Latent Differential Graphical model for Multi-Tissue and Multi-Omics integration to identify molecular interaction networks

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Biological background: Radiation Exposure and Thyroid Cancer Risk

- Ionizing radiation induces **DNA damage**, which can lead to **mutations**.
- In proliferating cells, mutations can be **propagated and accumulate through cell divisions**.

➔ This increases the **frequency of mutated cells** and the risk of carcinogenic transformation.

- The thyroid is particularly **radiosensitive during childhood**, when thyroid cells are actively proliferating.

- Epidemiological studies demonstrate an **increased risk of thyroid cancer at radiation doses >100 mGy**.
- At **low doses (<100 mGy)**, radiation-associated effects are **difficult to detect** due to limited statistical power and low absolute risk.

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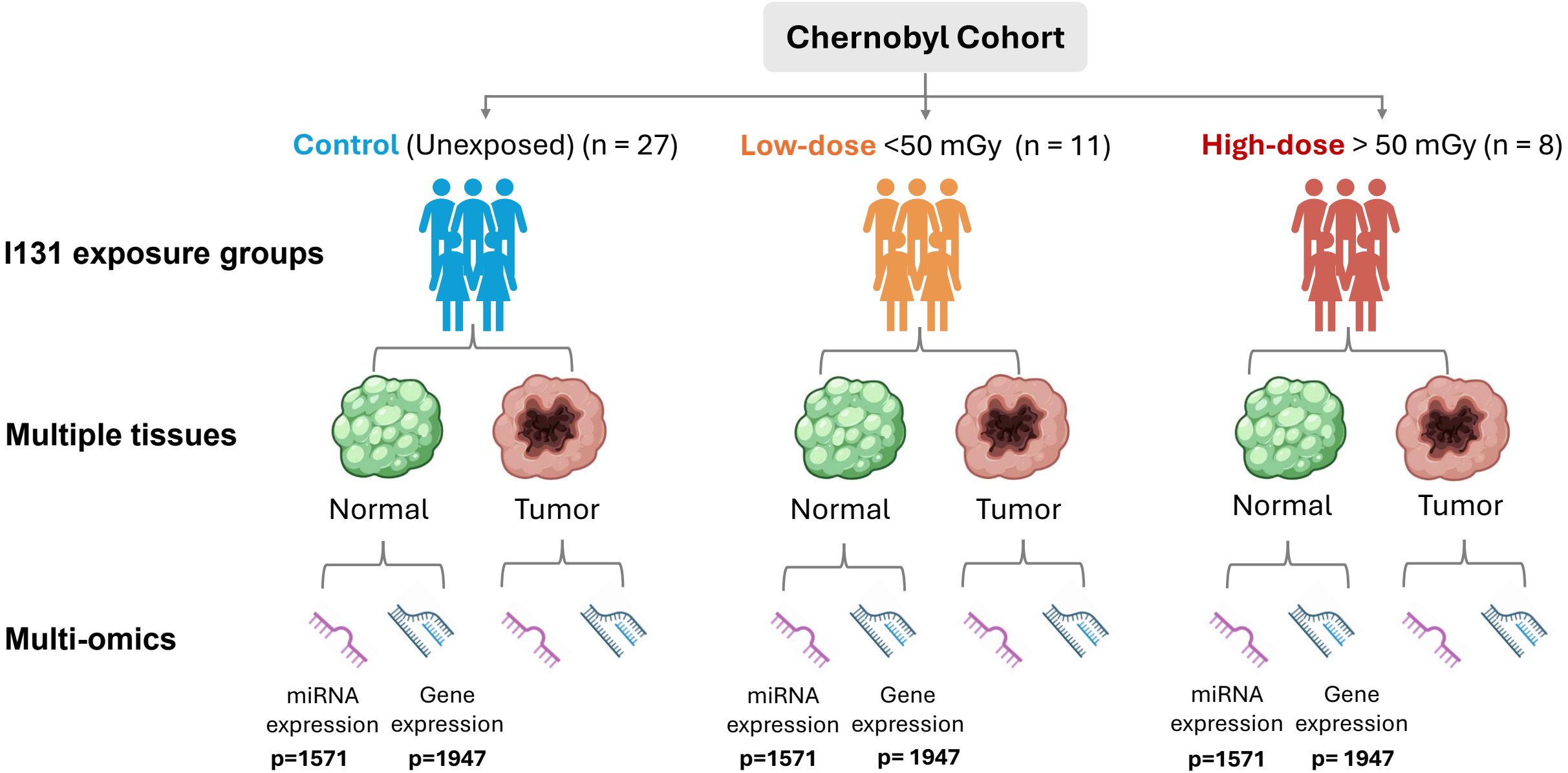
Understand the impact of low-dose radiation exposure (<100 mGy) on molecular mechanisms of thyroid cancer

Our Chernobyl Cohort study design



State-of-the-Art in Network Inference

Signatures detection through feature selection

Our previous study **[1]** identified radiation-associated molecular **signatures.**

But such biomarker approaches are not designed to **explore** **low-dose** specific interaction networks.

Gaussian Graphical models

Sparse Graphical models enable the reconstruction of molecular networks.

But existing graphical models do not **simultaneously** handle all the constraints of **our design study**:

multi-group, multi-tissue and multi-omics.

[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.

State-of-the-Art in Network Inference

Existing approaches typically address only a subset of the problem

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

Method	Multi-group	Multi-tissue	Multi-omics
FGL [2]	✓		
CoGLasso [3]			✓
Hetero-difgraph [4]	✓		
DIABLO [5]	✓		✓
multiSLICE [6]		✓	✓

[2] Danaher et al., *The Joint Graphical Lasso for Inverse Covariance Estimation Across Multiple Classes*, 2014.
[3] Albanese et al., *Multi-Omics Network Reconstruction with Collaborative Graphical Lasso*, 2026.
[4] Li et al., *Subgroup Analysis of Differential Networks with Latent Variables*, 2025.
[5] Singh et al., *DIABLO: An Integrative Approach for Identifying Key Molecular Drivers from Multi-Omics Assays*, 2019.
[6] Ondrus et al., *A Latent Multilayer Graphical Model for Complex, Interdependent Systems*, 2026.

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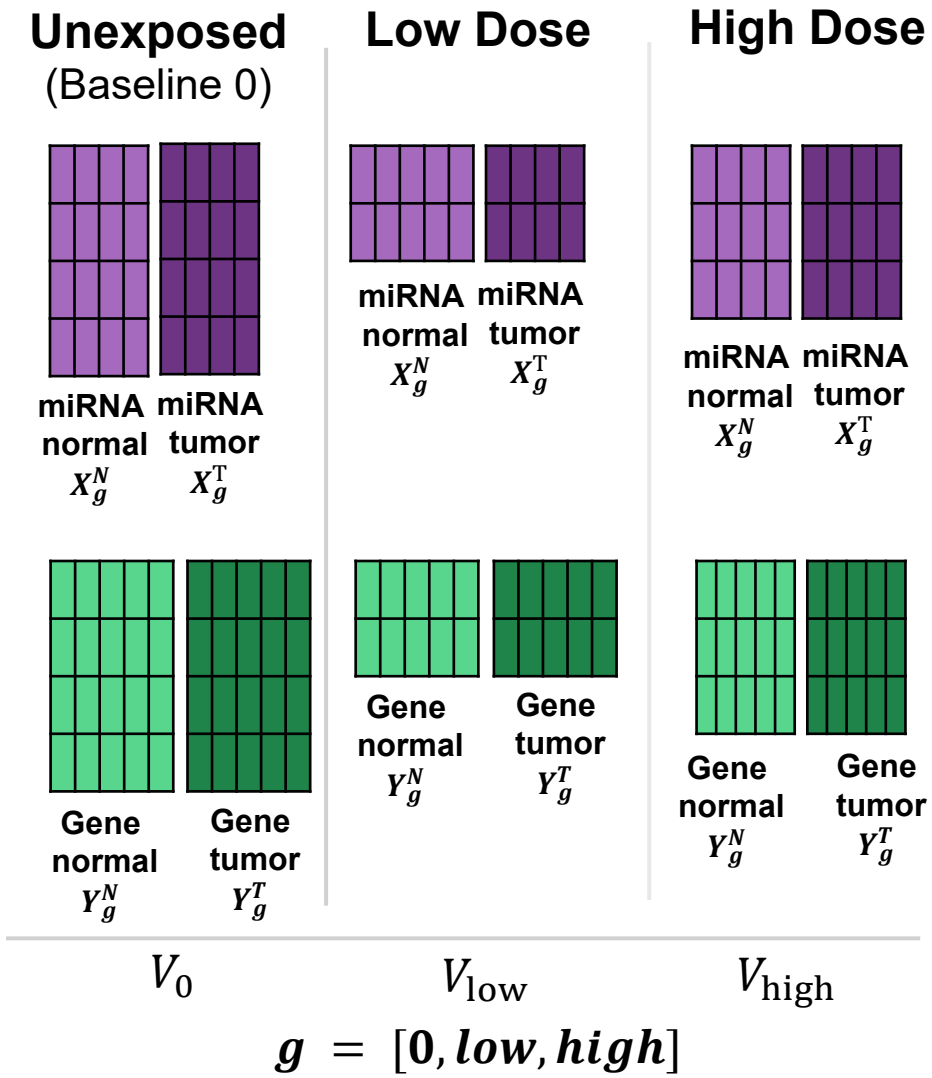
DIABLO	✓		✓
multiSLICE		✓	✓
Multi-DiffNet (our model)	✓	✓	✓

Gap: jointly model multi-omics × multi-tissue × multi-group data

Multi-DiffNet: Joint Multi-Tissue Multi-Omics Network Inference

From Multi-Omics Data to Differential Networks

Multi-tissue multi-omics measurements



Multi-DiffNet: Joint Multi-Tissue Multi-Omics Network Inference

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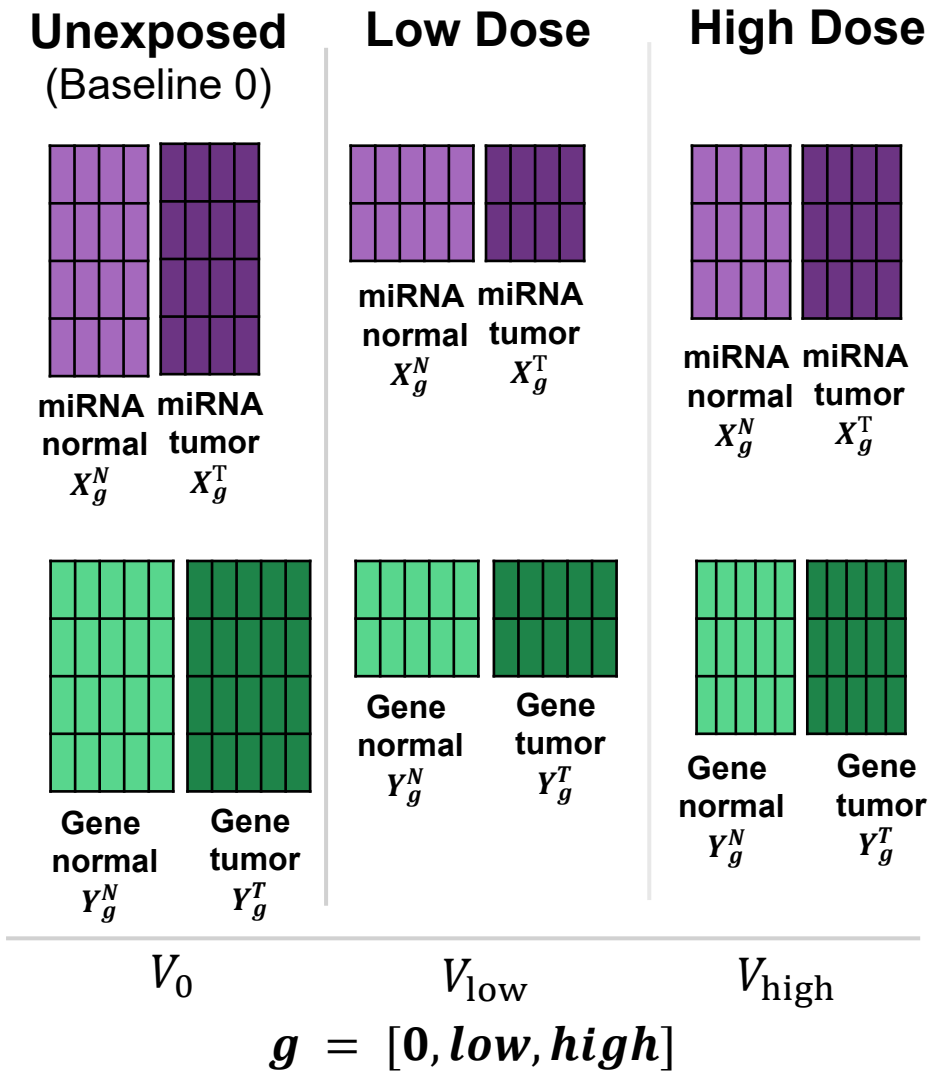

Multi-tissue multi-omics Integration

Shared latent Z_g

Captures the dependence structure across tissues and omics

$$Z_g \qquad V_g = \begin{bmatrix} X_g^N \\ X_g^T \\ Y_g^N \\ Y_g^T \end{bmatrix}$$

$$V_g = UZ_g + \varepsilon_g$$

$$L_0 = -UU^T$$

$$\theta_0 = S_0 + L_0$$

Multi-DiffNet Framework

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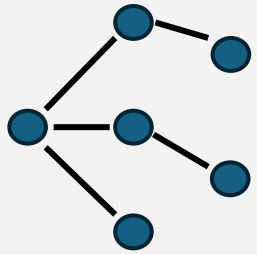
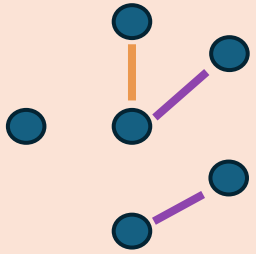
Example of network decomposition for a single tissue-omic layer

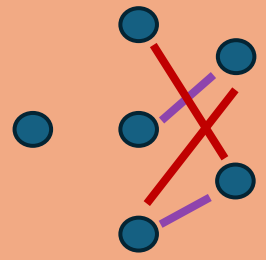
Shared baseline network θ_0



Low-dose network Δ_{low}



High-dose network Δ_{high}



Sparse latent differential graphical model

Joint network inference

$$\theta_{low} = \theta_0 + \Delta_{low},$$

$$\theta_{high} = \theta_0 + \Delta_{high},$$

Radiation-induced perturbation Δ_{rad}

Specific to Low-dose perturbation $\Delta_{spec-low}$

Specific to High-dose perturbation $\Delta_{spec-high}$

Multi-DiffNet: Model Formulation and Regularization

Objective Function

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

$$\mathcal{L}(S_0, L_0, \{\Delta_k\}) = n_0\left[-\log\det(\Theta_0) + \mathrm{Tr}\left(\widehat{\Sigma_0}\Theta_0\right)\right] + \lambda_1\|S_0\|_1 + \mu_0\|L_0\|_* + \sum_{k\in\{\mathbf{low},\,\mathbf{high}\}} n_k\left[-\log\det(\Theta_0 + \Delta_k) + \mathrm{Tr}\left(\widehat{\Sigma_k}(\Theta_0 + \Delta_k)\right)\right] + \sum_{k\in\{\mathbf{low},\,\mathbf{high}\}} \lambda_2^{(k)}\|\Delta_k\|_1 + \lambda_3\left\|\Delta_{\mathbf{low}} - \Delta_{\mathbf{high}}\right\|_1.$$

- $\Theta_0 = S_0 - L_0$: baseline network with sparse (S_0) and latent (L_0) components.
- Δ_k: dose-specific differential network ($k \in \{\mathbf{low}, \mathbf{high}\}$)
- $\widehat{\Sigma_0}$, $\widehat{\Sigma_k}$: empirical covariance matrices.
- λ_1: baseline sparsity penalty.
- $\lambda_2^{(k)}$: differential sparsity penalty.
- λ_3: similarity penalty between differential networks.
- μ_0: latent low-rank regularization parameter.

Simulation Study

Validation under controlled ground-truth networks

- **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.
- Validation through **multiple scenarios.**

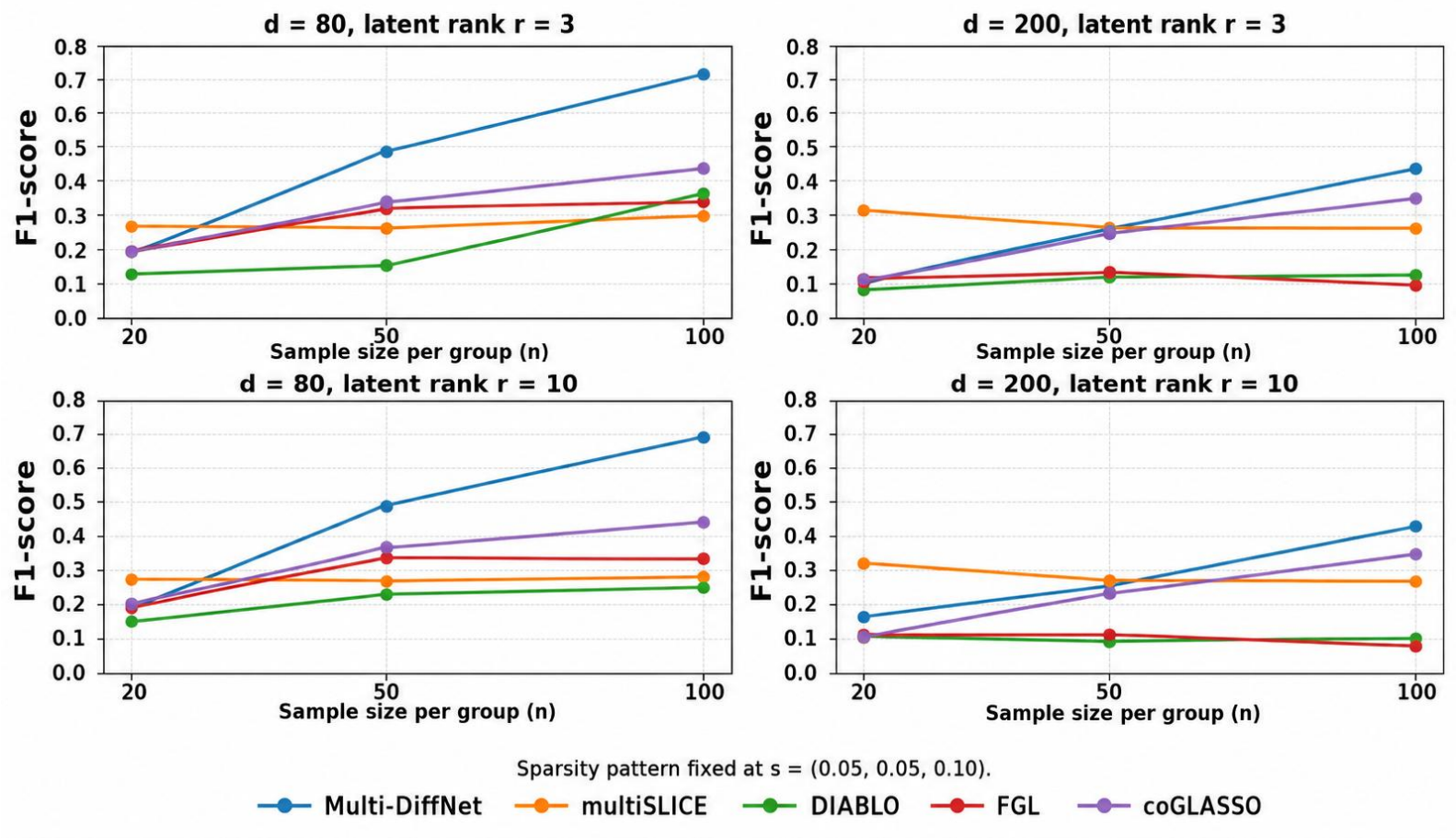
Dimension	Sample size	Latent rank	Replications
d = 80; 200	n = 20; 50; 100	r = 3; 10	50 per scenario

Compared methods: **multiSLICE • DIABLO • FGL • CoGLasso**

Evaluation: **Precision • Recall • F1-score • Edge estimation bias**

Multi-DiffNet Shows Consistent Gains Across Simulation Settings

Multi-DiffNet improves edge recovery compared to other methods across most scenarios



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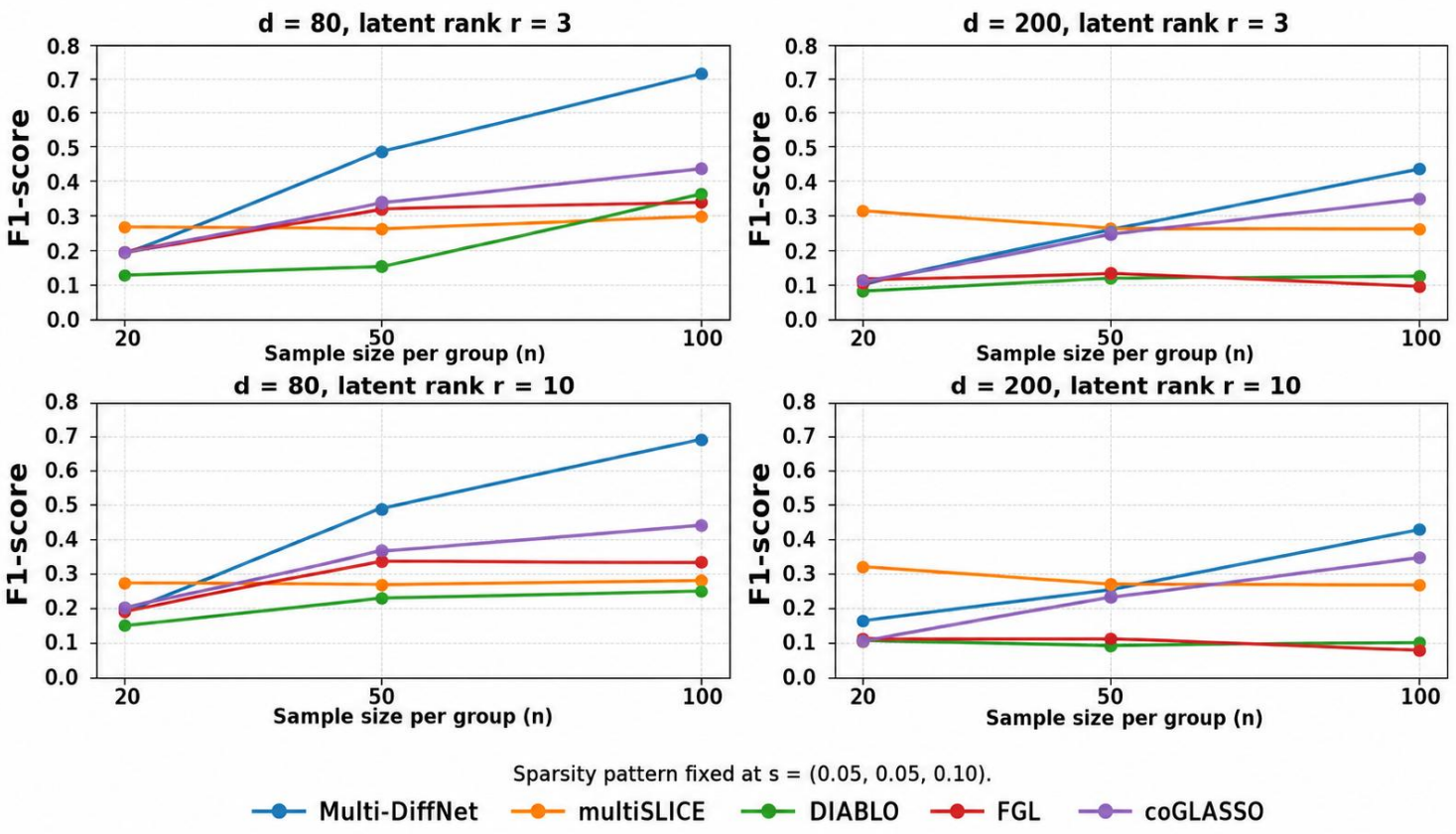


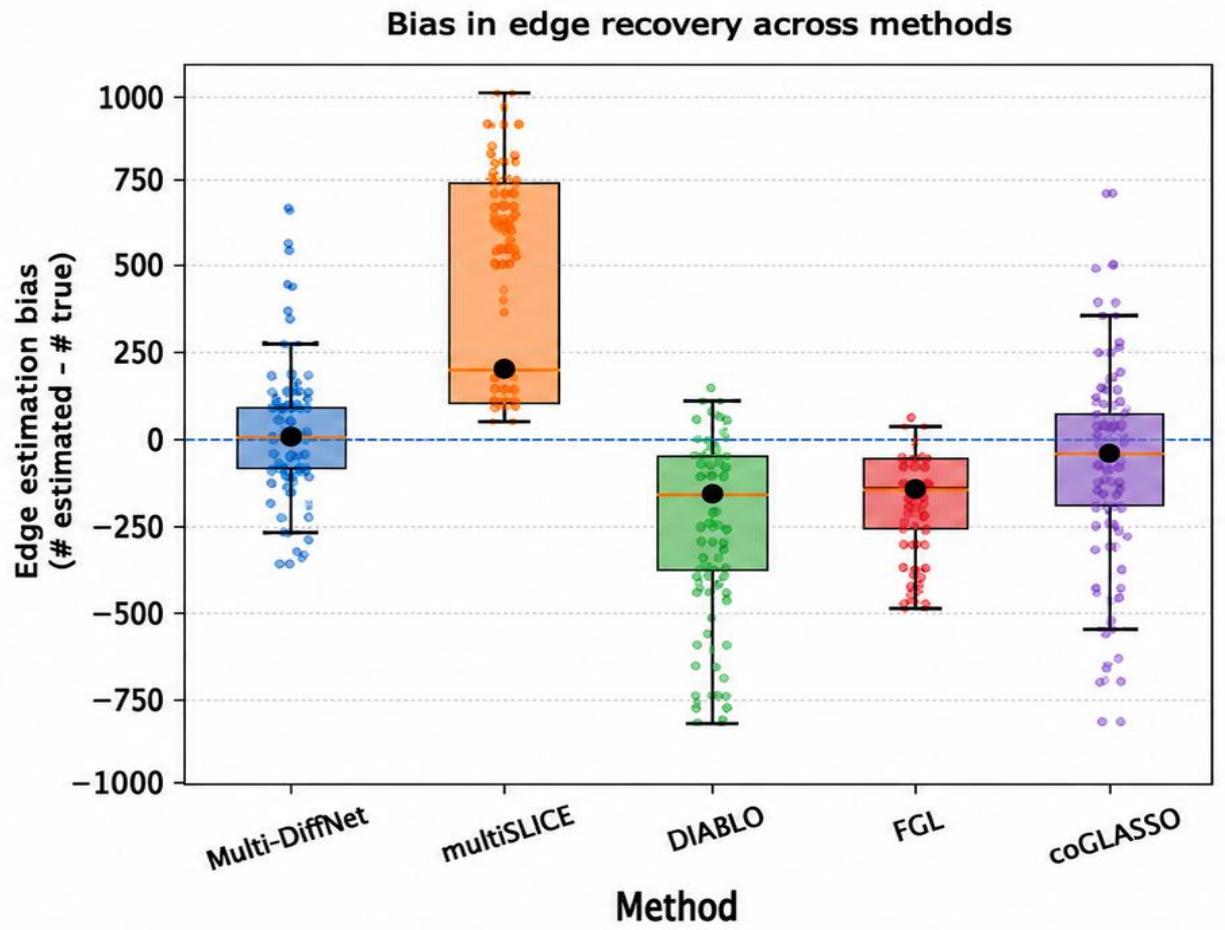
F1-score improves with sample size

n=20	n=50	n=100
0.20	0.49	0.72

Example: d = 80, r = 3

Multi-DiffNet Achieves the Most Accurate Edge Recovery

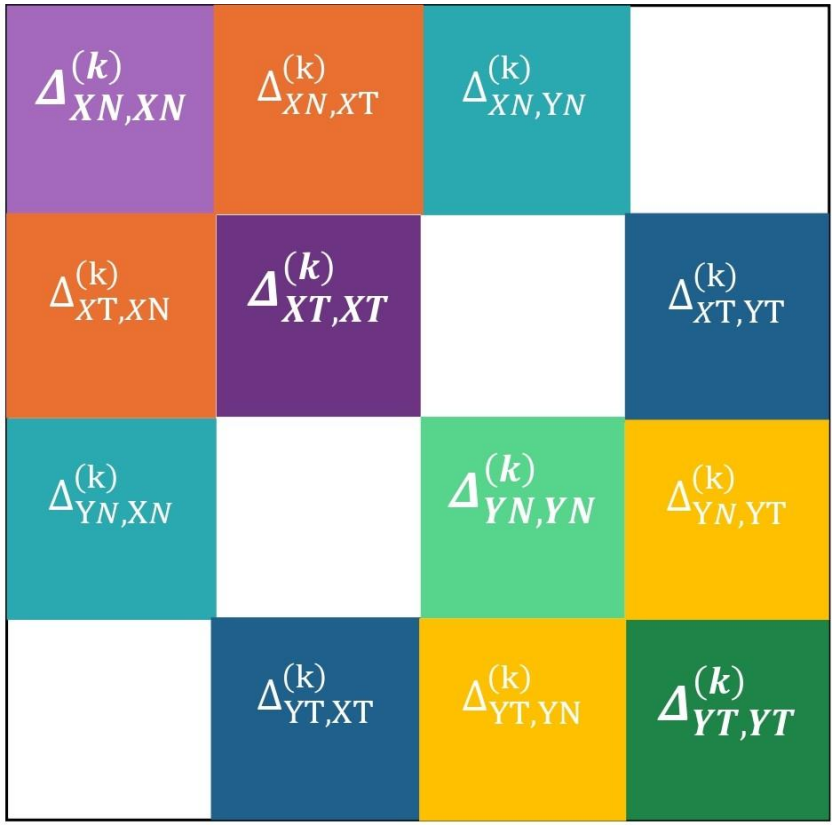
Multi-DiffNet: edge bias closest to zero



multiSLICE → overestimation | DIABLO / FGL → underestimation

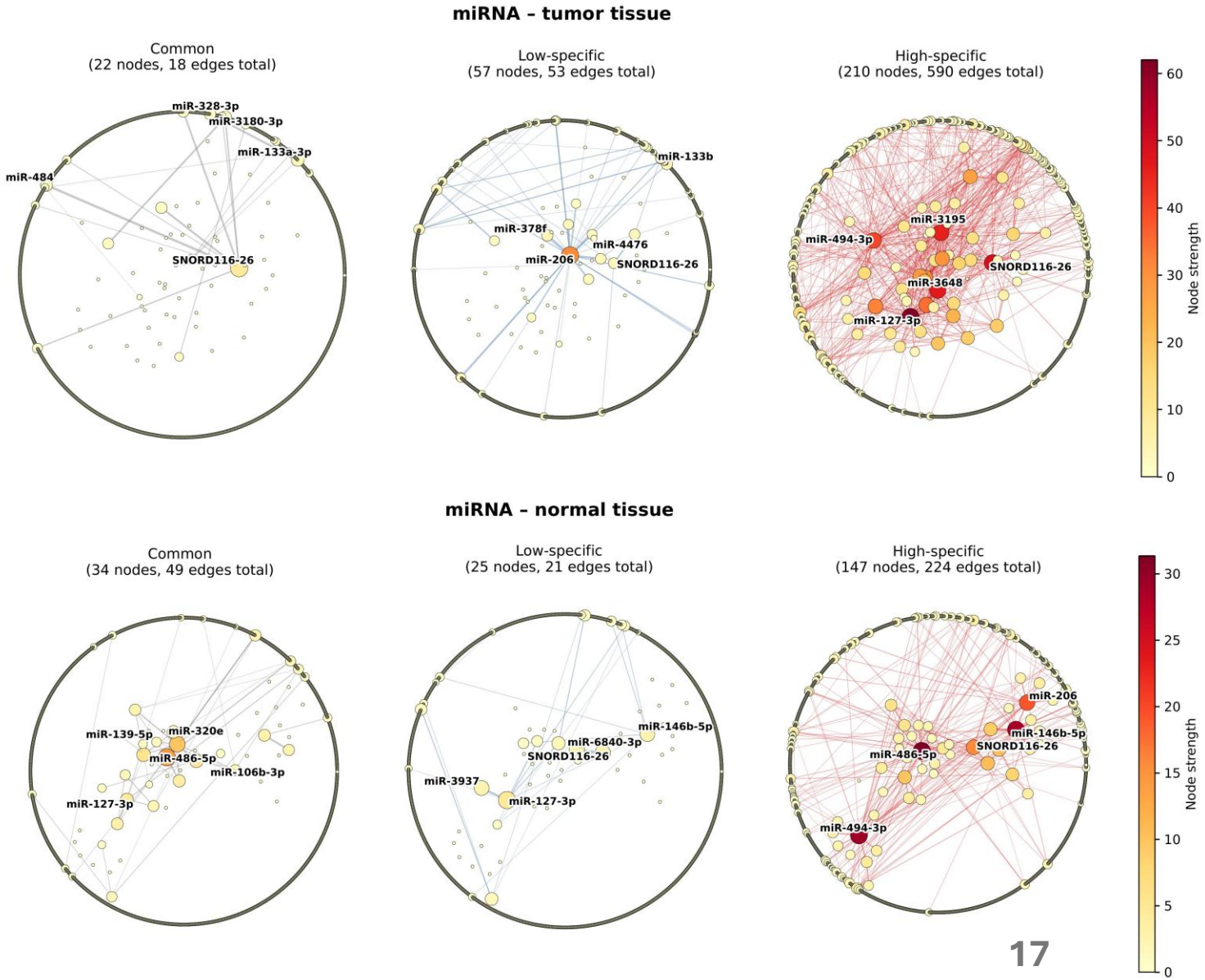
Multi-DiffNet Captures Interactions Across Omics and Tissues

Differential matrices provide intra-omics, cross-omics and cross-tissue interactions



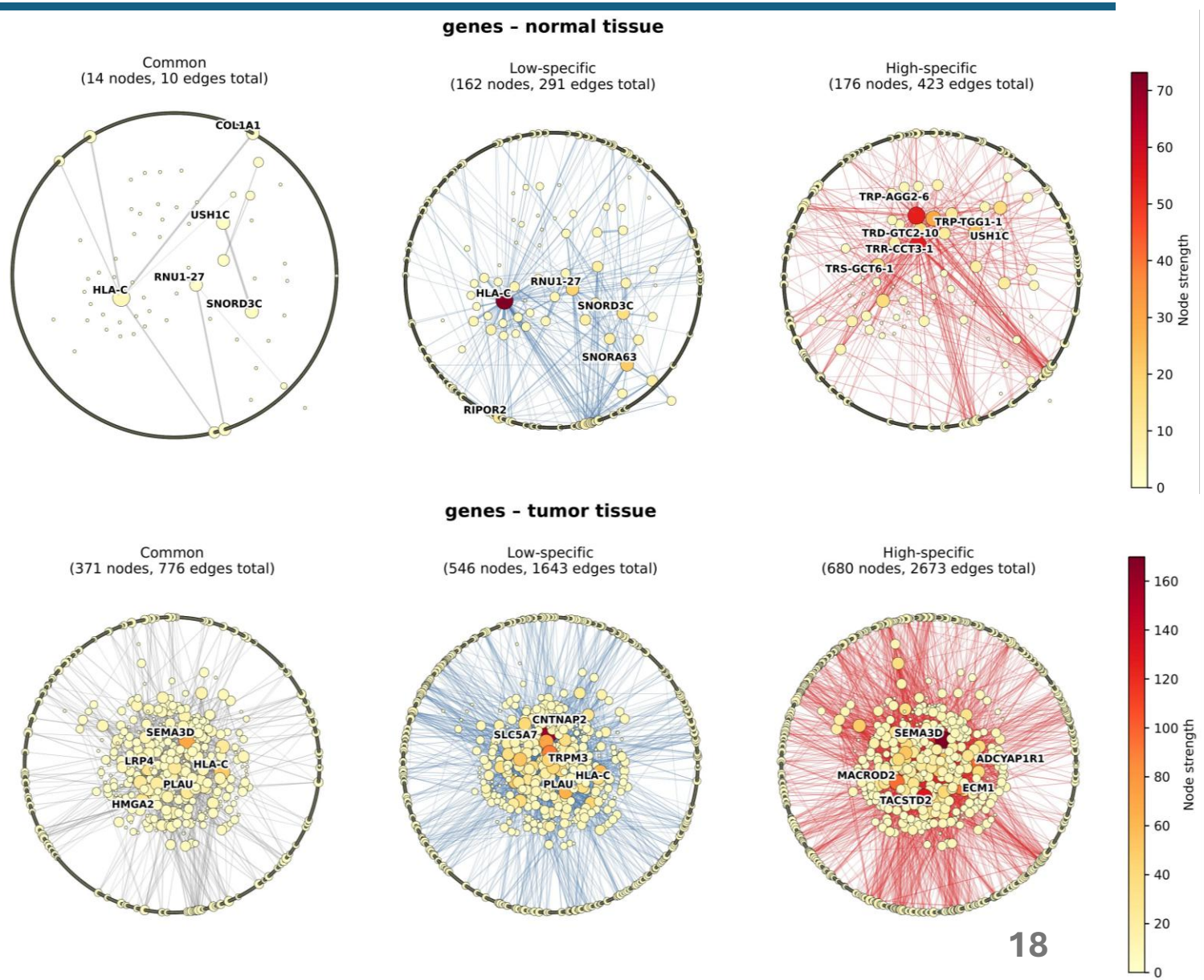
Radiation Exposure Drives Stronger miRNA Network Rewiring in Tumor Tissue

- **Tumor** networks are **more connected** than normal-tissue networks.
- **High**-dose exposure induces **stronger** network rewiring than **low**-dose exposure.
- **Common** interactions across both exposure groups reveal a **shared radiation-associated** response.

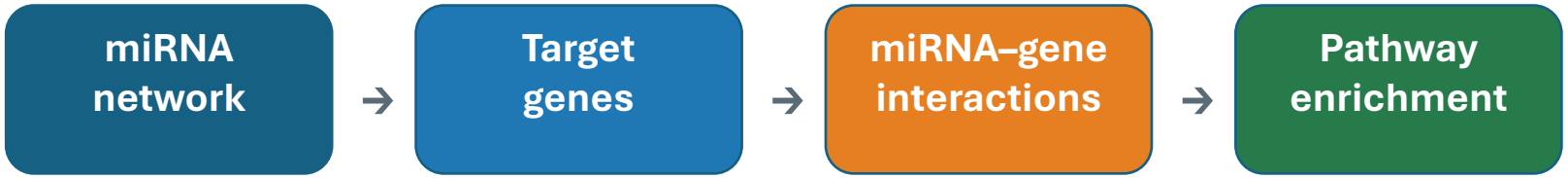


Radiation Exposure Drives Stronger Gene Network Rewiring in Tumor Tissue

- **Tumor gene networks** are **more connected** than normal-tissue networks.
- **High-dose** exposure induces **the strongest** gene network rewiring, particularly in tumor tissue.
- **Low-dose specific interactions remain detectable**, revealing distinct molecular alterations even at low exposure levels.



Cross-Omics Networks Reveal Dose-Dependent Radiation-Related Pathways



LOW DOSE

- **Integrin pathway**
- **EGR1-regulated pathway**
- **PLAU, FN1**

HIGH DOSE

- **PLAU–PLAUR pathway**
- **SERPINE1**
- **Matrix remodeling**
- **Vascular programs and Stress-related responses**

➔ Discovered genes and pathways **linked to radiation response and radiosensitivity**, and **previously reported** as **dysregulated in post-Chernobyl** and **post-radiotherapy thyroid tumors** (Abend et al., 2012; Ory et al., 2011; Stein et al., 2010; Ugolin et al., 2017; Detours et al., 2007; Mitsutake et al., 2011).

Conclusion and future work

Conclusion

- **Multi-DiffNet: Unified integration** of multi-group , multi-tissue and multi-omics.
- **Latent modeling** captures shared dependencies.
- Identifies **shared and dose-specific network perturbations**.
- **Well-balanced edge recovery** in simulations.
- Reveals **dose- and tissue-specific networks**, including **low-dose effects**.

Multi-DiffNet Code

Future work

- **Stability selection** for more robust edge inference and **hyperparameter selection**.
- Extended simulations to **more challenging high-dimensional settings with** $n \ll p$.
- **Reproducibility:** Validate **interactions and radiation-associated pathways in independent external datasets**.

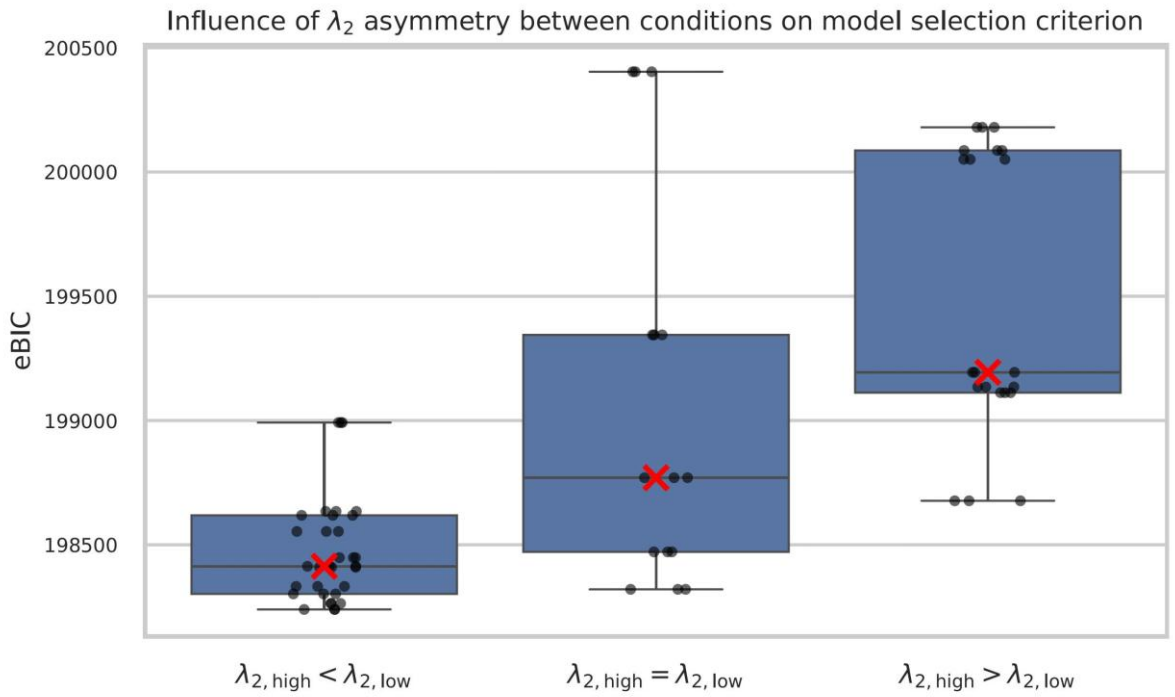
Acknowledgments

- **My co-authors:**
  - Charline Jouannet
  - Maâmar Souidi
  - **Catherine Ory**
  - **Mohamed Amine Benadjaoud**
- All members of the **LRAcc team**
- **ASNR, CEA, and EDF** for their support

Thank you for attention

MultiDiffNet model Selection Reveals an Asymmetric Differential Sparsity

Optimal model selection reveals dose-specific network sparsity



Selected model

$\lambda_1 = 0.1$

λ_2 low = 0.7

λ_2 high = 0.6

$\lambda_3 = 0.01$

$\mu_0 = 2.5$

Estimated latent rank = 27

Simulation results