TRANSITUS

Received
December 19, 2025

Revised
January 10, 2026

Accepted
January 15, 2026

Published
January 27, 2026

Keywords
MetaGraph, Iterated MetaGraph, Molecular MetaGraph, Molecular Iterated MetaGraph.

Molecular MetaGraph and Molecular Iterated MetaGraph in Chemistry and BioChemistry

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DOI/url: https://journalmanager.transitus.in/index.php/jamss

Abstract

Graph theory investigates mathematical structures consisting of vertices and edges, providing a foundation for modeling relationships and connectivity. A *MetaGraph* is a higher-level graph in which the vertices are themselves graphs, with edges representing specified relations among these graphs. An *Iterated MetaGraph* extends this concept recursively: its vertices are MetaGraphs, thereby forming a hierarchy of graph-of-graphs structures across multiple levels. In this paper, we introduce two new extensions, the *Molecular MetaGraph* and the *Molecular Iterated MetaGraph*, which generalize the concept of molecular graphs through the frameworks of MetaGraphs and Iterated MetaGraphs. Furthermore, we provide illustrative applications of these models in biochemistry. These applications demonstrate how an iterative, meta-level perspective can be applied to molecular graphs, offering new insights into biochemical structures and processes.

1 Preliminaries

This section presents the fundamental concepts and definitions that underpin the discussions in this paper. Unless otherwise noted, all graphs considered here are *finite*.

1.1 MetaGraph(Graph of Graph)

Graph theory investigates mathematical structures consisting of vertices and edges to model relationships and connectivity [1,2]. A MetaGraph is a graph whose vertices are themselves graphs, with edges representing specified relations between those graphs (cf. [3–5]).

Definition 1.1 (Metagraph (graph of graphs))**.** (cf. [6]) Fix a nonempty universe $\mathfrak{G}$ of finite graphs (undirected, loopless by default) and a nonempty family of binary relations

$$\mathcal{R} \subseteq \mathcal{P}\big(\mathfrak{G} \times \mathfrak{G}\big).$$

A *metagraph over* $(\mathfrak{G}, \mathcal{R})$ is a directed, labelled multigraph

$$M = (V, E, s, t, \lambda)$$

with

$$V \subseteq \mathfrak{G}, \qquad s, t : E \to V, \qquad \lambda : E \to \mathcal{R},$$

satisfying the incidence constraint

$$\forall e \in E : \ \big(s(e),\, t(e)\big) \in \lambda(e).$$

Elements of V are *meta-vertices* (each is a graph $G \in \mathfrak{G}$). For $e \in E$ with $\lambda(e) = R$, we write $s(e) \xrightarrow{R} t(e)$ and call e a *meta-edge*. If $\mathcal{R} = \{R\}$ is a singleton, labels may be omitted. If every $R \in \mathcal{R}$ is symmetric, M can be viewed as an undirected labelled multigraph.

Remark 1.2. We fix a common base universe $\mathfrak{G}$ of finite, loopless graphs that encode biochemical modules. Each $G \in \mathfrak{G}$ comes with a vertex-labeling $\ell_V : V(G) \to \Sigma_V$ (e.g. metabolite/protein/gene names) and, when needed, an edge-labeling $\ell_E : E(G) \to \Sigma_E$ (e.g. reaction/interaction types). We use the following chemically meaningful binary relations on $\mathfrak{G}$:

$$\begin{aligned}
R_{\text{shareM}}(G,H) &:\iff \{\text{metabolite names in } G\} \cap \{\text{metabolite names in } H\} \neq \emptyset,\\
R_{\text{shareP}}(G,H) &:\iff \{\text{protein names in } G\} \cap \{\text{protein names in } H\} \neq \emptyset,\\
R_{\text{GRN}\Delta}(G,H) &:\iff E(G) \triangle E(H) \neq \emptyset \quad \text{(directed GRNs; activation/inhibition labels allowed).}
\end{aligned}$$

Set $\mathcal{R} := \{R_{\text{shareM}}, R_{\text{shareP}}, R_{\text{GRN}\Delta}\}$.

Each example specifies a metagraph $\mathsf{M} = (V, E, s, t, \lambda)$ over $(\mathfrak{G}, \mathcal{R})$ and verifies the incidence constraint.

Example 1.3 (Metabolic module metagraph: glycolysis–link–TCA)**.** Let the pathway graphs be

$$\begin{aligned}
G_{\text{Gly}} &: \ V = \{\text{Glc}, \text{G6P}, \text{F6P}, \text{Pyr}\},\ E = \{\text{Glc} \to \text{G6P},\ \text{G6P} \to \text{F6P},\ \text{F6P} \to \text{Pyr}\},\\
G_{\text{PDH}} &: \ V = \{\text{Pyr}, \text{AcCoA}, \text{CO}_2\},\ E = \{\text{Pyr} \to \text{AcCoA}\},\\
G_{\text{TCA}} &: \ V = \{\text{AcCoA}, \text{OAA}, \text{Citrate}, \text{Succinate}, \text{Malate}\},\ E = \{\text{AcCoA} + \text{OAA} \to \text{Citrate},\ \ldots\}.
\end{aligned}$$

Define the metagraph $\mathsf{M}_{\text{metab}}$ by

$$V = \{G_{\text{Gly}}, G_{\text{PDH}}, G_{\text{TCA}}\}, \qquad E = \{e_1, e_2\},$$

$$s(e_1) = G_{\text{Gly}},\ t(e_1) = G_{\text{PDH}},\ \lambda(e_1) = R_{\text{shareM}} \quad \text{(witness Pyr)},$$

$$s(e_2) = G_{\text{PDH}},\ t(e_2) = G_{\text{TCA}},\ \lambda(e_2) = R_{\text{shareM}} \quad \text{(witness AcCoA)}.$$

For each $e \in E$, $(s(e), t(e)) \in \lambda(e)$ by the indicated shared metabolite, so the incidence constraint holds.

Example 1.4 (Protein-complex metagraph: shared subunits)**.** Let simple complex graphs be

$$G_{\mathrm{CplxA}}:\ V=\{E_1,E_2\},\ E=\big\{\{E_1,E_2\}\big\},$$
$$G_{\mathrm{CplxB}}:\ V=\{E_2,E_3\},\ E=\big\{\{E_2,E_3\}\big\},$$
$$G_{\mathrm{CplxC}}:\ V=\{E_4\},\ E=\emptyset.$$

Define the metagraph $\mathsf{M}_{\mathrm{cplx}}$ by

$$V=\{G_{\mathrm{CplxA}},G_{\mathrm{CplxB}},G_{\mathrm{CplxC}}\},\quad E=\{e_{AB}\},\quad s(e_{AB})=G_{\mathrm{CplxA}},\ t(e_{AB})=G_{\mathrm{CplxB}},\ \lambda(e_{AB})=R_{\mathrm{shareP}},$$

witnessed by the shared subunit E_2. Then $(s(e_{AB}),t(e_{AB}))\in R_{\mathrm{shareP}}$; no edge is drawn to G_{CplxC} because E_{CplxC} shares no protein.

Example 1.5 (Condition-specific GRN metagraph: differential regulation)**.** Let directed GRNs (edges labeled by $\{\mathrm{act},\mathrm{inh}\}$) be

$$G^{(A)}_{\mathrm{GRN}}:\ V=\{\mathrm{TF1},\mathrm{G1},\mathrm{G2}\},\ E=\{\mathrm{TF1}\xrightarrow{\mathrm{act}}\mathrm{G1},\ \mathrm{TF1}\xrightarrow{\mathrm{act}}\mathrm{G2}\},$$
$$G^{(B)}_{\mathrm{GRN}}:\ V=\{\mathrm{TF1},\mathrm{G1},\mathrm{G2}\},\ E=\{\mathrm{TF1}\xrightarrow{\mathrm{act}}\mathrm{G1}\},$$
$$G^{(C)}_{\mathrm{GRN}}:\ V=\{\mathrm{TF2},\mathrm{G2}\},\ E=\{\mathrm{TF2}\xrightarrow{\mathrm{inh}}\mathrm{G2}\}.$$

Define $\mathsf{M}_{\mathrm{grn}}$ by

$$V=\{G^{(A)}_{\mathrm{GRN}},G^{(B)}_{\mathrm{GRN}},G^{(C)}_{\mathrm{GRN}}\},\quad E=\{e_{AB},e_{AC}\},$$
$$s(e_{AB})=G^{(A)}_{\mathrm{GRN}},\ t(e_{AB})=G^{(B)}_{\mathrm{GRN}},\ \lambda(e_{AB})=R_{\mathrm{GRN}\Delta}\ \ (\text{witness: edge TF1}\to\text{G2 present only in } A),$$
$$s(e_{AC})=G^{(A)}_{\mathrm{GRN}},\ t(e_{AC})=G^{(C)}_{\mathrm{GRN}},\ \lambda(e_{AC})=R_{\mathrm{GRN}\Delta}\ \ (\text{many-edge difference}).$$

Thus $(s(e),t(e))\in\lambda(e)$ for each e, so $\mathsf{M}_{\mathrm{grn}}$ is a valid metagraph.

1.2 Iterated MetaGraph(Graph of Graph of ... of Graph)

An Iterated MetaGraph is a graph whose vertices are metagraphs, recursively extending graph-of-graphs structure to multiple hierarchical levels [7].

Definition 1.6 (Unit metagraph embedding)**.** [7] For $X\in\mathfrak{G}$ define the *unit metagraph*

$$\mathsf{U}(X)\ :=\ \big(\{X\},\emptyset,\_,\_,\_\big).$$

This gives an injective map $\mathsf{U}:\mathfrak{G}\hookrightarrow\mathrm{Obj}\big(\mathrm{Meta}(\mathfrak{G},\mathcal{R})\big)$.

Definition 1.7 (Relation lifting)**.** Given $\mathcal{R}$ on $\mathfrak{G}$, define its *lift* $\mathcal{R}^{\uparrow}$ on finite metagraphs over $(\mathfrak{G},\mathcal{R})$ by

$$\forall R\in\mathcal{R},\quad (M_1,M_2)\in R^{\uparrow}\iff\exists\,x\in V(M_1),\,y\in V(M_2):\ (x,y)\in R.$$

Set $\mathcal{R}^{\uparrow}:=\{R^{\uparrow}:R\in\mathcal{R}\}$.

Definition 1.8 (Iterated object and relation universes)**.** Define recursively for $t\in\mathbb{N}_0$:

$$\mathfrak{G}^{(0)}:=\mathfrak{G},\qquad\mathcal{R}^{(0)}:=\mathcal{R},$$
$$\mathfrak{G}^{(t+1)}:=\Big\{\text{finite metagraphs over }\big(\mathfrak{G}^{(t)},\mathcal{R}^{(t)}\big)\Big\},\qquad\mathcal{R}^{(t+1)}:=\big(\mathcal{R}^{(t)}\big)^{\uparrow}.$$

Definition 1.9 (Iterated MetaGraph of depth t)**.** For $t \in \mathbb{N}_0$, an *iterated metagraph of depth* t is a metagraph

$$M^{(t)} = (V^{(t)}, E^{(t)}, s^{(t)}, t^{(t)}, \lambda^{(t)})$$

over $\big(\mathfrak{G}^{(t)}, \mathcal{R}^{(t)}\big)$, i.e., $V^{(t)} \subseteq \mathfrak{G}^{(t)}$, $\lambda^{(t)} : E^{(t)} \to \mathcal{R}^{(t)}$ and

$$\forall e \in E^{(t)} : \ \big(s^{(t)}(e),\, t^{(t)}(e)\big) \in \lambda^{(t)}(e).$$

Remark 1.10. We use the relation lifting of the preliminaries: for $R \in \mathcal{R}$ and metagraphs $\mathsf{M}_1, \mathsf{M}_2$ over $(\mathfrak{G}, \mathcal{R})$,

$$(\mathsf{M}_1, \mathsf{M}_2) \in R^{\uparrow} \iff \exists X \in V(\mathsf{M}_1),\ \exists Y \in V(\mathsf{M}_2) \text{ such that } (X, Y) \in R.$$

Example 1.11 (Depth $t = 1$: Metabolism vs. complexes, linked by an annotation map)**.** Let $\mathsf{M}_{\text{metab}}$ and M_{cplx} be as above. Define a base cross-relation $R_{\text{annot}} \subseteq \mathfrak{G} \times \mathfrak{G}$ by

$$(G, H) \in R_{\text{annot}} \iff \exists \text{enzyme } E \in V(H) \text{ that catalyzes some edge of } G.$$

(Equivalently, fix an annotation map κ : {enzymes} $\to$ {reactions} and require $\kappa(E) \in E(G)$.) Assume $\kappa(E_1) = \text{G6P} \to \text{F6P}$ (a step in G_{Gly}) and $E_1 \in V(G_{\text{CplxA}})$. Then $(G_{\text{Gly}}, G_{\text{CplxA}}) \in R_{\text{annot}}$. Form the depth-1 metagraph

$$\mathsf{N}_1^{(1)} = \big(\ \{\, \mathsf{M}_{\text{metab}}, \mathsf{M}_{\text{cplx}} \,\},\ \{f\},\ s^{(1)}, t^{(1)}, \lambda^{(1)}\ \big),$$

with $s^{(1)}(f) = \mathsf{M}_{\text{metab}}$, $t^{(1)}(f) = \mathsf{M}_{\text{cplx}}$, and $\lambda^{(1)}(f) = R_{\text{annot}}^{\uparrow}$. By the witness $(G_{\text{Gly}}, G_{\text{CplxA}})$, $(s^{(1)}(f), t^{(1)}(f)) \in \lambda^{(1)}(f)$, so $\mathsf{N}_1^{(1)}$ is valid.

Example 1.12 (Depth $t = 1$: Comparative metabolism across species)**.** Build two organism-specific metagraphs using R_{shareM}:

$$\mathsf{M}_{\text{met}}^{\text{Ec}} :\ V = \{G_{\text{Gly}}^{\text{Ec}}, G_{\text{TCA}}^{\text{Ec}}\},\ E = \big\{G_{\text{Gly}}^{\text{Ec}} \xrightarrow{R_{\text{shareM}}} G_{\text{TCA}}^{\text{Ec}}\big\}$$

with witness metabolite AcCoA (via the explicit PDH-link included in $G_{\text{Gly}}^{\text{Ec}}$), and

$$\mathsf{M}_{\text{met}}^{\text{Sc}} :\ V = \{G_{\text{Gly}}^{\text{Sc}}, G_{\text{TCA}}^{\text{Sc}}\},\ E = \big\{G_{\text{Gly}}^{\text{Sc}} \xrightarrow{R_{\text{shareM}}} G_{\text{TCA}}^{\text{Sc}}\big\}$$

with the same witness. At depth 1, set

$$\mathsf{N}_2^{(1)} = (\{\mathsf{M}_{\text{met}}^{\text{Ec}}, \mathsf{M}_{\text{met}}^{\text{Sc}}\},\ \{g\},\ s^{(1)}, t^{(1)}, \lambda^{(1)}), \quad s^{(1)}(g) = \mathsf{M}_{\text{met}}^{\text{Ec}},\ t^{(1)}(g) = \mathsf{M}_{\text{met}}^{\text{Sc}},\ \lambda^{(1)}(g) = R_{\text{shareM}}^{\uparrow}.$$

Since $G_{\text{TCA}}^{\text{Ec}}$ and $G_{\text{TCA}}^{\text{Sc}}$ both contain the metabolite *Citrate*, $(G_{\text{TCA}}^{\text{Ec}}, G_{\text{TCA}}^{\text{Sc}}) \in R_{\text{shareM}}$, which witnesses $(s^{(1)}(g), t^{(1)}(g)) \in \lambda^{(1)}(g)$.

Example 1.13 (Depth $t = 2$: Linking depth-1 projects by double lift)**.** Let $\mathsf{N}_1^{(1)}$ and $\mathsf{N}_2^{(1)}$ be as above. Consider the depth-2 metagraph

$$\mathsf{Q}^{(2)} = (V^{(2)}, E^{(2)}, s^{(2)}, t^{(2)}, \lambda^{(2)}), \qquad V^{(2)} = \{\mathsf{N}_1^{(1)}, \mathsf{N}_2^{(1)}\},\ E^{(2)} = \{h\}.$$

Define

$$s^{(2)}(h) = \mathsf{N}_1^{(1)}, \quad t^{(2)}(h) = \mathsf{N}_2^{(1)}, \quad \lambda^{(2)}(h) = (R_{\text{shareM}}^{\uparrow})^{\uparrow}.$$

To witness $(s^{(2)}(h), t^{(2)}(h)) \in \lambda^{(2)}(h)$, pick $X = \mathsf{M}_{\text{metab}} \in V(\mathsf{N}_1^{(1)})$ and $Y = \mathsf{M}_{\text{met}}^{\text{Ec}} \in V(\mathsf{N}_2^{(1)})$. Since $G_{\text{TCA}} \in V(X)$ and $G_{\text{TCA}}^{\text{Ec}} \in V(Y)$ share metabolite *Citrate*, we have $(G_{\text{TCA}}, G_{\text{TCA}}^{\text{Ec}}) \in R_{\text{shareM}}$, hence $(X, Y) \in R_{\text{shareM}}^{\uparrow}$, which by definition yields $(s^{(2)}(h), t^{(2)}(h)) \in (R_{\text{shareM}}^{\uparrow})^{\uparrow}$. Thus $\mathsf{Q}^{(2)}$ is a valid depth-2 iterated metagraph.

1.3 Molecular Graph

A *Molecular Graph* models a molecule with atoms as vertices and bonds as edges, thereby representing its structural connectivity [8–10]. Related concepts include the *Molecular HyperGraph* [11,12] and the *Molecular SuperHyperGraph* [13, 14], which provide generalized frameworks for capturing higher-order interactions in molecular structures. Also the related concepts such as Chemical Graphs [15, 16], Neutrosophic Chemical Graphs [17], and Molecular Fuzzy Graphs [18] are also well known.

Definition 1.14 (Molecular Graph)**.** (cf. [19, 20]) A *molecular graph* is a finite, simple, undirected graph $G = (V, E)$ in which each vertex $v \in V$ represents an atom and each edge $e = \{u, v\} \in E$ represents a chemical bond between atoms u and v. (Optionally, vertex/edge labels may encode atom types and bond types or orders.)

Example 1.15 (Water H_2O as a molecular graph)**.** Let

$$V = \{O, H_1, H_2\}, \qquad E = \big\{\{O, H_1\},\ \{O, H_2\}\big\}.$$

Then $G = (V, E)$ is a finite, simple, undirected molecular graph: each vertex represents an atom (oxygen O, hydrogens H_1, H_2) and each edge represents an O–H bond. Optionally, one may add labels

$$\tau(O) = \mathrm{O}, \quad \tau(H_i) = \mathrm{H}\ (i = 1, 2), \qquad \beta(\{O, H_i\}) = \text{single},$$

and the adjacency matrix (ordering O, H_1, H_2) is

$$A = \begin{pmatrix} 0 & 1 & 1 \\ 1 & 0 & 0 \\ 1 & 0 & 0 \end{pmatrix}, \quad \deg(O) = 2,\ \deg(H_1) = \deg(H_2) = 1.$$

2 Main Results of this Paper

This section presents the main results established in this paper.

2.1 Molecular MetaGraph

A Molecular MetaGraph is a higher-level graph where vertices are molecular graphs and edges encode chemically invariant relations among them. We first fix a typed setting for molecules.

Definition 2.1 (Typed molecular graph and type-preserving isomorphism)**.** Let Σ_V be a finite set of *atom types* (e.g. element symbols, hybridizations, charges) and Σ_E a finite set of *bond types* (e.g. single, double, triple, aromatic). A *typed molecular graph* is a quadruple

$$G = (V, E, \tau, \beta),$$

where V is a finite vertex set (atoms), $E \subseteq \binom{V}{2}$ (bonds), $\tau : V \to \Sigma_V$ assigns each atom its type, and $\beta : E \to \Sigma_E$ assigns each bond its type. A bijection $\varphi : V(G) \to V(H)$ between typed molecular graphs G and H is a *type-preserving isomorphism* (notation $G \cong H$) if

$$\{u, v\} \in E(G) \iff \{\varphi(u), \varphi(v)\} \in E(H), \quad \tau_H(\varphi(v)) = \tau_G(v), \quad \beta_H(\{\varphi(u), \varphi(v)\}) = \beta_G(\{u, v\}).$$

Let $\mathfrak{Mol}$ denote the universe of all finite typed molecular graphs (Definition 2.1).

Definition 2.2 (Chemically invariant relations)**.** A binary relation $R \subseteq \mathfrak{Mol} \times \mathfrak{Mol}$ is *chemically invariant* if for all $G, H, G', H' \in \mathfrak{Mol}$,

$$G \cong G' \text{ and } H \cong H' \text{ and } (G, H) \in R \implies (G', H') \in R.$$

Let $\mathcal{R}_{\text{chem}}$ be any nonempty family of chemically invariant relations. Typical examples (not required for the theory) include: substructure (R_{sub}), reaction-step (R_{rxn}), isomer-of (R_{iso}), scaffold-similarity-at-threshold-θ ($R_{\text{sim},\theta}$), etc.

Definition 2.3 (Molecular MetaGraph)**.** A *Molecular MetaGraph over* $(\mathfrak{Mol}, \mathcal{R}_{\text{chem}})$ is a directed, labelled multigraph

$$\mathsf{M} = (V, E, s, t, \lambda)$$

with

$$V \subseteq \mathfrak{Mol}, \qquad s, t : E \to V, \qquad \lambda : E \to \mathcal{R}_{\text{chem}},$$

satisfying the metagraph incidence constraint

$$\forall e \in E : \quad \big(s(e),\, t(e)\big) \in \lambda(e).$$

The elements of V are *meta-vertices* (each is a molecular graph), and each $e \in E$ is a *meta-edge* labelled by a chemical relation $\lambda(e)$ that holds on its endpoints.

Remark 2.4. We use the chemically invariant base relations

$$R_{\text{sub}},\ R_{\text{rxn}},\ R_{\text{iso}},\ R_{\text{sim},\theta},\ R_{\text{eq}} \ \in\ \mathcal{R}_{\text{chem}},$$

where R_{sub} denotes "is a (typed) substructure of," R_{rxn} denotes "reactant-to-product in a fixed elementary step," R_{iso} denotes "constitutional isomers," $R_{\text{sim},\theta}$ denotes "scaffold similarity at threshold θ," and R_{eq} is molecular identity (type-preserving isomorphism). Recall that a Molecular MetaGraph is $\mathsf{M} = (V, E, s, t, \lambda)$ with $V \subseteq \mathfrak{Mol}$ and $\forall e \in E :\ (s(e), t(e)) \in \lambda(e)$.

Example 2.5 (Molecular MetaGraph I: A single-step reaction mini-network (Fischer esterification))**.** Let the molecular vertices be

$$V = \{G_{\text{AA}}, G_{\text{EtOH}}, G_{\text{EA}}, G_{\text{H}_2\text{O}}\},$$

standing for acetic acid (SMILES `CC(=O)O`), ethanol (`CCO`), ethyl acetate (`CCOC(=O)C`), and water (`O`). Define four directed meta-edges encoding reactant→product incidence in the esterification step:

$$E = \{e_1, e_2, e_3, e_4\}, \qquad \begin{aligned} s(e_1) &= G_{\text{AA}},\ t(e_1) = G_{\text{EA}},\ \lambda(e_1) = R_{\text{rxn}},\\ s(e_2) &= G_{\text{EtOH}},\ t(e_2) = G_{\text{EA}},\ \lambda(e_2) = R_{\text{rxn}},\\ s(e_3) &= G_{\text{AA}},\ t(e_3) = G_{\text{H}_2\text{O}},\ \lambda(e_3) = R_{\text{rxn}},\\ s(e_4) &= G_{\text{EtOH}},\ t(e_4) = G_{\text{H}_2\text{O}},\ \lambda(e_4) = R_{\text{rxn}}. \end{aligned}$$

Then $\mathsf{M}_{\text{ester}} = (V, E, s, t, \lambda)$ is a Molecular MetaGraph over $(\mathfrak{Mol}, \mathcal{R}_{\text{chem}})$.

Example 2.6 (Molecular MetaGraph II: Substructure & similarity on simple aromatics)**.** Let

$$V = \{G_{\text{Bz}}, G_{\text{Tol}}, G_{\text{Ph}}\},$$

for benzene (`c1ccccc1`), toluene (`Cc1ccccc1`), and phenol (`Oc1ccccc1`). Define

$$E = \{e_1, e_2, e_3\},$$

with

$$s(e_1) = G_{\mathrm{Bz}},\ t(e_1) = G_{\mathrm{Tol}},\ \lambda(e_1) = R_{\mathrm{sub}},$$
$$s(e_2) = G_{\mathrm{Bz}},\ t(e_2) = G_{\mathrm{Ph}},\ \lambda(e_2) = R_{\mathrm{sub}},$$
$$s(e_3) = G_{\mathrm{Tol}},\ t(e_3) = G_{\mathrm{Ph}},\ \lambda(e_3) = R_{\mathrm{sim},\,0.6}.$$

Interpreting $R_{\mathrm{sim},0.6}$ as "Tanimoto (scaffold) similarity ≥ 0.6," $\mathsf{M}_{\mathrm{arom}} = (V, E, s, t, \lambda)$ is a Molecular MetaGraph in which benzene is a typed substructure of toluene and phenol, and toluene is scaffold-similar to phenol.

Example 2.7 (Molecular MetaGraph III: Constitutional isomers of C_3H_8O)**.** Let

$$V = \{G_{n\text{-PrOH}}, G_{i\text{-PrOH}}, G_{\mathrm{MeOEt}}\},$$

for 1-propanol (`CCCO`), isopropanol (`CC(O)C`), and methoxyethane (`CCOC`). Since R_{iso} is symmetric, we realize it as a bidirected triangle:

$$E = \{e_{12}, e_{21}, e_{13}, e_{31}, e_{23}, e_{32}\},$$

where, writing $(1, 2, 3) = (n\text{-PrOH}, i\text{-PrOH}, \mathrm{MeOEt})$,

$$s(e_{ij}) = G_i, \quad t(e_{ij}) = G_j, \quad \lambda(e_{ij}) = R_{\mathrm{iso}} \quad (i \neq j).$$

Then $\mathsf{M}_{\mathrm{isoC3H8O}} = (V, E, s, t, \lambda)$ is a Molecular MetaGraph whose meta-edges encode isomerism.

Theorem 2.8 (Every Molecular MetaGraph is a MetaGraph)**.** *With $\mathfrak{G} := \mathfrak{Mol}$ and $\mathcal{R} := \mathcal{R}_{\mathrm{chem}}$, every structure M as in Definition 2.3 is a metagraph over $(\mathfrak{G}, \mathcal{R})$ in the sense of the preliminaries.*

Proof. Comparing Definition 2.3 with the metagraph schema $M = (V, E, s, t, \lambda)$, we must verify $V \subseteq \mathfrak{G}$, $s, t : E \to V$, $\lambda : E \to \mathcal{R}$, and the incidence condition $\big(s(e), t(e)\big) \in \lambda(e)$ for all $e \in E$. By construction, $V \subseteq \mathfrak{Mol} = \mathfrak{G}$, s, t, λ have the required codomains, and the last property is explicitly imposed in Definition 2.3. Therefore M is a metagraph over $(\mathfrak{G}, \mathcal{R})$. □

Next we show that Molecular MetaGraphs *generalize* ordinary molecular graphs by a faithful embedding that preserves all atom and bond information.

Definition 2.9 (Atomic one-vertex templates)**.** For each $a \in \Sigma_V$, let $K_1^{(a)}$ denote the one-vertex graph with vertex-type a and no edges; formally,

$$K_1^{(a)} = \big(\{*\},\ \emptyset,\ \tau_{K_1^{(a)}}(*) := a,\ \beta \text{ undefined}\big) \in \mathfrak{Mol}.$$

Definition 2.10 (Bond-labelled meta-relations)**.** For each $b \in \Sigma_E$, define a relation $R_{\mathrm{bond},b} \subseteq \mathfrak{Mol} \times \mathfrak{Mol}$ by

$$\big(K_1^{(a)}, K_1^{(a')}\big) \in R_{\mathrm{bond},b}$$

$\iff$ "there exists a molecular graph containing a b-bond between an a-atom and an a'-atom".

This relation is chemically invariant (it depends only on types), hence $R_{\mathrm{bond},b} \in \mathcal{R}_{\mathrm{chem}}$ after enlarging $\mathcal{R}_{\mathrm{chem}}$ if necessary.

Definition 2.11 (Canonical embedding $J : \mathfrak{Mol} \hookrightarrow \mathrm{MolMeta}$)**.** Given $G = (V, E, \tau, \beta) \in \mathfrak{Mol}$, define a Molecular MetaGraph

$$J(G) \ := \ \big(V^*, E^*, s^*, t^*, \lambda^*\big)$$

as follows:

$$\begin{aligned} V^* &:= \{\, K_1^{(\tau(v))} \mid v \in V \,\}, \\ E^* &:= \{\, e^*_{uv} \mid \{u,v\} \in E \,\} \ \text{(a multiset if needed)}, \\ s^*(e^*_{uv}) &:= K_1^{(\tau(u))}, \quad t^*(e^*_{uv}) := K_1^{(\tau(v))}, \\ \lambda^*(e^*_{uv}) &:= R_{\text{bond},\,\beta(\{u,v\})}. \end{aligned}$$

Let $\pi : V^* \to V$ be the bijection $\pi\Big(K_1^{(\tau(v))}\Big) := v$.

Theorem 2.12 (Molecular MetaGraphs generalize molecular graphs)**.** *For every typed molecular graph $G = (V, E, \tau, \beta)$, the "collapse" of $J(G)$ recovers G exactly:*

$$\mathrm{col}\big(J(G)\big) \;=\; G,$$

where

$$\mathrm{col}\big(J(G)\big) := \Big(\, V,\ E,\ \tau,\ \beta \,\Big)$$

with V and τ, β taken from G and E reconstructed from $J(G)$ by

$$E \;=\; \Big\{\ \{\pi(s^*(e^*)),\, \pi(t^*(e^*))\} \ :\ e^* \in E^*,\ \lambda^*(e^*) = R_{\text{bond},\,\beta(\{\pi(s^*(e^*)),\pi(t^*(e^*))\})}\ \Big\}.$$

Consequently, J is injective on isomorphism classes and embeds the category of typed molecular graphs (with type-preserving isomorphisms) fully and faithfully into the category of Molecular MetaGraphs whose edges use only $\{R_{\text{bond},b} : b \in \Sigma_E\}$.

Proof. Fix $G = (V, E, \tau, \beta)$ and build $J(G)$ as in Definition 2.11. By construction, $\pi : V^* \to V$ is a bijection. We verify equality of edge sets and labels by direct elementwise computation.

($\subseteq$) Let $e^* = e^*_{uv} \in E^*$. Then by definition,

$$s^*(e^*) = K_1^{(\tau(u))}, \quad t^*(e^*) = K_1^{(\tau(v))}, \quad \lambda^*(e^*) = R_{\text{bond},\,\beta(\{u,v\})}.$$

Applying π we obtain

$$\{\pi(s^*(e^*)), \pi(t^*(e^*))\} = \{u, v\} \in E,$$

and the recovered bond type is

$$\beta\big(\{\pi(s^*(e^*)), \pi(t^*(e^*))\}\big) = \beta(\{u, v\}),$$

which matches the label index of $\lambda^*(e^*)$. Hence every meta-edge contributes exactly the original bond.

($\supseteq$) Conversely, let $\{u, v\} \in E$. Then $e^*_{uv} \in E^*$ by construction, and

$$\{\pi(s^*(e^*_{uv})), \pi(t^*(e^*_{uv}))\} = \{u, v\}, \quad \lambda^*(e^*_{uv}) = R_{\text{bond},\,\beta(\{u,v\})},$$

so the edge $\{u, v\}$ is recovered in $\mathrm{col}(J(G))$ with the correct bond type.

Thus the recovered edge multiset and labels coincide elementwise with those of G, and vertex types are preserved by π:

$$\tau\big(\pi(K_1^{(\tau(v))})\big) = \tau(v).$$

Therefore $\mathrm{col}(J(G)) = G$ as graphs with types. This proves that J is injective on objects up to isomorphism and, by the explicit reconstruction, that hom-sets are preserved (faithfulness). □

2.2 Molecular Iterated MetaGraph

A Molecular Iterated MetaGraph recursively treats Molecular MetaGraphs as vertices, building multi-level hierarchies of graph-of-graphs structures across chemistry. We lift chemically invariant relations level by level, as in the iterated metagraph construction from the preliminaries, but restricted to $\mathfrak{Mol}$ and $\mathcal{R}_{\mathrm{chem}}$.

Definition 2.13 (Lifted chemical relations)**.** Set $\mathfrak{Mol}^{(0)} := \mathfrak{Mol}$ and $\mathcal{R}_{\mathrm{chem}}^{(0)} := \mathcal{R}_{\mathrm{chem}}$. Given $\mathfrak{Mol}^{(t)}$ and $\mathcal{R}_{\mathrm{chem}}^{(t)}$, define

$$\mathfrak{Mol}^{(t+1)} := \Big\{ \text{ finite Molecular MetaGraphs over } \big(\mathfrak{Mol}^{(t)}, \mathcal{R}_{\mathrm{chem}}^{(t)}\big) \Big\},$$

and for each $R \in \mathcal{R}_{\mathrm{chem}}^{(t)}$ its lift $R^{\uparrow} \subseteq \mathfrak{Mol}^{(t+1)} \times \mathfrak{Mol}^{(t+1)}$ by

$$\big(\mathsf{M}_1, \mathsf{M}_2\big) \in R^{\uparrow} \quad \Longleftrightarrow \quad \exists\, X \in V(\mathsf{M}_1),\, Y \in V(\mathsf{M}_2) \text{ with } (X, Y) \in R.$$

Set $\mathcal{R}_{\mathrm{chem}}^{(t+1)} := \{R^{\uparrow} : R \in \mathcal{R}_{\mathrm{chem}}^{(t)}\}$.

Definition 2.14 (Molecular Iterated MetaGraph of depth t)**.** For $t \in \mathbb{N}_0$, a *Molecular Iterated MetaGraph of depth t* is a metagraph

$$\mathsf{M}^{(t)} = (V^{(t)}, E^{(t)}, s^{(t)}, t^{(t)}, \lambda^{(t)})$$

over $\big(\mathfrak{Mol}^{(t)}, \mathcal{R}_{\mathrm{chem}}^{(t)}\big)$, i.e.,

$$V^{(t)} \subseteq \mathfrak{Mol}^{(t)}, \qquad \lambda^{(t)} : E^{(t)} \to \mathcal{R}_{\mathrm{chem}}^{(t)}, \qquad \forall e \in E^{(t)} :\ \big(s^{(t)}(e), t^{(t)}(e)\big) \in \lambda^{(t)}(e).$$

Remark 2.15. For iterated examples we use the lifted relations of Definition 2.14: for $R \in \mathcal{R}_{\mathrm{chem}}^{(t)}$, its lift $R^{\uparrow}$ satisfies

$$(\mathsf{M}_1, \mathsf{M}_2) \in R^{\uparrow} \iff \exists X \in V(\mathsf{M}_1),\ \exists Y \in V(\mathsf{M}_2) \text{ with } (X, Y) \in R.$$

Example 2.16 (Molecular Iterated MetaGraph I (depth $t = 1$): Substructure lifted across two meta-graphs)**.** Let $\mathsf{M}_A = \mathsf{M}_{\mathrm{arom}}$ from Example 2 restricted to $V_A = \{G_{\mathrm{Bz}}, G_{\mathrm{Tol}}\}$ and edge $G_{\mathrm{Bz}} \xrightarrow{R_{\mathrm{sub}}} G_{\mathrm{Tol}}$. Let M_B have $V_B = \{G_{\mathrm{Bz}}, G_{\mathrm{Ph}}\}$ and edge $G_{\mathrm{Bz}} \xrightarrow{R_{\mathrm{sub}}} G_{\mathrm{Ph}}$. Define a depth-1 iterated meta-graph

$$\mathsf{N}^{(1)} = (V^{(1)}, E^{(1)}, s^{(1)}, t^{(1)}, \lambda^{(1)}),$$

with

$$V^{(1)} = \{\mathsf{M}_A, \mathsf{M}_B\}, \qquad E^{(1)} = \{f\}, \qquad s^{(1)}(f) = \mathsf{M}_A,\ t^{(1)}(f) = \mathsf{M}_B,\ \lambda^{(1)}(f) = R_{\mathrm{sub}}^{\uparrow}.$$

Since $(G_{\mathrm{Bz}}, G_{\mathrm{Ph}}) \in R_{\mathrm{sub}}$ with $G_{\mathrm{Bz}} \in V(\mathsf{M}_A)$ and $G_{\mathrm{Ph}} \in V(\mathsf{M}_B)$, we have $f \in R_{\mathrm{sub}}^{\uparrow}$ by definition, so $\mathsf{N}^{(1)}$ is a valid Molecular Iterated MetaGraph of depth 1.

Example 2.17 (Molecular Iterated MetaGraph II (depth $t = 1$): Equality-lift between forward and reverse steps)**.** Let $\mathsf{M}_{\mathrm{ester}}$ be Example 1 (forward esterification). Let $\mathsf{M}_{\mathrm{hydr}}$ be the corresponding hydrolysis meta-graph with edges $G_{\mathrm{EA}} \to G_{\mathrm{AA}}, G_{\mathrm{EA}} \to G_{\mathrm{EtOH}}, G_{\mathrm{H_2O}} \to G_{\mathrm{AA}}, G_{\mathrm{H_2O}} \to G_{\mathrm{EtOH}}$ all labelled R_{rxn}. Define

$$\mathsf{H}^{(1)} = (\{\, \mathsf{M}_{\mathrm{ester}}, \mathsf{M}_{\mathrm{hydr}} \,\}, \{g_1, g_2\}, s^{(1)}, t^{(1)}, \lambda^{(1)}),$$

with

$$s^{(1)}(g_1) = \mathsf{M}_{\mathrm{ester}},\ t^{(1)}(g_1) = \mathsf{M}_{\mathrm{hydr}},\ s^{(1)}(g_2) = \mathsf{M}_{\mathrm{hydr}},\ t^{(1)}(g_2) = \mathsf{M}_{\mathrm{ester}},\ \lambda^{(1)}(g_1) = \lambda^{(1)}(g_2) = R_{\mathrm{eq}}^{\uparrow}.$$

Because both meta-graphs contain G_{EA} (and other common molecules), there exist $X = Y = G_{\mathrm{EA}}$ with $(X, Y) \in R_{\mathrm{eq}}$; hence $(\mathsf{M}_{\mathrm{ester}}, \mathsf{M}_{\mathrm{hydr}}) \in R_{\mathrm{eq}}^{\uparrow}$ and $\mathsf{H}^{(1)}$ is a valid depth-1 Molecular Iterated MetaGraph.

Example 2.18 (Molecular Iterated MetaGraph III (depth $t = 2$): Project-level linkage via double lift)**.** Form two depth-1 nodes:

$$\mathsf{P}_1^{(1)} := (\{\mathsf{M}_A, \mathsf{M}_{\text{ester}}\}, \{p\}, s^{(1)}, t^{(1)}, \lambda^{(1)}), \quad s^{(1)}(p) = \mathsf{M}_A,\ t^{(1)}(p) = \mathsf{M}_{\text{ester}},\ \lambda^{(1)}(p) = R_{\text{eq}}^{\uparrow},$$

witnessed by the shared molecule $G_{\text{H}_2\text{O}}$ (or any chosen common species), and

$$\mathsf{P}_2^{(1)} := (\{\mathsf{M}_B, \mathsf{M}_{\text{hydr}}\}, \{q\}, s^{(1)}, t^{(1)}, \lambda^{(1)}), \quad s^{(1)}(q) = \mathsf{M}_B,\ t^{(1)}(q) = \mathsf{M}_{\text{hydr}},\ \lambda^{(1)}(q) = R_{\text{eq}}^{\uparrow},$$

witnessed by G_{AA} or G_{EtOH}. Now define a depth-2 meta-graph

$$\mathsf{Q}^{(2)} = (V^{(2)}, E^{(2)}, s^{(2)}, t^{(2)}, \lambda^{(2)}), \quad V^{(2)} = \{\mathsf{P}_1^{(1)}, \mathsf{P}_2^{(1)}\},\ E^{(2)} = \{r\},$$

with

$$s^{(2)}(r) = \mathsf{P}_1^{(1)}, \quad t^{(2)}(r) = \mathsf{P}_2^{(1)}, \quad \lambda^{(2)}(r) = \big(R_{\text{eq}}^{\uparrow}\big)^{\uparrow}.$$

To see $r \in (R_{\text{eq}}^{\uparrow})^{\uparrow}$, take $X = \mathsf{M}_{\text{ester}} \in V(\mathsf{P}_1^{(1)})$ and $Y = \mathsf{M}_{\text{hydr}} \in V(\mathsf{P}_2^{(1)})$; we already have $(X, Y) \in R_{\text{eq}}^{\uparrow}$ (Example 6), so by the lift definition $(\mathsf{P}_1^{(1)}, \mathsf{P}_2^{(1)}) \in (R_{\text{eq}}^{\uparrow})^{\uparrow}$. Thus $\mathsf{Q}^{(2)}$ is a Molecular Iterated MetaGraph of depth 2.

Theorem 2.19 (Molecular Iterated MetaGraphs are Iterated MetaGraphs)**.** *For every $t \in \mathbb{N}_0$, any $\mathsf{M}^{(t)}$ as in Definition 2.14 is an iterated metagraph of depth t in the sense of the preliminaries (with base universe $\mathfrak{Mol}$ and base relations $\mathcal{R}_{\text{chem}}$).*

Proof. By Definition 2.13, $(\mathfrak{Mol}^{(t)}, \mathcal{R}_{\text{chem}}^{(t)})$ is obtained from $(\mathfrak{Mol}^{(t-1)}, \mathcal{R}_{\text{chem}}^{(t-1)})$ by the same lifting scheme used for general iterated metagraphs. Thus $V^{(t)} \subseteq \mathfrak{Mol}^{(t)}$, $\lambda^{(t)}$ takes values in $\mathcal{R}_{\text{chem}}^{(t)}$, and each edge satisfies the required incidence. Therefore $\mathsf{M}^{(t)}$ is a metagraph over $\big(\mathfrak{Mol}^{(t)}, \mathcal{R}_{\text{chem}}^{(t)}\big)$, i.e. an iterated metagraph of depth t. □

3 Additional Results: Some Applications in Biochemistry

Biochemistry is the scientific study of chemical processes, reactions, and molecular interactions occurring within living organisms [21]. This section presents application examples of the Molecular MetaGraph and Molecular Iterated MetaGraph, as defined in this paper, within the field of biochemistry.

Example 3.1 (ATP-dependent phosphorylation (hexokinase step))**.** ATP-dependent phosphorylation is a biochemical process where ATP donates its phosphate group to a substrate, regulating energy transfer and cellular signaling (cf. [22, 23]). Let the molecular vertex set be

$$V = \{\, G_{\text{ATP}},\ G_{\text{ADP}},\ G_{\text{Glc}},\ G_{\text{G6P}} \,\},$$

representing ATP, ADP, glucose, and glucose-6-phosphate. Model the hexokinase reaction

$$\text{ATP} + \text{Glc} \ \longrightarrow\ \text{ADP} + \text{G6P}\ (+\text{H}^+)$$

by the directed meta-edges

$$E = \{e_1, e_2\}, \quad s(e_1) = G_{\text{ATP}},\ t(e_1) = G_{\text{ADP}},\ \lambda(e_1) = R_{\text{rxn}}, \qquad s(e_2) = G_{\text{Glc}},\ t(e_2) = G_{\text{G6P}},\ \lambda(e_2) = R_{\text{rxn}}.$$

Then

$$\mathsf{M}_{\text{HK}} \ :=\ (V, E, s, t, \lambda)$$

is a Molecular MetaGraph over $(\mathfrak{Mol}, \mathcal{R}_{\text{chem}})$ because each edge satisfies the incidence constraint $\big(s(e_i), t(e_i)\big) \in R_{\text{rxn}} = \lambda(e_i)$ $(i = 1, 2)$.

Example 3.2 (NADH-coupled reduction (lactate dehydrogenase step))**.** Let

$$V = \{\, G_{\mathrm{NAD^+}},\ G_{\mathrm{NADH}},\ G_{\mathrm{Pyr}},\ G_{\mathrm{Lac}} \,\},$$

representing NAD^+, NADH, pyruvate, and lactate. For the LDH reaction

$$\mathrm{NADH} + \mathrm{Pyr} \ \longrightarrow\ \mathrm{NAD}^+ + \mathrm{Lac},$$

take

$$E = \{e_1, e_2\}, \quad s(e_1) = G_{\mathrm{NADH}},\ t(e_1) = G_{\mathrm{NAD^+}},\ \lambda(e_1) = R_{\mathrm{rxn}}, \qquad s(e_2) = G_{\mathrm{Pyr}},\ t(e_2) = G_{\mathrm{Lac}},\ \lambda(e_2) = R_{\mathrm{rxn}}.$$

Thus $\mathsf{M}_{\mathrm{LDH}} = (V, E, s, t, \lambda)$ is a valid Molecular MetaGraph since $\big(s(e_i), t(e_i)\big) \in R_{\mathrm{rxn}} = \lambda(e_i)$ for $i = 1, 2$.

We use the lifted relations of Definition 2.13. Recall:

$$(\mathsf{M}_1, \mathsf{M}_2) \in R^{\uparrow} \iff \exists X \in V(\mathsf{M}_1),\ \exists Y \in V(\mathsf{M}_2) \text{ with } (X, Y) \in R.$$

Example 3.3 (Depth $t = 1$: Linking consecutive glycolytic steps via a lifted equality)**.** Let M_{HK} be the hexokinase meta-graph from the first example. Define the phosphoglucose isomerase (PGI) [24] meta-graph

$$\mathsf{M}_{\mathrm{PGI}}:\ V' = \{G_{\mathrm{G6P}}, G_{\mathrm{F6P}}\}, \quad E' = \{e_1', e_2'\},$$

with

$$s(e_1') = G_{\mathrm{G6P}},\ t(e_1') = G_{\mathrm{F6P}},\ \lambda(e_1') = R_{\mathrm{rxn}}, \qquad s(e_2') = G_{\mathrm{F6P}},\ t(e_2') = G_{\mathrm{G6P}},\ \lambda(e_2') = R_{\mathrm{rxn}}.$$

Form a depth-1 iterated meta-graph

$$\mathsf{N}^{(1)}_{\mathrm{Gly}} = (V^{(1)}, E^{(1)}, s^{(1)}, t^{(1)}, \lambda^{(1)}),$$

with

$$V^{(1)} = \{\, \mathsf{M}_{\mathrm{HK}},\ \mathsf{M}_{\mathrm{PGI}} \,\}, \quad E^{(1)} = \{f\}, \quad s^{(1)}(f) = \mathsf{M}_{\mathrm{HK}},\ t^{(1)}(f) = \mathsf{M}_{\mathrm{PGI}},\ \lambda^{(1)}(f) = R_{\mathrm{eq}}^{\uparrow}.$$

Since $G_{\mathrm{G6P}} \in V(\mathsf{M}_{\mathrm{HK}}) \cap V(\mathsf{M}_{\mathrm{PGI}})$, we have $(G_{\mathrm{G6P}}, G_{\mathrm{G6P}}) \in R_{\mathrm{eq}}$, so by definition $\big(s^{(1)}(f), t^{(1)}(f)\big) \in R_{\mathrm{eq}}^{\uparrow} = \lambda^{(1)}(f)$. Hence $\mathsf{N}^{(1)}_{\mathrm{Gly}}$ is a valid Molecular Iterated MetaGraph of depth 1.

Example 3.4 (Depth $t = 2$: Dehydrogenase family coupling via double lift)**.** (cf. [25, 26]) Construct three Molecular MetaGraphs on redox-coupled steps:

(i) LDH (already defined) with molecules $\{G_{\mathrm{NAD^+}}, G_{\mathrm{NADH}}, G_{\mathrm{Pyr}}, G_{\mathrm{Lac}}\}$.

(ii) MDH (malate dehydrogenase):

$$\mathsf{M}_{\mathrm{MDH}}:\ V = \{G_{\mathrm{NAD^+}}, G_{\mathrm{NADH}}, G_{\mathrm{OAA}}, G_{\mathrm{Mal}}\}, \quad E = \{e_1, e_2\},$$

$$s(e_1) = G_{\mathrm{NADH}},\ t(e_1) = G_{\mathrm{NAD^+}},\ \lambda(e_1) = R_{\mathrm{rxn}}, \qquad s(e_2) = G_{\mathrm{OAA}},\ t(e_2) = G_{\mathrm{Mal}},\ \lambda(e_2) = R_{\mathrm{rxn}}.$$

(iii) GAPDH (glyceraldehyde-3-phosphate dehydrogenase):

$$\mathsf{M}_{\mathrm{GAPDH}}:\ V = \{G_{\mathrm{NAD^+}}, G_{\mathrm{NADH}}, G_{\mathrm{G3P}}, G_{\text{1,3-BPG}}\}, \quad E = \{e_1, e_2\},$$

$$s(e_1) = G_{\mathrm{NAD^+}},\ t(e_1) = G_{\mathrm{NADH}},\ \lambda(e_1) = R_{\mathrm{rxn}}, \qquad s(e_2) = G_{\mathrm{G3P}},\ t(e_2) = G_{\text{1,3-BPG}},\ \lambda(e_2) = R_{\mathrm{rxn}}.$$

Create two depth-1 nodes using lifted equality (they share NAD^+/NADH):

$$\mathsf{P}^{(1)}_1 = (\{\mathsf{M}_{\mathrm{LDH}}, \mathsf{M}_{\mathrm{MDH}}\}, \{p\}, s^{(1)}, t^{(1)}, \lambda^{(1)})$$

with $s^{(1)}(p) = \mathsf{M}_{\mathrm{LDH}}$, $t^{(1)}(p) = \mathsf{M}_{\mathrm{MDH}}$, $\lambda^{(1)}(p) = R_{\mathrm{eq}}^{\uparrow}$, witnessed by the common molecule $G_{\mathrm{NAD^+}}$ (or G_{NADH}); and

$$\mathsf{P}_2^{(1)} = (\{\mathsf{M}_{\mathrm{GAPDH}}, \mathsf{M}_{\mathrm{LDH}}\}, \{q\}, s^{(1)}, t^{(1)}, \lambda^{(1)})$$

with $s^{(1)}(q) = \mathsf{M}_{\mathrm{GAPDH}}$, $t^{(1)}(q) = \mathsf{M}_{\mathrm{LDH}}$, $\lambda^{(1)}(q) = R_{\mathrm{eq}}^{\uparrow}$, witnessed again by $\mathrm{NAD^+/NADH}$.

Now define a depth-2 Molecular Iterated MetaGraph

$$\mathsf{Q}^{(2)} = (V^{(2)}, E^{(2)}, s^{(2)}, t^{(2)}, \lambda^{(2)}), \quad V^{(2)} = \{\mathsf{P}_1^{(1)}, \mathsf{P}_2^{(1)}\}, \ E^{(2)} = \{r\},$$

with

$$s^{(2)}(r) = \mathsf{P}_1^{(1)}, \quad t^{(2)}(r) = \mathsf{P}_2^{(1)}, \quad \lambda^{(2)}(r) = \left(R_{\mathrm{eq}}^{\uparrow}\right)^{\uparrow}.$$

To verify incidence, choose $X = \mathsf{M}_{\mathrm{LDH}} \in V(\mathsf{P}_1^{(1)})$, $Y = \mathsf{M}_{\mathrm{LDH}} \in V(\mathsf{P}_2^{(1)})$. Because X and Y each contain $G_{\mathrm{NAD^+}}$ (hence $(G_{\mathrm{NAD^+}}, G_{\mathrm{NAD^+}}) \in R_{\mathrm{eq}}$), we get $(X, Y) \in R_{\mathrm{eq}}^{\uparrow}$, which witnesses $\left(s^{(2)}(r), t^{(2)}(r)\right) \in (R_{\mathrm{eq}}^{\uparrow})^{\uparrow}$. Therefore $\mathsf{Q}^{(2)}$ is a valid depth-2 Molecular Iterated MetaGraph.

4 Conclusion

In this paper, we studied new extensions called the *Molecular MetaGraph* and the *Molecular Iterated MetaGraph*, which generalize the notion of molecular graphs using the frameworks of MetaGraphs and Iterated MetaGraphs.

In future work, we aim to investigate further extensions based on alternative graph frameworks, such as *Fuzzy Graphs* [27], *Neutrosophic Graphs* [28,29], *Directed Graphs* [30], HyperFuzzy Graphs [31], HyperGraph [32], SuperHyperGraph [33,34], *Bidirected Graphs* [35], and *Plithogenic Graphs* [36]. Moreover, we hope that this line of research will advance toward applications in the field of chemistry as well as the development of algorithms.

Funding

No external funding was received for this work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this work.

Acknowledgments

We thank all colleagues, reviewers, and readers whose comments and questions have greatly improved this manuscript. We are also grateful to the authors of the works cited herein for providing the theoretical foundations that underpin our study. Finally, we appreciate the institutional and technical support that enabled this research.

Data Availability

This paper is theoretical and did not generate or analyze any empirical data. We welcome future studies that apply and test these concepts in practical settings.

Research Integrity

The author confirms that this manuscript is original, has not been published elsewhere, and is not under consideration by any other journal.

Use of Computational Tools

All proofs and derivations were performed manually; no computational software (e.g., Mathematica, SageMath, Coq) was used.

Code Availability

No code or software was developed for this study.

Ethical Approval

This research did not involve human participants or animals, and therefore did not require ethical approval.

Use of Generative AI and AI-Assisted Tools

We use generative AI and AI-assisted tools for tasks such as English grammar checking, and We do not employ them in any way that violates ethical standards.

Supplementary Information

No supplementary materials accompany this paper.

Disclaimer

The ideas presented here are theoretical and have not yet been validated through empirical testing. While we have strived for accuracy and proper citation, inadvertent errors may remain. Readers should verify any referenced material independently. The opinions expressed are those of the authors and do not necessarily reflect the views of their institutions.

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