Isomorphic_cell

2025.01.21 - Choice of Data Preprocessing

We use subgraph representation as it is easier to pass this to the `Intact` portion of the model. We can then use the `perturbed_genes` for the collection of the perturbed set during perturbed set separation.

```
dataset[40]
HeteroData(
  gene={
    node_ids=[6605],
    num_nodes=6605,
    ids_pert=[2],
    cell_graph_idx_pert=[2],
    x=[6605, 64],
    x_pert=[2, 64],
    gene_interaction=[1],
    gene_interaction_p_value=[1],
    fitness=[1],
    fitness_std=[1],
  },
  metabolite={
    num_nodes=2534,
    node_ids=[2534],
  },
  (gene, physical_interaction, gene)={
    edge_index=[2, 144199],
    num_edges=144199,
  },
  (gene, regulatory_interaction, gene)={
    edge_index=[2, 16089],
    num_edges=16089,
  },
  (metabolite, reaction-genes, metabolite)={
    hyperedge_index=[2, 20939],
    stoichiometry=[20939],
    reaction_to_genes=dict(len=4881),
    reaction_to_genes_indices=dict(len=4881),
    num_edges=4875,
  }
)
```

Batched

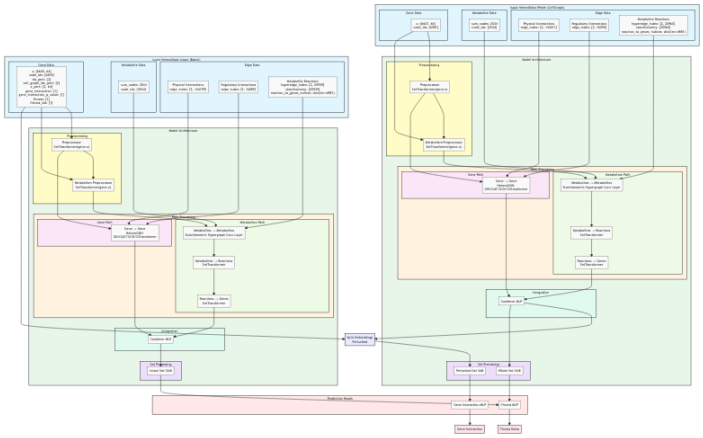
```
batch
HeteroDataBatch(
  gene={
    node_ids=[2],
    num_nodes=13210,
    ids_pert=[2],
    cell_graph_idx_pert=[4],
    x=[13210, 64],
    x_batch=[13210],
    x_ptr=[3],
    x_pert=[4, 64],
    x_pert_batch=[4],
    x_pert_ptr=[3],
    gene_interaction=[2],
    gene_interaction_p_value=[2],
```

```
    fitness=[2],
    fitness_std=[2],
    batch=[13210],
    ptr=[3],
  },
  metabolite={
    num_nodes=5068,
    node_ids=[2],
    batch=[5068],
    ptr=[3],
  },
  (gene, physical_interaction, gene)={
    edge_index=[2, 287499],
    num_edges=[2],
  },
  (gene, regulatory_interaction, gene)={
    edge_index=[2, 32180],
    num_edges=[2],
  },
  (metabolite, reaction-genes, metabolite)={
    hyperedge_index=[2, 41914],
    stoichiometry=[41914],
    reaction_to_genes=dict(len=4881),
    reaction_to_genes_indices=dict(len=4881),
    num_edges=[2],
  }
)
```

This is the base graph that will get pass through the model first `dataset.cell_graph`. We only need to pass one object not batched then expand after the combiner.

```
dataset.cell_graph
HeteroData(
  gene={
    num_nodes=6607,
    node_ids=[6607],
    x=[6607, 64],
  },
  metabolite={
    num_nodes=2534,
    node_ids=[2534],
  },
  (gene, physical_interaction, gene)={
    edge_index=[2, 144211],
    num_edges=144211,
  },
  (gene, regulatory_interaction, gene)={
    edge_index=[2, 16095],
    num_edges=16095,
  },
  (metabolite, reaction-genes, metabolite)={
    hyperedge_index=[2, 20960],
    stoichiometry=[20960],
    num_edges=4881,
    reaction_to_genes=dict(len=4881),
    reaction_to_genes_indices=dict(len=4881),
  }
)
```

2025.01.21 - Updated Mermaid Diagram



2025.01.21 - Algorithm

Algorithm Definitions

1. **Gene Graph** (G):
   - n: Number of genes (nodes in the gene graph).
   - d_G: Feature dimension of the genes.
   - $\mathcal{N}_G \in \mathbb{R}^{n \times d_G}$: Node features representing the genes.
   - $\mathcal{E}_G \in \{0,1\}^{n \times n}$: Multiple edge indices representing physical and regulatory interactions between genes.
   - $X_G \in \mathbb{R}^{n \times h}$: Node feature matrix after transformation, where h is the hidden feature dimension.
2. **Metabolite Hypergraph** (H):
   - m: Number of metabolites (nodes in the metabolite hypergraph).
   - d_H: Feature dimension of the metabolites.
   - $\mathcal{N}_H \in \mathbb{R}^{m \times d_H}$: Node features representing the metabolites.
   - e_H: Number of hyperedges (reactions) in the hypergraph.
   - $\mathcal{E}_H \in \{0,1\}^{m \times e_H}$: Hyperedge matrix representing reactions linking metabolites to genes.
   - $I_{\text{met}} \in \{0,1\}^{m \times n}$: Incidence matrix linking metabolites to genes via gene-protein-reaction associations.
3. **Stoichiometry and Reaction Mapping**:
   - $E_H \in \mathbb{R}^{e_H \times h}$: Edge feature matrix after applying the Stoichiometric Hypergraph Convolution layer.
   - $X_{\text{rxn}} \in \mathbb{R}^{n \times h}$: Reaction embeddings derived from edge features mapped back to genes.
   - $X_{\text{gene}} \in \mathbb{R}^{n \times h}$: Final gene representations from reaction embeddings.
4. **Perturbed Set**:
   - p: Number of perturbed genes.
   - perturbed_ids $\in \mathbb{R}^p$: Indices of the perturbed genes in the dataset.
   - $Z_p \in \mathbb{R}^{p \times h}$: Embeddings for the perturbed genes selected from the Whole Graph embeddings.

Algorithm Steps

Step 1: Whole Graph Processing (Left-Hand Side)

1. **Preprocessing**:
   - Input: $\mathcal{N}_G \in \mathbb{R}^{n \times d_G}$
   - Output: $X_G = \text{SetTransformer}(\mathcal{N}_G) \in \mathbb{R}^{n \times h}$
2. **Gene-Gene Interaction**:
   - Input: $X_G \in \mathbb{R}^{n \times h}, \mathcal{E}_G \in \{0,1\}^{n \times n}$
   - Output: $X_G = \text{HeteroGNN}(X_G, \mathcal{E}_G) \in \mathbb{R}^{n \times h}$
3. **Metabolism Preprocessing**:
   - Input: $X_G \in \mathbb{R}^{n \times h}$
   - Output: $X_H = \text{SetTransformer}(X_G) \in \mathbb{R}^{m \times h}$
4. **Stoichiometric Hypergraph**:
   - Input: $X_H \in \mathbb{R}^{m \times h}, I_{\text{met}} \in \{0,1\}^{m \times n}$
   - Output: $E_H = \text{StoichiometricHypergraphConv}(X_H, I_{\text{met}}) \in \mathbb{R}^{e_H \times h}$
5. **Reaction-to-Gene Mapping**:
   - Input: $E_H \in \mathbb{R}^{e_H \times h}, I_{\text{rxn}} \in \{0,1\}^{e_H \times n}$
   - Output: $X_{\text{rxn}} = \text{SetTransformer}(E_H, I_{\text{rxn}}) \in \mathbb{R}^{n \times h}$
   - Input: $X_{\text{rxn}} \in \mathbb{R}^{n \times h}, I_{\text{gene}} \in \{0,1\}^{n \times g}$
   - Output: $X_{\text{gene}} = \text{SetTransformer}(X_{\text{rxn}}, I_{\text{gene}}) \in \mathbb{R}^{n \times h}$
6. **Combining Representations**:
   - Input: $X_G \in \mathbb{R}^{n \times h}, X_{\text{gene}} \in \mathbb{R}^{n \times h}$
   - Output: $Z_w = \text{MLP}([X_G \| X_{\text{gene}}]) \in \mathbb{R}^{n \times h}$
7. **Pooling Whole Set**:
   - Input: $Z_w \in \mathbb{R}^{n \times h}$
   - Output: $S_w = \text{MLP}(\text{ISAB}(Z_w)) \in \mathbb{R}^1$

Step 2: Intact Graph Processing (Right-Hand Side)

1. **Preprocessing**:

- Same steps as the Whole Graph, but with perturbed data fields:
- Output: $Z_1 = \text{MLP}([X_G \| X_{\text{gene}}]) \in \mathbb{R}^{n \times h}$

2. **Pooling Intact Set**:
   - Input: $Z_1 \in \mathbb{R}^{n \times h}$
   - Output: $S_1 = \text{MLP}(\text{ISAB}(Z_1)) \in \mathbb{R}^1$

Step 3: Fitness Ratio Computation

1. **Compute Fitness Ratio**:
   - Input: $S_1 \in \mathbb{R}^1, S_w \in \mathbb{R}^1$
   - Output: $\hat{y}_{\text{fitness}} = \frac{S_1}{S_w} \in \mathbb{R}^1$

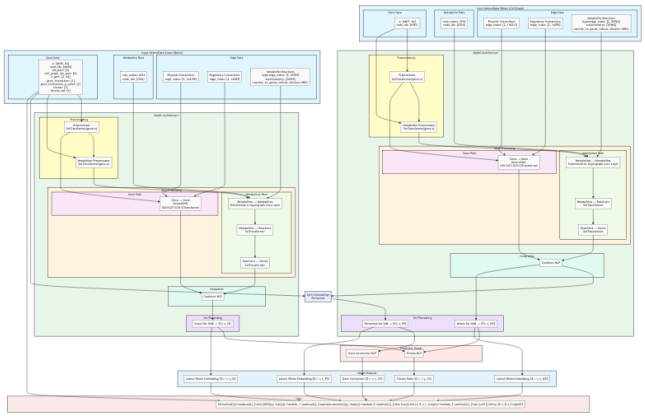
Step 4: Perturbed Set Processing

1. **Select Perturbed Embeddings**:
   - Input: $Z_w \in \mathbb{R}^{n \times h}, \text{perturbed\_ids} \in \mathbb{R}^p$
   - Output: $Z_p = \text{Select}(Z_w, \text{perturbed\_ids}) \in \mathbb{R}^{p \times h}$
2. **Pooling Perturbed Set**:
   - Input: $Z_p \in \mathbb{R}^{p \times h}$
   - Output: $S_p = \text{MLP}(\text{SAB}(Z_p)) \in \mathbb{R}^1$
3. **Gene Interaction Prediction**:
   - Input: $S_p \in \mathbb{R}^1$
   - Output: $\hat{y}_{\text{gene\_interaction}} = S_p \in \mathbb{R}^1$

Final Outputs

1. **Fitness Ratio**: $\hat{y}_{\text{fitness}} \in \mathbb{R}^1$
2. **Gene Interaction Predictions**: $\hat{y}_{\text{gene\_interaction}} \in \mathbb{R}^1$

2025.01.22 - Update Mermaid



2025.01.22 - Algorithm

Graph Types and Processing

1. Whole Graph (Cell Graph)

- Base graph $\mathcal{G}_{\text{whole}}$ that represents the unperturbed cell
- Single instance (batch size = 1) since it never changes
- Contains complete set of genes, metabolites, and their interactions
- Serves as reference point for measuring perturbation effects
- Data structure matches cell_graph format:

```
dataset.cell_graph

HeteroData(
  gene={
    num_nodes=6607,
    node_ids=[6607],
    x=[6607, 64],
  },
  metabolite={
    num_nodes=2534,
    node_ids=[2534],
  },
  (gene, physical_interaction, gene)={
    edge_index=[2, 144211],
    num_edges=144211,
  },
  (gene, regulatory_interaction, gene)={
    edge_index=[2, 16095],
    num_edges=16095,
  },
  (metabolite, reaction-genes, metabolite)={
    hyperedge_index=[2, 20960],
    stoichiometry=[20960],
    num_edges=4881,
    reaction_to_genes=dict(len=4881),
    reaction_to_genes_indices=dict(len=4881),
  }
)
```

2. Intact Graphs (Perturbed Instances)

- Collection of perturbed instances $\{\mathcal{G}_{\text{intact}}^{(i)}\}_{i=1}^{b}$ where b is batch size
- Each graph is derived from whole graph but with specific perturbations
- Processed in batches during training
- Contains additional perturbation-related data:

```
dataset[40]

HeteroData(
  gene={
    node_ids=[6605],
    num_nodes=6605,
    ids_pert=[2],
    cell_graph_idx_pert=[2],
    x=[6605, 64],
    x_pert=[2, 64],
    gene_interaction=[1],
    gene_interaction_p_value=[1],
```

```
    fitness=[1],
    fitness_std=[1],
  },
  metabolite={
    num_nodes=2534,
    node_ids=[2534],
  },
  (gene, physical_interaction, gene)={
    edge_index=[2, 144199],
    num_edges=144199,
  },
  (gene, regulatory_interaction, gene)={
    edge_index=[2, 16089],
    num_edges=16089,
  },
  (metabolite, reaction-genes, metabolite)={
    hyperedge_index=[2, 20939],
    stoichiometry=[20939],
    reaction_to_genes=dict(len=4881),
    reaction_to_genes_indices=dict(len=4881),
    num_edges=4875,
  }
)
```

Processing Flow

1. Whole Graph Processing:
   - Single pass through base cell graph
   - Outputs used as reference and for querying perturbed embeddings
2. Intact Graph Processing:
   - Batch processing of perturbed instances
   - Each instance compared against whole graph for fitness calculation
   - Perturbation effects measured relative to whole graph state

1. Gene-Gene Interaction Multigraph Let $\mathcal{G}_g = (\mathcal{V}_g, \mathcal{E}_g, \phi)$ represent the gene-gene interaction multigraph where:

- $\mathcal{V}_g$ is the set of gene vertices with $|\mathcal{V}_g| = n_g$ vertices
- $\mathcal{E}_g = \mathcal{E}_p \cup \mathcal{E}_r$ is the multiset of edges where:
  - $\mathcal{E}_p$ is the set of physical interaction edges
  - $\mathcal{E}_r$ is the set of regulatory interaction edges
- $\phi : \mathcal{E}_g \to \{\text{physical}, \text{regulatory}\}$ is the edge type mapping
- $X_g \in \mathbb{R}^{n_g \times d}$ is the gene feature matrix where d is the feature dimension

2. Metabolic Hypergraph Let $\mathcal{H}_m = (\mathcal{V}_m, \mathcal{E}_r, I_{m\to r}, I_{r\to g}, S)$ represent the metabolic hypergraph where:

- $\mathcal{V}_m$ is the set of metabolite vertices with $|\mathcal{V}_m| = n_m$ vertices
- $\mathcal{E}_r$ is the set of reaction hyperedges with $|\mathcal{E}_r| = n_r$ edges
- $I_{m\to r} \in \{0,1\}^{n_m \times n_r}$ is the metabolite-to-reaction incidence matrix
- $I_{r\to g} \in \{0,1\}^{n_r \times n_g}$ is the reaction-to-gene incidence matrix
- $S \in \mathbb{R}^{n_r}$ contains the stoichiometric coefficients
- $E_m \in \mathbb{R}^{n_m \times h}$ is the metabolite embedding lookup table

3. Label Data Structures For each batch of size b:

- $y_{\text{fitness}} \in \mathbb{R}^b$ (fitness ratio labels)
- $y_{\text{gene\_interaction}} \in \mathbb{R}^b$ (gene interaction labels)
- $P \in \mathbb{N}^p$ (perturbed gene indices for each sample)

Forward Pass Architecture

Base Forward Function Takes a graph $\mathcal{G}$ and outputs latent embeddings Z and pooled representation z

forward$(\mathcal{G}) \rightarrow (Z, z)$:

1. Preprocessing:
   - $H_g = \text{MLP}(X_g) \in \mathbb{R}^{n_g \times h}$, where $n_g = 6607$ (gene nodes)
   - $H_r = \text{SAB}(H_g, I_{r \rightarrow g}) \in \mathbb{R}^{n_r \times h}$, where $n_r = 4881$ (reactions)
2. Parallel Processing:

   Gene Path:
   - $Z_g = \text{HeteroGNN}(H_g, \mathcal{E}_g) \in \mathbb{R}^{n_g \times h}$

   Metabolic Path:
   - $Z_m = \text{StoichiometricHypergraphConv}(E_m, H_r, \mathcal{E}_r, S) \in \mathbb{R}^{n_m \times h}$, where $n_m = 2534$ (metabolites)
   - $Z_r = \text{SAB}(Z_m, I_{m \rightarrow r}) \in \mathbb{R}^{n_r \times h}$
   - $Z_{mg} = \text{SAB}(Z_r, I_{r \rightarrow g}) \in \mathbb{R}^{n_g \times h}$
3. Integration:
   - $Z = \text{MLP}([Z_g \| Z_{mg}]) \in \mathbb{R}^{n_g \times h}$
   - $z = \text{ISAB}(Z) \in \mathbb{R}^h$

   Return: (Z, z)

Model Workflow

1. Process Whole Graph:
   - $(Z_W, z_W) = \text{forward}(\mathcal{G}_{\text{whole}})$
   - $Z_W \in \mathbb{R}^{n_g \times h}, z_W \in \mathbb{R}^h$
2. Process Intact Graph:
   - $(Z_I, z_I) = \text{forward}(\mathcal{G}_{\text{intact}})$
   - $Z_I \in \mathbb{R}^{n_g \times h}, z_I \in \mathbb{R}^h$
3. Query Perturbed Set:
   - Let $P \in \mathbb{N}^p$ be indices of perturbed genes from `ids_pert`, where $p = 2$ (perturbed genes) in the example data
   - $Z_P = Z_W[P] \in \mathbb{R}^{p \times h}$
   - $z_P = \text{SAB}(Z_P) \in \mathbb{R}^h$

Prediction Heads

1. Growth and Fitness Calculation:
   - $\text{growth}_W = \text{MLP}_{\text{growth}}(z_W) \in \mathbb{R}^1$
   - $\text{growth}_I = \text{MLP}_{\text{growth}}(z_I) \in \mathbb{R}^1$
   - $\hat{y}_{\text{fitness}} = \text{growth}_I / \text{growth}_W \in \mathbb{R}^1$
2. Gene Interaction:
   - $\hat{y}_{\text{gene\_interaction}} = \text{MLP}_{\text{interaction}}(z_P) \in \mathbb{R}^1$

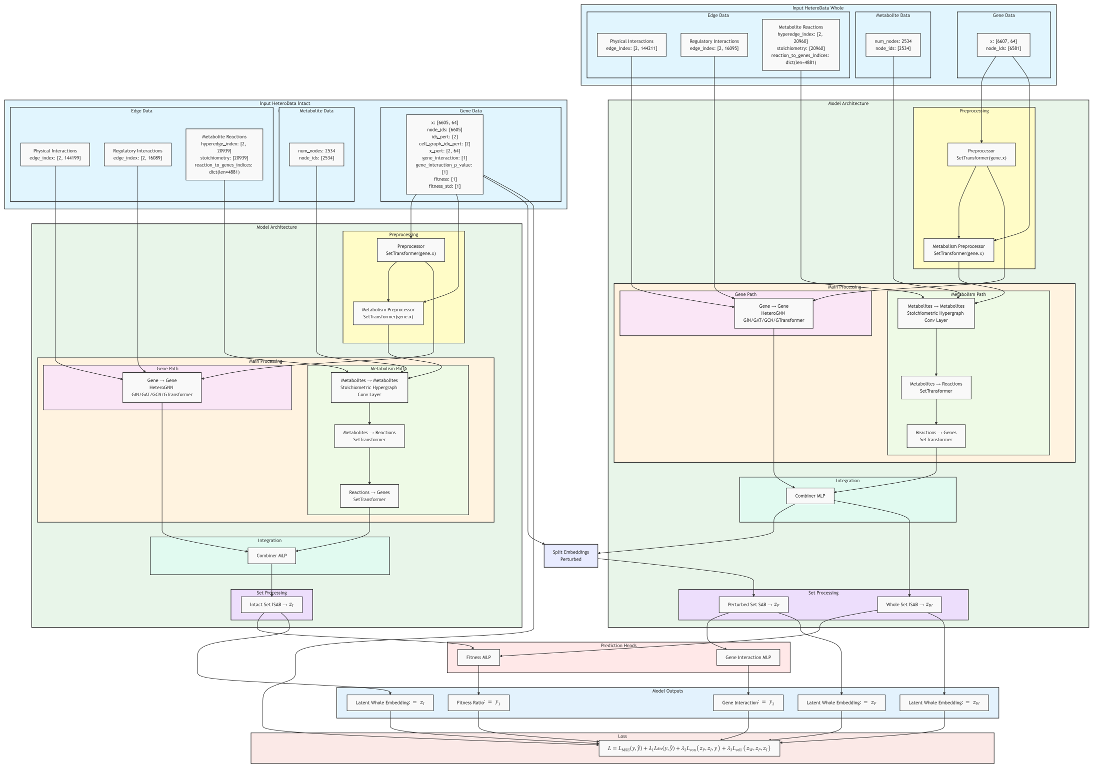
For a batch of size b: $\hat{Y} = [\hat{y}_{\text{fitness}} \| \hat{y}_{\text{gene\_interaction}}] \in \mathbb{R}^{2 \times b}$

Loss Computation The total loss with domain-specific weighting:

$$\mathcal{L} = \mathcal{L}_{\text{MSE}}(Y, \hat{Y}) + \lambda_1 \mathcal{L}_{\text{dist}}(Y, \hat{Y}) + \lambda_2 \mathcal{L}_{\text{SupCR}}(z_P, z_I, Y) + \lambda_3 \mathcal{L}_{\text{cell}}(z_W, z_P, z_I)$$

Where:

- $Y, \hat{Y} \in \mathbb{R}^{2 \times b}$ (ground truth and predictions)
- $z_P, z_I, z_W \in \mathbb{R}^h$ (latent representations)
- $\lambda_1, \lambda_2, \lambda_3 \in \mathbb{R}^+$ (loss weights)


Input HeteroData Whole
Edge Data
Physical Interactions
edge_index: [2, 144211]
Regulatory Interactions
edge_index: [2, 16095]
Metabolite Reactions
hyperedge_index: [2, 20960]
stoichiometry: [20960]
reaction_to_genes_indices: dict(len=4881)
Metabolite Data
num_nodes: 2534
node_ids: [2534]
Gene Data
x: [6607, 64]
node_ids: [6581]
Input HeteroData Intact
Edge Data
Physical Interactions
edge_index: [2, 144199]
Regulatory Interactions
edge_index: [2, 16089]
Metabolite Reactions
hyperedge_index: [2, 20939]
stoichiometry: [20939]
reaction_to_genes_indices: dict(len=4881)
Metabolite Data
num_nodes: 2534
node_ids: [2534]
Gene Data
x: [6605, 64]
node_ids: [6605]
ids_pert: [2]
cell_graph_idx_pert: [2]
x_pert: [2, 64]
gene_interaction: [1]
gene_interaction_p_value: [1]
fitness: [1]
fitness_std: [1]
Model Architecture
Preprocessing
Preprocessor
SetTransformer(gene.x)
Metabolism Preprocessor
SetTransformer(gene.x)
Main Processing
Gene Path
Gene → Gene
HeteroGNN
GIN/GAT/GCN/GTransformer
Metabolism Path
Metabolites → Metabolites
Stoichiometric Hypergraph
Conv Layer
Metabolites → Reactions
SetTransformer
Reactions → Genes
SetTransformer
Integration
Combiner MLP
Set Processing
Intact Set ISAB → z_I
Split Embeddings
Perturbed
Perturbed Set SAB → z_P
Whole Set ISAB → z_W
Prediction Heads
Fitness MLP
Gene Interaction MLP
Model Outputs
Latent Whole Embedding $:= z_I$
Fitness Ratio $:= y_1$
Gene Interaction $:= y_2$
Latent Whole Embedding $:= z_P$
Latent Whole Embedding $:= z_W$
Loss
$L = L_{\text{MSE}}(y, \hat{y}) + \lambda_1 L_{\text{div}}(y, \hat{y}) + \lambda_2 L_{\text{con}}(z_P, z_I, y) + \lambda_3 L_{\text{cell}}(z_W, z_P, z_I)$