# Latent Differential Graphical model for Multi-Tissue and Multi-Omics integration to model molecular interaction networks under multiple Radiation Exposure groups

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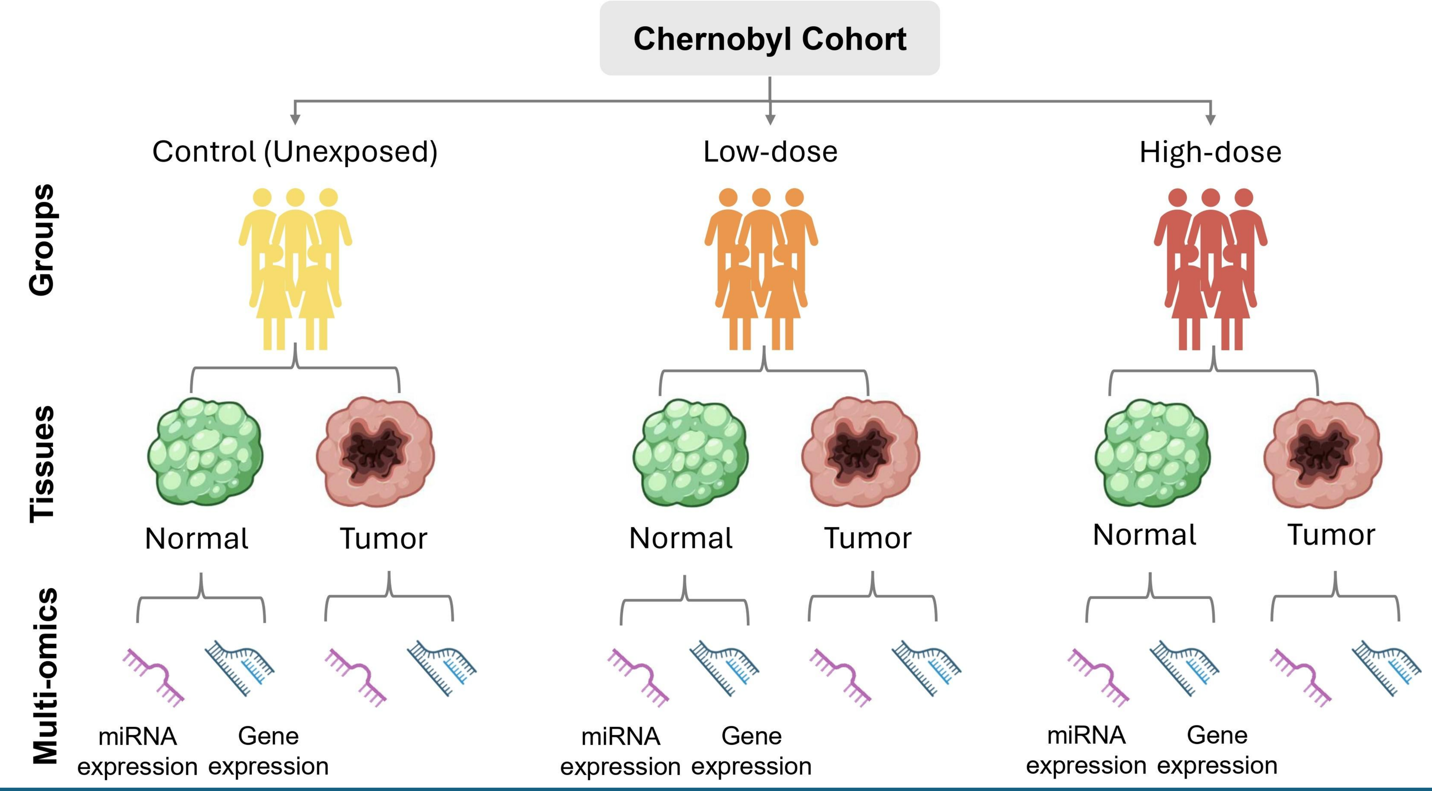
## Background and challenges

- Exposure to ionizing radiation during childhood is associated with an increased risk of **papillary thyroid carcinoma**.
- Understanding the biological effects of **low-dose radiation exposure** remains a major challenge.
- **High dimensional** data with **multiple modalities**: multiple radiation exposure groups, multiple biological tissues and multiple omics layers.




## State-of-the-art in Network Inference

- **Our previous study** identified radiation-associated molecular **signatures**[1].
- **But** characterizing **low-dose** specific mechanisms using conventional integrative approaches such as **feature selection** is **challenging**.

➔ Sparse **Graphical models** enable the reconstruction of molecular networks.

- Existing graphical models do not **simultaneously** handle all these modalities.

➔ **Lack a unified framework** for jointly modeling **complex hierarchical structures**.

| Method | Multi-omics | Multi-tissue | Multi-group | Latent |
|---|---|---|---|---|
| FGL[2] | | | X | |
| CoGLasso[3] | X | | | |
| Hetero−difgraph[4] | | | X | X |
| DIABLO[5] | X | | X | X |
| multiSLICE[6] | X | X | | X |
| **Multi-DiffNet** (our model) | X | X | X | X |

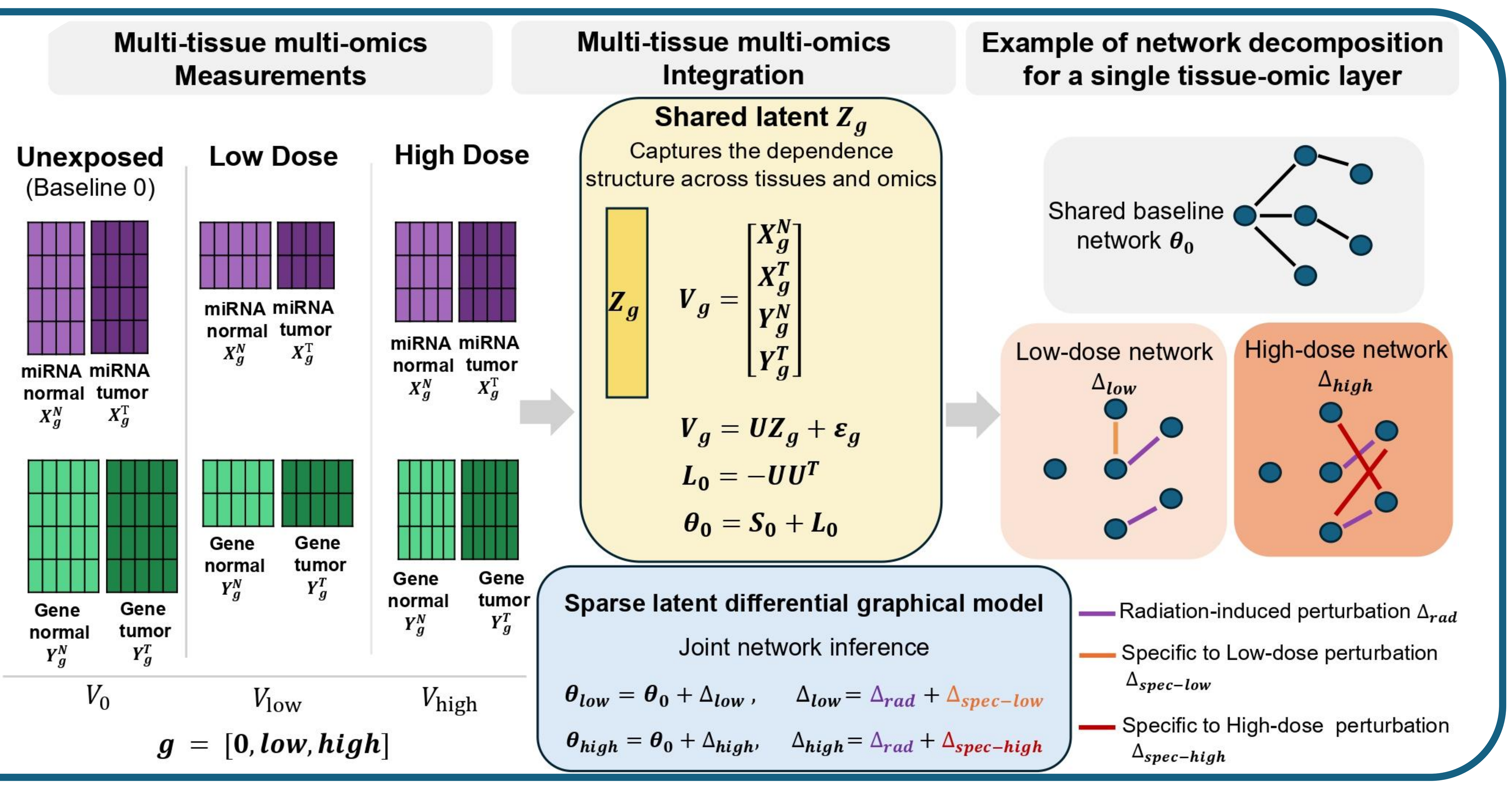
➔ **Goal:** Develop an **integrative framework** based on graphical gaussian models for differential network inference across multiple omics, tissues, groups.

## Contribution: Multi-DiffNet

Latent differential graphical model for multi-tissue and multi-omics network inference to identify **shared** and **exposure-specific** (**low** and **high**) interactions:

$$\mathcal{L}(S_0, L_0, \{\Delta_k\}) = n_0\left[-\log\det(\Theta_0) + \mathrm{Tr}(\widehat{\Sigma}_0\Theta_0)\right] + \lambda_1\|S_0\|_1 + \mu_0\|L_0\|_* + \sum_{k\in\{\text{low},\,\text{high}\}} n_k\left[-\log\det(\Theta_0+\Delta_k) + \mathrm{Tr}\left(\widehat{\Sigma}_k(\Theta_0+\Delta_k)\right)\right] + \sum_{k\in\{\text{low},\,\text{high}\}} \boxed{\lambda_2^{(k)}\|\Delta_k\|_1} + \boxed{\lambda_3\left\|\Delta_{\text{low}}-\Delta_{\text{high}}\right\|_1}.$$

- $\Theta_0 = S_0 - L_0$: baseline network with sparse ($S_0$) and latent ($L_0$) components.
- $\Delta_k$: dose-specific differential network ($k \in \{\text{low}, \text{high}\}$)
- $\widehat{\Sigma}_0, \widehat{\Sigma}_k$: empirical covariance matrices.
- $\lambda_1$: baseline sparsity penalty.
- $\lambda_2^{(k)}$: differential sparsity penalty.
- $\lambda_3$: similarity penalty between differential networks.
- $\mu_0$: latent low-rank regularization parameter.

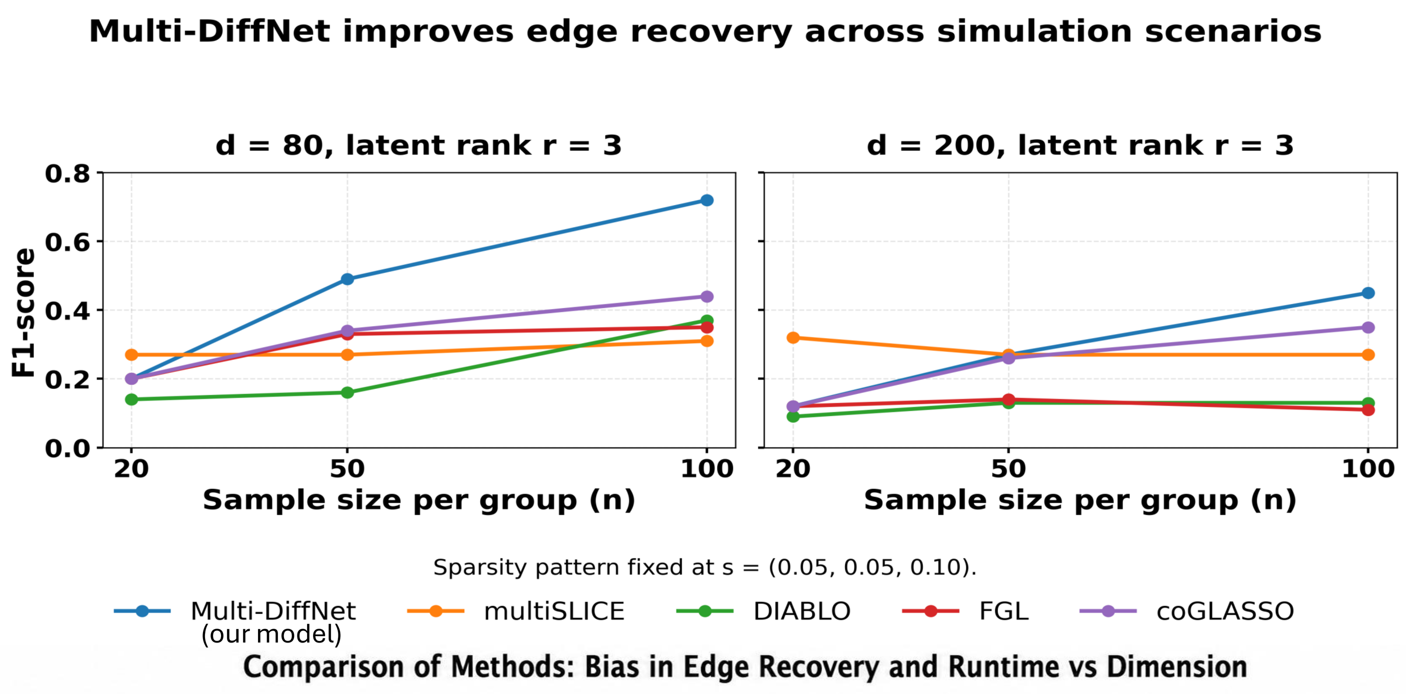


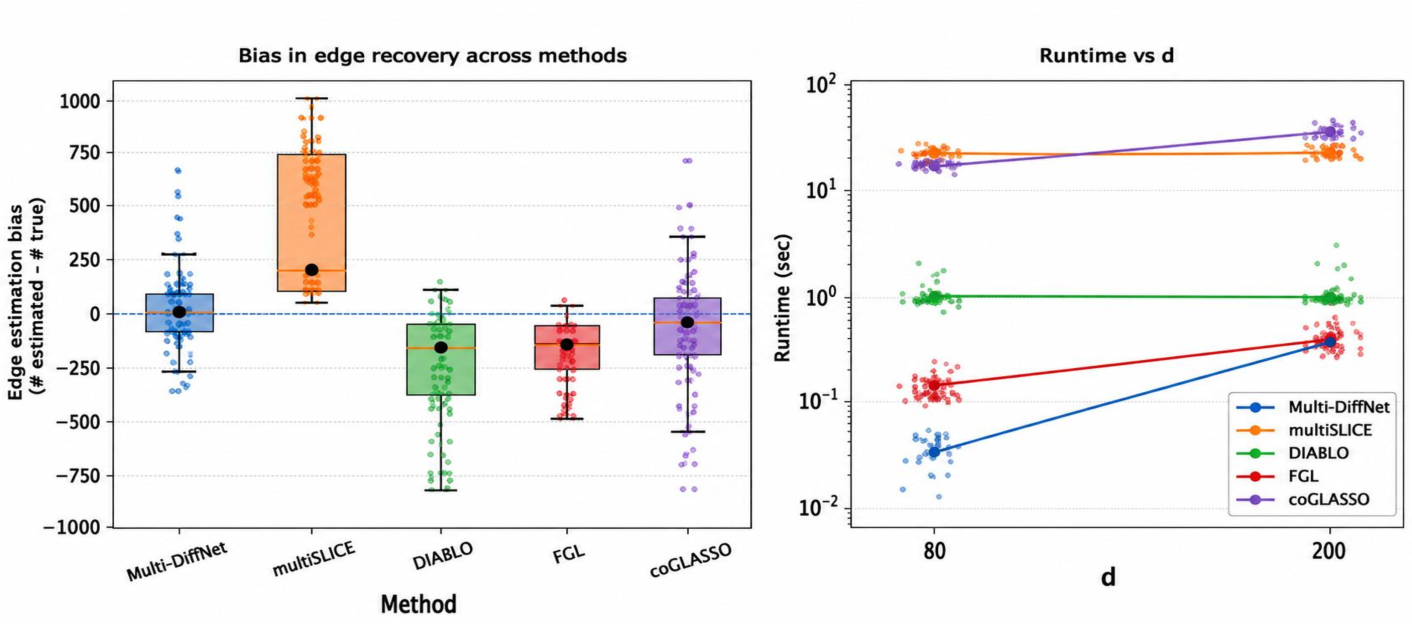

## Simulated data

**Multiple group Gaussian data** (unexposed, low-dose and high-dose) with:

- a **shared latent structure** across tissues and omics
- a **sparse baseline** network
- sparse **exposure-specific** perturbations.

**Scenarios:** sample size (n =20, 50, 100), dimension (d = 80, 200), latent rank (r = 3,10).

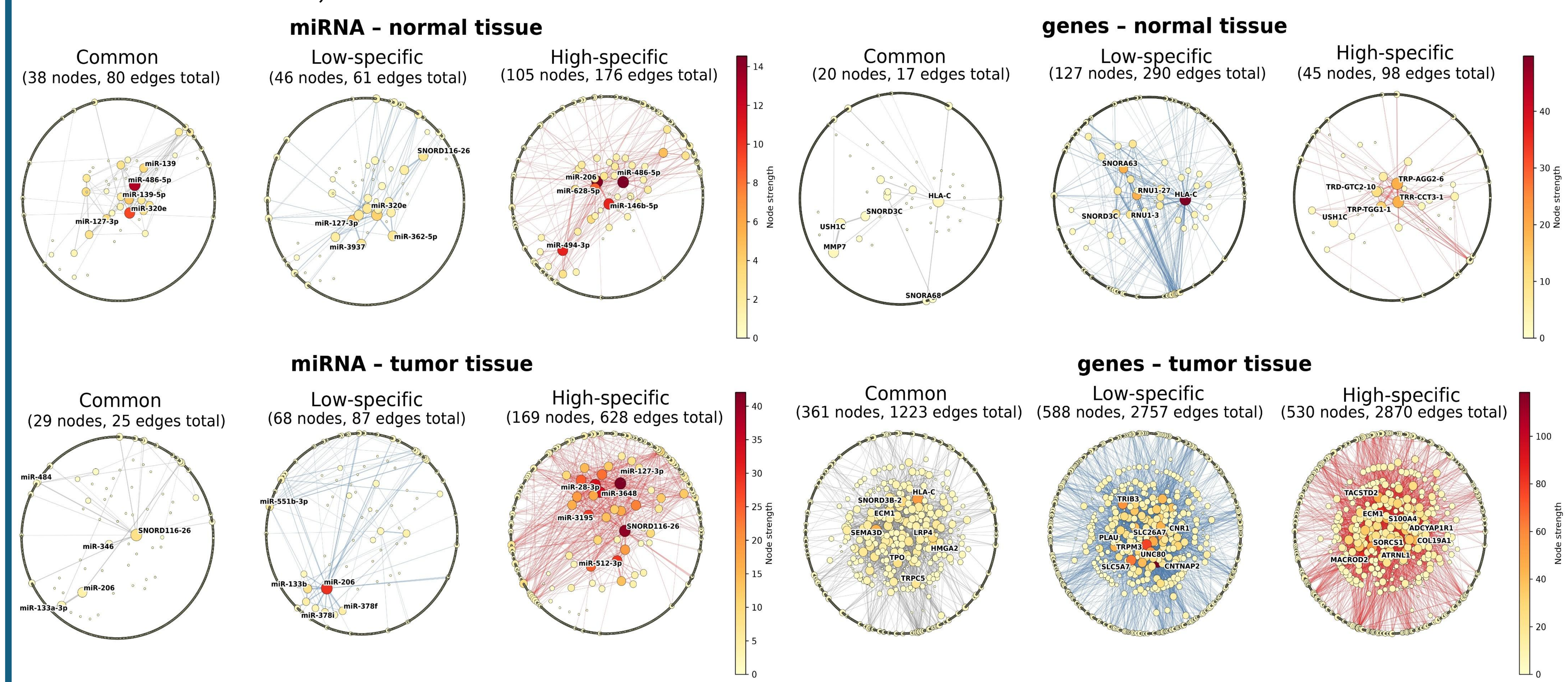



➔ **Multi-DiffNet** consistently **outperforms** competing methods in differential **edge recovery**, achieving the **highest F1-scores**, **reduced estimation bias**, and **competitive runtimes** across all simulation scenarios.

## Chernobyl Tissue Bank (CTB) Thyroid Cancer Cohort [7]

- **47 individuals** (28 unexposed, 11 low-dose (< 50 mGy), 8 high-dose (> 500 mGy)).
- **Features** retained after **differential expression analysis**: 1,571 miRNAs and 1,947 genes.
- **Tissues:** Normal, Tumor.




➔**High-dose** irradiation group induces markedly **denser and more connected** differential networks than **low-dose** irradiation group, particularly in **tumor tissue**, across both miRNA and gene omics.

## Network Inference interactions

- Inference of **intra-omics**, **cross-omics**, **intra-tissue** and **cross-tissue** interactions.
- Inference of **shared** and **dose-specific** radiation-associated networks.

**Multi-DiffNet Code**

### References

[1] Ory et al., *Post-Chornobyl Thyroid Papillary Carcinomas Display Distinct Past 131I Exposure and Radiation-Associated Carcinogenesis Molecular Signatures at Low and High Thyroid Doses*, 2026.
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[4] Li et al., *Subgroup Analysis of Differential Networks with Latent Variables*, 2025.
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[7] Likhtarov et al., *Reconstruction of Individual Thyroid Doses to the Ukrainian Subjects Enrolled in the Chernobyl Tissue Bank*, 2013.