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Modeling Molecular Interactions with Hyper-Networks and Super-Hyper-networks

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Authors' contributions

This work was carried out in collaboration among all authors. Author TF was responsible for conceptual development, mathematical analysis, manuscript editing and writing, as well as self-review. Authors MG and AAG conducted the review of the manuscript and verified its validity. Each contributor is also conducting any additional checks and adjustments as needed. All authors read and approved the final manuscript.

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ABSTRACT

Graph theory examines the structure of networks by treating entities as vertices and the connections between them as edges. A Hyper-Graph enhances this framework by permitting a single Hyper-edge to link multiple vertices at once. Building on that idea, a Super-Hyper-Graph introduces layers of recursively nested powersets, which create hierarchical and self-referential relationships among its Hyper-edges. These extended models—often called Hyper-Networks and Super-Hyper-networks—capture complex, higher-order associations that ordinary graphs cannot. Such constructions find important applications in the life sciences. For example, a Molecular Interaction Network represents biochemical systems by assigning each molecule to a node and using edges to denote pairwise interactions or chemical reactions, thereby facilitating the analysis of intricate molecular pathways.

In this paper, we extend the concept of Molecular Interaction Networks by proposing two new frameworks: the *Molecular Interaction Hyper-network* and the *Molecular Interaction Super-Hyper-network*, both grounded in the structures of Hyper-Networks and Super-Hyper-networks. These frameworks offer new insights into multi-scale biochemical systems, with potential applications in drug target identification and pathway analysis. We hope that future research will further explore the mathematical, biological, and computational aspects of the *Molecular Interaction Hyper-network* and the Molecular Interaction Super-Hyper-network.

Keywords: Super-hyper-graph; hyper-graph; molecular Interaction networks; hyper-networks; super-hyper-networks.

1 INTRODUCTION

1.1 Theories of Graphs, Hyper-Graphs and Super-Hyper-Graphs

Graph theory is a branch of mathematics focused on the study of networks, where nodes (called vertices) are connected by links (called edges)(Diestel, 2005). Graphs have been extensively studied and applied in a wide range of disciplines, including social science, artificial intelligence, graph neural networks (GNNs), and general network analysis (cf.(Feng et al., 2019; Gao et al., 2022; Guo et al., 2022)).

Mathematical structures can often be extended into *Hyper-structures* and *Super-Hyper-structures* by utilizing the power set and n-th iterated powerset constructions (Smarandache, 2024c, 2023b; Fujita, 2025a; Smarandache, 2023a). These generalized frameworks are particularly useful for modeling hierarchical and multi-layered systems in both theoretical and practical contexts.

When applied to graph theory, these extensions give rise to two important generalizations: the *Hyper-Graph*(Berge, 1984; Bretto, 2013) and the *Super-Hyper-Graph* (Fujita and Smarandache, 2024a; Smarandache, 2020, 2019). A hypergraph allows each edge—called a *Hyper-edge*—to connect more than two vertices simultaneously, capturing complex many-to-many relationships. A Super-Hyper-Graph goes further by incorporating recursively nested powerset structures, enabling hierarchical and self-referential relationships among collections of Hyper-edges. These models can also be extended into various directions, such as directed graphs (Jose et al., 2023; Fujita, 2025h; George et al., 2024), bidirected graphs (Kita, 2017; Xu and Zhang, 2005; Gonz'alez and Mr'oz, 2023), and multidirected graphs (Pardo-Guerra et al., 2025, 2024).

1.2 Graph theory and Network Theory

Network theory investigates the structure and behavior of systems composed of interconnected nodes and edges, with emphasis on the analysis of relationships, flows, and dynamic interactions in complex environments. Examples of networks include biological networks(Girvan and Newman, 2001; Maere et al., 2005), ecological networks (Kurtz et al., 2014; Delmas et al., 2018), electrical networks(Balabanian and Bickart, 1969; Berglind and Gillner, 1994), social network(Pryke, 2005; Nagy and Pecho, 2009; Salama et al., 2014), telecommunications networks(Schoonderwoerd et al., 1996; Frost and Melamed, 1994), business networks (Håkansson and Snehota, 1995; Håkansson and Ford, 2002; Alcácer et al., 2016), and supply networks (Villena and Gioia, 2018; Ang et al., 2017).

Graphs are commonly employed as foundational tools for representing such networks. In this context, *Hyper-Networks* and *Super-Hyper-networks* emerge as

network-based analogues of Hyper-Graphs and Super-Hyper-Graphs, respectively, allowing for the modeling of higher-order and hierarchical relationships in networked systems (cf.(Fujita, 2025d; Hamidi et al., 2023)).

1.3 Graph in Biology and Biochemistry

Graph-based and network-based approaches have also played a central role in many studies in biology (N. and B.V., 2023; Durga et al., 2019), chemistry(Trinajstic, 2018; García-Domenech et al., 2008; Wagner and Wang, 2018), biophysics(Srivastava et al., 2023), bioelectricity(Gawthrop and Pan, 2021), bioinformatics(Yi et al., 2022; Have and Jensen, 2013; Zhang and Wiemann, 2009), and biochemistry(Thiede et al., 2022). Examples of graph concepts in biology and biochemistry include the Molecular Graph(Faulon, 1998; Hanser et al., 1996; Lu et al., 2024), Protein–Protein Interaction (PPI) Graph(Theofilatos et al., 2015; Kritikos et al., 2011; Brevier et al., 2007), Signal Transduction Network (Galperin, 2004; Robbins et al., 2012; Wang and Albert, 2011), Phylogenetic Tree (Kapli et al., 2020; Mooers and Heard, 1997; Huelsenbeck et al., 2002), and RNA Secondary Structure Graph(Le et al., 1989; Koessler et al., 2010). Hyper-Graphs are likewise employed in fields such as biology and biochemistry (Feng et al., 2021; Franzese et al., 2019; Jin et al., 2023; Dai and Gao, 2023). As such, graph-based models are widely utilized across various domains in the life sciences.

In this paper, we focus on a class of graph-based models known as *Molecular Interaction Networks*, which describe biochemical interactions among molecules. In such models, nodes represent molecular entities (e.g., proteins, genes, or metabolites), and edges represent pairwise interactions or chemical reactions (Ideker et al., 2002; Alfarano et al., 2004; Gawron et al., 2016; Lee et al., 2008).

1.4 Our Contributions in this paper

This paper introduces two novel generalizations: the *Molecular Interaction Hyper-network* and the *Molecular Interaction Super-Hyper-network*, which extend the structure of Molecular Interaction Networks using the frameworks of Hyper-Networks and Super-Hyper-networks, respectively. We present their formal definitions, investigate their mathematical properties, and provide concrete real-world examples. These newly proposed models are intended to support future research on hierarchical and multi-scale representations of molecular interaction networks.

1.5 Structure of this research paper

This subsection outlines the structure of the paper. Section 2 presents the *Preliminaries and Definitions*, including foundational concepts such as Classical Structure, Hyper-structure, and n-Super-Hyper-structure, as well as Hyper-Graph, Super-Hyper-Graph, and Molecular Interaction Networks. Section 3 introduces and defines *Molecular Interaction Hyper-Networks*, while Section 4 focuses on the definition and analysis of *Molecular Interaction Super-Hyper-networks*. For each, concrete examples and related mathematical theorems are discussed. Finally, Section 5 provides the *conclusion* of the paper along with directions for *future work*.

2 PRELIMINARIES

This section reviews the key concepts and definitions that underpin our results. Throughout, all graphs are assumed finite unless stated otherwise.

2.1 Classical Structures, Hyperstructures and n-Superhyperstructures

A *classical structure* is any mathematical system defined on a set S. Replacing S by its powerset $\mathrm{POWSET}(S)$ yields a *hyperstructure*. By iterating this process n times—forming $\mathrm{POWSET}^n(S)$—one obtains an *n-superhyperstructure* (Fujita, 2025j; Adebisi and Ajuebishi, 2025; Fujita, 2025b; Smarandache, 2024b). In other words, $\mathrm{POWSET}^n(S)$ is the result of applying the powerset operator n consecutive times (Smarandache, 2024a; Fujita, 2025c; Al-Odhari, 2025; Fujita, 2025b). Below we introduce these notions formally and give simple examples.

Definition 2.1 (Base Set)**.** Let S be a nonempty set, called the *base set*. Formally,

$$S = \{\, e \mid e \text{ belongs to the specified domain} \}.$$

Every element of constructions such as $\mathrm{POWSET}(S)$ or $\mathrm{POWSET}_n(S)$ is drawn from S.

Definition 2.2 (Powerset)**.** (Fujita, 2024c) The (finite) *powerset* of a set S, denoted $\mathrm{POWSET}(S)$, is the collection of all possible subsets of S, including both the empty set and S itself. Formally, it is expressed as:

$$\mathrm{POWSET}(S) = \{A \mid A \subseteq S\}.$$

Example 2.3 (Post-translational Modification Combinations)**.** Post-translational modifications are chemical changes made to proteins after synthesis, altering their activity, localization, stability, or interaction with other molecules (cf.(Mann and Jensen, 2003; Krishna and Wold, 1993; Ramazi and Zahiri, 2021)). Consider a protein domain that can undergo three types of post-translational modifications:

$$S = \{\mathrm{P},\ \mathrm{Ac},\ \mathrm{Me}\},$$

where P = phosphorylation, Ac = acetylation, Me = methylation. Then the powerset $\mathrm{POWSET}(S)$ enumerates all possible modification states:

$$\mathrm{POWSET}(S) = \big\{\,\emptyset,\ \{\mathrm{P}\},\ \{\mathrm{Ac}\},\ \{\mathrm{Me}\},\ \{\mathrm{P},\mathrm{Ac}\},\ \{\mathrm{P},\mathrm{Me}\},\ \{\mathrm{Ac},\mathrm{Me}\},\ \{\mathrm{P},\mathrm{Ac},\mathrm{Me}\}\big\}.$$

- $\emptyset$: unmodified protein.
- $\{\mathrm{P}\}$, $\{\mathrm{Ac}\}$, $\{\mathrm{Me}\}$: single modification states.
- $\{\mathrm{P},\mathrm{Ac}\}$, $\{\mathrm{P},\mathrm{Me}\}$, $\{\mathrm{Ac},\mathrm{Me}\}$: dual-modification states.
- $\{\mathrm{P},\mathrm{Ac},\mathrm{Me}\}$: fully modified protein.

This enumeration guides the design of experiments probing cross-talk between different modifications and their combinatorial effects on protein function.

Definition 2.4 (n-th Powerset)**.** (Smarandache, 2024b; Fujita, 2024c, 2025d) Let H be any (finite) set. Its *n-th powerset*, denoted $\mathrm{POWSET}_n(H)$, is defined by

$$\mathrm{POWSET}_1(H) = \mathrm{POWSET}(H), \quad \mathrm{POWSET}_{n+1}(H) = \mathrm{POWSET}\big(\mathrm{POWSET}_n(H)\big), \quad n \geq 1.$$

The *n-th nonempty powerset* $\mathrm{POWSET}^*_n(H)$ omits the empty set at each stage:

$$\mathrm{POWSET}^*_1(H) = \mathrm{POWSET}(H) \setminus \{\varnothing\}, \quad \mathrm{POWSET}^*_{n+1}(H) = \mathrm{POWSET}\big(\mathrm{POWSET}^*_n(H)\big) \setminus \{\varnothing\}.$$

Example 2.5 (Gene Regulatory Programs via POWSET_n)**.** (Zoller et al., 2022; Dillon and Sabbattini, 2000) Let the set of regulatory elements be

$$H = \{,,\}.$$

Level 1 (POWSET_1): all single-gene programs,

$$\mathrm{POWSET}_1(H) = \mathrm{POWSET}(H) = \{\varnothing, \{\}, \{\}, \{\}, \{,\}, \{,\}, \{,\}, \{,\}, \{,,\}\}.$$

Level 2 (POWSET_2): multi-gene programs. Choose

$$A_1 = \{\}, \quad A_2 = \{,\}, \quad A_3 = \{,\},$$

then

$$\mathrm{POWSET}_2(H) = \mathrm{POWSET}\big(\mathrm{POWSET}_1(H)\big), \quad M_1 = \{A_1, A_2\}, \quad M_2 = \{A_2, A_3\}.$$

Level 3 (POWSET_3): tissue-level programs,

$$\mathrm{POWSET}_3(H) = \mathrm{POWSET}\big(\mathrm{POWSET}_2(H)\big), \quad T = \{M_1, M_2\}.$$

Thus the sequence

$$H \longrightarrow \mathrm{POWSET}_1(H) \longrightarrow \mathrm{POWSET}_2(H) \longrightarrow \mathrm{POWSET}_3(H)$$

captures successively higher-order regulatory combinations from individual elements up to tissue-level programs.

Definition 2.6 (Classical Structure)**.** (cf.(Smarandache, 2024b, 2022)) A *Classical Structure* is a mathematical framework defined on a non-empty set H, equipped with one or more *Classical Operations* that satisfy specified *Classical Axioms*. Specifically:

A *Classical Operation* is a function of the form:

$$\#_0 : H^m \to H,$$

where $m \geq 1$ is a positive integer, and H^m denotes the m-fold Cartesian product of H. Common examples include addition and multiplication in algebraic structures such as groups, rings, and fields.

Definition 2.7 (Hyper-Operation)**.** (cf.(Vougioukli, 2020a,b; Rezaei et al., 2021; Vougioukli, 2023)) A *Hyper-Operation* is a generalization of a binary operation where the result of combining two elements is a set, not a single element. Formally, for a set S, a Hyper-Operation $\circ$ is defined as:

$$\circ : S \times S \to \mathrm{POWSET}(S),$$

where $\mathrm{POWSET}(S)$ is the powerset of S.

Definition 2.8 (Hyper-structure)**.** (cf.(Smarandache, 2024b; Fujita, 2024c; Smarandache, 2022)) A *Hyper-structure* extends the notion of a Classical Structure by operating on the powerset of a base set. Formally, it is defined as:

$$\mathcal{H} = (\mathrm{POWSET}(S), \circ),$$

where S is the base set, $\mathrm{POWSET}(S)$ is the powerset of S, and $\circ$ is an operation defined on subsets of $\mathrm{POWSET}(S)$. Hyper-structures allow for generalized operations that can apply to collections of elements rather than single elements.

Example 2.9 (Metabolic Pathway Hyper-structure of Glycolysis)**.** A metabolic pathway is a series of enzyme-catalyzed biochemical reactions that convert substrates into products, sustaining cellular processes and energy flow (cf.(Brown et al., 2016; Milone et al., 2014)). In biochemistry, metabolic pathways involve sequences of enzyme-catalyzed reactions converting substrates into products. We model part of the glycolysis pathway as a Hyper-structure

$$\mathcal{H} = \big(\mathrm{POWSET}(S),\, \circ\big),$$

where the *base set* of metabolites is

$$S = \big\{\, \text{Glucose},\ \text{ATP},\ \text{ADP},\ \text{Glucose-6-Phosphate},\ \text{Fructose-6-Phosphate},\ \text{Fructose-1, 6-Bisphosphate} \big\},$$

and the *Hyper-Operation*

$$\circ : S \times S \ \longrightarrow\ \mathrm{POWSET}(S)$$

is defined on single metabolites by the stoichiometry of key reactions:

$$\begin{aligned} \text{Glucose} \circ \text{ATP} &= \{\text{Glucose-6-Phosphate},\ \text{ADP}\}, \\ \text{Fructose-6-Phosphate} \circ \text{ATP} &= \{\text{Fructose-1, 6-Bisphosphate},\ \text{ADP}\}, \\ x \circ y &= \{\, x, y\} \quad \text{if no direct reaction occurs.} \end{aligned}$$

We extend $\circ$ to mixtures by

$$A \circ B = \bigcup_{a \in A,\ b \in B} (a \circ b), \quad A, B \subseteq S.$$

Concrete computations:

$$\{\text{Glucose}\} \circ \{\text{ATP}\} = \{\text{Glucose-6-Phosphate},\ \text{ADP}\},$$

$$\begin{aligned} &\{\text{Glucose}, \text{ATP}\} \circ \{\text{Fructose-6-Phosphate}, \text{ATP}\} \\ &= \big(\text{Glucose} \circ \text{Fructose-6-Phosphate}\big) \ \cup\ \big(\text{ATP} \circ \text{ATP}\big) \ \cup\ \ldots \end{aligned}$$

$$= \{\text{Glucose}, \text{Fructose-6-Phosphate}, \dots\}.$$

Thus $\mathcal{H}$ captures the many-to-many relationships of metabolites in glycolysis: combining substrates yields all possible products, and mixing mixtures yields the union of individual reaction outcomes, modeling both single-step and multi-step biochemical processes within one algebraic framework.

Definition 2.10 (Super-Hyper-Operation)**.** (Smarandache, 2024b) Let H be a nonempty set, and write $\mathrm{POWSET}(H)$ for its powerset. Define recursively

$$\mathrm{POWSET}^0(H) = H, \qquad \mathrm{POWSET}^{k+1}(H) = \mathrm{POWSET}\big(\mathrm{POWSET}^k(H)\big), \quad k \geq 0.$$

An (m,n)-*Super-Hyper-Operation* is an m-ary map

$$\circ^{(m,n)} : H^m \longrightarrow \mathrm{POWSET}^n_*(H),$$

where $\mathrm{POWSET}^n_*(H)$ denotes the n-th powerset of H, either excluding the empty set (yielding a *classical-type* (m,n)-Super-Hyper-Operation) or including it (yielding a *Neutrosophic* (m,n)-Super-Hyper-Operation). These higher-order operations extend ordinary Hyper-Operations by producing multi-level subsets via iterated powerset constructions.

Definition 2.11 (n-Super-Hyper-structure)**.** (Smarandache, 2024b; Fujita, 2024d) Let S be a nonempty set and define its n-th powerset $\mathrm{POWSET}_n(S)$ as above. An n-*Super-Hyper-structure* is the pair

$$\mathrm{SuHySt}_n \;=\; \big(\mathrm{POWSET}_n(S), \circ\big),$$

where $\circ$ is a (multi-ary) operation on elements of $\mathrm{POWSET}_n(S)$. By iterating the powerset, this framework captures hierarchical and multi-scale relationships within S, generalizing the notion of a Hyper-structure to deeper levels.

Example 2.12 (2-Super-Hyper-structure of Protein Complex Assembly)**.** Protein complex assembly is the biological process where multiple protein subunits interact and bind to form a functional multi-protein complex (cf.(Hung and Sheng, 2002; Makhnevych and Houry, 2012; Natarajan et al., 2020)). In cellular biochemistry(Banani et al., 2017), many functional units arise by hierarchical assembly of protein subunits.

- **Base set** S of protein subunits:

$$S = \{\text{Actin, Myosin, Tropomyosin, Troponin}\}.$$

- **First-level complexes** $\mathrm{POWSET}^1(S)$:

$$C_1 = \{\text{Actin, Myosin}\} \quad (\text{actomyosin}),$$
$$C_2 = \{\text{Actin, Tropomyosin, Troponin}\} \quad (\text{thin filament regulatory unit}),$$
$$C_3 = \{\text{Myosin, Troponin}\} \quad (\text{myosin–troponin interaction}).$$

- **Second-level supervertices** $\mathrm{POWSET}^2(S)$:

$$M_1 = \{C_1, C_2\}, \quad M_2 = \{C_1, C_3\}, \quad M_3 = \{C_2, C_3\}.$$

Define the Super-Hyper-Operation

$$\star : \mathrm{POWSET}^2(S) \times \mathrm{POWSET}^2(S) \longrightarrow \mathrm{POWSET}\big(\mathrm{POWSET}^2(S)\big)$$

by

$$X \star Y = \big\{\, X \cup Y,\; X \cap Y,\; X \triangle Y \,\big\}, \quad X, Y \subseteq \mathrm{POWSET}^2(S),$$

where $X \triangle Y$ is the symmetric difference. For example,

$$M_1 \star M_2 = \big\{\, \{C_1, C_2, C_3\},\; \{C_1\},\; \{C_2, C_3\} \big\}.$$

Thus $\big(\mathrm{POWSET}^2(S), \star\big)$ is a 2-Super-Hyper-structure modeling the hierarchical assembly of protein complexes—first forming binary and ternary subcomplexes, then organizing them into larger functional modules such as the sarcomeric apparatus in muscle fibers.

2.2 Super-Hyper-Graph

A Hyper-Graph extends the classical graph by allowing each Hyper-edge to join any number of vertices, thereby capturing higher-order relationships among elements (Berge, 1984). Several important variants have been developed, including directed Hyper-Graphs (Xiao et al., 2022; Akram and Luqman, 2017b; Pretolani, 2013), fuzzy Hyper-Graphs (Samanta and Pal, 2012; Mordeson and Nair, 2012; Wang and Gong, 2020), regular Hyper-Graphs (Ellis and Linial, 2013; Dumitriu and Zhu, 2019), soft Hyper-Graphs (Akram and Nawaz, 2023; Amini et al., 2022; GEORGE et al., 2023), and neutrosophic Hyper-Graphs (Luqman et al., 2019; Malik et al., 2022; Akram et al., 2018; Akram and Luqman, 2017a).

The *Super-Hyper-Graph* framework goes further by embedding iterated powerset constructions into the Hyper-Graph structure, generating nested connectivity layers that reveal hierarchical and self-referential patterns (Fujita, 2024b; Parra Gallardo et al., 2024; Cao, 2025; Fujita, 2025d). Extensions such as the fuzzy Super-Hyper-Graph (Hamidi et al., 2023) and the plithogenic Super-Hyper-Graph (Smarandache and Martin, 2020; Marcos et al., 2025; Jácome Mogro et al., 2024; Mogro Cepeda et al., 2024) incorporate uncertainty and multi-valued logic into these multi-level models.

Below, we present the formal definitions of Hyper-Graphs, Super-Hyper-Graphs, and their related extensions, accompanied by concrete examples.

Definition 2.13 (Hyper-Graph)**.** (Bretto, 2013; Berge, 1984) A *Hyper-Graph* $H = (V, E)$ is defined by

- a nonempty vertex set V, and
- a collection $E \subseteq \mathrm{POWSET}(V) \setminus \{\varnothing\}$ of *Hyper-edges*, each of which is a nonempty subset of V.

By allowing Hyper-edges to join any number of vertices, Hyper-Graphs naturally capture higher-order relationships. In this work, we assume both V and E are finite.

Definition 2.14 (SubHyper-Graph)**.** (Bretto, 2013; Berge, 1984) Given a Hyper-Graph $H = (V, E)$, a *subHyper-Graph* is any $H' = (V', E')$ satisfying

$$V' \subseteq V, \quad E' \subseteq \{\, e \in E \mid e \subseteq V' \}.$$

Equivalently, one obtains H' by selecting a subset of vertices V' and retaining exactly those Hyper-edges of H that lie entirely within V'.

Example 2.15 (Citric Acid Cycle as a Hyper-Graph)**.** The Citric Acid Cycle is a central metabolic pathway that generates energy by oxidizing acetyl-CoA into carbon dioxide and high-energy molecules (cf.(Owen et al., 2002; Williamson and Cooper, 1980; Wan et al., 1989; Akram, 2014)). Model the key steps of the citric acid (TCA) cycle as a Hyper-Graph $H = (V, E)$:

Vertices (metabolites):

$$V = \{\, \text{Acetyl-CoA},\ \text{Oxaloacetate},\ \text{Citrate},\ \text{Isocitrate},\ \alpha\text{-KG},\ \text{Succinate},\ \text{Fumarate},\ \text{Malate} \,\}.$$

Hyper-edges (enzyme-catalyzed reactions):

$$\begin{aligned}
e_1 &= \{\text{Acetyl-CoA},\ \text{Oxaloacetate},\ \text{Citrate}\},\\
e_2 &= \{\text{Citrate},\ \text{Isocitrate}\},\\
e_3 &= \{\text{Isocitrate},\ \alpha\text{-KG}\},\\
e_4 &= \{\alpha\text{-KG},\ \text{Succinate}\},\\
e_5 &= \{\text{Succinate},\ \text{Fumarate}\},\\
e_6 &= \{\text{Fumarate},\ \text{Malate}\},\\
e_7 &= \{\text{Malate},\ \text{Oxaloacetate}\}.
\end{aligned}$$

Here each Hyper-edge e_i connects all substrates and products of the i-th step simultaneously, capturing the stoichiometry of that reaction.

Interpretation:

- e_1 (citrate synthase) consumes Acetyl-CoA + Oxaloacetate to form Citrate.
- e_4 (α-ketoglutarate dehydrogenase) transforms α-KG into Succinate (via intermediates), etc.
- Representing each reaction as a Hyper-edge highlights multi-component interactions in one step, unlike a simple pairwise graph.

This Hyper-Graph formalism aids pathway analysis by recognizing reactions involving more than two metabolites as single cohesive units.

Definition 2.16 (n-Super-Hyper-Graph)**.** (Smarandache, 2019, 2020)
Let V_0 be a finite base set of vertices. For each integer $k \geq 0$, define the iterative powerset by

$$\mathrm{POWSET}^0(V_0) = V_0, \quad \mathrm{POWSET}^{k+1}(V_0) = \mathrm{POWSET}(\mathrm{POWSET}^k(V_0)),$$

where $\mathrm{POWSET}(\cdot)$ denotes the usual powerset operation. An *n-Super-Hyper-Graph* is then a pair

$$\mathrm{SupHypG}^{(n)} = (V, E),$$

with

$$V \subseteq \mathrm{POWSET}^n(V_0) \quad \text{and} \quad E \subseteq \mathrm{POWSET}^n(V_0).$$

Each element of V is called an *n-super-vertex* and each element of E an *n-super-edge*.

Example 2.17 (Global Climate Research Consortia as a 2-Super-Hyper-Graph)**.** Global climate refers to the long-term patterns and averages of temperature, humidity, wind, and precipitation across the entire Earth(cf.(Karl and Trenberth, 2003; Coen et al., 2020; Willis, 2020)). Let the base set of researchers be

$$V_0 = \{\text{Ayame, Ziro, Taro, Shinzou}\}.$$

First-level research groups (1-supervertices in $\mathrm{POWSET}^1(V_0)$) are:

$$R_1 = \{\text{Ayame, Ziro}\}, \quad R_2 = \{\text{Ziro, Taro}\}, \quad R_3 = \{\text{Taro, Shinzou}\}.$$

Second-level consortia (2-supervertices in $\mathrm{POWSET}^2(V_0)$) are:

$$C_\alpha = \{R_1, R_2\}, \quad C_\beta = \{R_2, R_3\}.$$

We then form the 2-Super-Hyper-Graph

$$\mathrm{SupHypG}^{(2)} = (V, E)$$

by

$$V = \{C_\alpha, C_\beta\}, \qquad E = \{\{C_\alpha, C_\beta\}\}.$$

Here:

- Each 2-super-vertex C_α and C_β represents a research consortium composed of overlapping labs.
- The single 2-super-edge $\{C_\alpha, C_\beta\}$ models a joint international summit bringing together both consortia.
- This structure captures three hierarchical levels: individual researchers $\rightarrow$ lab groups $\rightarrow$ consortia $\rightarrow$ inter-consortium collaboration.

Example 2.18 (2-Super-Hyper-Graph of Protein Complex Hierarchies)**.** Protein complex hierarchy refers to the multi-level organization of proteins into subunits, complexes, and higher-order assemblies with distinct biological functions (cf.(Piljic and Schultz, 2008; Matthews, 2015; Meldal et al., 2015)). In muscle contraction, proteins assemble hierarchically into complexes and higher-order modules. We model this as a 2-Super-Hyper-Graph:

Base set of proteins:

$$V_0 = \{\text{MyosinII},\ \text{Actin},\ \text{Tropomyosin},\ \text{Troponin}\}.$$

First-level complexes ($\mathrm{POWSET}^1(V_0)$):

$$C_1 = \{\text{MyosinII, Actin}\},\quad C_2 = \{\text{Actin, Tropomyosin, Troponin}\},\quad C_3 = \{\text{MyosinII, Troponin}\}.$$

Second-level supervertices ($\mathrm{POWSET}^2(V_0)$):

$$M_1 = \{C_1,\, C_2\},\quad M_2 = \{C_1,\, C_3\},\quad M_3 = \{C_2,\, C_3\}.$$

Define the 2-Super-Hyper-Graph

$$\mathrm{SupHypG}^{(2)} = (V,\, E),$$

with

$$V = \{M_1,\, M_2,\, M_3\},\quad E = \big\{\{M_1,\, M_2\},\, \{M_2,\, M_3\}\big\}.$$

Interpretation:

- Each M_i is a *2-super-vertex* representing a higher-order module of protein complexes (e.g. thick vs. thin filament assemblies).
- Each $\{M_i, M_j\} \in E$ is a *2-super-edge* linking modules that coexist or interact within the sarcomeric unit during contraction.

Thus $\big(\mathrm{POWSET}^2(V_0), E\big)$ captures the hierarchical organization from individual proteins to complexes and then to functional modules in muscle biochemistry.

Example 2.19 (Corporate Hierarchy as a 3-Super-Hyper-Graph)**.** Let the base set of employees be

$$V_0 = \{\text{Ayame, Ziro, Taro, Shinzou, Eve, Mamoru}\}.$$

First-level committees (1-supervertices in $\mathrm{POWSET}^1(V_0)$) might be:

$$C_1 = \{\text{Ayame, Ziro}\},\quad C_2 = \{\text{Taro, Shinzou}\},\quad C_3 = \{\text{Eve, Mamoru}\},\quad C_4 = \{\text{Ziro, Taro}\}.$$

Second-level departments (2-supervertices in $\mathrm{POWSET}^2(V_0)$) could group these committees into:

$$D_{\text{Sales}} = \{C_1,\, C_4\},\quad D_{\text{Engineering}} = \{C_2,\, C_3\}.$$

Third-level divisions (3-supervertices in $\mathrm{POWSET}^3(V_0)$) then organize departments into:

$$U_{\text{Commercial}} = \{D_{\text{Sales}}\},\quad U_{\text{Technical}} = \{D_{\text{Engineering}}\}.$$

We form the 3-Super-Hyper-Graph

$$\mathrm{SupHypG}^{(3)} = (V,\, E)$$

by setting

$$V = \{\, U_{\text{Commercial}},\, U_{\text{Technical}}\,\},\qquad E = \big\{\{\, U_{\text{Commercial}},\, U_{\text{Technical}}\,\}\big\}.$$

Interpretation:

- $\mathrm{POWSET}^0(V_0)$: individual employees.
- $\mathrm{POWSET}^1(V_0)$: cross-functional committees C_i.
- $\mathrm{POWSET}^2(V_0)$: departments D_{Sales} and $D_{\text{Engineering}}$.
- $\mathrm{POWSET}^3(V_0)$: top-level divisions $U_{\text{Commercial}}$ and $U_{\text{Technical}}$.
- The single 3-super-edge $\{U_{\text{Commercial}}, U_{\text{Technical}}\}$ models a company-wide strategic initiative linking both divisions.

This example illustrates how a 3-Super-Hyper-Graph captures four hierarchical layers—employees, committees, departments, divisions—and their inter-division collaboration in one unified structure.

2.3 Molecular Interaction Networks

Molecular interaction networks represent biochemical relationships, where nodes correspond to molecules (such as proteins, genes, or metabolites), and edges denote physical or functional interactions among them(Nasirian and Menichetti, 2023; Panditrao et al., 2022; Di Rocco et al., 2022; Manica et al., 2021). Due to their biochemical significance, molecular interaction networks have been the subject of extensive research across various disciplines(Hu et al., 2024; Lin et al., 2024; Weng et al., 2025; Weng and Mittal, 2025). The formal definition of molecular interaction networks is provided below.

Definition 2.20 (Network)**.** (Estrada, 2013; Pryke, 2005) A *network* (or *graph*) is a triple

$$N = (V, E, w)$$

where:

- V is a nonempty, finite set of *vertices* (or *nodes*);
- For an undirected network, $E \subseteq \big\{\{u, v\} \mid u, v \in V,\ u \neq v\big\}$ is the set of *edges*, each connecting two distinct vertices. In a directed network, one replaces E by an *arc* set $A \subseteq V \times V$, where each $(u, v) \in A$ is an oriented link from u to v.
- $w\colon E \to \mathrm{R}_{\geq 0}$ (or $w\colon A \to \mathrm{R}_{\geq 0}$) is an optional *weight function* assigning a nonnegative value to each edge (or arc).

Optionally, a *vertex labeling* $\ell_V : V \to L_V$ may be included to specify types or identifiers for the vertices.

Definition 2.21 (Molecular Interaction Network)**.** (Nasirian and Menichetti, 2023; Panditrao et al., 2022; Di Rocco et al., 2022; Manica et al., 2021) A *molecular interaction network* is a labeled Hyper-Graph

$$\mathcal{N} = (V, \mathcal{I}, \ell_V, \ell_{\mathcal{I}})$$

where:

- V is a finite set of *molecular entities* (e.g. proteins, metabolites, genes);
- $\mathcal{I} \subseteq \mathrm{POWSET}(V) \setminus \{\varnothing\}$ is a collection of *interactions*, each $I \in \mathcal{I}$ being a nonempty subset of V whose members participate jointly in a biochemical event (e.g. complex assembly, enzymatic catalysis, regulatory binding);
- $\ell_V\colon V \to L_V$ assigns to each entity a label (e.g. “kinase,” “ligand,” “metabolite”);
- $\ell_{\mathcal{I}}\colon \mathcal{I} \to L_{\mathcal{I}}$ assigns to each interaction a category or set of attributes (e.g. “binding,” “phosphorylation,” confidence score).

One may also define a weight function $w\colon \mathcal{I} \to \mathrm{R}_{\geq 0}$ to quantify interaction strengths or probabilities.

Example 2.22 (Yeast Protein–Protein Interaction Network)**.** Yeast protein–protein interaction refers to physical or functional associations between yeast proteins, essential for cellular processes and regulatory networks (cf.(Bader and Hogue, 2002; Han et al., 2004; Causier and Davies, 2002)). Let

$$V = \{\mathrm{P53}, \mathrm{MDM2}, \mathrm{ATM}, \mathrm{CHK2}\},$$
$$\mathcal{I} = \big\{\{\mathrm{P53}, \mathrm{MDM2}\},\ \{\mathrm{ATM}, \mathrm{P53}\},\ \{\mathrm{ATM}, \mathrm{CHK2}\},\ \{\mathrm{CHK2}, \mathrm{P53}\}\big\}.$$

Define

$$\ell_V(x) = \text{“protein”} \quad (\forall x \in V),$$
$$\ell_{\mathcal{I}}(\{\mathrm{P53}, \mathrm{MDM2}\}) = \text{“ubiquitination”}, \quad \ell_{\mathcal{I}}(\{\mathrm{ATM}, \mathrm{P53}\}) = \text{“phosphorylation”},$$
$$\ell_{\mathcal{I}}(\{\mathrm{ATM}, \mathrm{CHK2}\}) = \text{“activation”}, \quad \ell_{\mathcal{I}}(\{\mathrm{CHK2}, \mathrm{P53}\}) = \text{“phosphorylation”}.$$

If we include confidence scores:

$$w(\{\mathrm{P53}, \mathrm{MDM2}\}) = 0.95,\ w(\{\mathrm{ATM}, \mathrm{P53}\}) = 0.80,\ w(\{\mathrm{ATM}, \mathrm{CHK2}\}) = 0.85,\ w(\{\mathrm{CHK2}, \mathrm{P53}\}) = 0.90.$$

Then $\mathcal{N} = (V, \mathcal{I}, \ell_V, \ell_{\mathcal{I}}, w)$ models a small yeast protein–protein interaction network, capturing both the participants and the types and strengths of their interactions.

3 MOLECULAR INTERACTION HYPER-NETWORK

A *Molecular Interaction Hyper-network* is a mathematical framework developed to represent complex biochemical systems, where interactions may involve multiple molecular entities simultaneously. We now present the formal definition of a Molecular Interaction Hyper-network.

Definition 3.1 (Hyper-network)**.** A *Hyper-network* is a triple

$$H = \big(V,\ \mathcal{E},\ w\big)$$

where:

- V is a nonempty, finite set of *nodes*;
- $\mathcal{E} \subseteq \mathrm{POWSET}(V) \setminus \{\varnothing\}$ is the collection of *Hyper-edges*, each $e \in \mathcal{E}$ being a nonempty subset of V, thus permitting interactions among multiple nodes;
- $w\colon \mathcal{E} \to \mathbb{R}_{\geq 0}$ is an optional *weight function* on Hyper-edges.

A *directed Hyper-network* can be obtained by taking $\mathcal{E}$ to consist of ordered tuples of nodes or by distinguishing head and tail subsets within each e. One may also include

$$\ell_V\colon V \to L_V, \quad \ell_{\mathcal{E}}\colon \mathcal{E} \to L_{\mathcal{E}}$$

to attach labels or attributes to nodes and Hyper-edges, respectively.

Definition 3.2 (Molecular Interaction Hyper-network)**.** A (finite) *molecular interaction Hyper-network* is a quintuple

$$\mathcal{H} = \big(V,\ \mathcal{I},\ \ell_V,\ \ell_{\mathcal{I}},\ w\big)$$

where:

- V is a finite set of *molecular entities* (e.g. proteins, metabolites, genes);
- $\mathcal{I} \subseteq \mathrm{POWSET}(V) \setminus \{\varnothing\}$ is the set of *interaction Hyper-edges*, each representing the group of entities involved in a single biochemical event (e.g. complex assembly, multi-enzyme catalysis);
- $\ell_V\colon V \to L_V$ assigns a type or identifier to each entity (e.g. “kinase”, “ligand”);
- $\ell_{\mathcal{I}}\colon \mathcal{I} \to L_{\mathcal{I}}$ assigns a category or descriptor to each interaction (e.g. “binding”, “phosphorylation cascade”);
- $w\colon \mathcal{I} \to \mathbb{R}_{\geq 0}$ gives a nonnegative weight or confidence score for each interaction.

Example 3.3 (Eukaryotic DNA Replication Pre-Initiation as a Molecular Interaction Hyper-network)**.** DNA replication is the biological process of copying a cell’s DNA, producing two identical DNA molecules before cell division (cf.(Kornberg and Baker, 2005; Kunkel and Bebenek, 2000; Bell and Dutta, 2002)). Consider the assembly and activation of the eukaryotic DNA replication pre-initiation complex. Let

$$V = \{\,\mathrm{ORC},\ \mathrm{Cdc6},\ \mathrm{Cdt1},\ \mathrm{MCM2\text{–}7},\ \mathrm{CDK2},\ \mathrm{DDK}\}$$

be the set of molecular entities: the origin recognition complex (ORC), loading factors Cdc6 and Cdt1, the MCM2–7 helicase, and the two kinases CDK2 and DDK. Define two interaction Hyper-edges:

$$\mathcal{I} = \{\,I_{\mathrm{loading}},\ I_{\mathrm{activation}}\,\},$$

where

$$I_{\mathrm{loading}} = \{\mathrm{ORC}, \mathrm{Cdc6}, \mathrm{Cdt1}, \mathrm{MCM2\text{–}7}\}, \quad I_{\mathrm{activation}} = \{\mathrm{MCM2\text{–}7}, \mathrm{CDK2}, \mathrm{DDK}\}.$$

Label each node by its functional class:

$$\ell_V(x) = \begin{cases} \text{“origin-binding factor”}, & x = \mathrm{ORC}, \\ \text{“helicase loader”}, & x = \mathrm{Cdc6}, \mathrm{Cdt1}, \\ \text{“replicative helicase”}, & x = \mathrm{MCM2–7}, \\ \text{“kinase”}, & x = \mathrm{CDK2}, \mathrm{DDK}. \end{cases}$$

Label each Hyper-edge by its biological process:

$$\ell_{\mathcal{I}}(I_{\mathrm{loading}}) = \text{“MCM2–7 helicase loading”}, \quad \ell_{\mathcal{I}}(I_{\mathrm{activation}}) = \text{“helicase activation by phosphorylation”}.$$

Optionally, assign confidence scores based on experimental evidence:

$$w(I_{\mathrm{loading}}) = 0.92, \quad w(I_{\mathrm{activation}}) = 0.88.$$

- I_{loading} models the coordinated loading of the MCM2–7 helicase onto origin DNA by ORC, Cdc6, and Cdt1.
- $I_{\mathrm{activation}}$ captures the subsequent activation of the loaded helicase by CDK2 and DDK phosphorylation.

This Hyper-network illustrates a multi-step, multi-protein process in which Hyper-edges represent higher-order interactions essential for DNA replication initiation.

Example 3.4 (Human Hemoglobin Interaction Hyper-network)**.** Human hemoglobin is a protein in red blood cells that transports oxygen from the lungs to body tissues and organs(cf.(Itano, 1953; Hill and Koningsberg, 1962)). Let

$$V = \{\alpha_1,\ \alpha_2,\ \beta_1,\ \beta_2,\ \mathrm{O}_2\}$$

be the set of molecular entities (four globin subunits and oxygen). Define the set of interaction Hyper-edges

$$\mathcal{I} = \{\, E_{\mathrm{tetramer}},\ E_{\mathrm{O}_2} \,\},$$

where

$$E_{\mathrm{tetramer}} = \{\alpha_1, \alpha_2, \beta_1, \beta_2\}, \quad E_{\mathrm{O}_2} = \{\alpha_1, \alpha_2, \beta_1, \beta_2, \mathrm{O}_2\}.$$

The labeling functions are

$$\ell_V(\alpha_i) = \text{“globin subunit”}, \quad \ell_V(\beta_i) = \text{“globin subunit”}, \quad \ell_V(\mathrm{O}_2) = \text{“oxygen molecule”},$$
$$\ell_{\mathcal{I}}(E_{\mathrm{tetramer}}) = \text{“hemoglobin tetramer assembly”}, \quad \ell_{\mathcal{I}}(E_{\mathrm{O}_2}) = \text{“oxygen binding”}.$$

Optionally, assign confidence scores:

$$w(E_{\mathrm{tetramer}}) = 1.00, \quad w(E_{\mathrm{O}_2}) = 0.98.$$

Here:

- E_{tetramer} captures the multi-protein assembly of two α and two β chains into the functional hemoglobin tetramer.
- E_{O_2} captures the cooperative binding of molecular oxygen to the assembled tetramer.

This example illustrates a molecular interaction Hyper-network where Hyper-edges represent complex biochemical events involving more than two entities.

Example 3.5 (Pyruvate Dehydrogenase Complex as a Molecular Interaction Hyper-network)**.** Pyruvate Dehydrogenase Complex is a multi-enzyme system that converts pyruvate into acetyl-CoA, linking glycolysis to the Krebs cycle (Patel and Korotchkina, 2006; Harris et al., 2002; Patel et al., 2014; Tovar-Méndez et al., 2003). Let

$$V = \{\, \mathrm{E1},\ \mathrm{E2},\ \mathrm{E3},\ \mathrm{Pyruvate},\ \mathrm{CoA},\ \mathrm{NAD}^+ \},$$

be the set of molecular entities: the three enzyme subunits of the pyruvate dehydrogenase complex (E1, E2, E3) and its substrates/cofactors (pyruvate, coenzyme A, NAD^+). Define the interaction Hyper-edges

$$\mathcal{I} = \{\, I_{\text{assembly}},\ I_{\text{catalysis}} \,\},$$

where

$$I_{\text{assembly}} = \{\text{E1}, \text{E2}, \text{E3}\}, \quad I_{\text{catalysis}} = \{\text{E1}, \text{E2}, \text{E3}, \text{Pyruvate}, \text{CoA}, \text{NAD}^+\}.$$

Label each node by its type:

$$\ell_V(\text{E1}) = \ell_V(\text{E2}) = \ell_V(\text{E3}) = \text{“enzyme subunit”}, \quad \ell_V(\text{Pyruvate}) = \ell_V(\text{CoA}) = \ell_V(\text{NAD}^+) = \text{“substrate/cofactor”}.$$

Label each Hyper-edge by its biological process:

$$\ell_{\mathcal{I}}(I_{\text{assembly}}) = \text{“complex assembly”}, \quad \ell_{\mathcal{I}}(I_{\text{catalysis}}) = \text{“oxidative decarboxylation reaction”}.$$

Optionally, assign confidence scores:

$$w(I_{\text{assembly}}) = 0.90, \quad w(I_{\text{catalysis}}) = 0.85.$$

Here:

- I_{assembly} models the multi-enzyme assembly of E1, E2, and E3 into the functional pyruvate dehydrogenase complex.
- $I_{\text{catalysis}}$ captures the coordinated catalytic event converting pyruvate plus CoA and NAD^+ into acetyl-CoA and NADH.

This example demonstrates a molecular interaction Hyper-network in which Hyper-edges represent both the assembly of a multi-protein complex and its multi-participant enzymatic reaction.

Theorem 3.6 (Hyper-network Property)**.** *Every molecular interaction Hyper-network $\mathcal{H} = (V, \mathcal{I}, \ell_V, \ell_{\mathcal{I}}, w)$ is a Hyper-network in the sense of Definition.*

Proof. Let $\mathcal{H} = (V, \mathcal{I}, \ell_V, \ell_{\mathcal{I}}, w)$ be a molecular interaction Hyper-network. We verify each condition of Definition [Hyper-network]:

1. **Node set:** By hypothesis, V is a nonempty finite set of molecular entities.
2. **Hyper-edge set:** By construction,
   $$\mathcal{I} \subseteq \text{POWSET}(V) \setminus \{\emptyset\},$$
   and each $I \in \mathcal{I}$ is a nonempty subset of V.
3. **Weight function:** The map $w : \mathcal{I} \to \mathbb{R}_{\geq 0}$
   assigns a nonnegative real weight or confidence score to each Hyper-edge, as required.
4. **Optional labels:** The node-labeling $\ell_V : V \to L_V$
   and Hyper-edge-labeling
   $\ell_{\mathcal{I}} : \mathcal{I} \to L_{\mathcal{I}}$ are admissible extensions under the general Hyper-network definition and do not violate any axioms.

Since all structural requirements of a Hyper-network are satisfied, $\mathcal{H}$ is indeed a Hyper-network in the sense of Definition. □

Theorem 3.7 (Generalization of Molecular Interaction Networks)**.** *Let $\mathcal{N} = (V, \mathcal{I}_2, \ell_V, \ell_{\mathcal{I}}, w)$ be a molecular interaction network in which every interaction involves at most two entities, i.e. $\mathcal{I}_2 \subseteq \big\{\{u, v\} \mid u, v \in V\big\} \cup \{\{v\} \mid v \in V\}$. Then $\mathcal{N}$ is a special case of the molecular interaction Hyper-network $\mathcal{H}$ obtained by setting $\mathcal{I} = \mathcal{I}_2$.*

Proof. Let $\mathcal{H} = (V, \mathcal{I}, \ell_V, \ell_\mathcal{I}, w)$ be the candidate Hyper-network obtained by taking $\mathcal{I} = \mathcal{I}_2$. We check that $\mathcal{H}$ satisfies the definition of a molecular interaction Hyper-network:

1. *Node set:* By hypothesis, V is a finite set of molecular entities.
2. *Hyper-edges:* Since $\mathcal{I}_2 \subseteq \big\{\{u, v\} \mid u, v \in V\big\} \cup \{\{v\} \mid v \in V\}$, we have
$$\mathcal{I} \subseteq \mathrm{POWSET}(V) \setminus \{\emptyset\},$$
and each element of $\mathcal{I}$ is a nonempty subset of V of cardinality one or two.
3. *Node-labeling:* The map $\ell_V : V \to L_V$ is unchanged and labels each entity by its type or identifier.
4. *Hyper-edge-labeling:* The map $\ell_\mathcal{I} : \mathcal{I} \to L_\mathcal{I}$ likewise remains valid, assigning each interaction its category.
5. *Weight function:* The function $w : \mathcal{I} \to \mathbb{R}_{\geq 0}$ assigns a nonnegative score to each interaction.

All conditions of Definition [Molecular Interaction Hyper-network] are thus met. Moreover, because every interaction in $\mathcal{I}$ involves at most two entities, $\mathcal{H}$ is precisely the original molecular interaction network $\mathcal{N}$, viewed as a special case of a Hyper-network where Hyper-edges have size ≤ 2. Therefore, $\mathcal{N}$ embeds directly into the Hyper-network framework without alteration. □

Theorem 3.8 (Induced SubHyper-network)**.** *Let $\mathcal{H} = (V, \mathcal{I}, \ell_V, \ell_\mathcal{I}, w)$ be a molecular interaction Hyper-network and let $U \subseteq V$ be any nonempty subset of molecular entities. Define*

$$\mathcal{I}_U = \{\, I \in \mathcal{I} : I \subseteq U\},$$

and restrict labels and weights accordingly. Then

$$\mathcal{H}[U] = (U,\ \mathcal{I}_U,\ \ell_V|_U,\ \ell_\mathcal{I}|_{\mathcal{I}_U},\ w|_{\mathcal{I}_U})$$

is itself a molecular interaction Hyper-network.

Proof.
1. U is nonempty and finite since $U \subseteq V$.
2. $\mathcal{I}_U \subseteq \mathrm{POWSET}(U) \setminus \{\emptyset\}$ by construction, and each $I \in \mathcal{I}_U$ remains a nonempty interaction Hyper-edge.
3. The restricted maps $\ell_V|_U$ and $\ell_\mathcal{I}|_{\mathcal{I}_U}$ still assign valid labels to nodes and Hyper-edges.
4. The restricted weight $w|_{\mathcal{I}_U}$ remains a nonnegative function on $\mathcal{I}_U$.

Thus $\mathcal{H}[U]$ satisfies all axioms of Definition [Molecular Interaction Hyper-network]. □

Theorem 3.9 (Primal Graph Theorem)**.** *Let $\mathcal{H} = (V, \mathcal{I}, \ell_V, \ell_\mathcal{I}, w)$ be a molecular interaction Hyper-network. Its* primal graph *$G(\mathcal{H})$ is the labeled simple graph*

$$G(\mathcal{H}) = \big(V,\ E,\ \ell_V,\ \psi\big)$$

where

$$E = \big\{\{u, v\} \subseteq V : \exists\, I \in \mathcal{I},\ \{u, v\} \subseteq I\big\}, \quad \psi(\{u, v\}) = \max_{I \ni u, v} w(I).$$

Then $G(\mathcal{H})$ is a molecular interaction network.

Proof.
- V is finite and nonempty.
- Each $\{u, v\} \in E$ arises from some Hyper-edge $I \subseteq V$, so $E \subseteq \{\{u, v\} \mid u, v \in V\}$.
- The node-labeling ℓ_V is unchanged.
- The bond-order labeling ψ assigns a nonnegative weight to each edge, taking the maximum confidence among all Hyper-edges that contain both u and v.

Hence $G(\mathcal{H})$ meets the definition of a molecular interaction network (a special case of Definition with Hyper-edges of size at most two). □

Theorem 3.10 (Coverage of Entities)**.** *In any molecular interaction Hyper-network $\mathcal{H} = (V, \mathcal{I}, \ell_V, \ell_{\mathcal{I}}, w)$, every entity participates in at least one interaction:*

$$\bigcup_{I \in \mathcal{I}} I \;=\; V.$$

Proof. By the biochemical semantics of molecular interaction Hyper-Networks, each entity $v \in V$ must appear in at least one biochemical event $I \in \mathcal{I}$. Formally, if some v did not appear in any I, then v would be isolated and never part of an interaction—contradicting the intended modeling. Therefore the union of all Hyper-edges equals V. □

4 MOLECULAR INTERACTION N-SUPER-HYPER-NETWORK

A (finite) *Molecular Interaction n-Super-Hyper-network* is a mathematical framework designed to model hierarchical biochemical systems. It captures multi-scale molecular interactions using n-level nested groupings of molecular entities and their associated interaction events. We formally define a Molecular Interaction n-Super-Hyper-network as follows.

Definition 4.1 (n-Super-Hyper-network)**.** (Fujita, 2025d) Let V_0 be a finite base set of *nodes*. Define the n-th iterated powerset recursively by

$$\mathrm{POWSET}^0(V_0) = V_0, \qquad \mathrm{POWSET}^{k+1}(V_0) = \mathrm{POWSET}\big(\mathrm{POWSET}^k(V_0)\big) \quad (k \geq 0).$$

An *n-Super-Hyper-network* is a tuple

$$\mathcal{N}^{(n)} \;=\; \big(V,\ \mathcal{E},\ w\big)$$

where

- $V \subseteq \mathrm{POWSET}^n(V_0)$ is a finite set of *n-super-nodes*;
- $\mathcal{E} \subseteq \mathrm{POWSET}^n(V_0)$ is a finite set of *n-super-edges*, each super-edge $e \in \mathcal{E}$ being a nonempty subset of V;
- $w\colon \mathcal{E} \to \mathbb{R}_{\geq 0}$ is an optional *weight function* assigning a nonnegative real weight (or confidence) to each super-edge.

In other words, both vertices and Hyper-edges of the network are drawn from the n-th powerset of the base node set, capturing up to n levels of hierarchical grouping.

Example 4.2 (Disaster Response as a 2-Super-Hyper-network)**.** Disaster response involves coordinated actions by emergency services, governments, and communities to manage and mitigate the impact of disasters (cf.(O'Neill, 2005; Imran et al., 2014; Berkoune et al., 2012)). Let the base set of individual responders be

$$V_0 = \{\text{Ayame},\ \text{Ziro},\ \text{Taro},\ \text{Shinzou}\}.$$

First-level collections (teams, in $\mathrm{POWSET}^1(V_0)$) are

$$T_1 = \{\text{Ayame}, \text{Ziro}\}, \quad T_2 = \{\text{Ziro}, \text{Taro}\}, \quad T_3 = \{\text{Taro}, \text{Shinzou}\}.$$

Second-level collections (task forces, in $\mathrm{POWSET}^2(V_0)$) are

$$F_A = \{T_1, T_2\}, \quad F_B = \{T_2, T_3\}.$$

Define the 2-Super-Hyper-network

$$\mathcal{N}^{(2)} = (V, \mathcal{E}, w)$$

by

$$V = \{\, F_A, F_B\}, \qquad \mathcal{E} = \big\{\{F_A, F_B\}\big\},$$

with weights

$$w(\{F_A, F_B\}) = 0.85.$$

Here:

- Each super-node $F_A, F_B \in V$ is a *2-super-node*, representing a pair of overlapping teams working together.
- The single super-edge $\{F_A, F_B\}$ connects these two task forces, modeling a joint multi-team operation.
- The weight 0.85 might represent the confidence or coordination efficiency of that joint operation.

This construction captures individual responders $\rightarrow$ teams $\rightarrow$ task forces and the cooperative relations among those forces, all within a single unified 2-Super-Hyper-network framework.

Definition 4.3 (Molecular Interaction n-Super-Hyper-network)**.** Let V_0 be a finite set of molecular entities (e.g. proteins, metabolites, genes). For each integer $n \geq 1$, define the iterated powerset

$$\mathrm{POWSET}^0(V_0) = V_0, \quad \mathrm{POWSET}^{k+1}(V_0) = \mathrm{POWSET}\big(\mathrm{POWSET}^k(V_0)\big) \quad (k \geq 0).$$

A *molecular interaction n-Super-Hyper-network* is a quintuple

$$\mathcal{H}^{(n)} \;=\; \big(V^{(n)},\, \mathcal{I}^{(n)},\, \ell_V^{(n)},\, \ell_{\mathcal{I}}^{(n)},\, w^{(n)}\big)$$

where

- $V^{(n)} \subseteq \mathrm{POWSET}^n(V_0)$ is a finite set of *n-super-nodes*;
- $\mathcal{I}^{(n)} \subseteq \mathrm{POWSET}^n(V_0) \setminus \{\emptyset\}$ is a finite set of *n-super-edges*, each $I \in \mathcal{I}^{(n)}$ being a nonempty subset of $V^{(n)}$;
- $\ell_V^{(n)} \colon V^{(n)} \to L_V$ labels each n-super-node by its biological or chemical role (e.g. “multi-protein complex”);
- $\ell_{\mathcal{I}}^{(n)} \colon \mathcal{I}^{(n)} \to L_{\mathcal{I}}$ labels each n-super-edge by its interaction type (e.g. “cascade”, “assembly”);
- $w^{(n)} \colon \mathcal{I}^{(n)} \to \mathbb{R}_{\geq 0}$ assigns a nonnegative confidence score to each n-super-interaction.

Example 4.4 (EGF Receptor Signaling Pathway as a Molecular Interaction 2-Super-Hyper-network)**.** The EGF receptor signaling pathway is a molecular cascade activated by epidermal growth factor, regulating cell growth, differentiation, survival, and proliferation through kinase-mediated interactions (cf. (Wells, 1999; Wee and Wang, 2017; Normanno et al., 2006; Oda et al., 2005; Shigematsu and Gazdar, 2006)). Let the base set of molecular entities be

$$V_0 = \{\,\mathrm{EGF},\, \mathrm{EGFR},\, \mathrm{GRB2},\, \mathrm{SOS},\, \mathrm{RAS},\, \mathrm{RAF},\, \mathrm{MEK},\, \mathrm{ERK}\}.$$

First-level interaction Hyper-edges (in $\mathrm{POWSET}^1(V_0)$) are the elementary binding or activation events:

$$\begin{aligned} E_1 &= \{\mathrm{EGF},\, \mathrm{EGFR}\}, \quad E_2 = \{\mathrm{EGFR},\, \mathrm{GRB2},\, \mathrm{SOS}\},\\ E_3 &= \{\mathrm{SOS},\, \mathrm{RAS}\}, \quad E_4 = \{\mathrm{RAS},\, \mathrm{RAF}\},\\ E_5 &= \{\mathrm{RAF},\, \mathrm{MEK}\}, \quad E_6 = \{\mathrm{MEK},\, \mathrm{ERK}\}. \end{aligned}$$

These form the set of 1-super-nodes:

$$V^{(1)} = \{E_1, E_2, E_3, E_4, E_5, E_6\} \;\subseteq\; \mathrm{POWSET}^1(V_0).$$

Next, group related events into functional modules (2-super-nodes in $\mathrm{POWSET}^2(V_0)$):

$$F_R = \{E_1, E_2\}, \quad F_S = \{E_3, E_4\}, \quad F_M = \{E_5, E_6\}.$$

Thus

$$V^{(2)} = \{\,F_R,\, F_S,\, F_M\} \;\subseteq\; \mathrm{POWSET}^2(V_0).$$

Finally, define the 2-super-interaction Hyper-edges (in $\mathrm{POWSET}^2(V_0)$) linking these modules:

$$\mathcal{I}^{(2)} = \big\{\{F_R, F_S\},\; \{F_S, F_M\}\big\}.$$

Labeling functions assign biological roles and interaction types:

$\ell_V^{(2)}(F_R)$ = "Receptor complex assembly",
$\ell_V^{(2)}(F_S)$ = "RAS activation module",
$\ell_V^{(2)}(F_M)$ = "MAPK phosphorylation cascade",
$\ell_{\mathcal{I}}^{(2)}(\{F_R, F_S\})$ = "Signal propagation (receptor → RAS)",
$\ell_{\mathcal{I}}^{(2)}(\{F_S, F_M\})$ = "Signal propagation (RAS → MAPK)".

Weights (confidence scores) might be

$$w^{(2)}(\{F_R, F_S\}) = 0.95, \quad w^{(2)}(\{F_S, F_M\}) = 0.90,$$

reflecting high-confidence pathway activation.

In this 2-Super-Hyper-network:

- Level 0 (V_0) are individual proteins.
- Level 1 ($V^{(1)}$) are elementary interactions.
- Level 2 ($V^{(2)}$) are functional modules grouping those interactions.
- Hyper-edges $\mathcal{I}^{(2)}$ connect modules to model the hierarchical signal-transduction cascade.

Example 4.5 (Glycolytic Pathway as a Molecular Interaction 2-Super-Hyper-network)**.** The glycolytic pathway is a series of enzymatic reactions that convert glucose into pyruvate, generating ATP and NADH in cells (cf. (Fothergill-Gilmore, 1986; Vander Heiden et al., 2010)). Let the base set of molecular entities be

$$V_0 = \{\,\mathrm{Glucose},\ \mathrm{ATP},\ \mathrm{HK},\ \mathrm{G6P},\ \mathrm{PGI},\ \mathrm{F6P},\ \mathrm{PFK},\ \mathrm{FBP},\ \mathrm{ALD},\ \mathrm{GAP},\ \mathrm{TPI}\}.$$

Define the first-level interaction Hyper-edges (1-super-nodes in $\mathrm{POWSET}^1(V_0)$) corresponding to the elementary enzymatic steps:

$$\begin{aligned} E_1 &= \{\mathrm{Glucose},\ \mathrm{HK},\ \mathrm{ATP}\},\\ E_2 &= \{\mathrm{G6P},\ \mathrm{PGI}\},\\ E_3 &= \{\mathrm{F6P},\ \mathrm{PFK},\ \mathrm{ATP}\},\\ E_4 &= \{\mathrm{FBP},\ \mathrm{ALD}\},\\ E_5 &= \{\mathrm{GAP},\ \mathrm{TPI}\}. \end{aligned}$$

Thus

$$V^{(1)} = \{\,E_1, E_2, E_3, E_4, E_5\} \ \subseteq\ \mathrm{POWSET}^1(V_0).$$

Next, group these into two functional modules (2-super-nodes in $\mathrm{POWSET}^2(V_0)$):

$$F_{\mathrm{prep}} = \{\,E_1,\ E_2,\ E_3\}, \qquad F_{\mathrm{payoff}} = \{\,E_4,\ E_5\}.$$

Hence

$$V^{(2)} = \{\,F_{\mathrm{prep}},\ F_{\mathrm{payoff}}\} \ \subseteq\ \mathrm{POWSET}^2(V_0).$$

Finally, define the second-level interaction Hyper-edges (2-super-edges):

$$\mathcal{I}^{(2)} = \big\{\,\{F_{\mathrm{prep}},\ F_{\mathrm{payoff}}\}\big\}.$$

Label each 2-super-node and the 2-super-edge:

$\ell_V^{(2)}(F_{\mathrm{prep}})$ = "Preparatory phase of glycolysis",
$\ell_V^{(2)}(F_{\mathrm{payoff}})$ = "Payoff phase of glycolysis",
$\ell_{\mathcal{I}}^{(2)}\big(\{F_{\mathrm{prep}}, F_{\mathrm{payoff}}\}\big)$ = "Phase transition in glycolysis".

Optionally, assign a confidence score:

$$w^{(2)}\big(\{F_{\text{prep}}, F_{\text{payoff}}\}\big) = 0.90.$$

In this 2-Super-Hyper-network:

- Level 0 (V_0): individual metabolites and enzymes.
- Level 1 ($V^{(1)}$): elementary enzymatic interactions.
- Level 2 ($V^{(2)}$): functional modules (preparatory vs. payoff phase).
- 2-super-edge $\{F_{\text{prep}}, F_{\text{payoff}}\}$ models the hierarchical linkage between the two phases of glycolysis.

Example 4.6 (EGFR Signaling as a Molecular Interaction 3-Super-Hyper-network)**.** Let the base set of entities be

$$V_0 = \{\,\text{EGF},\ \text{EGFR},\ \text{GRB2},\ \text{SOS},\ \text{RAS},\ \text{RAF},\ \text{MEK},\ \text{ERK},\ \text{PI3K},\ \text{AKT},\ \text{mTOR}\}.$$

First-level interaction Hyper-edges (1-super-nodes in $\text{POWSET}^1(V_0)$) correspond to elementary binding or activation events:

$$\begin{aligned} E_1 &= \{\text{EGF}, \text{EGFR}\}, & E_2 &= \{\text{EGFR}, \text{GRB2}, \text{SOS}\},\\ E_3 &= \{\text{SOS}, \text{RAS}\}, & E_4 &= \{\text{RAS}, \text{RAF}\},\\ E_5 &= \{\text{RAF}, \text{MEK}\}, & E_6 &= \{\text{MEK}, \text{ERK}\},\\ E_7 &= \{\text{EGFR}, \text{PI3K}\}, & E_8 &= \{\text{PI3K}, \text{AKT}\},\\ E_9 &= \{\text{AKT}, \text{mTOR}\}. \end{aligned}$$

Thus

$$V^{(1)} = \{E_1, E_2, \ldots, E_9\} \ \subseteq\ \text{POWSET}^1(V_0).$$

Second-level modules (2-super-nodes in $\text{POWSET}^2(V_0)$) group these into functional units:

$$F_R = \{E_1, E_2\}, \quad F_M = \{E_3, E_4, E_5, E_6\}, \quad F_P = \{E_7, E_8, E_9\}.$$

Hence

$$V^{(2)} = \{F_R, F_M, F_P\} \ \subseteq\ \text{POWSET}^2(V_0).$$

Third-level supermodules (3-super-nodes in $\text{POWSET}^3(V_0)$) capture overarching signaling branches:

$$\mathsf{U}_1 = \{F_R, F_M\}, \quad U_2 = \{F_R, F_P\}.$$

Thus

$$V^{(3)} = \{U_1, U_2\} \ \subseteq\ \text{POWSET}^3(V_0).$$

Define the single 3-super-interaction Hyper-edge

$$\mathcal{I}^{(3)} = \{\{\,U_1, U_2\}\}.$$

Labeling functions record functional roles:

$$\begin{aligned} \ell_V^{(3)}(U_1) &= \text{“EGFR}\rightarrow\text{MAPK signaling supermodule”},\\ \ell_V^{(3)}(U_2) &= \text{“EGFR}\rightarrow\text{PI3K–AKT–mTOR supermodule”},\\ \ell_{\mathcal{I}}^{(3)}\big(\{U_1, U_2\}\big) &= \text{“Integrated proliferative and survival signaling”}. \end{aligned}$$

Optionally, assign a confidence weight:

$$w^{(3)}(\{U_1, U_2\}) = 0.95.$$

- *Level 0* (V_0): individual molecular entities.
- *Level 1* ($V^{(1)}$): elementary interactions (ligand–receptor, adapter binding, kinase activation).
- *Level 2* ($V^{(2)}$): functional modules (receptor complex, MAPK cascade, PI3K–AKT–mTOR branch).
- *Level 3* ($V^{(3)}$): supermodules integrating MAPK-driven proliferation and PI3K–AKT–mTOR-driven survival pathways.
- $\mathcal{I}^{(3)}$ captures the coordination between these two critical signaling branches.

Example 4.7 (Insulin Signaling Pathway as a Molecular Interaction 3-Super-Hyper-network)**.** The insulin signaling pathway regulates glucose uptake and metabolism by transmitting signals from insulin receptors to intracellular effectors like AKT and GLUT4 (cf. (Saltiel and Pessin, 2002; Pessin et al., 2000; Taha and Klip, 1999)). Let the base set of molecular entities be

$$V_0 = \{\,\mathrm{Insulin},\ \mathrm{IR},\ \mathrm{IRS},\ \mathrm{PI3K},\ \mathrm{PDK1},\ \mathrm{AKT},\ \mathrm{AS160},\ \mathrm{GLUT4}\}.$$

First-level interaction Hyper-edges (1-super-nodes in $\mathrm{POWSET}^1(V_0)$) correspond to elementary signaling steps:

$$\begin{aligned} E_1 &= \{\mathrm{Insulin},\ \mathrm{IR}\}, & E_2 &= \{\mathrm{IR},\ \mathrm{IRS}\},\\ E_3 &= \{\mathrm{IRS},\ \mathrm{PI3K}\}, & E_4 &= \{\mathrm{PI3K},\ \mathrm{PDK1}\},\\ E_5 &= \{\mathrm{PDK1},\ \mathrm{AKT}\}, & E_6 &= \{\mathrm{AKT},\ \mathrm{AS160}\},\\ E_7 &= \{\mathrm{AS160},\ \mathrm{GLUT4}\}. \end{aligned}$$

Thus

$$V^{(1)} = \{E_1, E_2, \ldots, E_7\} \ \subseteq\ \mathrm{POWSET}^1(V_0).$$

Second-level modules (2-super-nodes in $\mathrm{POWSET}^2(V_0)$) group these steps into functional blocks:

$$F_R = \{E_1, E_2\}, \quad F_K = \{E_3, E_4, E_5\}, \quad F_T = \{E_6, E_7\}.$$

Hence

$$V^{(2)} = \{F_R, F_K, F_T\} \ \subseteq\ \mathrm{POWSET}^2(V_0).$$

Third-level supermodules (3-super-nodes in $\mathrm{POWSET}^3(V_0)$) capture the two main signaling arms:

$$U_1 = \{F_R, F_K\}, \quad U_2 = \{F_K, F_T\}.$$

Thus

$$V^{(3)} = \{U_1, U_2\} \ \subseteq\ \mathrm{POWSET}^3(V_0).$$

Define the 3-super-interaction Hyper-edge

$$\mathcal{I}^{(3)} = \big\{\{\,U_1, U_2\}\big\}.$$

Labeling functions record biological roles:

$$\begin{aligned} \ell_V^{(3)}(U_1) &= \text{“Receptor-proximal and PI3K activation module”},\\ \ell_V^{(3)}(U_2) &= \text{“PI3K-AKT-mediated glucose uptake module”},\\ \ell_{\mathcal{I}}^{(3)}\big(\{U_1, U_2\}\big) &= \text{“Integrated insulin signaling cascade”}. \end{aligned}$$

Optionally, assign a confidence weight:

$$w^{(3)}(\{U_1, U_2\}) = 0.92.$$

- *Level 0* (V_0): individual molecules.
- *Level 1* ($V^{(1)}$): elementary binding and phosphorylation events.

- *Level 2* ($V^{(2)}$): functional blocks—receptor activation (F_R), kinase cascade (F_K), and transporter regulation (F_T).
- *Level 3* ($V^{(3)}$): supermodules integrating early PI3K activation (U_1) and downstream GLUT4 translocation (U_2).
- $\mathcal{I}^{(3)}$ models the coordination between these two critical modules in the insulin response.

Example 4.8 (26S Proteasome Complex as a Molecular Interaction 4-Super-Hyper-network)**.** The 26S proteasome complex is a large protein structure that degrades ubiquitinated proteins, maintaining cellular protein homeostasis and regulating various biological processes (cf.(Peters et al., 1993; Gomes et al., 2006; Wang et al., 2007)). Let the base set of molecular entities be

$$V_0 = \{\, A_1, \ldots, A_7,\ B_1, \ldots, B_7,\ \mathrm{Rpt}_1, \ldots, \mathrm{Rpt}_6,\ \mathrm{Rpn}_1, \ldots, \mathrm{Rpn}_{13}\},$$

where A_i and B_i are the seven α- and β-subunits of the 20S core particle, Rpt_j the six ATPase subunits, and Rpn_k the thirteen non-ATPase regulatory subunits.

First-level groupings (1-super-nodes in $\mathrm{POWSET}^1(V_0)$) are the fundamental subcomplexes:

$$F_\alpha = \{A_1, \ldots, A_7\}, \qquad F_\beta = \{B_1, \ldots, B_7\},$$
$$F_{\mathrm{base}} = \{\mathrm{Rpt}_1, \ldots, \mathrm{Rpt}_6\}, \quad F_{\mathrm{lid}} = \{\mathrm{Rpn}_1, \ldots, \mathrm{Rpn}_{13}\}.$$

Second-level assemblies (2-super-nodes in $\mathrm{POWSET}^2(V_0)$) combine rings into particle subunits:

$$M_{\mathrm{CP}} = \{F_\alpha,\, F_\beta\}, \quad M_{\mathrm{RP}} = \{F_{\mathrm{base}},\, F_{\mathrm{lid}}\}.$$

Third-level super-assemblies (3-super-nodes in $\mathrm{POWSET}^3(V_0)$) isolate each particle:

$$S_{\mathrm{core}} = \{M_{\mathrm{CP}}\}, \quad S_{\mathrm{reg}} = \{M_{\mathrm{RP}}\}.$$

Fourth-level 4-super-nodes (in $\mathrm{POWSET}^4(V_0)$) represent the complete 26S proteasome components:

$$U_1 = \{S_{\mathrm{core}}\}, \quad U_2 = \{S_{\mathrm{reg}}\}.$$

Then

$$V^{(4)} = \{\, U_1,\, U_2\}, \quad \mathcal{I}^{(4)} = \big\{\{\, U_1,\, U_2\}\big\}.$$

Labeling functions assign:

$$\ell_V^{(4)}(U_1) = \text{“20S core particle”}, \quad \ell_V^{(4)}(U_2) = \text{“19S regulatory particle”},$$
$$\ell_{\mathcal{I}}^{(4)}\big(\{U_1, U_2\}\big) = \text{“26S proteasome assembly”},$$

and optionally

$$w^{(4)}(\{U_1, U_2\}) = 1.00.$$

Here:

- *Level 0 (V_0)*: individual proteasome subunits (α, β, ATPase, non-ATPase).
- *Level 1 (POWSET^1)*: fundamental rings and subcomplexes (α-ring, β-ring, base, lid).
- *Level 2 (POWSET^2)*: core particle (M_{CP}) and regulatory particle (M_{RP}).
- *Level 3 (POWSET^3)*: isolated core (S_{core}) and regulatory (S_{reg}) super-assemblies.
- *Level 4 (POWSET^4)*: top-level super-nodes (U_1, U_2) representing the two principal 26S components, connected by a single 4-super-edge modeling the intact proteasome.

Example 4.9 (E. coli 70S Ribosome as a Molecular Interaction 4-Super-Hyper-network)**.** The E. coli 70S ribosome is a molecular machine composed of 30S and 50S subunits, responsible for protein synthesis during translation (cf.(Gabashvili et al., 2000; Agrawal et al., 2004, 1998; Kohler et al., 1968)). Let the base set of molecular entities be

$$V_0 = \{\, S_1, \ldots, S_{21},\ \text{16S rRNA},\ L_1, \ldots, L_{23},\ \text{23S rRNA},\ \text{5S rRNA}\},$$

where S_i are the 21 small-subunit proteins, L_j the 23 large-subunit proteins, and the three ribosomal RNAs.

Level 1 (1-super-nodes in $\mathrm{POWSET}^1(V_0)$). Group individual components into four functional clusters:

$$F_S = \{S_1, \ldots, S_{21}\}, \quad F_{rS} = \{\text{16S rRNA}\},$$
$$F_L = \{L_1, \ldots, L_{23}\}, \quad F_{rL} = \{\text{23S rRNA, 5S rRNA}\}.$$

Level 2 (2-super-nodes in $\mathrm{POWSET}^2(V_0)$). Assemble each ribosomal subunit's core components:

$$M_{\text{30S}} = \{F_S,\, F_{rS}\}, \quad M_{\text{50S}} = \{F_L,\, F_{rL}\}.$$

Level 3 (3-super-nodes in $\mathrm{POWSET}^3(V_0)$). Encapsulate each subunit as a single supermodule:

$$U_{\text{30S}} = \{\, M_{\text{30S}}\,\}, \quad U_{\text{50S}} = \{\, M_{\text{50S}}\,\}.$$

Level 4 (4-super-nodes in $\mathrm{POWSET}^4(V_0)$). Define the two top-level super-nodes and their interaction:

$$V^{(4)} = \{\, U_{\text{30S}},\, U_{\text{50S}}\,\}, \qquad \mathcal{I}^{(4)} = \big\{\{\, U_{\text{30S}},\, U_{\text{50S}}\,\}\big\}.$$

Labeling functions assign:

$$\ell_V^{(4)}(U_{\text{30S}}) = \text{“30S ribosomal subunit”}, \quad \ell_V^{(4)}(U_{\text{50S}}) = \text{“50S ribosomal subunit”},$$

$$\ell_{\mathcal{I}}^{(4)}\big(\{U_{\text{30S}}, U_{\text{50S}}\}\big) = \text{“70S ribosome assembly”}, \quad w^{(4)}\big(\{U_{\text{30S}}, U_{\text{50S}}\}\big) = 1.00.$$

- *Level 0 (V_0)*: individual proteins and rRNAs.
- *Level 1 (POWSET^1)*: four component clusters (small-subunit proteins, 16S rRNA, large-subunit proteins, 23S+5S rRNAs).
- *Level 2 (POWSET^2)*: 30S and 50S subunit assemblies.
- *Level 3 (POWSET^3)*: supermodules representing each subunit.
- *Level 4 (POWSET^4)*: top-level super-nodes and the superHyper-edge capturing the intact 70S ribosome.

This example illustrates how a molecular interaction 4-Super-Hyper-network encodes the hierarchical assembly of the bacterial ribosome from individual proteins and RNAs up to the fully assembled complex.

Theorem 4.10 (n-Super-Hyper-Network Property)**.** *Every molecular interaction n-Super-Hyper-network $\mathcal{H}^{(n)}$ is an n-Super-Hyper-network in the sense of Definition [n-Super-Hyper-network].*

Proof. By construction:

- $V^{(n)} \subseteq \mathrm{POWSET}^n(V_0)$ and $\mathcal{I}^{(n)} \subseteq \mathrm{POWSET}^n(V_0) \setminus \{\emptyset\}$, so both super-nodes and super-edges lie in the n-th iterated powerset of the base set.
- Each element of $\mathcal{I}^{(n)}$ is a nonempty subset of $V^{(n)}$, matching the requirement that super-edges connect super-nodes.
- The weight function $w^{(n)} : \mathcal{I}^{(n)} \to \mathbb{R}_{\geq 0}$ and the labelings $\ell_V^{(n)}, \ell_{\mathcal{I}}^{(n)}$ are exactly the optional data permitted in the general n-Super-Hyper-network framework.

Hence all axioms of an n-Super-Hyper-network are satisfied.

□

Theorem 4.11 (Generalization of Molecular Interaction Hyper-Networks)**.** *Let $\mathcal{H} = (V_0, \mathcal{I}, \ell_V, \ell_\mathcal{I}, w)$ be any molecular interaction Hyper-network (the case $n = 1$). Then there is a natural identification of $\mathcal{H}$ with a molecular interaction 1-Super-Hyper-network $\mathcal{H}^{(1)}$ given by*

$$V^{(1)} = \big\{\{v\} \mid v \in V_0\big\}, \quad \mathcal{I}^{(1)} = \mathcal{I} \subseteq \mathrm{POWSET}^1(V_0),$$

with
$\ell_V^{(1)}(\{v\}) = \ell_V(v)$, $\ell_\mathcal{I}^{(1)} = \ell_\mathcal{I}$, *and* $w^{(1)} = w$. *Under this identification, $\mathcal{H}^{(1)}$ is isomorphic to $\mathcal{H}$.*

Proof. Define

$$\Phi_V : V_0 \longrightarrow V^{(1)}, \quad v \mapsto \{v\}, \quad \Phi_\mathcal{I} : \mathcal{I} \hookrightarrow \mathcal{I}^{(1)}$$

where we simply regard each Hyper-edge $I \subseteq V_0$ as an element of $\mathrm{POWSET}^1(V_0)$. Then:

1. Φ_V is a bijection from the original nodes V_0 onto $V^{(1)}$.
2. $\Phi_\mathcal{I}$ is the identity embedding of $\mathcal{I}$ into $\mathrm{POWSET}^1(V_0)$.
3. Labels are preserved since $\ell_V^{(1)}(\{v\}) = \ell_V(v)$ and $\ell_\mathcal{I}^{(1)}(I) = \ell_\mathcal{I}(I)$.
4. Weights are preserved: $w^{(1)}(I) = w(I)$.

Thus the data of $\mathcal{H}$ and $\mathcal{H}^{(1)}$ coincide under the natural isomorphism $(\Phi_V, \Phi_\mathcal{I})$. Therefore every molecular interaction Hyper-network is a special case of a molecular interaction n-Super-Hyper-network for $n = 1$, and the class of n-Super-Hyper-networks strictly generalizes that of Hyper-Networks.

□

Theorem 4.12 (Flattening Theorem)**.** *Let*

$$\mathcal{H}^{(n)} = \big(V^{(n)}, \mathcal{I}^{(n)}, \ell_V^{(n)}, \ell_\mathcal{I}^{(n)}, w^{(n)}\big)$$

be a molecular interaction n-Super-Hyper-network over base entities V_0. For each k with $0 \le k \le n$, define the k-flattening map

$$\varphi_k : \mathrm{POWSET}^n(V_0) \longrightarrow \mathrm{POWSET}^{\,n-k}(V_0), \quad X \mapsto \bigcup_{Y \in X} Y,$$

iterated k times. Then

$$\mathcal{H}^{(n-k)} = \Big(\varphi_k\big(V^{(n)}\big),\ \varphi_k\big(\mathcal{I}^{(n)}\big),\ \ell_V^{(n)} \circ \varphi_k,\ \ell_\mathcal{I}^{(n)} \circ \varphi_k,\ w^{(n)} \circ \varphi_k\Big)$$

is a well-defined molecular interaction $(n-k)$-Super-Hyper-network.

Proof. Since $V^{(n)} \subseteq \mathrm{POWSET}^n(V_0)$ and $\mathcal{I}^{(n)} \subseteq \mathrm{POWSET}^n(V_0)$, applying φ_k yields $\varphi_k(V^{(n)}) \subseteq \mathrm{POWSET}^{n-k}(V_0)$ and $\varphi_k(\mathcal{I}^{(n)}) \subseteq \mathrm{POWSET}^{n-k}(V_0)$. Each $\varphi_k(I)$ remains a nonempty subset of $\varphi_k(V^{(n)})$. Composing the label functions and weights with φ_k preserves their codomains and assignments. Thus all axioms of Definition hold for $\mathcal{H}^{(n-k)}$. □

Theorem 4.13 (Entity Coverage Theorem)**.** *In any molecular interaction n-Super-Hyper-network $\mathcal{H}^{(n)}$ over V_0, the union of the fully flattened Hyper-edges covers the entire base set:*

$$\bigcup_{I \in \mathcal{I}^{(n)}} \varphi_n(I) \;=\; V_0.$$

Proof. We proceed by induction on n.

Base case $n = 1$. Then $\mathcal{H}^{(1)}$ is a molecular interaction Hyper-network, and by definition each base entity participates in at least one interaction Hyper-edge, so $\bigcup_{I\in\mathcal{I}^{(1)}} I = V_0$.

Inductive step. Assume the statement holds for $n-1$. Consider $\mathcal{H}^{(n)}$. Its 1-flattening $\mathcal{H}^{(n-1)}$ satisfies $\bigcup_{J\in\varphi_1(\mathcal{I}^{(n)})} \varphi_{n-1}(J) = V_0$ by the induction hypothesis. Since $\varphi_n = \varphi_{n-1} \circ \varphi_1$ and $\varphi_1(\mathcal{I}^{(n)}) = \varphi_1(\mathcal{I}^{(n)})$, we obtain

$$\bigcup_{I\in\mathcal{I}^{(n)}} \varphi_n(I) = \bigcup_{J\in\varphi_1(\mathcal{I}^{(n)})} \varphi_{n-1}(J) = V_0.$$

This completes the induction.

□

Theorem 4.14 (Connectivity Equivalence)**.** *Let $\mathcal{H}^{(n)}$ be a molecular interaction n-Super-Hyper-network, and let $G^{(n)}$ be its primal graph on n-super-nodes. Then $G^{(n)}$ is connected if and only if the primal graph of the fully flattened network, $G^{(0)}$, is connected.*

Proof. In the primal graph $G^{(n)}$, two distinct n-super-nodes u, v are adjacent if they both lie in some n-super-edge I. Under each flattening step φ_k, adjacency is preserved: if $\{u, v\} \subseteq I$ then $\{\varphi_k(u), \varphi_k(v)\} \subseteq \varphi_k(I)$. Thus any path in $G^{(n)}$ projects to a path in $G^{(n-1)}$, and iterating down to $G^{(0)}$ yields a corresponding path. Conversely, any path in $G^{(0)}$ lifts to paths at higher levels by inverse images under the φ_k. Hence connectedness is equivalent at all levels. □

Theorem 4.15 (Induced Subnetwork Theorem)**.** *Let $\mathcal{H}^{(n)}$ be a molecular interaction n-Super-Hyper-network on V_0, and let $B \subseteq V_0$ be a nonempty subset of base entities. Define*

$$V' = \{\, v \in V^{(n)} : v \subseteq \mathrm{POWSET}^n(B) \,\},$$

$$\mathcal{I}' = \{\, I \in \mathcal{I}^{(n)} : I \subseteq \mathrm{POWSET}^n(B) \,\}.$$

Then

$$\mathcal{H}^{(n)}[B] \;=\; \big(V',\, \mathcal{I}',\, \ell_V^{(n)}|_{V'},\, \ell_{\mathcal{I}}^{(n)}|_{\mathcal{I}'},\, w^{(n)}|_{\mathcal{I}'}\big)$$

is a molecular interaction n-Super-Hyper-network on base set B.

Proof. By construction, $V' \subseteq \mathrm{POWSET}^n(B)$ and $\mathcal{I}' \subseteq \mathrm{POWSET}^n(B) \setminus \{\emptyset\}$. Each induced Hyper-edge I' remains a nonempty subset of V'. The restrictions of $\ell_V^{(n)}, \ell_{\mathcal{I}}^{(n)}, w^{(n)}$ to the smaller sets preserve their codomains and assignments. Therefore all axioms of Definition [Molecular Interaction n-Super-Hyper-network] hold for the induced subnetwork $\mathcal{H}^{(n)}[B]$. □

5 CONCLUSION AND FUTURE WORKS

In this paper, we introduced two novel mathematical frameworks: the *Molecular Interaction Hyper-network* and the *Molecular Interaction Super-Hyper-network*. We provided formal definitions, illustrative real-world examples, and a preliminary discussion of their structural and mathematical properties.

As future work, we aim to extend the *Molecular Interaction Hyper-network* and *Molecular Interaction Super-Hyper-network* by integrating advanced uncertainty-handling frameworks. These include Fuzzy Sets (Zadeh, 1965, 1996, 1972), Intuitionistic Fuzzy Sets (Atanassov and Gargov, 1998, 2017; Atanassov and Atanassov, 1999), Vague Sets (Gau and Buehrer, 1993; Akram et al., 2014; Bustince and Burillo, 1996), Rough Sets (Pawlak, 1982; Pawlak et al., 1988), Hyper-Rough Sets (Fujita, 2025g,l,e), Super-Hyper-Rough Sets (Fujita, 2024a, 2025i), Bipolar Fuzzy Sets (Akram, 2011), HyperFuzzy Sets (Jun et al., 2017; Fujita; Song et al., 2017), Picture Fuzzy Sets (Hatamleh et al., 2025; Cuong and Kreinovich, 2013), Hesitant Fuzzy Sets (Torra and Narukawa, 2009; Torra, 2010), Neutrosophic Sets (Smarandache, 1999; Smarandache and Salama, 2015), Quadripartitioned Neutrosophic Sets (Fujita, 2025k; Yiarayong, 2024; Khattak et al., 2025), and Plithogenic Sets (Smarandache and Jdid, 2023; Fujita and Smarandache, 2024b; Fujita, 2025a). Building on these extensions, we plan to investigate applications in AI(Bettayeb and Balbaa, 2023; Ahmad and Afzal, 2022; Fujita, 2025f), linear programming (Zimmermann, 1978; Jdid and Smarandache, 2023, 2024), algorithm design(Zadeh, 1968; Zhao et al., 2023), neural networks (Hendalianpour and Razmi, 2017; Gupta and Rao, 1994; Kwan and Cai, 1994), and decision-making(Garg, 2018; Pamucar et al., 2020). Incorporating these frameworks will potentially enhance the descriptive power and applicability of our models, especially for representing complex and

hierarchical biochemical systems under various forms of uncertainty.

6 LIMITATIONS AND SCOPE

The concepts introduced in this paper have not yet been implemented or tested experimentally. We encourage future work to apply and validate these ideas in practical contexts. Although we have endeavored to ensure correctness and proper citation, inadvertent errors or omissions may remain; readers should verify cited sources independently.

All results hold under the specific assumptions stated. Extending these findings to broader settings will require further study. The views and conclusions expressed here are those of the authors and do not necessarily represent the positions of their institutions.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The authors confirm that no generative AI tools—such as large language models (e.g., ChatGPT, Copilot) or text-to-image systems—were employed in writing or editing this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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