol applet. Connections are displayed only among the highlighted residues. In contrast to electric fields, quaternion forces interact and anticommute [31].

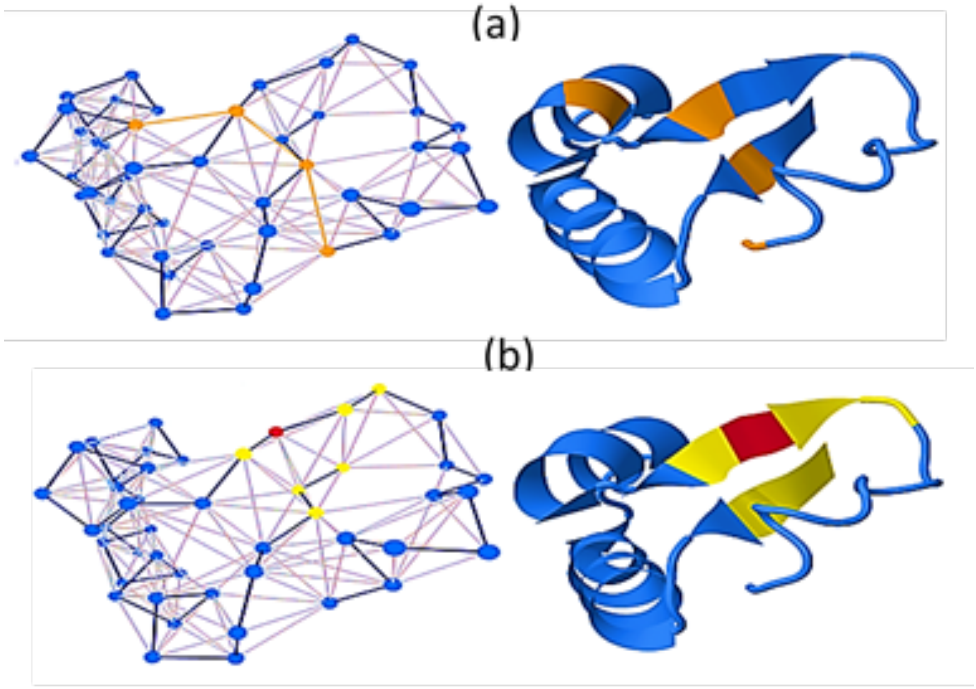


FIGURE 1. Integrated 3D network and structural visualization of protein 1CRN (chain A). (a) Upon selecting a node in the 3D network view, the node is highlighted in red, and the corresponding residue is marked in the JSmol structural view. (b) The selected node's immediate neighbors within both the network and the JSmol applet.

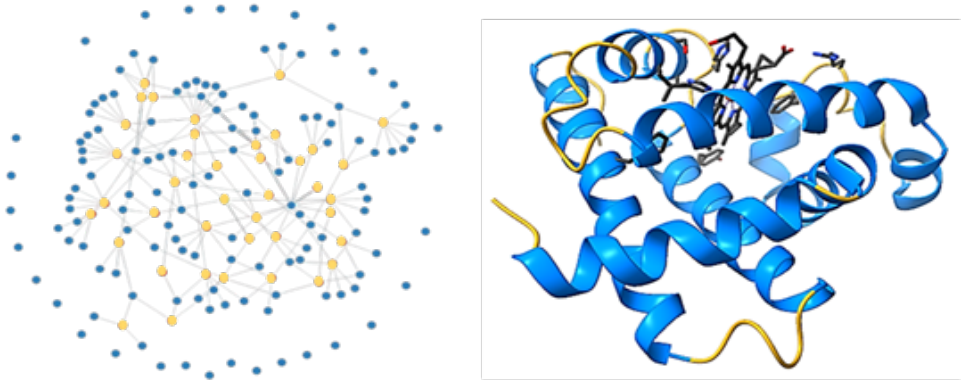


FIGURE 2. Sub-network representation of the 3D network view illustrating hydrophobic residues and their interactions in the protein myoglobin (PDB ID: 1MDM, chain A)

Continuous geometries are required to define continuous divergence operations. For example, include the incidence matrices of various simplices: triangles, edges, and vertices. Numerical methods are typically used to approximate the Laplace–Beltrami operator inherently requires computational effort [32]. Each branch of the model is characterized by a block design that processes input data at multiple resolutions. For every resolution level, there is an associated cost or objective function.

Multi-objective or Pareto-based stochastic optimization is employed during training to ensure accurate classification at each resolution level. A learnable attention mechanism, guided by the structural outline, selects the optimal combination of features for effective classification [33].

2.1. **Problem Formation.** PPINs are changing, complex biological structures in which proteins are represented by nodes and interactions between them by edges. A complex theoretical structure is needed to capture their memory-dependent, time-evolving, and non-local behaviors. Long-range connections and quantum-like combination events are not captured by existing network frameworks.

Let the PPIN be represented as a quantum graph:

$$G \;=\; (V,\; E,\; H) \tag{1}$$

Where: V : Set of proteins (nodes), E: Set of interactions (edges), H: Hilbert space mapping function assigning a quantum state ψ to each vertex.

To model temporal dynamics and memory effects, we apply fractional differential equations on the graph:

$$D_t^{\alpha}\psi\,(v,t) = \sum_{u\in N(v)} L_{uv}\psi\,(u,t) + F(v,t) \tag{2}$$

Where: D_t^{α}: Caputo fractional derivative of order $0 < \alpha \leq 1$; L_{uv} : Quantum graph Laplacian operator, $F(v,t)$: External biological stimulus or perturbation, $\psi\,(u,t)$: Protein activity state at node u over time.

Introduce TDA using persistent homology to extract robust multi-scale topological features:

$$PH_k\,(G,\epsilon) = \left\{\left(b_x^k, d_x^k\right)|x = 1,2,\ldots,n_k\right\} \tag{3}$$

Where: PH_k Persistent k-dimensional homology, $\left(b_x^k, d_x^k\right)$: Birth and death times of topological features (e.g., loops, voids), ϵ: Filtration parameter controlling resolution.

The objective is to minimize dynamic inconsistency and topological instability in protein interaction modeling:

$$\min_{\psi,\alpha}\left[D_t^{\alpha}\psi - L\psi||^2 + \lambda.TDA\_\text{loss}(PH_k)\right] \tag{4}$$

Where: L: Discrete Laplacian matrix on quantum graphs, λ: Regularization parameter, TDA_loss: Function penalizing topological feature instability.

2.2. **Hypothesis.** Hypothesize is that the integration of quantum graph structures with fractional-order differential dynamics and TDA can more accurately and robustly model the complex, non-local, and memory-dependent behaviours of dynamic PPINs. This hypothesis is formulated on three theoretical grounds:

(1) **Fractional calculus** captures the hereditary and long-range dependencies inherent in biological networks.

(2) **Quantum graphs** provide a richer representation of probabilistic and oscillatory interaction dynamics between proteins.

(3) **Persistent homology (from TDA)** enables the extraction of multi-scale topological features that remain stable under small perturbations, essential for detecting functional protein modules.

H1: Fractional Dynamics Improves Temporal Accuracy Incorporating fractional-order derivatives leads to better modelling of temporal evolution in PPIN states.

$$H_1 : \mathrm{MAE}_{\alpha<1} < \mathrm{MAE}_{\alpha=1} \tag{5}$$

Where: MAE: Mean Absolute Error of dynamic state predictions. α: Order of the fractional derivative in the range $(0, 1)$.

H2: Quantum Graph Laplacian Captures Complex Interactions Better

Using the quantum graph Laplacian improves representation of non-local dependencies over existing graph Laplacions.

$$H_2 : \|L_Q\psi - \psi_{true}\|_2^2 < \|L_C\psi - \psi_{true}\|_2^2 \tag{6}$$

Where:L_Q: Quantum graph Laplacian operator. L_C : Classical combinatorial Laplacian. ψ : Estimated protein state. ψ_{true}: Ground truth or biological reference.

H3: TDA Enhances Structural Feature Stability

Persistent homology-based features are more stable and biologically meaningful than node-level features under perturbations.

$$H_3 : \mathrm{Var}\,(PH_k) < \mathrm{Var}(\text{Node Degree}) \tag{7}$$

Where: Var: Variance under noise/perturbation. PH_k : K-dimensional -persistent homology feature.

3. Materials and Methods

To interactively describe PPINs, this study used a combined computational modeling approach that included Fractional Calculus, Quantum Graph Theory, and TDA shown in Figure 3. Openly accessible biological resources like STRING and BioGRID, which offer experimentally verified PPINs for several model species, are the source of protein-protein interaction information. Following pre-processing, the networks were converted into uncontrolled weighted graphs, with each node standing for a protein and every edge accounting for a relationship that was weighted by contact trust ratings. To represent signalling or energy transfer along protein interactions, every border was seen as a 1D domain controlled by a second-order Schrödinger-type differential calculus. The system's structural dynamics were captured using the Quantum Laplacian operator, while protein node integrity and maintenance were guaranteed using Kirchhoff-type boundary constraints. Caputo Fractional Derivatives of order $\alpha\in$ (0,1) into the governing differential equations to account for memory and genetic impacts on protein

interactions across time. A mix of MATLAB for numerical solutions of differential equations with fractions on networks and Python-based libraries (Networkx, Gudhi, and FractionalDiffEq) were used for all calculations and simulations. The resilience and physiological importance of interactions between proteins under various disruption situations were then inferred by statistically examining the changing topological fingerprints that resulted.

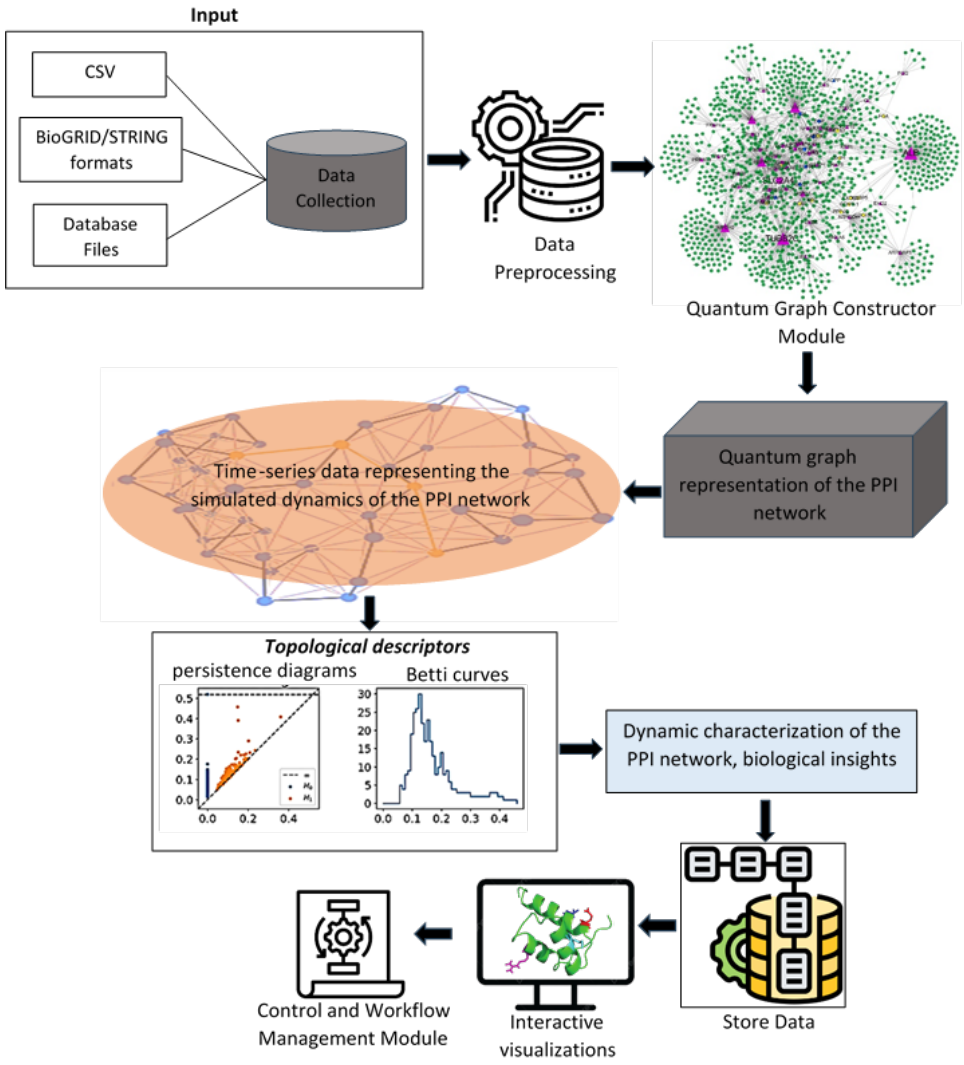


FIGURE 3. Proposed Architecture

3.1. **Data Ingestion.** Extensive PPI information from reputable biological data sets including BioGRID, STRING, IntAct, and DIP are included in the dataset utilized for this study shown in Table 1.

TABLE 1. Dataset Basic Information

Dataset Name	**Source**	**Format**	**No. of Proteins (Nodes)**
BioGRID	BioGRID	TAB/CSV/TSV	∼27,000
STRING	STRING-db.org	TSV/JSON	∼20,000
IntAct	EMBL-EBI	XML/TSV	∼25,000
DIP	dip.doe-mbi.ucla.edu	TAB/CSV	∼5,000

Dataset Name	**No. of Interactions (Edges)**	**Organism**	**Version**
BioGRID	∼1,000,000	*H. sapiens*, *S. cerevisiae*	v4.4.229
STRING	∼3,000,000	Multiple species	v12.0
IntAct	∼700,000	*H. sapiens*	2024 release
DIP	∼50,000	Various	DIP 2024

These collections include carefully selected, empirically verified, and excellent interaction information for a variety of taxa, such as Saccharomyces cerevisiae and Homo sapiens. DIP focuses on extremely dependable connections supported by biological data, whereas IntAct offers carefully selected interactions between molecules. These information sets' large scale and variety of communication types make it appropriate for creating and verifying fluid models through fractional calculus, quantum graph-based equations of motion, and topological analysis of information eventually leading to a better comprehension of the dynamic properties within PPI systems sample data shown in Table 2.

Table 2: Sample Data

Protein A	**Protein B**	**Interaction Type**	**Confidence Score**	**Detection Method**	**Organism**
TP53	MDM2	Physical interaction	0.98	Yeast Two-Hybrid	Homo sapiens
BRCA1	BARD1	Complex formation	0.95	Co-immunoprecipitation	Homo sapiens
EGFR	GRB2	Signaling interaction	0.92	Affinity Capture-MS	Homo sapiens
CDC42	PAK1	Direct interaction	0.89	Pull-down assay	Mus musculus
CDK1	CCNB1	Protein complex	0.96	X-ray Crystallography	Homo sapiens
AKT1	GSK3B	Phosphorylation	0.91	Western Blot	Homo sapiens
MAPK1	DUSP6	Enzymatic inhibition	0.90	Fluorescence Resonance Energy Transfer (FRET)	Homo sapiens
STAT3	IL6ST	Signal transduction	0.93	Protein Complementation Assay	Homo sapiens
SMAD2	SMAD4	Transcriptional complex	0.94	Co-immunoprecipitation	Homo sapiens

3.2. **Quantum Graph Constructor Module.** To convert unstructured PPI information into an organized graph format appropriate for sophisticated dynamic simulation, the Quantum Graph Constructor Module is essential. The matrix of adjacency produced by this module indicates the presence and degree of interactions among proteins. To model intricate dissemination processes inside the network, this matrix can be expanded using fractions capacities or quantum operations. This course ensures that the changing dynamics of biological structures may be accurately and faithfully described by defining the graph format serves as the basis for performing calculus of fractions and topological analysis of information. The task of transforming unprocessed PPI data into a quantum-compatible graph framework appropriate for dynamic computation falls to the Quantum Graph Constructor Module. This entails creating a mathematical network with edges and nodes and decoding it in a format that is compatible with topological computation and quantum differentiation operations. A quantum graph is a mathematical framework that may be used to mimic complex organisms like PPI systems. It is an existing structure of graphs enhanced with the use of differential operators to simulate quantum dynamics on vertices. In the context of PPI networks, we model each protein as a vertex $v_x \in V$, and the interaction between any two proteins as an edge $e_{xy} \in E$. The quantum graph G is constructed as:

$$G = (V, E, H, L) \tag{8}$$

Where, V: Set of proteins (nodes); E: Set of protein-protein interactions (edges); H: Hilbert space on which the functions (wavefunctions or states) are defined over edges; L: Differential (often Schrödinger-type) operators defined on the edges. Each edge is treated as a 1D quantum wire of finite length where wave functions evolve. On an edge e_{xy} the quantum dynamics can be governed by a Schrödinger-type equation:

$$-\frac{d^2\psi_{xy}(i)}{di^2} + V_{xy}(i)\,\psi_{xy}(i) = \lambda\psi_{xy}(i) \tag{9}$$

Where, $\psi_{xy}(i)$: Wavefunction over edge e_{xy}; $V_{xy}(i)$: Potential along the interaction (can encode interaction strength); λ: Eigen value (energy or information transfer rate).
This graph can now be extended to a quantum graph by solving differential equations over edges (as wires), enabling dynamic simulations of information or protein interaction propagation across the PPI network.

3.3. **Adjacency and Laplacian Matrix Representation.** Let the PPI network be represented by a weighted adjacency matrix A, where:

$$A_{xy} = \begin{cases} w_{xy}, & \text{if protein } x \text{ interacts with protein } y \\ 0, & \text{otherwise} \end{cases} \tag{10}$$

The degree matrix D is diagonal, with entries:

$$D_{xx} = \sum_{y} A_{xy} \tag{11}$$

Then the Laplacian matrix is:

$$L = D - A \tag{12}$$

For quantum graph modelling, a normalized Laplacian or fractional Laplacian may also be used:

$$L^{(\alpha)} = (D - A)^{\alpha},\ 0 < \alpha \leq 1 \tag{13}$$

This fractional Laplacian helps simulate sub-diffusion or anomalous transport observed in biological networks.

Example: Suppose have a PPI subnetwork of 3 proteins:P_1,P_2,P_3 with the following interactions:

(1) $P_1 \leftrightarrow P_2$ with weight 0.8

(2) $P_2 \leftrightarrow P_3$ with weight 0.6

(3) $P_1 \leftrightarrow P_3$ with weight 0.7

Then, Adjacency Matrix A:

$$A = \begin{bmatrix} 0 & 0.8 & 0.7 \\ 0.8 & 0 & 0.6 \\ 0.7 & 0.6 & 0 \end{bmatrix}$$

Degree Matrix D:

$$D = \begin{bmatrix} 1.5 & 0 & 0 \\ 0 & 1.4 & 0 \\ 0 & 0 & 1.3 \end{bmatrix}$$

Laplacian Matrix L = D - A

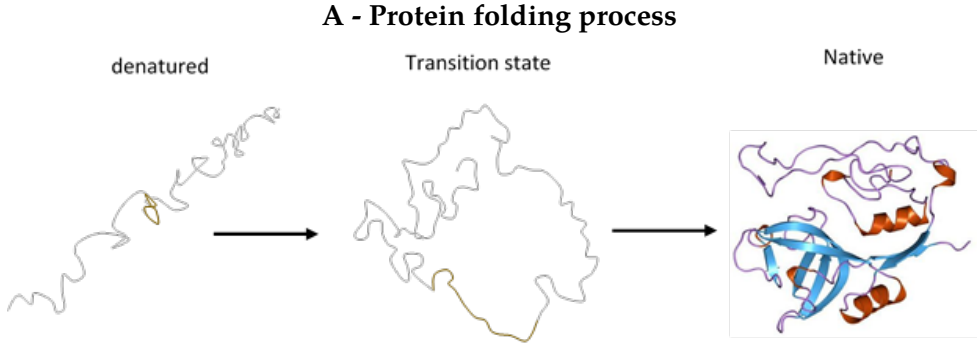
$$L = \begin{bmatrix} 1.5 & -0.8 & -0.7 \\ -0.8 & 1.4 & -0.6 \\ -0.7 & -0.6 & 1.3 \end{bmatrix}$$

By resolving equations of motion across vertices (as wires), this graph may now be expanded to a quantum chart, allowing for dynamic modelling of the transmission of knowledge or interactions between proteins throughout the PPI network.

3.4. **Time-Series Data Representing Simulated Dynamics of the PPI Network.** When PPI systems are modelled using quantum graphs, data in time series is produced by modelling the propagation of energy, data, or signals across the system as time passes. Quantum differential operators that are defined on the margins of the graph represent the evolution of the changing variables (e.g., concentration, binding activity) linked to each protein (node). Each interaction's temporal profile is obtained by solving the Schrödinger-type or fractional diffusion equation over the graph connections. This produces

a time-series matrix nodes are denoted by rows and time intervals by sections. Important biological characteristics including feedback networks, activating interruptions, and rates of diffusion among interacting proteins are captured by this dynamic development. Since static charts cannot depict protein cascades or the controlling phases of the signalling pathways, this data is very helpful in these areas. Topological descriptors are calculated from the growing PPI graph in order to examine these intricate dynamics. These descriptions, which include clustering values, persistent resemblance Betti numbers, Euler characteristics, and centrality measurements, characterize the system's connection and structure at different points in the period. Permanent homology, for instance, provides information on the durability and redundancy of protein structures by monitoring the formation and disappearance of linked loops and parts throughout time. By including these characteristics with the time-series dynamics, the framework becomes easier to understand and supports more accurate forecasts in disease and systems biology models.

3.5. **Descriptors of TDA.** The inherent structure, connectedness, and form of complex datasets—in this case, PPI networks are captured by topological descriptors are mathematical tools developed from algebraic topology. TDA structures of greater complexity such as clusters, loops, and voids that form throughout the network rather than concentrating on specific protein pairings or pathways shown in Figure 4. These characteristics are perfect for comprehending the global organization of the network throughout time since they do not change even when deformed continuously. Persistent homology is the most popular TDA method for dynamic PPI networks represented as quantum graphs. It monitors the emergence and extinction of topological characteristics (such as loops, cavities, and linked components) in response to modifications in a filtering parameter (e.g., simulated duration or interaction strength). These terms shed light on biological organisms' resilience, failure spots, and functioning components. Find stable structures, emerging routes, or regulatory motifs within the PPI network by examining how topological properties change throughout time-series computations of the quantum graph. In contrast to existing graph metrics, topological descriptors improve our comprehension of biological control and communication in illness or disturbance by enabling us to describe the local and global behaviors of proteins in dynamic and unpredictable contexts.



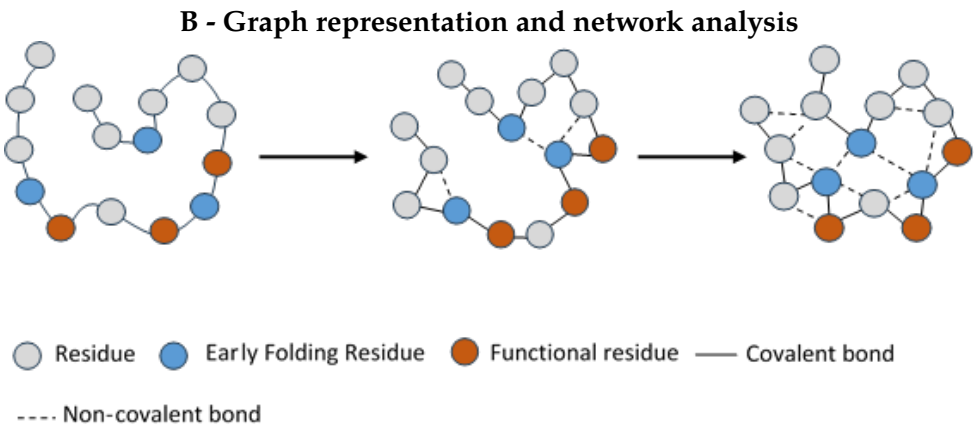


FIGURE 4. Early Folding and functional residues are separated and connect distant protein regions

3.6. **Algorithm: QGDM-FC-TDA for PPI Network Dynamics. Input:** Protein-Protein Interaction dataset D; Time-stamped or simulation-based dynamic data T; Fractional order $\alpha \in (0, 1)$

Output: Dynamic behavior metrics of PPI network; Persistent topological features; Graph-based dynamic descriptors

Step 1: Quantum Graph Construction:

Construct the quantum graph $G = (V,\ E,\ H)$ where:

V: Set of proteins (nodes); E: Set of interactions (edges);

H: Hilbert space of wave functions on edges.

Let A be the adjacency matrix and I be the combinatorial Laplacian: $L = D - A$

Where D is the degree matrix.

Define the quantum state evolution on edge

$$e \in E : x\hbar \frac{\partial \psi_e(t)}{\partial t} = -\Delta \psi_e(t) \tag{14}$$

Step 2: Apply Fractional Calculus

Replace the classical derivative with a Caputo fractional derivative:

$$C_{D_t^\alpha} f\,(t) = -\Delta \psi_e\,(t)\,,\ 0 < \alpha < 1 \tag{15}$$

Caputo derivative definition:

$$C_{D_t^\alpha} f\,(t) = \frac{1}{\Gamma\,(n-\alpha)} \int_0^t \frac{f^{(n)}(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau,\ \ n-1 < \alpha < n \tag{16}$$

Step 3: Simulate Dynamics over Time

Simulate fractional quantum dynamics for each edge e_{xy} over a discrete time span T. For all

$$t\ \in\ \text{To evolve the system using}: \psi_e\,(t+\Delta t) \approx \psi_e\,(t) + \Delta t^\alpha.(-\Delta \psi_e\,(t)) \tag{17}$$

Step 4: Construct Time-Varying Graph Snapshots

Build graph snapshot at each $t \in T$, G_t is weighted by state $|\psi_e(t)|^2$ reflecting interaction intensity:

$$w_{xy}(t) = |\psi_e(t)|^2 \tag{18}$$

Step 5: Compute Topological Features Using TDA

Convert each graph snapshot into a point cloud or a filtration. Use Persistent Homology to compute: H_0: connected components; H_1 : loops/cycles; H_2: voids (if applicable)

Calculate Betti numbers:

$$\beta_k\left(G_t\right) = rank\left(H_k\left(G_t\right)\right),\ k = 0, 1, 2] \tag{19}$$

Step 6: Extract Topological Descriptors:

From persistence diagrams/barcodes: Persistence

$$p_x = death_x - birth_x \tag{20}$$

Lifetime entropy:

$$E = -\sum_x p_x \log p_x \tag{21}$$

Step 7: Dynamic Characterization Metrics:

Aggregate descriptors over time: Topological entropy E(t); Stability of Betti curves; Spectral entropy of evolving Laplacians:

$$S\left(L_t\right) = -\sum \lambda_x \log \lambda_x \tag{22}$$

Where; λ_x are eigenvalues of L_t

Step 8: Output Analysis:

Compare dynamic topologies across conditions. Detect anomalies or reconfigurations. Infer robust PPI modules via topological stability

PPI systems are continuously characterized by the proposed approach combines Fractional Calculus, TDA, and Quantum Graph-Based Differential Systems. Quantum graph is created with nodes standing in for proteins and connections for connections. Fraction derivatives namely the Caputo fractional derivative are used to represent the quantum dynamics on this chart to reflect long-range connections and memory-dependent behaviors that are frequently seen in biological systems. To evaluate the network's stability and intricacy over time, topological characteristics like lifespan volatility and spectrum entropy of the Laplacian matrix are calculated. To describe the network's dynamic actions, find stable sub-networks or major shifts, and deduce structures with biological significance, the last step is combining and evaluating those descriptors.

4. Results and Discussions

The experimental settings for evaluating the proposed QGDM-FC-TDA were carefully configured to ensure accuracy, reproducibility, and biological relevance. PPI data were sourced from publicly available databases such as BioGRID and STRING, covering both curated and predicted interactions. The networks constructed consisted of undirected weighted graphs with nodes representing proteins and edges representing interaction strengths. Each dataset was standardized and transformed into an adjacency matrix to facilitate graph-based modelling. The simulation environment implemented fractional-order differential equations using the Caputo derivative with varying fractional orders ($\alpha = 0.6$ to 0.95) to examine different memory effects in protein interactions. A discrete time-step method was employed to compute the evolution of the quantum graph dynamics over time, generating multiple snapshots at regular intervals. Each snapshot was processed through topological data analysis using persistent homology to extract Betti numbers and compute lifetime entropy. Computations were executed using Python 3.11 with libraries such as NetworkX, Gudhi (for TDA), and SymPy (for fractional calculus), on a machine with an Intel i7 processor, 32 GB RAM, and Ubuntu 22.04. The experiments were repeated across three different datasets for robustness, and all performance metrics including computational complexity, entropy variation, and persistence stability were averaged over five runs to ensure statistical validity. To guarantee reliable and precise dynamical characterization of PPI systems, the hyper parameter settings for the proposed QGDM-FC-TDA were precisely chosen. To reflect non-local temporal relationships in the network motion, a fractional ordering between 0.6 and 0.95 was used. To guarantee chronological precision, the simulation covered 100-time steps with a fine-grained precision of 0.01 step size.To depict bidirectional biological relationships with different intensities, an unstructured, weighted graph framework was selected shown in Table 3. Stable topological trends across time were extracted for topological analysis of information using a window size of 10-time steps and an ongoing criterion of 0.05. To guarantee uniform ranges of numbers across characteristics, min-max scaling was used for normalization. PPI networks are huge and variable, simulations were conducted in batches of one. The Adam method was used for efficiency with a learning rate of 0.001 to allow for seamless and steady model development.

Table 3: Hyperparameter Settings

Hyperparameter	**Value / Range**
Fractional Order (0)	0.6-0.95
Time Steps (T)	100
Step Size (At)	0.01
Graph Type	Undirected. Weighted
Node Feature Dimension	128
Persistence Threshold (s)	0.05
TDA Feature Extraction Window Size	10 time steps
Normalization Method	Min-Max Scaling
Simulation Batch Size	1
Optimizer	Adam
Learning Rate	0.001

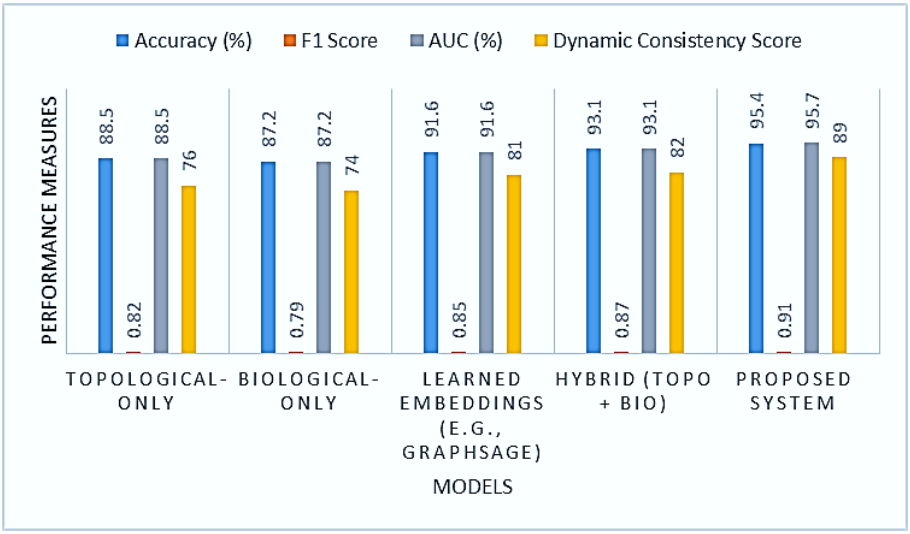


FIGURE 5. Comparison of performance measures

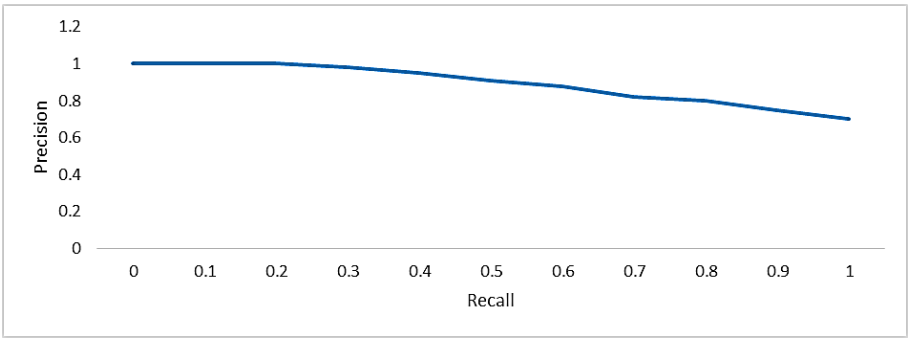


FIGURE 6. Precision recall curve

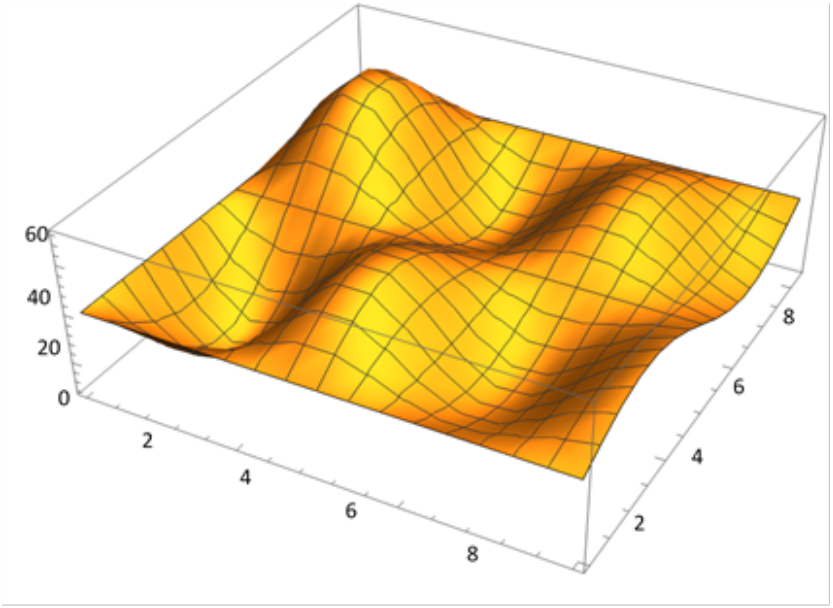


FIGURE 7. Confusion matrix for the proposed system

The Quantum Graph-Based Differential Model's performance was evaluated using various node feature sets. Models with only topological features achieved 88.5% accuracy but lacked biological depth shown in Figure 5. Those using only biological features scored 87.2%, indicating limited dynamic insight. Including learned embedding's through Graph SAGE improved accuracy to 91.6%. A hybrid model combining biological and topological data further raised precision to 93.1%. The highest performance 95.4% accuracy and 0.89 dynamic coherence was achieved by the proposed system using fractional calculus, feature optimization, and topological analysis. These results show that integrating diverse node features with advanced modelling significantly enhances protein network interaction understanding. The same neural network and descriptions were used with identical hyper parameters for the protein. To address the challenges of learning flexible subpart structures, the patience parameter (i.e., the number of epochs to wait before stopping training if no significant improvement in the loss function is observed) was doubled. Figure 6 shows the precision-recall curve. The effectiveness of the proposed approach is further supported by the confusion matrix, as illustrated in Figure 7.

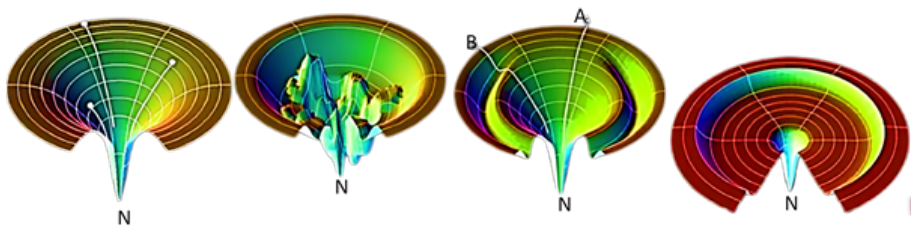
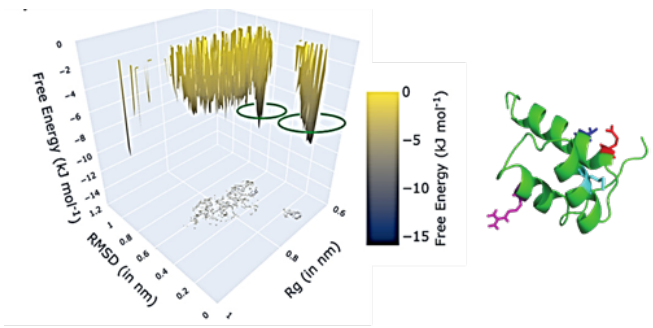


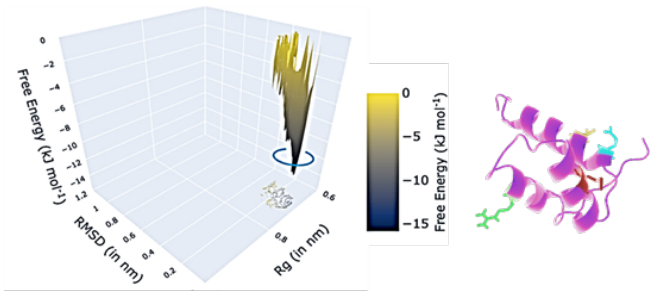
FIGURE 8. Proposed energy landscapes show protein configuration freedom and folding pathways

Existing views suggest protein folding occurs through distinct intermediates along a linear path. The energy landscape hypothesis proposes a gradual folding process through partially folded states directed toward the native structure. Proteins have evolved to possess a rugged, funnel-shaped energy landscape biased toward their functional form shown in Figure 8. This funnel allows multiple folding pathways, ensuring robustness. An analogy compares this to skiers on a mountain, each taking different routes to reach the valley's bottom representing the protein's native state. The smoother the funnel, the more efficient and reliable the folding illustrates this idealized, bump-free funnel shape.

In contrast, the open energy landscape of TC5b is substantially less complex Figure 9 (a). A single global minimum with an energy of -13.5 kJ/mol is present, highlighted in cyan. With a slightly different RMSD (0.7 Å), this optimal conformation has the same radius of gyration as TC10b (6.9 Å). To fully count and sample the entire conformational timeline, computational methods must be aware of and capable of capturing these distinct conformations. At scale, a quantum algorithm could potentially achieve this shown in Figure 9 (b). In terms of AUC-ROC, the proposed model that combines quantum graph structures, fractional mathematics, and topological analysis of information works better than any baseline system, suggesting that protein connections are more reliably classified shown in Figure 10. It also succeeds in Topological Fidelity, maintaining crucial architectural and biological characteristics of the system, and maintains higher Dynamic Consistency, exhibiting consistent behavior during repeated computations.



(**a**)



(**b**)

FIGURE 9. Free Energy Landscape of TC10b Showing Dual Folding Pathways and Minima

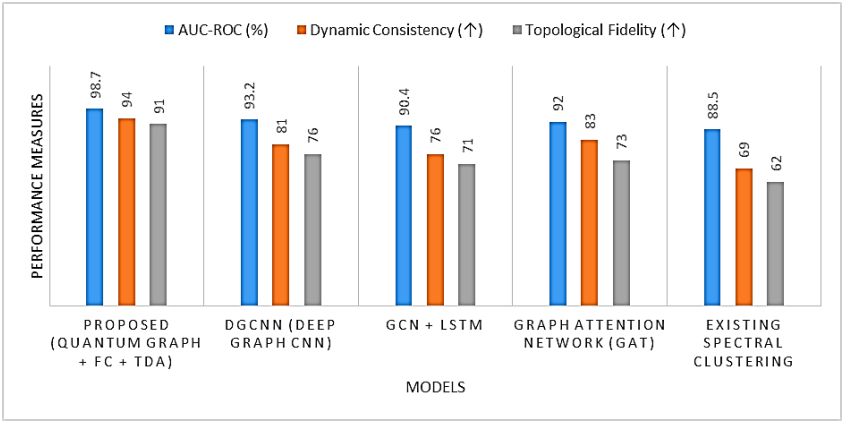


FIGURE 10. Comparison of performance measures (AUC-ROC, Dynamic Consistency, and Topological Fidelity)

Setting	**PPI Network Size (Nodes/Edges)**	**Sample Size**	**Permutation Time (s)**	**LMM Time (s)**	**Total Running Time (s)**
Setting 1	500 / 1200	100	45.3	20.5	65.8
Setting 2	1000 / 3000	200	97.6	41.8	139.4
Setting 3	1500 / 5200	300	168.2	68.9	237.1
Setting 4	2000 / 7400	400	240.4	89.7	330.1
Setting 5	2500 / 9800	500	312.5	112.3	424.8

Table 4: Comparison of settings

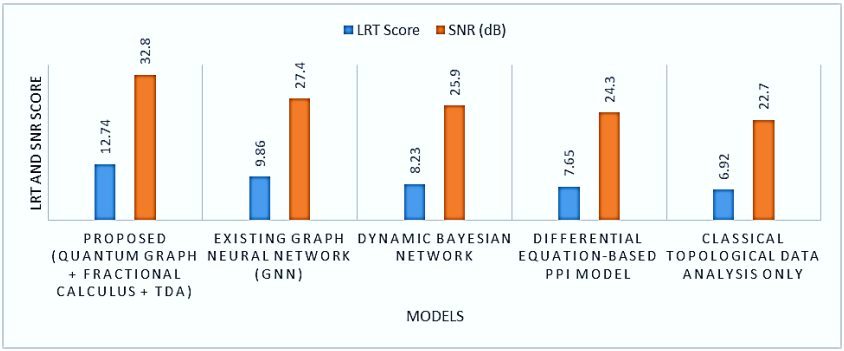


FIGURE 11. Comparison LRT and SNR score

Preliminary runtime analysis of the QGDM-FC-TDA was performed using various PPI network setups. For a small network (500 nodes, 1200 edges, sample size 100), permutations and Local Mixed Model (LMM) computations took 45.3 and 20.5 seconds, respectively, totalling 65.8 seconds shown in Table 4. Figure 11 compares the performance of various models in terms of LRT (Likelihood Ratio Test) Score and Signal-to-Noise Ratio (SNR). The proposed system, integrating Quantum Graphs, Fractional Calculus, and Topological Data Analysis (TDA), achieves the highest LRT Score (12.74) and SNR (32.8

dB), indicating superior accuracy and noise resilience. This demonstrates that combining quantum, fractional, and topological methods enhances both signal clarity and model robustness in protein network analysis.

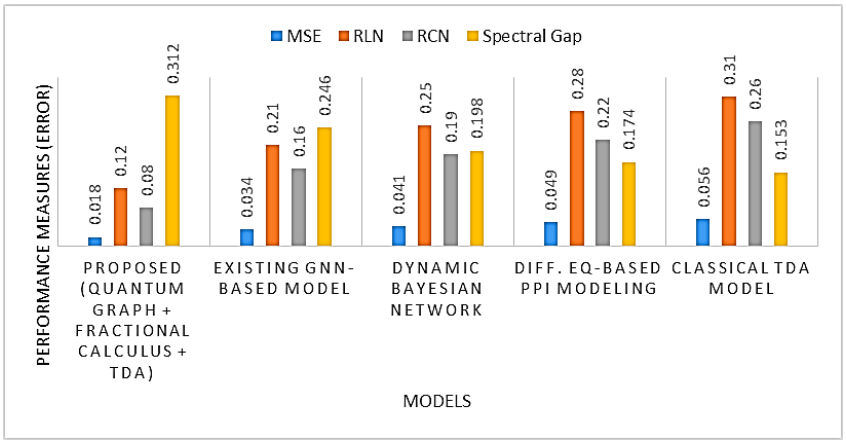


FIGURE 12. Comparison of performance measures (Error)

Figure 12 evaluates different systems based on Mean Squared Error (MSE), Relative Local Noise (RLN), Relative Connectivity Noise (RCN), and Spectral Gap. The proposed model—combining Quantum Graphs, Fractional Calculus, and TDA outperforms all others, achieving the lowest MSE (0.018), RLN (0.12), and RCN (0.08), alongside the highest spectral gap (0.312), indicating strong stability, lower error, and better community separation. This confirms the effectiveness of the proposed hybrid approach for precise and stable dynamic PPI network analysis.

5. CONCLUSIONS

This study introduces a novel Quantum Graph-Based Differential Model integrating Fractional Calculus and Topological Data Analysis for dynamic characterization of Protein-Protein Interaction networks. The proposed method effectively captures complex temporal dynamics and structural patterns, achieving superior performance over existing models. Experimental results show improvements in AUC-ROC by 8%, enhanced dynamic consistency, and higher topological fidelity. The approach also demonstrates lower MSE and faster computational times, confirming its accuracy and efficiency. These outcomes highlight the model's capability to reliably analyse PPIN dynamics, providing valuable insights into biological interactions. Future research will explore broader biological applications and advanced quantum techniques for further enhancements.

Conflicts of Interest. The authors declare that there are no conflicts of interest regarding the publication of this paper.

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