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Glossary

synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) when they are viable if inactivated separately.

Acronyms

ANOVA	Analysis of Variance.
SLIPT	Synthetic lethal interaction prediction tool.

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 simulation procedure (as applied in Section 3.3) with further refinements. The SLIPT methodology (and the equivalent χ^2 test alone) were applied across a range of pa-

rameters (including altering 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

The SLIPT methodology (as it has been applied throughout Chaptersr 4and 5) was compared to alternative computational approaches to detecting synthetic lethality in simulated gene expression data. As discussed in Section 3.3, this procedure enables testing the performance of detecting known synthetic lethal partner genes by sampling from a statistical model of synthetic lethality. While comprehensive benchmarking has not been performed, several approaches to synthetic lethal detection are considered (e.g., Pearson's correlation, the χ^2 test, and testing for bimodality) to evaluate the strengths of the SLIPT methodology, including modifications to the parameters of SLIPT.

Further testing of the performance of the SLIPT software R package (which is publicly released on GitHub as described in Section 3.5) has been left to third party researchers to impartially compare it to other software for synthetic lethal detection which is outside the scope of this thesis. The following comparisons of simulations of computational detection of synthetic lethality with different statistical rationales suffice to discuss the strengths of SLIPT, evaluate whether it is appropriate for further application in genomics research, and identify limitations which may be addressed

with further developments. Some potential avenues for further development of computational synthetic lethal discovery will be discussed in Section 7.2.

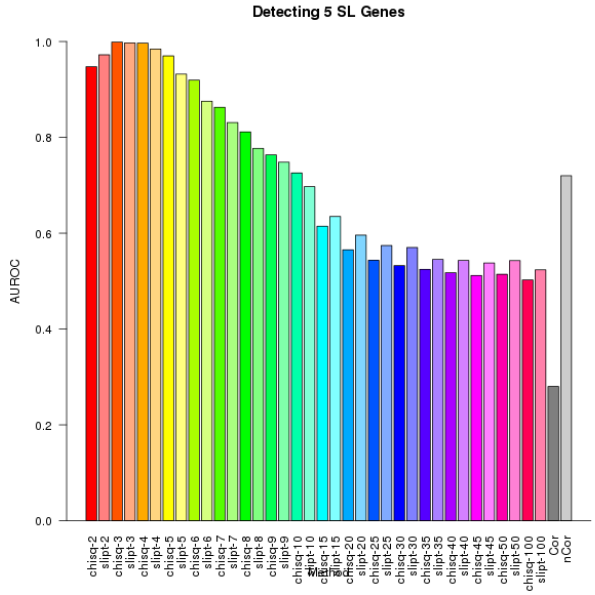
6.1.1 Performance of SLIPT and χ^2 across Quantiles

Simulated datasets with synthetic lethal partner genes were generated using the multivariate normal simulation procedure (as described in Section 3.2.2) with performance assessed using area under the reciever operating characteristic (AUROC) analysis (as described in Section 2.3.5). Synthetic lethal detection was compared for modifications to the SLIPT methdology (as described in Section 3.1), namely that the quantiles used to define low and high expression was varied. Rather than $\frac{1}{3}$ (as used throughout this thesis) the samples below the lowest $\frac{1}{n}$ quantile and above the highest $\frac{1}{n}$ quantile were used for SLIPT (and the χ^2-test) to detect lowly and highly expressing samples respectively. The quantiles tested range from 2, splitting at the $\frac{1}{2}$ quantile (the median), to 100, using the lowest (1%) and highest (99%) percentiles.

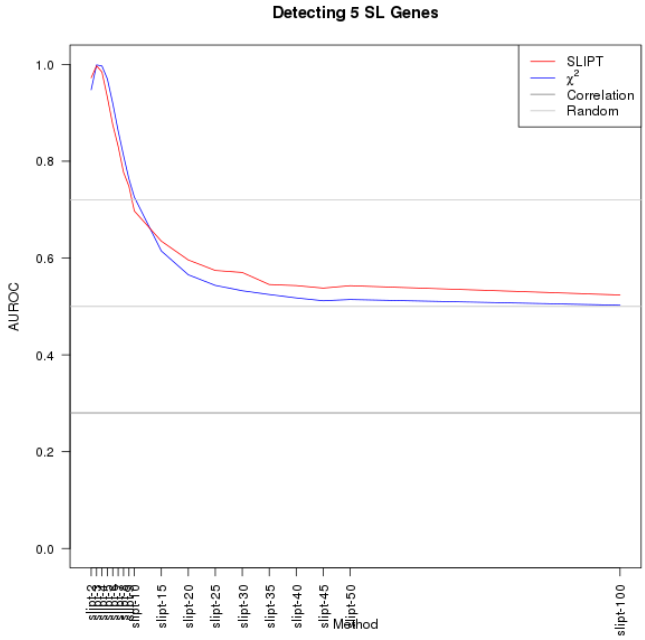
This enables testing of the threshold for lowly expressing genes which is most able to distinguish synthetic lethal genes, even with higher-order synthetic lethal interactions (as discussed in Section 3.2.1). Both SLIPT with the directional criteria for synthetic lethality and significance of the equivalent χ^2 test were performed for each quantile. Pearson's correlation was also tested on simulated continuous expression data for synthetic lethal detection in simulated data, considering both positive and negative correlations separately as predictors of synthetic lethality for comparison with χ^2 based approaches, using discete categories fo gene function deriving from quantiles.

The results presented throughout this section use the example of 5 synthetic lethal partners to illustrate the differences in performance between the standard SLIPT procedure (slipt-3) to n quantiles (slipt-n), the χ^2-test on the same quantiles, and positive or negative correlation. However, similar results across different numbers of known synthetic lethal genes are shown in Appendix N. The synthetic lethal detection procedures were compared with 10,000 simulations of a small dataset of 100 genes and 1000 samples without correlation structure between genes as performed in Section 3.3.2) . As shown in Figure 6.1, the 3-quantiles previously used have optimal performance and SLIPT has a comparable or higher performance than the χ^2-test alone across quantiles.

Pearson's correlation performed worse than random (with an AUROC lower than 0.5) as thus coexpression of genes is not predictive of synthetic lethality in simulated data. Conversely, negative correlation is predictive of synthetic lethality, consistent with synthetic lethal gene activity being mutually exclusive. However, neither correla-



(a) Barplot of χ^2, SLIPT, and correlation.



(b) Lineplot of χ^2, SLIPT, and correlation.

Figure 6.1: **Performance of χ^2 and SLIPT across quantiles**. Synthetic lethal detection (of 5 genes) with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). The line plot is coloured according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$-quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2.

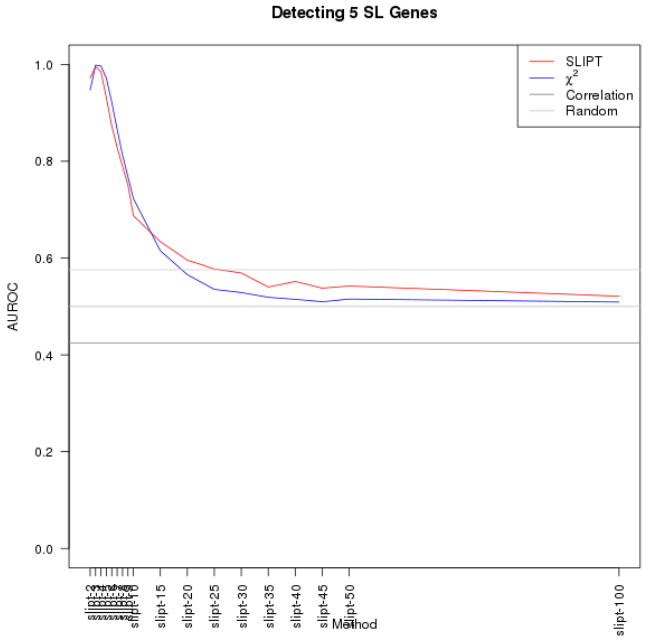


Figure 6.2: **Performance of χ^2 and SLIPT across quantiles with more genes**. Synthetic lethal detection (of 5 genes in 20,000) with quantiles as in axis labels. The line plot is coloured according to the legend. As for simulations with fewer genes, SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$-quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2.

tion approach performed as well as the optimal quantiles for the SLIPT procedure or χ^2-test.

These results are shown in both a bargraph and lineplot to show the individual results of each parameter and compare SLIPT with the χ^2-test side-by-side across quantiles. Similarly, these plots are given for detecting a range of known synthetic lethal partners in the simulations in Figures N.1 and N.2. These demonstrate that the findings shown for 5 synthetic lethal genes is robust across different numbers of underlying synthetic lethal genes.

The synthetic lethal detection procedures were also tested with 1000 simulations of a larger dataset of 20,000 genes and 1000 samples. While fewer simulations gives a less accurate reciever operating characteristic (ROC) result, this is sufficient to replicate the above findings with a feasible human of genes in a human gene expression dataset and assess the impact of a higher proportion of non synthetic lethal genes (potential

false positives). Simulated datasets of this size were also used in Section 3.3.2 to test the specificity in a number of genes similar to that in experimental datasets for cancer genomes. As shown in Figure 6.2, the above findings were replicated in simulations of a larger dataset with 20,000 genes. These were also robustly replicated across varying numbers of underlying synthetic lethal genes (as shown in Figure N.3).

6.1.1.1 Correlated Query Genes affects Specificity

As discussed in Section 3.3.2.2, postively correlated genes (with the query gene) have an impact of on the performance of synthetic lethal detection. SLIPT able to distinguish these from synthetic lethal partners and hence has a higher specificity in datasets which include postively correlated genes with the query gene (as expected in gene expression data). The synthetic lethal detection procedures were compared with 10,000 simulations of a small dataset of 100 genes (with 5 correlated with the query gene) and 1000 samples otherwise without correlation structure between genes. As shown in Figure 6.3, this specficity is reflected in the increased AUROC performance values for SLIPT (in contrast to Figure 6.1). This specficity can be attributed to the directional criteria (as described in Section 3.1) since the χ^2-test alone performs comparatively poorly with positively correlated genes.

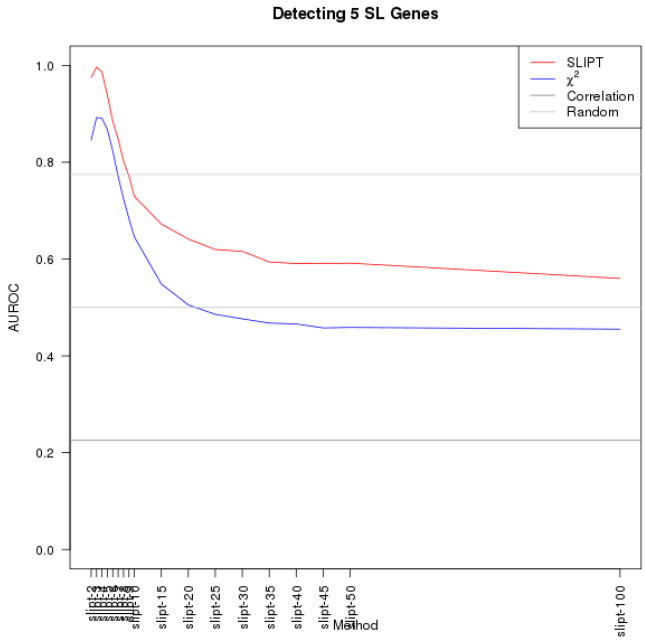


Figure 6.3: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with χ^2 with query correlation genes.

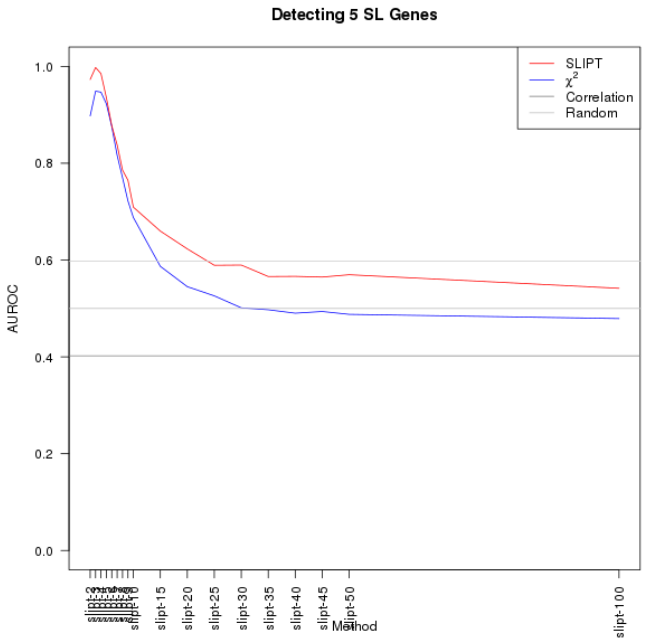


Figure 6.4: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with χ^2 with query correlation and more genes.

The synthetic lethal detection procedures were also compared with 1000 simulations of a larger dataset of 20,000 genes (with 1000 correlated with the query gene) and 1000 samples otherwise without correlation structure between genes. This simulation increases the number of genes (and proportion of negative genes) to those feasible in a human gene expression dataset while maintaining a comparable 5% of postively correlated genes. SLIPT still outperforms χ^2 or negative correlation and is optimal at the 3-quantile. However, the difference between SLIPT and χ^2 were less pronounced in a larger dataset since the sheer number of negative genes (as potential false postives) affects the specficity of SLIPT which distinguishes it from χ^2-test alone and is an important consideration in large-scale genomics analysis.

Nevertheless, SLIPT with 3-quantiles (as performed throughout Chapters 4 and 5), has higher performance than other quantiles, particularly with postive correlations (replicating the Section 3.3.2.2). These findings hold across different numbers of underlying synthetic lethal genes (as shown in Figures N.5 and N.6).

Together these results support the use of SLIPT, particularly the use of quantiles as thresholds for gene function and specific use of 3-quantiles which perform well compared to other quantiles. A particular concern in the design of SLIPT for expression data was

sufficient samples size when the data is divided into quantiles. The SLIPT methdology further peforms better for 3-quantiles (and other moderate values), irrespective of sample size or p-value threshold as AUROC values are independent from them. Such quantiles ensure that there are a sufficent number of samples expected below and above them so that deviations from these are statistically detectable. Thhese quantiles were also optimal for the χ^2 as both significance and the SLIPT directional conditions rely use the same expected values.

This categorical approach for gene function to detect synthetic lethality also outperforms correlations which use continuous data directly. Correlation performing poorly as a synthetic lethal detection strategy consistent with there not necessarily being a relationship between syntethic lethal partners which can be in distinct biological pathways, expressed at different times or in different cell types. Nevertheless, correlation is among the alternative detection methods considered in further detail.

6.1.2 Alternative Synthetic Lethal Detection Strategies

6.1.2.1 Correlation for Synthetic Lethal Detection

Text

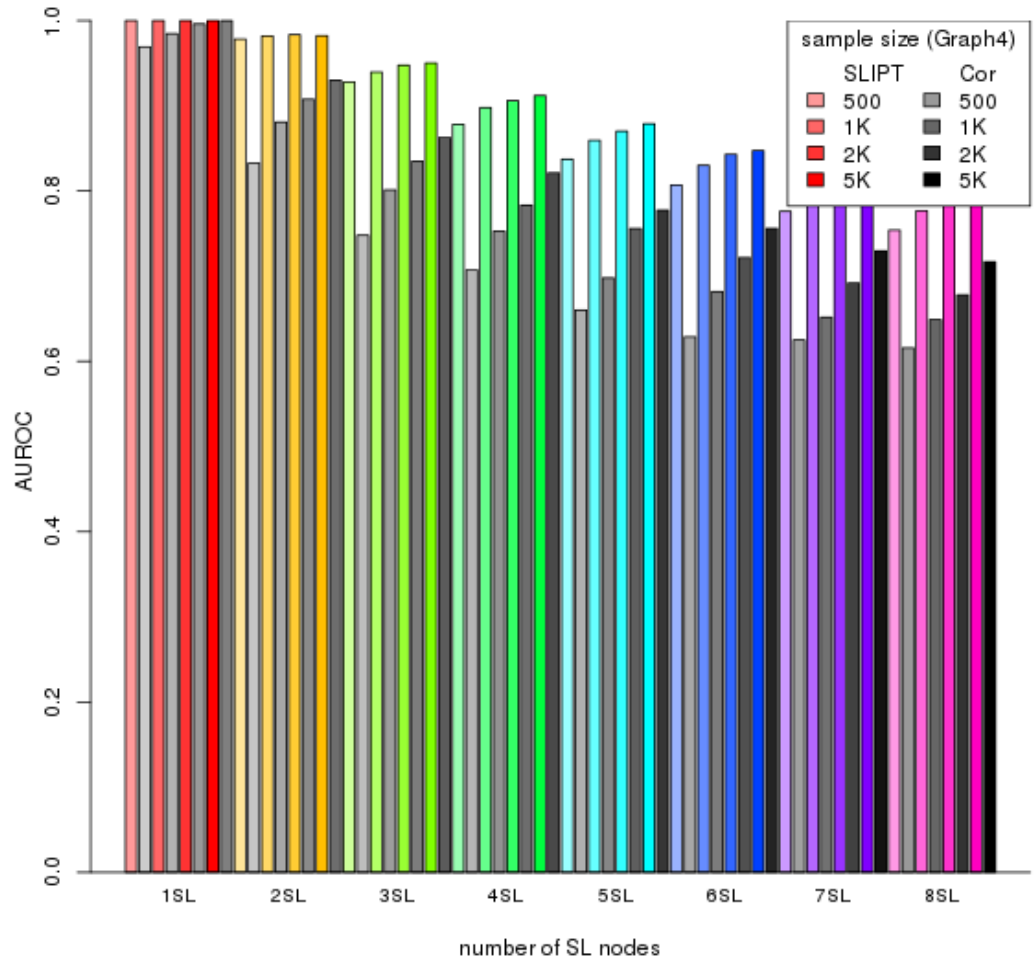


Figure 6.5: **Performance on Graph Structures**. Synthetic Lethal Detection Compared with negative correlation.

6.1.2.2 Testing for Bimodality with BiSEp

Computer says No

- Designed for global SL
- Unable to detect SL partners in TCGA data
- Source code modified to test partners of query gene (R package)
- Still unable to identify SL genes for CDH1 in TCGA

- Computationally-intensive, longer to run than SLIPT, more difficult to evaluate many iterations
- Unable to identify SL candidates in a limited number of simulations
- Assumes Bi-modal distribution detectable: not appropriate for normalised expression data (standard in the RNA-Seq analysis) or ranked (metagenes) – may be applicable to other datasets
- Comparing software is non-trivial (even those released as R packages), the above results are sufficent to evaluate SLIPT, and further benchmarking out of scope.

6.1.2.2.1 Implementation and Computation Time

Compare runtime?

6.1.2.3 Testing Synthetic Lethal Genes with Linear Models

[Move to future Dir??]

- Strategy to detect SL with linear models by fit to curve (significance) and slope (direction)
- Amenable to conditioning on known SL or iterative conditioning on strongest SL to detect other partners of higher-order SL
- All attempts: linear, GLM, and linear polynomial (quadratic, cubic, or quintic) underperform SLIPT, similar to Pearson's correlation results
- Linear models and regression may still be an avenue for further detection of SL (e.g., with Bayes)

6.2 Simulations with Graph Structures

Simulations of synthetic lethality in Section 3.3 included correlated blocks of genes as a rudimentary model of pathway structure and co-regulated genes. Here the simulation procedure was expanded to account for more complex graph structures by sampling from multivariate normal distributions with correlation structure derived from graph structures (as described in Section 3.4.2). This approach enables simulation of synthetic lethal pathways with known correlation structure and known partners (of a gene not in the pathway) and evaluation of the performance of SLIPT under simple controlled

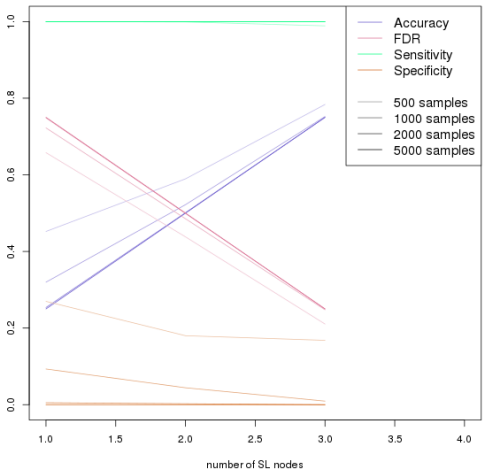
correlation structures and complex correlations such as those derived from biological networks (such as those described in Chapter 5). The SLIPT methdology will be tested both in artificial constructed networks to evaluate the effect of pathway structure on synthetic lethal detection and on large biologically feasible pathways to test whether SLIPT is robust under complex correlation structures and applicable to such complex genomics data.

These simulations combine the approach of prior simulation analyses (in Sections 3.3 and 6.1) with the graph structures for biological pathways (as used in Chapter 5). This enables testing whether subtle or large differences in pathway structure affect synthetic lethal detection, whether inhibiting relationships (or inverse correlations) between genes affects synthetic lethal detection, and whether synthetic lethal detection varies across which gene is synthetic lethal or affects proximal genes in the pathway structure. In addition, large numbers of synthetic lethal genes and biologically feasible numbers of genes (with many non-synthetic lethal genes) will be tested to replicate the findings of Sections 3.3 and 6.1 in correlated structures derived from pathway graphs, including examples of biological pathways from Reactome.

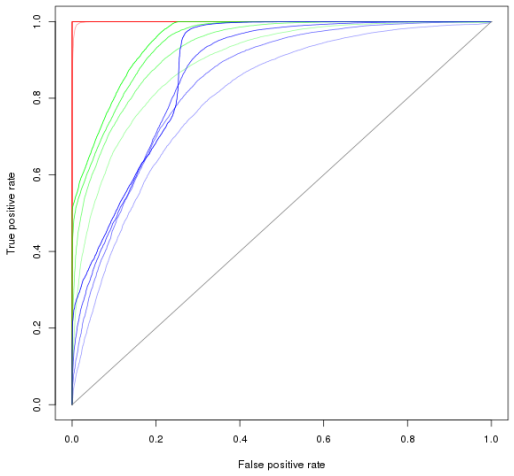
6.2.1 Performance over a Graph Structure

6.2.1.1 Simple Graph Structures

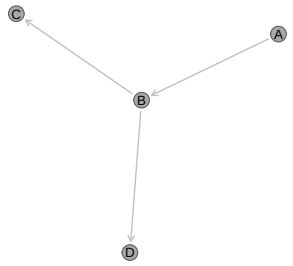
6.2.1.2 Constructed Graph Structures



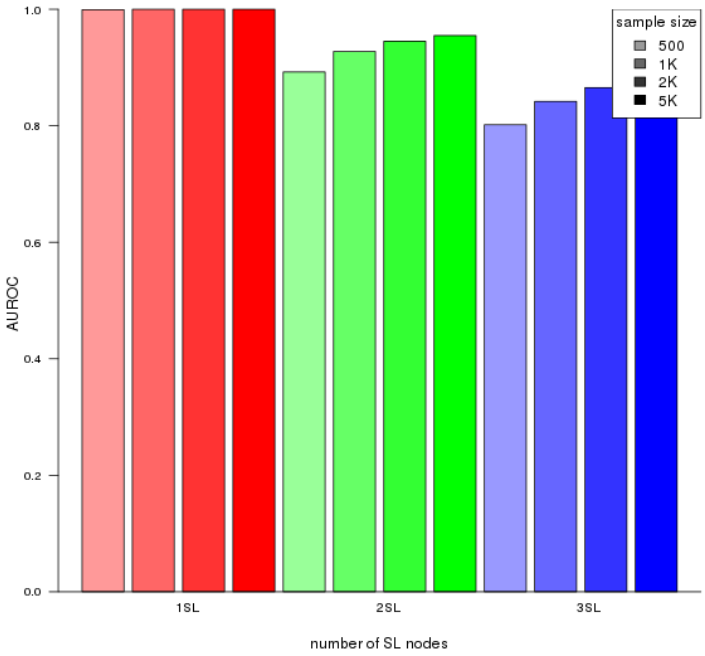
(a) Statistical evaluation



(b) Receiver operating characteristic

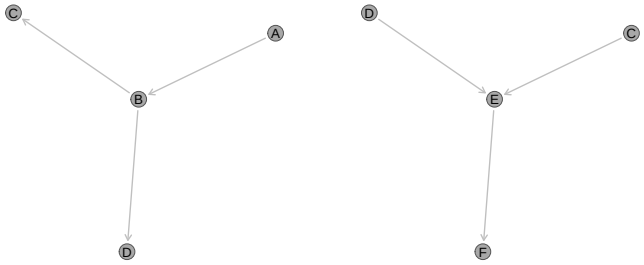


(c) Graph Structure

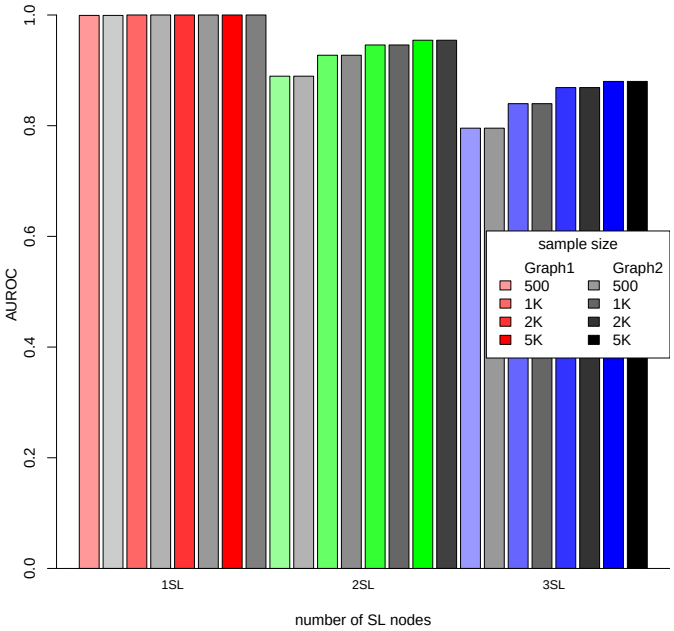


(d) Statistical performance

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.

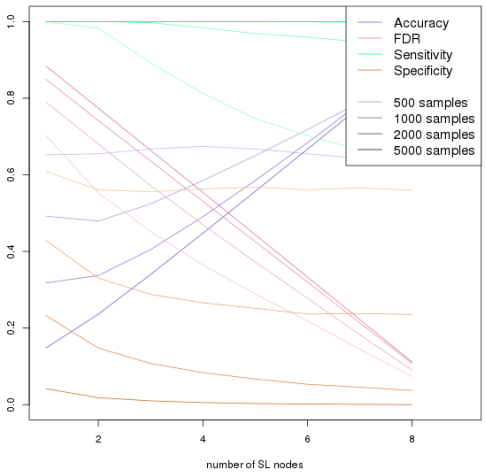


(a) Graph Structure (b) Graph Structure

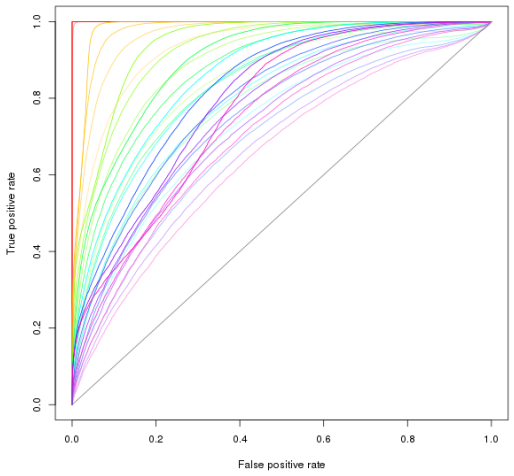


(c) Gene category in simulations

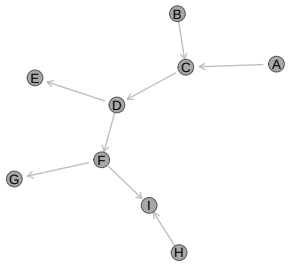
Figure 6.7: **Performance of simulations is similar in simple graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across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



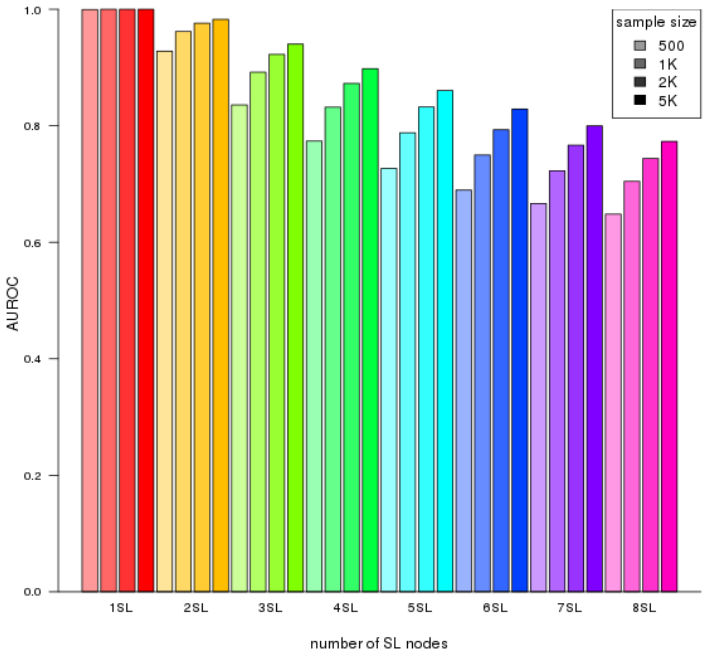
(a) Statistical evaluation



(b) Receiver operating characteristic

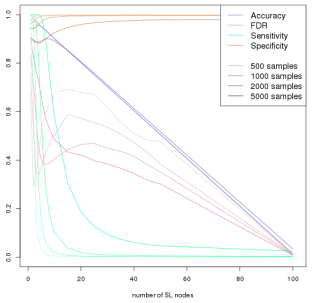


(c) Graph Structure

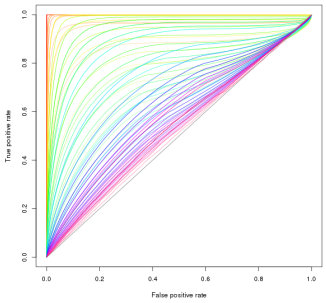


(d) Statistical performance

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.

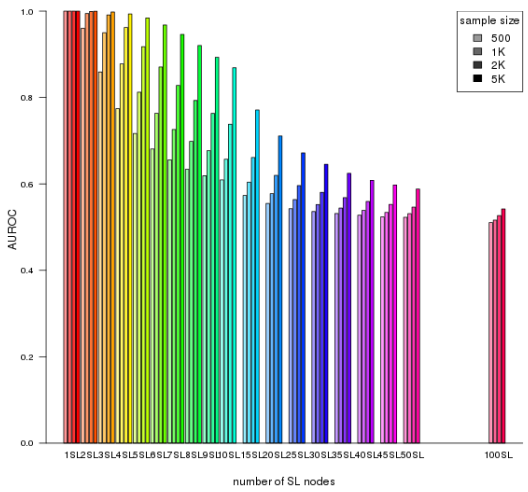


(a) Statistical evaluation



(b) Receiver operating characteristic

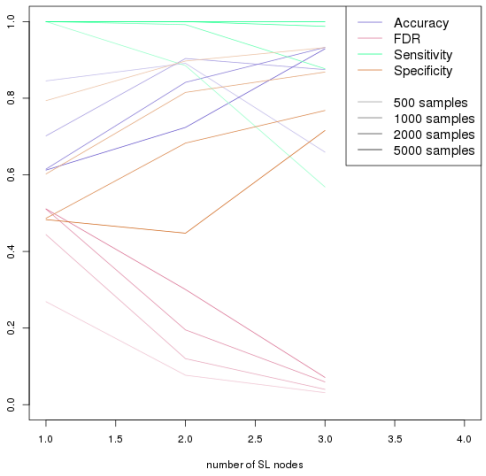
(c) Graph Structure



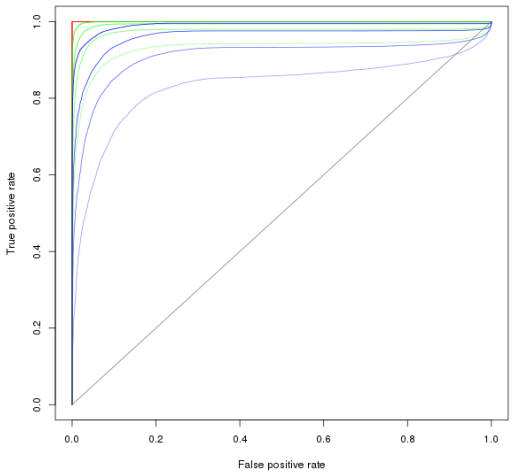
(d) Statistical performance

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.

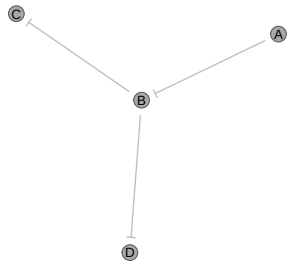
6.2.2 Performance with Inhibitions



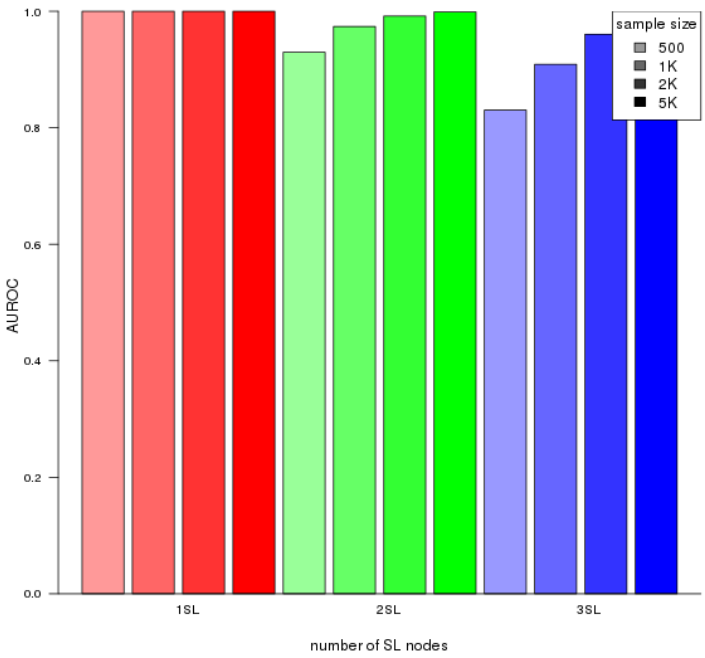
(a) Statistical evaluation



(b) Receiver operating characteristic

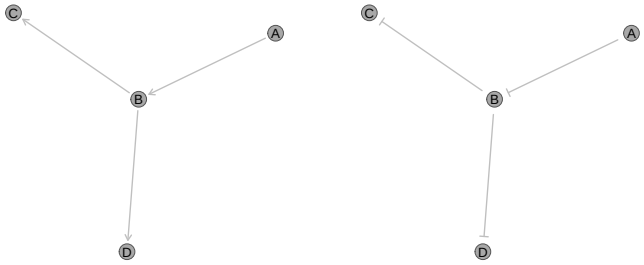


(c) Graph Structure

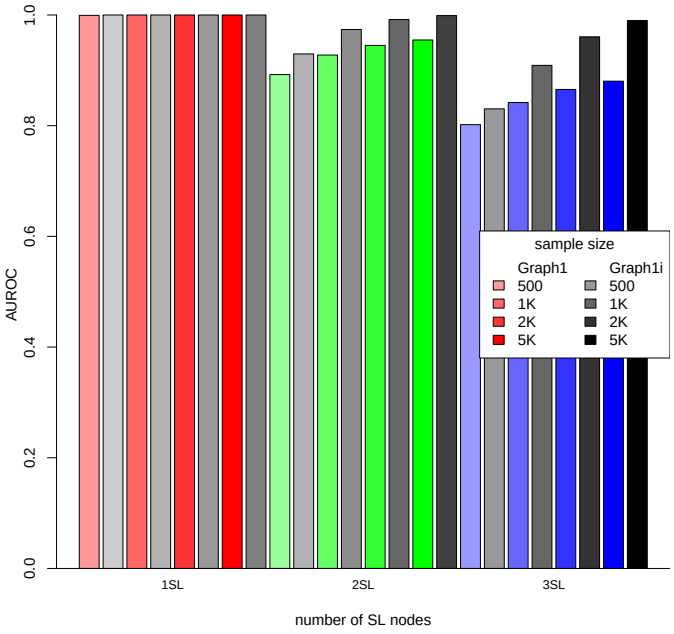


(d) Statistical performance

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.

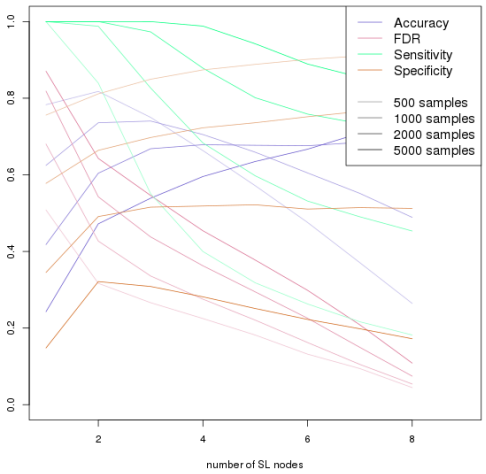


(a) Graph Structure (b) Graph Structure

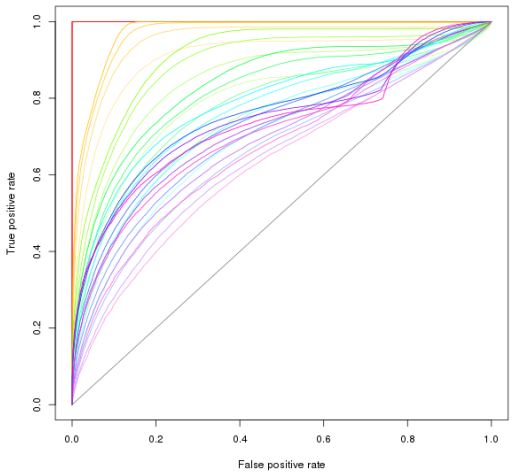


(c) Gene category in simulations

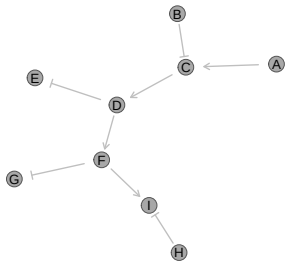
Figure 6.11: **Performance is higher on a simple inhibiting graph.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across simulations.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



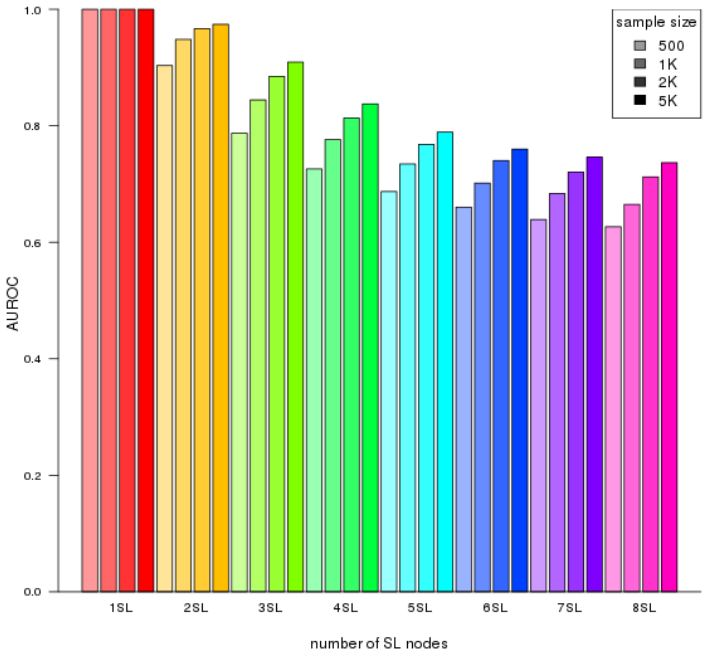
(a) Statistical evaluation



(b) Receiver operating characteristic

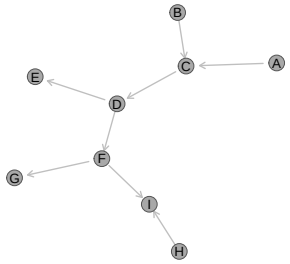


(c) Graph Structure

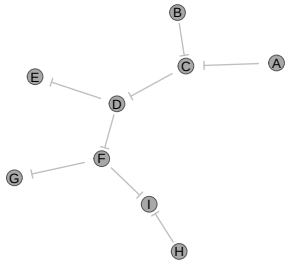


(d) Statistical performance

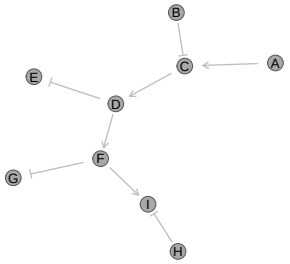
Figure 6.12: **Performance of simulations on an inhibiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (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.



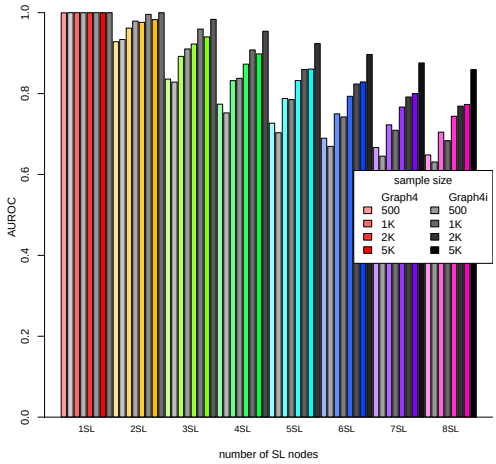
(a) Graph Structure



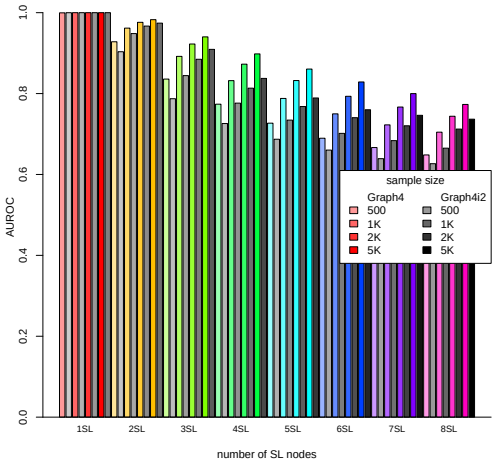
(b) Graph Structure



(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 χ^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 χ^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

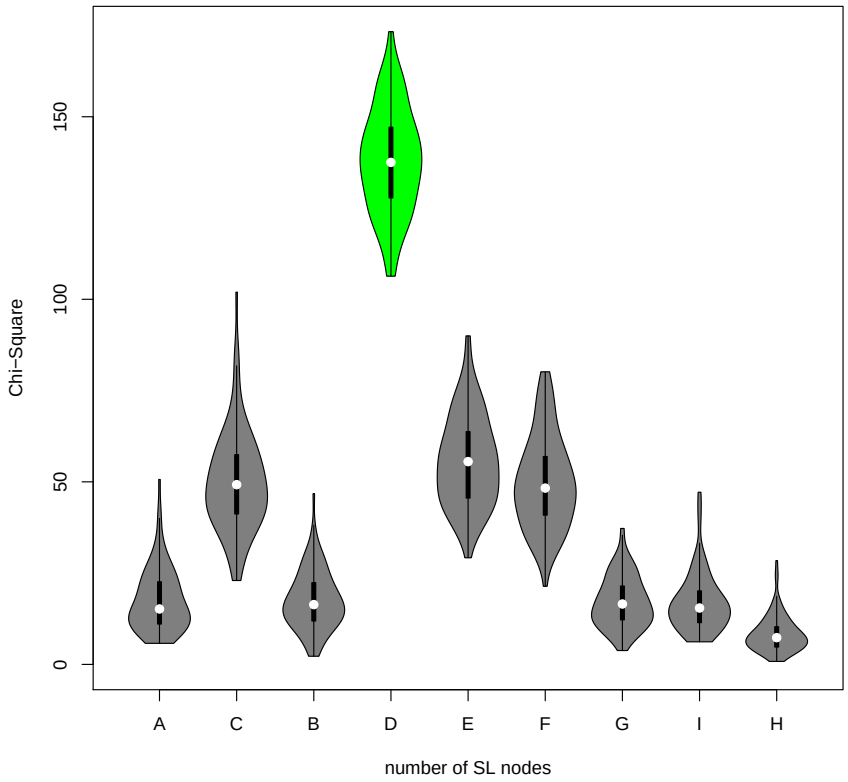
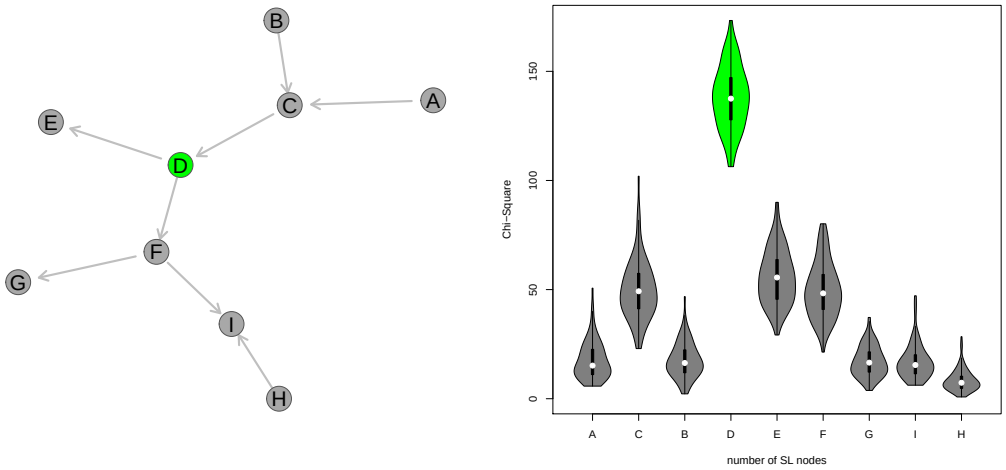


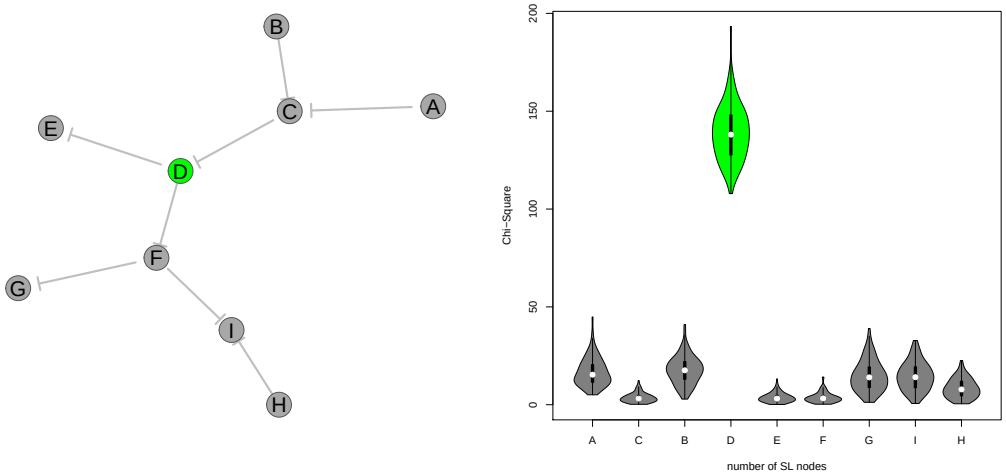
Figure 6.14: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The χ^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

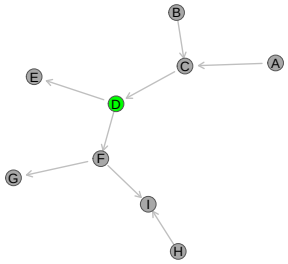
Figure 6.15: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across simulations.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



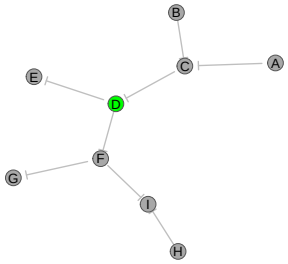
(a) Graph Structure

(b) Graph Structure

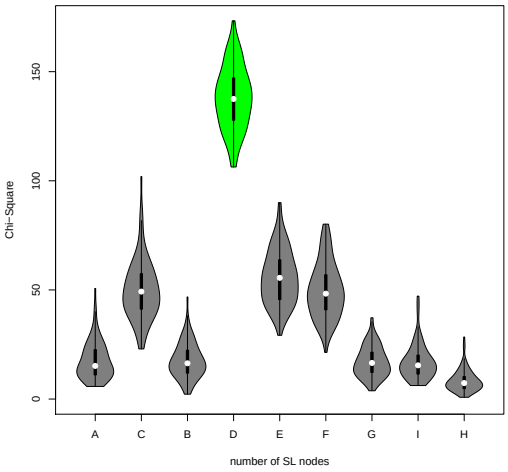
Figure 6.16: **Performance is affected by inhibition in graphs.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across simulations.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



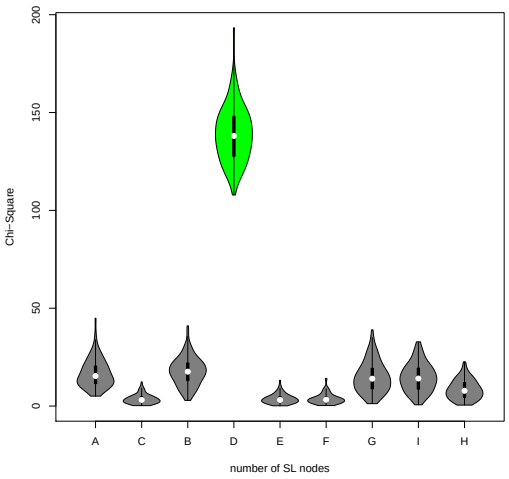
(a) Graph Structure



(b) Graph Structure



(c) Graph Structure



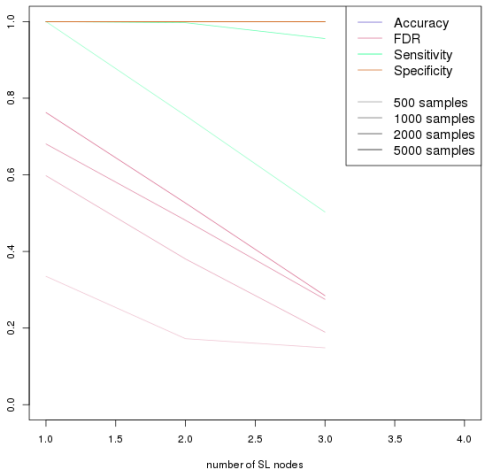
(d) Graph Structure

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 χ^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 χ^2 values show a clear threshold for SL and correlated genes when there are fewer of them, distinguishable from correlated genes in this case.

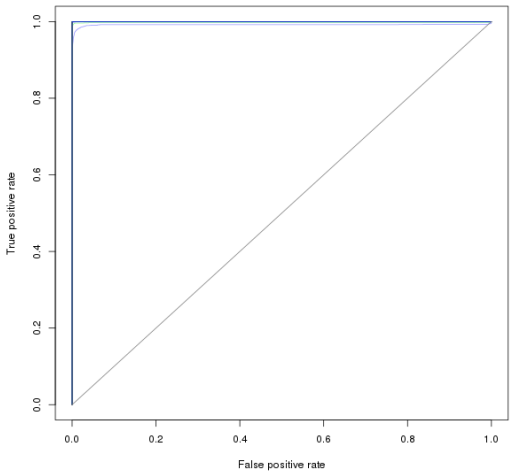
6.2.4 Performance with Feasible Gene Numbers (20,000)

6.2.4.1 Simple Graph Structures in a Genome

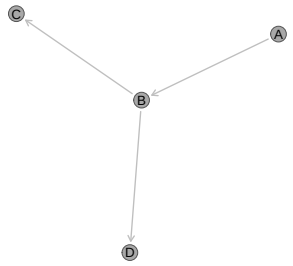
6.2.4.2 Constructed Graph Structures in a Genome



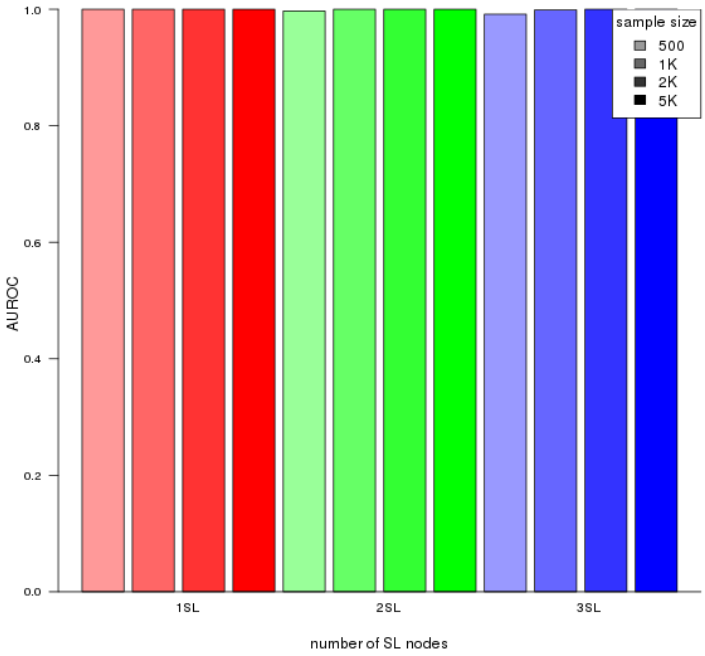
(a) Statistical evaluation



(b) Receiver operating characteristic

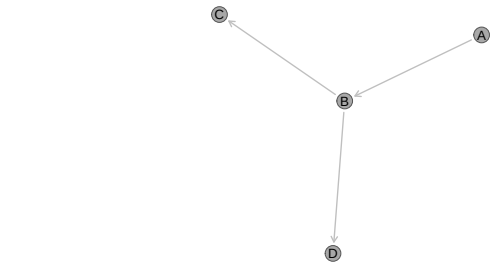


(c) Graph Structure

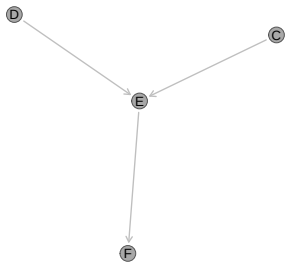


(d) Statistical performance

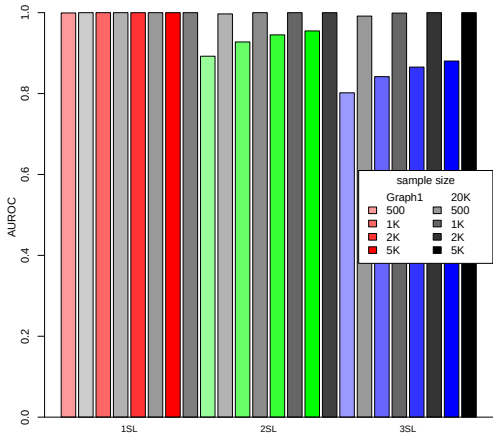
Figure 6.18: **Performance of simulations including a simple graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (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.



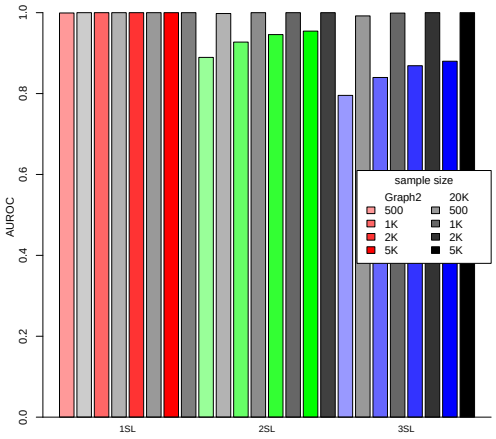
(a) Graph Structure



(b) Graph Structure

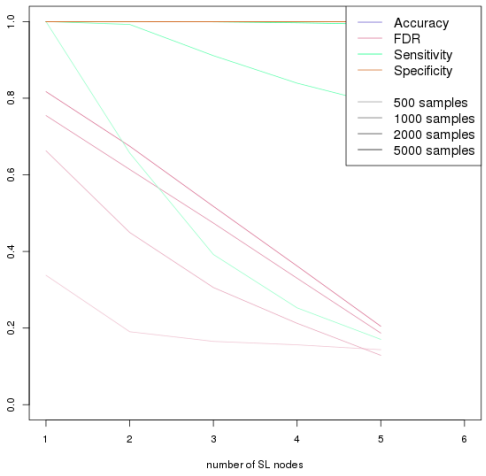


(c) Gene category in simulations

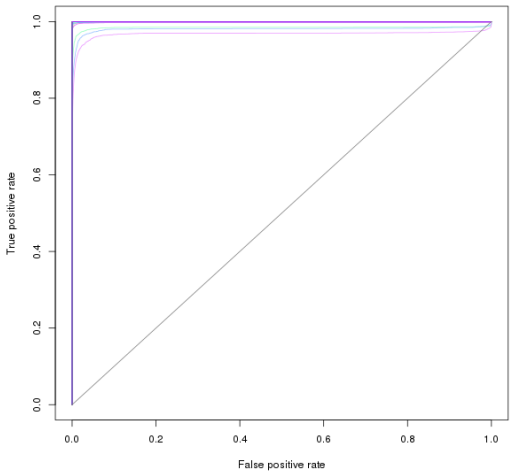


(d) Gene category in simulations

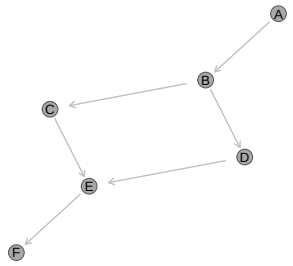
Figure 6.19: **Performance on a simple graph improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across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



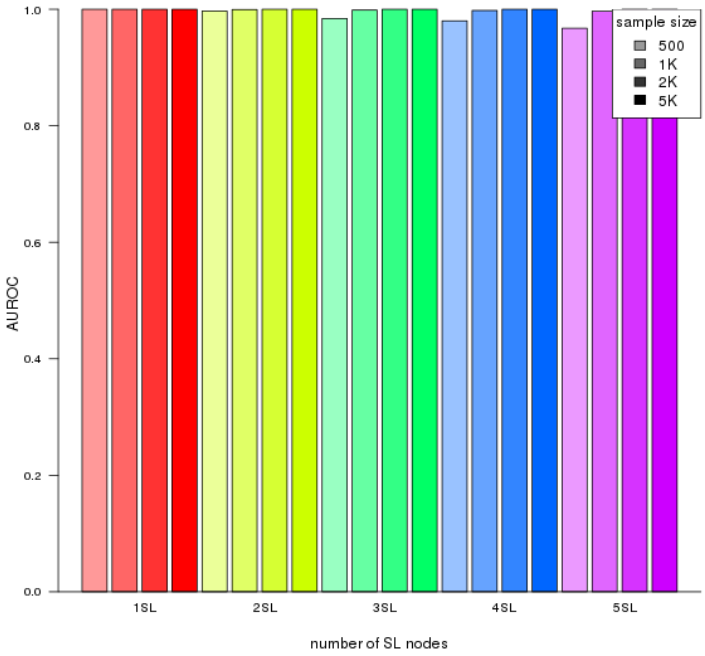
(a) Statistical evaluation



(b) Receiver operating characteristic

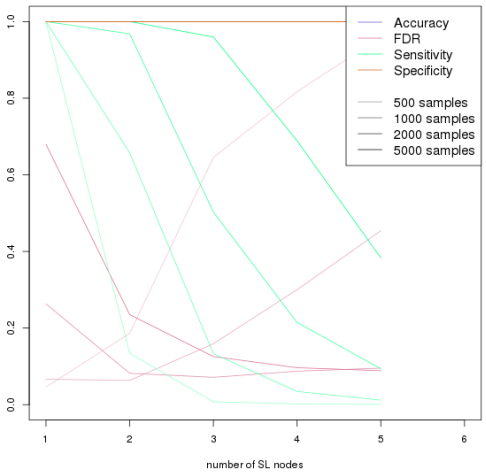


(c) Graph Structure

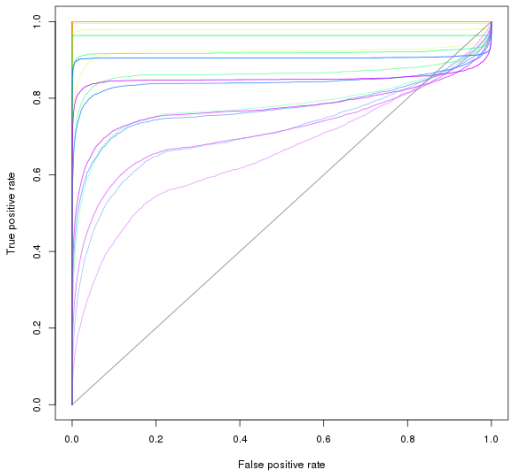


(d) Statistical performance

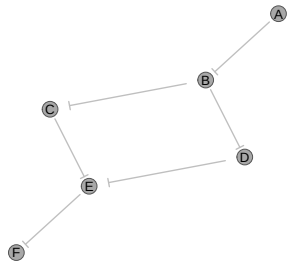
Figure 6.20: **Performance of simulations including a graph structure.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample 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.



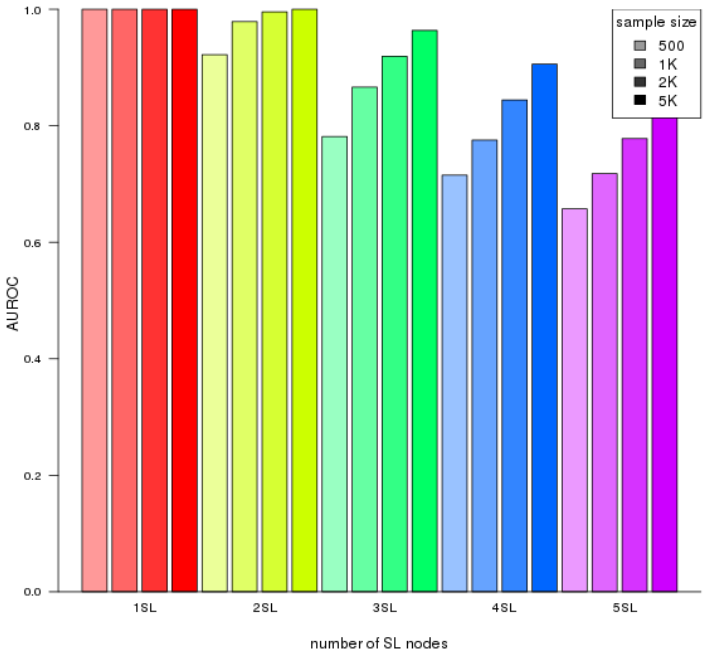
(a) Statistical evaluation



(b) Receiver operating characteristic

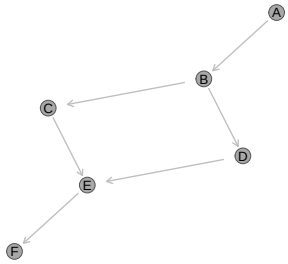


(c) Graph Structure

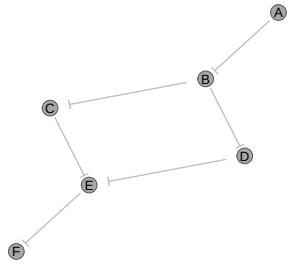


(d) Statistical performance

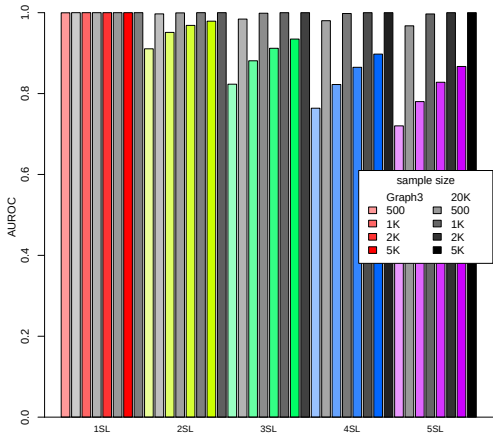
Figure 6.21: **Performance of simulations including an inhbiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample 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.



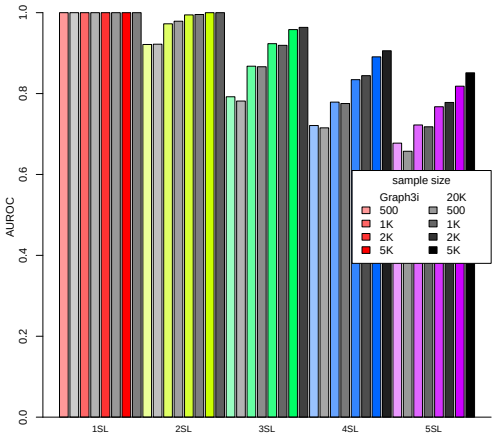
(a) Graph Structure



(b) Graph Structure

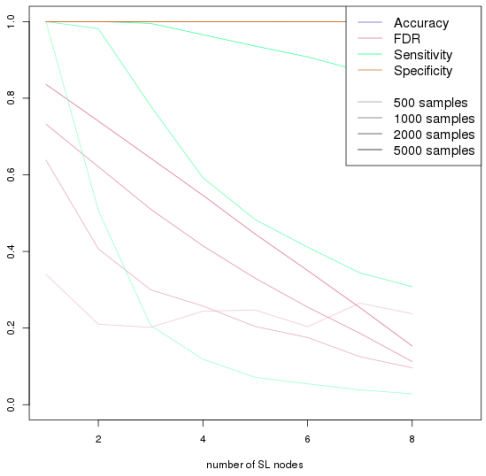


(c) Gene category in simulations

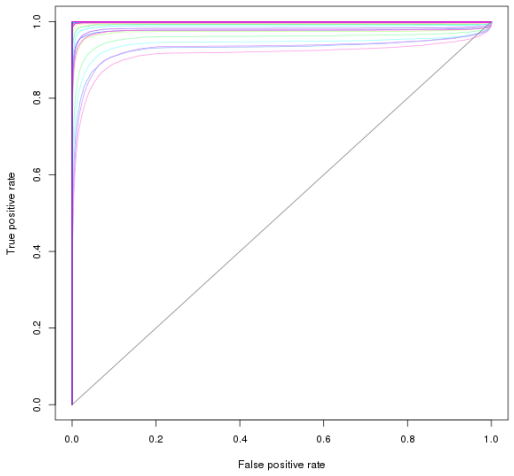


(d) Gene category in simulations

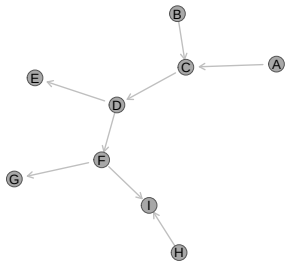
Figure 6.22: **Performance on an inhibiting graph improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown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



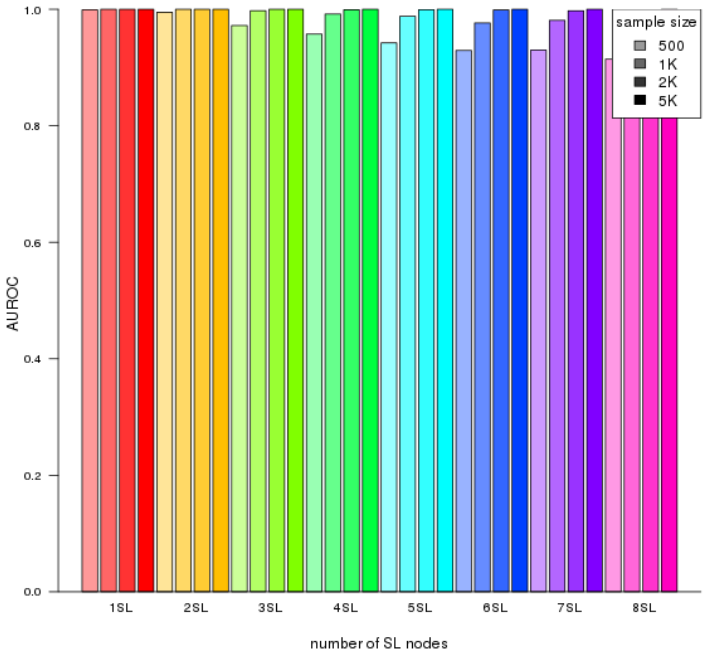
(a) Statistical evaluation



(b) Receiver operating characteristic

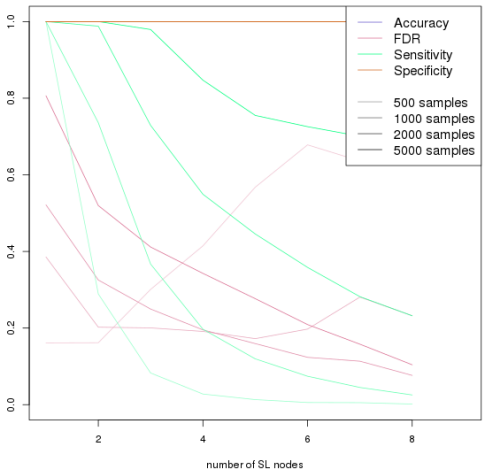


(c) Graph Structure

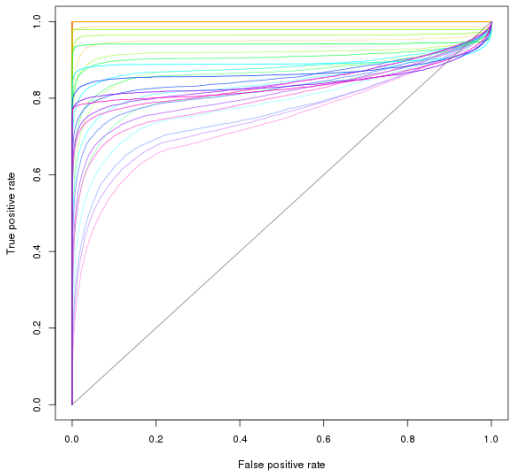


(d) Statistical performance

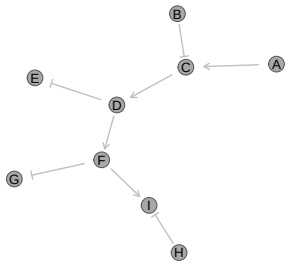
Figure 6.23: **Performance of simulations including a graph structure.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample 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.



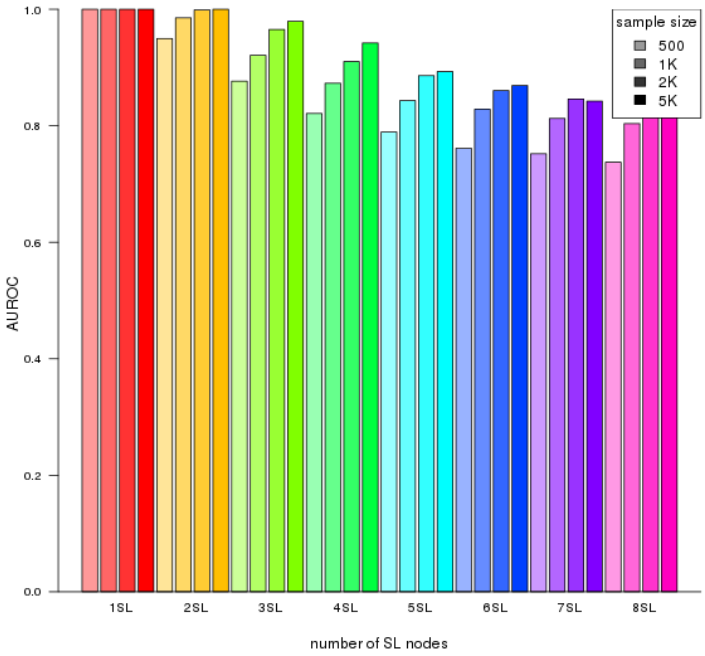
(a) Statistical evaluation



(b) Receiver operating characteristic

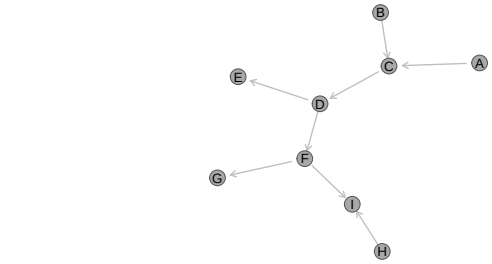


(c) Graph Structure

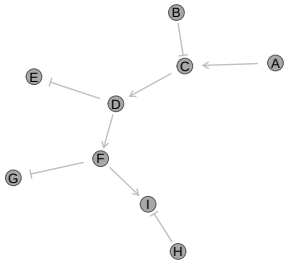


(d) Statistical performance

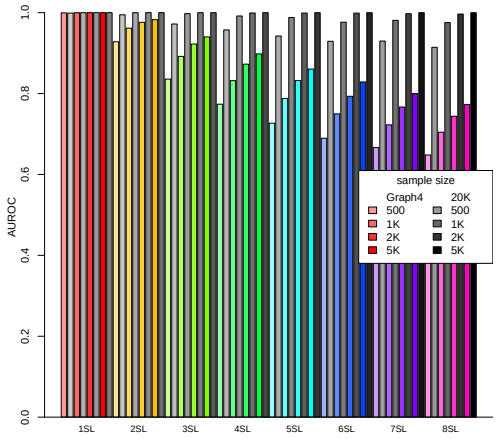
Figure 6.24: **Performance of simulations including an inhibiting graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample 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.



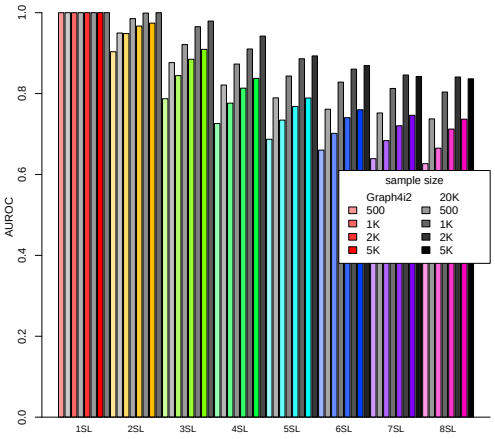
(a) Graph Structure



(b) Graph Structure



(c) Gene category in simulations

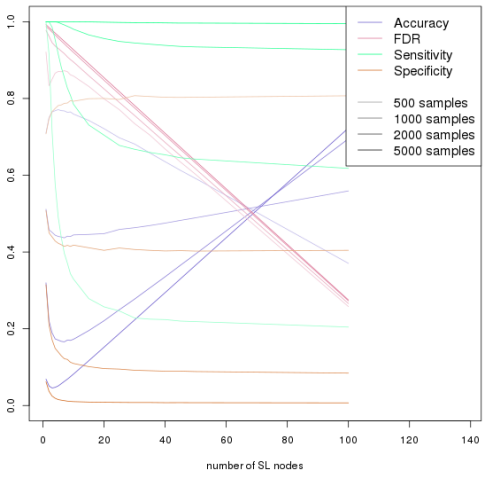


(d) Gene category in simulations

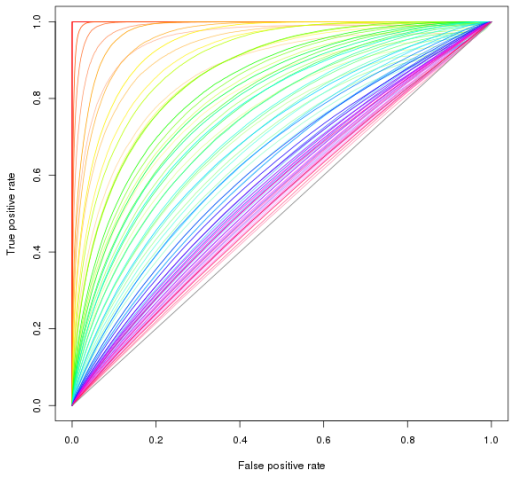
Figure 6.25: **Performance on an inhibiting graph improves with more genes.** The gene category (blue for query, cyan for query-correlated, red for SL, orange for SL-correlated, forest green for non-SL-correlated, and green for non-SL) ordered by χ^2 signed by the SLIPT directional condition is shown across simulations. For each of 1–10 SL partners, 10 simulations demonstrate that the increasing numbers of SL partners become harder detect. The χ^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

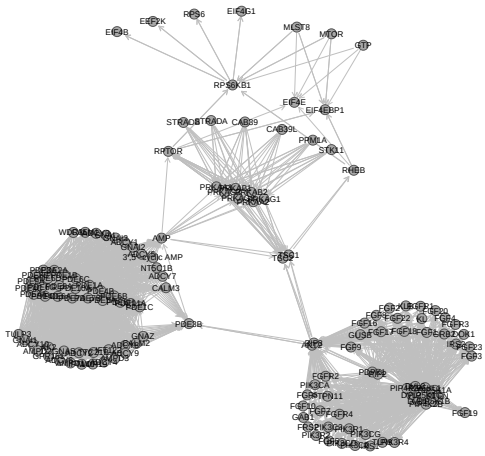
Text



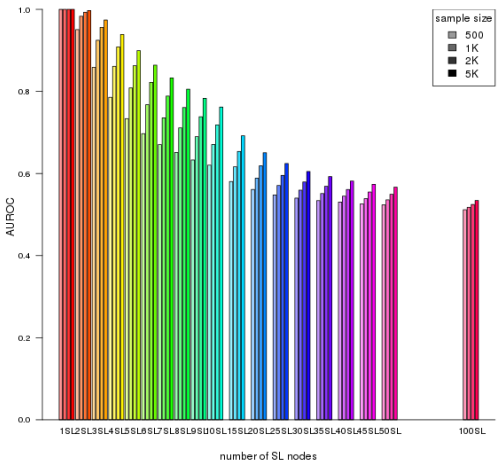
(a) Statistical evaluation



(b) Receiver operating characteristic

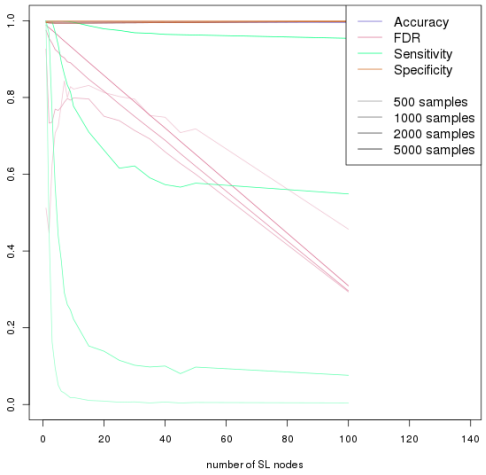


(c) Graph Structure

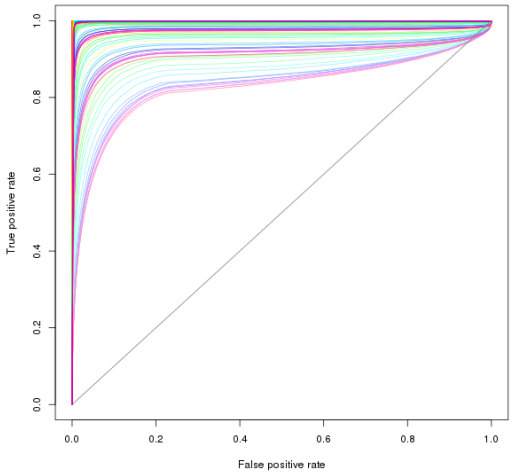


(d) Statistical performance

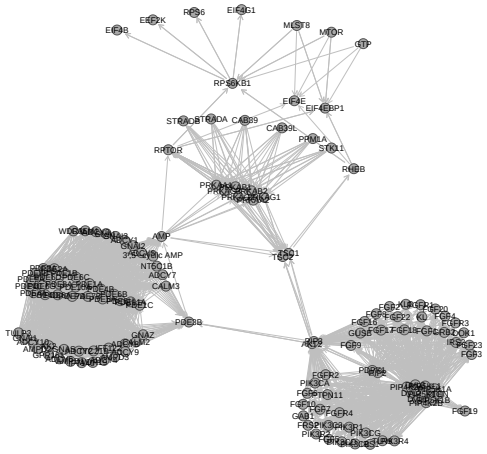
Figure 6.26: **Performance of simulations on the PI3K cascade.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (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.



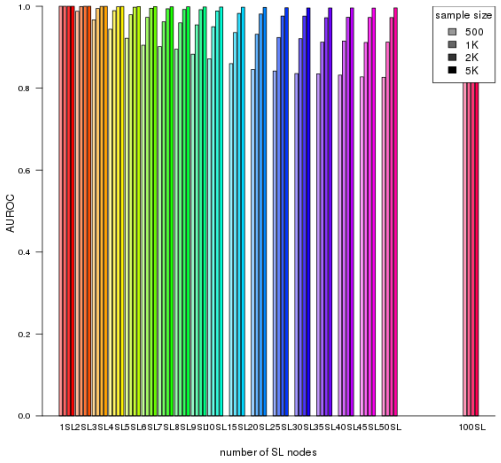
(a) Statistical evaluation



(b) Receiver operating characteristic



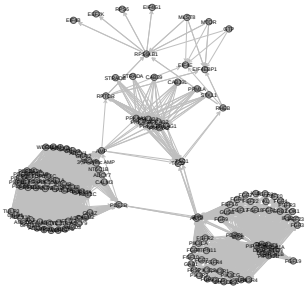
(c) Graph Structure



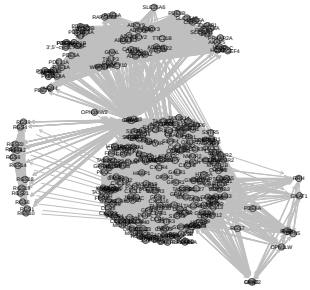
(d) Statistical performance

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.

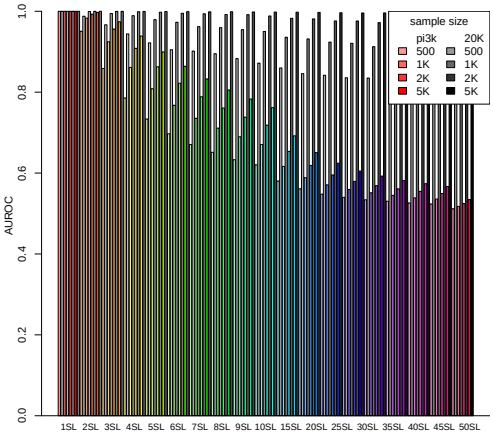
6.3.1 Pathway Structures in a Genome



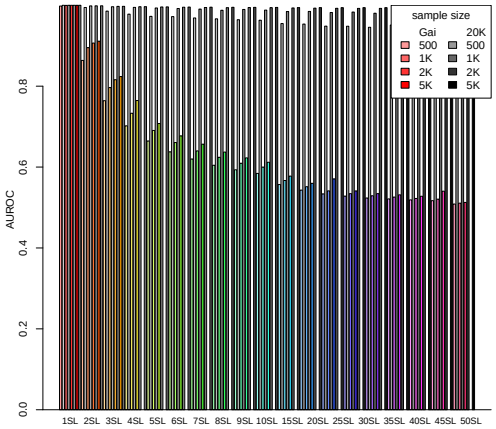
(a) Graph Structure



(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 χ^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 χ^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

Text

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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