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Glossary

E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
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).
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
TCGA	The Cancer Genome Atlas (genomics project).

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Appendix J

Performance of SLIPT and χ^2

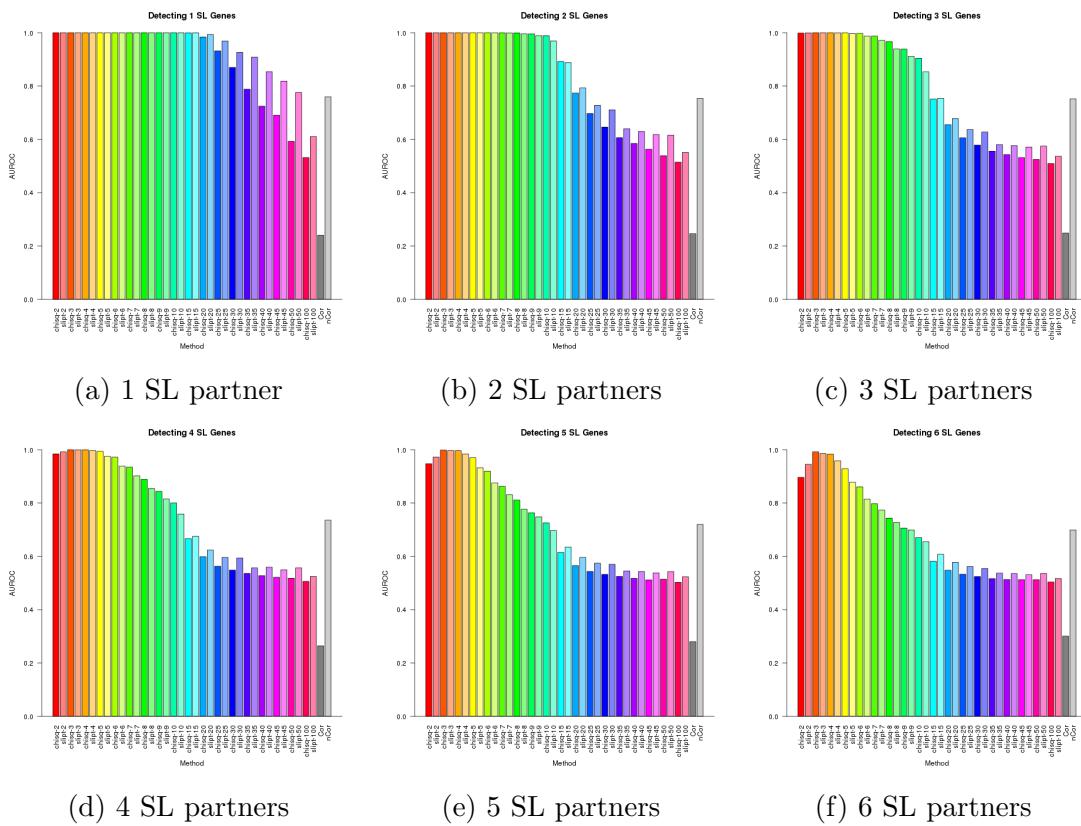


Figure J.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

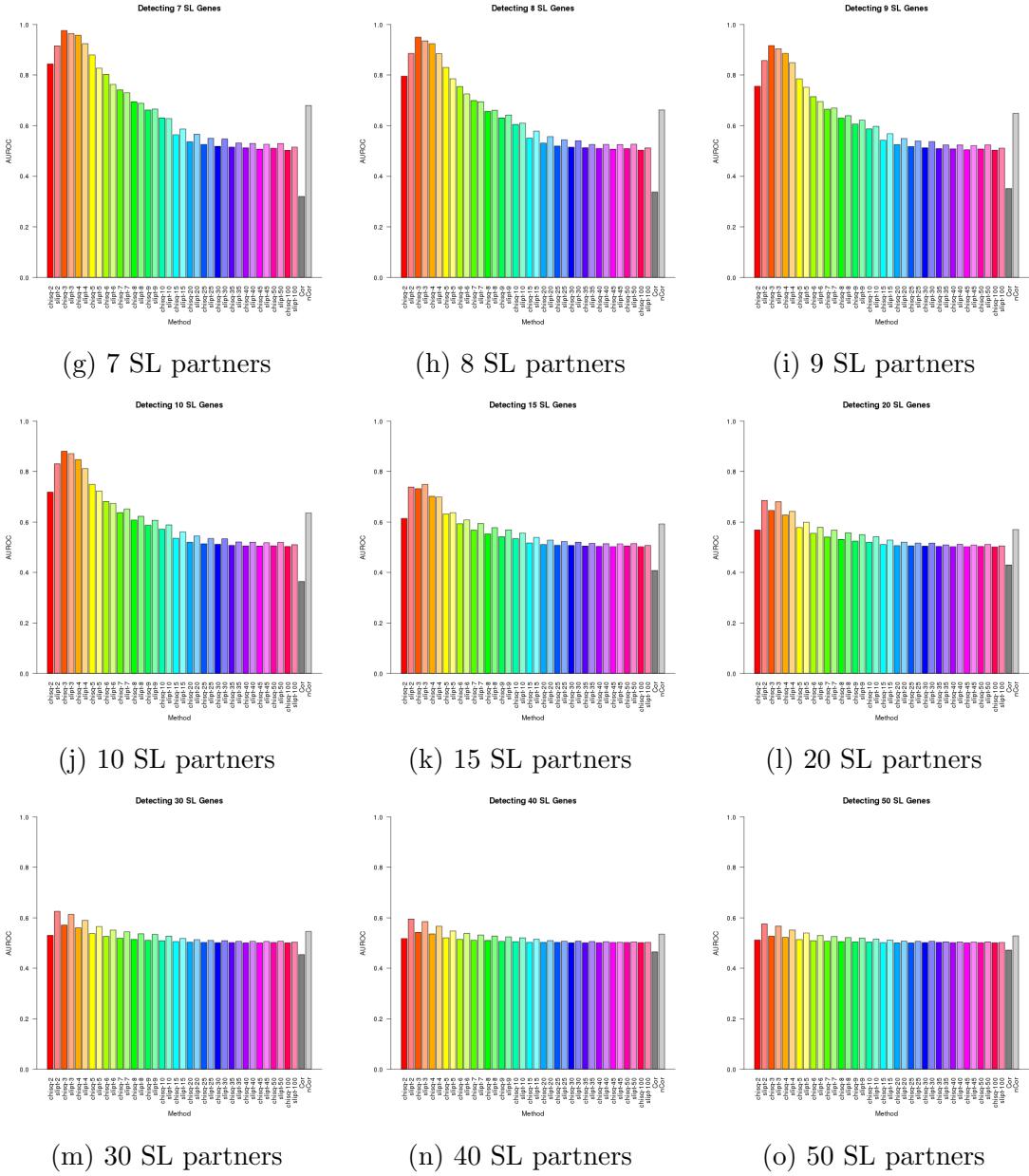


Figure J.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings are robust across different numbers of underlying synthetic lethal genes in 10,000 simulations of 100 genes and 1000 samples. SLIPT performs better than χ^2 for higher numbers of synthetic lethal genes and finer quantiles.

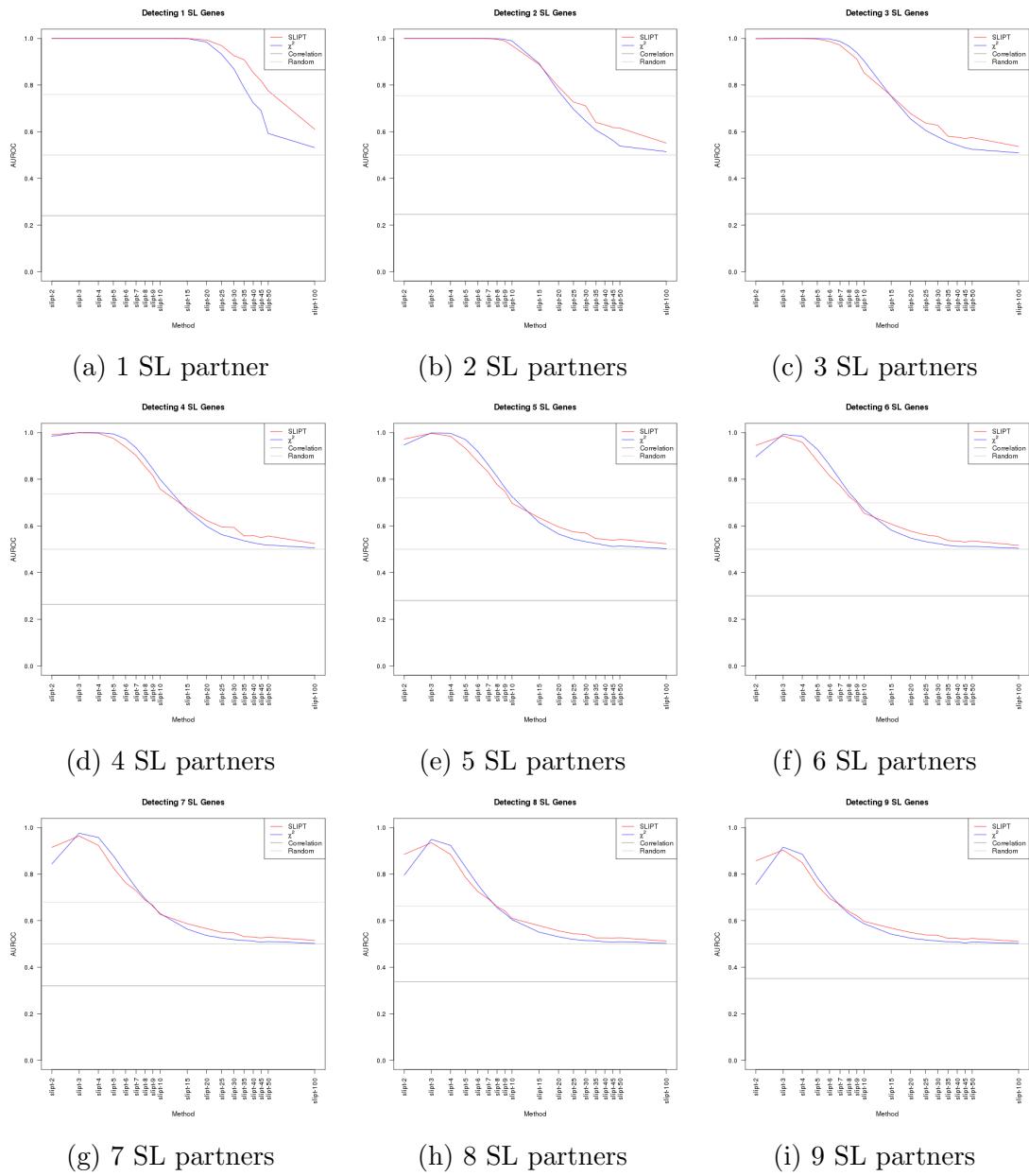


Figure J.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

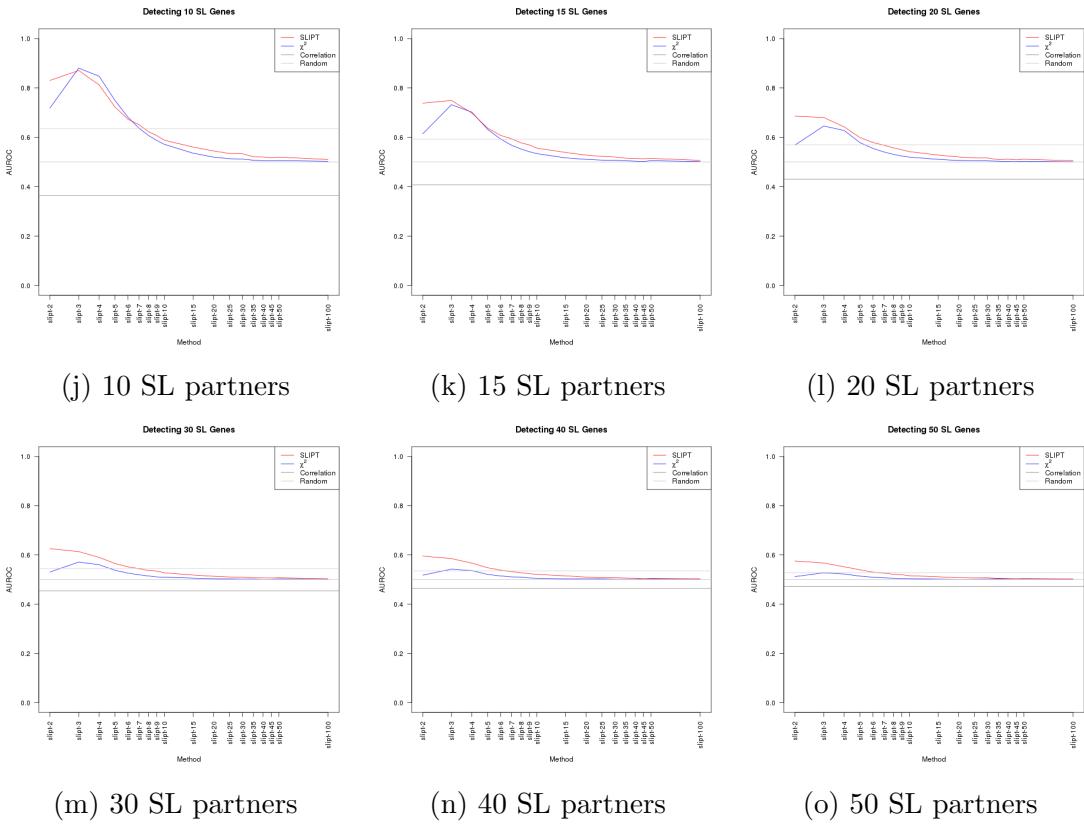


Figure J.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles and converging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

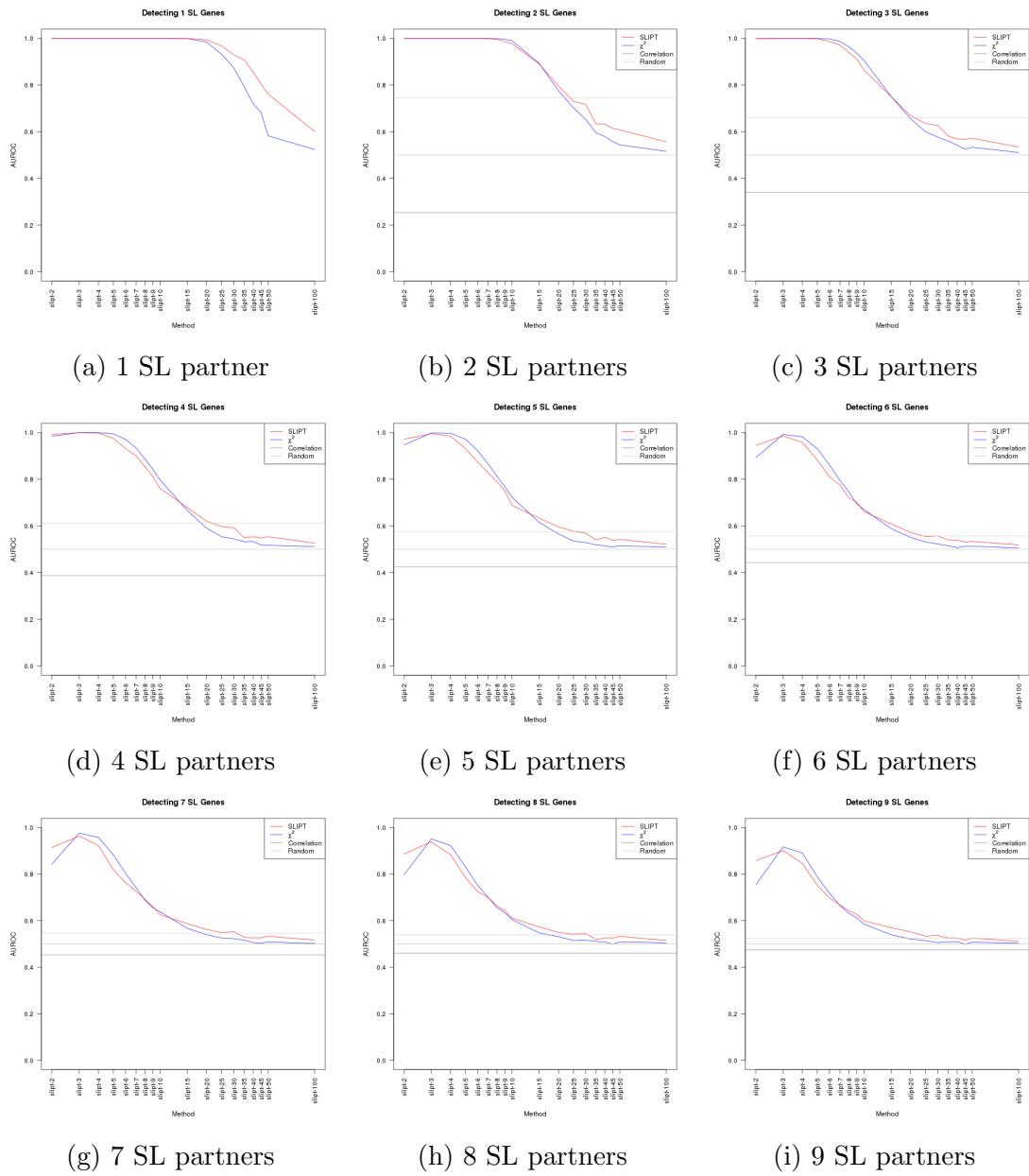


Figure J.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

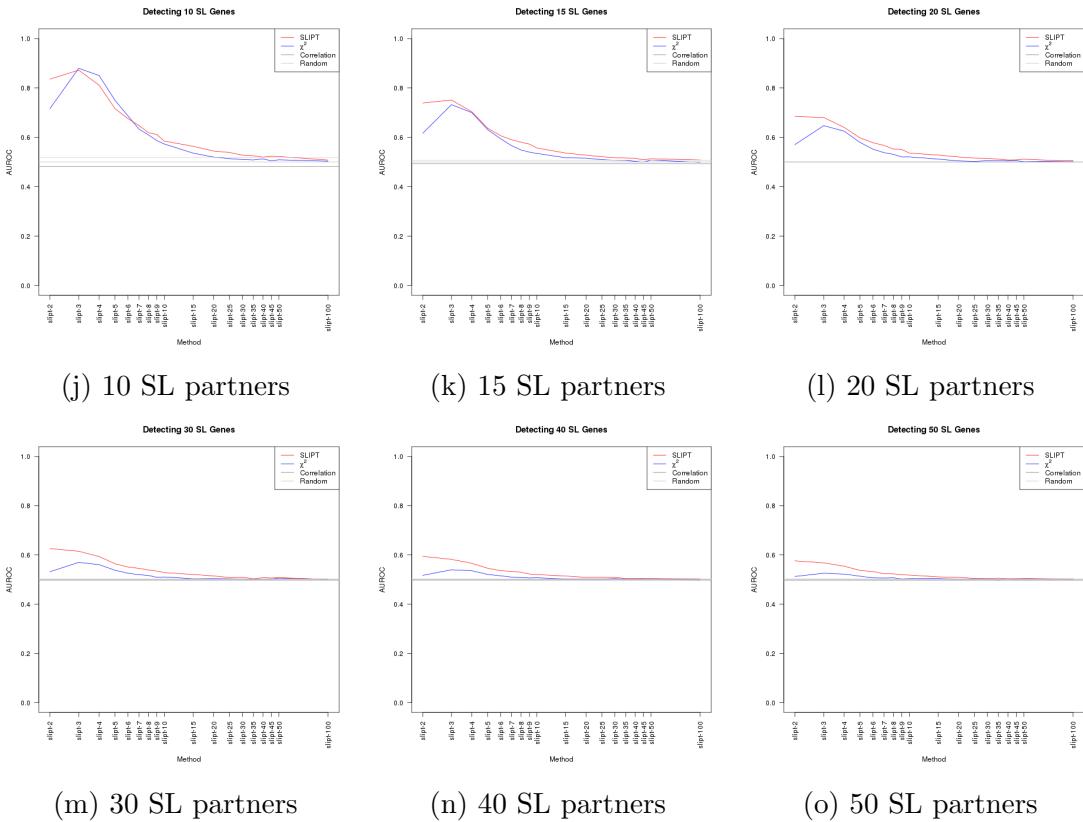


Figure J.3: Performance of χ^2 and SLIPT across quantiles with more genes.
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles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

J.1 Correlated Query Genes affects Specificity

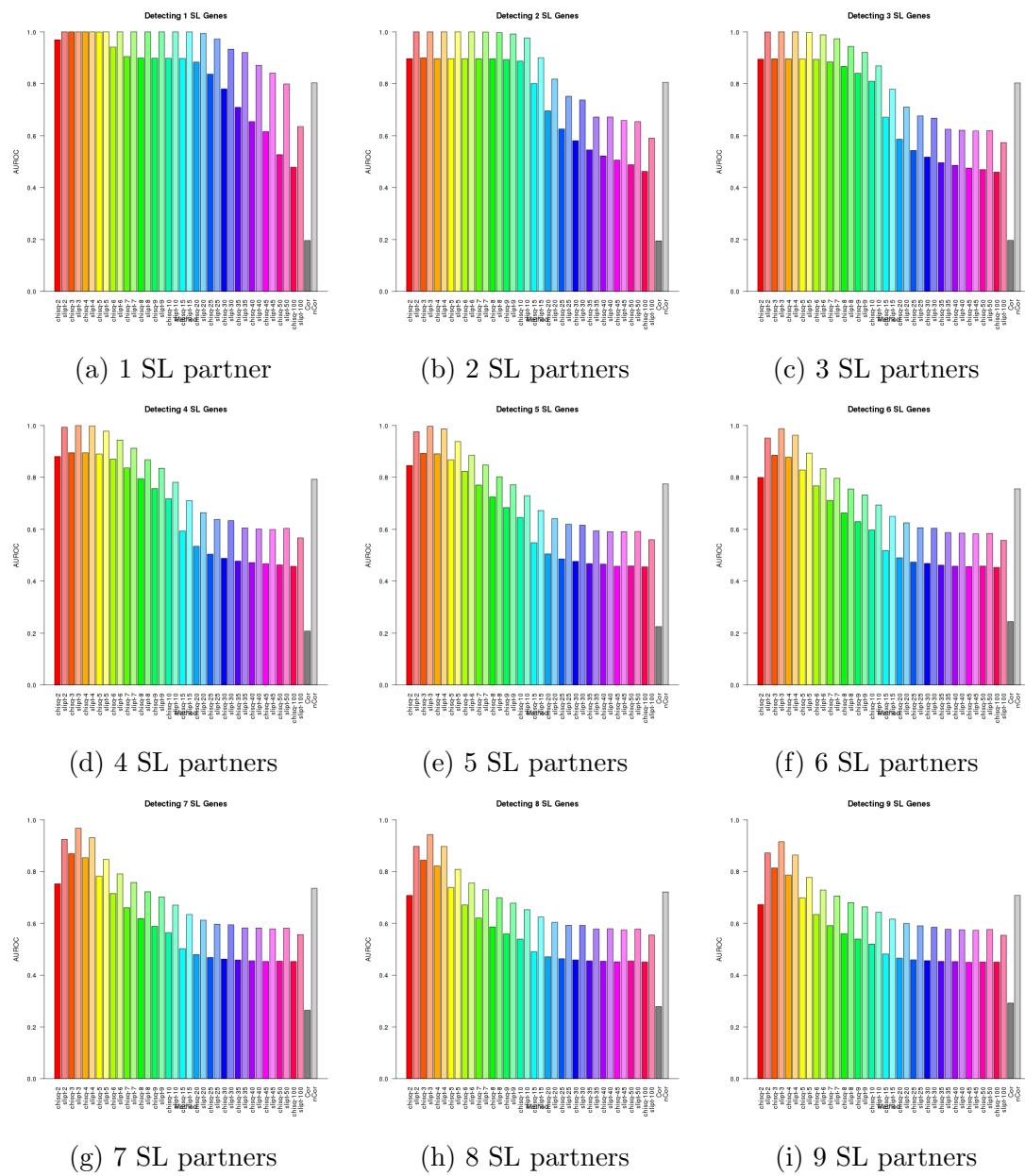


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. (continued on next page)

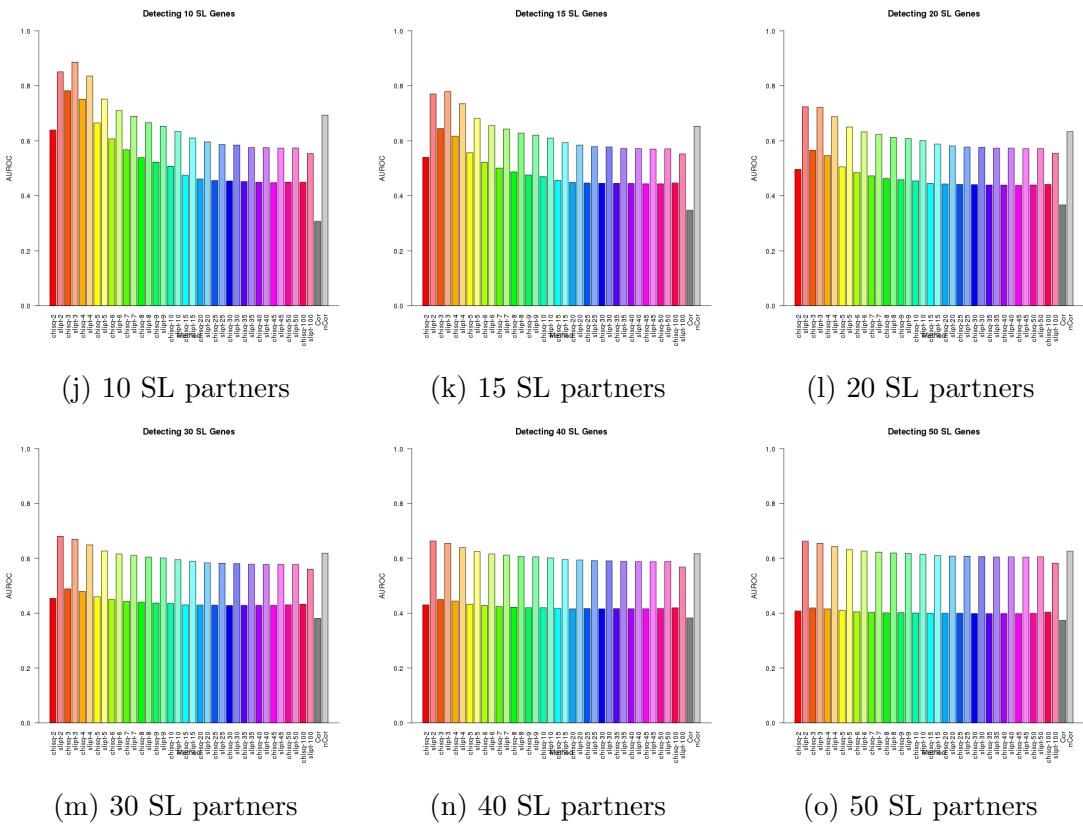


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking 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 . These findings are 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 performs consistently better than χ^2 with positively correlated genes.

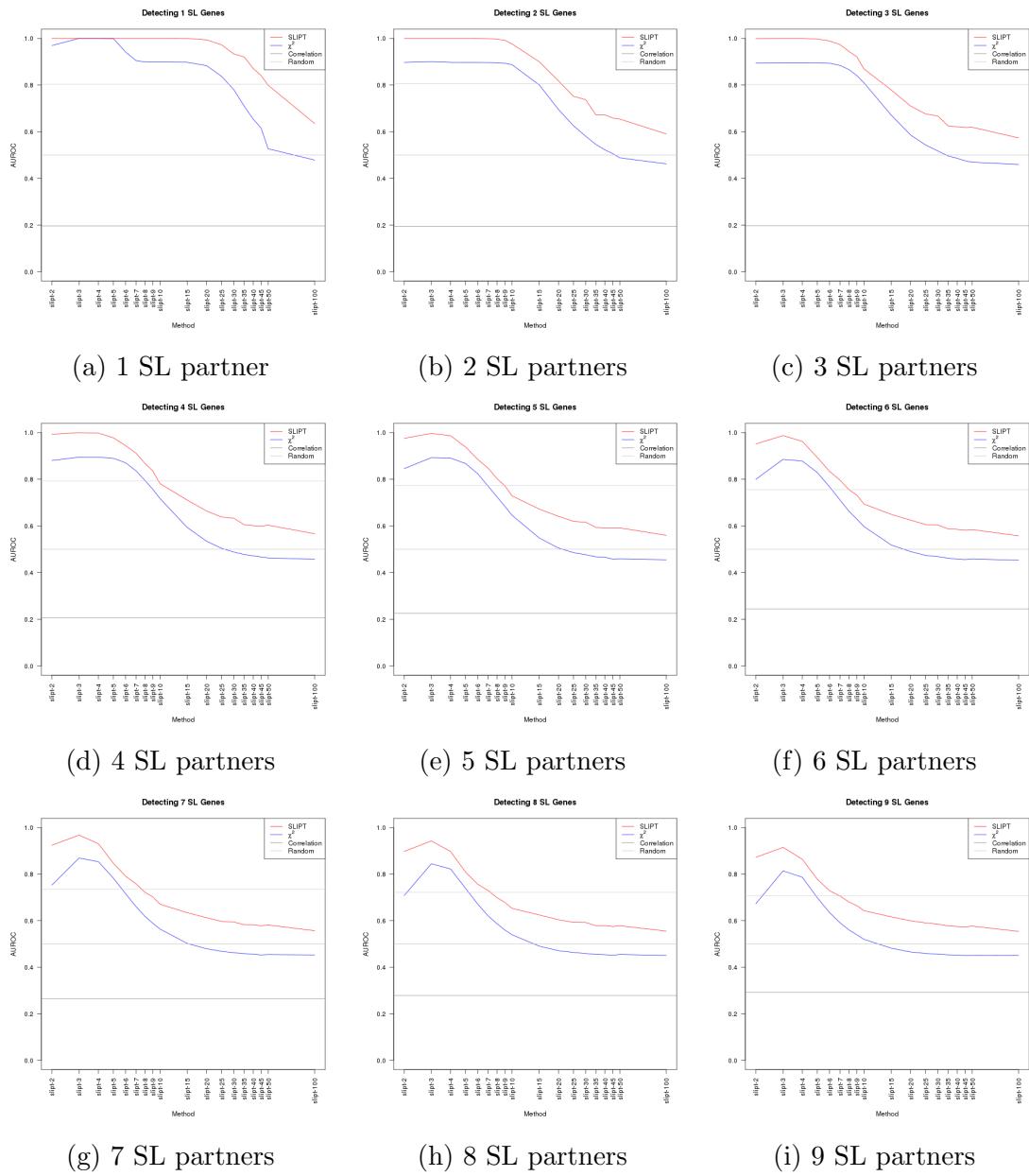


Figure J.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

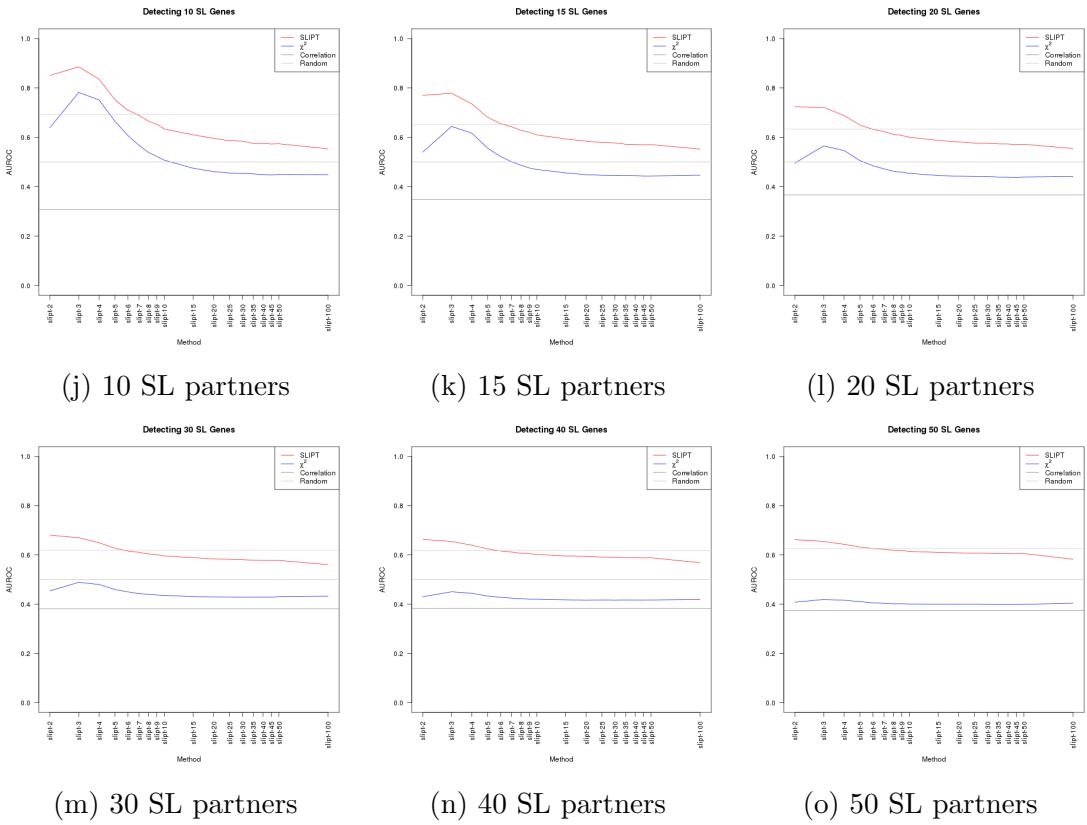


Figure J.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles and converging to random (0.5). Negative correlation was higher than positive but not optimal quantiles for SLIPT or χ^2 . These findings are 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 performs consistently better than χ^2 with positively correlated genes.

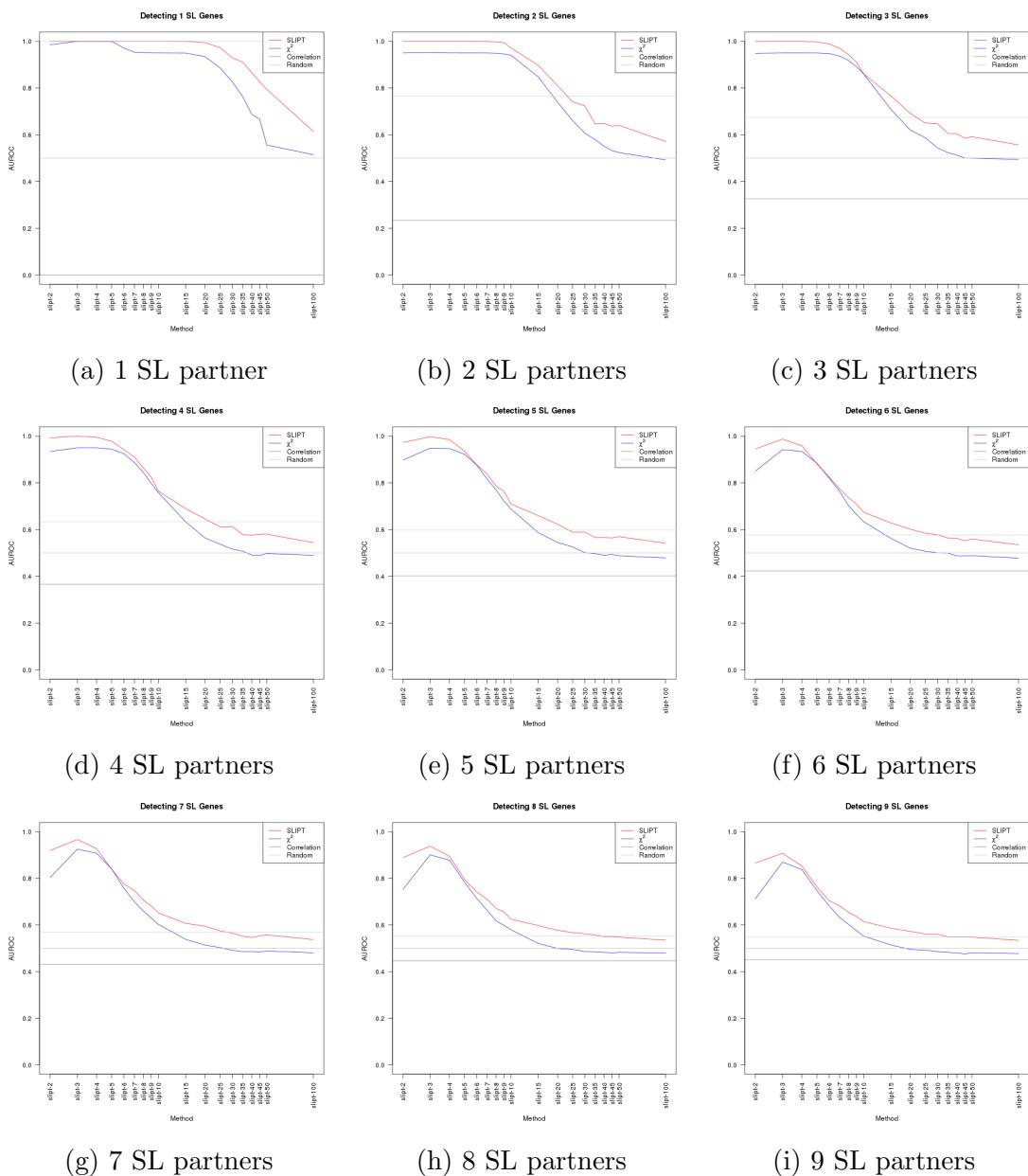


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. (continued on next page)

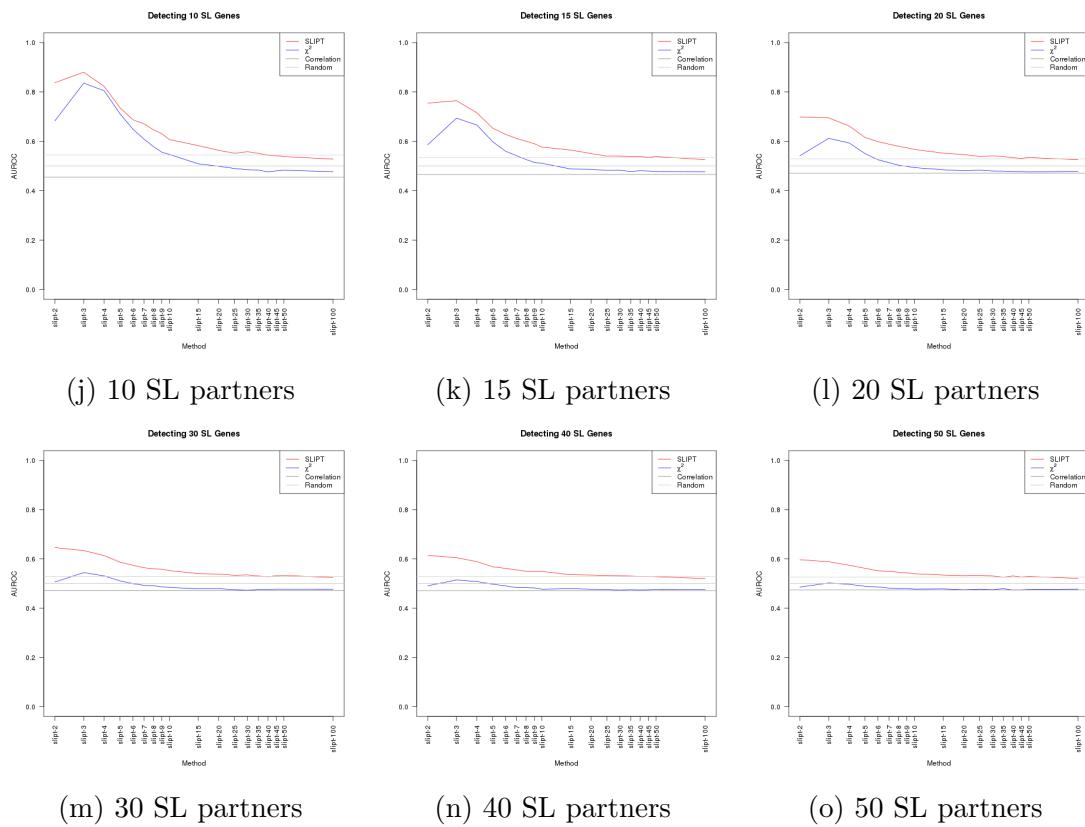


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking 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 . These findings are 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 performs consistently better than χ^2 with positively correlated genes.

Appendix K

Graph Structures

K.1 Simulations from Simple Graph Structures

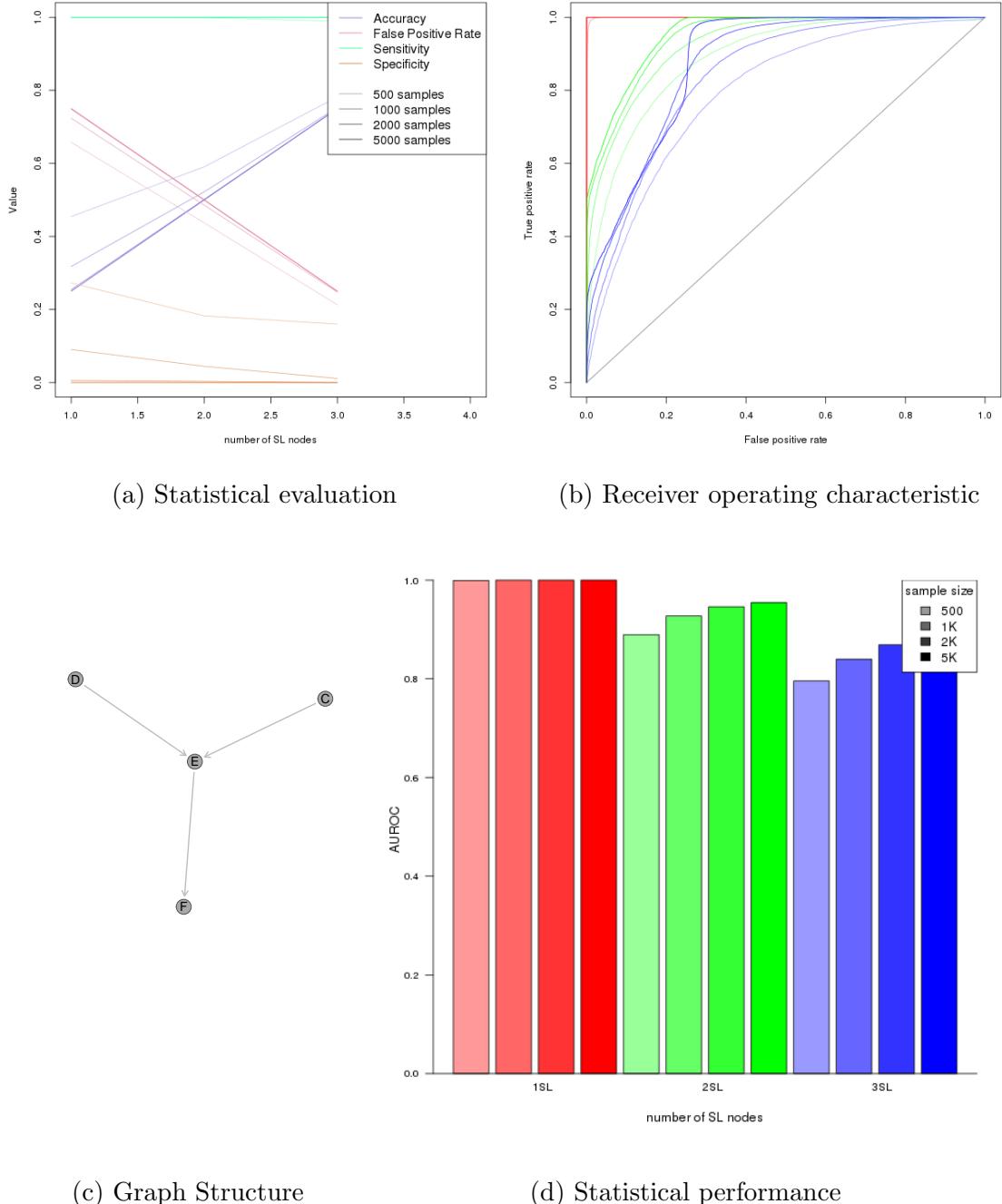


Figure K.1: Performance of simulations on a simple graph. Simulation of synthetic lethality was performed using a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.1b match Figure K.1d.

K.1.1 Simulations from Inhibiting Graph Structures

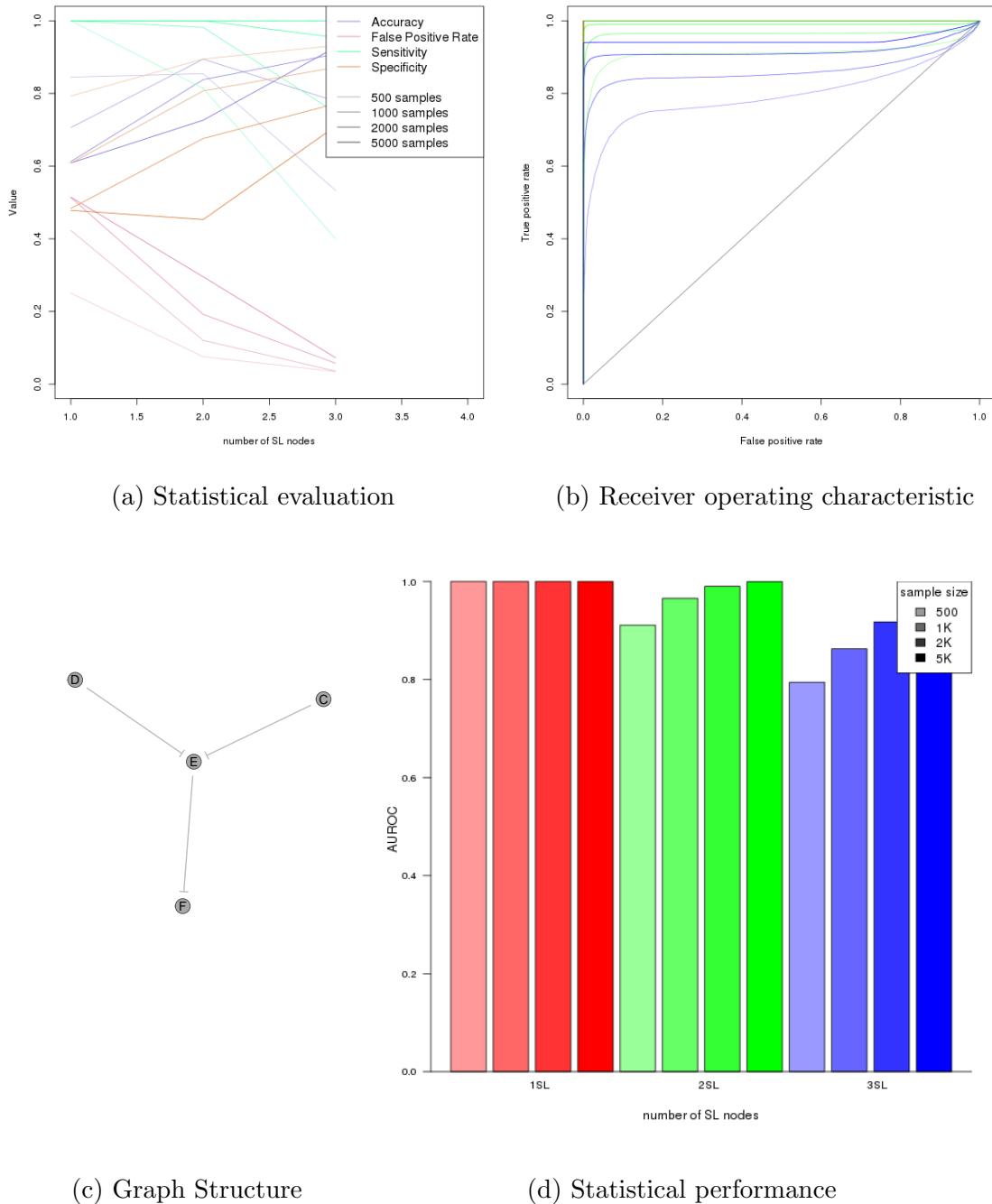
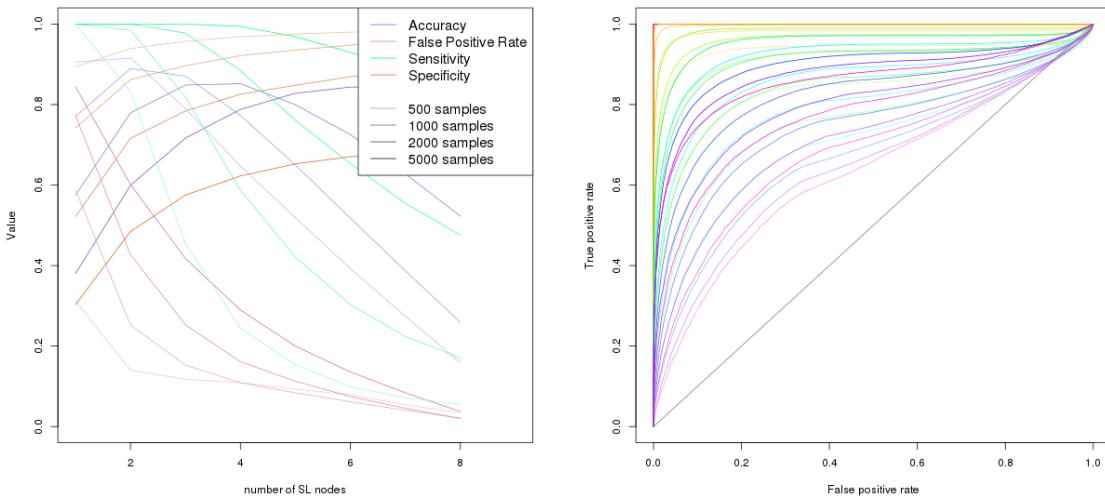
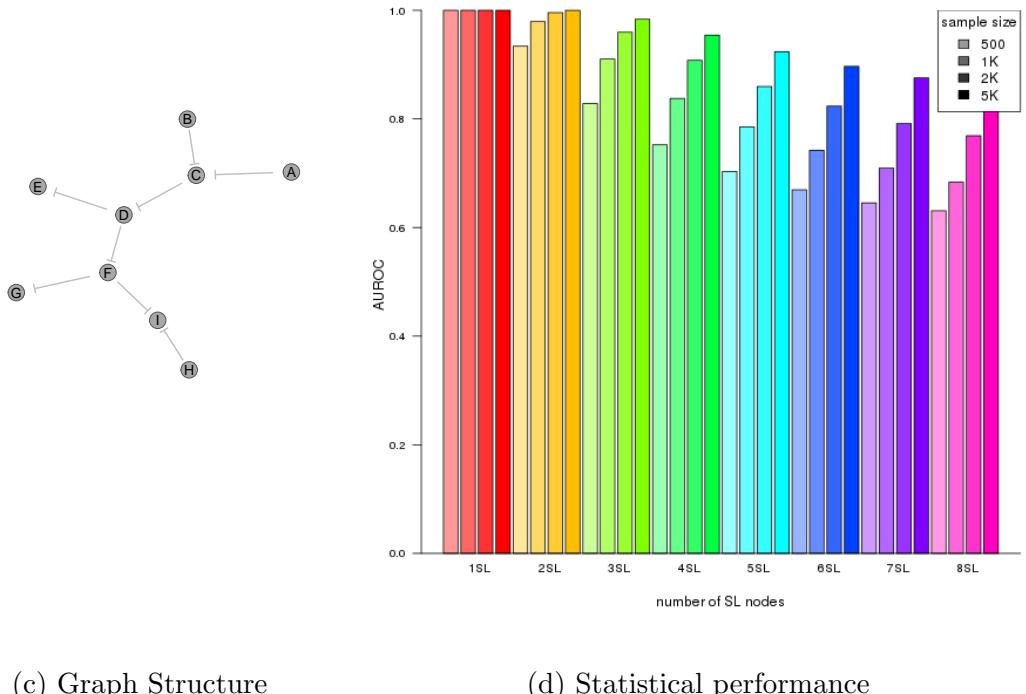


Figure K.2: Performance of simulations on an inhibiting graph. Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.



(a) Statistical evaluation

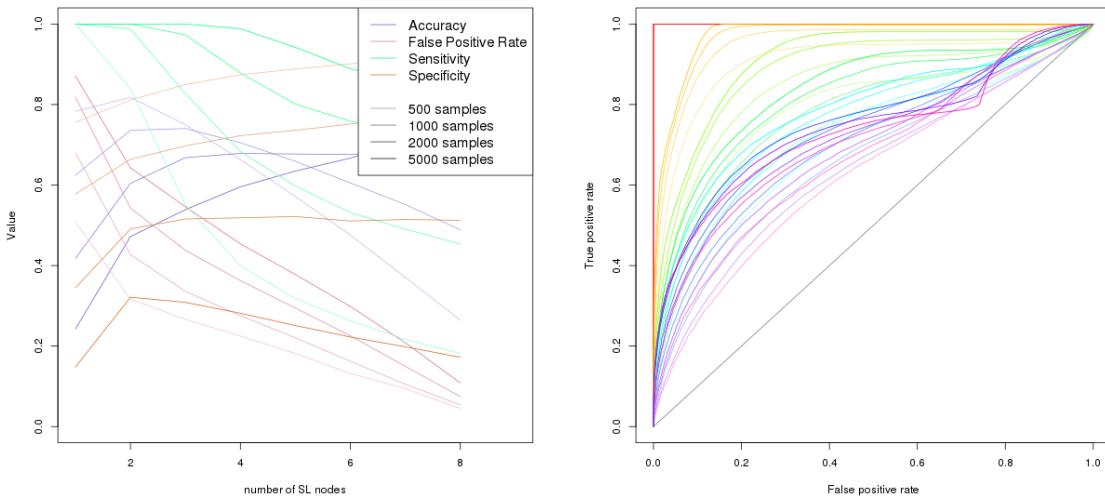
(b) Receiver operating characteristic



(c) Graph Structure

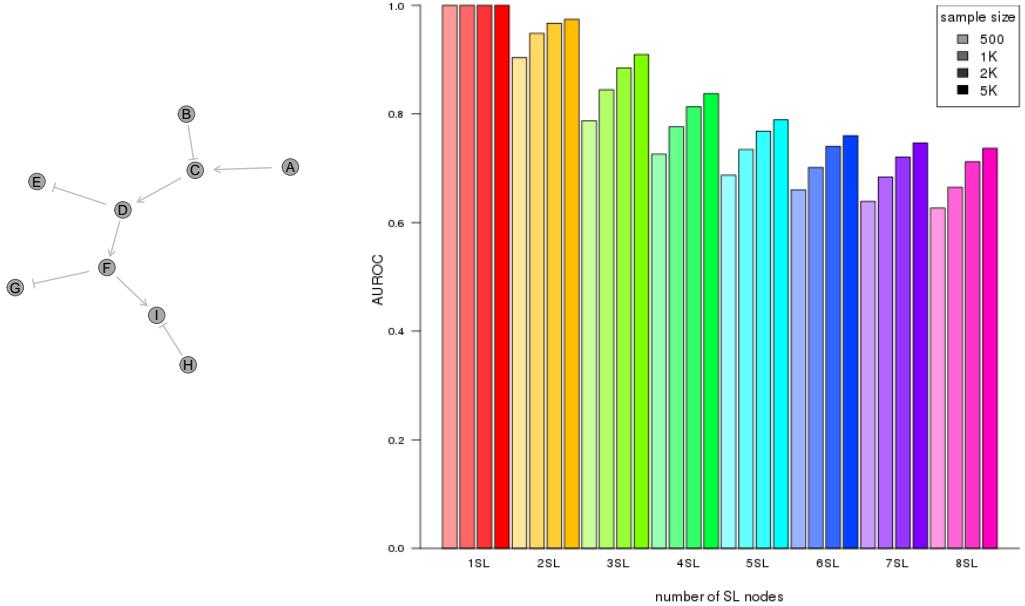
(d) Statistical performance

Figure K.3: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph4 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation

(b) Receiver operating characteristic

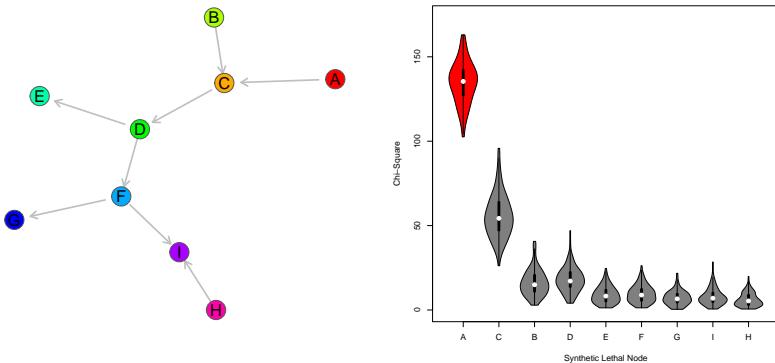


(c) Graph Structure

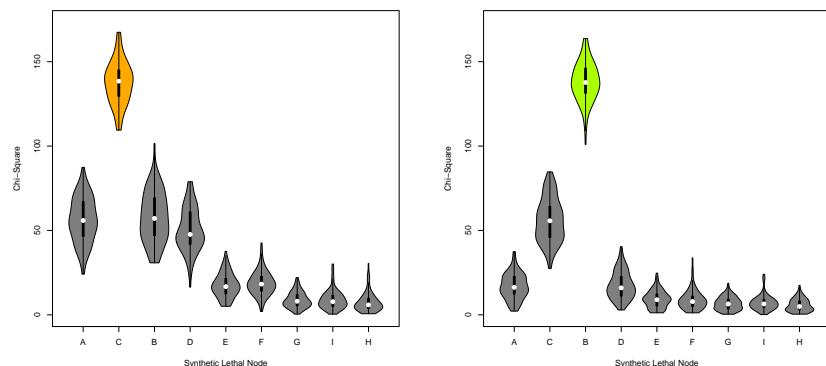
(d) Statistical performance

Figure K.4: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph4 with a combination of inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.

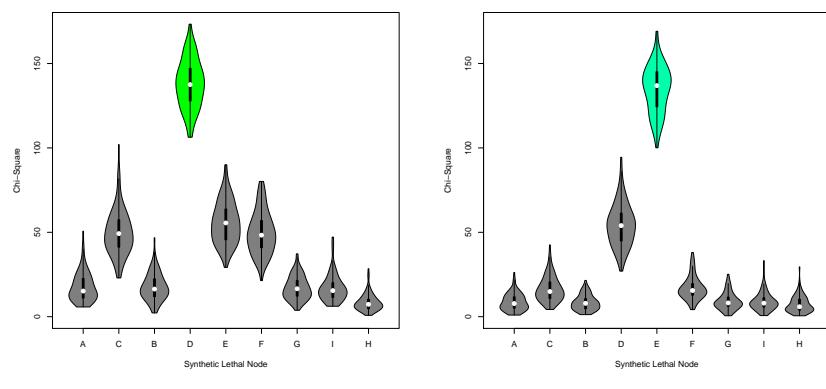
K.2 Simulation across Graph Structures



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

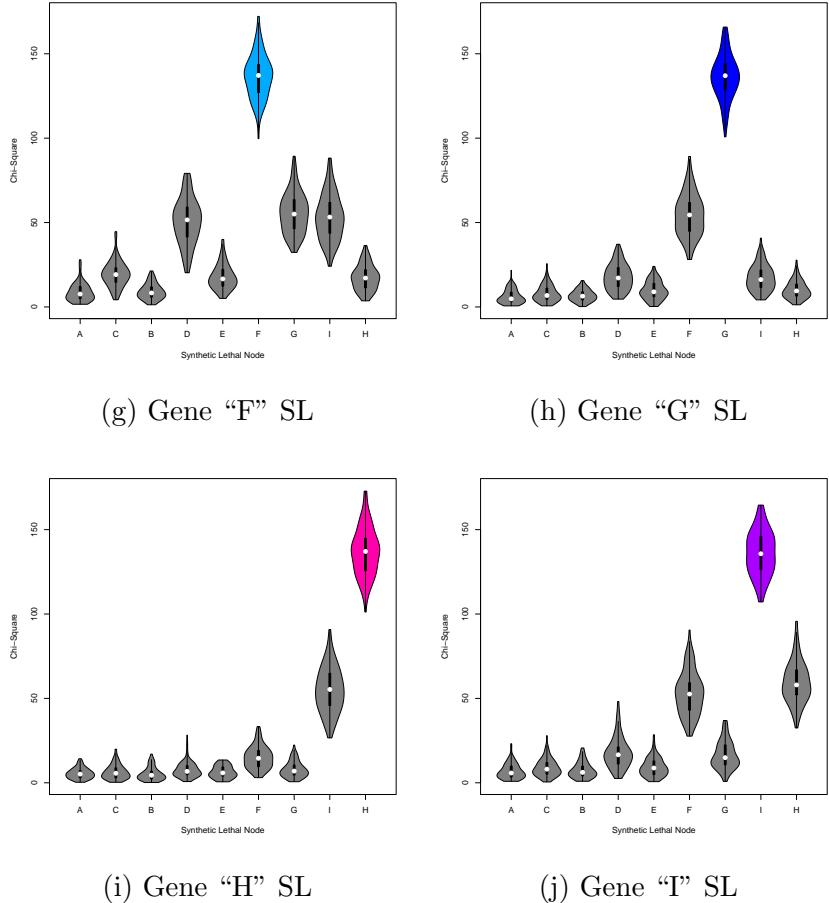
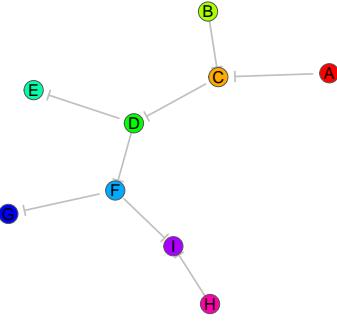
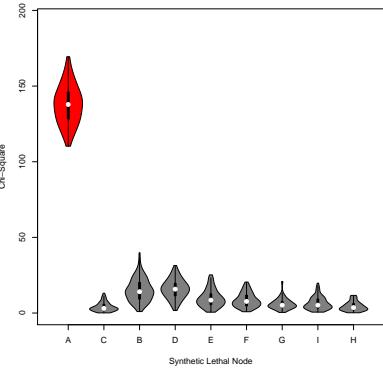


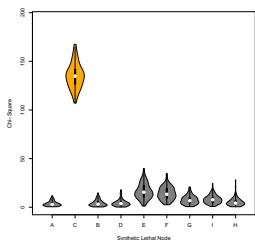
Figure K.5: Detection of synthetic lethality within a graph structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed 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.



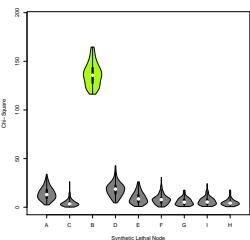
(a) Inhibiting Graph Structure



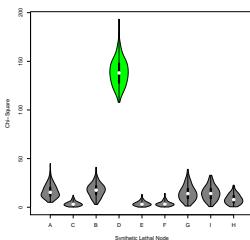
(b) χ^2 distribution for "A" SL



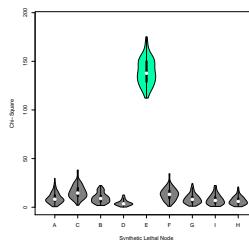
(c) Gene "B" SL



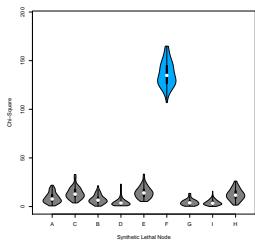
(d) Gene "C" SL



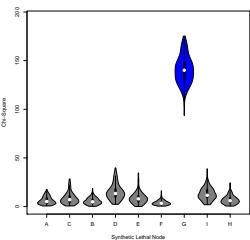
(e) Gene "D" SL



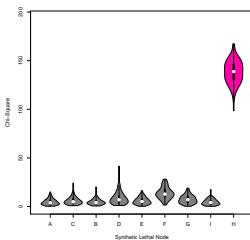
(f) Gene "E" SL



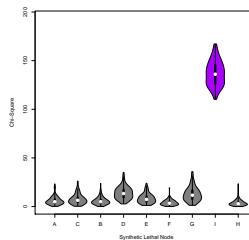
(g) Gene "F" SL



(h) Gene "G" SL

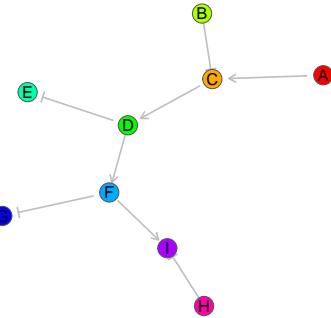


(i) Gene "H" SL

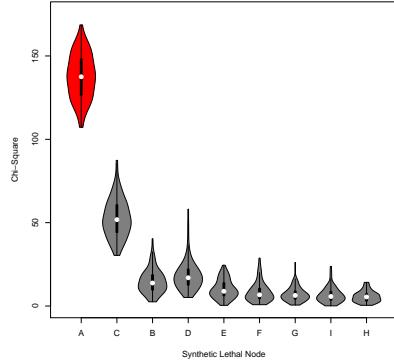


(j) Gene "I" SL

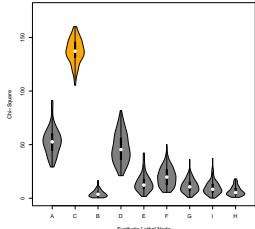
Figure K.6: Detection of synthetic lethality within an inhibiting graph. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in the respective 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.



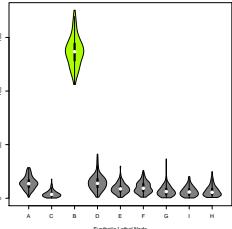
(a) Inhibiting Graph Structure



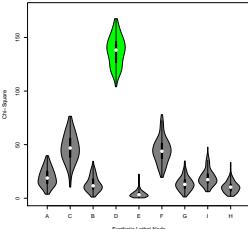
(b) χ^2 distribution for "A" SL



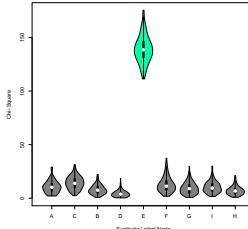
(c) Gene "B" SL



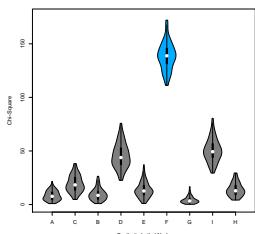
(d) Gene "C" SL



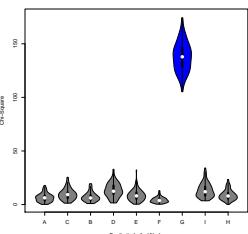
(e) Gene "D" SL



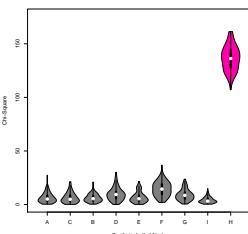
(f) Gene "E" SL



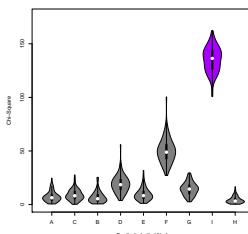
(g) Gene "F" SL



(h) Gene "G" SL



(i) Gene "H" SL



(j) Gene "I" SL

Figure K.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.

K.3 Simulations from Complex Graph Structures

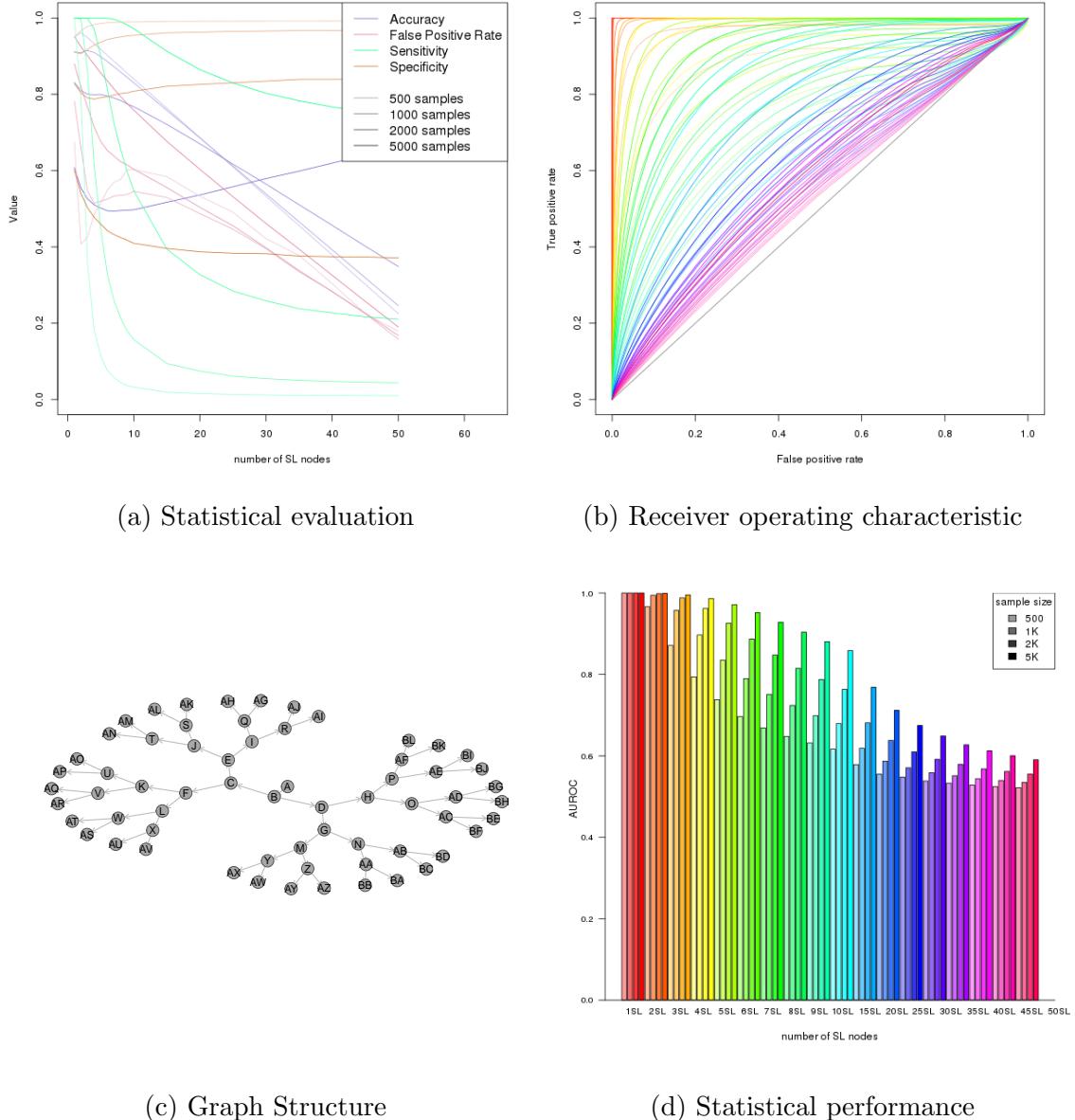
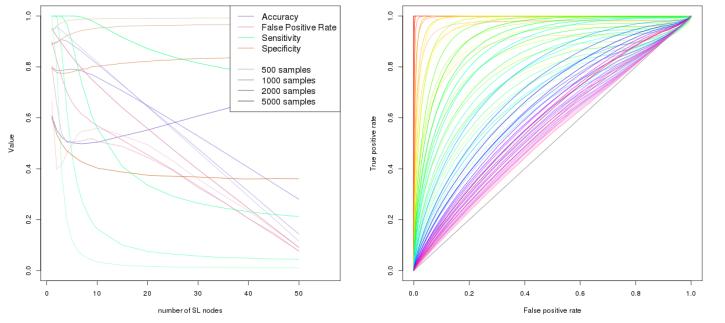
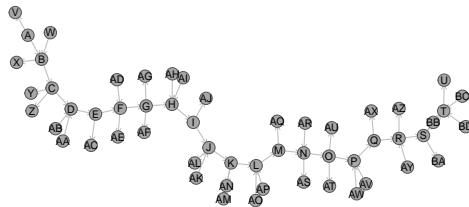


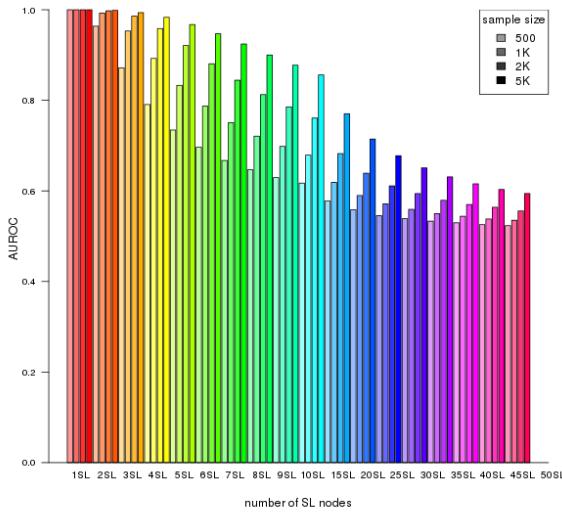
Figure K.8: **Performance of simulations on a branching graph.** Simulation of synthetic lethality used a multivariate normal distribution from a branching graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.



(a) Statistical evaluation (b) Receiver operating characteristic

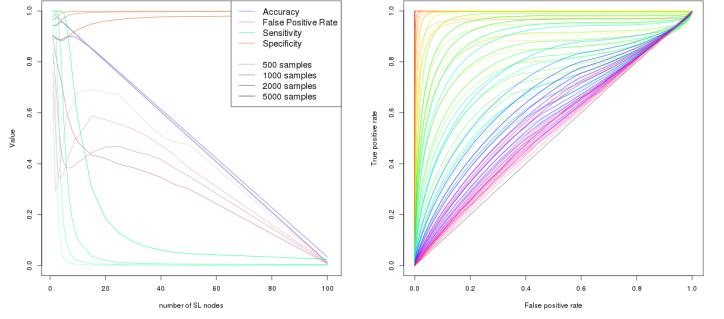


(c) Graph Structure

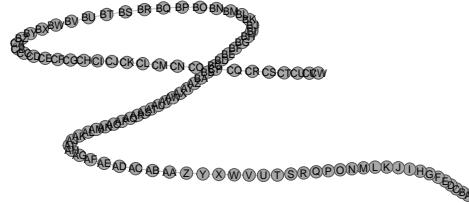


(d) Statistical performance

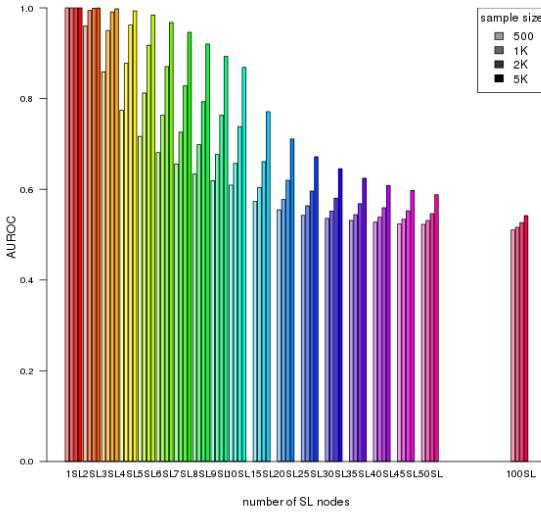
Figure K.9: **Performance of simulations on a complex graph.** Simulation of synthetic lethality used a multivariate normal distribution from a complex graph. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used. Colours in Figure K.9b match Figure K.9d.



(a) Statistical evaluation (b) Receiver operating characteristic



(c) Graph Structure



(d) Statistical performance

Figure K.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 K.10b match Figure K.10d.

K.3.1 Simulations from Complex Inhibiting Graphs

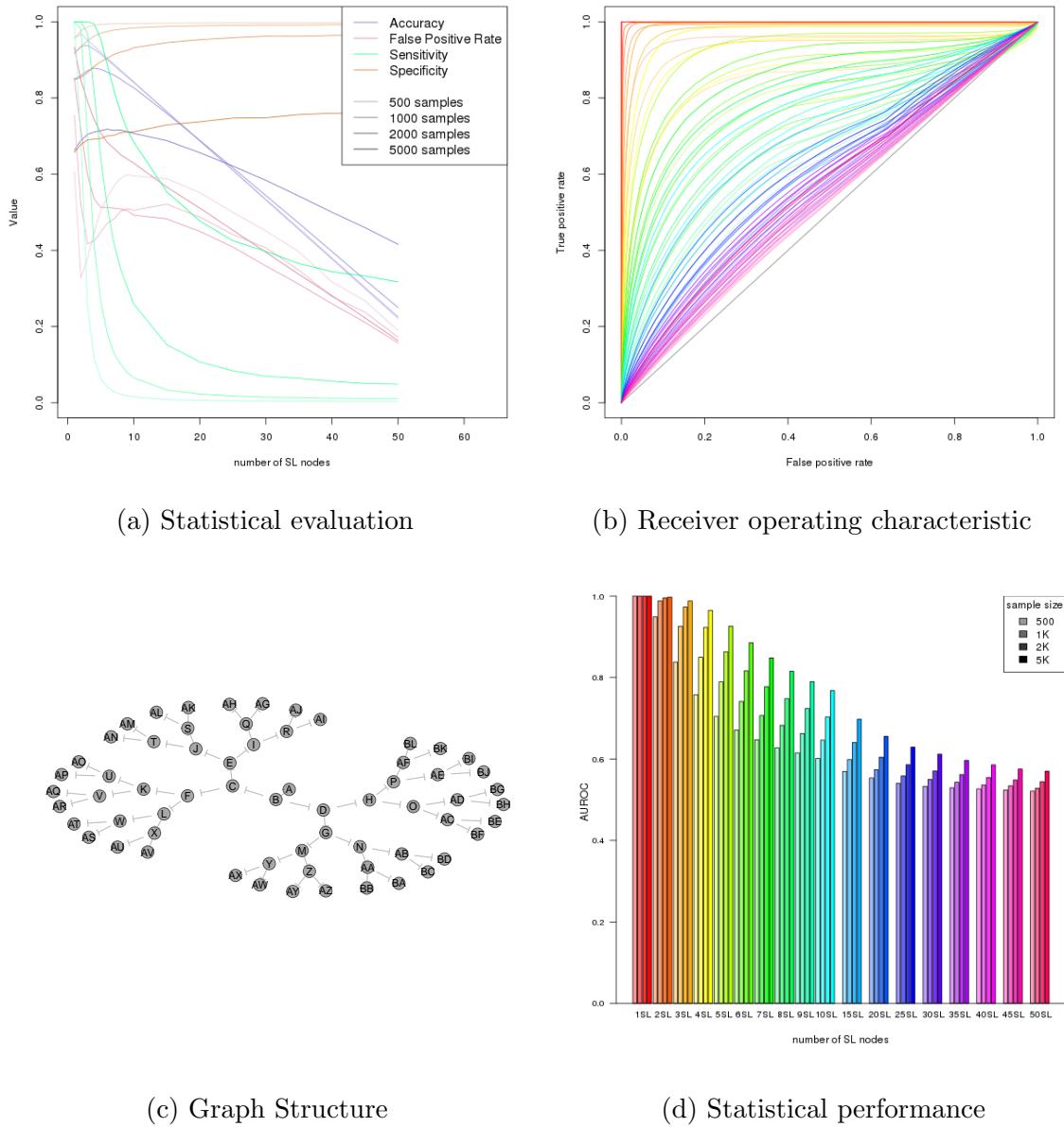
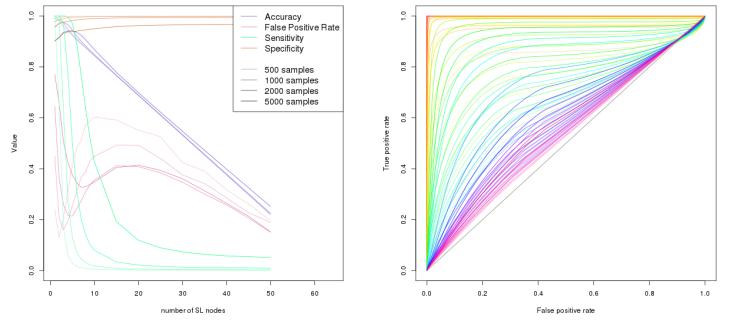
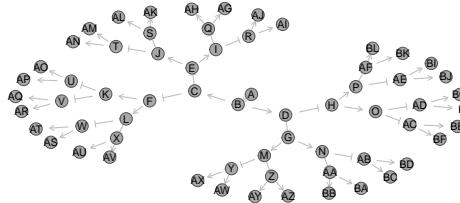


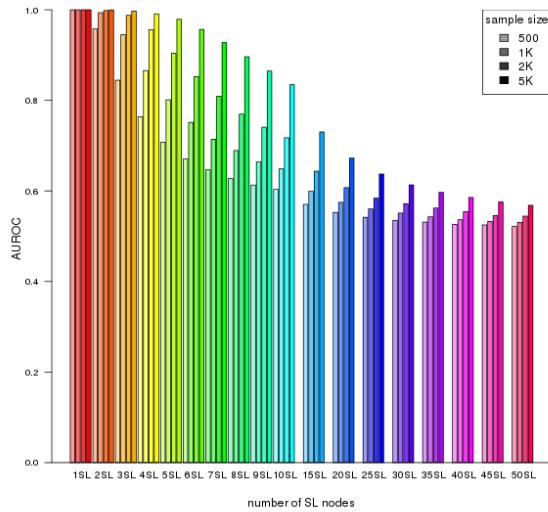
Figure K.11: Performance of simulations on a branching graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph6 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

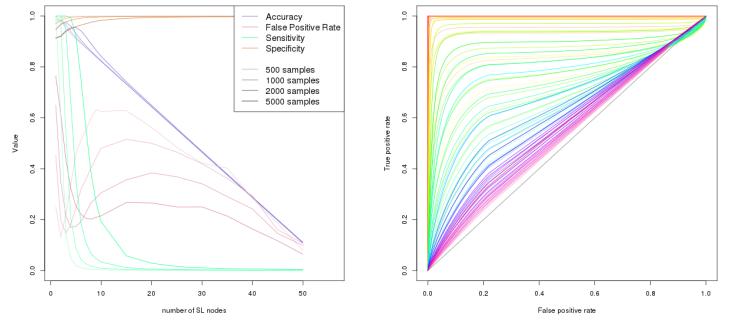


(c) Graph Structure

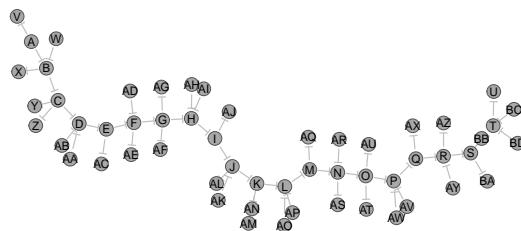


(d) Statistical performance

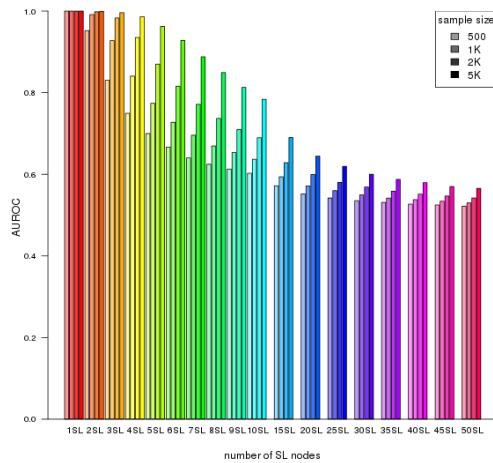
Figure K.12: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph6 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

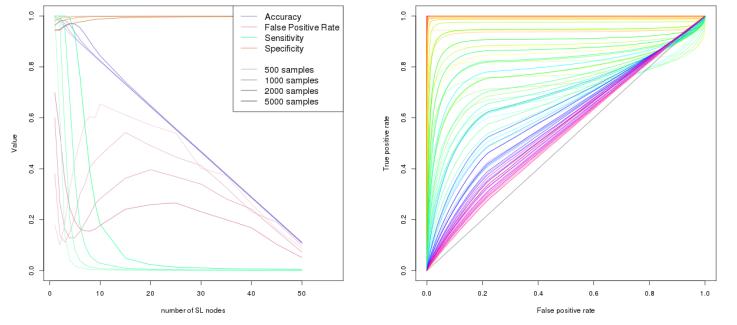


(c) Graph Structure

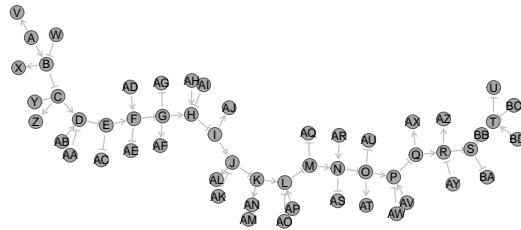


(d) Statistical performance

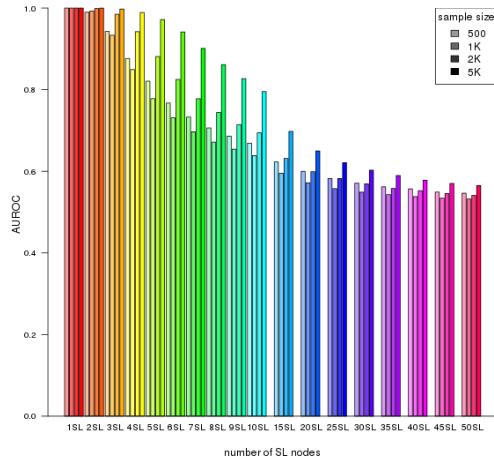
Figure K.13: Performance of simulations on a complex graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph7 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

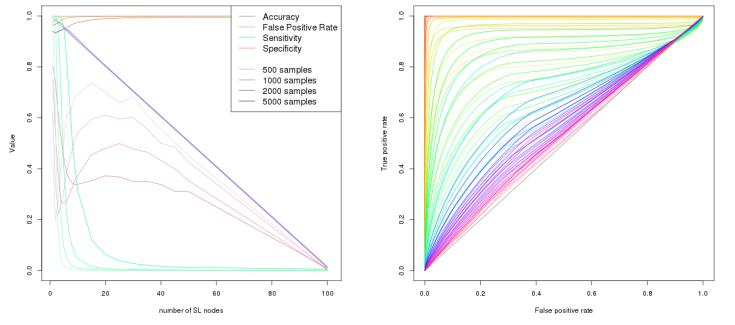


(c) Graph Structure

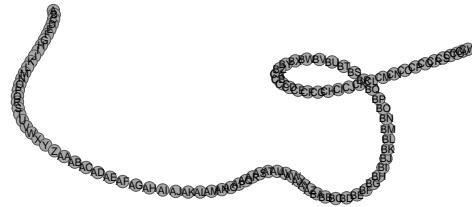


(d) Statistical performance

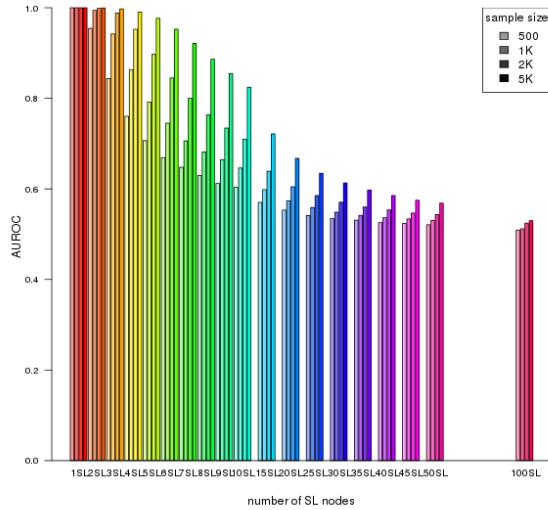
Figure K.14: Performance of simulations on a complex graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph7 with a combination of relationships. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

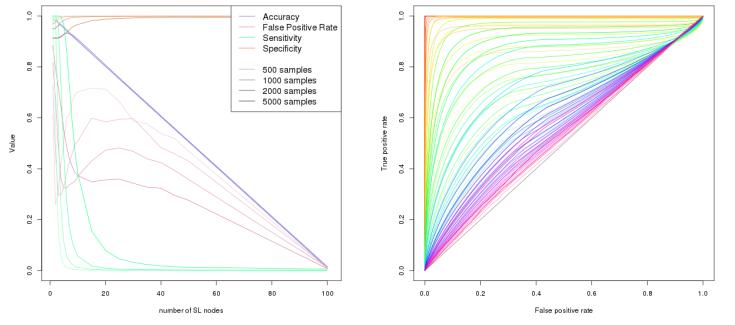


(c) Graph Structure



(d) Statistical performance

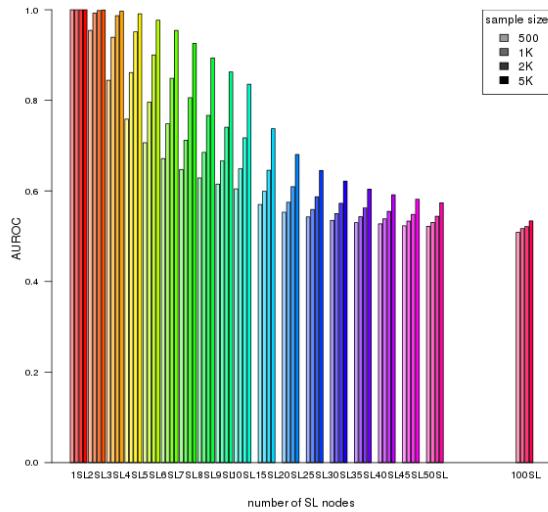
Figure K.15: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph5 with only inhibitions. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic



(c) Graph Structure



(d) Statistical performance

Figure K.16: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph5 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.

K.4 Simulations from Pathway Graph Structures

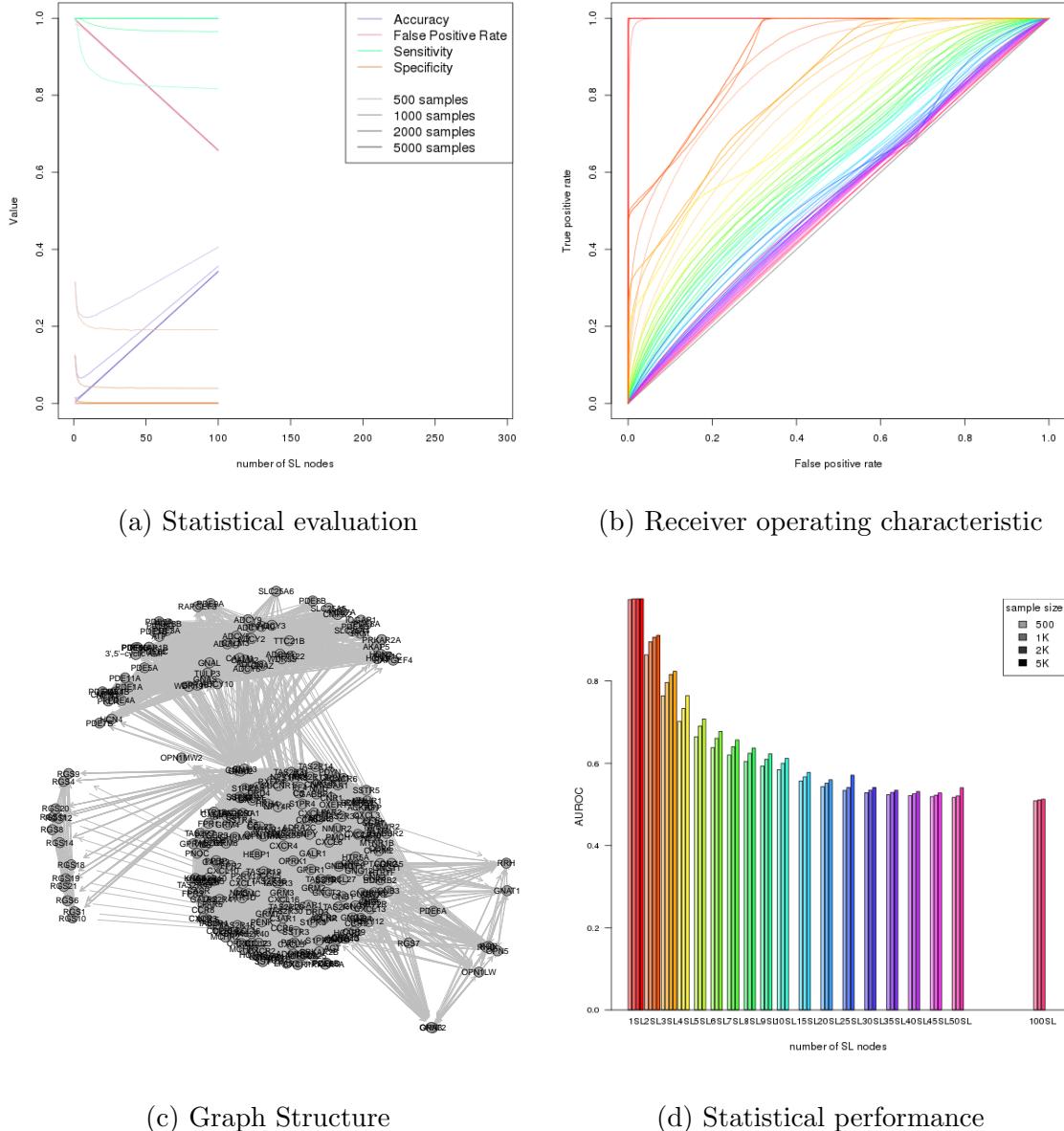


Figure K.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters for detecting synthetic lethality in the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

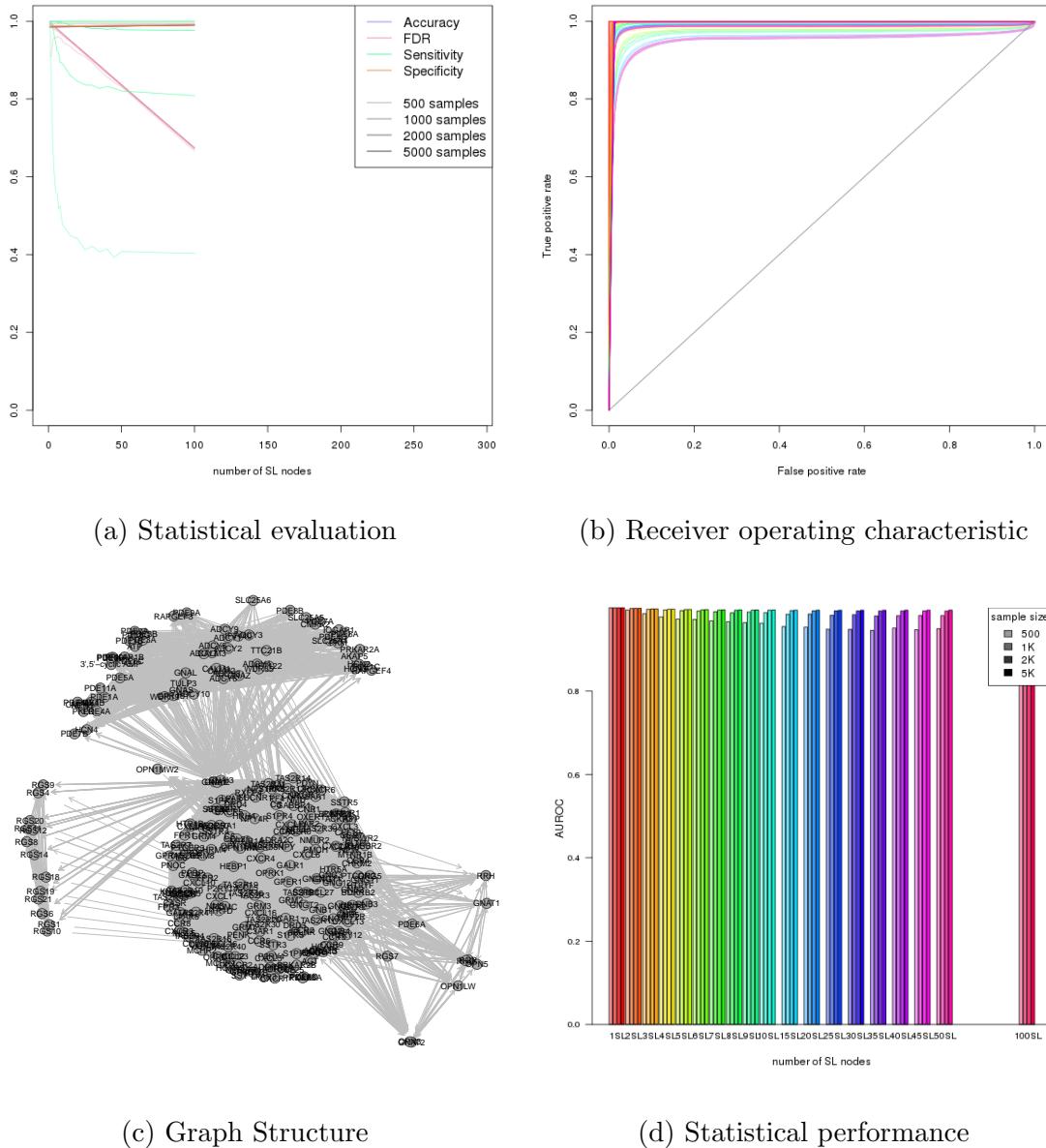


Figure K.18: Performance of simulations including the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters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