# Contents

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# Chapter 6

# Simulation and Modeling of Synthetic Lethal Pathways

Simulation and modelling of synthetic lethality in gene expression will be revisited in greater detail in this chapter, building upon the results provided to support the use of Synthetic Lethal Interaction Prediction Tool (SLIPT) in Section 3.3. A simulation procedure for generating simulated data with underlying (known) synthetic lethal partners of a query gene, such as *CDH1*, was developed (as described in Section 3.2.2) by sampling from a Multivariate normal distribution based on a statistical model of synthetic lethality in expression data (as described in Section 3.2.1). This simulation framework was applied to simulated data (in Section 3.3), including simple correlation structures to assess the statistical performance of the SLIPT methodology and support it's use a computational approach for detecting synthetic lethal candidates from expression data throughout this thesis (in Chapters 4 and 5).

While this basic framework was sufficent to support the use of SLIPT in prior Chapters, further investigations with simulations were conducted to assess the strengths and limitations of the SLIPT methodology, compare it to alternative statistical approaches to synthetic lethal detection, and assess it's performance upon more complex correlation structures. Together these simulation investigations assess the performance of the SLIPT methdology, including on pathway graph structures (such as those discussed in Chapter 5) and determine whether the SLIPT methdology (or similar refined bioinformatics strategies) are statistically rigourous or suitable for wider genomics applications.

These simulation investigations continue to utilise the Multivariate Normal procedure (as applied in Section 3.3) with further refinements. The SLIPT methodology (and it's equivalent $\chi^2$ test) were applied across a range of parameters (including al-

tering the quantiles for detecting synthetic lethal direction and compared correlation. This was also applied to with query correlated genes (as performed in Section 3.3).

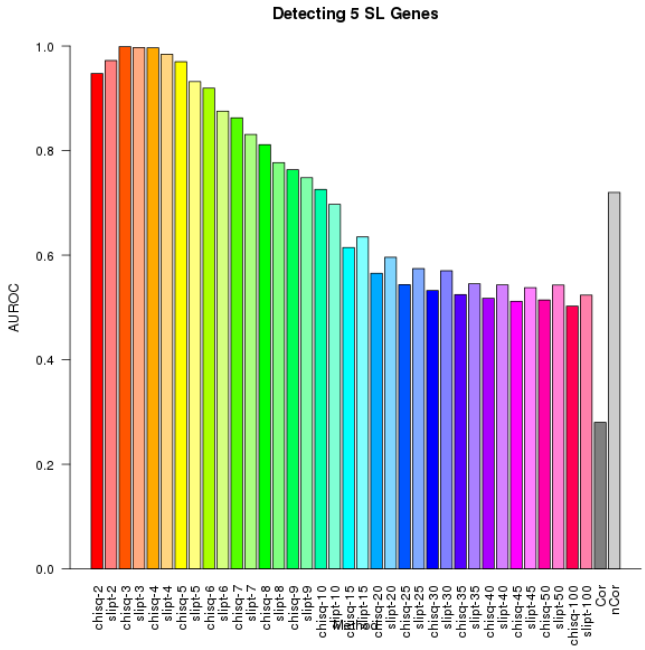
A refined simulation procedure was developed specifically to extend the simulation procedure (described in Section 3.2) to utilise pathway graph structures for the correlation structures of simulated datasets (as described in Section 3.4.2). This methdology can be applied to simulated correlation structures across simple graph structures to test specfic network modules or use pathway structures based on biological pathways (as discussed in Chapter 5). Thus graph structure and simulation approaches were combined to test whether a gene locus in a pathway affects detection by SLIPT and whether SLIPT performance is affected by pathway structure. The simulation procedure based on graph structures were applied in a computational pipeline across many parameters with high-performance computing (as discussed in Section 2.5.3) and the core simulation functions have been released as a software package for wider use to test bioinformatics and statistical methods on graph structures (as described in Section 3.5.3).

## 6.1 Comparing methods

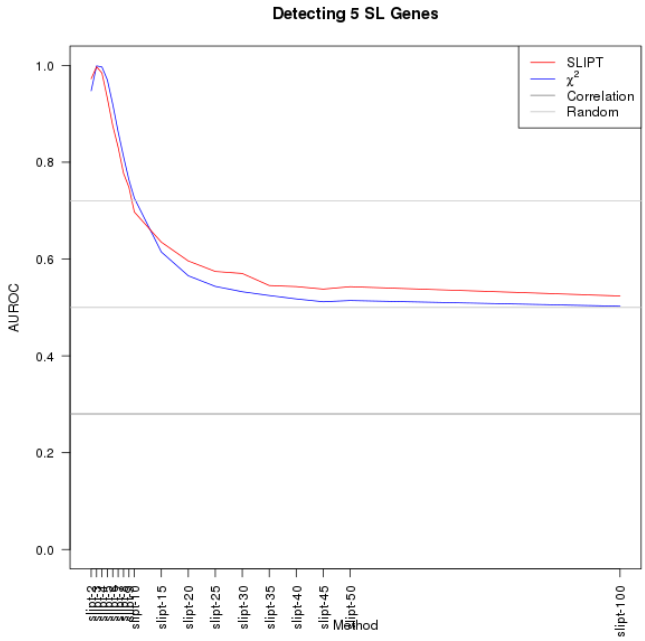
Methods were compared ...

### 6.1.1 Performance of SLIPT and $\chi^2$ across Quantiles

Text




(a) Performance of $\chi^2$ and SLIPT




(b) Comparison to Correlation

Figure 6.1: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with $\chi$.

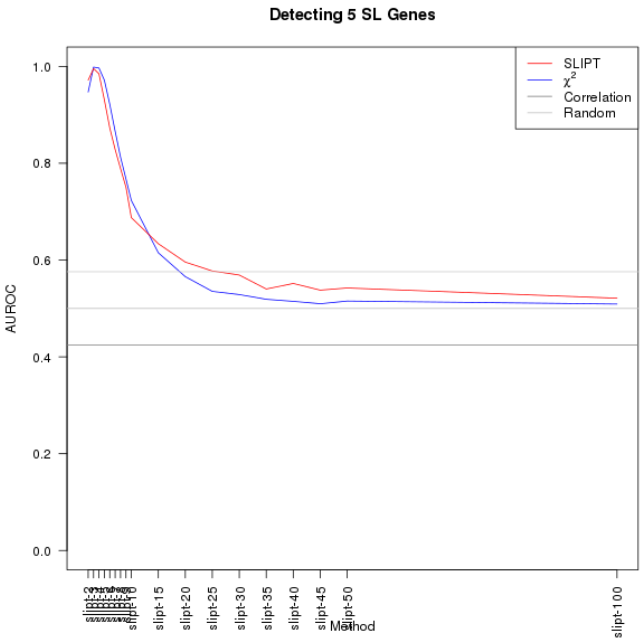



Figure 6.2: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with $\chi$ with more genes.

#### 6.1.1.1 Correlated Query Genes affects Specificity

Text

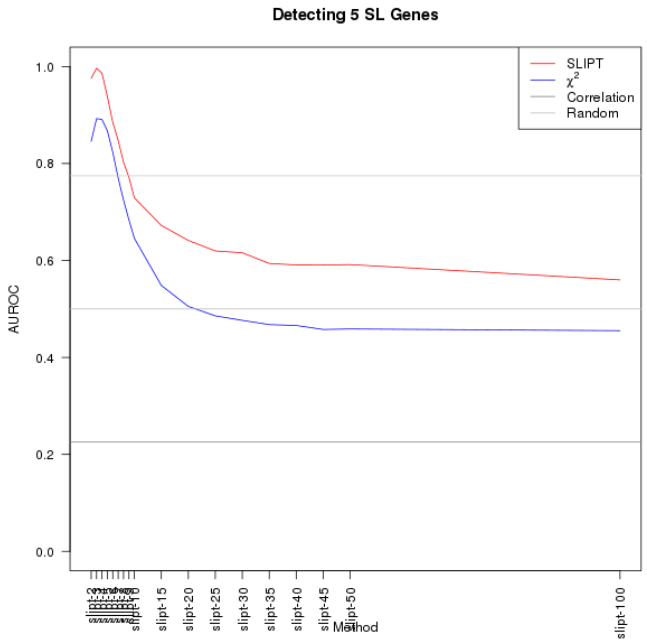



Figure 6.3: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with $\chi$ with query correlation genes.

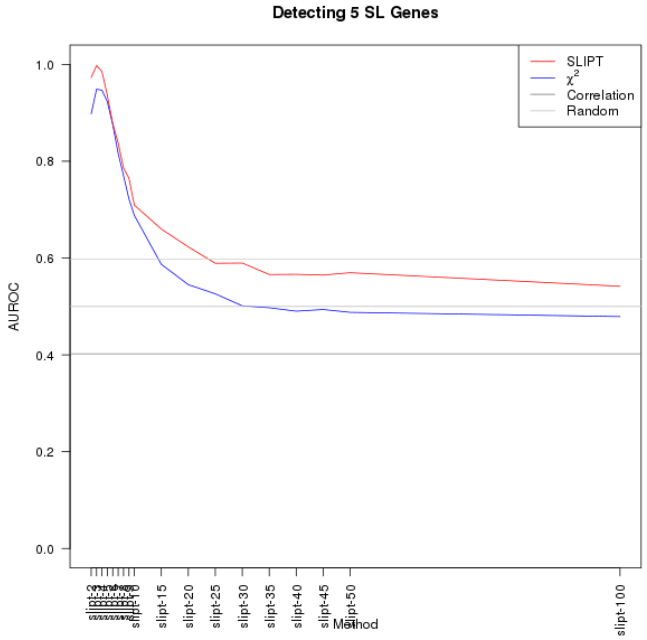



Figure 6.4: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with $\chi$ with query correlation and more genes.

### 6.1.2 Correlation as a Synthetic Lethal Detection Strategy

Text

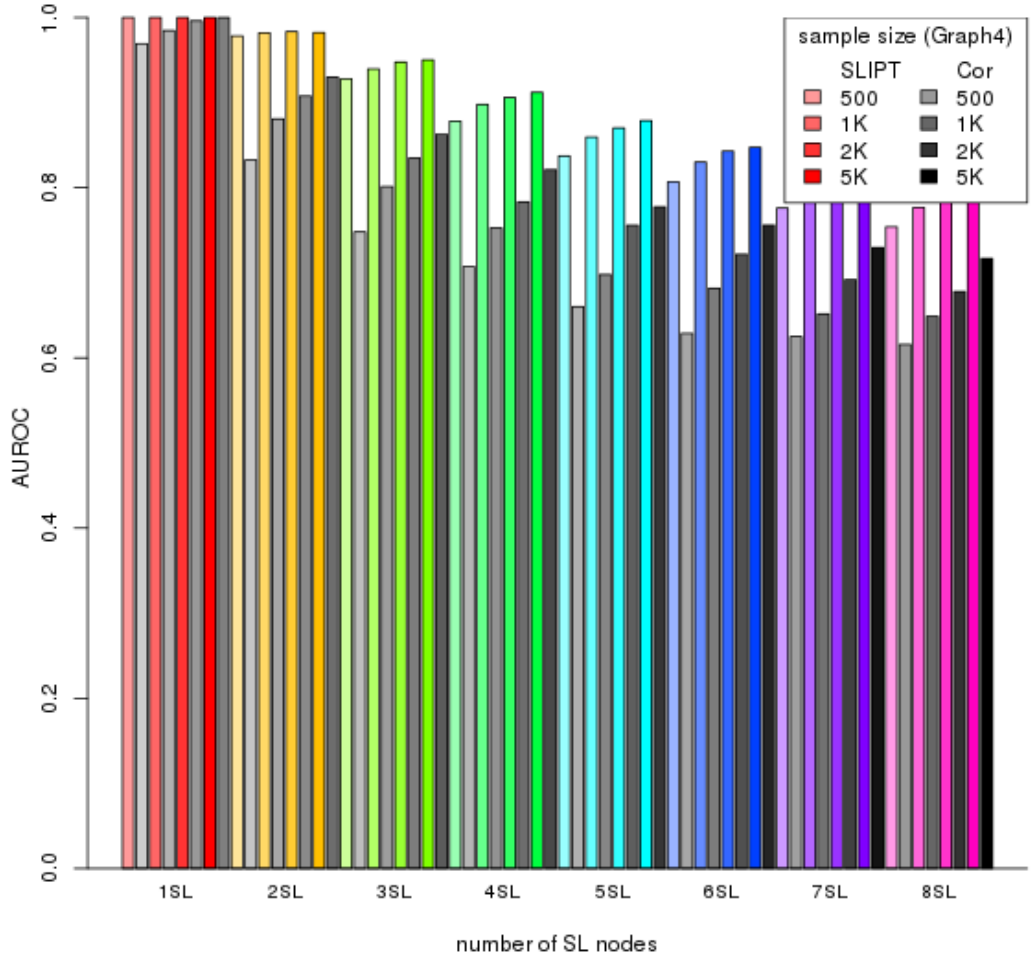



Figure 6.5: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with negative correlation.

### 6.1.3 Testing for Bimodality with BiSEp

Computer says No

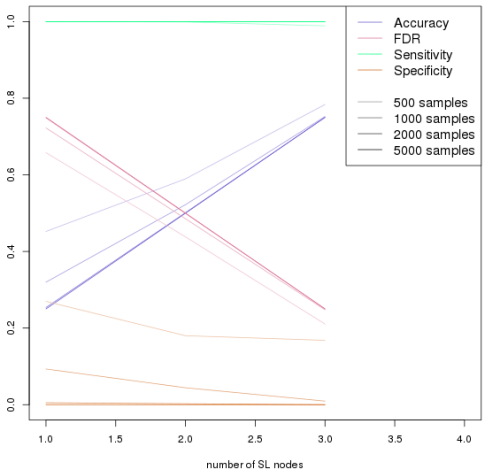
### 6.1.4 Testing Synthetic Lethal Genes with Linear Models

Text

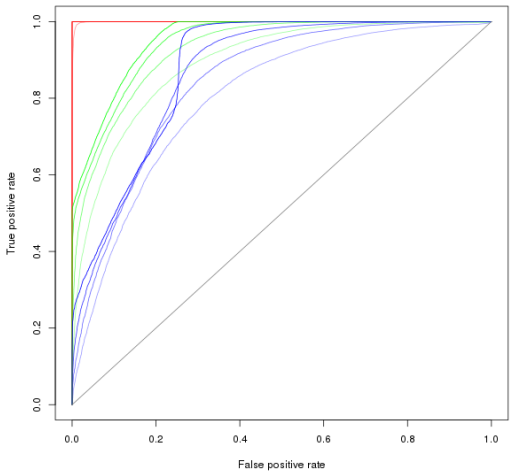
## 6.2 Simulations with Graph Structures

Text

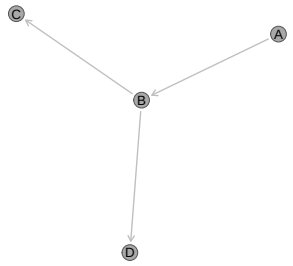
### 6.2.1 Performance over a Graph Structure



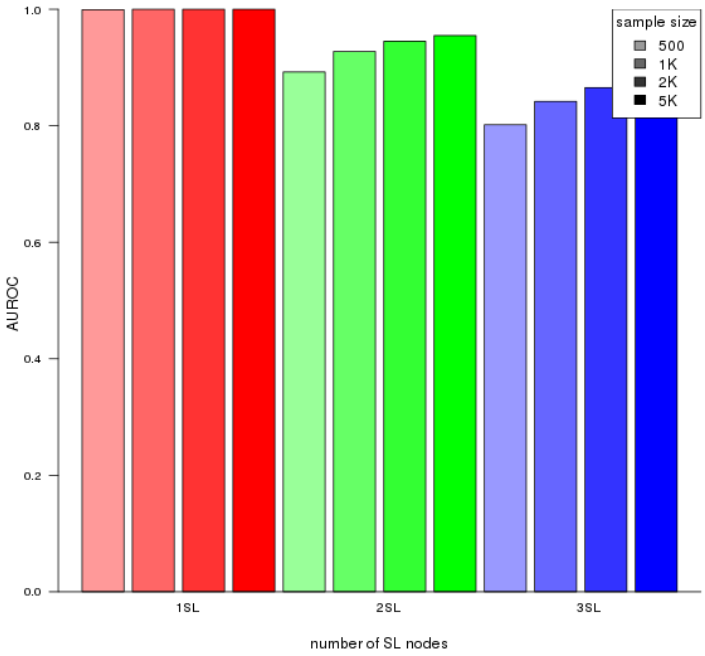

(a) Statistical evaluation




(b) Receiver operating characteristic

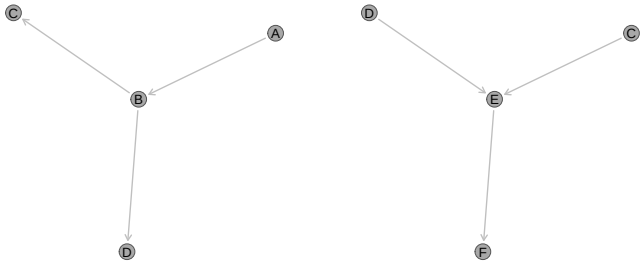



(c) Graph Structure

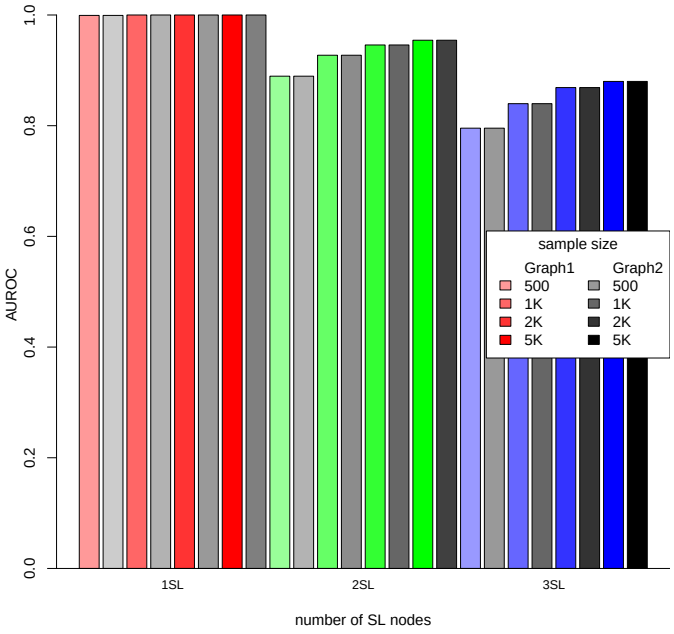



(d) Statistical performance

Figure 6.6: **Performance of simulations on a simple graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

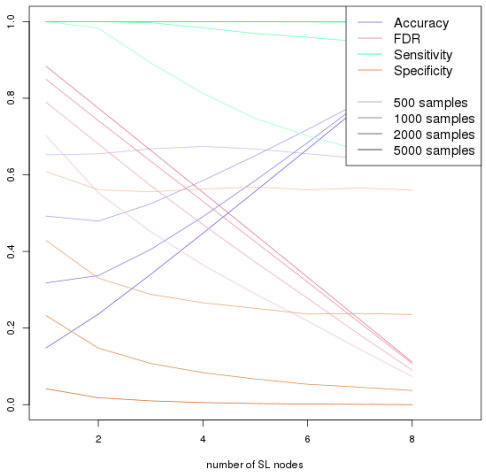



(a) Graph Structure (b) Graph Structure

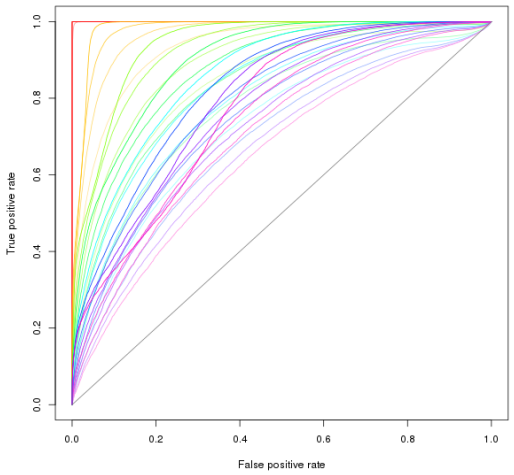



(c) Gene category in simulations

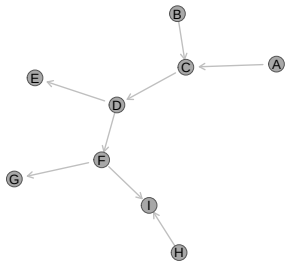
Figure 6.7: **Performance of simulations is similar in simple graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.



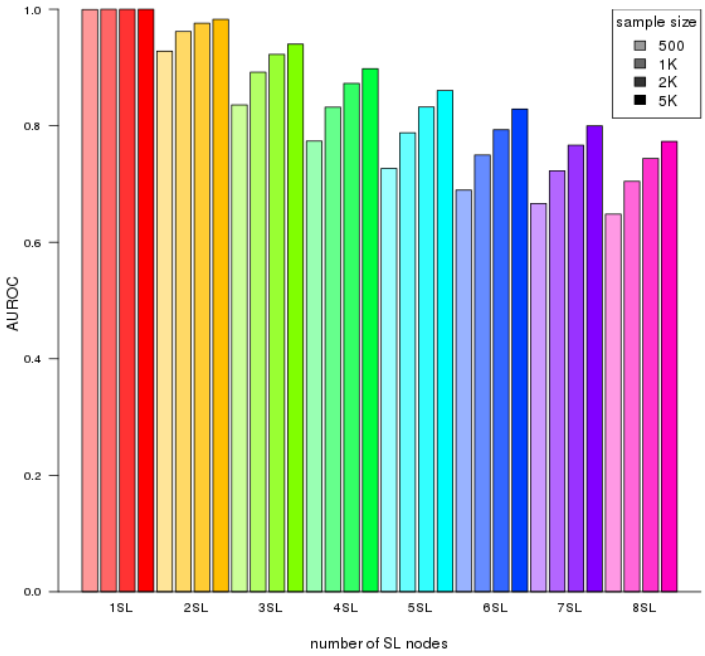

(a) Statistical evaluation




(b) Receiver operating characteristic

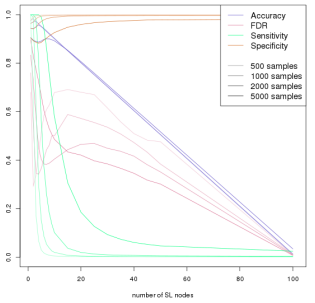



(c) Graph Structure

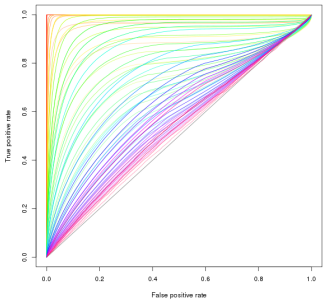



(d) Statistical performance

Figure 6.8: **Performance of simulations on a graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

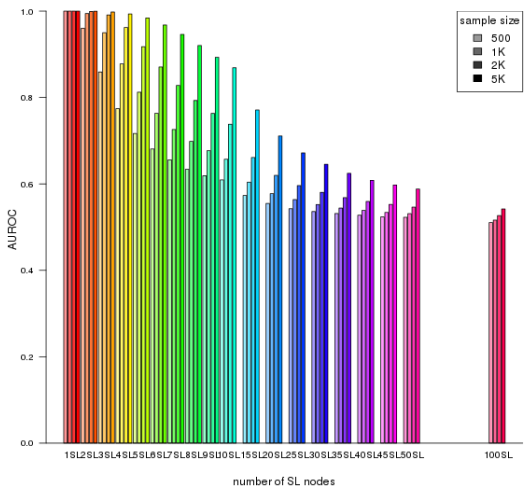



(a) Statistical evaluation




(b) Receiver operating characteristic

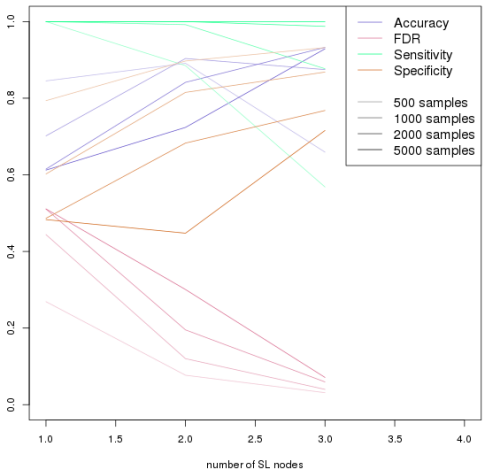
(c) Graph Structure



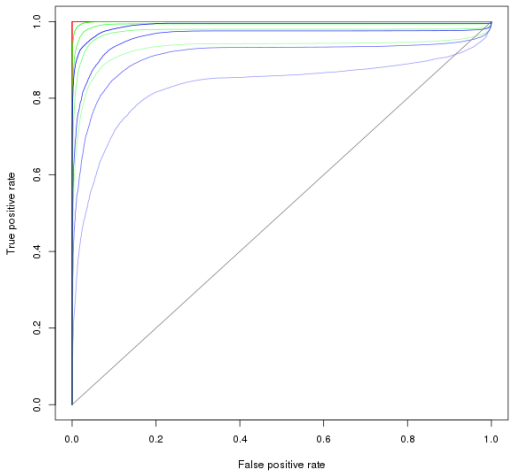

(d) Statistical performance

Figure 6.9: **Performance of simulations on a large graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

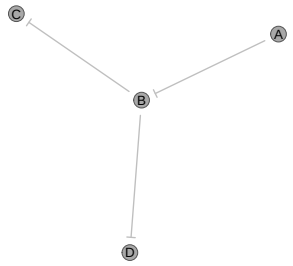
### 6.2.2 Performance with Inhibitions



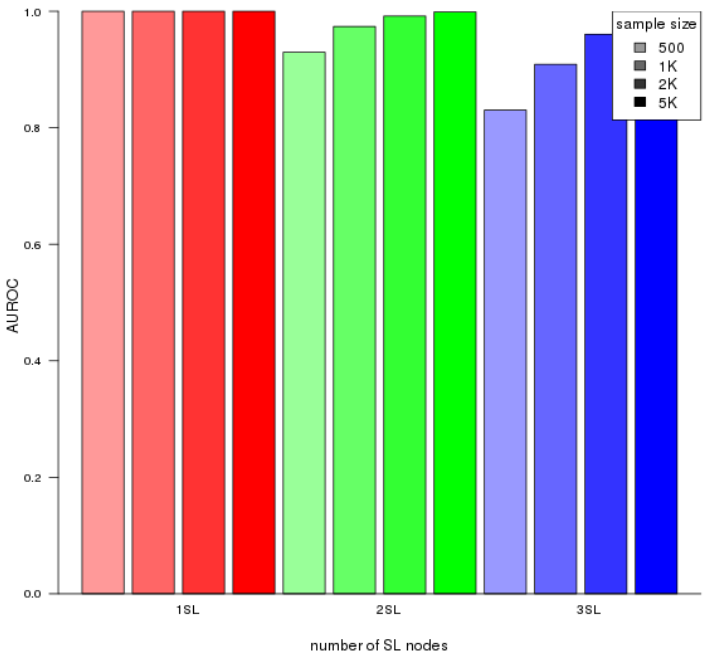

(a) Statistical evaluation




(b) Receiver operating characteristic

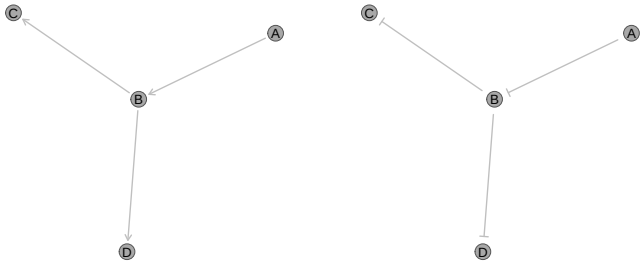



(c) Graph Structure

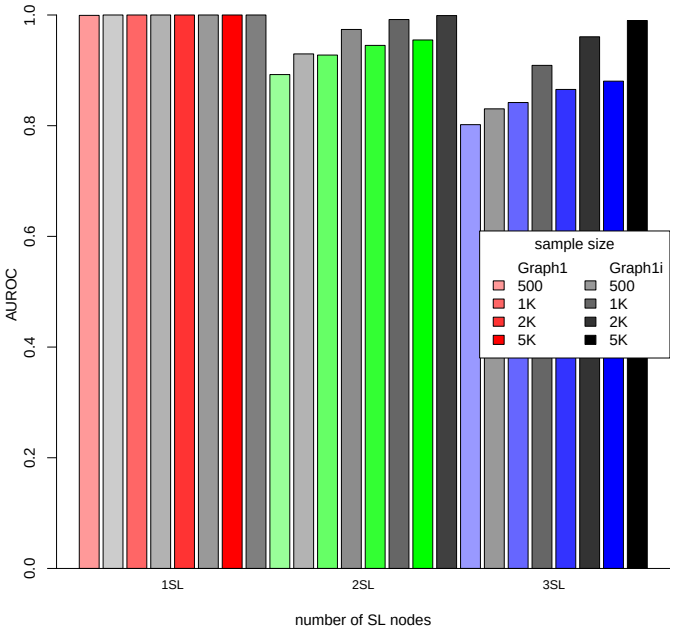



(d) Statistical performance

Figure 6.10: **Performance of simulations on a simple inhibiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

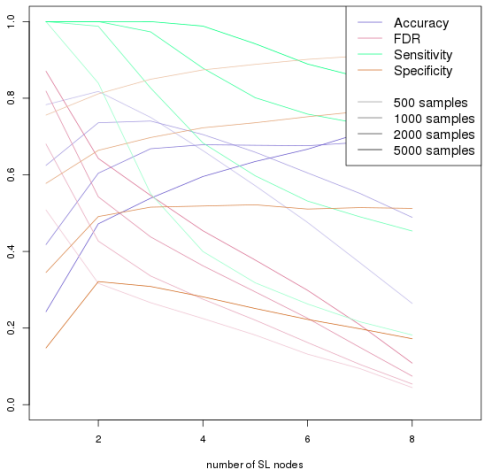



(a) Graph Structure (b) Graph Structure

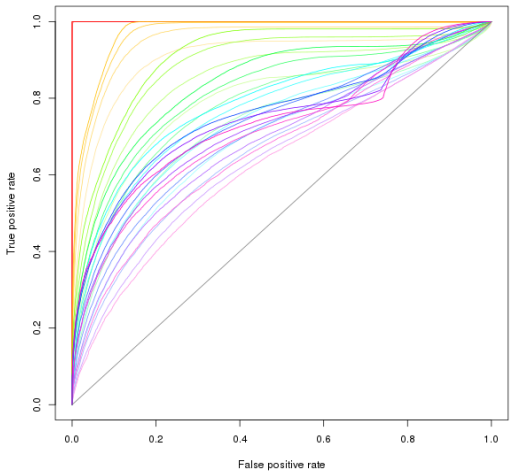



(c) Gene category in simulations

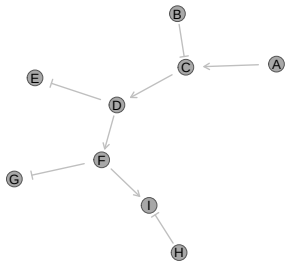
Figure 6.11: **Performance is higher on a simple inhibiting graph.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.



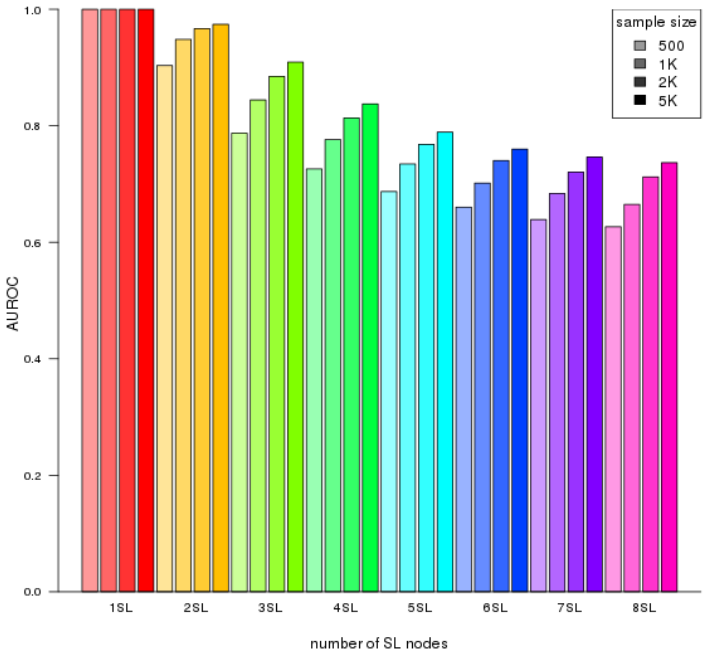

(a) Statistical evaluation




(b) Receiver operating characteristic

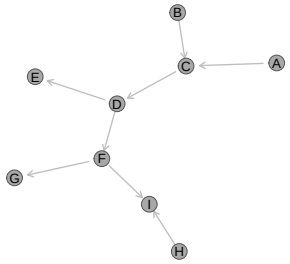



(c) Graph Structure

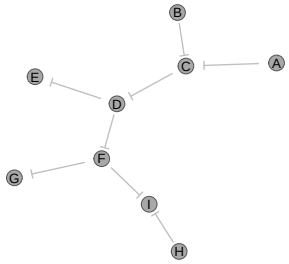



(d) Statistical performance

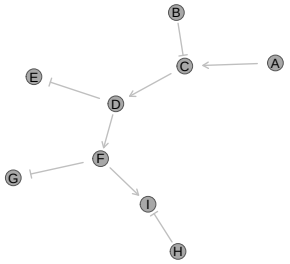
Figure 6.12: **Performance of simulations on an inhibiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



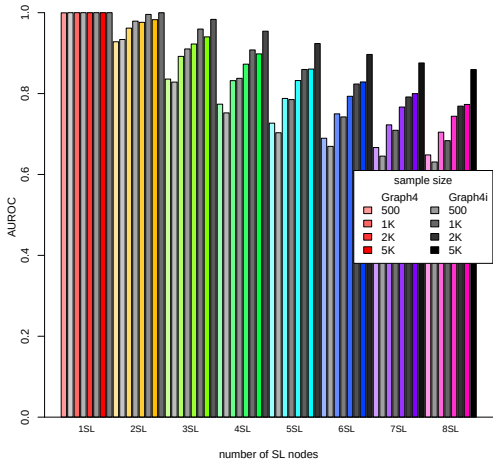

(a) Graph Structure



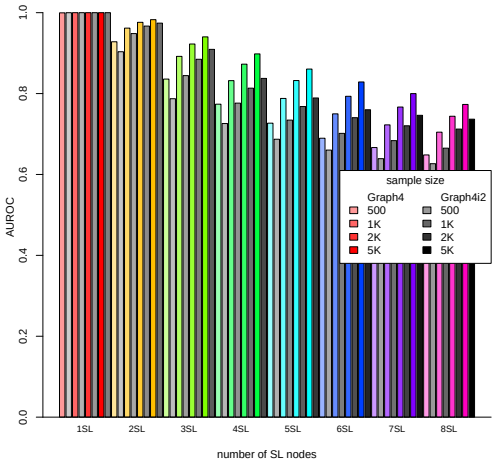

(b) Graph Structure




(c) Graph Structure




(d) Gene category in simulations




(e) Gene category in simulations

Figure 6.13: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.

### 6.2.3 Synthetic Lethality across Graph Structures

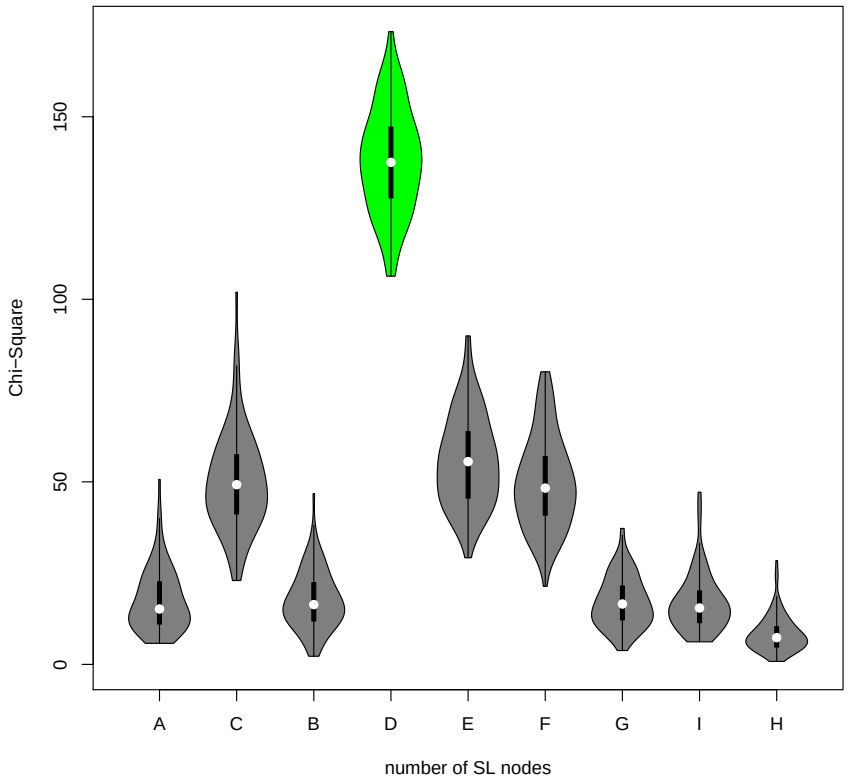
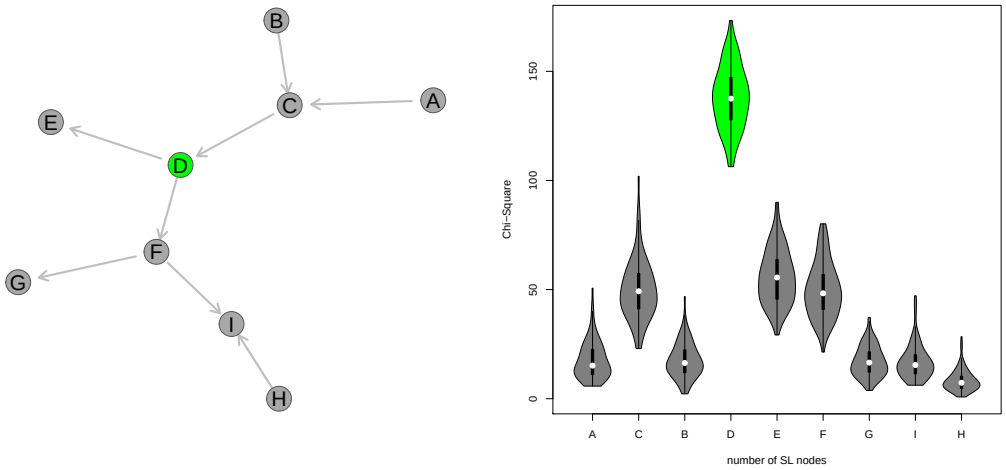


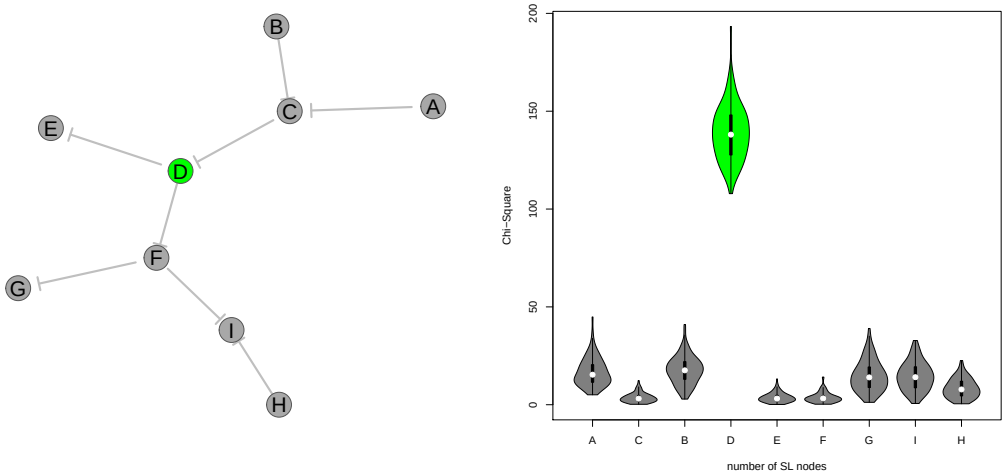

Figure 6.14: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.




(a) Graph Structure

(b) Graph Structure

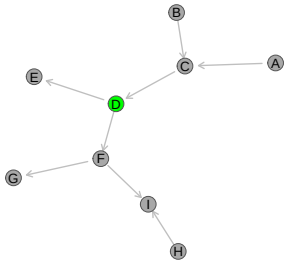
Figure 6.15: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.



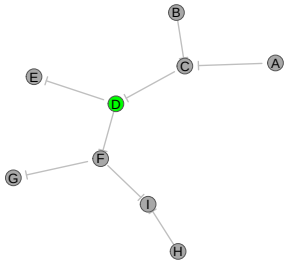

(a) Graph Structure

(b) Graph Structure

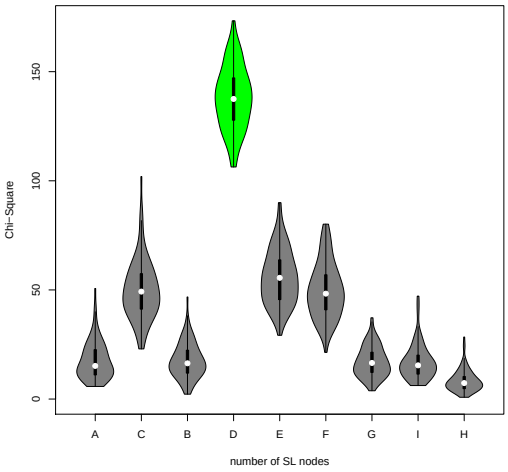
Figure 6.16: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.



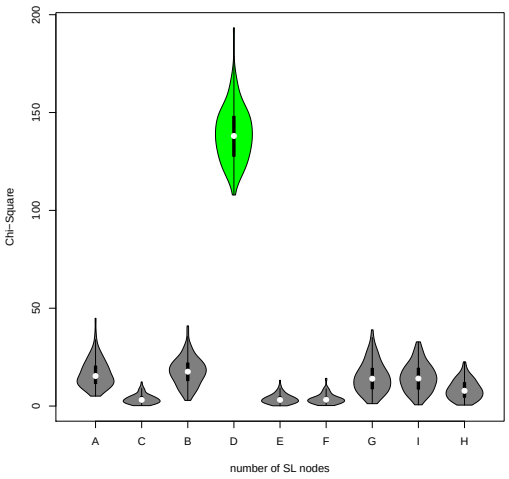

(a) Graph Structure




(b) Graph Structure



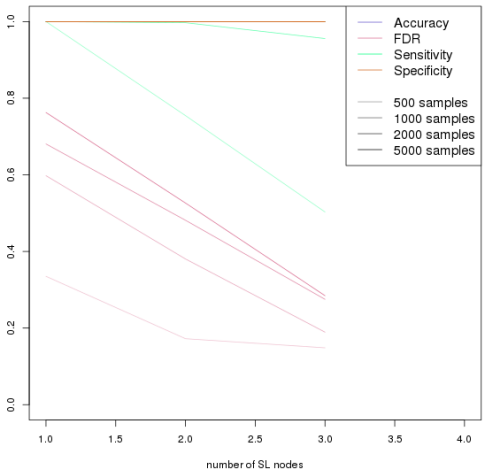

(c) Graph Structure



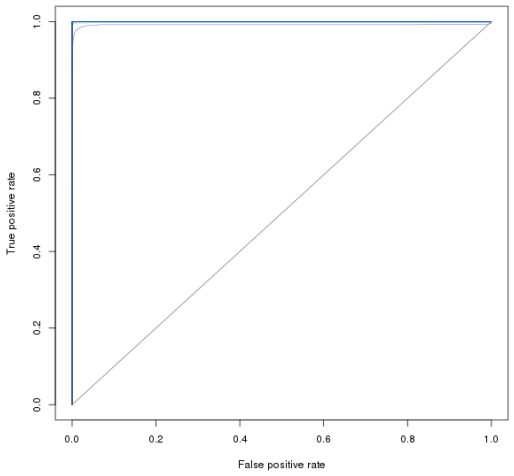

(d) Graph Structure

Figure 6.17: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.

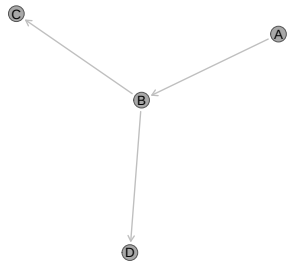
### 6.2.4 Performance with feasible gene numbers (20,000)



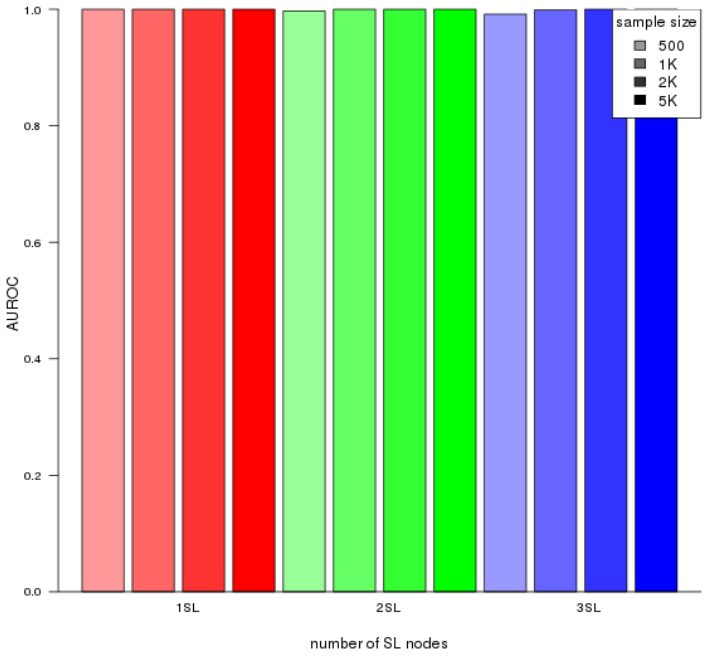

(a) Statistical evaluation




(b) Receiver operating characteristic

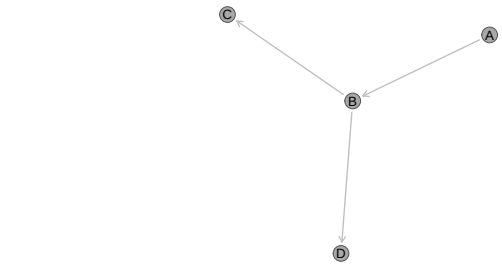



(c) Graph Structure

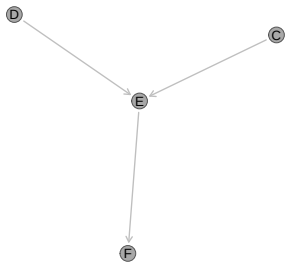



(d) Statistical performance

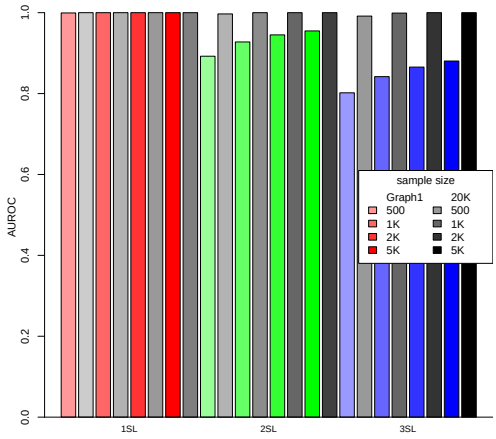
Figure 6.18: **Performance of simulations including a simple graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



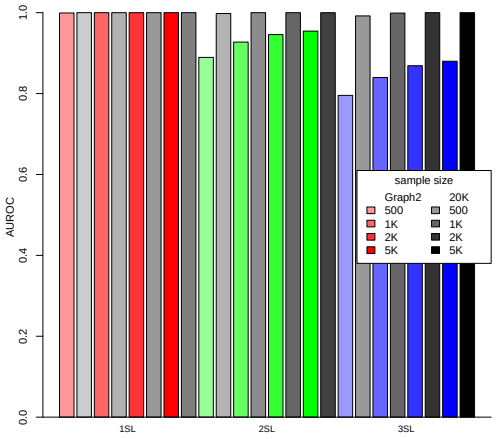

(a) Graph Structure




(b) Graph Structure

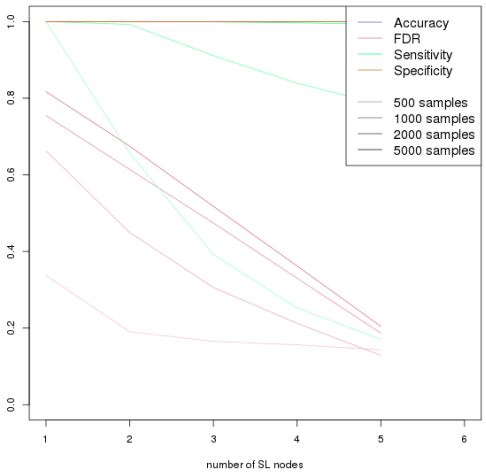



(c) Gene category in simulations

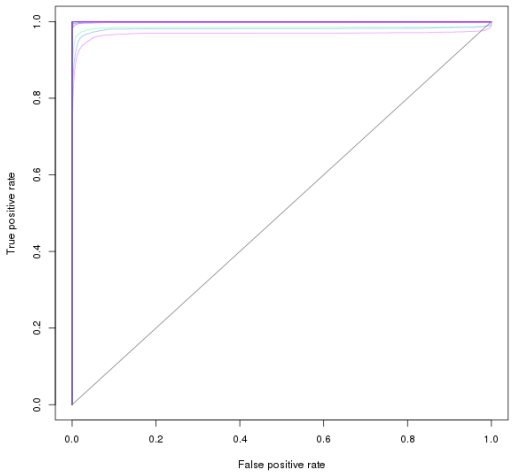



(d) Gene category in simulations

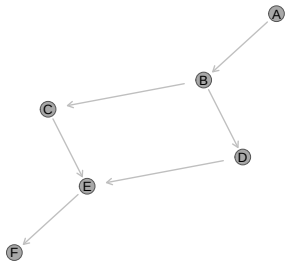
Figure 6.19: **Performance on a simple graph improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.



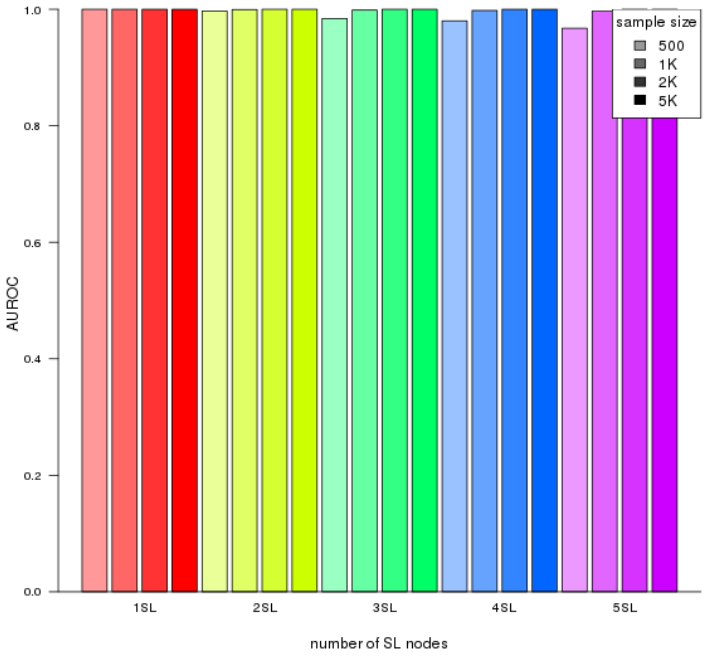

(a) Statistical evaluation




(b) Receiver operating characteristic

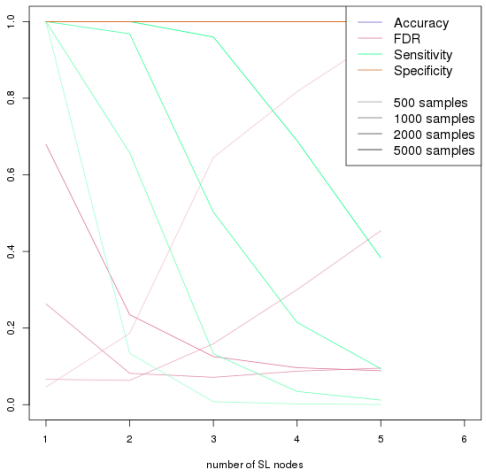



(c) Graph Structure

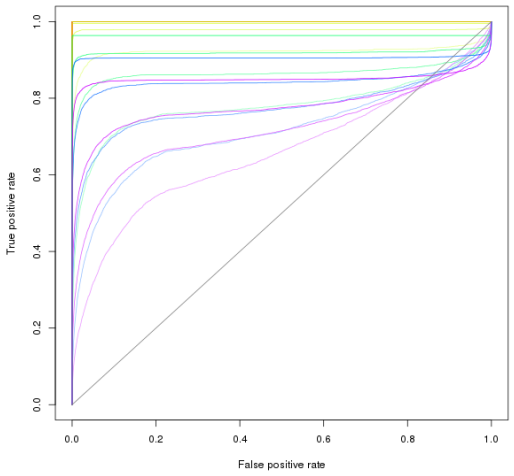



(d) Statistical performance

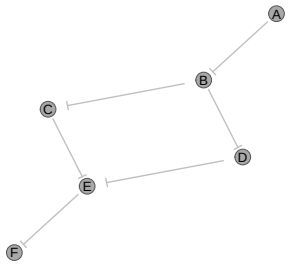
Figure 6.20: **Performance of simulations including a graph structure.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



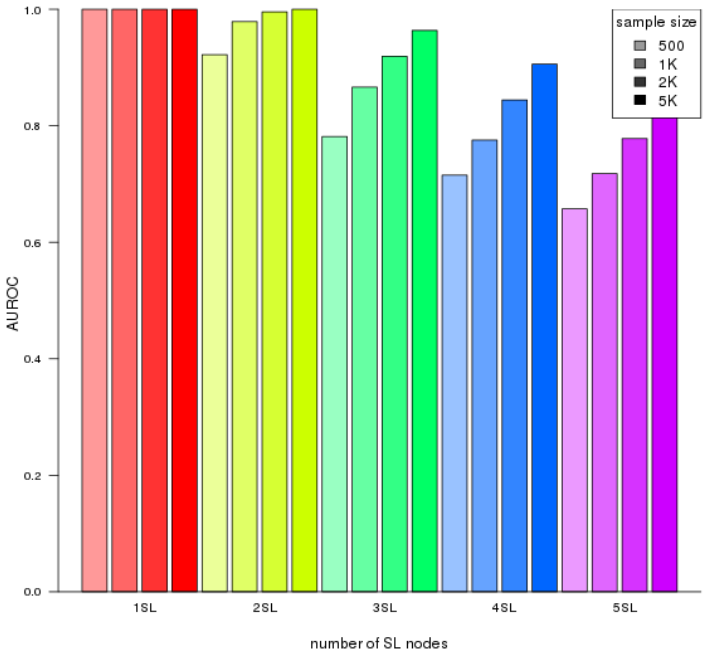

(a) Statistical evaluation




(b) Receiver operating characteristic

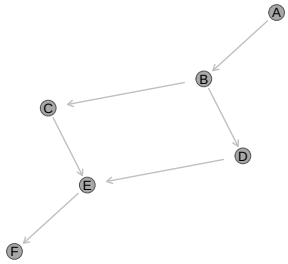



(c) Graph Structure

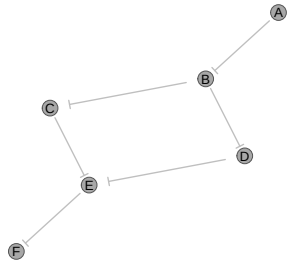



(d) Statistical performance

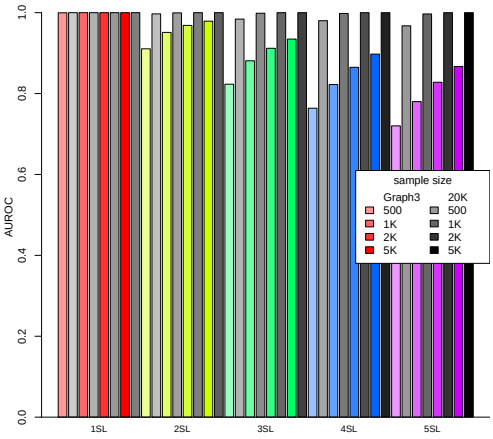
Figure 6.21: **Performance of simulations including an inhbiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



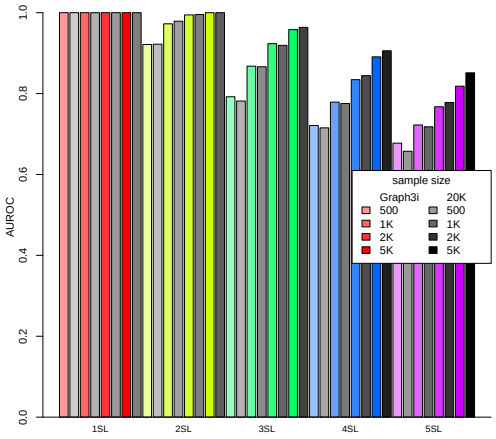

(a) Graph Structure




(b) Graph Structure

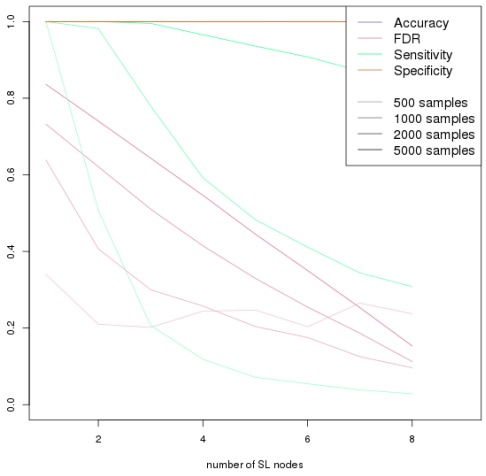



(c) Gene category in simulations

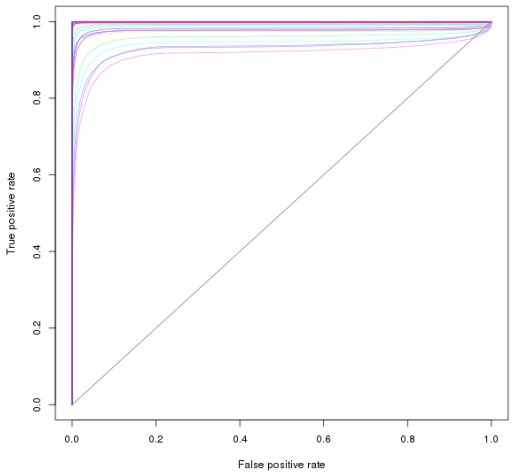



(d) Gene category in simulations

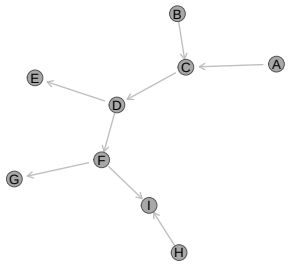
Figure 6.22: **Performance on an inhibiting graph improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.



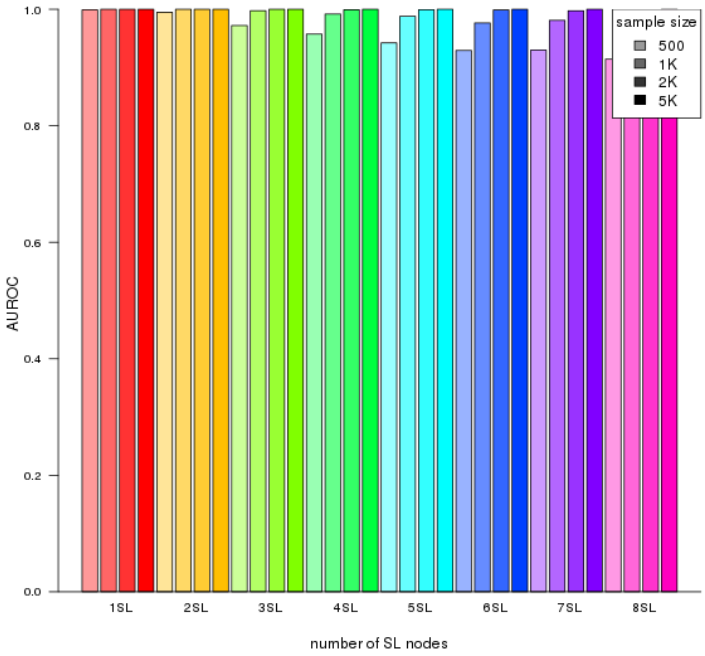

(a) Statistical evaluation




(b) Receiver operating characteristic

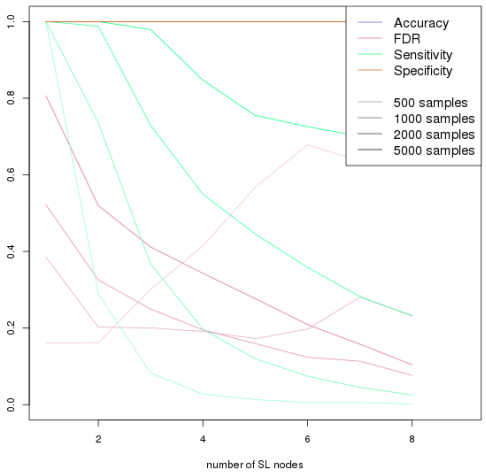



(c) Graph Structure

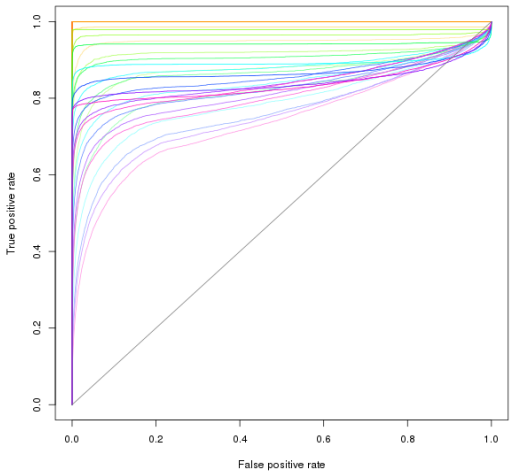



(d) Statistical performance

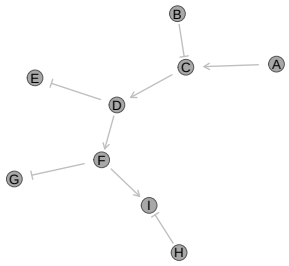
Figure 6.23: **Performance of simulations including a graph structure.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



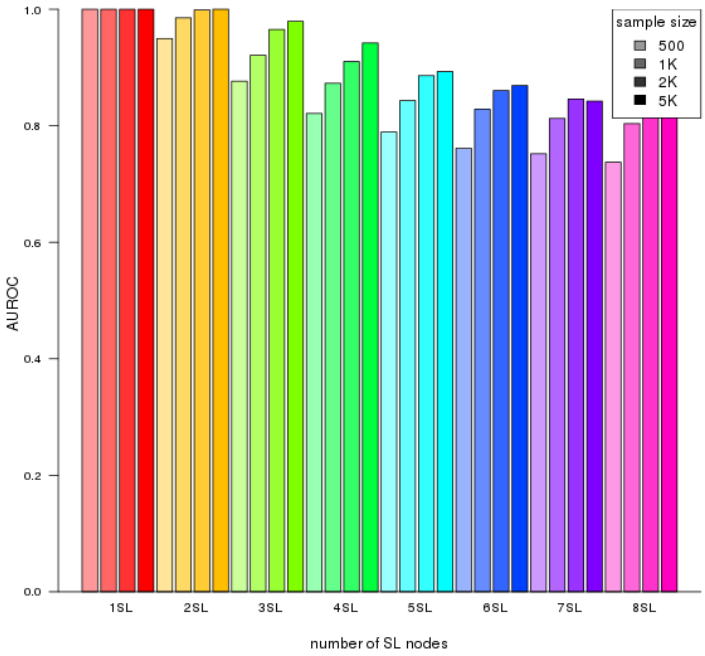

(a) Statistical evaluation




(b) Receiver operating characteristic

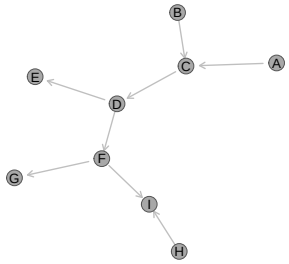



(c) Graph Structure

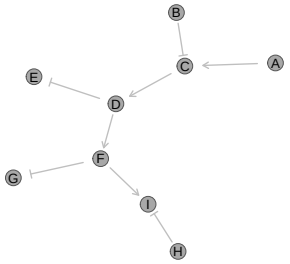



(d) Statistical performance

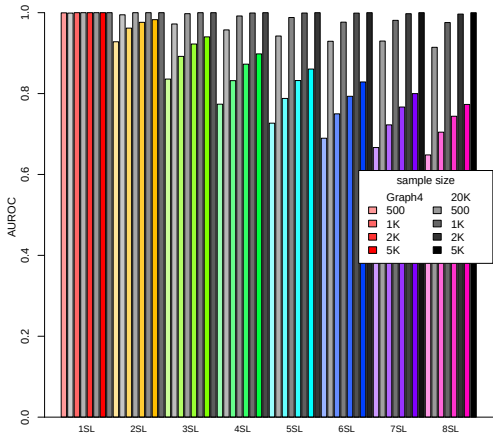
Figure 6.24: **Performance of simulations including an inhibiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



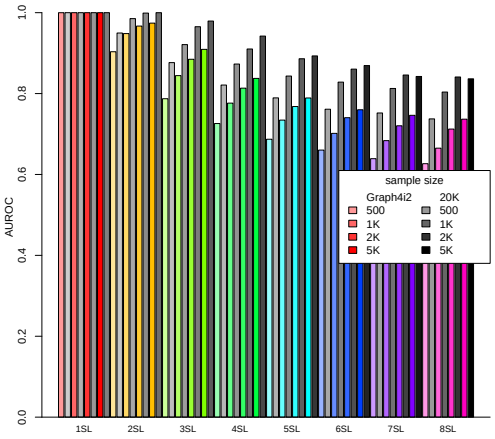

(a) Graph Structure




(b) Graph Structure




(c) Gene category in simulations

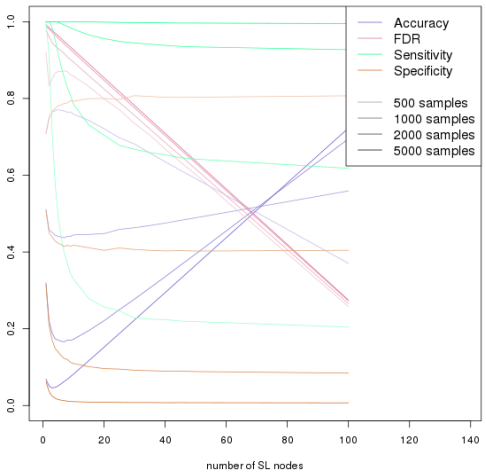



(d) Gene category in simulations

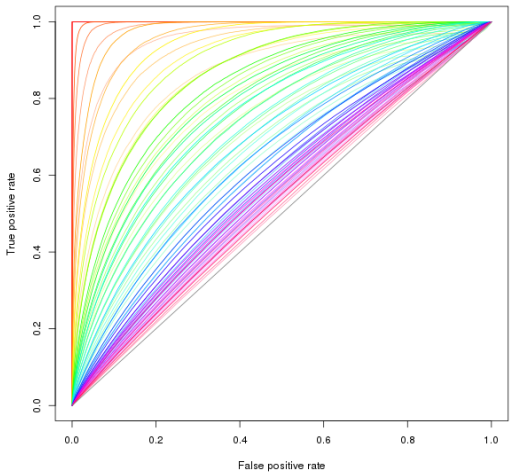
Figure 6.25: **Performance on an inhibiting graph improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.

## 6.3 Simulations over pathway-based graphs

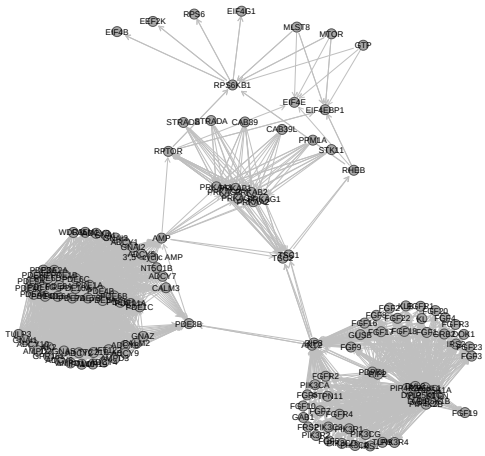
Text



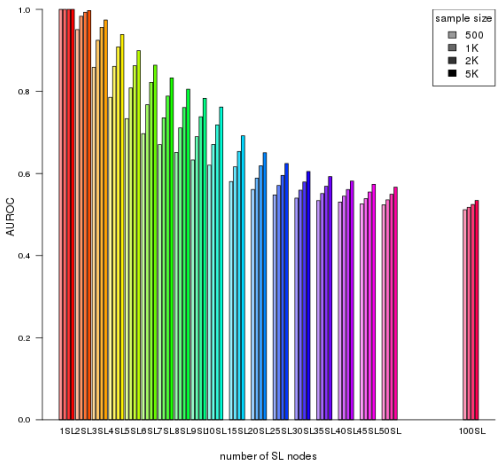

(a) Statistical evaluation




(b) Receiver operating characteristic

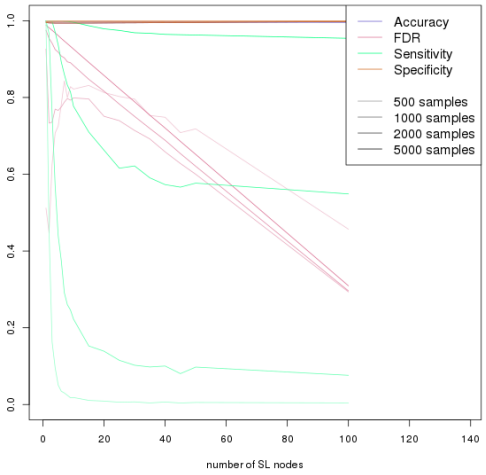


(c) Graph Structure

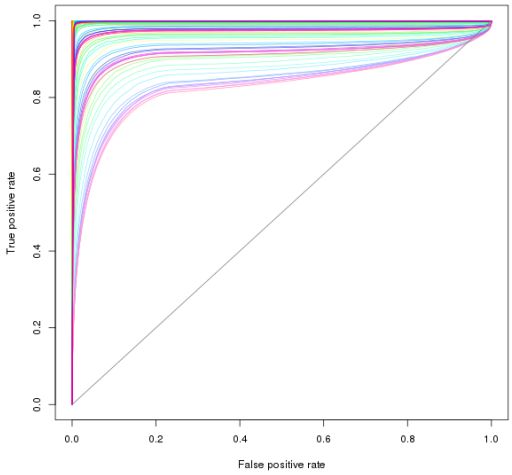



(d) Statistical performance

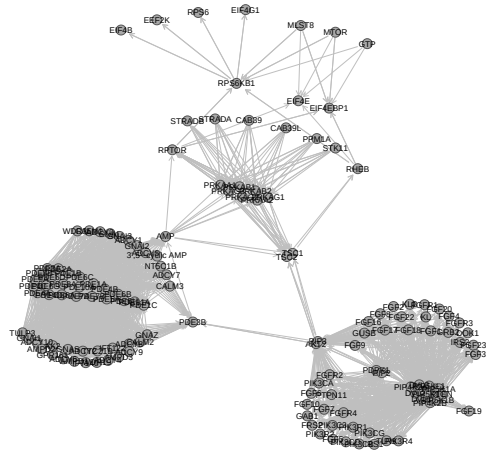
Figure 6.26: **Performance of simulations on the PI3K cascade.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



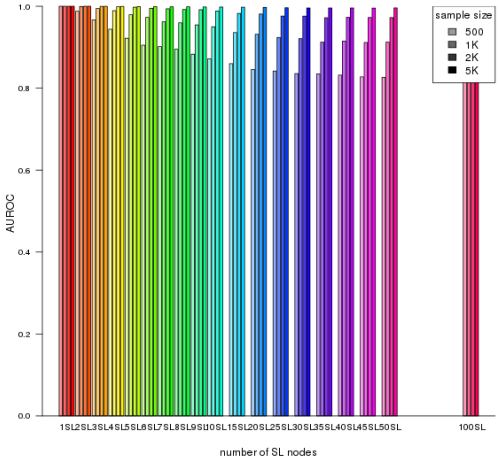

(a) Statistical evaluation




(b) Receiver operating characteristic

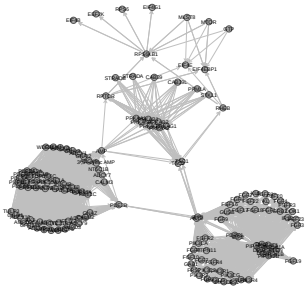


(c) Graph Structure

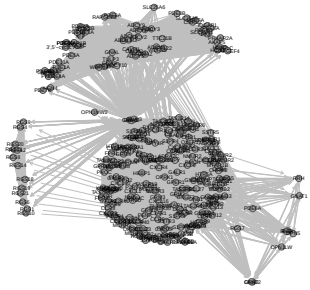



(d) Statistical performance

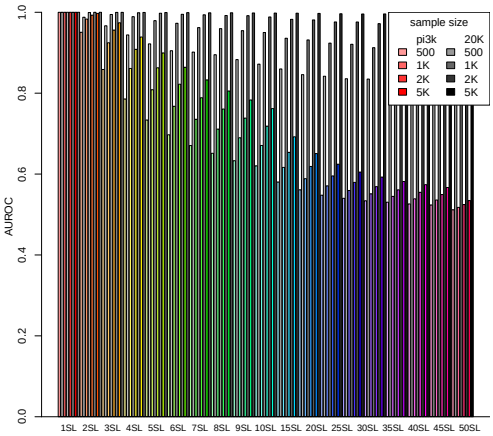
Figure 6.27: **Performance of simulations including the PI3K cascade.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



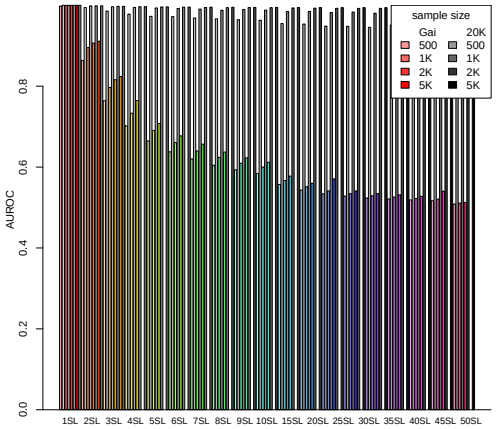
(a) Graph Structure



(b) Graph Structure




(c) Gene category in simulations




(d) Gene category in simulations

Figure 6.28: **Performance on pathways improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by $\chi^2$ signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The $\chi^2$ values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.

## 6.4 Discussion

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## 6.5 Summary

Text

**Aims**

- A Model of Synthetic Lethal Genes in Gene Expression Data
- Comparison of SLIPT to Alternative Approaches
- Simulations of Known Synthetic Lethal Genes within Pathway Networks

**Summary**

- We have designed a straight-forward rational query-based synthetic lethal detection method with the example of application to *CDH1* in cancer gene expression
- I have developed a simulation pipeline to generate continuous gene expression with pathway structure including a procedure to simulate synthetic lethality
- The simulation procedure shows that SLIPT is robust across pathway structures and has desirable performance compared to other statistical techniques

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