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Biological Networks, HyperNetworks, and SuperHyperNetworks in Biomedicine

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Abstract. Graph theory has been widely applied across diverse scientific domains. Hypergraphs extend classical graphs by allowing hyperedges to connect arbitrary subsets of vertices, while superhypergraphs further enrich this structure through iterated powersets that capture hierarchical and self-referential relationships. Graphs are also extensively used in chemical and biological contexts. A biological network typically represents genes, proteins, or metabolites as vertices, with pairwise regulatory, signaling, or metabolic interactions encoded as weighted edges. In this paper, we investigate *biological hypernetworks* and *biological superhypernetworks* as natural generalizations of biological networks, achieved through the frameworks of hypergraphs and superhypergraphs, respectively. Furthermore, we briefly consider application examples of Biological Networks, HyperNetworks, and SuperHyperNetworks in biomedicine.

Keywords. Superhypergraph, Hypergraph, Biological Network, HyperNetworks, SuperHyperNetworks

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1 Preliminaries

This section introduces the set-theoretic and hypergraph-theoretic notation used throughout the paper. All sets are finite. The elements of every biological base set are regarded as atomic labels; in particular, they are not themselves interpreted as sets in the recursive constructions below.

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1.1 Power Set and Iterated Power Sets

The power set of a set contains all of its subsets, including the empty set and the set itself. Iterated power sets are obtained by repeatedly applying the power-set operator [1, 2].

Definition 1.1 (Power set)**.** [3] For a set S, its *power set*, denoted by $\mathrm{POWS}(S)$, is

$$\mathrm{POWS}(S) := \{X : X \subseteq S\}.$$

Example 1.2 (Biology: CRISPR Knockout Design Space)**.** Let the target gene set be

$$S = \{\mathrm{TP53},\ \mathrm{KRAS},\ \mathrm{EGFR}\}.$$

The power set $\mathrm{POWS}(S)$ enumerates all knockout combinations (experimental conditions), totaling $2^{|S|} = 2^3 = 8$:

$$\mathrm{POWS}(S) = \big\{\varnothing,\ \{\mathrm{TP53}\},\ \{\mathrm{KRAS}\},\ \{\mathrm{EGFR}\},\ \{\mathrm{TP53}, \mathrm{KRAS}\},$$
$$\{\mathrm{TP53}, \mathrm{EGFR}\},\ \{\mathrm{KRAS}, \mathrm{EGFR}\},$$
$$\{\mathrm{TP53}, \mathrm{KRAS}, \mathrm{EGFR}\}\big\}.$$

Here, $\varnothing$ is the no-KO control; each nonempty subset specifies a single- or multi-gene CRISPR knockout to test.

Definition 1.3 (Iterated Power Set)**.** [4] For each integer $n \geq 1$, define the n-fold iterated power set of S by

$$\mathrm{POWS}^1(S) = \mathrm{POWS}(S),$$
$$\mathrm{POWS}^{k+1}(S) = \mathrm{POWS}\big(\mathrm{POWS}^k(S)\big) \quad (k \geq 1).$$

Equivalently, one may write $P_n(S) = \mathrm{POWS}^n(S)$.

Definition 1.4 (Nonempty Iterated Power Set)**.** [4] Define the nonempty iterated power set by

$$\mathrm{POWS}^*_1(S) = \mathrm{POWS}(S) \setminus \{\varnothing\},$$
$$\mathrm{POWS}^*_{k+1}(S) = \mathrm{POWS}^*\big(\mathrm{POWS}^*_k(S)\big) \quad (k \geq 1),$$

where $\mathrm{POWS}^*(X) = \mathrm{POWS}(X) \setminus \{\varnothing\}$ for any set X.

Example 1.5 (Chemical reaction participants and their grouped contexts (size-3 base set))**.** *Base set.* Let

$$S = \{\mathrm{GLC\ (glucose)},\ \mathrm{ATP},\ \mathrm{HK\ (hexokinase)}\}, \qquad |S| = 3.$$

Level 1: nonempty power set.

$$\mathrm{POWS}^*_1(S) = \{\{\mathrm{GLC}\}, \{\mathrm{ATP}\}, \{\mathrm{HK}\}, \{\mathrm{GLC}, \mathrm{ATP}\},$$
$$\{\mathrm{GLC}, \mathrm{HK}\}, \{\mathrm{ATP}, \mathrm{HK}\}, \{\mathrm{GLC}, \mathrm{ATP}, \mathrm{HK}\}\}.$$

Hence

$$|\mathrm{POWS}^*_1(S)| = 2^{|S|} - 1 = 2^3 - 1 = 7.$$

Interpretation. Each element of $\mathrm{POWS}^*_1(S)$ is a *nonempty group of participants* that can co-occur in an experimental or mechanistic context, e.g., $\{\mathrm{GLC}, \mathrm{ATP}\}$ "substrates only," or $\{\mathrm{GLC}, \mathrm{ATP}, \mathrm{HK}\}$ "full reactive triad."

Level 2: nonempty power set of Level 1.

$$\mathrm{POWS}^*_2(S) = \mathrm{POWS}^*\big(\mathrm{POWS}^*_1(S)\big) = \mathrm{POWS}\big(\mathrm{POWS}^*_1(S)\big) \setminus \{\varnothing\},$$

so

$$|\mathrm{POWS}^*_2(S)| = 2^{|\mathrm{POWS}^*_1(S)|} - 1 = 2^7 - 1 = 127.$$

Interpretation. An element of $\mathrm{POWS}_2^*(S)$ is a *nonempty family of nonempty participant-groups*, i.e., a small "protocol library" of admissible co-occurrences. For instance, two concrete elements of $\mathrm{POWS}_2^*(S)$ are

$$F_1 = \big\{\{\mathrm{GLC}, \mathrm{ATP}\}, \{\mathrm{HK}\}\big\}, \qquad F_2 = \big\{\{\mathrm{GLC}\}, \{\mathrm{GLC}, \mathrm{ATP}, \mathrm{HK}\}\big\},$$

encoding, respectively, (i) a two-step preparation set (substrates present; enzyme separate) and (ii) a minimal/maximal pairing rule.

Example 1.6 (Protein complex assembly and inhibitory subassemblies (size-4 base set))**.** *Base set.* Consider three protein subunits and one inhibitor,

$$S = \{A, B, C, I\}, \qquad |S| = 4,$$

where A, B, C are complex-forming subunits and I is an inhibitor.

Level 1: nonempty power set.

$$|\mathrm{POWS}_1^*(S)| = 2^4 - 1 = 15.$$

Representative members (from singletons to larger subassemblies) include

$$\{A\},\ \{B\},\ \{C\},\ \{I\},\ \{A, B\},\ \{A, C\},\ \{B, C\},\ \{A, B, C\},\ \{A, B, I\},\ \{A, B, C, I\},$$

each interpretable as a *possible subassembly state* (e.g., $\{A, B, C\}$ active trimer; $\{A, B, I\}$ inhibited dimer).

Level 2: families of subassemblies.

$$\mathrm{POWS}_2^*(S) = \mathrm{POWS}^*\big(\mathrm{POWS}_1^*(S)\big),$$

$$|\mathrm{POWS}_2^*(S)| = 2^{15} - 1 = 32767.$$

Each element of $\mathrm{POWS}_2^*(S)$ is a *nonempty collection of admissible subassemblies*. Two concrete examples are

$$\mathcal{F}_{\text{active}} = \big\{\{A, B\}, \{B, C\}, \{A, B, C\}\big\},$$

$$\mathcal{F}_{\text{inhibited}} = \big\{\{A, B, I\}, \{A, C, I\}, \{B, C, I\}, \{A, B, C, I\}\big\}.$$

Here $\mathcal{F}_{\text{active}}$ enumerates active assemblies, while $\mathcal{F}_{\text{inhibited}}$ lists inhibited states containing I. Thus, Level-2 elements compactly encode *design rules or admissible state-sets* for complex formation under inhibitory conditions.

Definition 1.7 (Iterated power set)**.** [4] For every integer $k \geq 0$, define

$$\mathrm{POWS}^0(S) := S, \qquad \mathrm{POWS}^{k+1}(S) := \mathrm{POWS}\big(\mathrm{POWS}^k(S)\big).$$

Thus, $\mathrm{POWS}^k(S)$ is the k-fold iterated power set of S.

Definition 1.8 (Recursively nonempty iterated power set)**.** [4] Write

$$\mathrm{POWS}^*(X) := \mathrm{POWS}(X) \setminus \{\varnothing\}.$$

The recursively nonempty iterated power sets are defined by

$$\mathrm{POWS}_1^*(S) := \mathrm{POWS}^*(S), \qquad \mathrm{POWS}_{k+1}^*(S) := \mathrm{POWS}^*\big(\mathrm{POWS}_k^*(S)\big) \quad (k \geq 1).$$

If $m_k := |\mathrm{POWS}_k^*(S)|$, then

$$m_1 = 2^{|S|} - 1, \qquad m_{k+1} = 2^{m_k} - 1.$$

1.2 Hypergraphs and SuperHypergraphs

Hypergraphs extend ordinary graphs by allowing each *hyperedge* to connect an arbitrary, nonempty subset of vertices; this mechanism naturally captures higher–order relations among elements [5–7]. Related concepts include the Directed HyperGraph [8, 9], MultiHyperGraph [10, 11], Fuzzy HyperGraph [12–15], and Neutrosophic HyperGraph [16, 17]. A *SuperHyperGraph* goes a step further by employing iterated powersets, thereby encoding multi-layered and self-referential couplings among hyperedges [18–22].

Definition 1.9 (Hypergraph)**.** [23, 24] Let V be a finite set of *vertices*. A *hypergraph* is a pair

$$H = \big(V,\ E\big), \qquad E \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\},$$

where each element of E is a *hyperedge*. There is no a priori bound on the size of a hyperedge.

Example 1.10 (Illustrative hypergraphs from chemistry and biology)**.** (i) **Chemistry: functional groups in ethanol.** Let the vertices be the atoms of ethanol,

$$V = \{\mathrm{C}_1, \mathrm{C}_2, \mathrm{O}, \mathrm{H}_1, \ldots, \mathrm{H}_6\}.$$

Define hyperedges at the group level (instead of single bonds):

$$E = \big\{\{\mathrm{C}_1, \mathrm{O}, \mathrm{H}_1\},\ \{\mathrm{C}_1, \mathrm{C}_2, \mathrm{H}_2, \mathrm{H}_3\},\ \{\mathrm{C}_2, \mathrm{H}_4, \mathrm{H}_5, \mathrm{H}_6\}\big\}.$$

The first hyperedge represents the hydroxyl group $-\mathrm{OH}$; the remaining ones represent the methyl/methylene groups. Thus, the molecule is modeled at the level of functional groupings.

(ii) **Biology: multi-protein signaling complexes.** Let vertices denote proteins in a signaling cascade,

$$V = \{\mathrm{EGFR}, \mathrm{Grb2}, \mathrm{SOS}, \mathrm{RAS}, \mathrm{RAF}, \mathrm{MEK}, \mathrm{ERK}\}.$$

Introduce hyperedges for multi-protein complexes:

$$E = \big\{\{\mathrm{EGFR}, \mathrm{Grb2}, \mathrm{SOS}\},\ \{\mathrm{RAS}, \mathrm{RAF}, \mathrm{MEK}\},\ \{\mathrm{RAF}, \mathrm{MEK}, \mathrm{ERK}\}\big\}.$$

Each hyperedge records a complex required for transducing the signal, thereby going beyond pairwise interactions to capture higher-order biochemical assemblies.

Definition 1.11 (n-SuperHyperGraph)**.** (cf. [20]) Let V_0 be a finite nonempty base set and let $n \geq 0$. An *n-SuperHyperGraph* over V_0 is a pair

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

such that

$$\varnothing \neq V \subseteq \mathrm{POWS}^n(V_0), \qquad \varnothing \neq E \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\}.$$

The elements of V are called n-supervertices, and the elements of E are called n-superedges. For $n = 0$, this is an ordinary hypergraph on the vertex set $V \subseteq V_0$.

Example 1.12 (Level-2 SuperHyperGraph for pathway–complex coupling (chemical biology, $n = 2$))**.** *Objective.* Represent, at two hierarchical levels, (i) a glycolytic entry reaction, (ii) a multi-subunit enzyme complex, and (iii) a TCA-entry step, and connect them by several 2-superedges, including one event spanning all three modules.

Base set (entities).

$$V_0 = \{\mathrm{GLC}, \mathrm{ATP}, \mathrm{G6P}, \mathrm{ADP}, \mathrm{E1}, \mathrm{E2}, \mathrm{E3},\ \mathrm{PYR}, \mathrm{CoA}, \mathrm{AcCoA}, \mathrm{CO2}, \mathrm{NAD}^+, \mathrm{NADH}\}.$$

Level-1 sets (in $\mathrm{POWS}(V_0)$*).*

$$\begin{aligned} L_{\text{hex}} &= \{\text{GLC}, \text{ATP}, \text{G6P}, \text{ADP}\} && \text{(hexokinase participants)},\\ L_{\text{pdh-sub}} &= \{\text{E1}, \text{E2}, \text{E3}\} && \text{(PDH subunits)},\\ L_{\text{pdh-rxn}} &= \{\text{PYR}, \text{CoA}, \text{AcCoA}, \text{CO2}, \text{NAD}^+, \text{NADH}\} && \text{(PDH reaction species)}. \end{aligned}$$

Level-2 supervertices (in $\mathrm{POWS}^2(V_0)$*).*

$$v_{\text{gly}} = \{L_{\text{hex}}\}, \qquad v_{\text{pdh}} = \{L_{\text{pdh-sub}}, L_{\text{pdh-rxn}}\}, \qquad v_{\text{tca}} = \{\,\{\text{AcCoA}\}\,\}.$$

Define

$$V = \{v_{\text{gly}}, v_{\text{pdh}}, v_{\text{tca}}\} \subseteq \mathrm{POWS}^2(V_0).$$

2*-superedges (nonempty subsets of* V*).*

$$E = \Big\{\, e_1 = \{v_{\text{gly}}, v_{\text{pdh}}\},\ \ e_2 = \{v_{\text{pdh}}, v_{\text{tca}}\},\ \ e_3 = \{v_{\text{gly}}, v_{\text{pdh}}, v_{\text{tca}}\} \,\Big\} \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\}.$$

Verification. Since $V \subseteq \mathrm{POWS}^2(V_0)$ and each e_i is a nonempty subset of V, we obtain $\mathrm{SHG}^{(2)} = (V, E)$ as an n-SuperHyperGraph with $n = 2$. Semantically, e_3 expresses a cross-step constraint (flow from glycolysis through PDH to TCA entry) that would be obscured by a single ordinary hyperedge on V_0.

Example 1.13 (Level-3 SuperHyperGraph for paracrine signaling and transcriptional response ($n = 3$))**.** *Objective.* Across three levels, encode (i) cell clusters and ligand/receptor families, (ii) their modular groupings (source/target modules and TF/promoter module), and (iii) a single 3-superedge linking communication to response.

Base set (entities).

$$V_0 = \{\text{Mac1}, \text{Mac2}, \text{T1}, \text{T2},\ \text{IL6}, \text{TNF}, \text{IL6R}, \text{TNFR},\ \text{STAT3}, \text{NF}\kappa\text{B},\ \text{G1}, \text{G2}\ \}.$$

Level-1 sets (in $\mathrm{POWS}(V_0)$*): cell clusters, ligand/receptor pools, TF and promoter sets.*

$$\begin{aligned} C_M &= \{\text{Mac1}, \text{Mac2}\}, & C_T &= \{\text{T1}, \text{T2}\},\\ L &= \{\text{IL6}, \text{TNF}\}, & R &= \{\text{IL6R}, \text{TNFR}\},\\ T &= \{\text{STAT3}, \text{NF}\kappa\text{B}\}, & P &= \{\text{G1}, \text{G2}\}. \end{aligned}$$

Level-2 supervertices (in $\mathrm{POWS}^2(V_0)$*).*

$$v_{\text{src}} = \{C_M, L\}, \qquad v_{\text{dst}} = \{C_T, R\}, \qquad v_{\text{resp}} = \{T, P\}.$$

Level-3 supervertices (in $\mathrm{POWS}^3(V_0)$*).*

$$u_{\text{channel}} = \{v_{\text{src}}, v_{\text{dst}}\}, \qquad u_{\text{program}} = \{v_{\text{resp}}\}.$$

Set

$$V = \{u_{\text{channel}}, u_{\text{program}}\} \subseteq \mathrm{POWS}^3(V_0).$$

3*-superedges (nonempty subsets of* V*).*

$$E = \Big\{\, e = \{u_{\text{channel}}, u_{\text{program}}\} \,\Big\} \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\}.$$

Since $V \subseteq \mathrm{POWS}^3(V_0)$ and $E \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\}$, we obtain $\mathrm{SHG}^{(3)} = (V, E)$ as an n-SuperHyperGraph with $n = 3$. Here, u_{channel} encodes paracrine communication

(macrophage cluster → T-cell cluster via ligand/receptor families), while u_{program} encodes the downstream transcriptional machinery (TF module and promoters). The single 3-superedge e asserts that the *communication channel* and the *gene program* participate jointly in one higher-level biological event (e.g., cytokine-driven activation producing a defined transcriptional response), preserving hierarchical structure across cells, molecules, and regulatory targets.

2 Main Results

This section gives mathematically consistent definitions of biological networks, biological hypernetworks, and biological superhypernetworks. The event-indexed formulation used below permits distinct biological events to have the same participant set, different directions, or different annotations.

2.1 Biological networks

A biological network represents molecular or cellular entities by vertices and pairwise interactions by arcs [25–28].

Notation 2.1 (Types, interaction classes, and arc data)**.** *Let $\mathcal{T}$ be a finite set of biological types and let $\mathcal{I}$ be a finite set of interaction classes. Fix a total order $\preceq$ on $\mathcal{I}$; it will only be used to resolve exact ties in projected interaction labels. For a finite set V, write*

$$\Delta_V := \{(v, v) : v \in V\}.$$

Definition 2.2 (Biological network)**.** A *biological network* is a tuple

$$\mathcal{G} = (V, A, \tau, \rho, \sigma, w),$$

where

- V is a finite nonempty set of biological entities;
- $A \subseteq (V \times V) \setminus \Delta_V$ is a set of directed, loopless arcs;
- $\tau : V \to \mathcal{T}$ is a type map;
- $\rho : A \to \mathcal{I}$ is an interaction-class map;
- $\sigma : A \to \{-1, 0, +1\}$ is a sign map;
- $w : A \to \mathbb{R}_{\geq 0}$ is a nonnegative weight map.

An undirected biological network is represented by a symmetric arc set: $(u, v) \in A$ if and only if $(v, u) \in A$, with equal annotations in both directions.

For $u \in V$, define

$$k_{\text{out}}(u) := |\{v : (u, v) \in A\}|, \qquad k_{\text{in}}(u) := |\{v : (v, u) \in A\}|.$$

Example 2.3 (Regulatory network: two transcription factors and two genes)**.** Let

$$V = \{\text{TFA}, \text{TFB}, \text{G1}, \text{G2}\},$$

with

$$\tau(\text{TFA}) = \tau(\text{TFB}) = \text{protein}, \qquad \tau(\text{G1}) = \tau(\text{G2}) = \text{gene}.$$

Set

$$A = \{(\text{TFA}, \text{G1}), (\text{TFB}, \text{G1}), (\text{TFA}, \text{TFB}), (\text{TFB}, \text{G2})\}.$$

Let $\rho(a) =$ regulates for every $a \in A$, and define

$$\begin{aligned}
\sigma(\text{TFA}, \text{G1}) &= +1, \quad & w(\text{TFA}, \text{G1}) &= 0.90, \\
\sigma(\text{TFB}, \text{G1}) &= -1, \quad & w(\text{TFB}, \text{G1}) &= 0.70, \\
\sigma(\text{TFA}, \text{TFB}) &= +1, \quad & w(\text{TFA}, \text{TFB}) &= 0.50, \\
\sigma(\text{TFB}, \text{G2}) &= +1, \quad & w(\text{TFB}, \text{G2}) &= 0.85.
\end{aligned}$$

This is a typed, signed, weighted biological network.

Example 2.4 (Protein–protein interaction network as a symmetric digraph)**.** Let

$$V = \{\text{TP53}, \text{MDM2}, \text{RB1}, \text{E2F1}\}, \qquad \tau(v) = \text{protein} \quad (v \in V).$$

Let

$$F = \big\{\{\text{TP53}, \text{MDM2}\}, \{\text{RB1}, \text{E2F1}\}, \{\text{MDM2}, \text{RB1}\}\big\}$$

and define the symmetric arc set

$$A := \{(u, v) \in V \times V : \{u, v\} \in F\}.$$

For both orientations of each pair, take $\rho =$ binds, $\sigma = 0$, and

$$\begin{aligned}
w(\text{TP53}, \text{MDM2}) &= w(\text{MDM2}, \text{TP53}) = 0.95, \\
w(\text{RB1}, \text{E2F1}) &= w(\text{E2F1}, \text{RB1}) = 0.90, \\
w(\text{MDM2}, \text{RB1}) &= w(\text{RB1}, \text{MDM2}) = 0.30.
\end{aligned}$$

Example 2.5 (Metabolic substrate graph as a symmetric clique)**.** For the reaction Glucose+ ATP $\longrightarrow$ G6P + ADP, let

$$V = \{\text{Glucose}, \text{ATP}, \text{G6P}, \text{ADP}\}, \qquad \tau(v) = \text{metabolite} \quad (v \in V).$$

The corresponding substrate graph is represented by

$$A := \{(u, v) \in V \times V : u \neq v\},$$

with $\rho =$ co-participates, $\sigma = 0$, and $w \equiv 1$. Its underlying undirected graph is the complete graph K_4.

Definition 2.6 (Underlying simple graph and standard measures)**.** Let $\mathcal{G} = (V, A, \tau, \rho, \sigma, w)$ be a biological network. Its underlying simple graph is

$$G^{\mathrm{u}} = (V, F), \qquad F := \big\{\{u, v\} \subseteq V : (u, v) \in A \text{ or } (v, u) \in A\big\}.$$

Let $N := |V|$.

- If G^{u} is connected and $d(i, j)$ denotes its shortest-path distance, then the mean shortest-path length is

$$\langle \ell \rangle := \frac{2}{N(N-1)} \sum_{\{i,j\} \in \binom{V}{2}} d(i, j).$$

  For a sequence of connected networks with $N \to \infty$, logarithmic growth $\langle \ell \rangle = O(\log N)$ is one characteristic commonly associated with small-world behavior.
- For $i \in V$, let $N(i)$ be its neighbor set in G^{u}, let $k_i := |N(i)|$, and let m_i be the number of edges induced by $N(i)$. Define

$$C_i := \begin{cases} \dfrac{2m_i}{k_i(k_i - 1)}, & k_i \geq 2, \\ 0, & k_i < 2, \end{cases} \qquad \langle C \rangle := \frac{1}{N} \sum_{i \in V} C_i.$$

The global transitivity

$$C_{\mathrm{tr}} := \frac{3\,\#\{\text{triangles in } G^{\mathrm{u}}\}}{\#\{\text{connected triples in } G^{\mathrm{u}}\}}$$

is a related but generally different statistic.

- The empirical degree distribution is

$$P(k) := \frac{|\{v \in V : \deg_{G^{\mathrm{u}}}(v) = k\}|}{N}.$$

Example 2.7 (Mean shortest-path length on a four-vertex path)**.** Let

$$V = \{1,2,3,4\}, \qquad F = \{\{1,2\},\{2,3\},\{3,4\}\}.$$

The six pairwise distances are $1, 2, 3, 1, 2, 1$. Hence

$$\langle \ell \rangle = \frac{2}{4 \cdot 3}(1+2+3+1+2+1) = \frac{5}{3}.$$

Example 2.8 (Clustering and degree distribution on a triangle with a tail)**.** Let

$$F = \{\{1,2\},\{2,3\},\{3,1\},\{3,4\}\}.$$

Then $(k_1, k_2, k_3, k_4) = (2, 2, 3, 1)$ and

$$(C_1, C_2, C_3, C_4) = \left(1, 1, \frac{1}{3}, 0\right), \qquad \langle C \rangle = \frac{7}{12}.$$

The empirical degree distribution is

$$P(1) = \frac{1}{4}, \qquad P(2) = \frac{1}{2}, \qquad P(3) = \frac{1}{4}.$$

2.2 Biological hypernetworks

A biological hypernetwork uses event-indexed hyperedges to encode joint biological events involving several entities simultaneously.

Notation 2.9 (Event supports, roles, and orientation)**.** *Let $\mathcal{R}$ be a finite set of role labels and let*

$$\pi : \mathcal{R} \to \{\mathrm{in}, \mathrm{out}, \mathrm{neu}\}$$

be an orientation map. Let $\mathcal{E}$ be a finite event set and let

$$\partial : \mathcal{E} \to \mathrm{POWS}(V) \setminus \{\varnothing\}$$

be an incidence or support map. For $e \in \mathcal{E}$, a role map is $\lambda_e : \partial(e) \to \mathcal{R}$ and a stoichiometry map is $s_e : \partial(e) \to \mathbb{N}_{>0}$. Define

$$\mathrm{In}(e) := \{u \in \partial(e) : \pi(\lambda_e(u)) = \mathrm{in}\},$$
$$\mathrm{Out}(e) := \{u \in \partial(e) : \pi(\lambda_e(u)) = \mathrm{out}\},$$
$$\mathrm{Neu}(e) := \{u \in \partial(e) : \pi(\lambda_e(u)) = \mathrm{neu}\}.$$

These three sets form a partition of $\partial(e)$.

Definition 2.10 (Biological hypernetwork)**.** A *biological hypernetwork* is a tuple

$$\mathcal{H} = \big(V, \mathcal{E}, \partial, \tau, \rho, \{\lambda_e\}_{e\in\mathcal{E}}, \{s_e\}_{e\in\mathcal{E}}, \sigma, w\big),$$

where

- V is a finite nonempty set of biological entities;
- $\mathcal{E}$ is a finite nonempty set of biological events;
- $\partial : \mathcal{E} \to \mathrm{POWS}(V) \setminus \{\varnothing\}$ assigns a nonempty participant set to each event;
- $\tau : V \to \mathcal{T}$ and $\rho : \mathcal{E} \to \mathcal{I}$ assign entity types and interaction classes;

- $\lambda_e : \partial(e) \to \mathcal{R}$ and $s_e : \partial(e) \to \mathbb{N}_{>0}$ assign roles and positive stoichiometric coefficients;
- $\sigma : \mathcal{E} \to \{-1, 0, +1\}$ and $w : \mathcal{E} \to \mathbb{R}_{\geq 0}$ assign signs and weights.

The map ∂ need not be injective. Consequently, two distinct events may have the same participant set while retaining different directions, labels, signs, or weights.

Remark 2.11 (Identification convention)**.** When ∂ is injective and no ambiguity can arise, an event may be identified notationally with its support. Thus, writing $e = \{u_1, \ldots, u_r\}$ is shorthand for $\partial(e) = \{u_1, \ldots, u_r\}$.

Example 2.12 (Hexokinase reaction)**.** Let

$$V = \{\mathrm{GLC}, \mathrm{ATP}, \mathrm{G6P}, \mathrm{ADP}, \mathrm{HK}, \mathrm{Mg}^{2+}\},$$

with metabolites, protein, and ion typed in the natural way. Let $\mathcal{E} = \{e_{\mathrm{hex}}\}$ and

$$\partial(e_{\mathrm{hex}}) = V, \qquad \rho(e_{\mathrm{hex}}) = \text{reaction}, \qquad \sigma(e_{\mathrm{hex}}) = 0, \qquad w(e_{\mathrm{hex}}) = 1.$$

Assign roles

$$\begin{aligned} &\lambda_{e_{\mathrm{hex}}}(\mathrm{GLC}) = \lambda_{e_{\mathrm{hex}}}(\mathrm{ATP}) = \texttt{reactant}, \\ &\lambda_{e_{\mathrm{hex}}}(\mathrm{G6P}) = \lambda_{e_{\mathrm{hex}}}(\mathrm{ADP}) = \texttt{product}, \\ &\lambda_{e_{\mathrm{hex}}}(\mathrm{HK}) = \texttt{enzyme}, \qquad \lambda_{e_{\mathrm{hex}}}(\mathrm{Mg}^{2+}) = \texttt{cofactor}, \end{aligned}$$

with $s_{e_{\mathrm{hex}}} \equiv 1$. Under the orientation reactant$\mapsto$ in, product$\mapsto$ out, and enzyme/cofactor$\mapsto$ neu, this is a biological hypernetwork.

Example 2.13 (Cooperative transcriptional repression)**.** Let

$$V = \{\mathrm{TFA}, \mathrm{TFB}, \mathrm{HDAC}, \mathrm{G}\}, \qquad \mathcal{E} = \{e_{\mathrm{rep}}\}, \qquad \partial(e_{\mathrm{rep}}) = V.$$

Assign regulator roles to TFA and TFB, a coregulator role to HDAC, and a target role to G. Let regulator/coregulator map to in and target map to out. Taking

$$\rho(e_{\mathrm{rep}}) = \text{multi_regulation}, \qquad \sigma(e_{\mathrm{rep}}) = -1, \qquad w(e_{\mathrm{rep}}) = 2, \qquad s_{e_{\mathrm{rep}}} \equiv 1$$

represents the cooperative event without decomposing it into independent pairwise interactions.

Definition 2.14 (Role-aware directed 2-section)**.** Let $\mathcal{H}$ be a biological hypernetwork. Define

$$\mathcal{E}^{\to} := \{e \in \mathcal{E} : \mathrm{In}(e) \neq \varnothing \text{ and } \mathrm{Out}(e) \neq \varnothing\}.$$

For $e \in \mathcal{E}^{\to}$, put

$$Z_e := |\mathrm{In}(e)|\,|\mathrm{Out}(e)|$$

and define the event-specific contribution

$$c_e(u, v) := \begin{cases} \dfrac{w(e)}{Z_e}, & u \in \mathrm{In}(e),\ v \in \mathrm{Out}(e), \\ 0, & \text{otherwise.} \end{cases}$$

For $(u, v) \in V \times V$, let

$$\mathcal{E}_{uv} := \{e \in \mathcal{E}^{\to} : u \in \mathrm{In}(e),\ v \in \mathrm{Out}(e)\}.$$

The role-aware directed 2-section is

$$\mathcal{G}_\pi(\mathcal{H}) = (V, A_{\to}, \tau, \rho_{\to}, \sigma_{\to}, w_{\to}),$$

where

$$A_{\to} := \{(u, v) : \mathcal{E}_{uv} \neq \varnothing\}, \qquad w_{\to}(u, v) := \sum_{e \in \mathcal{E}_{uv}} c_e(u, v),$$

$$q_{\to}(u,v) := \sum_{e \in \mathcal{E}_{uv}} \sigma(e) c_e(u,v), \qquad \sigma_{\to}(u,v) := \operatorname{sgn}(q_{\to}(u,v)).$$

For $a \in \rho(\mathcal{E}_{uv})$, define

$$W_a(u,v) := \sum_{\substack{e \in \mathcal{E}_{uv} \\ \rho(e)=a}} c_e(u,v).$$

Then $\rho_{\to}(u,v)$ is the $\preceq$-least element of

$$\arg\max_{a \in \rho(\mathcal{E}_{uv})} W_a(u,v).$$

Because $\mathrm{In}(e) \cap \mathrm{Out}(e) = \varnothing$, the projected network is loopless. The fixed tie-breaking order makes every projected annotation well-defined.

Proposition 2.15 (Eventwise weight conservation)**.** *For every $e \in \mathcal{E}^{\to}$,*

$$\sum_{u \in \mathrm{In}(e)} \sum_{v \in \mathrm{Out}(e)} c_e(u,v) = w(e).$$

Proof. There are exactly $Z_e = |\mathrm{In}(e)|\,|\mathrm{Out}(e)|$ ordered pairs in $\mathrm{In}(e) \times \mathrm{Out}(e)$, and each receives the contribution $w(e)/Z_e$. □

Example 2.16 (Directed 2-section of a regulatory hypernetwork)**.** Let

$$V = \{\mathrm{TF1}, \mathrm{TF2}, \mathrm{TF3}, \mathrm{G1}, \mathrm{G2}\}, \qquad \mathcal{E} = \{e_{\mathrm{act}}, e_{\mathrm{rep}}\},$$

with

$$\partial(e_{\mathrm{act}}) = \{\mathrm{TF1}, \mathrm{TF2}, \mathrm{G1}, \mathrm{G2}\}, \qquad \partial(e_{\mathrm{rep}}) = \{\mathrm{TF3}, \mathrm{G2}\}.$$

Let

$$\mathrm{In}(e_{\mathrm{act}}) = \{\mathrm{TF1}, \mathrm{TF2}\}, \quad \mathrm{Out}(e_{\mathrm{act}}) = \{\mathrm{G1}, \mathrm{G2}\},$$
$$\mathrm{In}(e_{\mathrm{rep}}) = \{\mathrm{TF3}\}, \qquad \mathrm{Out}(e_{\mathrm{rep}}) = \{\mathrm{G2}\}.$$

Take

$$w(e_{\mathrm{act}}) = 3, \quad \sigma(e_{\mathrm{act}}) = +1, \quad w(e_{\mathrm{rep}}) = 1.5, \quad \sigma(e_{\mathrm{rep}}) = -1.$$

Then $Z_{e_{\mathrm{act}}} = 4$ and $Z_{e_{\mathrm{rep}}} = 1$. Hence the first event contributes weight 0.75 to each of

$$(\mathrm{TF1}, \mathrm{G1}), (\mathrm{TF1}, \mathrm{G2}), (\mathrm{TF2}, \mathrm{G1}), (\mathrm{TF2}, \mathrm{G2}),$$

and the second contributes weight 1.5 to $(\mathrm{TF3}, \mathrm{G2})$. Eventwise conservation gives $4(0.75) = 3$ and $1(1.5) = 1.5$.

Theorem 2.17 (Underlying support hypergraph)**.** *Let $\mathcal{H}$ be a biological hypernetwork and define*

$$E_{\mathrm{supp}} := \{\partial(e) : e \in \mathcal{E}\}.$$

Then (V, E_{supp}) is a hypergraph. If ∂ is not injective, this support hypergraph forgets the multiplicity and annotations of events having the same support.

Proof. For every $e \in \mathcal{E}$, $\partial(e)$ is a nonempty subset of V. Hence $E_{\mathrm{supp}} \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\}$. □

Theorem 2.18 (Biological hypernetworks strictly generalize biological networks)**.** *Every biological network can be embedded into a biological hypernetwork so that its role-aware directed 2-section is exactly the original network. The inclusion is proper because biological hypernetworks may contain events with support size greater than two.*

Proof. Let $\mathcal{G} = (V, A, \tau, \rho, \sigma, w)$ be a biological network. Set $\mathcal{E} := A$ and, for each event $e = (u, v) \in A$, define

$$\partial(e) := \{u, v\}, \qquad \lambda_e(u) = \texttt{source}, \qquad \lambda_e(v) = \texttt{target},$$

where $\pi(\texttt{source}) = \text{in}$ and $\pi(\texttt{target}) = \text{out}$. Let $s_e \equiv 1$ and retain the same $\rho(e)$, $\sigma(e)$, and $w(e)$. Distinct antiparallel arcs remain distinct events even though they have the same unordered support. For every $e = (u, v)$, $Z_e = 1$, and e contributes only the arc (u, v) with its original annotations. Therefore $\mathcal{G}_\pi(\mathcal{H}) = \mathcal{G}$.

To see that the inclusion is proper, take an event e with $|\partial(e)| \geq 3$. Such an event is a genuine multiway object and is not itself an arc of a pairwise network. □

Proposition 2.19 (Undirected clique 2-section)**.** *Let*

$$\mathcal{E}_{\geq 2} := \{e \in \mathcal{E} : |\partial(e)| \geq 2\}.$$

Define

$$F_c := \left\{\{u, v\} \in \tbinom{V}{2} : \exists e \in \mathcal{E}_{\geq 2},\ \{u, v\} \subseteq \partial(e)\right\}$$

and

$$c_e^{\mathrm{u}}(\{u, v\}) := \begin{cases} \dfrac{w(e)}{\binom{|\partial(e)|}{2}}, & \{u, v\} \subseteq \partial(e), \\ 0, & \textit{otherwise}, \end{cases}$$

$$w_c(\{u, v\}) := \sum_{e \in \mathcal{E}_{\geq 2}} c_e^{\mathrm{u}}(\{u, v\}).$$

Then (V, F_c, w_c) is a weighted simple graph. Moreover, conservation holds eventwise and globally:

$$\sum_{\{u,v\} \in \binom{\partial(e)}{2}} c_e^{\mathrm{u}}(\{u, v\}) = w(e) \quad (e \in \mathcal{E}_{\geq 2}),$$

$$\sum_{f \in F_c} w_c(f) = \sum_{e \in \mathcal{E}_{\geq 2}} w(e).$$

In general, $\sum_{f \in \binom{\partial(e)}{2}} w_c(f)$ need not equal $w(e)$, because w_c also contains contributions from other overlapping events.

Proof. The first identity follows because $\partial(e)$ induces exactly $\binom{|\partial(e)|}{2}$ unordered pairs. The global identity follows by interchanging the two finite sums. □

2.3 Biological superhypernetworks

A biological superhypernetwork retains hierarchical groupings of biological entities while allowing biological events to couple those groupings.

Definition 2.20 (Level-indexed flattening)**.** Let V_0 be a finite nonempty base set. Define maps

$$\mathrm{flat}_n : \mathrm{POWS}^n(V_0) \to \mathrm{POWS}(V_0) \qquad (n \geq 0)$$

recursively by

$$\mathrm{flat}_0(u) := \{u\} \quad (u \in V_0),$$

$$\mathrm{flat}_{n+1}(X) := \bigcup_{Y \in X} \mathrm{flat}_n(Y) \quad \big(X \in \mathrm{POWS}^{n+1}(V_0)\big).$$

The admissible nondegenerate n-supervertices are

$$\mathfrak{B}_n(V_0) := \{X \in \mathrm{POWS}^n(V_0) : \mathrm{flat}_n(X) \neq \varnothing\}.$$

Definition 2.21 (Biological superhypernetwork at level n)**.** Fix $n \geq 1$. A *biological superhypernetwork at level n* is a tuple

$$\mathcal{SH}^{(n)} = \big(V, \mathcal{E}, \partial_n, \tau, \rho, \{\lambda_e\}_{e\in\mathcal{E}}, \{s_e\}_{e\in\mathcal{E}}, \sigma, w\big),$$

where

- $\varnothing \neq V \subseteq \mathfrak{V}_n(V_0)$ is a finite set of n-supervertices;
- $\mathcal{E}$ is a finite nonempty set of hierarchical biological events;
- $\partial_n : \mathcal{E} \to \mathrm{POWS}(V) \setminus \{\varnothing\}$ assigns a nonempty set of n-supervertices to each event;
- the base support of e is

$$\mathrm{supp}_0(e) := \bigcup_{X\in\partial_n(e)} \mathrm{flat}_n(X) \subseteq V_0;$$

- $\tau : V_0 \to \mathcal{T}$ and $\rho : \mathcal{E} \to \mathcal{I}$ assign base-entity types and event classes;
- $\lambda_e : \mathrm{supp}_0(e) \to \mathcal{R}$ and $s_e : \mathrm{supp}_0(e) \to \mathbb{N}_{>0}$ assign base-level roles and stoichiometry;
- $\sigma : \mathcal{E} \to \{-1, 0, +1\}$ and $w : \mathcal{E} \to \mathbb{R}_{\geq 0}$ assign signs and weights.

Since every $X \in V$ has nonempty flattening and $\partial_n(e)$ is nonempty, every base support $\mathrm{supp}_0(e)$ is nonempty.

For $e \in \mathcal{E}$, define $\mathrm{In}(e)$, $\mathrm{Out}(e)$, and $\mathrm{Neu}(e)$ on $\mathrm{supp}_0(e)$ by the same role-orientation rule as in the biological-hypernetwork case.

Remark 2.22 (Incidence signature)**.** For $e \in \mathcal{E}$, define $\eta_e \in \mathbb{Z}^{V_0}$ by

$$\eta_e(u) = \begin{cases} -s_e(u), & u \in \mathrm{In}(e), \\ +s_e(u), & u \in \mathrm{Out}(e), \\ 0, & u \notin \mathrm{In}(e) \cup \mathrm{Out}(e). \end{cases}$$

Because neutral entities receive coefficient zero,

$$\mathrm{supp}(\eta_e) = \mathrm{In}(e) \cup \mathrm{Out}(e),$$

not necessarily the full base support $\mathrm{supp}_0(e)$.

Definition 2.23 (Projection to a biological hypernetwork)**.** The *base-support projection* of $\mathcal{SH}^{(n)}$ is

$$\Pi_{n\to 0}(\mathcal{SH}^{(n)}) := \big(V_0, \mathcal{E}, \partial_0, \tau, \rho, \{\lambda_e\}, \{s_e\}, \sigma, w\big),$$

where

$$\partial_0(e) := \mathrm{supp}_0(e) \qquad (e \in \mathcal{E}).$$

No event aggregation is performed: distinct hierarchical events remain distinct even when they have the same flattened support.

Definition 2.24 (Base-layer role-aware directed 2-section)**.** Define

$$\mathcal{G}_\pi(\mathcal{SH}^{(n)}) := \mathcal{G}_\pi\big(\Pi_{n\to 0}(\mathcal{SH}^{(n)})\big),$$

where the right-hand side is the role-aware directed 2-section from Definition 2.14.

Example 2.25 (Transcriptional activation with complexes and promoter sets ($n = 2$))**.** Let

$$V_0 = \{\mathrm{TF1}, \mathrm{TF2}, \mathrm{MED}, \mathrm{G1}, \mathrm{G2}\}.$$

Define level-1 sets

$$L_{\mathrm{dim}} = \{\mathrm{TF1}, \mathrm{TF2}\}, \quad L_{\mathrm{med}} = \{\mathrm{MED}\}, \quad L_{\mathrm{prom}} = \{\mathrm{G1}, \mathrm{G2}\},$$

and level-2 supervertices

$$v_{\mathrm{mach}} = \{L_{\mathrm{dim}}, L_{\mathrm{med}}\}, \qquad v_{\mathrm{prom}} = \{L_{\mathrm{prom}}\}.$$

Let

$$V = \{v_{\mathrm{mach}}, v_{\mathrm{prom}}\}, \qquad \mathcal{E} = \{e\}, \qquad \partial_2(e) = \{v_{\mathrm{mach}}, v_{\mathrm{prom}}\}.$$

Then

$$\mathrm{supp}_0(e) = \{\mathrm{TF1}, \mathrm{TF2}, \mathrm{MED}, \mathrm{G1}, \mathrm{G2}\}.$$

Assign regulator roles to TF1, TF2, MED and target roles to G1, G2, with

$$w(e) = 2.4, \qquad \sigma(e) = +1.$$

Thus $Z_e = 3 \cdot 2 = 6$, and the base-layer 2-section assigns event-specific contribution $2.4/6 = 0.4$ to each regulator-to-target arc.

Example 2.26 (Paracrine signaling between cell clusters ($n = 2$))**.** Let

$$V_0 = \{\mathrm{M1}, \mathrm{M2}, \mathrm{T1}, \mathrm{T2}, \mathrm{IL6}, \mathrm{TNF}, \mathrm{IL6R}, \mathrm{TNFR}\}.$$

Put

$$C_M = \{\mathrm{M1}, \mathrm{M2}\}, \quad C_T = \{\mathrm{T1}, \mathrm{T2}\}, \quad L = \{\mathrm{IL6}, \mathrm{TNF}\}, \quad R = \{\mathrm{IL6R}, \mathrm{TNFR}\},$$
$$v_{\mathrm{src}} = \{C_M, L\}, \qquad v_{\mathrm{dst}} = \{C_T, R\}.$$

Let

$$V = \{v_{\mathrm{src}}, v_{\mathrm{dst}}\}, \quad \mathcal{E} = \{e_{\mathrm{signal}}\}, \quad \partial_2(e_{\mathrm{signal}}) = \{v_{\mathrm{src}}, v_{\mathrm{dst}}\}.$$

Assign source roles to $\{\mathrm{M1}, \mathrm{M2}, \mathrm{IL6}, \mathrm{TNF}\}$ and target roles to $\{\mathrm{T1}, \mathrm{T2}, \mathrm{IL6R}, \mathrm{TNFR}\}$. If $w(e_{\mathrm{signal}}) = 1.6$, then $Z_{e_{\mathrm{signal}}} = 16$, and each source-to-target pair receives event-specific contribution 0.1.

Example 2.27 (Metabolic step with neutral enzyme and cofactor ($n = 1$))**.** Let

$$v_{\mathrm{in}} = \{\mathrm{GLC}, \mathrm{ATP}, \mathrm{HK}, \mathrm{Mg}^{2+}\}, \qquad v_{\mathrm{out}} = \{\mathrm{G6P}, \mathrm{ADP}\},$$
$$V = \{v_{\mathrm{in}}, v_{\mathrm{out}}\}, \qquad \mathcal{E} = \{e\}, \qquad \partial_1(e) = \{v_{\mathrm{in}}, v_{\mathrm{out}}\}.$$

Take

$$\mathrm{In}(e) = \{\mathrm{GLC}, \mathrm{ATP}\}, \quad \mathrm{Out}(e) = \{\mathrm{G6P}, \mathrm{ADP}\}, \quad \mathrm{Neu}(e) = \{\mathrm{HK}, \mathrm{Mg}^{2+}\},$$

with $w(e) = 2$ and $\sigma(e) = 0$. Then $Z_e = 4$, so each of the four reactant-to-product arcs receives event-specific contribution 0.5. The neutral entities remain vertices of the base-layer network but generate no directed pairs for this event.

Theorem 2.28 (Underlying SuperHyperGraph structure)**.** *Let $\mathcal{SH}^{(n)}$ be a biological superhypernetwork and define*

$$E^{(n)}_{\mathrm{supp}} := \{\partial_n(e) : e \in \mathcal{E}\}.$$

Then $(V, E^{(n)}_{\mathrm{supp}})$ is an n-SuperHyperGraph over V_0.

Proof. By Definition 2.21, $\varnothing \neq V \subseteq \mathrm{POWS}^n(V_0)$ and every $\partial_n(e)$ is a nonempty subset of V. Therefore $\varnothing \neq E^{(n)}_{\mathrm{supp}} \subseteq \mathrm{POWS}(V) \setminus \{\varnothing\}$. □

Theorem 2.29 (Well-defined base-support projection)**.** *For every biological superhypernetwork $\mathcal{SH}^{(n)}$, the object $\Pi_{n\to 0}(\mathcal{SH}^{(n)})$ is a biological hypernetwork.*

Proof. For each event e, the set $\partial_n(e)$ is nonempty and consists of admissible supervertices with nonempty flattenings. Hence $\partial_0(e) = \mathrm{supp}_0(e)$ is a nonempty subset of V_0. All remaining maps already have the domains and codomains required by Definition 2.10. □

Theorem 2.30 (Biological superhypernetworks generalize biological hypernetworks)**.** *Every biological hypernetwork is the exact base-support projection of a level-*1 *biological superhypernetwork. Moreover, the projection is generally not injective, because distinct hierarchical groupings may have the same flattening.*

Proof. Let

$$\mathcal{H} = (V_0, \mathcal{E}, \partial, \tau, \rho, \{\lambda_e\}, \{s_e\}, \sigma, w)$$

be a biological hypernetwork. Define

$$V := \{\{v\} : v \in V_0\} \subseteq \mathrm{POWS}(V_0)$$

and, for each $e \in \mathcal{E}$,

$$\partial_1(e) := \{\{v\} : v \in \partial(e)\}.$$

Then

$$\mathrm{supp}_0(e) = \bigcup_{\{v\} \in \partial_1(e)} \mathrm{flat}_1(\{v\}) = \partial(e).$$

Keeping all annotations unchanged gives a level-1 biological superhypernetwork whose projection is exactly $\mathcal{H}$.

For noninjectivity, let $V_0 = \{a, b\}$. The distinct level-2 objects

$$X = \big\{\{a\}, \{b\}\big\}, \qquad Y = \big\{\{a, b\}\big\}$$

satisfy $\mathrm{flat}_2(X) = \mathrm{flat}_2(Y) = \{a, b\}$. Thus flattening may erase hierarchical structure. □

Corollary 2.31 (Biological superhypernetworks generalize biological networks)**.** *Every biological network is the base-layer directed* 2*-section of a biological superhypernetwork.*

Proof. First apply Theorem 2.18 to embed the biological network into a biological hypernetwork. Then apply Theorem 2.30 to embed that hypernetwork into a level-1 biological superhypernetwork. The two projections recover the original network exactly. □

3 Application Examples

The following examples illustrate the preceding definitions. The numerical weights are illustrative model parameters rather than experimentally estimated constants.

Example 3.1 (Biological network: JAK–STAT antiviral response)**.** Let

$$V = \{\mathrm{IFN}\alpha, \mathrm{IFNAR}, \mathrm{JAK1}, \mathrm{TYK2}, \mathrm{STAT1}, \mathrm{STAT2}, \mathrm{IRF9}, \mathrm{ISG}\}.$$

Assign type protein to all vertices except ISG, which is typed as a gene-program node. Let

$$\begin{aligned} A = \{&(\mathrm{IFN}\alpha, \mathrm{IFNAR}), (\mathrm{IFNAR}, \mathrm{JAK1}), (\mathrm{IFNAR}, \mathrm{TYK2}),\\ &(\mathrm{JAK1}, \mathrm{STAT1}), (\mathrm{TYK2}, \mathrm{STAT2}), (\mathrm{STAT1}, \mathrm{ISG}),\\ &(\mathrm{STAT2}, \mathrm{ISG}), (\mathrm{IRF9}, \mathrm{ISG})\}. \end{aligned}$$

Take $\rho \equiv$ regulates and $\sigma \equiv +1$. Define the weights in the displayed arc order by

$$(0.95, 0.90, 0.85, 0.88, 0.86, 0.60, 0.40, 0.20).$$

The illustrative total incoming weight at ISG is

$$0.60 + 0.40 + 0.20 = 1.20.$$

Example 3.2 (Biological network: p53 stress response)**.** Let

$$V = \{\text{DNA_damage}, \text{ATM}, \text{TP53}, \text{MDM2}, \text{p21}\},$$

where DNA_damage is a signal node, ATM, TP53, and MDM2 are proteins, and p21 is a gene-product node. Let

$$A = \{(\text{DNA_damage}, \text{ATM}), (\text{ATM}, \text{TP53}), (\text{TP53}, \text{MDM2}),$$
$$(\text{MDM2}, \text{TP53}), (\text{TP53}, \text{p21})\}.$$

Assign signs $(+1, +1, +1, -1, +1)$ and weights $(0.90, 0.80, 0.75, 0.85, 0.85)$ in this order. The multiplicative path score along

$$\text{DNA_damage} \to \text{ATM} \to \text{TP53} \to \text{p21}$$

is

$$0.90 \cdot 0.80 \cdot 0.85 = 0.612.$$

This product is an illustrative path score; it is not asserted to be a universal biochemical law.

Example 3.3 (Biological hypernetwork: extrinsic tenase event)**.** Let

$$V = \{\text{TF}, \text{FVIIa}, \text{FX}, \text{FXa}, \text{Ca}^{2+}, \text{PL}\}, \qquad \mathcal{E} = \{e\}, \qquad \partial(e) = V.$$

Assign

$$\text{In}(e) = \{\text{FX}\}, \qquad \text{Out}(e) = \{\text{FXa}\}, \qquad \text{Neu}(e) = \{\text{TF}, \text{FVIIa}, \text{Ca}^{2+}, \text{PL}\}.$$

Let $\rho(e) = \text{reaction}$, $\sigma(e) = +1$, $w(e) = 2.50$, and $s_e \equiv 1$. Since $Z_e = 1$, the role-aware directed 2-section receives the single event-specific contribution

$$c_e(\text{FX}, \text{FXa}) = 2.50.$$

Example 3.4 (Biological hypernetwork: multiplex CRISPR editing)**.** Let

$$V = \{\text{GeneA}, \text{GeneB}, \Delta\text{A}, \Delta\text{B}, \Delta\text{AB}, \text{Cas9}, \text{gA}, \text{gB}, \text{NHEJ}\},$$
$$\mathcal{E} = \{e\}, \qquad \partial(e) = V.$$

Set

$$\text{In}(e) = \{\text{GeneA}, \text{GeneB}\}, \quad \text{Out}(e) = \{\Delta\text{A}, \Delta\text{B}, \Delta\text{AB}\},$$
$$\text{Neu}(e) = \{\text{Cas9}, \text{gA}, \text{gB}, \text{NHEJ}\}.$$

If $w(e) = 1.80$, then $Z_e = 2 \cdot 3 = 6$, and each of the six input-to-output pairs receives event-specific contribution 0.30. Proposition 2.15 gives $6(0.30) = 1.80$.

Example 3.5 (Biological superhypernetwork: checkpoint immunotherapy ($n = 2$))**.** Let

$$V_0 = \{\text{antiPD1}, \text{antiCTLA4}, \text{PD1}, \text{PD-L1}, \text{CD8T}, \text{DC}, \text{Tumor}\}.$$

Define

$$T = \{\text{antiPD1}, \text{antiCTLA4}\}, \quad I = \{\text{PD1}, \text{PD-L1}\}, \quad C = \{\text{CD8T}, \text{DC}\}, \quad U = \{\text{Tumor}\},$$
$$v_{\text{therapy}} = \{T, I\}, \quad v_{\text{immune}} = \{C\}, \quad v_{\text{tumor}} = \{U\}.$$

Let

$$V = \{v_{\text{therapy}}, v_{\text{immune}}, v_{\text{tumor}}\}, \qquad \mathcal{E} = \{e_1, e_2\},$$
$$\partial_2(e_1) = \{v_{\text{therapy}}, v_{\text{immune}}\}, \qquad \partial_2(e_2) = \{v_{\text{immune}}, v_{\text{tumor}}\}.$$

For e_1, take

$$\text{In}(e_1) = \{\text{antiPD1}, \text{antiCTLA4}\}, \quad \text{Out}(e_1) = \{\text{CD8T}, \text{DC}\}, \quad \text{Neu}(e_1) = \{\text{PD1}, \text{PD-L1}\},$$

with $w(e_1) = 1.20$. Each of its four directed pairs receives 0.30. For e_2, take

$$\text{In}(e_2) = \{\text{CD8T}, \text{DC}\}, \qquad \text{Out}(e_2) = \{\text{Tumor}\}, \qquad w(e_2) = 0.60.$$

Each of its two directed pairs receives 0.30.

Example 3.6 (Biological superhypernetwork: multi-omics diagnostic pipeline ($n = 2$))**.** Let

$$V_0 = \{\text{Sample}, \text{BRCA1}, \text{BRCA2}, \text{TP53}, \text{CA125}, \text{HE4}, \text{Lactate}, \text{Pyruvate}, \text{Dx}\}.$$

Put

$$G = \{\text{BRCA1}, \text{BRCA2}, \text{TP53}\}, \quad P = \{\text{CA125}, \text{HE4}\}, \quad M = \{\text{Lactate}, \text{Pyruvate}\},$$

$$S = \{\text{Sample}\}, \quad D = \{\text{Dx}\}, \quad v_{\text{assay}} = \{G, P, M\}, \quad v_{\text{specimen}} = \{S\}, \quad v_{\text{report}} = \{D\}.$$

Let

$$V = \{v_{\text{specimen}}, v_{\text{assay}}, v_{\text{report}}\}, \qquad \mathcal{E} = \{e_1, e_2\},$$

$$\partial_2(e_1) = \{v_{\text{specimen}}, v_{\text{assay}}\}, \qquad \partial_2(e_2) = \{v_{\text{assay}}, v_{\text{report}}\}.$$

For e_1, take

$$\text{In}(e_1) = \{\text{Sample}\}, \qquad \text{Out}(e_1) = G \cup P \cup M, \qquad w(e_1) = 2.10.$$

For e_2, take

$$\text{In}(e_2) = G \cup P \cup M, \qquad \text{Out}(e_2) = \{\text{Dx}\}, \qquad w(e_2) = 2.10.$$

Both events have normalizer 7, so every generated base-layer pair receives event-specific contribution 0.30.

4 Conclusion

This paper formulated biological networks, biological hypernetworks, and biological superhypernetworks within one consistent event-indexed framework. Biological networks encode pairwise directed interactions, biological hypernetworks retain genuinely multiway events, and biological superhypernetworks additionally preserve nested organization through level-indexed supervertices. The support and flattening projections show precisely how the three model classes are related, while the event-indexed incidence maps prevent distinct reactions or reciprocal interactions from being inadvertently identified.

Future research may investigate fuzzy graphs [29, 30], intuitionistic fuzzy graphs [31, 32], neutrosophic graphs [33–35], picture fuzzy graphs [36], and plithogenic graphs [37, 38], together with algorithmic, statistical, and data-driven validation on biological datasets.

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Conflicts of Interest

The authors confirm that there are no conflicts of interest related to the research or its publication.

Code Availability

No code or software was developed for this study.

Use of Generative AI and AI-Assisted Tools

Generative AI and AI-assisted tools were used for tasks such as English grammar checking. These tools were not used in any manner that violates ethical standards.

Disclaimer

This work presents theoretical concepts that have not yet undergone practical testing or validation. Future researchers are encouraged to apply and assess these ideas in empirical contexts. While every effort has been made to ensure accuracy and appropriate referencing, unintentional errors or omissions may still exist. Readers are advised to verify referenced materials on their own. The views and conclusions expressed here are the authors' own and do not necessarily reflect those of their affiliated organizations.

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