Joint network inference comparative study for cancer characterization

Blanche Francheterre, Marc Chadeau-Hyam, Julien Chiquet
23/03/2026

MIA PARIS-SACLAY INRAE

Discern
Colorectal - Renal - Pancreatic - Cancers

IMPERIAL

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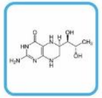
Figure 1: Iulianus in pisce

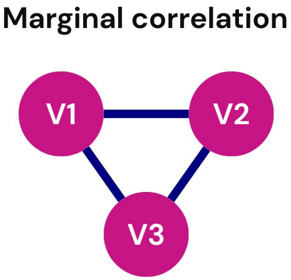
Motivation

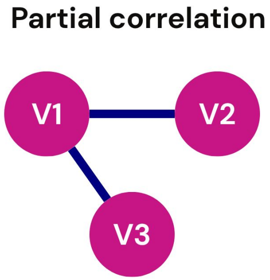
		Supporting Structure	Platforms (log10 order of magnitude)	Features
	Genome	DNA	Microarrays Sequencing	Categorical data Distance-driven correlation Extremely stable over time
	Epigenome	DNA methylation Histone modifications Non-coding RNA	Microarrays Bisulfite sequencing	Continuous data Affected by time and exposures (with reduced plasticity)
	Transcriptome	mRNA	Microarrays RNA sequencing	Continuous data Affected by time and exposures Strong measurement noise
	Proteome	Proteins	Microarrays Mass spectrometry	Continuous data Affected by time and exposures
	Metabolome	Small molecules	Mass spectrometry NMR spectroscopy	Continuous data Structured correlation Strongly affected by exposures
	Microbiome	Microbial DNA	Sequencing	Categorical/Count Data Structured correlation Affected by time and exposures

Motivation

Assumptions

- OMIC variables that are **involved in the same regulatory pathways** tend to be **correlated**
- **Gaussian graphical models** infer **direct associations** between variables by estimating **partial correlations** [Lauritzen, 1996]





Conditionnally on V1, V2 and V3 are independent

Motivation

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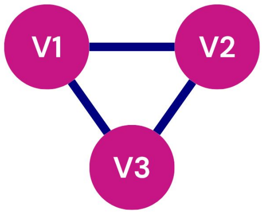
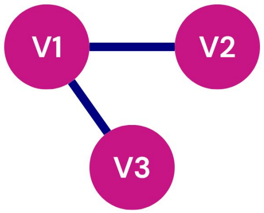
Marginal correlation



Partial correlation



Conditionnally on V1, V2 and V3 are independent

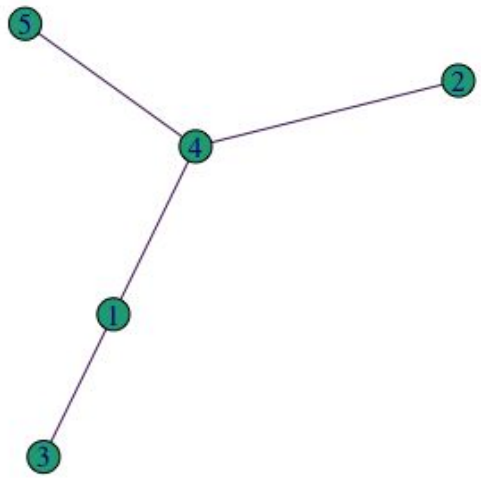
→ These **partial correlations** are encoded in **the precision matrix, Ω**

$$X_i \sim \mathcal{N}(\mu, \Omega^{-1})$$

Motivation

$$\Omega = \begin{pmatrix} 1.71 & 0 & 0.23 & 0.47 & 0 \\ 0 & 1.54 & 0 & -0.54 & 0 \\ 0.23 & 0 & 1.23 & 0 & 0 \\ 0.47 & -0.54 & 0 & 2.52 & 0.5 \\ 0 & 0 & 0 & 0.5 & 1.5 \end{pmatrix}$$

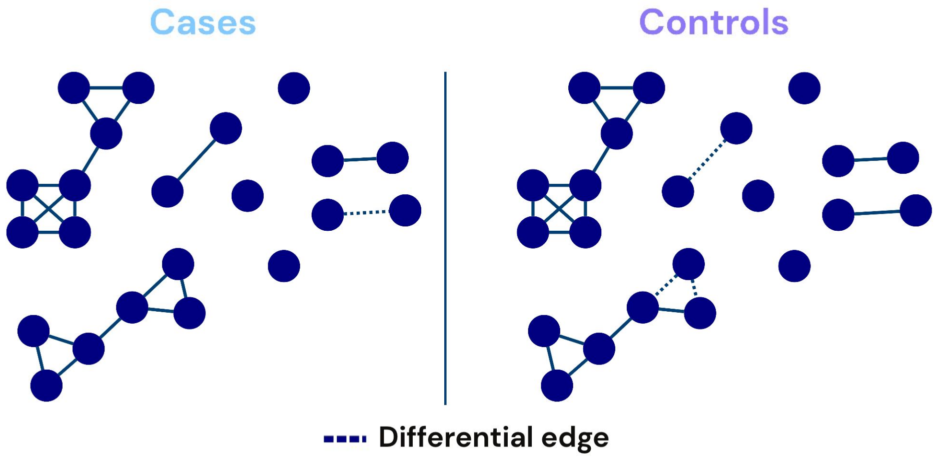
$$A = \begin{pmatrix} 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$



Hypothesis

Let $X \in \mathbb{R}^{n \times p}$ the matrix of observations and $Y \in \{1, 2, .., K\}$ the response variable.
Let $K = 2$, we assume that $X_1 \sim \mathcal{N}(\mu_1, \Sigma_1), X_2 \sim \mathcal{N}(\mu_2, \Sigma_2)$, where $X_1 = (\mathbf{x_i} : Y_i = 1)$ and $X_2 = (\mathbf{x_i} : Y_i = 2)$ such that:

$$\Sigma_1^{-1} = \Omega_1$$



$$\Sigma_2^{-1} = \Omega_2$$

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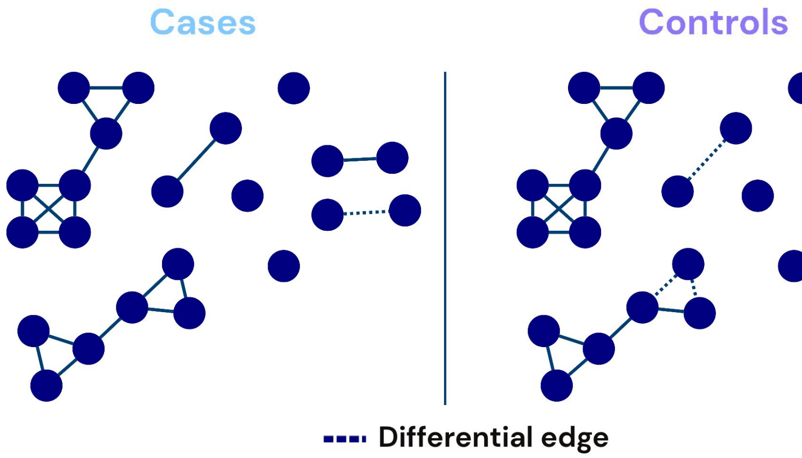

$$\Sigma_2^{-1} = \Omega_2$$

Graphs have a **shared structure** between classes with **differential edges**

→ **Joint network inference**

Objectives

Estimate

- For each condition k: $\mathcal{E}^{(k)} = \{(i,j) : \Omega_{ij}^{(k)} \neq 0,\ i \neq j\}$
- The differential structure

$$\mathcal{E}_{\text{suppdiff}}^{(kk')} = \mathcal{E}^{(k)} \triangle\, \mathcal{E}^{(k')},\ \text{where } \triangle \text{ denotes the symmetric difference and } k \neq k'$$

- The differential edge weights

$$\mathcal{E}_{\text{precdiff}}^{(kk')} = \{(i,j) : \Omega_{ij}^{(k)} \neq \Omega_{ij}^{(k')}\},\ \text{where } k \neq k'$$

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Research questions

➔ Considering joint and independent network estimation approaches, **under what conditions** do they perform best at **recovering shared and condition-specific network structure**?

➔ Which **hyperparameter calibration** strategy yields the most reliable edge detection?

Joint network inference methods

Method	Loss	Penalties
Graphical lasso (GL) [Yang et al, 2007, Danaher et al, 2014]	$\min_{\{\Omega\}_{k=1}^K} \sum_{k=1}^K n_k \left[\mathrm{tr}\left(\hat{\Sigma}^{(k)}\Omega^{(k)}\right) - \log\det(\Omega^{(k)})\right]$	• L1 penalty on edges • L1 penalty on edges + joint fused penalty • L1 penalty on edges + joint group penalty • L1 penalty on edges + node based penalty
Neighborhood selection (NS) [Meinshausen & Bühlmann, 2006]	$\min_{\{\beta\}_{k=1}^K} \sum_{k=1}^K \sum_{j=1}^p \frac{1}{2n_k} \left\Vert X_j^{(k)} - X_{-j}^{(k)} B_j^{(k)} \right\Vert_2^2$ $\beta_{ij}^{(k)} = 0 \Leftrightarrow \omega_{ij}^{(k)} = 0$	• L1 penalty on edges • L1 penalty on edges + joint fused penalty • L1 penalty on edges + joint group penalty • Data shared lasso
Partial correlation based neighborhood selection (PC) [Peng et al, 2009]	Let $\tilde{X}_i^{(k)} = \sqrt{\frac{\sigma_{ii}}{\sigma_{jj}}} X_i^{(k)}$ $\min_{\{\rho\}_{k=1}^K} \sum_{k=1}^K \sum_{j=1}^p \frac{1}{2n_k} \left\Vert X_j^{(k)} - \sum_{i \neq j} \rho_{ij}^{(k)} \tilde{X}_i^{(k)} \right\Vert_2^2$	• L1 penalty on edges • L1 penalty on edges + joint fused penalty • L1 penalty on edges + joint group penalty
Dtrace [Yuan et al, 2017]	Let $\Omega_{\text{diff}} = \Omega_2 - \Omega_1$ $\min_{\Omega_{\text{diff}}} \left[\frac{1}{2} \mathrm{Tr}\left(\Omega_{\text{diff}}^{\mathsf{T}} \hat{\Sigma}_1 \Omega_{\text{diff}} \hat{\Sigma}_2\right) - \mathrm{Tr}\left(\Omega_{\text{diff}}(\hat{\Sigma}_1 - \hat{\Sigma}_2)\right)\right]$	• L1 penalty on differential edges

Penalties

Individual edge penalty

$$\lambda_1 \sum_{k=1}^{K} \sum_{i \neq j} \left| \Omega_{ij}^{(k)} \right|$$

$$+$$

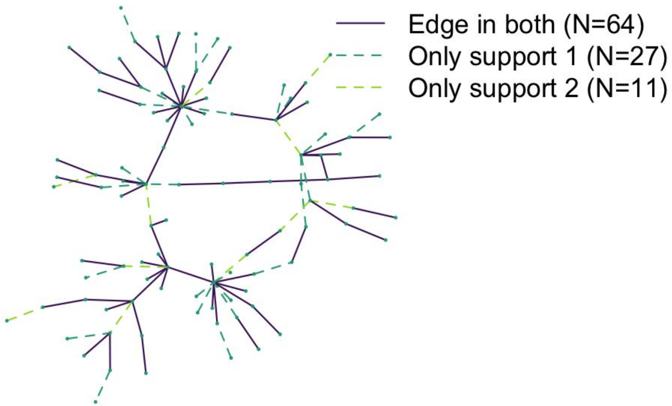
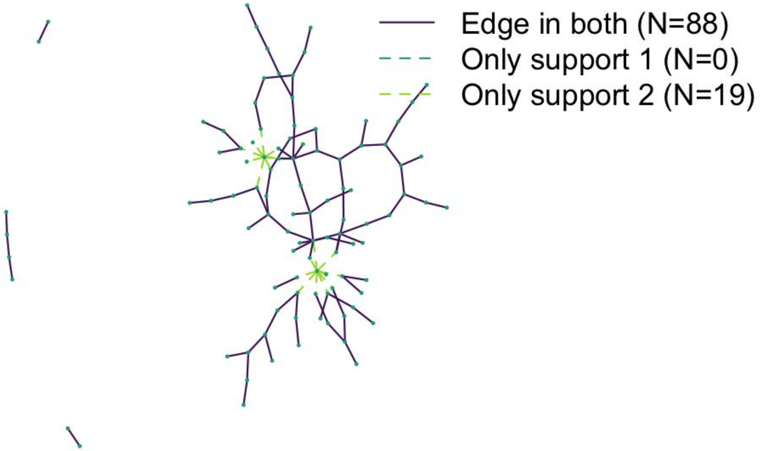
Joint fused penalty

$$\lambda_2 \sum_{k<k'} \sum_{i,j} \left| \Omega_{ij}^{(k)} - \Omega_{ij}^{(k')} \right|$$

Joint group penalty

$$\lambda_2 \sum_{i \neq j} \left(\sum_{k=1}^{K} {\Omega_{ij}^{(k)}}^2 \right)^{1/2}$$

Network generation

<table>
<tr><td>Number of nodes p</td><td colspan="2">30, 100, 300, 500</td></tr>
<tr><td rowspan="2">Topology</td><td>Scale-free</td><td>Random graph with hubs</td></tr>
<tr><td>
</td><td>
</td></tr>
<tr><td>Differential edge</td><td colspan="2">➔ Random
➔ Rewiring
➔ Hub-based</td></tr>
</table>

Data generation

- ➔ Generate **2 positive definite matrices** for the corresponding graphs
- ➔ **Σ_1, Σ_2**: computed as the **inverse of precision matrices**
- ➔ We simulate data from a **multivariate Normal distribution** $N(0,\Sigma_k)$, where $k \in \{1, 2\}$
- ➔ Sample sizes: **N = 50, 100, 200** per condition
- ➔ **50 independent replicates** of datasets X_1 and X_2

Performance evaluation

Evaluation of differential support edges

Compute over λ_2 :

- Area under the precision-recall curve (AUPR)
- Area under recall vs. false-positive rate (AUC)
- Area under power vs. FDR (AUPF)

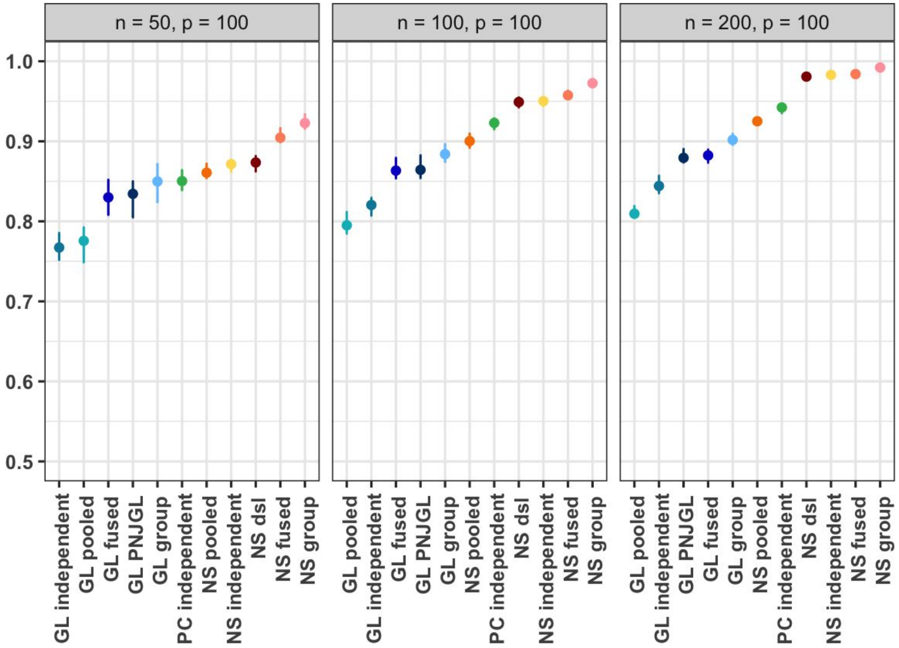
Evaluation of overall graph inference

- Apply the same metrics to assess graph recovery over λ_1

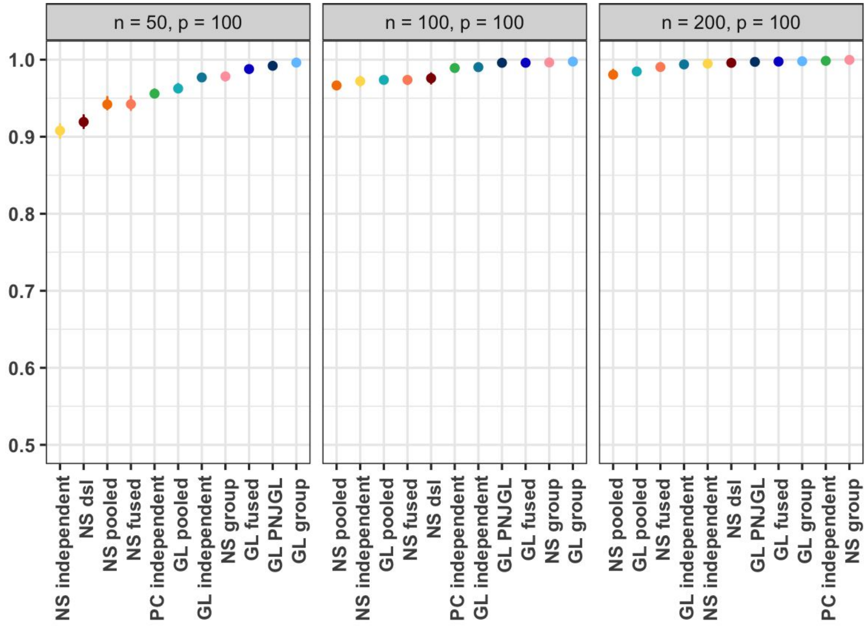
For each method, record the **maximum F1-score** in terms of edge recovery across λ_1 , λ_2 parameters and average it over the 50 simulated datasets

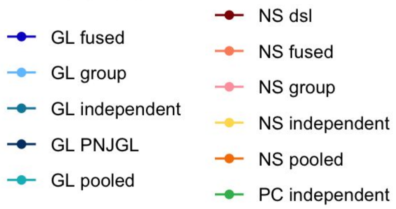
Results - hub based perturbations

Median AUPR of graphs support recovery



Median AUROC of graphs support recovery

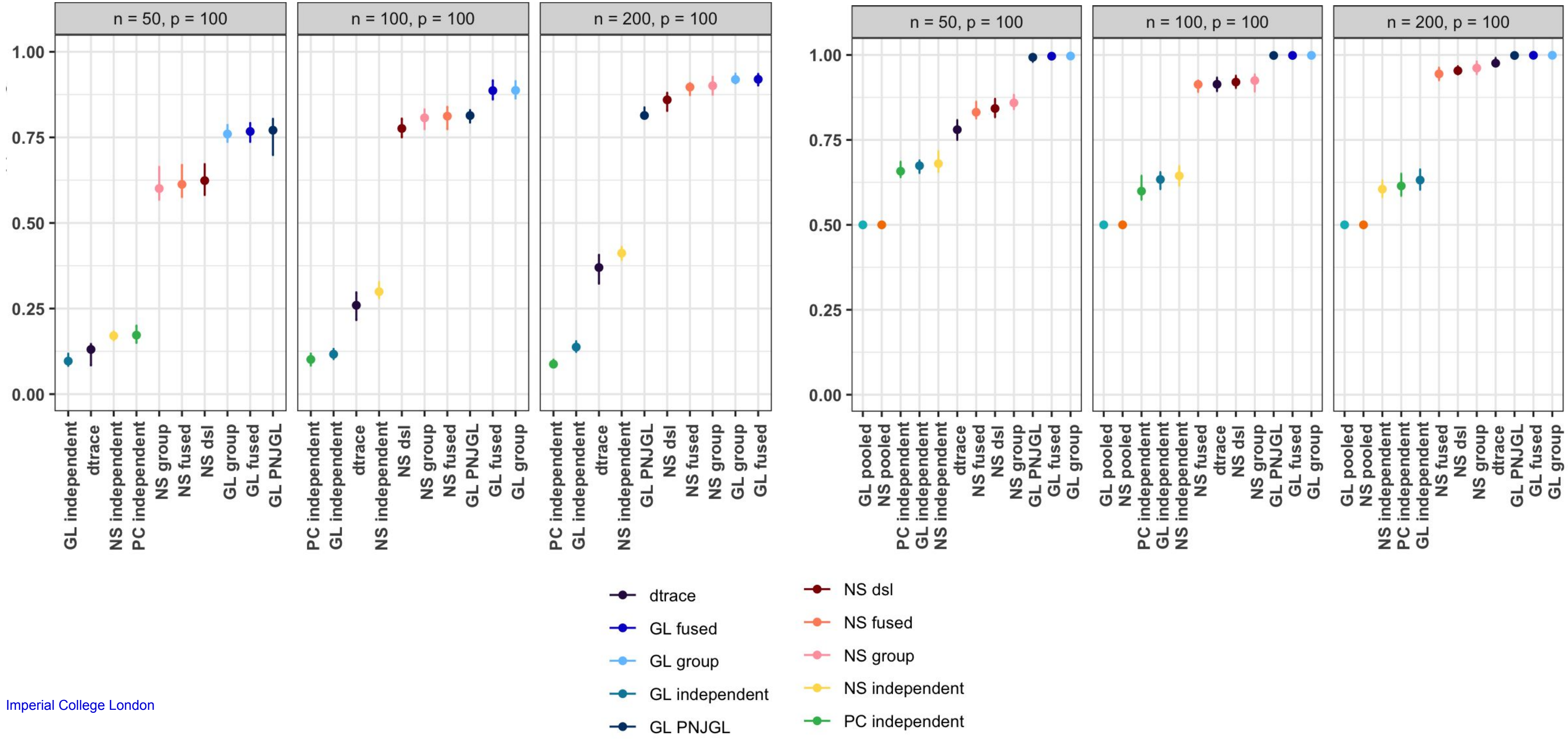




Results - hub based perturbations

Median AUPR of differential support recovery

Median AUROC of differential support recovery



Results - rewiring edge perturbations

Median AUPR of graphs support recovery

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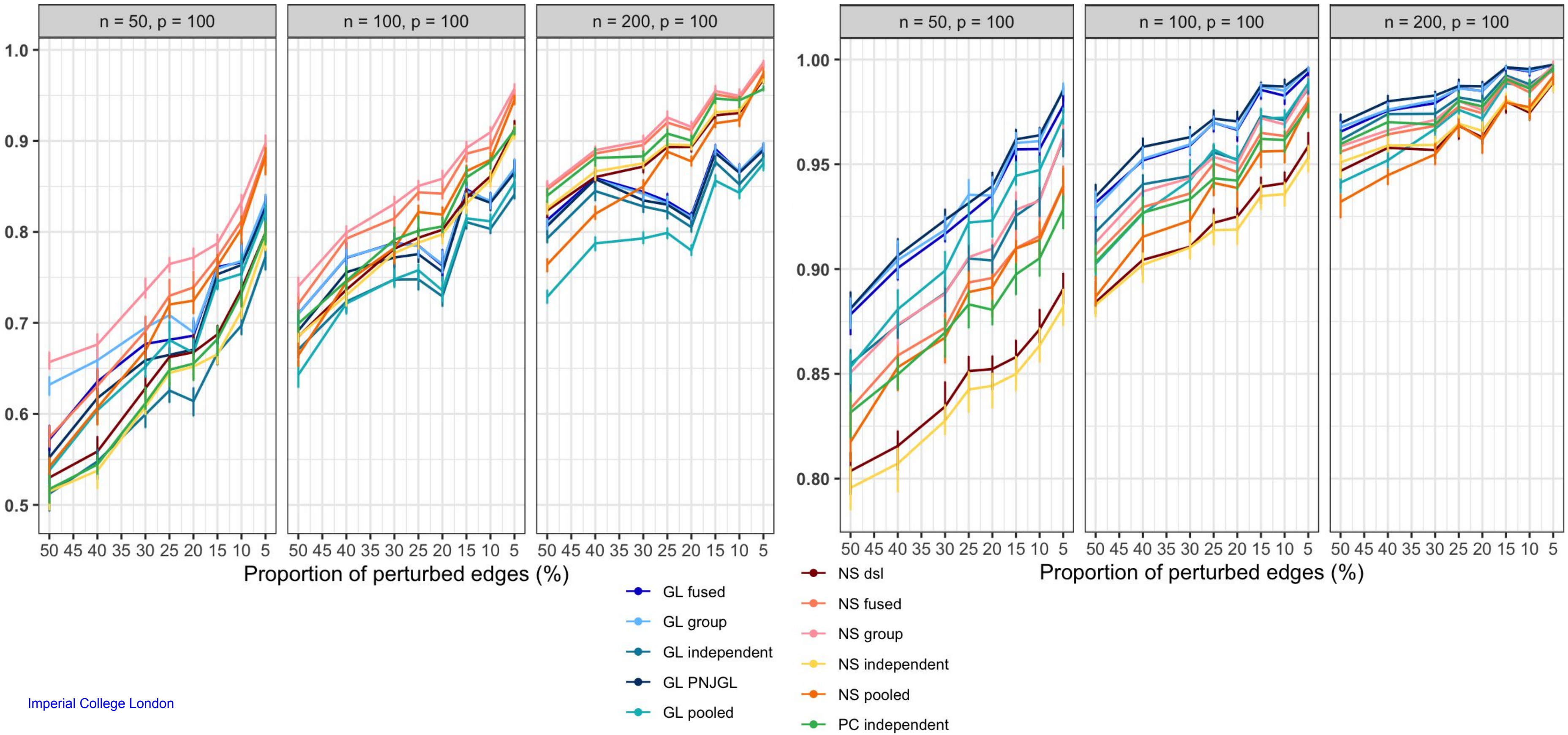

Results - rewiring edge perturbations

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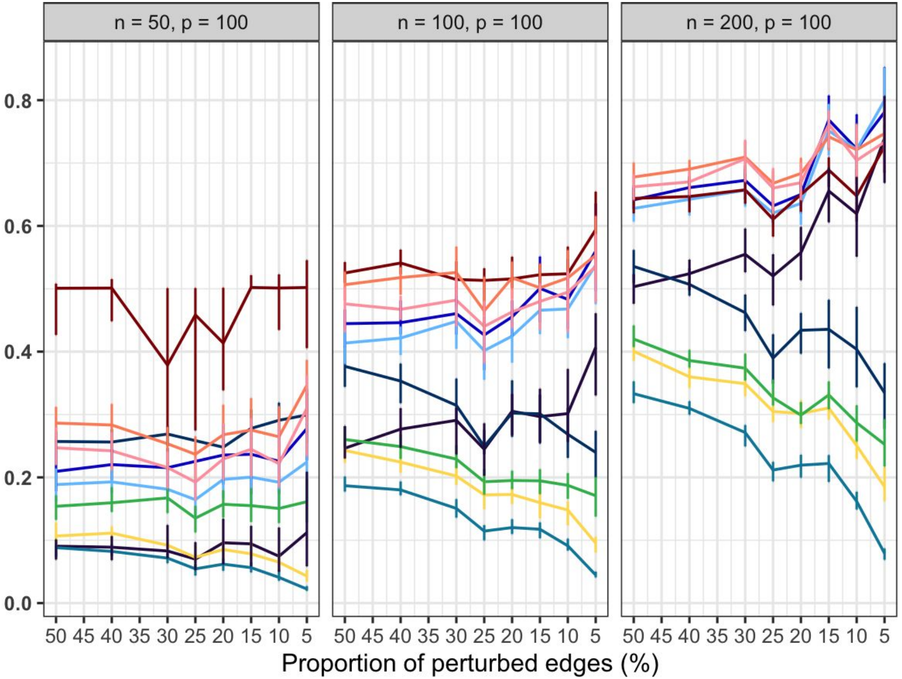

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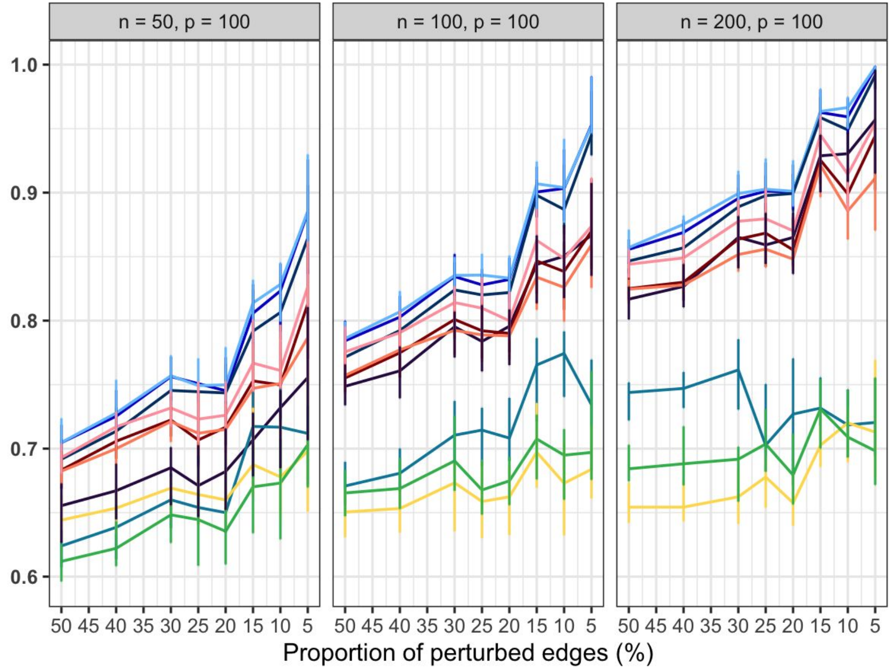


Model calibration

Information criteria

1. Obtain debiased precision matrices
2. Compute criteria: AIC, BIC, eBIC

$$\mathrm{eBIC}(\lambda_1, \lambda_2) = \sum_{k=1}^{K} \left[-2\ell(\hat{\Omega}^{(k)}(\lambda_1, \lambda_2) + |\mathcal{E}^{(k)}| \log(n_k) + 4\gamma |\mathcal{E}^{(k)}| \log(p) \right]$$

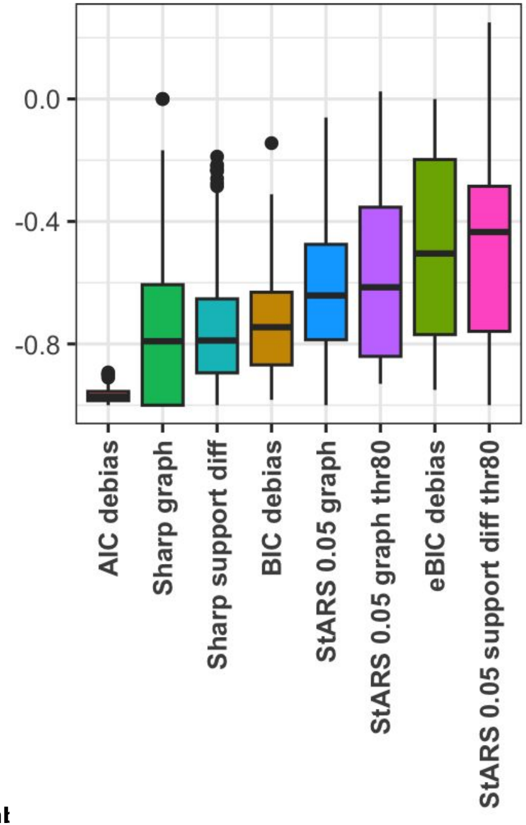
$\hat{\Omega}^{(k)}(\lambda_1, \lambda_2)$ is the estimated precision matrix for at (λ_1, λ_2), $|\mathcal{E}^{(k)}|$ is the number of edges

Subsampling-based calibration

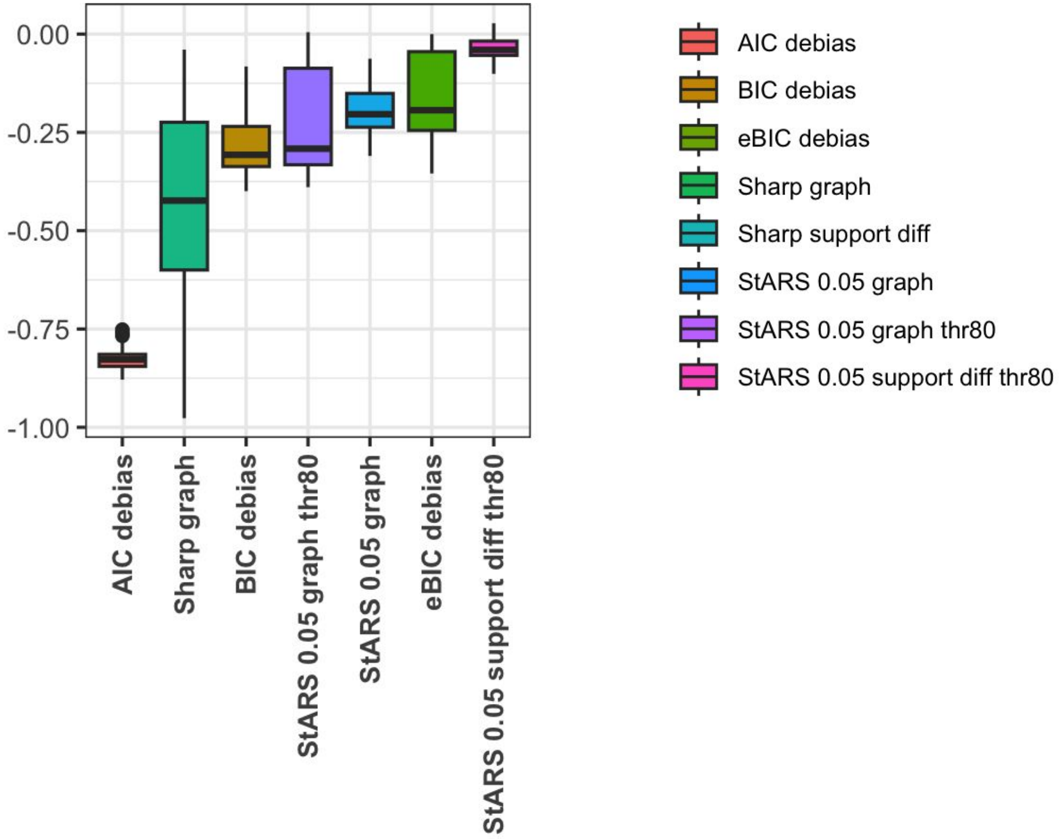
- StARS [Liu et al, 2010]
- Sharp [Bodinier et al, 2023]

Model calibration

Differential support recovery



Graphs support recovery

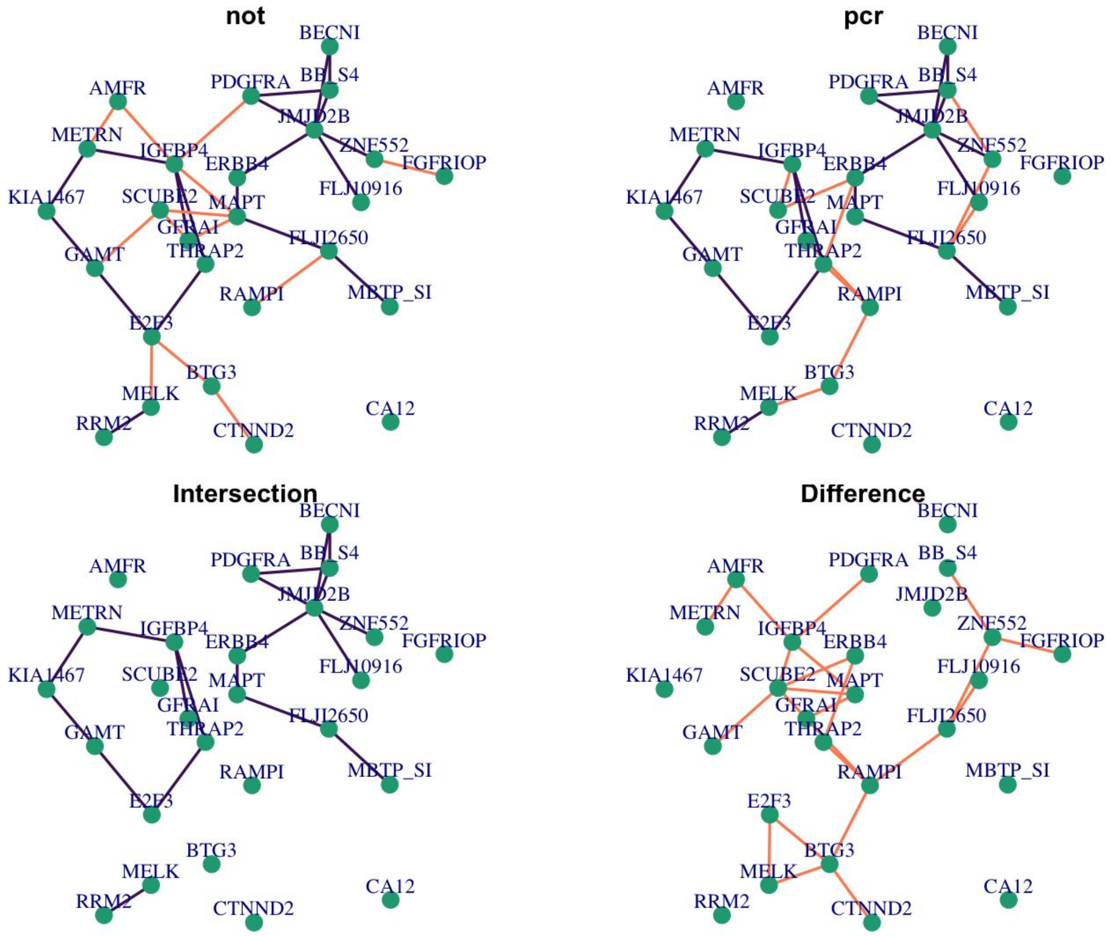


***neighl**

n=100 p=100

Application

- 133 patients with stage I-III breast cancer
- Patients were treated with **chemotherapy** prior to surgery.
- Patient response to treatment classified as **pathologic complete response** (pCR) or **residual disease** (not-pCR)
- 26 genes having a high predictive value



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Thank you

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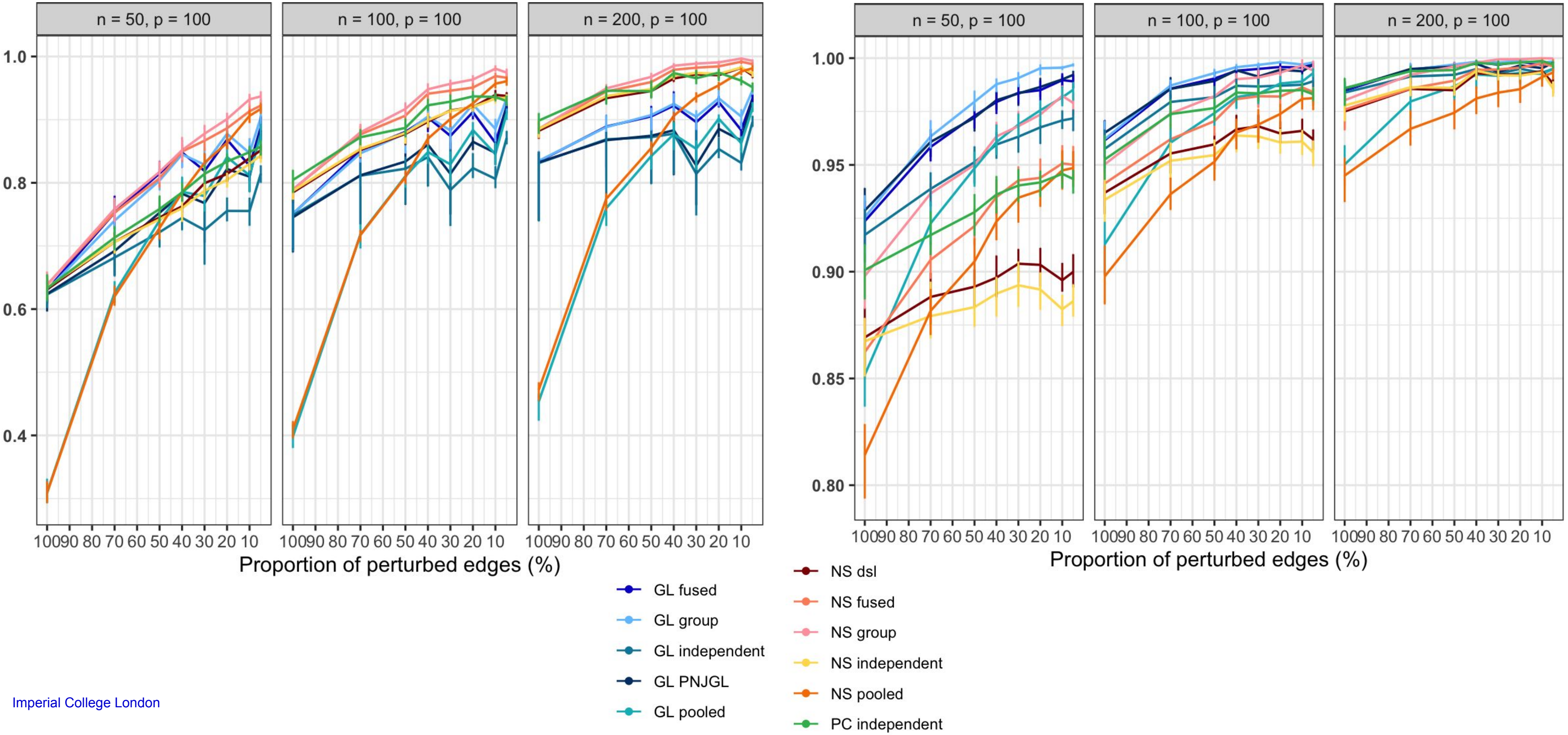
28/01/2026

Colorectal - Renal - Pancreatic - Cancers

Results - random edge perturbations

Median AUPR of graphs support recovery

Median AUROC of graphs support recovery



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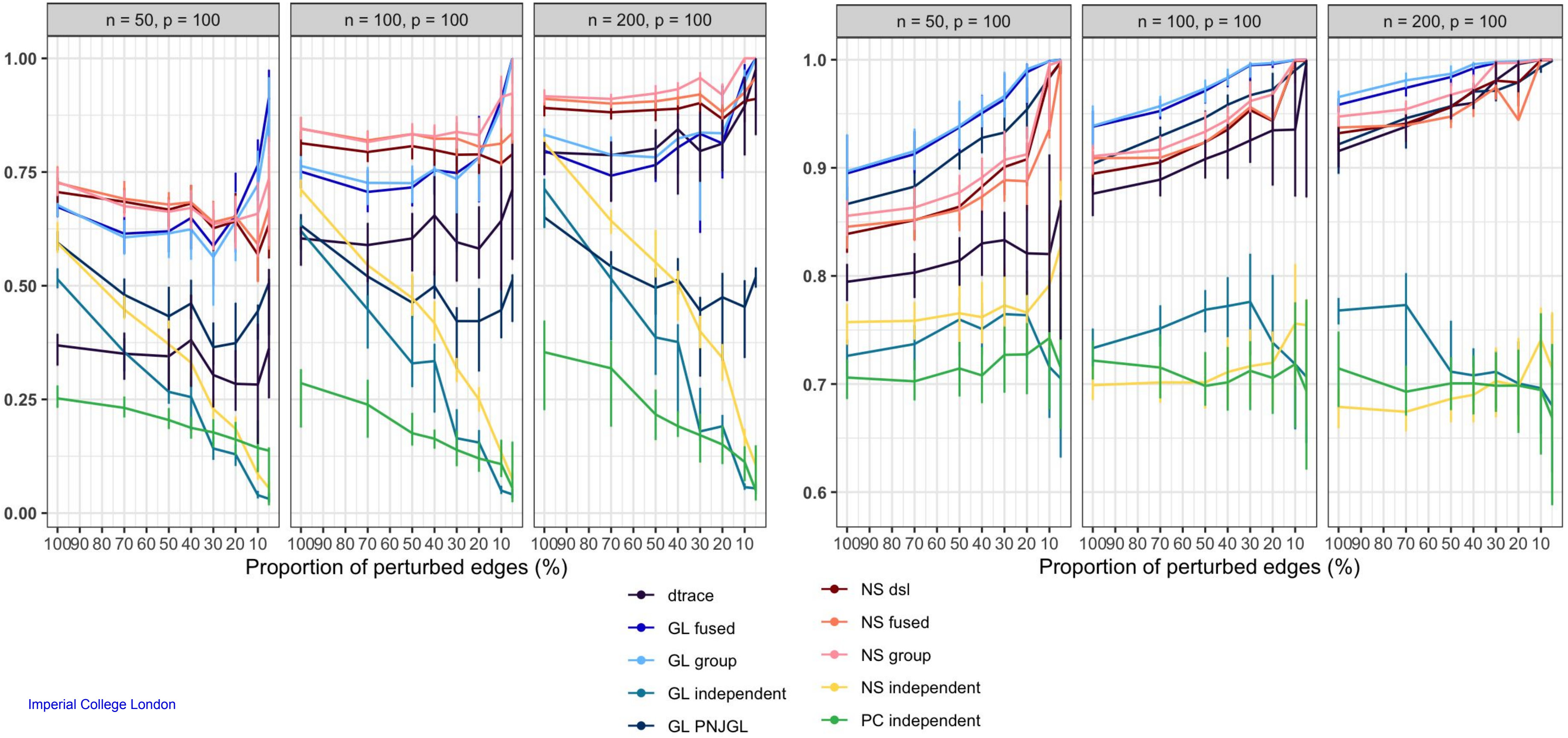


Weights

➔ **Improving edge selection** and incorporating **prior knowledge**

	Individual edges	**Joint fused**	**Joint group**
Penalty	$\lambda_1 \sum_{k=1}^{K} \sum_{i,j} \boldsymbol{w_{ij}^{(k)}} \left\lvert \beta_{ij}^{(k)} \right\rvert$	$\lambda_2 \sum_{k<k'} \sum_{i,j} \boldsymbol{w_{ij}^{(kk')}} \left\lvert \beta_{ij}^{(k)} - \beta_{ij}^{(k')} \right\rvert$	$\lambda_2 \sum_{i,j} \boldsymbol{w_{ij}} \left(\sum_{k=1}^{K} {\beta_{ij}^{(k)}}^2 \right)^{1/2}$
Adaptive weight	$w_{ij}^{(k)} = \frac{1}{\left\lvert \beta_{ij}^{(k)} \right\rvert}$	$w_{ij}^{(kk')} = \frac{1}{\left\lvert \beta_{ij}^{(k)} - \beta_{ij}^{(k')} \right\rvert}$	$w_{ij} = \frac{1}{\left(\sum_{k=1}^{K} {\beta_{ij}^{(k)}}^2 \right)^{1/2}}$
Degree-based weight	$w_{ij}^{(k)} = \frac{1}{\sqrt{(d_i^{(k)} + 1) \cdot (d_j^{(k)} + 1)}}$	$w_{ij}^{(kk')} = \frac{1}{\left\lvert \sqrt{(d_i^{(k)} + 1) \cdot (d_j^{(k)} + 1)} - \sqrt{(d_i^{(k')} + 1) \cdot (d_j^{(k')} + 1)} \right\rvert + \epsilon}$	$w_{ij} = \frac{w_{ij}^{(k)} + w_{ij}^{(k')}}{2}$

Weights

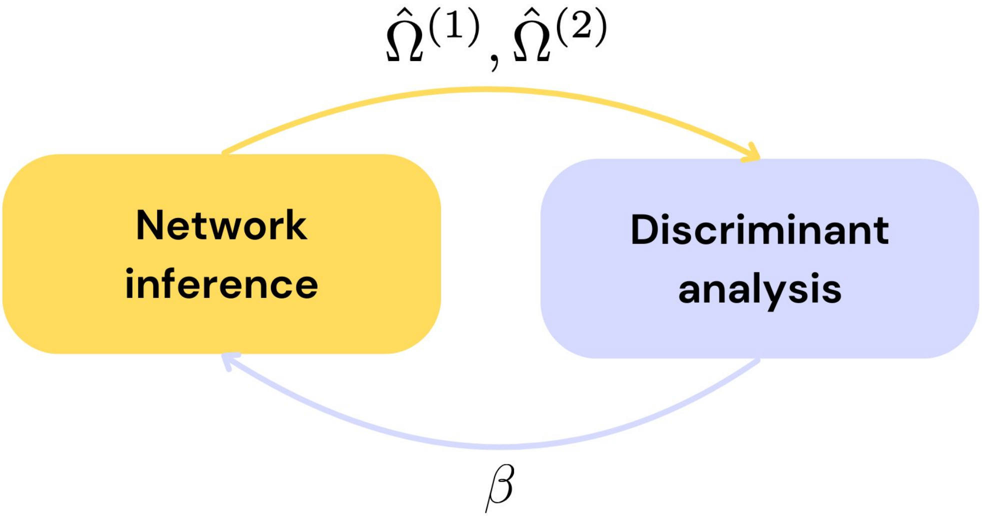
➔ **Improving edge selection** and incorporating **prior knowledge**

- Weights obtained from **Stochastic Block Model** clustering on the adjacency matrix [Ambroise et al, 2009]
- Weights obtained from **Multipartite Block Model** to account for multi-omics [unpublished Chiquet, 2018]

Next steps

➔ Combine joint network estimation and outcome discrimination to:

- improve **interpretability** and **discrimination**
- Identify both **structural** and **predictive differences** across classes



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