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Glossary

gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutation	A change in DNA sequence that disrupts gene function.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

Acronyms

ANOVA Analysis of Variance.

mtSLIPT Synthetic Lethal Interaction Prediction Tool
(against mutation).

ROC Reciever Operating Characteristic (curve).

siRNA Short Interfering RNA.

SLIPT Synthetic Lethal Interaction Prediction Tool.

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Appendix K

Performance of SLIPT and χ^2

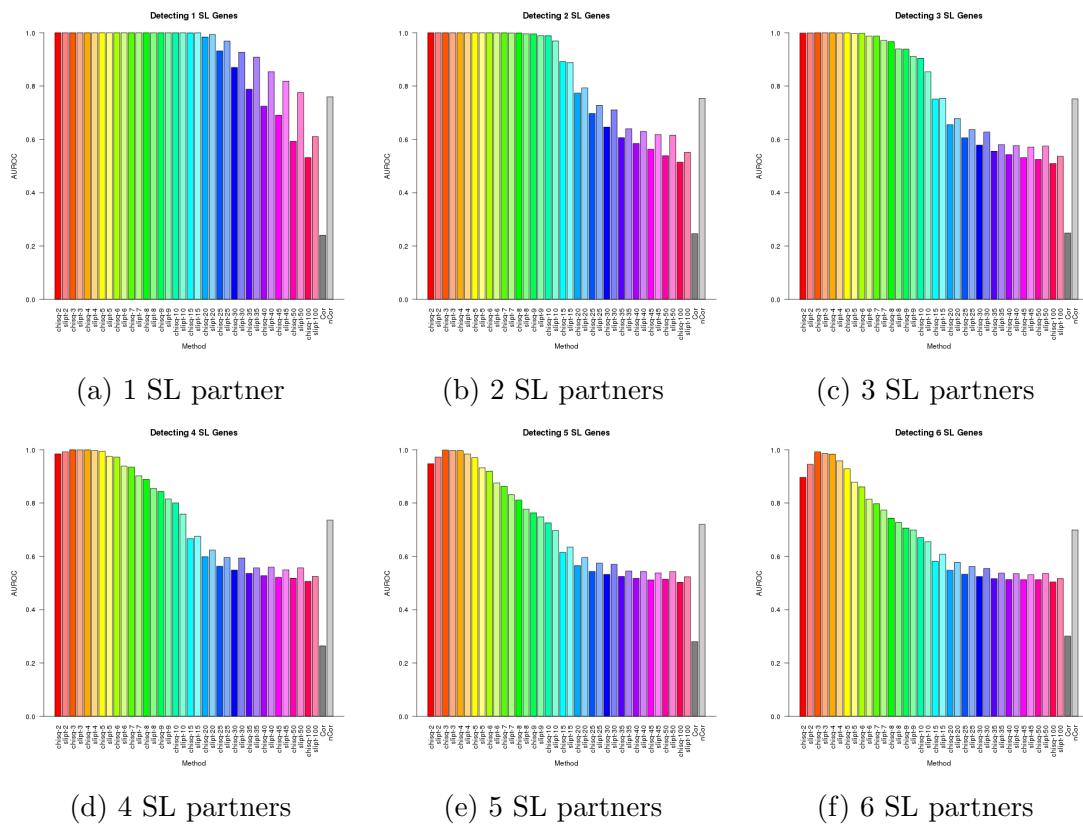


Figure K.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

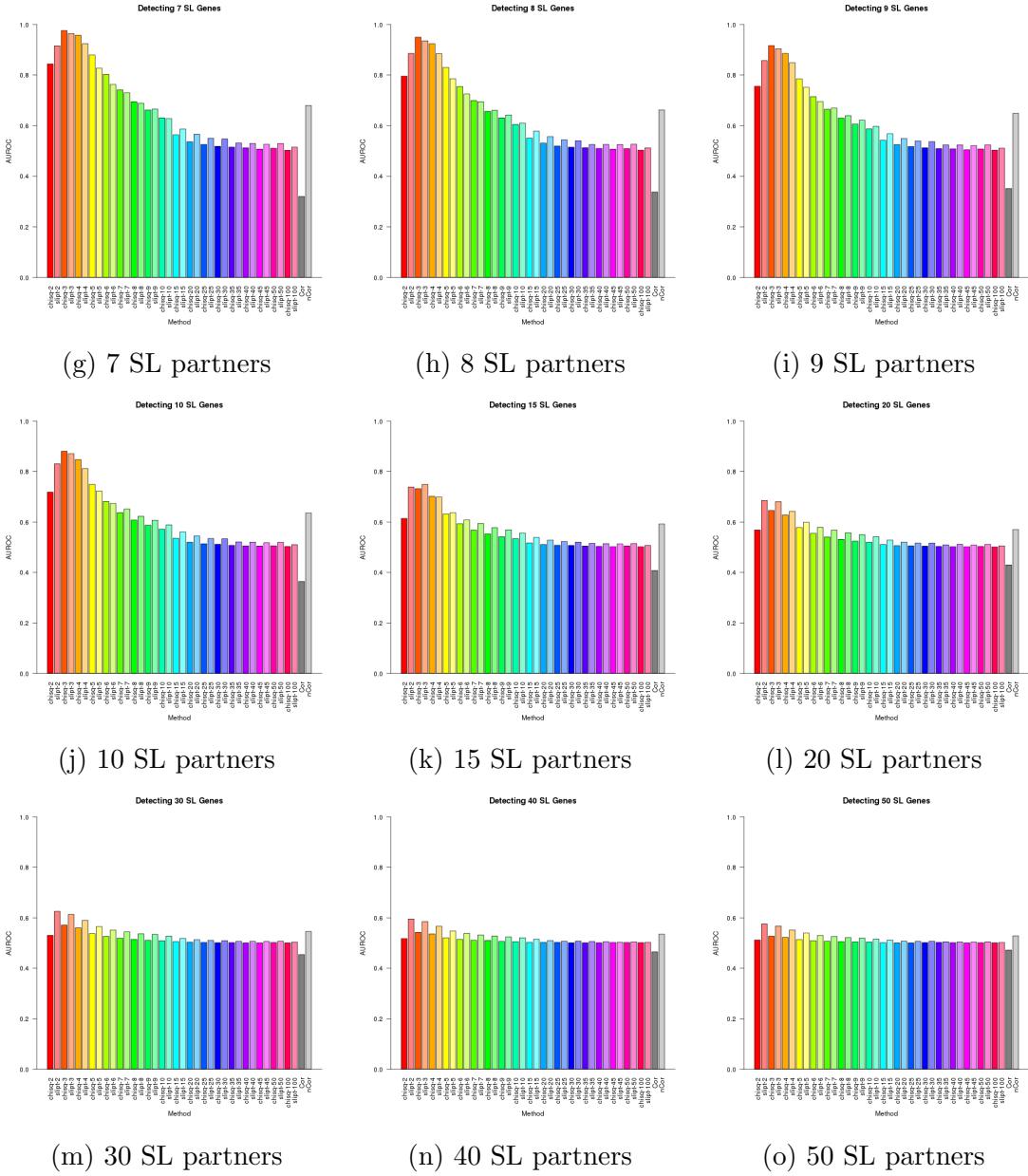


Figure K.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes and 1000 samples. SLIPT performed better than χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

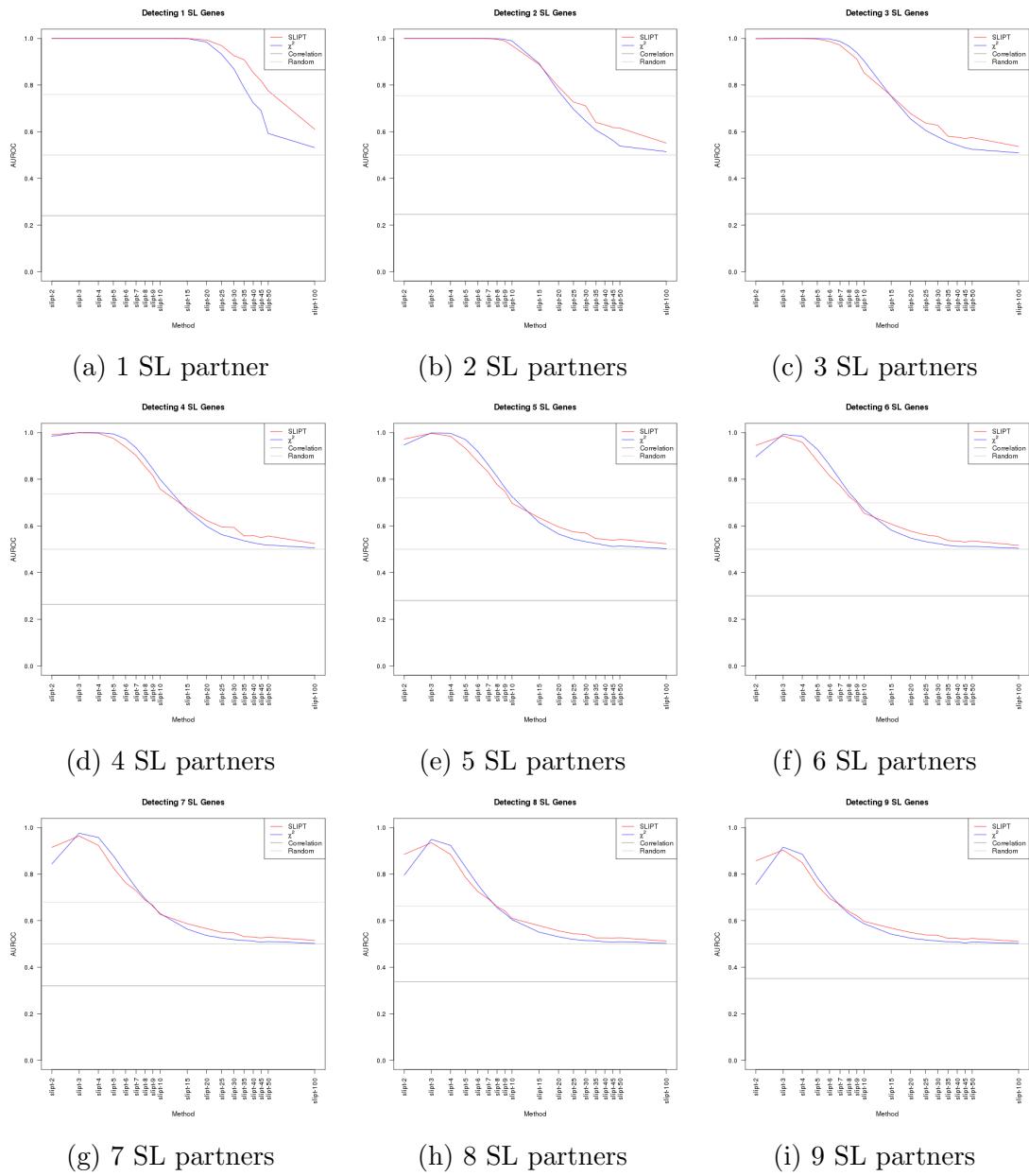


Figure K.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

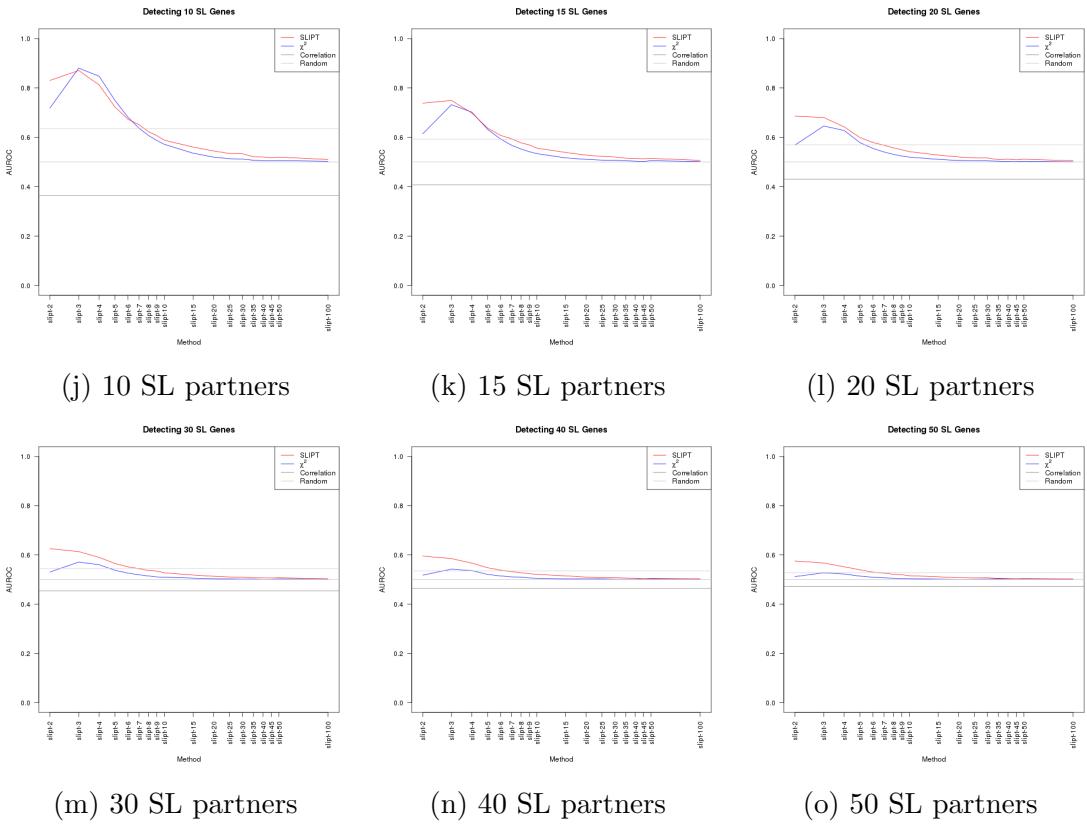


Figure K.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes and 1000 samples. SLIPT performed better than χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

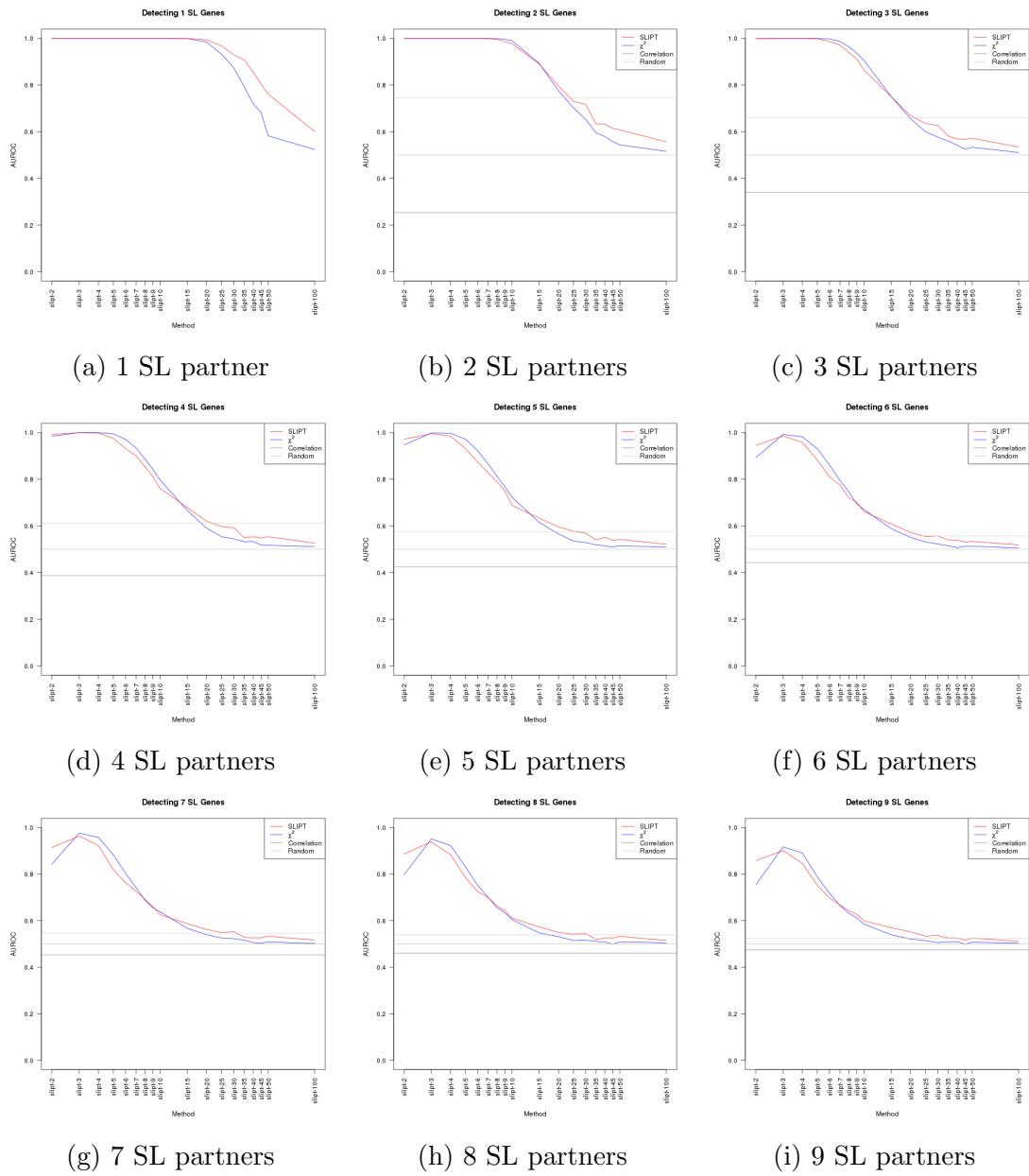


Figure K.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

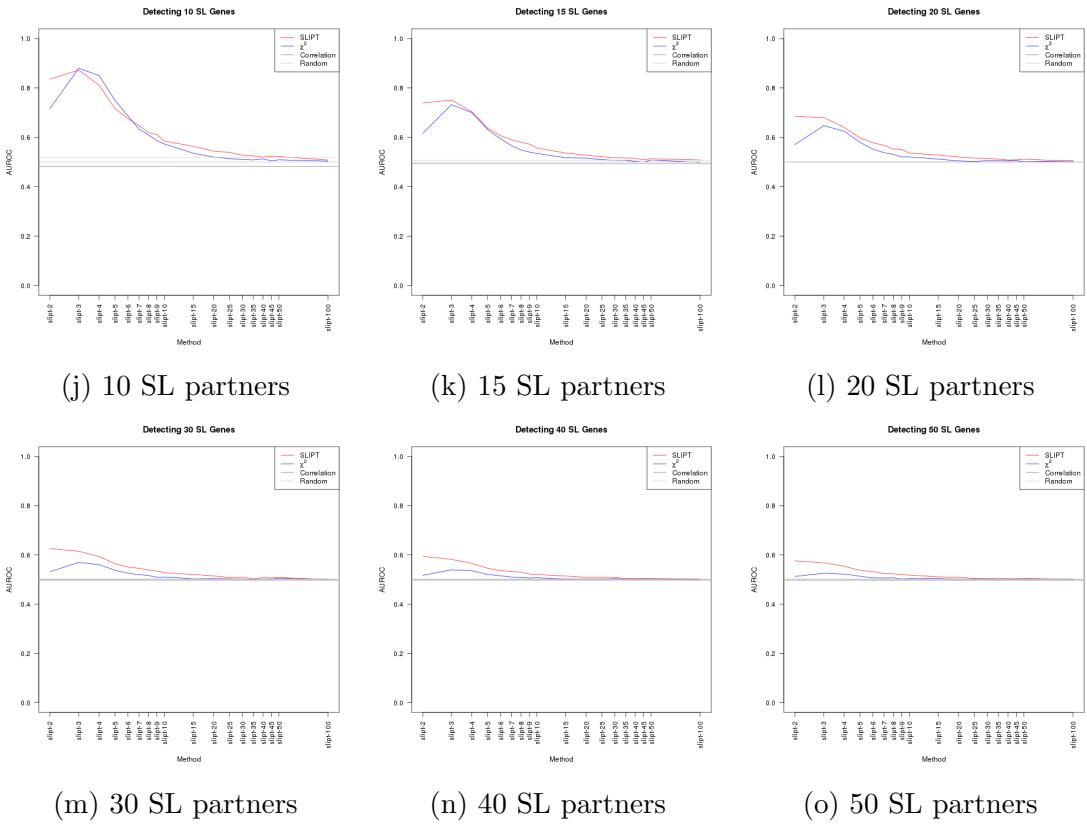


Figure K.3: Performance of χ^2 and SLIPT across quantiles with more genes.
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings were robust across different numbers of underlying synthetic lethal genes in 1000 simulations of 20,000 genes and 1000 samples. SLIPT performed better than χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

K.1 Correlated Query Genes affects Specificity

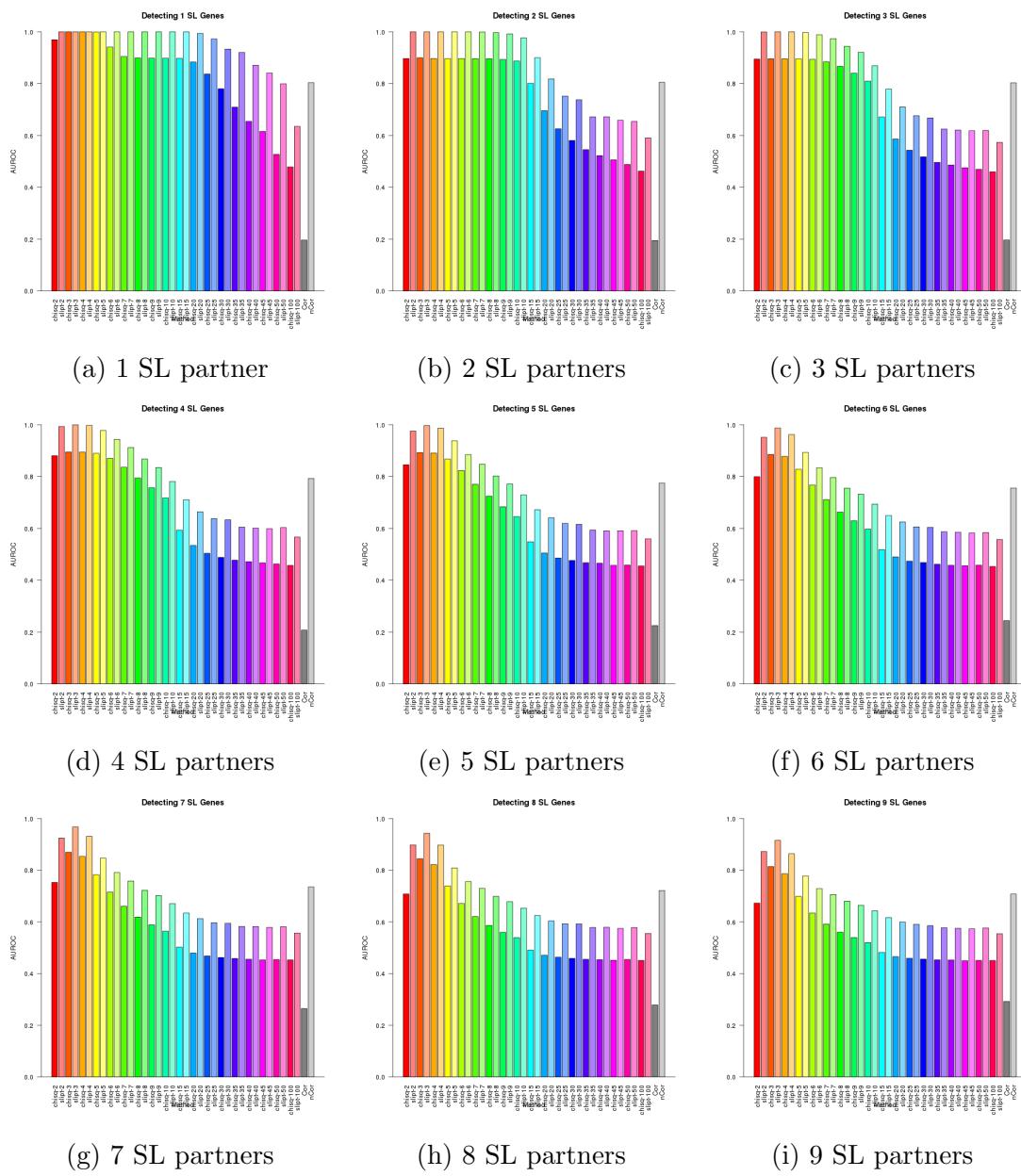


Figure K.4: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

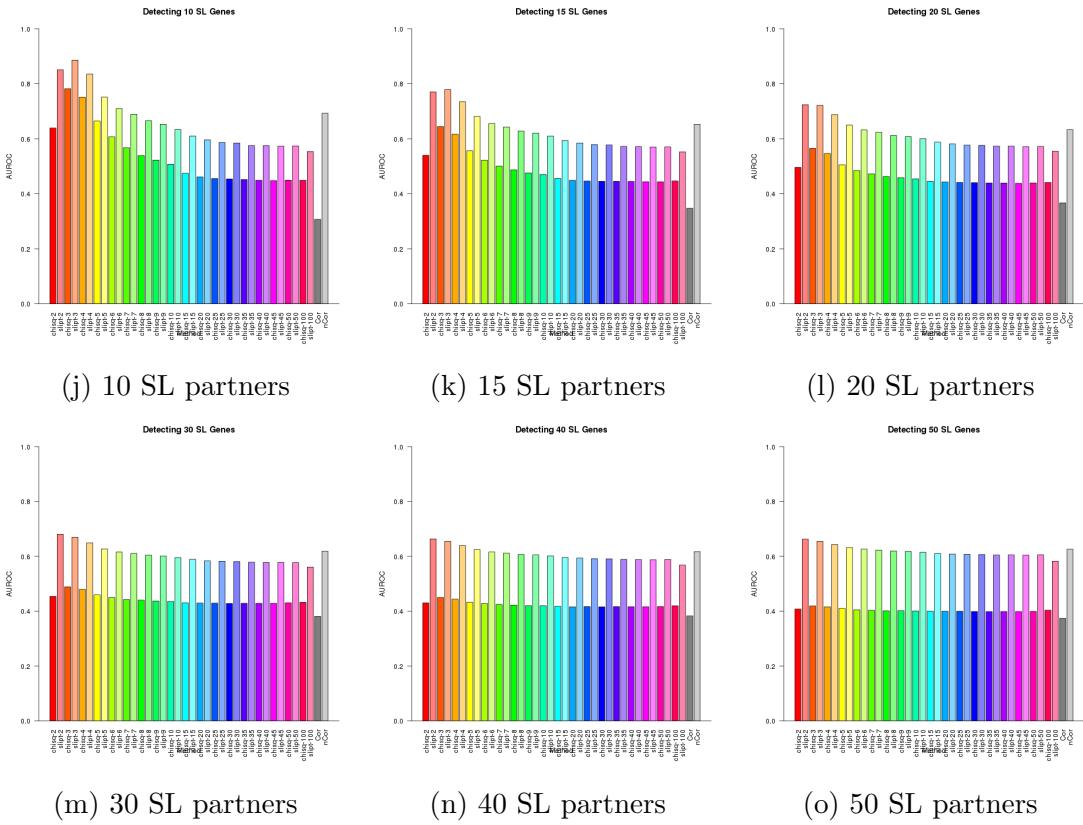


Figure K.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes (including 10 correlated with the query) and 1000 samples. SLIPT performed consistently better than χ^2 with positively correlated genes.

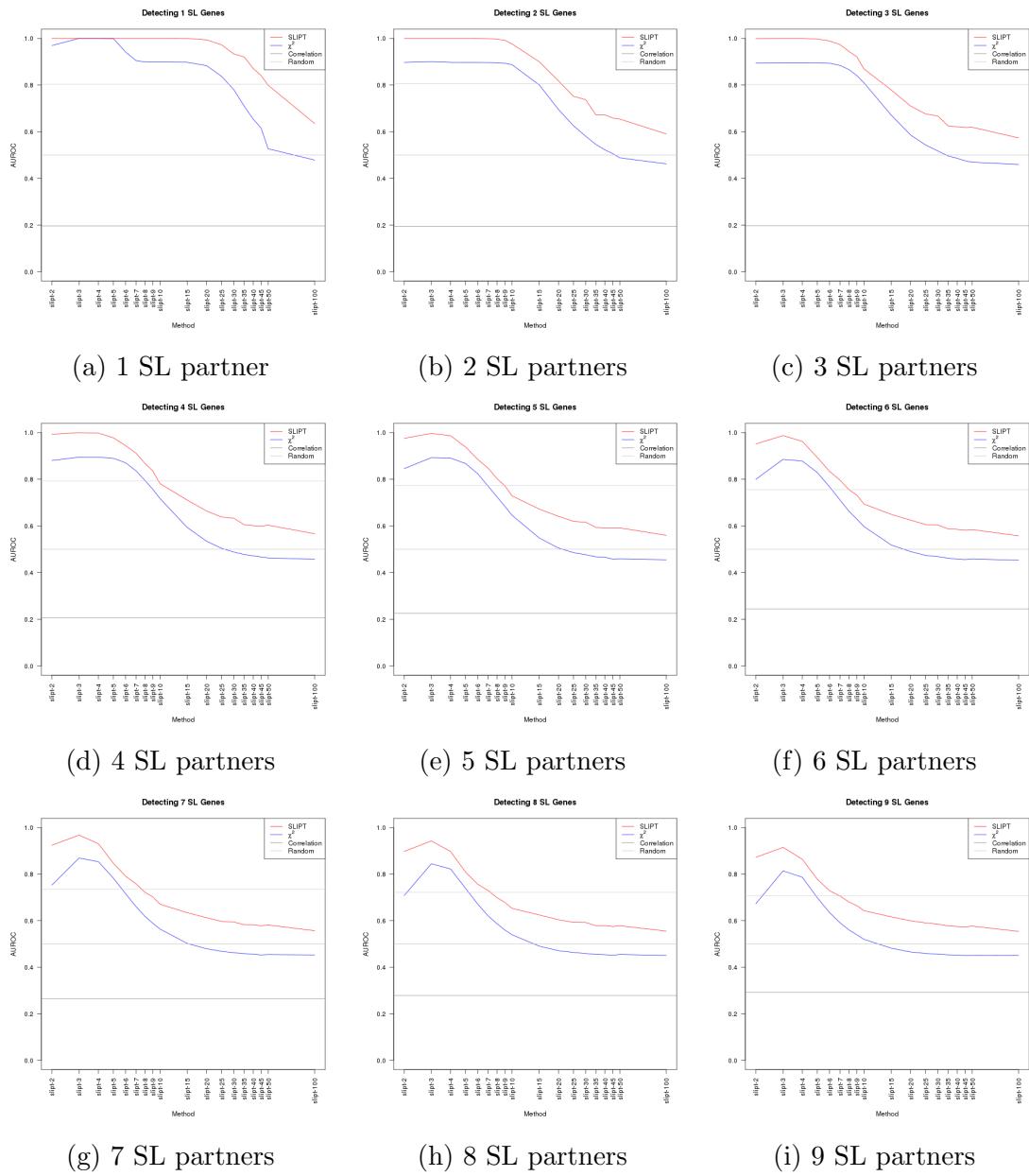


Figure K.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

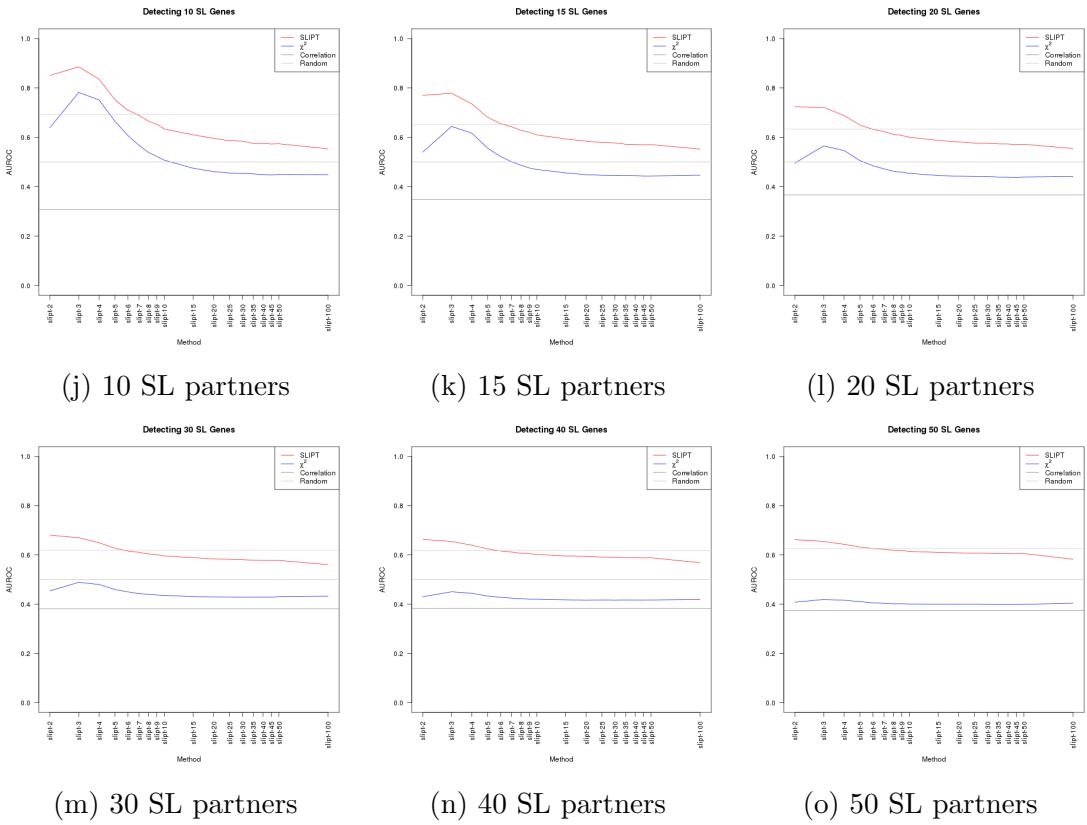


Figure K.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings were robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes (including 10 correlated with the query) and 1000 samples. SLIPT performed consistently better than χ^2 with positively correlated genes.

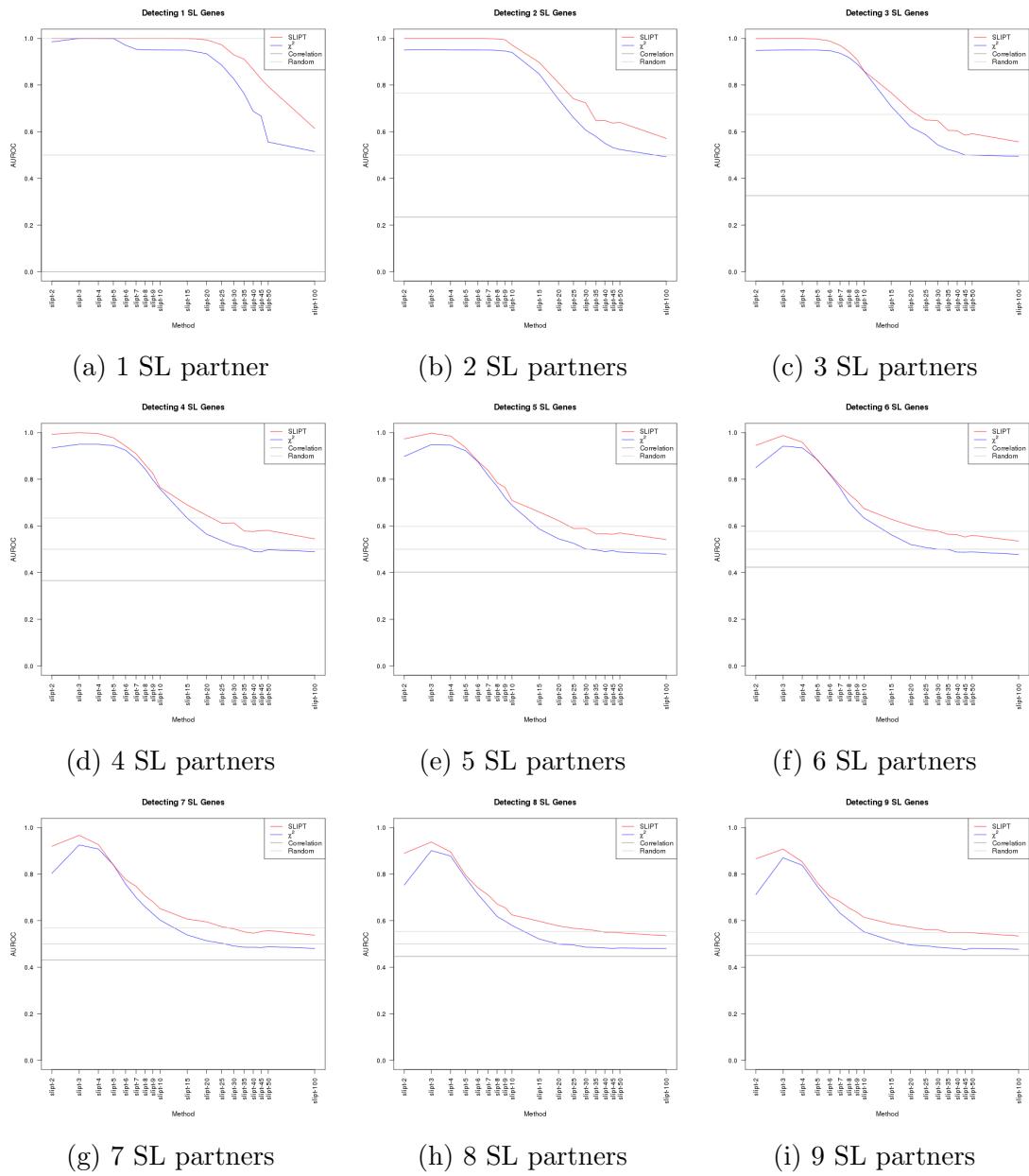


Figure K.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. (continued on next page)

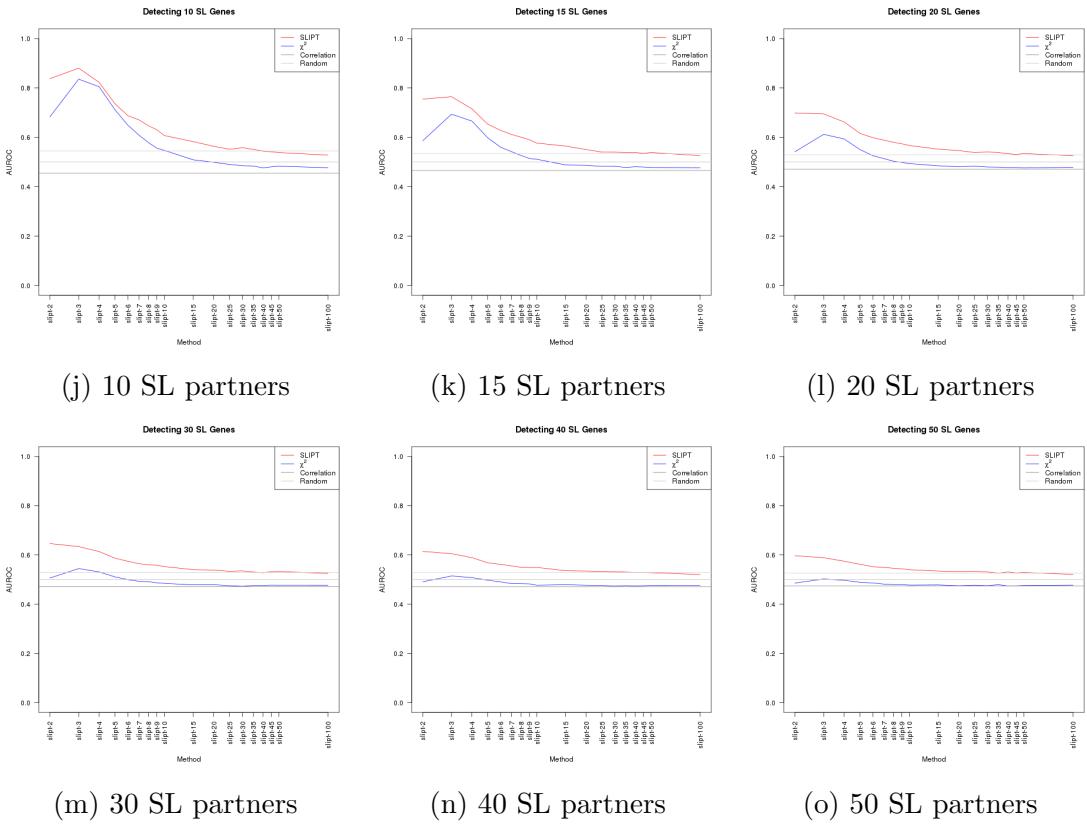


Figure K.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings were robust across different numbers of underlying synthetic lethal genes in 1000 simulations of 20,000 genes (including 1000 correlated with the query) and 1000 samples. SLIPT performed consistently better than χ^2 with positively correlated genes.

Appendix L

Simulations on Graph Structures

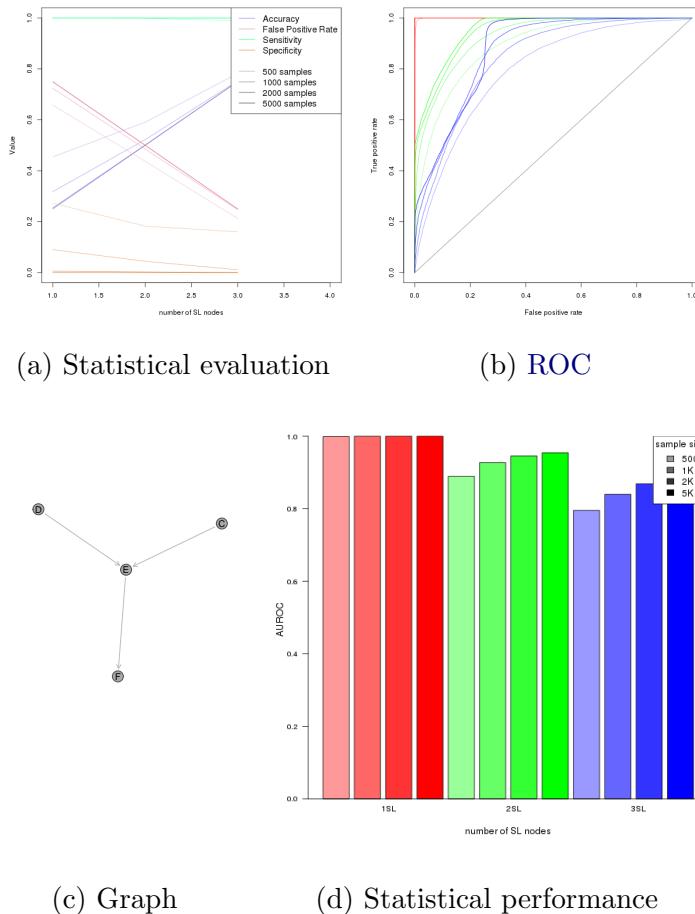


Figure L.1: Performance of simulations on a simple graph. Simulation of synthetic lethality was performed using a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure L.1b match Figure L.1d.

L.0.1 Simulations from Inhibiting Graph Structures

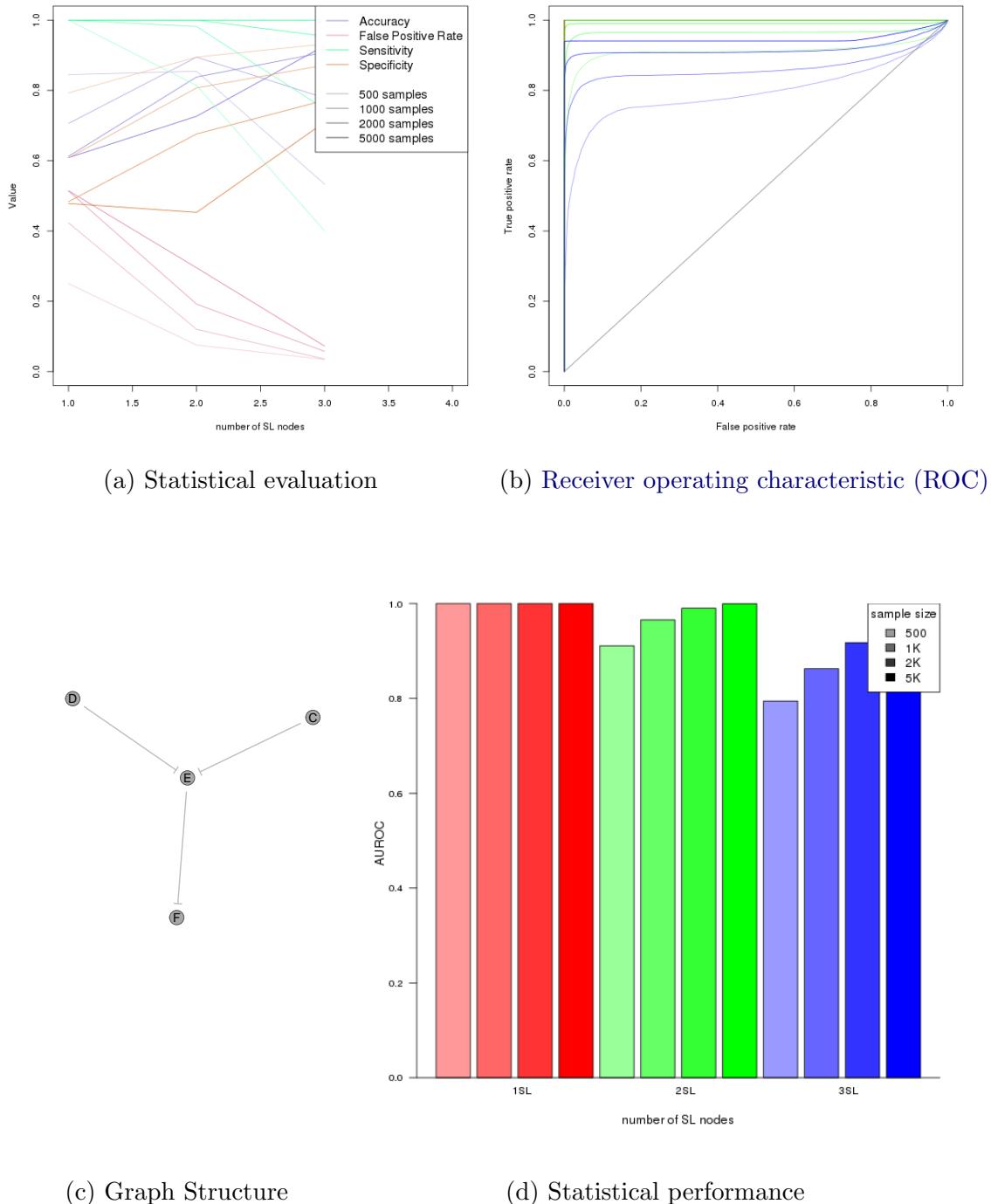
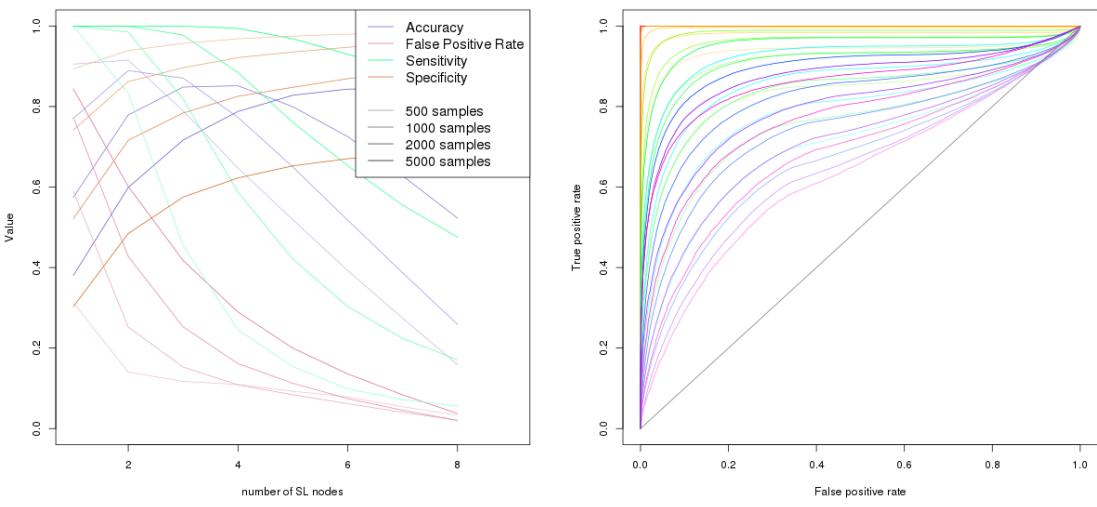
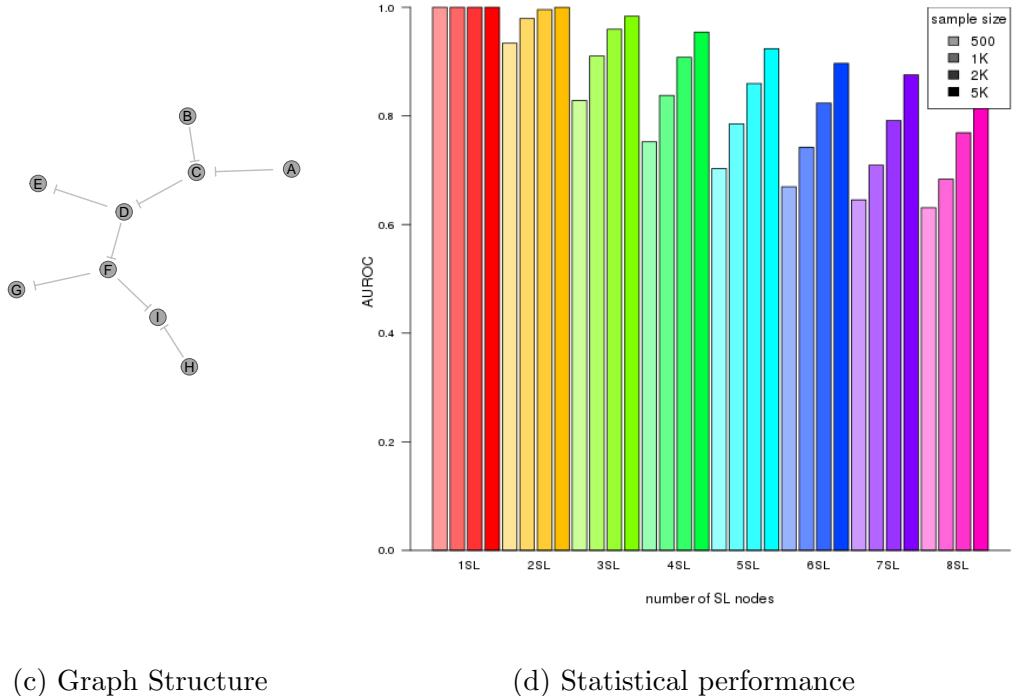


Figure L.2: **Performance of simulations on an inhibiting graph.** Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure L.2b match Figure L.2d.



(a) Statistical evaluation

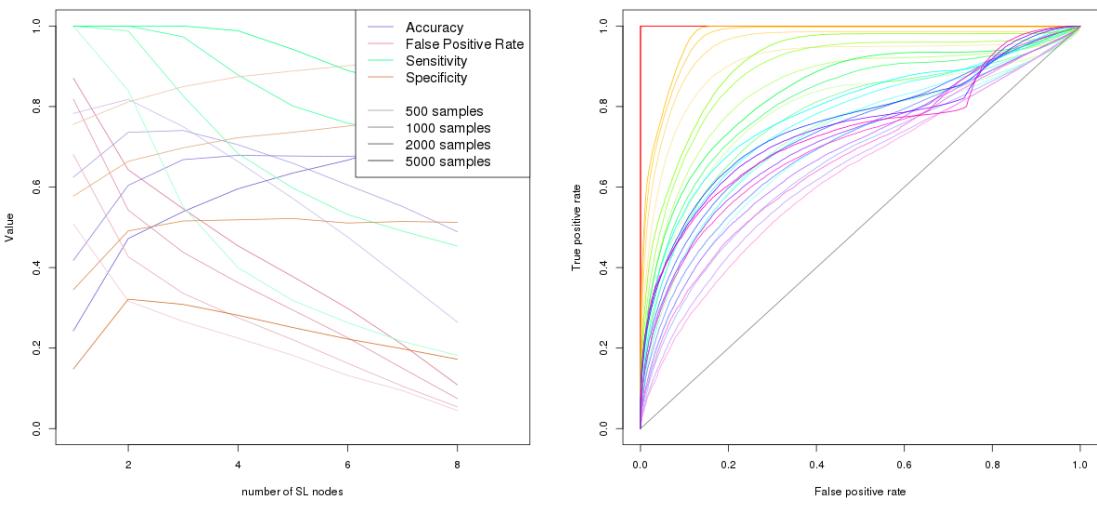
(b) ROC



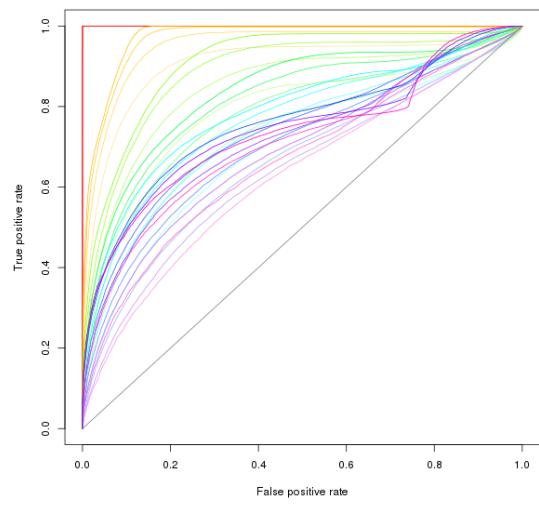
(c) Graph Structure

(d) Statistical performance

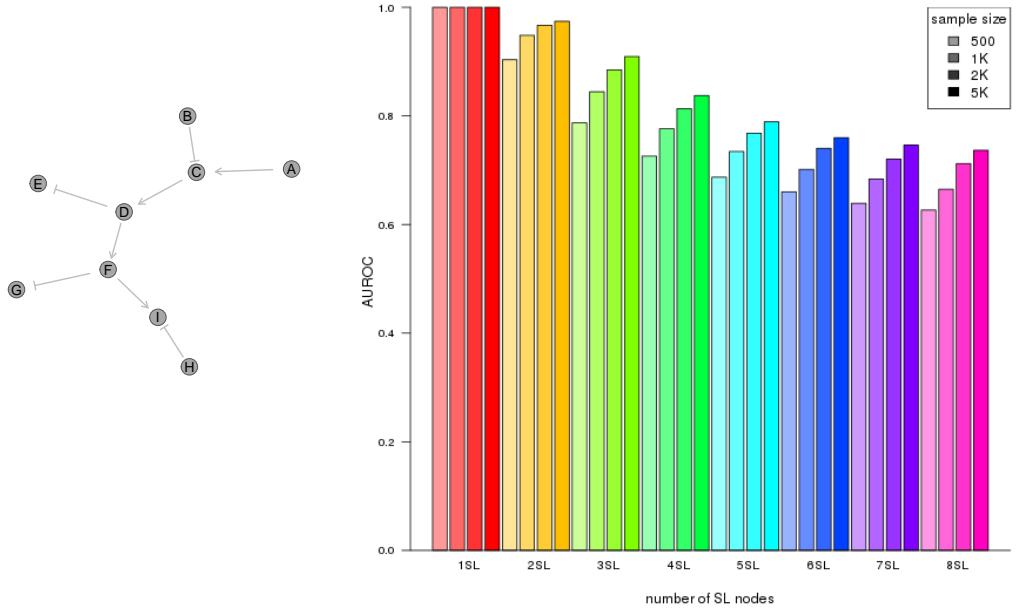
Figure L.3: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a pathway with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.3b match Figure L.3d.



(a) Statistical evaluation



(b) ROC

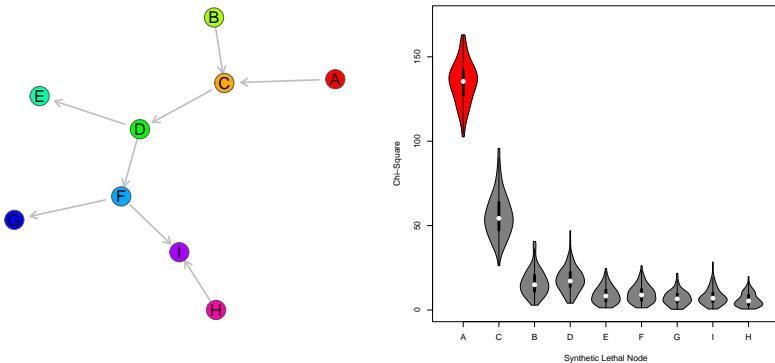


(c) Graph Structure

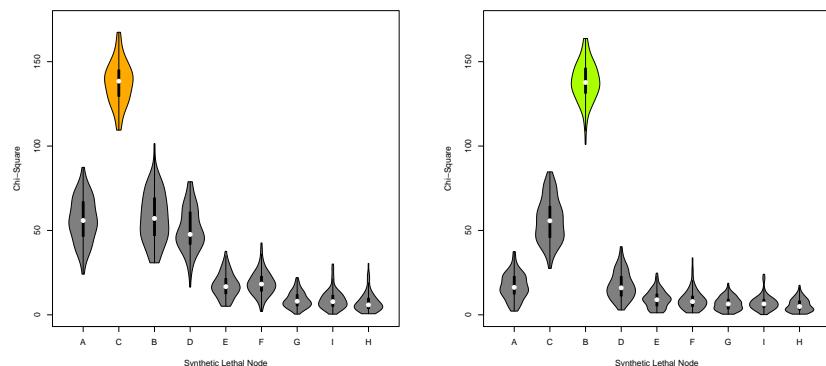
(d) Statistical performance

Figure L.4: Performance of simulations on a constructed graph with inhibition.
Simulation of synthetic lethality used a multivariate normal distribution from a pathway with a combination of inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.4b match Figure L.4d.

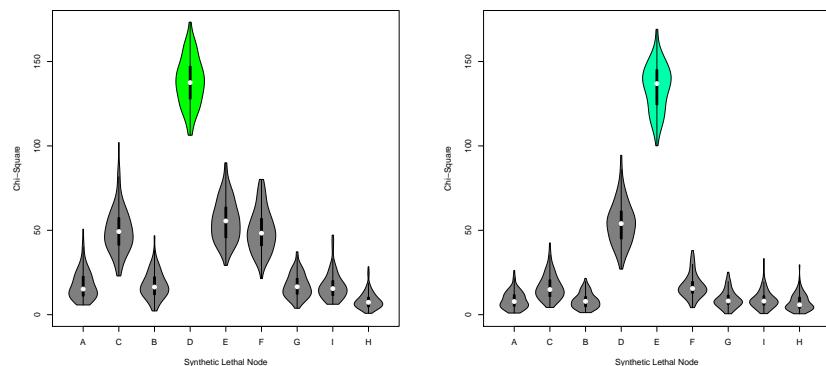
L.1 Simulation across Graph Structures



(a) Activating Graph Structure (b) χ^2 distribution for “A” SL



(c) Gene “B” SL (d) Gene “C” SL



(e) Gene “D” SL (f) Gene “E” SL

Figure L.5: **Detection of synthetic lethality within a graph Structure.** (continued on next page)

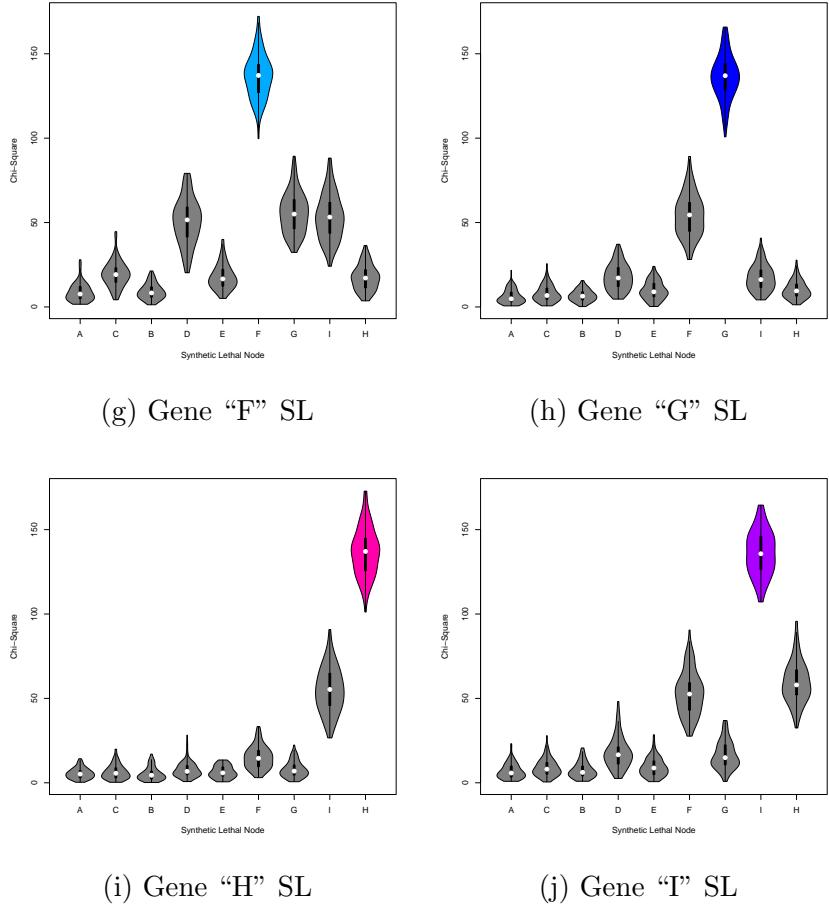
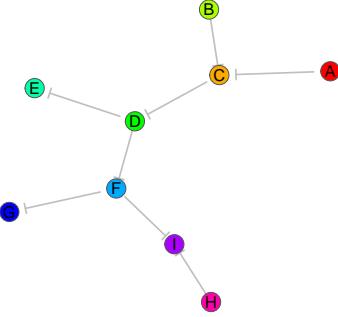
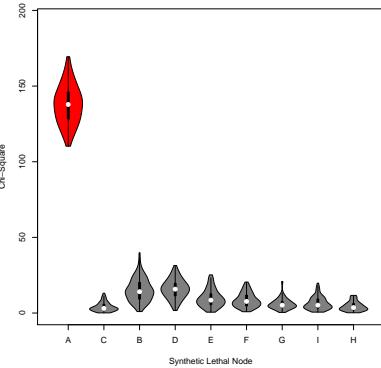


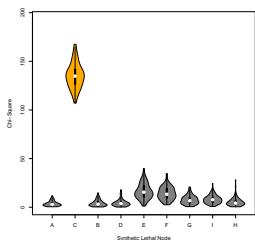
Figure L.5: Detection of synthetic lethality within a graph structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from [SLIPT](#) was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples. For each synthetic lethal gene, the adjacent genes in the network also had elevated test statistics.



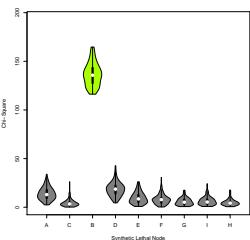
(a) Inhibiting Graph Structure



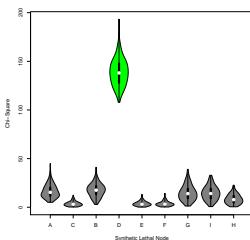
(b) χ^2 distribution for "A" SL



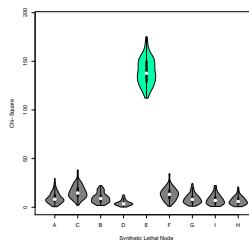
(c) Gene "B" SL



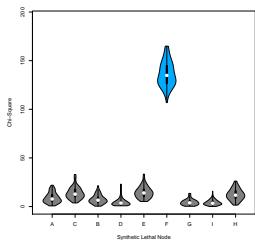
(d) Gene "C" SL



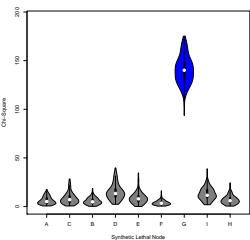
(e) Gene "D" SL



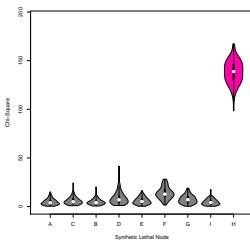
(f) Gene "E" SL



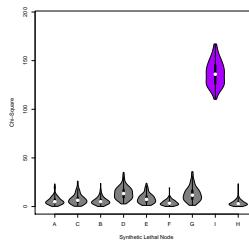
(g) Gene "F" SL



(h) Gene "G" SL

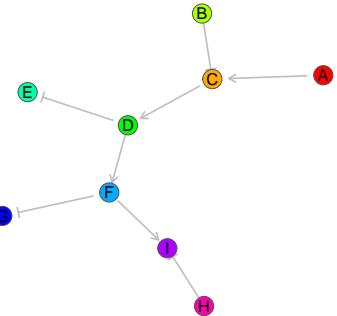


(i) Gene "H" SL

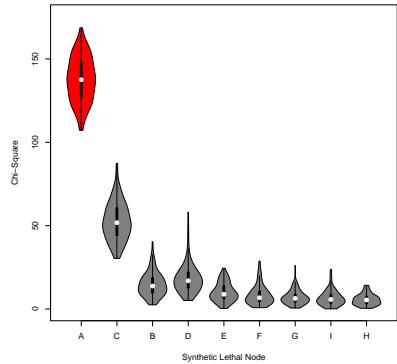


(j) Gene "I" SL

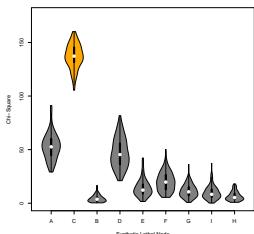
Figure L.6: Detection of synthetic lethality within an inhibiting graph. Each gene was designated to be synthetic lethal separately and the χ^2 value from [SLIPT](#) was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples. For each synthetic lethal gene, the adjacent genes exhibited lower χ^2 values with inhibiting relationships.



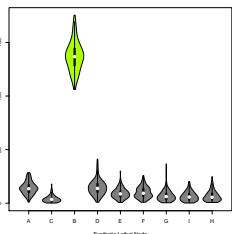
(a) Inhibiting Graph Structure



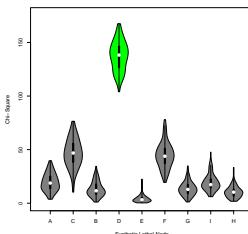
(b) χ^2 distribution for "A" SL



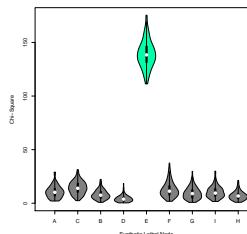
(c) Gene "B" SL



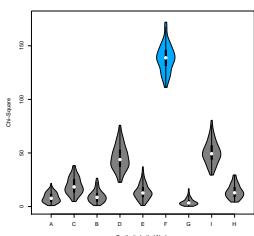
(d) Gene "C" SL



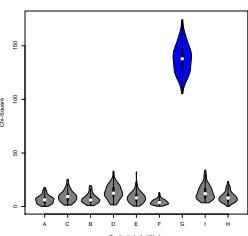
(e) Gene "D" SL



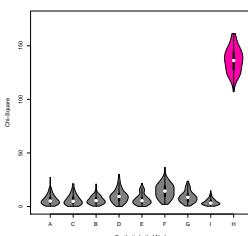
(f) Gene "E" SL



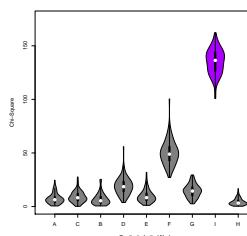
(g) Gene "F" SL



(h) Gene "G" SL



(i) Gene "H" SL



(j) Gene "I" SL

Figure L.7: Detection of synthetic lethality within an inhibiting graph. Each gene was designated to be synthetic lethal separately and the χ^2 value from [SLIPT](#) was computed for each gene across the graph structure with inhibiting and relationships. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples.

L.2 Simulations from Complex Graph Structures

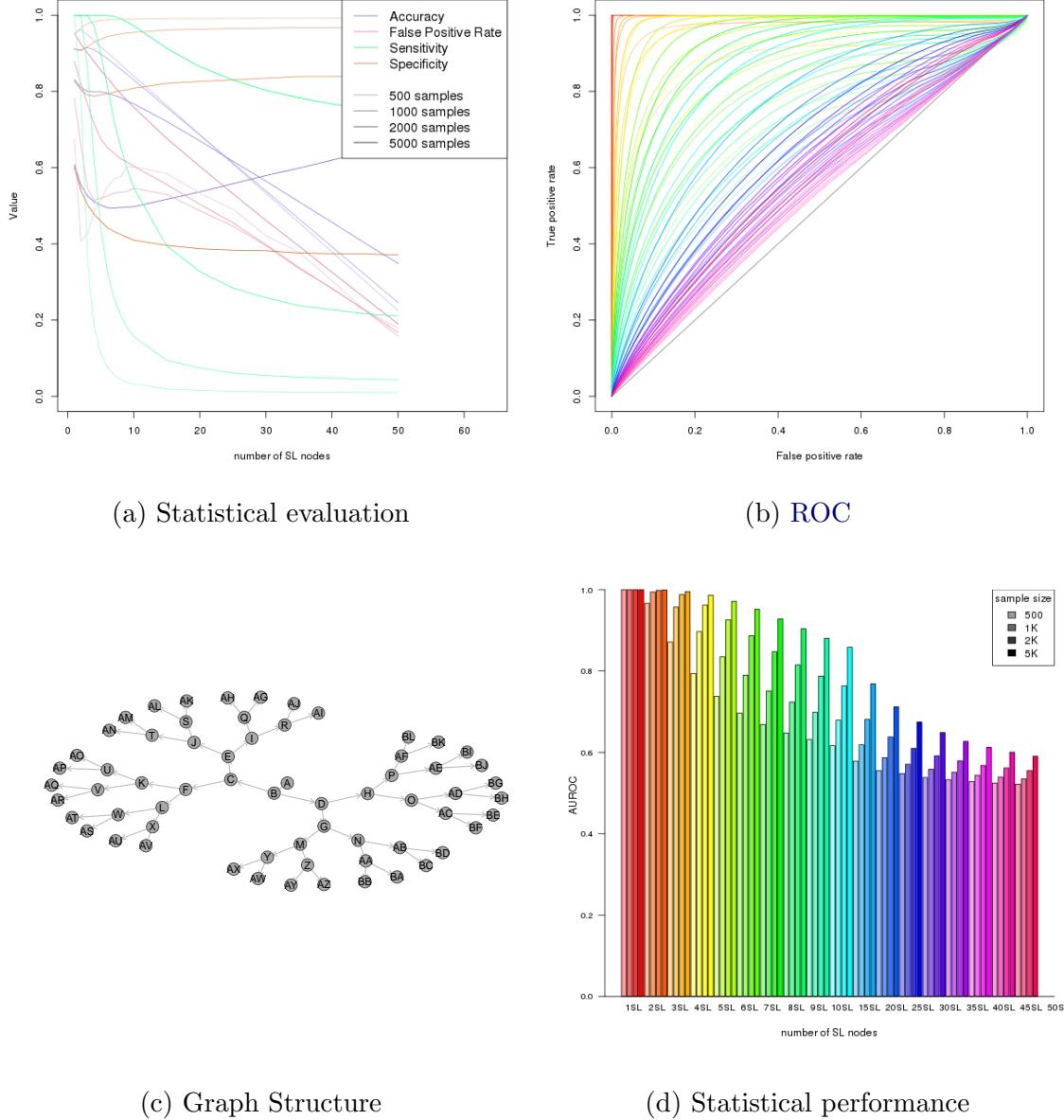
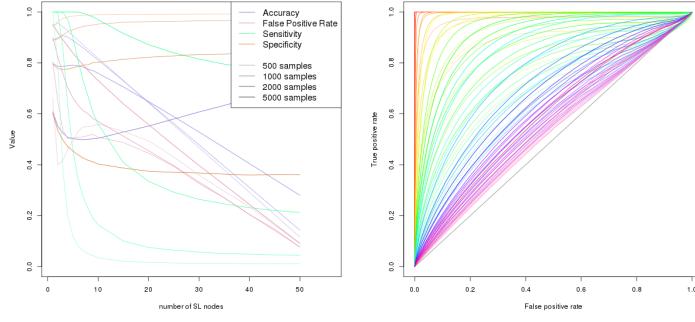
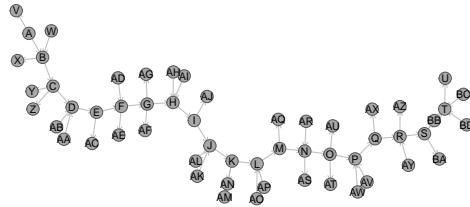


Figure L.8: **Performance of simulations on a branching graph.** Simulation of synthetic lethality used a multivariate normal distribution from a branching graph. For each parameter, 10,000 simulations were used. Colours in Figure L.8b match Figure L.8d.

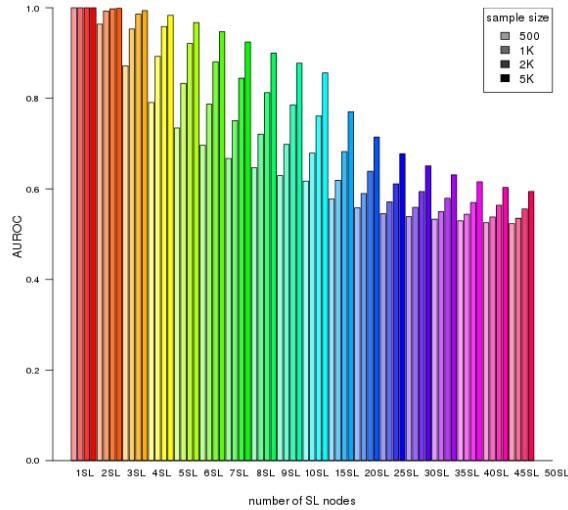


(a) Statistical evaluation

(b) ROC

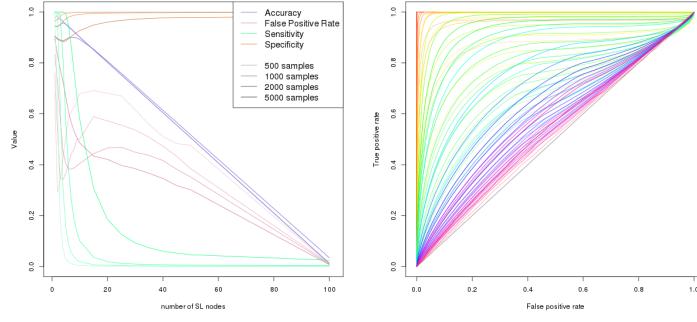


(c) Graph Structure

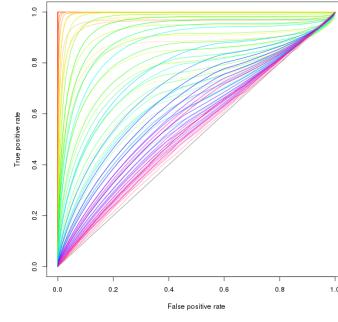


(d) Statistical performance

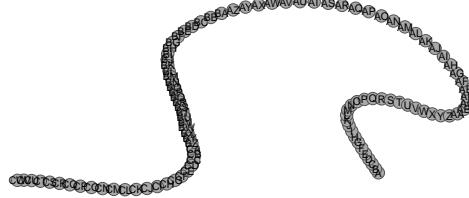
Figure L.9: Performance of simulations on a complex graph. Simulation of synthetic lethality used a multivariate normal distribution from a complex graph. For each parameter, 10,000 simulations were used. Colours in Figure L.9b match Figure L.9d.



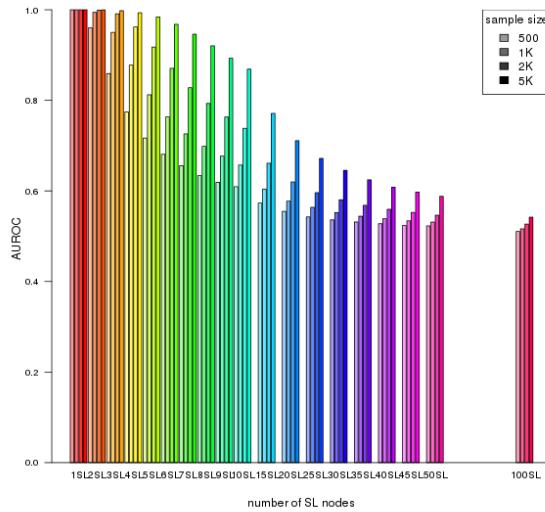
(a) Statistical evaluation



(b) ROC



(c) Graph Structure



(d) Statistical performance

Figure L.10: Performance of simulations on a large graph. Simulation of synthetic lethality used a multivariate normal distribution from a large graph. For each parameter, 10,000 simulations were used. Colours in Figure L.10b match Figure L.10d.

L.2.1 Simulations from Complex Inhibiting Graphs

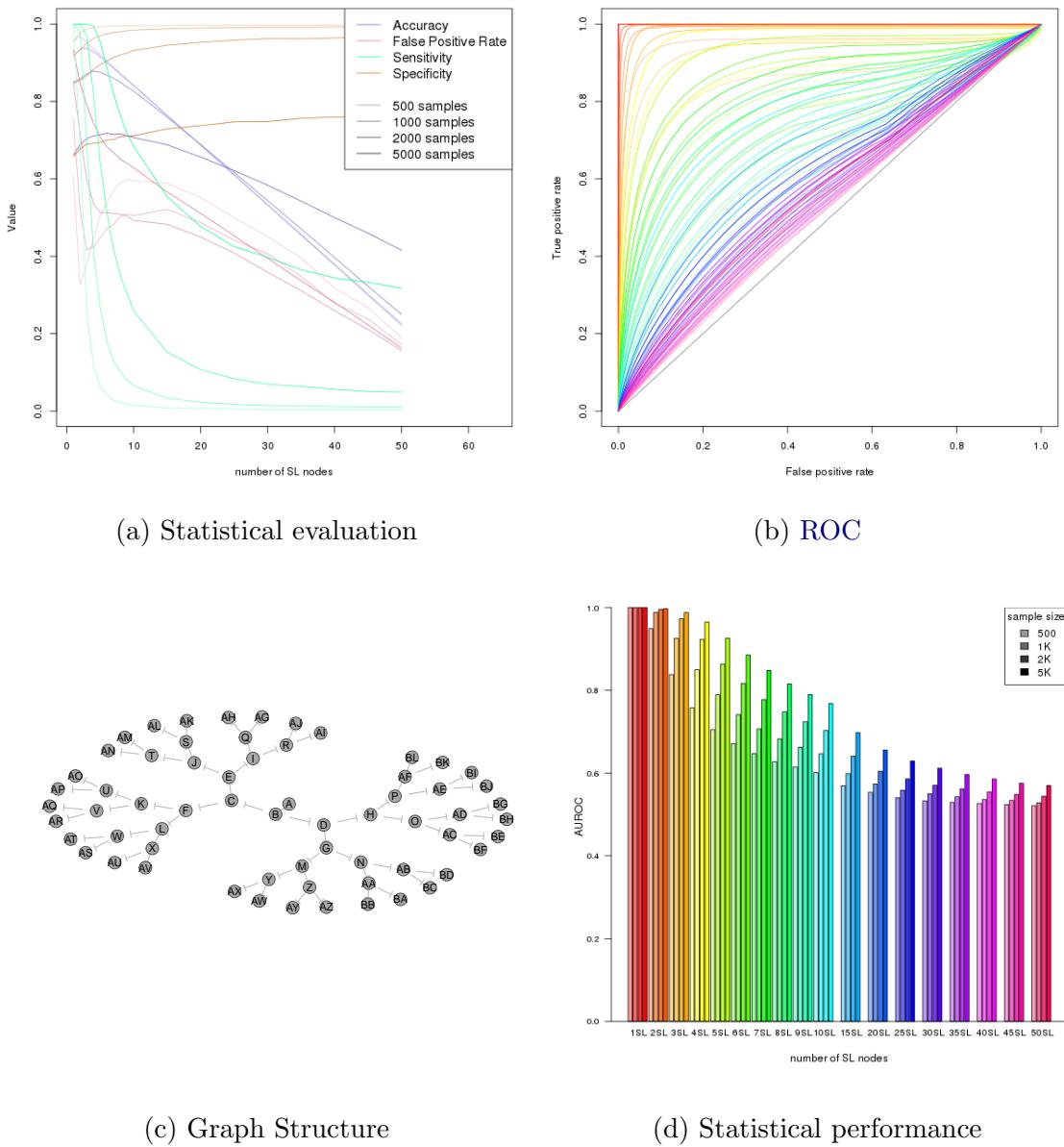
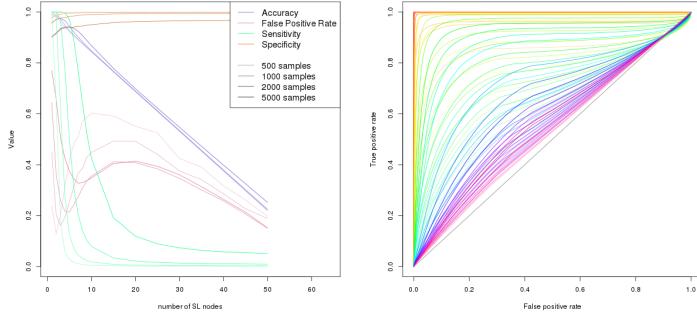
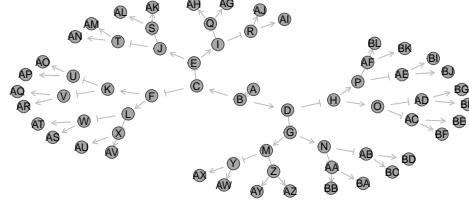


Figure L.11: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.11b match Figure L.11d.

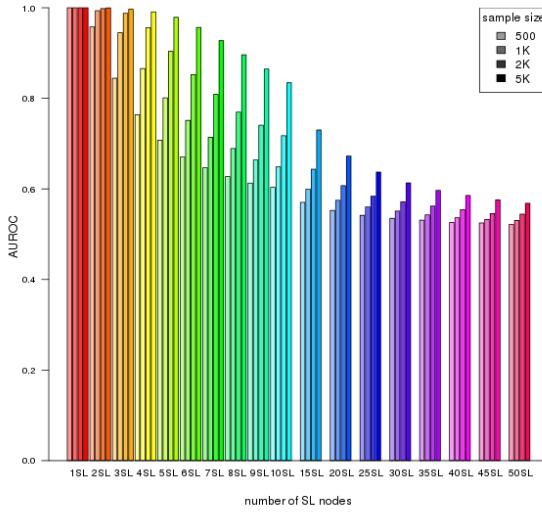


(a) Statistical evaluation

(b) ROC

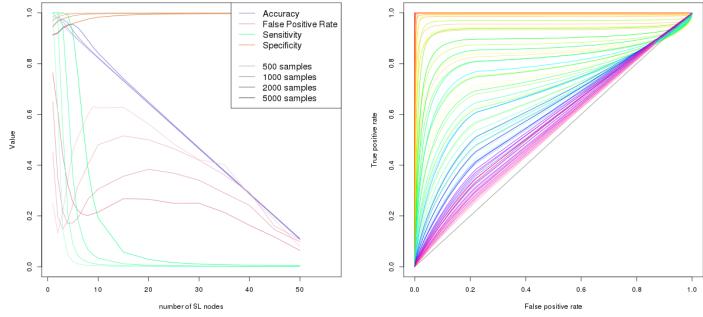


(c) Graph Structure



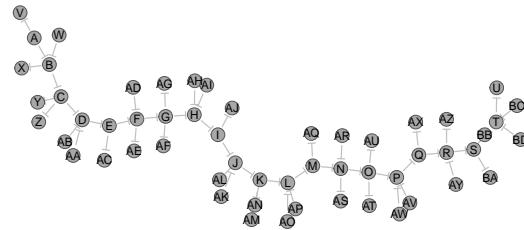
(d) Statistical performance

Figure L.12: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with alternating inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.12b match Figure L.12d.

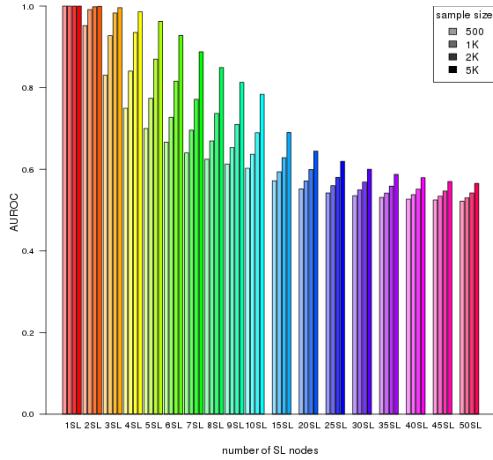


(a) Statistical evaluation

(b) ROC

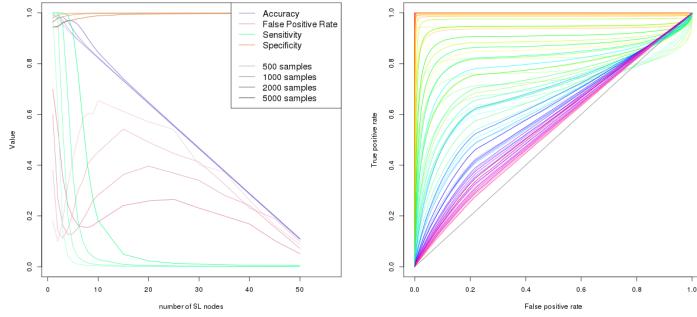


(c) Graph Structure



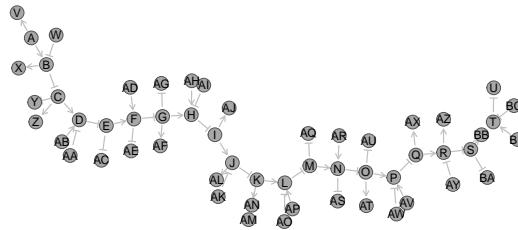
(d) Statistical performance

Figure L.13: Performance of simulations on a complex graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a complex graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.13b match Figure L.13d.

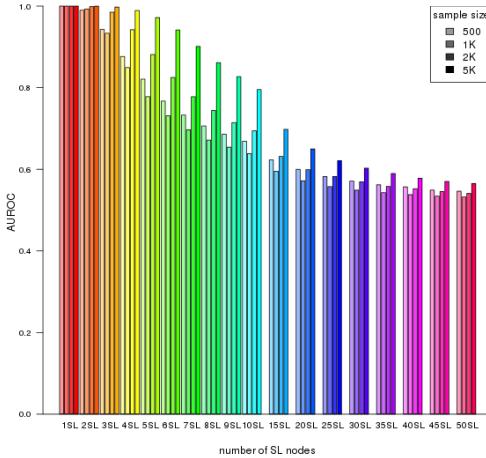


(a) Statistical evaluation

(b) ROC

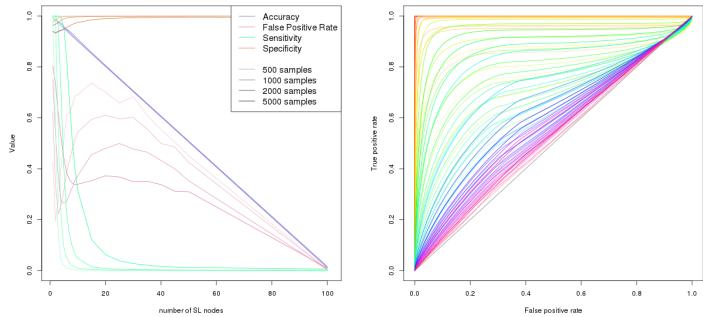


(c) Graph Structure



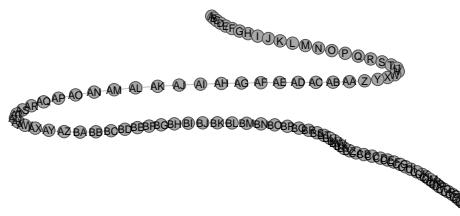
(d) Statistical performance

Figure L.14: Performance of simulations on a complex graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a complex graph with a combination of relationships. For each parameter, 10,000 simulations were used. Colours in Figure L.14b match Figure L.14d.

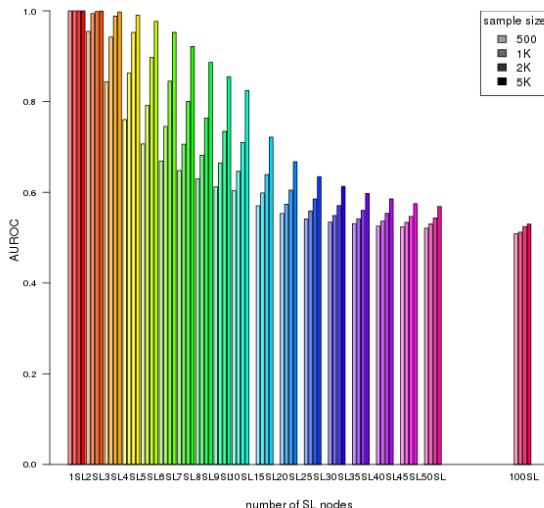


(a) Statistical evaluation

(b) ROC

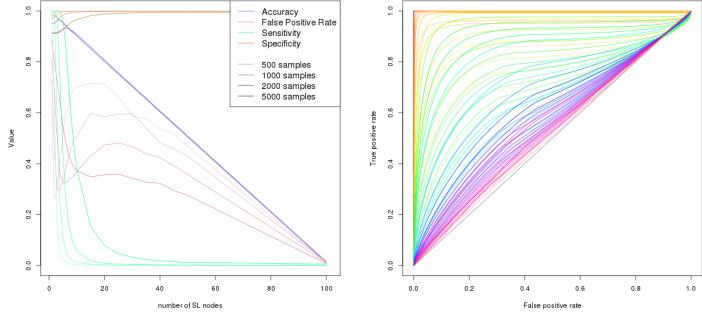


(c) Graph Structure

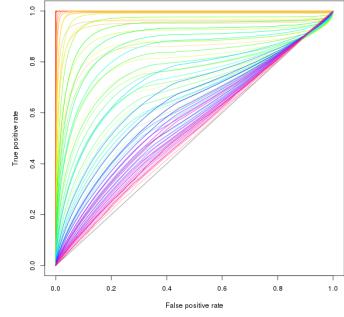


(d) Statistical performance

Figure L.15: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from a large graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.15b match Figure L.15d.



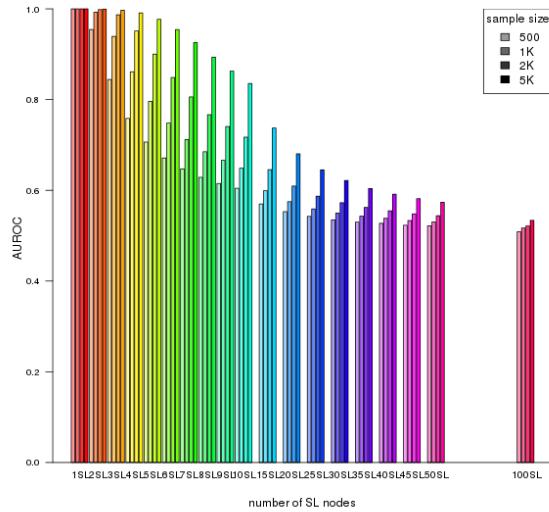
(a) Statistical evaluation



(b) ROC



(c) Graph Structure



(d) Statistical performance

Figure L.16: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from a large graph with alternating inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure L.16b match Figure L.16d.

L.3 Simulations from Pathway Graph Structures

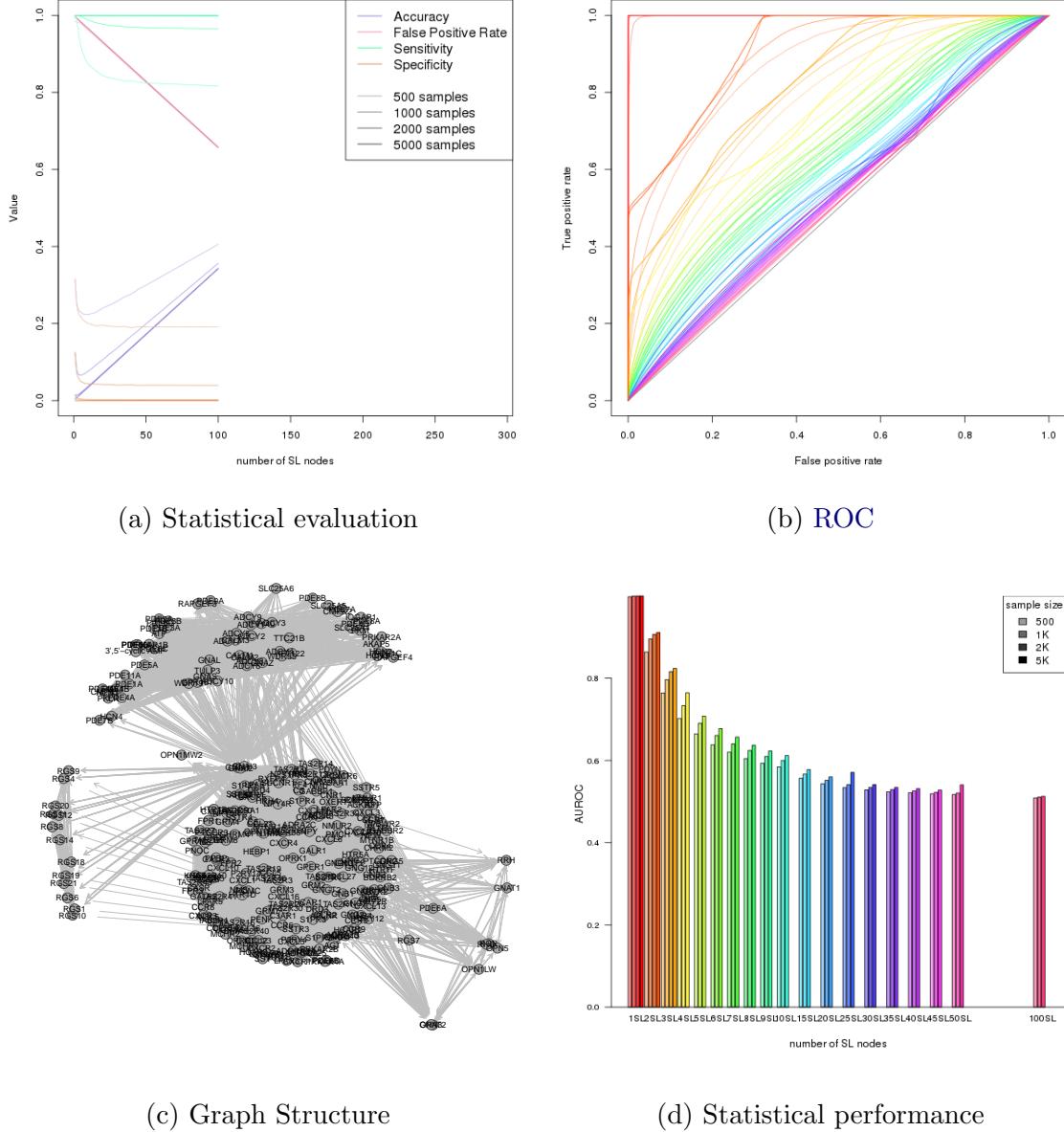


Figure L.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of **SLIPT** was high across parameters for detecting synthetic lethality in the graph structure within a larger dataset. The performance decreased for a greater number of true positives to detect but the accuracy increased with a low false positive rate.

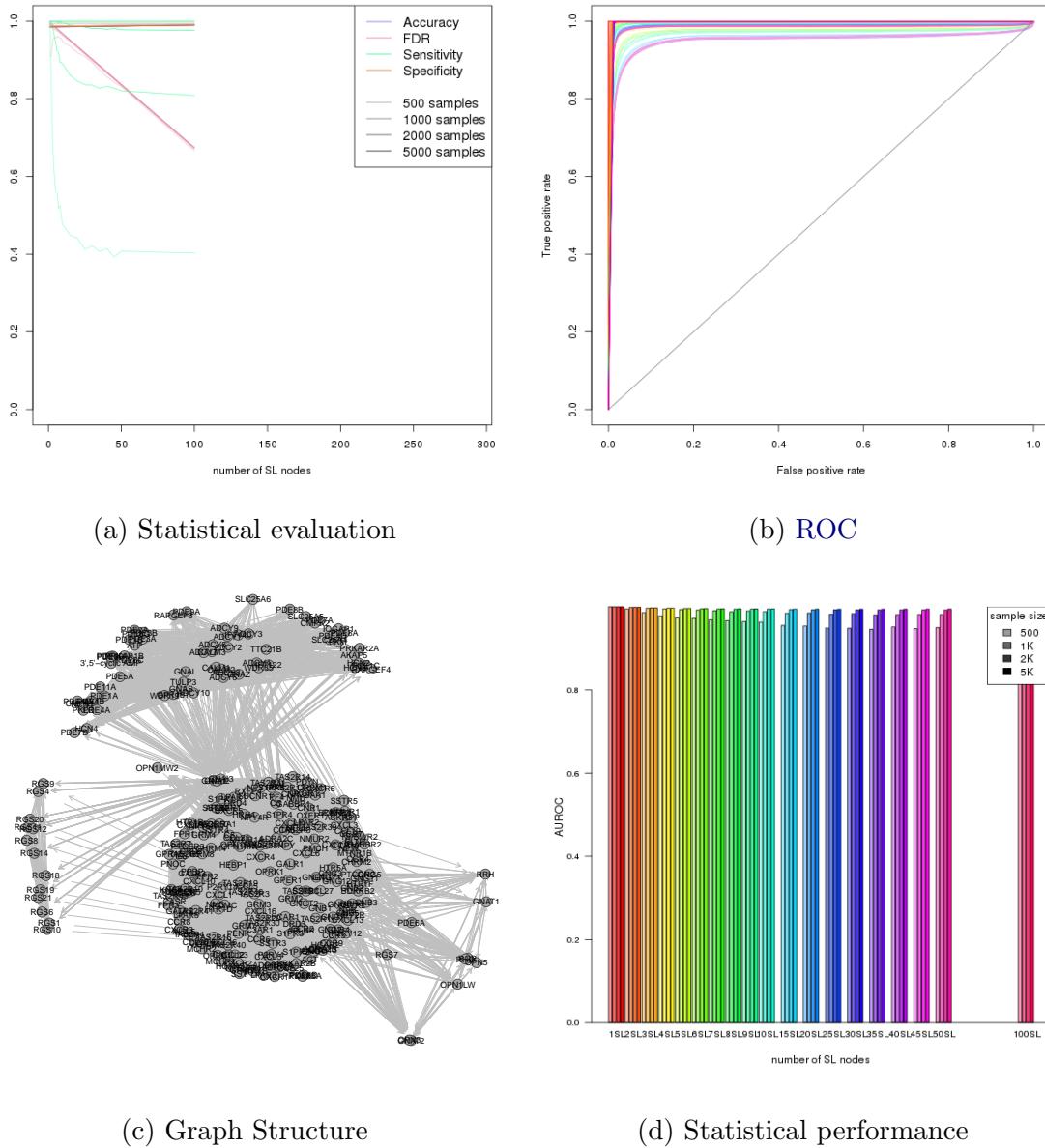


Figure L.18: **Performance of simulations including the $G_{\alpha i}$ signalling pathway.** Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome $G_{\alpha i}$ signalling pathway. Performance of **SLIPT** was high across parameters for detecting synthetic lethality in the graph structure within a larger dataset. The sensitivity decreased for a greater number of true positives to detect but the specificity remained high with a low false positive rate.