

Contents

Glossary	x
Acronyms	xi
2 Methods and Resources	41
2.1 Bioinformatics Resources for Genomics Research	41
2.1.1 Public Data and Software Packages	41
2.1.1.1 Cancer Genome Atlas Data	42
2.1.1.2 Reactome and Annotation Data	43
2.2 Data Handling	43
2.2.1 Normalisation	43
2.2.2 Sample Triage	43
2.2.3 Metagenes and the Singular Value Decomposition	44
2.2.4 Candidate Triage and Integration with Screen Data	46
2.3 Techniques	46
2.3.1 Statistical Procedures and Tests	47
2.3.2 Gene Set Over-representation Analysis	48
2.3.3 Clustering	48
2.3.4 Heatmap	48
2.3.5 Modelling and Simulations	49
2.3.5.1 Receiver Operating Characteristic Curves	50
2.3.6 Resampling Analysis	50
2.4 Pathway Structure Methods	51
2.4.1 Network and Graph Analysis	51
2.4.2 Sourcing Graph Structure Data	52
2.4.3 Constructing Pathway Subgraphs	52
2.4.4 Network Analysis Metrics	53
2.5 Implementation	54
2.5.1 Computational Resources and Linux Utilities	54
2.5.2 R Language and Packages	55
2.5.3 High Performance and Parallel Computing	58
3 Methods Developed During Thesis	60
3.1 A Synthetic Lethal Detection Methodology	60
3.2 Synthetic Lethal Simulation and Modelling	62
3.2.1 A Model of Synthetic Lethality in Expression Data	63

3.2.2	Simulation Procedure	67
3.3	Detecting Simulated Synthetic Lethal Partners	70
3.3.1	Binomial Simulation of Synthetic Lethality	70
3.3.2	Multivariate Normal Simulation of Synthetic Lethality	72
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	74
3.3.2.2	Specificity with Query-Correlated Pathways	80
3.4	Graph Structure Methods	84
3.4.1	Upstream and Downstream Gene Detection	84
3.4.1.1	Permutation Analysis for Statistical Significance	85
3.4.2	Simulating Gene Expression from Graph Structures	85
3.5	Customised Functions and Packages Developed	90
3.5.1	Synthetic Lethal Interaction Prediction Tool	90
3.5.2	Data Visualisation	91
3.5.3	Extensions to the iGraph Package	91
3.5.3.1	Sampling Simulated Data from Graph Structures	93
3.5.3.2	Plotting Directed Graph Structures	93
3.5.3.3	Computing Information Centrality	94
3.5.3.4	Testing Pathway Structure with Permutation Testing	94
3.5.3.5	Metapackage to Install iGraph Functions	95
4	Synthetic Lethal Analysis of Gene Expression Data	96
4.1	Synthetic Lethal Genes in Breast Cancer	97
4.1.1	Synthetic Lethal Pathways in Breast Cancer	98
4.1.2	Expression Profiles of Synthetic Lethal Partners	100
4.1.2.1	Subgroup Pathway Analysis	103
4.2	Comparing Synthetic Lethal Gene Candidates	105
4.2.1	Primary siRNA Screen Candidates	105
4.2.2	Comparison with Correlation	105
4.2.3	Comparison with Primary Screen Viability	108
4.2.4	Comparison with Secondary siRNA Screen Validation	110
4.2.5	Comparison to Primary Screen at Pathway Level	111
4.2.5.1	Resampling Genes for Pathway Enrichment	113
4.2.6	Integrating Synthetic Lethal Pathways and Screens	118
4.3	Synthetic Lethal Pathway Metagenes	119
4.4	Replication in Stomach Cancer	121
4.5	Discussion	122
4.5.1	Strengths of the SLIPT Methodology	122
4.5.2	Synthetic Lethal Pathways for E-cadherin	123
4.5.3	Replication and Validation	125
4.5.3.1	Integration with siRNA Screening	125
4.5.3.2	Replication across Tissues	126
4.6	Summary	126

5 Synthetic Lethal Pathway Structure	128
5.1 Synthetic Lethal Genes in Reactome Pathways	128
5.1.1 The PI3K/AKT Pathway	129
5.1.2 The Extracellular Matrix	131
5.1.3 G Protein Coupled Receptors	134
5.1.4 Gene Regulation and Translation	134
5.2 Network Analysis of Synthetic Lethal Genes	136
5.2.1 Gene Connectivity and Vertex Degree	137
5.2.2 Gene Importance and Centrality	138
5.2.2.1 Information Centrality	138
5.2.2.2 PageRank Centrality	140
5.3 Relationships between Synthetic Lethal Genes	141
5.3.1 Detecting Upstream or Downstream Synthetic Lethality	142
5.3.2 Resampling for Synthetic Lethal Pathway Structure	144
5.4 Discussion	146
5.5 Summary	148
6 Simulation and Modelling of Synthetic Lethal Pathways	149
6.1 Synthetic Lethal Detection Methods	150
6.1.1 Performance of SLIPT and χ^2 across Quantiles	151
6.1.1.1 Correlated Query Genes affects Specificity	154
6.1.2 Alternative Synthetic Lethal Detection Strategies	156
6.1.2.1 Correlation for Synthetic Lethal Detection	157
6.1.2.2 Testing for Bimodality with BiSEp	158
6.2 Simulations with Graph Structures	159
6.2.1 Performance over Graph Structures	160
6.2.1.1 Simple Graph Structures	160
6.2.1.2 Constructed Graph Structures	163
6.2.2 Performance with Inhibitions	165
6.2.3 Synthetic Lethality across Graph Structures	171
6.2.4 Performance within a Simulated Human Genome	174
6.3 Simulations in More Complex Graph Structures	179
6.3.1 Simulations over Pathway-based Graphs	180
6.3.2 Pathway Structures in a Simulated Human Genome	182
6.4 Discussion	185
6.4.1 Simulation Procedure	185
6.4.2 Comparing Methods with Simulated Data	186
6.4.3 Design and Performance of SLIPT	187
6.4.4 Simulations from Graph Structures	189
6.5 Summary	190
7 Discussion	192
7.1 Synthetic Lethality and <i>CDH1</i> Biology	192
7.1.1 Established Functions of <i>CDH1</i>	193
7.1.2 The Molecular Role of <i>CDH1</i> in Cancer	193
7.2 Significance	194

7.2.1	Synthetic Lethality in the Genomic Era	194
7.2.2	Clinical Interventions based on Synthetic Lethality	196
7.3	Future Directions	197
7.4	Conclusions	199
	Bibliography	201
A	Sample Quality	225
A.1	Sample Correlation	225
A.2	Replicate Samples in TCGA Breast Cancer Data	227
B	Software Used for Thesis	231
C	Mutation Analysis in Breast Cancer	240
C.1	Synthetic Lethal Genes and Pathways	240
C.2	Synthetic Lethal Expression Profiles	241
C.3	Comparison to Primary Screen	244
C.3.1	Resampling Analysis	246
C.4	Compare SLIPT genes	248
D	Metagene Analysis	250
D.1	Pathway Signature Expression	250
D.2	Synthetic Lethal Reactome Metagenes	254
E	Intrinsic Subtyping	255
F	Stomach Expression Analysis	257
F.1	Synthetic Lethal Genes and Pathways	257
F.2	Comparison to Primary Screen	261
F.2.1	Resampling Analysis	263
F.3	Metagene Analysis	265
G	Synthetic Lethal Genes in Pathways	266
H	Network Analysis for Mutation SLIPT	273
I	Pathway Structure for Mutation SLIPT	276
J	Performance of SLIPT and χ^2	278
J.1	Correlated Query Genes affects Specificity	284
K	Simulations on Graph Structures	290
K.0.1	Simulations from Inhibiting Graph Structures	291
K.1	Simulation across Graph Structures	294
K.2	Simulations from Complex Graph Structures	298
K.2.1	Simulations from Complex Inhibiting Graphs	301
K.3	Simulations from Pathway Graph Structures	307

List of Figures

2.1	Read count density	45
2.2	Read count sample mean	45
3.1	Framework for synthetic lethal prediction	61
3.2	Synthetic lethal prediction adapted for mutation	62
3.3	A model of synthetic lethal gene expression	64
3.4	Modelling synthetic lethal gene expression	65
3.5	Synthetic lethality with multiple genes	66
3.6	Simulating gene function	68
3.7	Simulating synthetic lethal gene function	68
3.8	Simulating synthetic lethal gene expression	69
3.9	Performance of binomial simulations	71
3.10	Comparison of statistical performance	71
3.11	Performance of multivariate normal simulations	73
3.12	Simulating expression with correlated gene blocks	75
3.13	Simulating expression with correlated gene blocks	76
3.14	Synthetic lethal prediction across simulations	78
3.15	Performance with correlations	79
3.16	Comparison of statistical performance with correlation structure	80
3.17	Performance with query correlations	81
3.18	Statistical evaluation of directional criteria	82
3.19	Performance of directional criteria	83
3.20	Simulated graph structures	86
3.21	Simulating expression from a graph structure	87
3.22	Simulating expression from graph structure with inhibitions	88
3.23	Demonstration of violin plots with custom features	92
3.24	Demonstration of annotated heatmap	92
3.25	Simulating graph structures	94
4.1	Synthetic lethal expression profiles of analysed samples	101
4.2	Comparison of SLIPT with siRNA	106
4.3	Comparison of SLIPT and siRNA genes with correlation	106
4.4	Comparison of SLIPT and siRNA genes with correlation	108
4.5	Comparison of SLIPT and siRNA genes with screen viability	109
4.6	Comparison of SLIPT genes with siRNA screen viability	109
4.7	Resampled intersection of SLIPT and siRNA candidate genes	114

5.1	Synthetic lethality in the PI3K cascade	130
5.2	Synthetic lethality in Elastic Fibre Formation	132
5.3	Synthetic lethality in Fibrin Clot Formation	133
5.4	Synthetic lethality in the GPCRs	135
5.5	Synthetic lethality and vertex degree	137
5.6	Synthetic lethality and centrality	139
5.7	Synthetic lethality and PageRank	141
5.8	Structure of synthetic lethality resampling	143
6.1	Performance of χ^2 and SLIPT across quantiles	152
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	153
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	154
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	155
6.5	Performance of negative correlation and SLIPT	158
6.6	Simple graph structures	161
6.7	Performance of simulations on a simple graph	162
6.8	Performance of simulations is similar in simple graphs	163
6.9	Performance of simulations on a pathway	164
6.10	Performance of simulations on a simple graph with inhibition	166
6.11	Performance is higher on a simple inhibiting graph	168
6.12	Performance of simulations on a constructed graph with inhibition . .	169
6.13	Performance is affected by inhibition in graphs	170
6.14	Detection of synthetic lethality within a graph structure	172
6.15	Performance of simulations including a simple graph	176
6.16	Performance on a simple graph improves with more genes	177
6.17	Performance on an inhibiting graph improves with more genes	178
6.18	Performance of simulations on the PI3K cascade	181
6.19	Performance of simulations including the PI3K cascade	183
6.20	Performance on pathways improves with more genes	184
A.1	Correlation profiles of removed samples	225
A.2	Correlation analysis and sample removal	226
A.3	Replicate excluded samples	227
A.4	Replicate samples with all remaining	228
A.5	Replicate samples with some excluded	229
C.1	Synthetic lethal expression profiles of analysed samples	242
C.2	Comparison of mtSLIPT to short interfering RNA (siRNA)	244
C.3	Compare mtSLIPT and siRNA genes with correlation	248
C.4	Compare mtSLIPT and siRNA genes with correlation	248
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	249
D.1	Pathway metagene expression profiles	252
D.2	Expression profiles for estrogen receptor related genes	253
F.1	Synthetic lethal expression profiles of stomach samples	259

F.2	Comparison of SLIPT in stomach to siRNA	261
G.1	Synthetic lethality in the PI3K/AKT pathway	266
G.2	Synthetic lethality in the PI3K/AKT pathway in cancer	267
G.3	Synthetic lethality in the Extracellular Matrix	268
G.4	Synthetic lethality in the GPCR Downstream	269
G.5	Synthetic lethality in the Translation Elongation	270
G.6	Synthetic lethality in the Nonsense-mediated Decay	271
G.7	Synthetic lethality in the 3' UTR	272
H.1	Synthetic lethality and vertex degree	273
H.2	Synthetic lethality and centrality	274
H.3	Synthetic lethality and PageRank	274
I.1	Structure of synthetic lethality resampling	276
J.1	Performance of χ^2 and SLIPT across quantiles	278
J.2	Performance of χ^2 and SLIPT across quantiles	280
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	282
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation	284
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation	286
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	288
K.1	Performance of simulations on a simple graph	290
K.2	Performance of simulations on an inhibiting graph	291
K.3	Performance of simulations on a constructed graph with inhibition	292
K.4	Performance of simulations on a constructed graph with inhibition	293
K.5	Detection of synthetic lethality within a graph structure	294
K.6	Detection of synthetic lethality within an inhibiting graph	296
K.7	Detection of synthetic lethality within an inhibiting graph	297
K.8	Performance of simulations on a branching graph	298
K.9	Performance of simulations on a complex graph	299
K.10	Performance of simulations on a large graph	300
K.11	Performance of simulations on a branching graph with inhibition	301
K.12	Performance of simulations on a branching graph with inhibition	302
K.13	Performance of simulations on a complex graph with inhibition	303
K.14	Performance of simulations on a complex graph with inhibition	304
K.15	Performance of simulations on a large constructed graph with inhibition	305
K.16	Performance of simulations on a large constructed graph with inhibition	306
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	307
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	308

List of Tables

2.1	Excluded samples by batch and clinical characteristics	44
2.2	Computers used during thesis	54
2.3	Linux utilities and applications used during thesis	55
2.4	R installations used during thesis	56
2.5	R Packages used during thesis	56
2.6	R packages developed during thesis	58
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	98
4.2	Pathways for <i>CDH1</i> partners from SLIPT	99
4.3	Pathways for clusters of <i>CDH1</i> partners from SLIPT	104
4.4	ANOVA for synthetic lethality and correlation with <i>CDH1</i>	107
4.5	Comparison of Synthetic Lethal Interaction Prediction Tool (SLIPT) genes against secondary siRNA screen	111
4.6	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	112
4.7	Pathways for <i>CDH1</i> partners from SLIPT	115
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen .	116
4.9	Examples of candidate metagenes synthetic lethal for <i>CDH1</i> from SLIPT	120
5.1	ANOVA for synthetic lethality and vertex degree	138
5.2	ANOVA for synthetic lethality and information centrality	139
5.3	ANOVA for synthetic lethality and PageRank centrality	140
5.4	Resampling for pathway structure of synthetic lethal detection methods	145
B.1	Complete list of R packages used during this thesis	231
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT . . .	240
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	241
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT	243
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA	245
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	246
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	247
D.1	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT . .	254
E.1	Comparison of intrinsic subtypes	255
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	257
F.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	258

F.3	Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT	260
F.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	262
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	263
F.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA	264
F.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer	265
H.1	ANOVA for synthetic lethality and vertex degree	275
H.2	ANOVA for synthetic lethality and information centrality	275
H.3	ANOVA for synthetic lethality and PageRank centrality	275
I.1	Resampling for pathway structure of synthetic lethal detection methods	277

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 J

Performance of SLIPT and χ^2

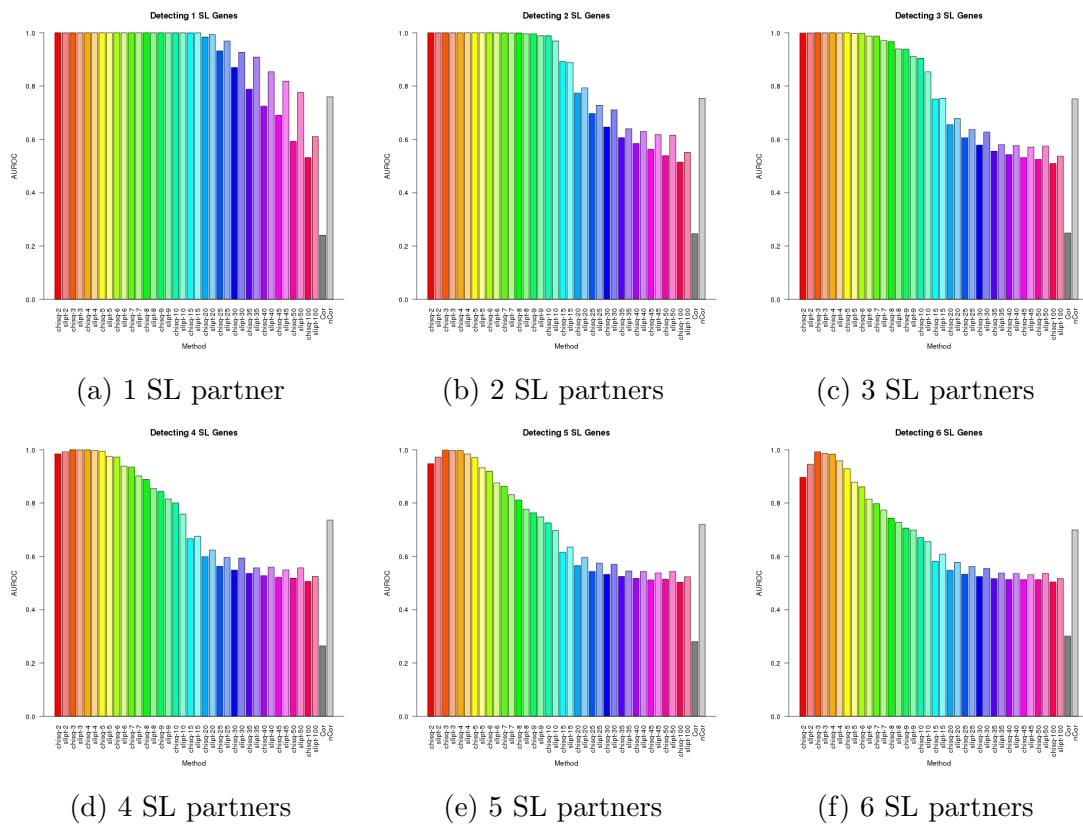


Figure J.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

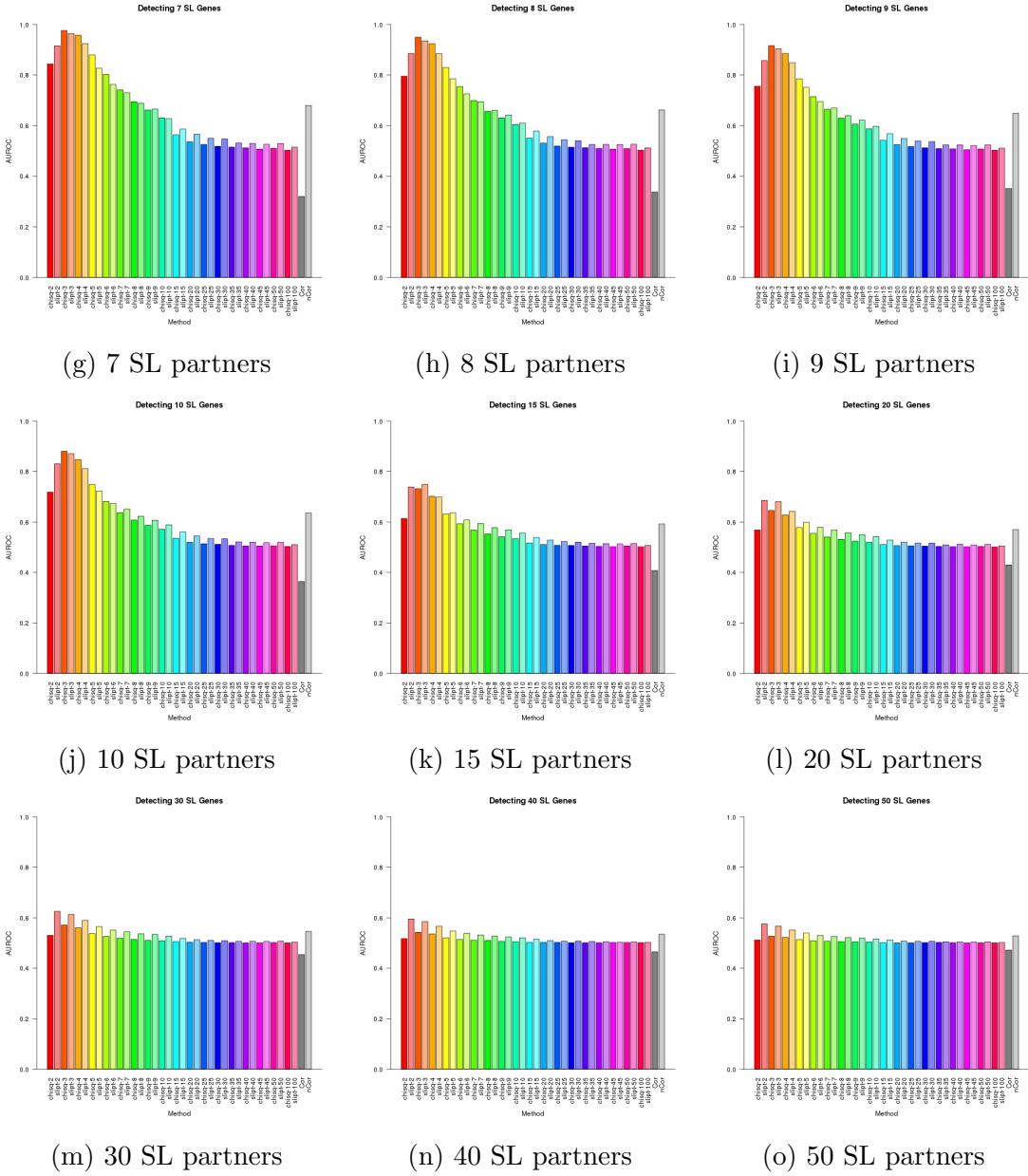


Figure J.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles 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.

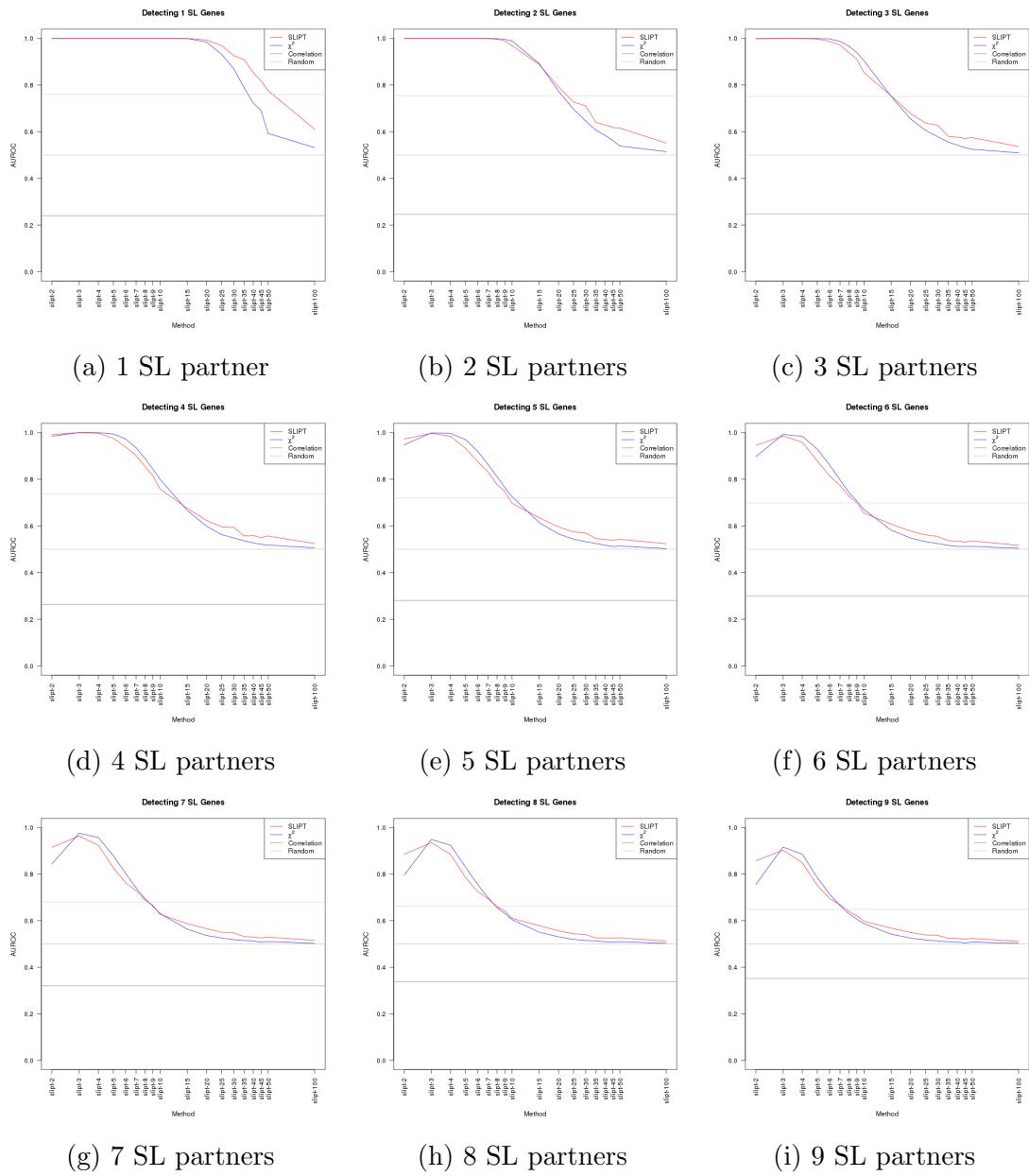


Figure J.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

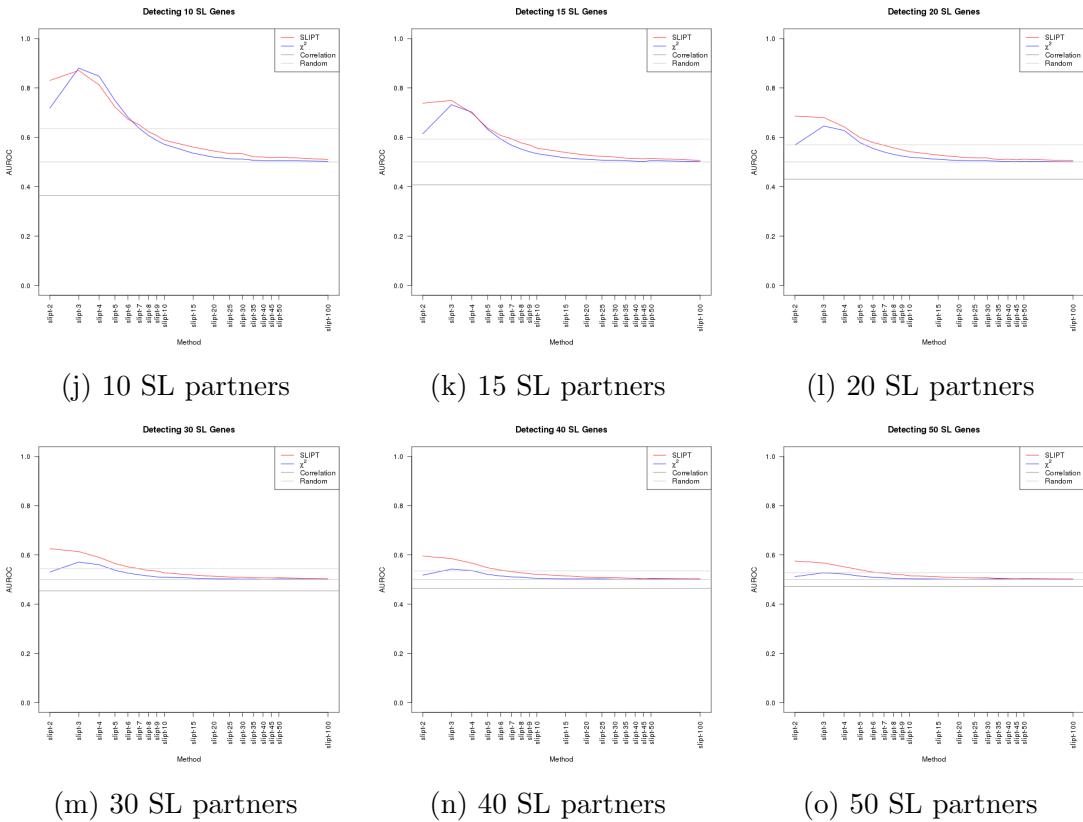


Figure J.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging 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.

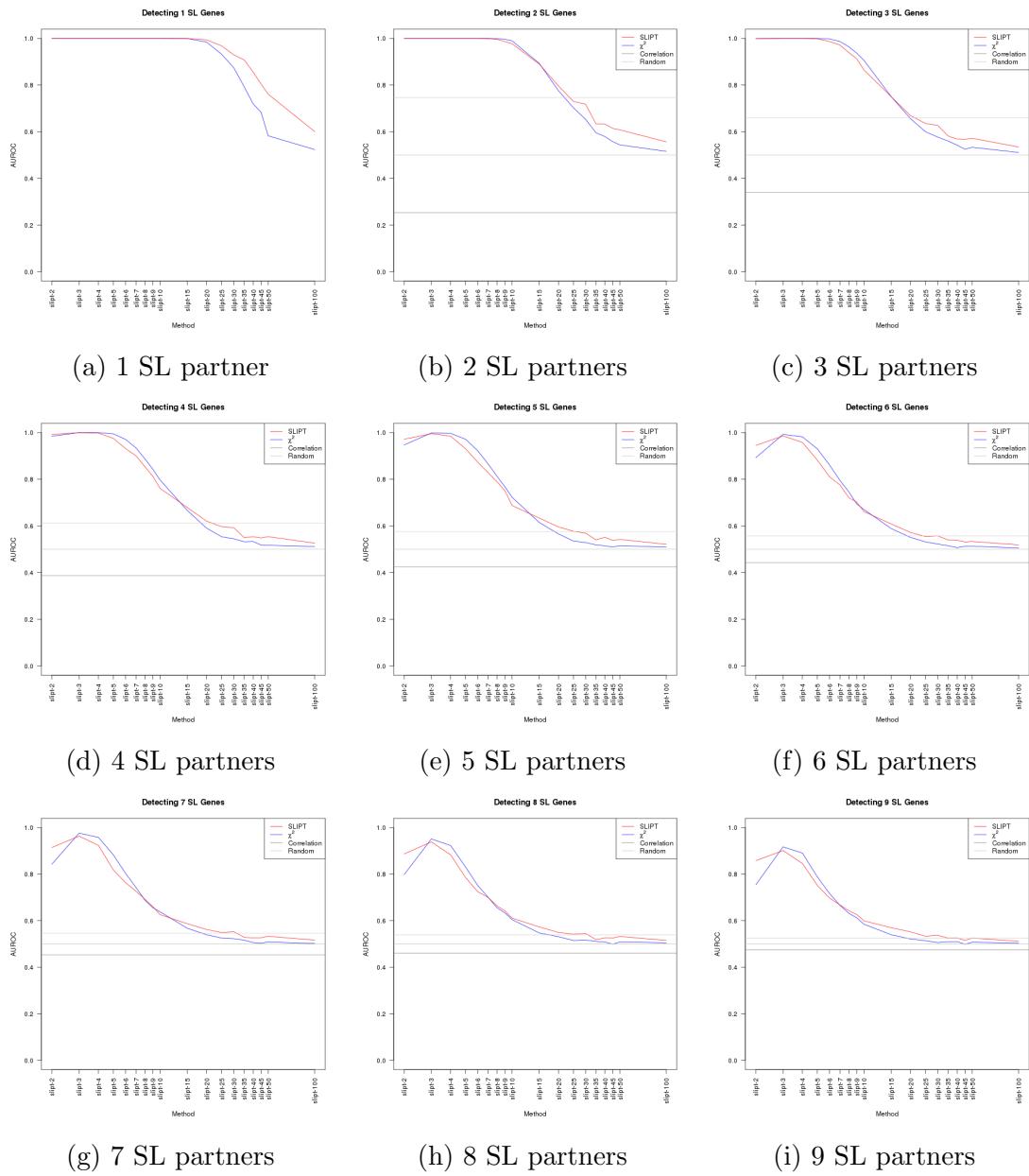


Figure J.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

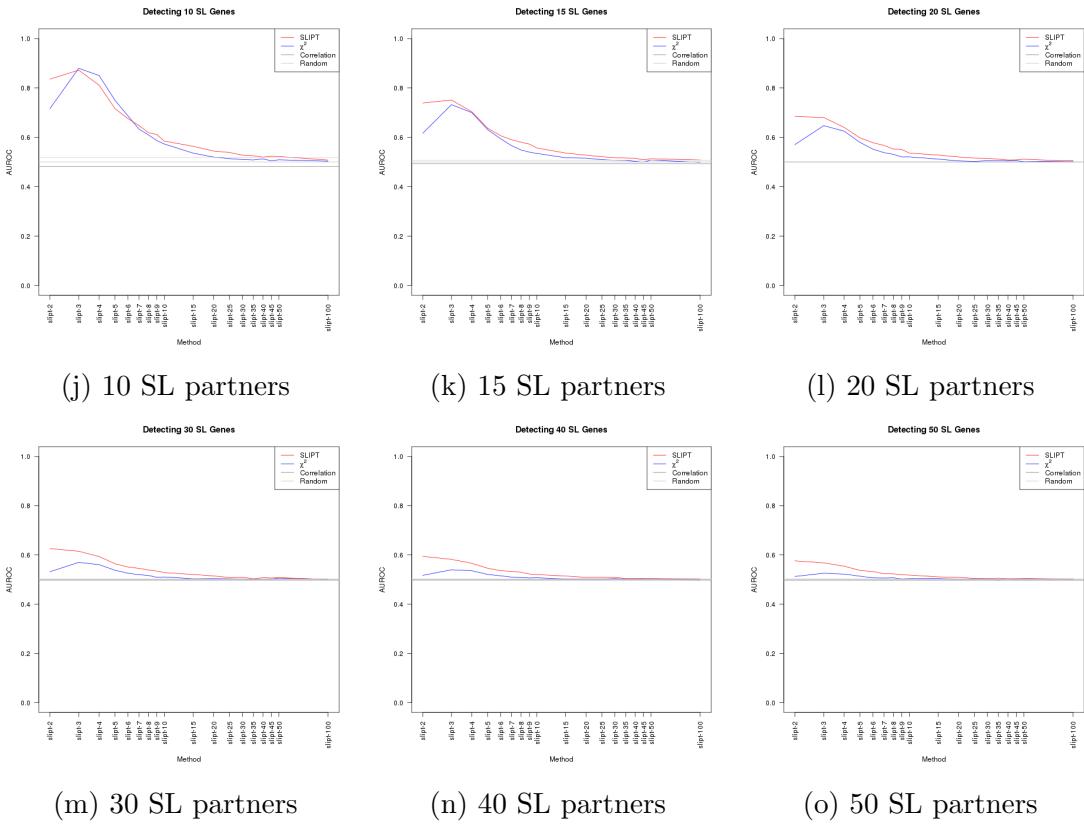


Figure J.3: Performance of χ^2 and SLIPT across quantiles with more genes.
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles 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.

J.1 Correlated Query Genes affects Specificity

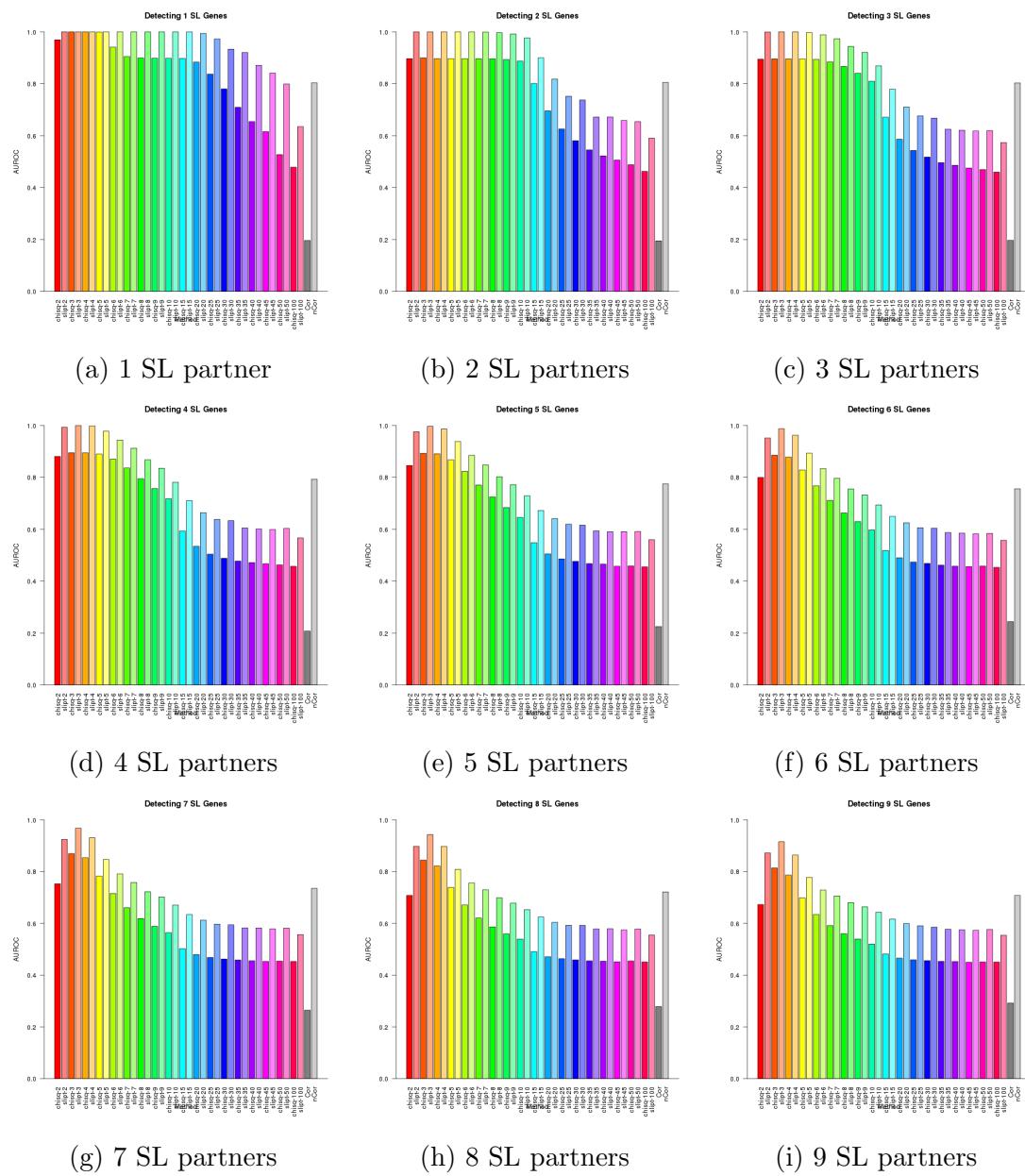


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. (continued on next page)

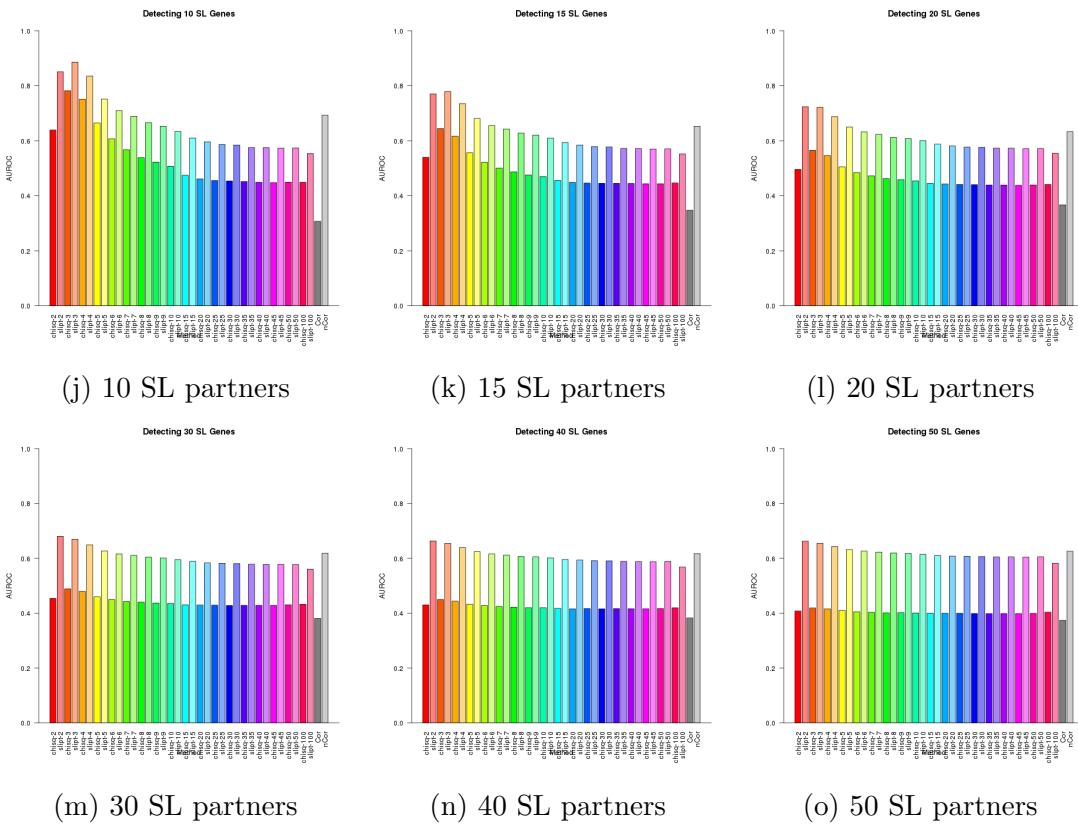


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking 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.

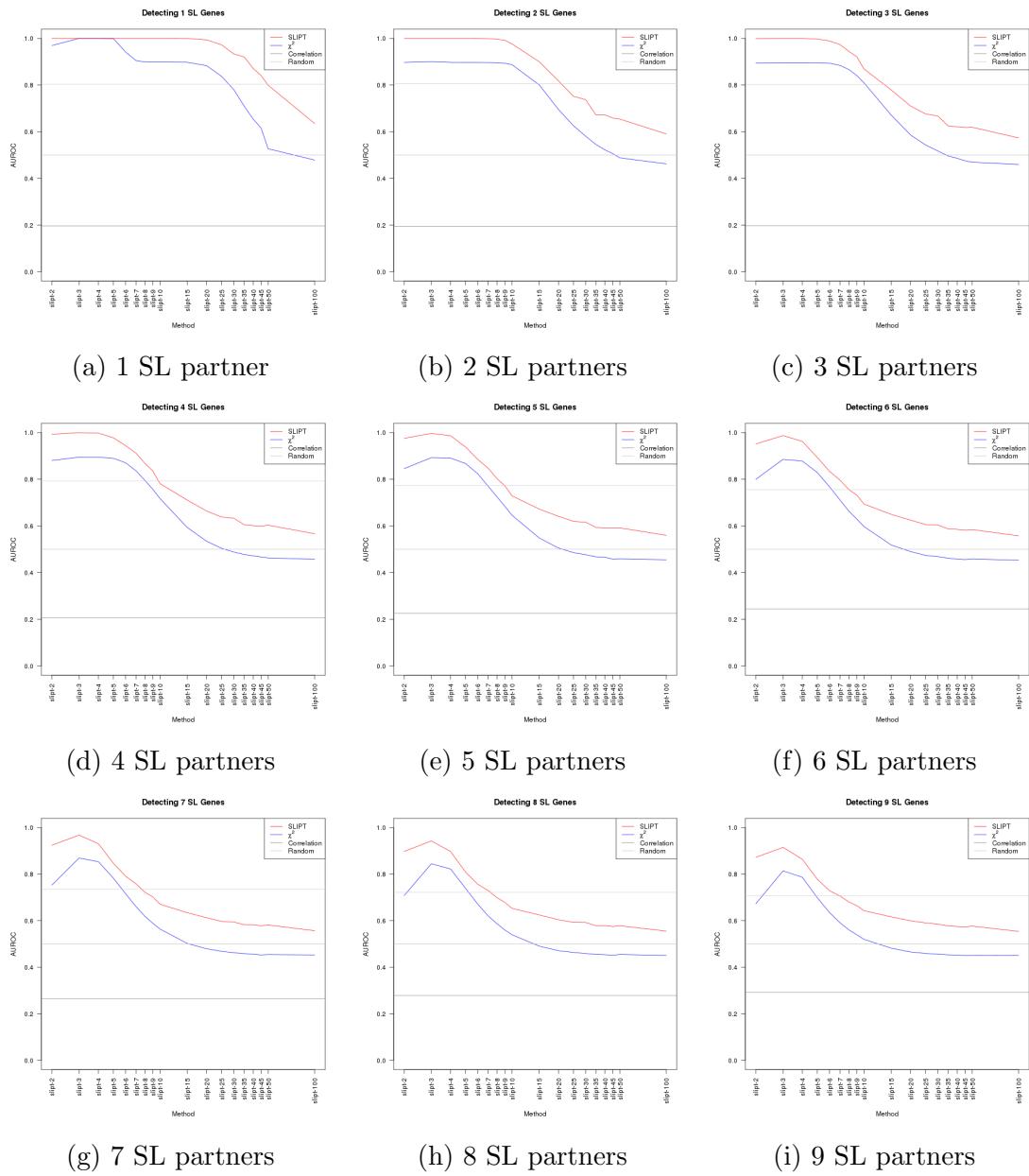


Figure J.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

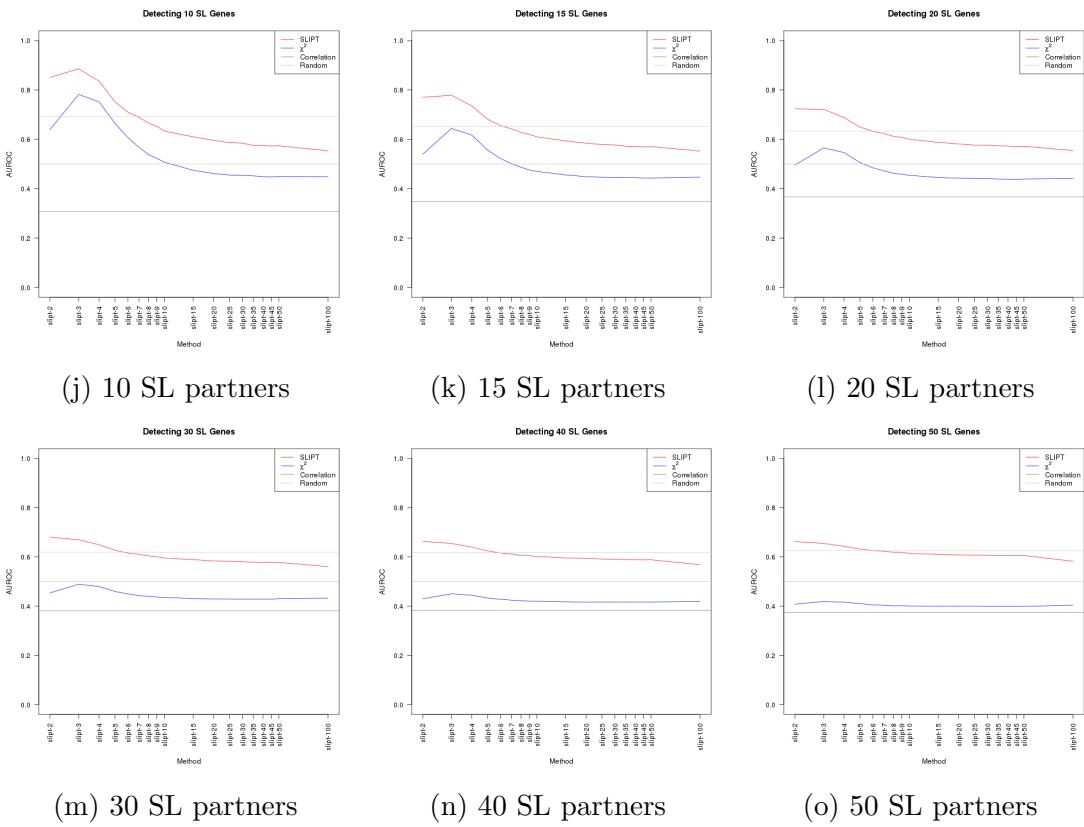


Figure J.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles 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.

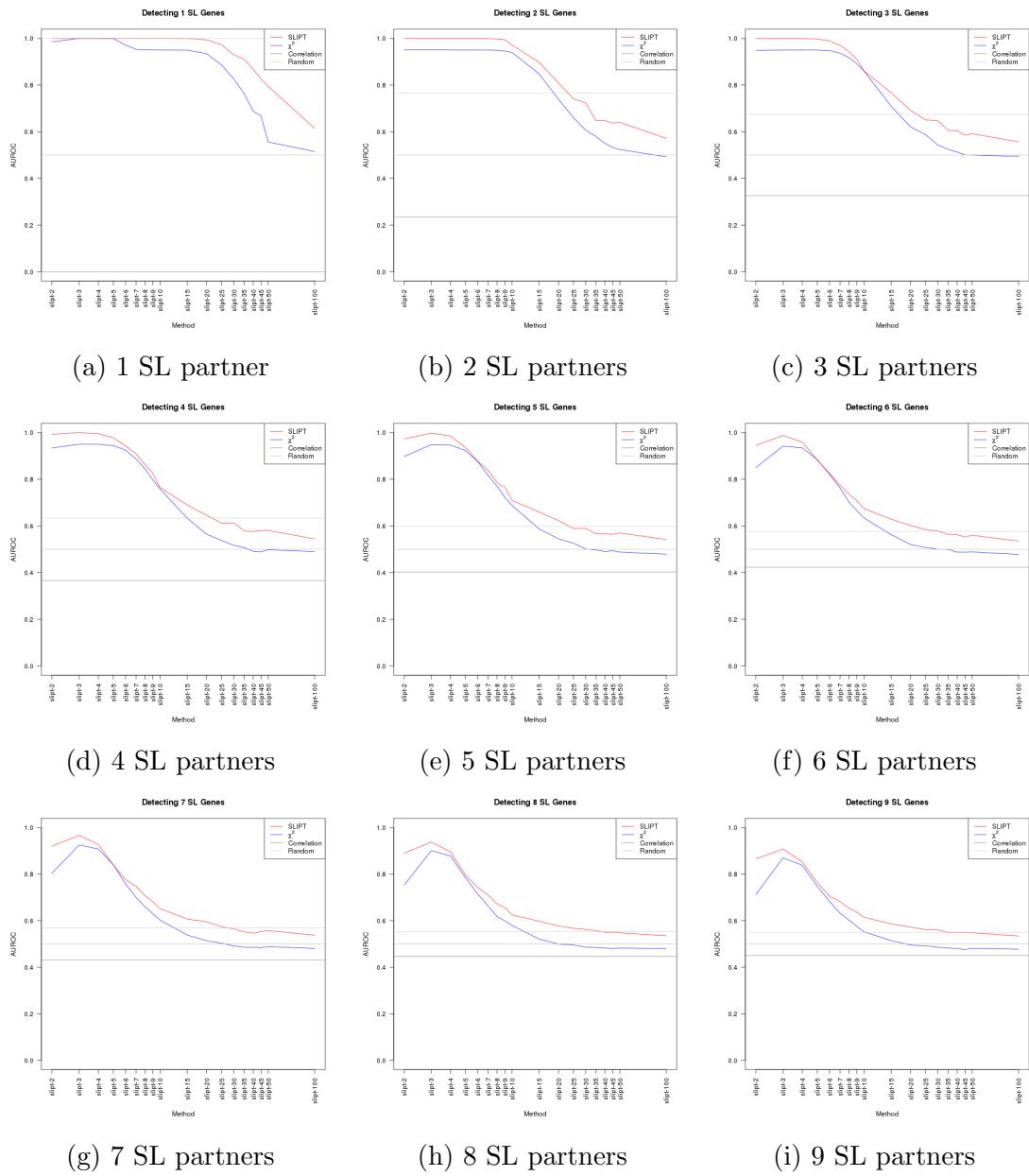


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. (continued on next page)

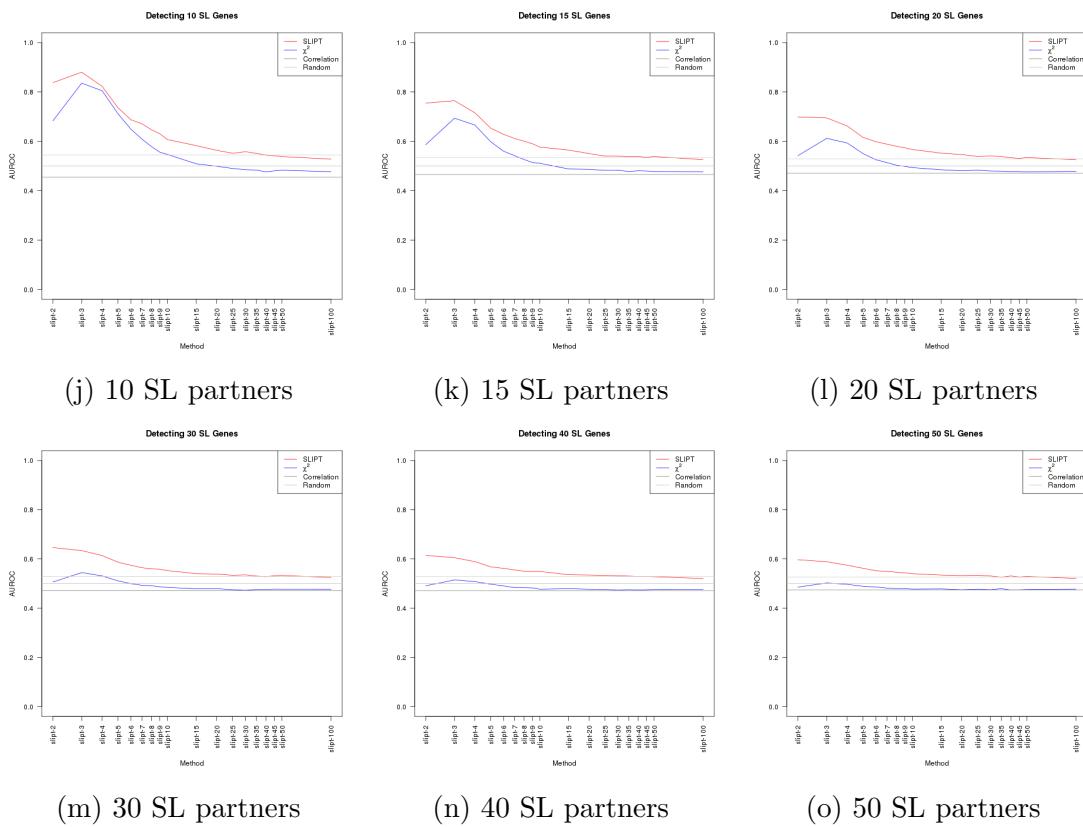


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking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

Simulations on Graph Structures

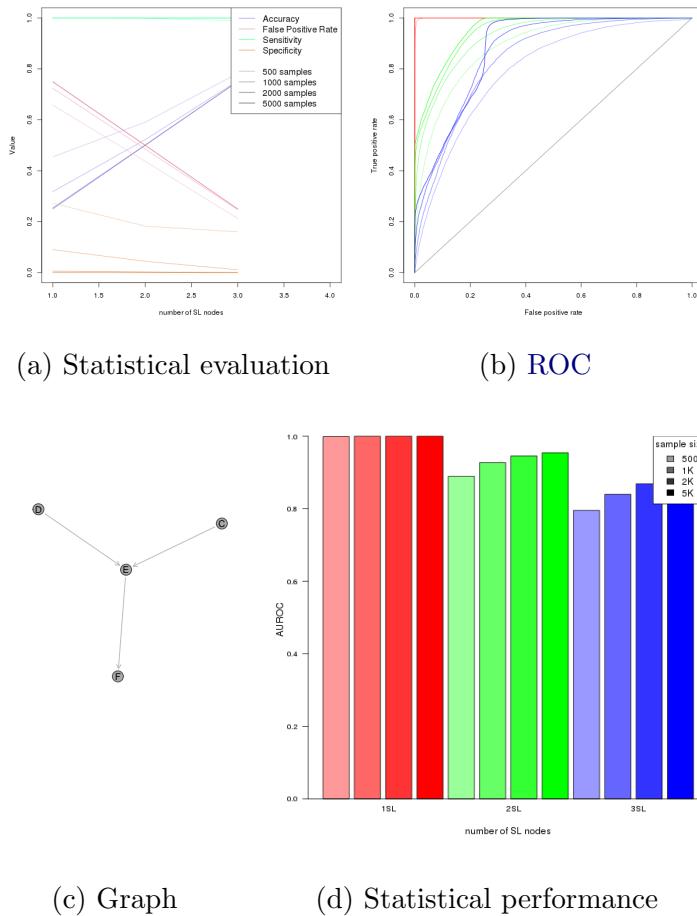


Figure K.1: **Performance of simulations on a simple graph.** Simulation of synthetic lethality was performed using a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.1b match Figure K.1d.

K.0.1 Simulations from Inhibiting Graph Structures

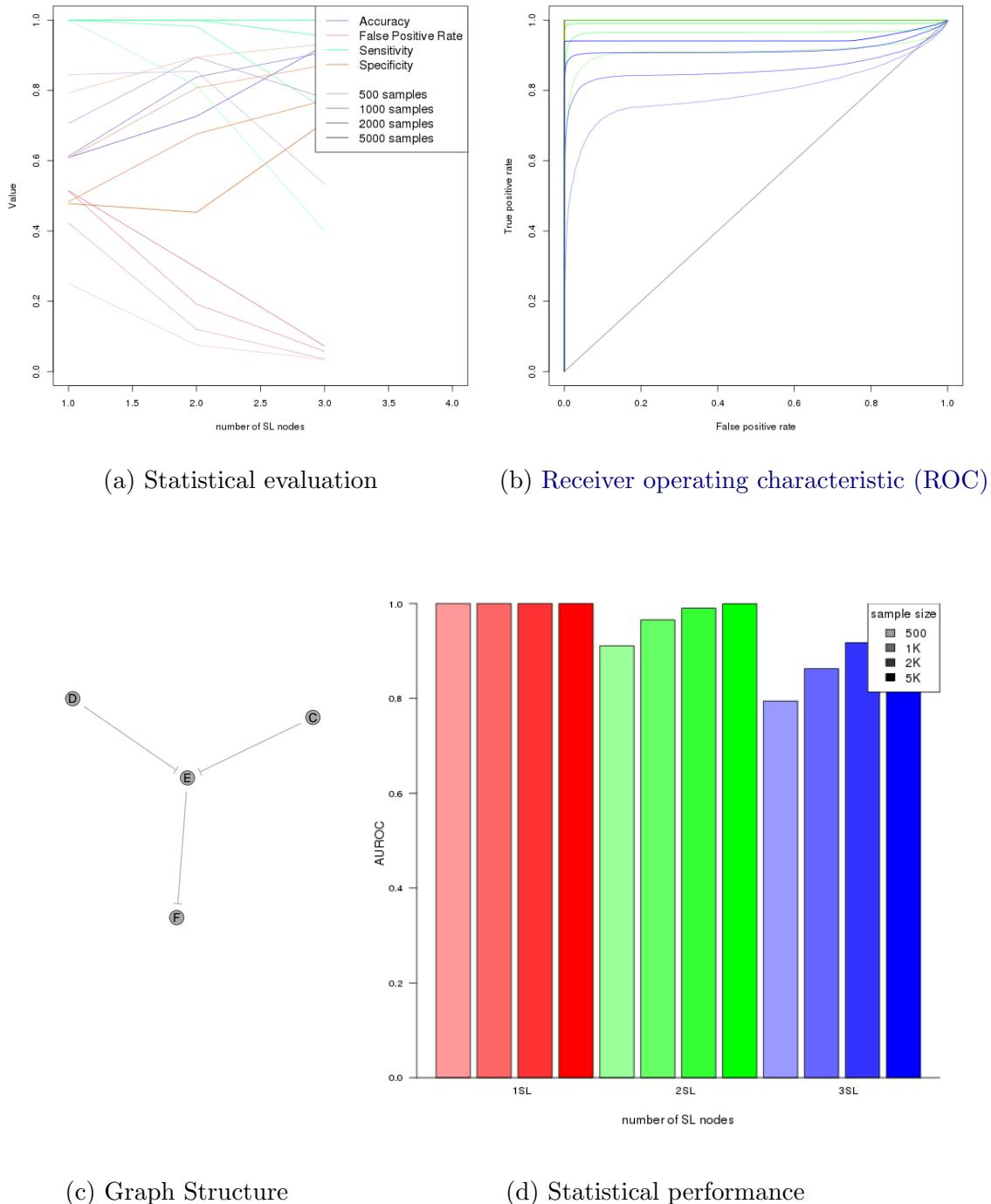


Figure K.2: **Performance of simulations on an inhibiting graph.** Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.

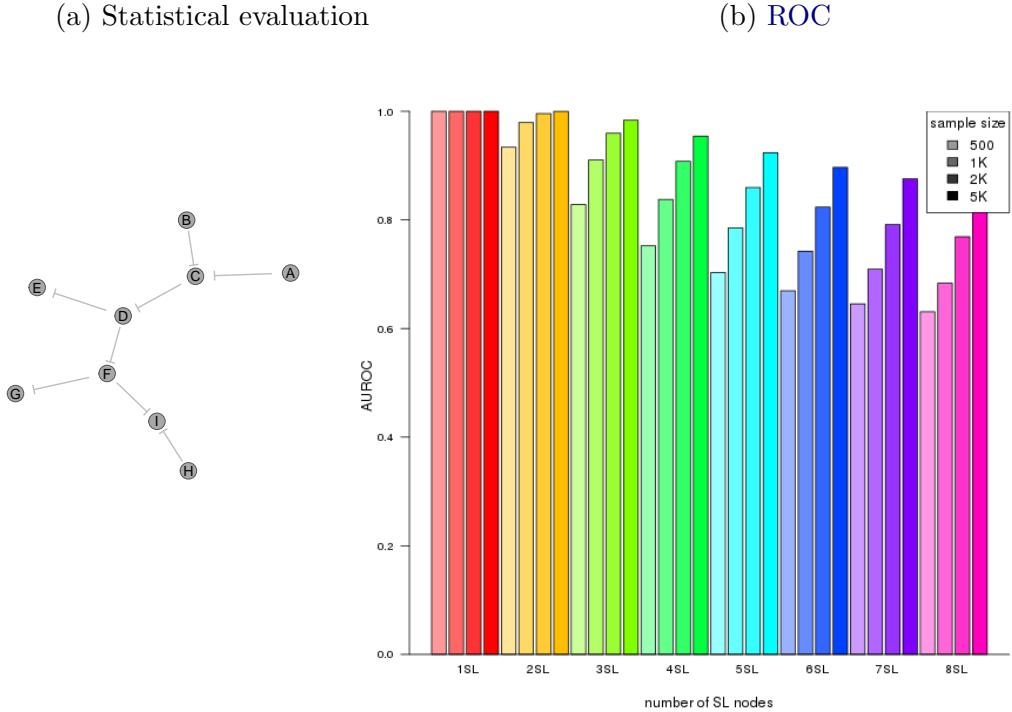
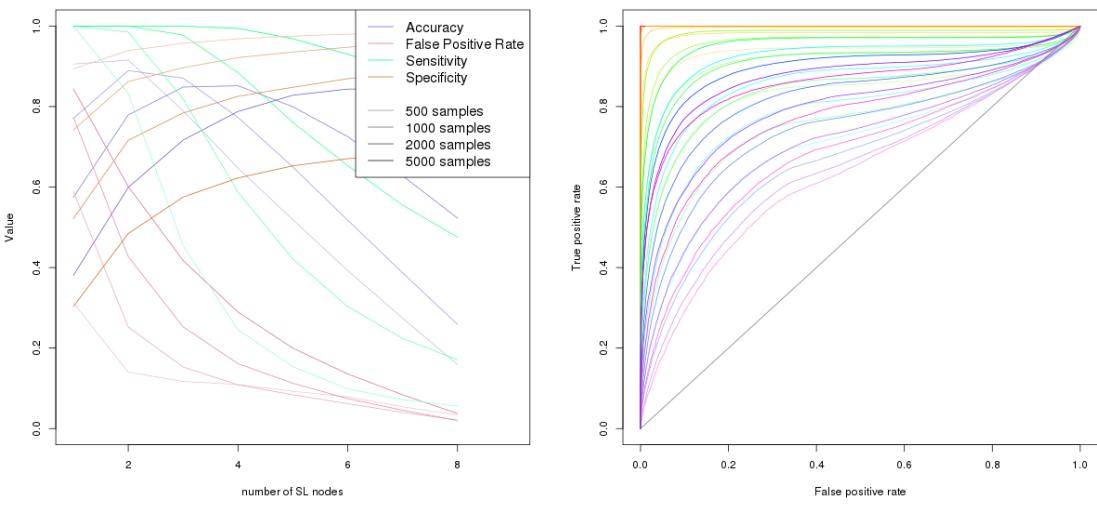
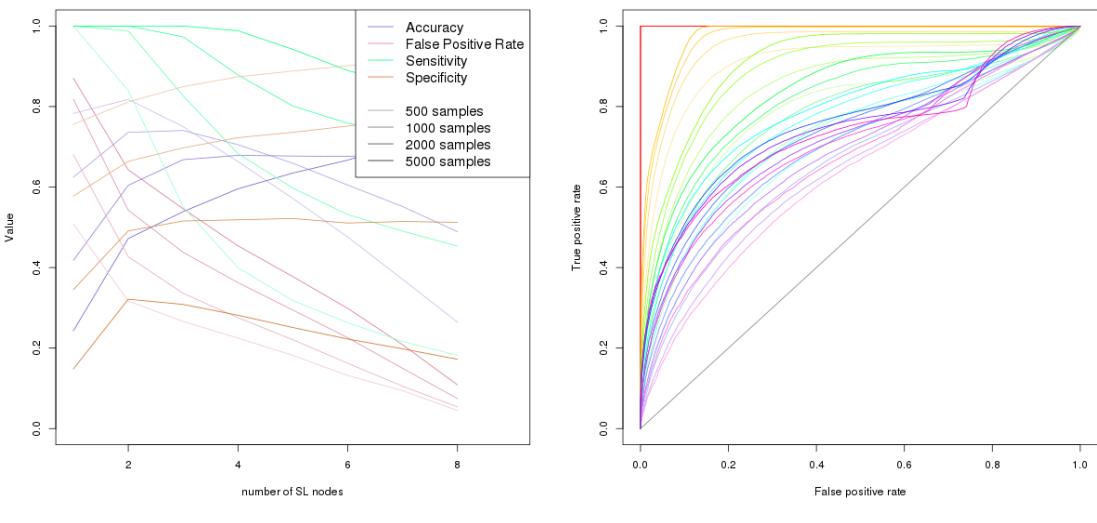
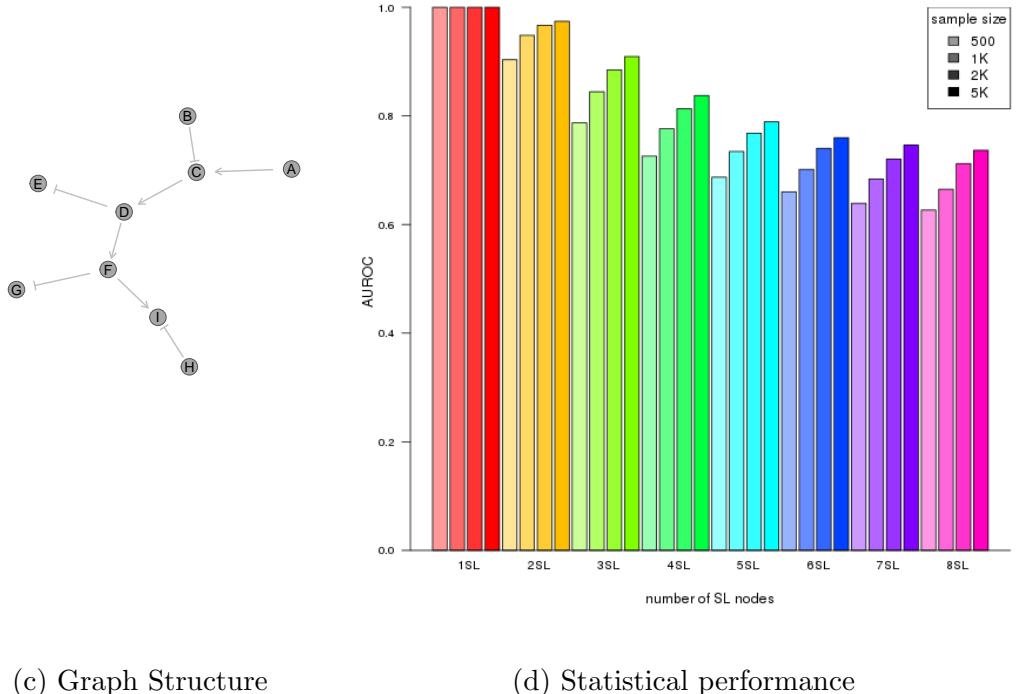


Figure K.3: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a pathway with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.3b match Figure K.3d.



(a) Statistical evaluation

(b) ROC

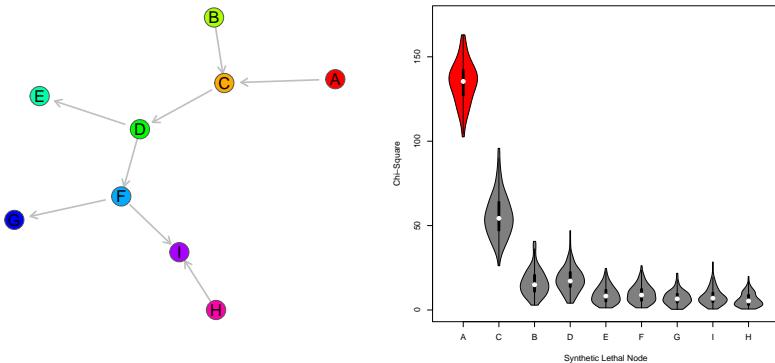


(c) Graph Structure

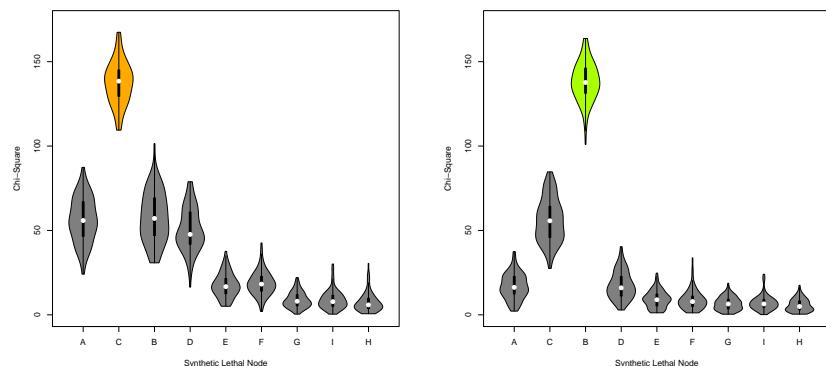
(d) Statistical performance

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

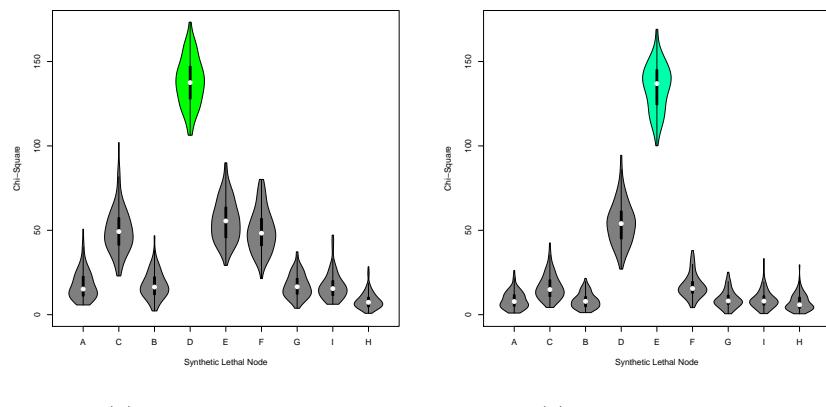
K.1 Simulation across Graph Structures



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

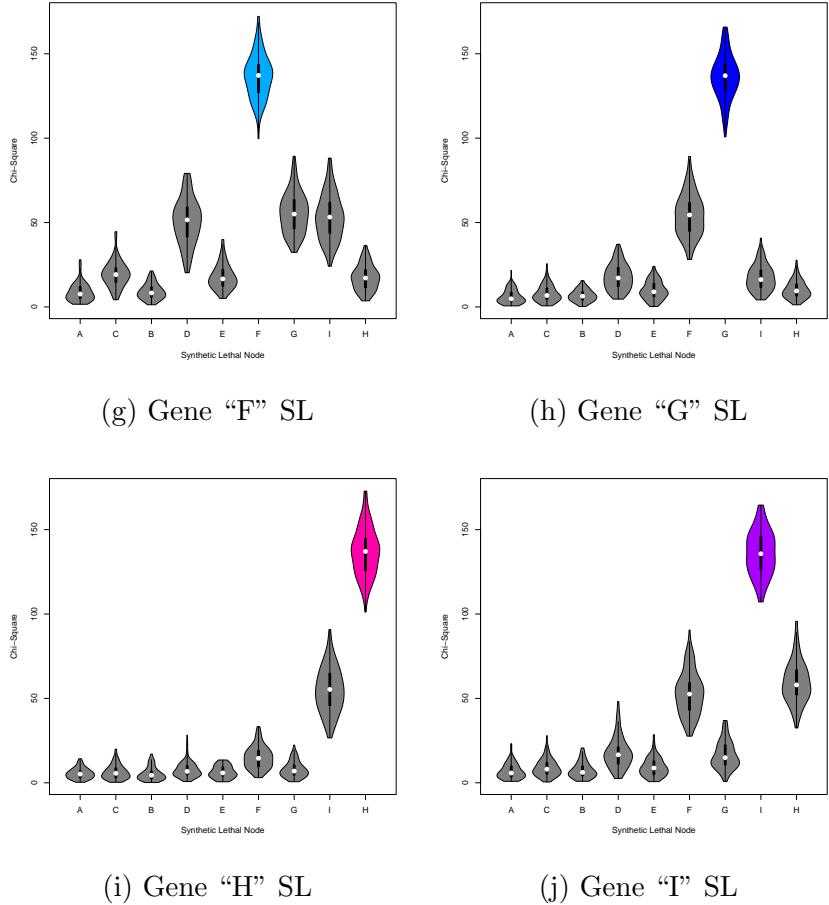
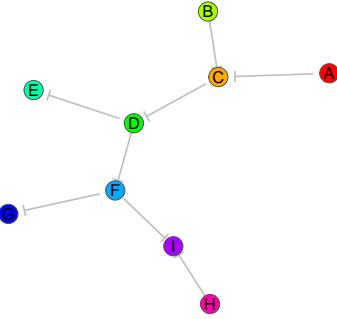
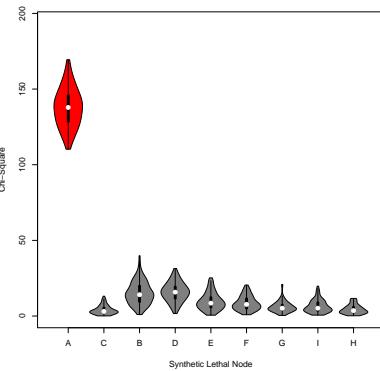


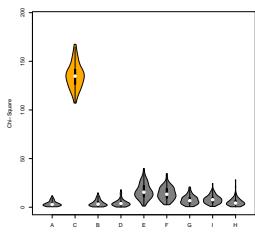
Figure K.5: Detection of synthetic lethality within a graph structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from [SLIPT](#) was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were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



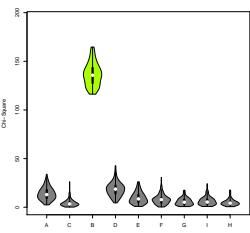
(a) Inhibiting Graph Structure



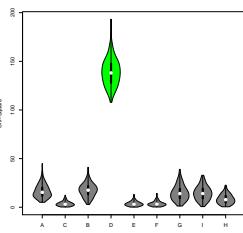
(b) χ^2 distribution for "A" SL



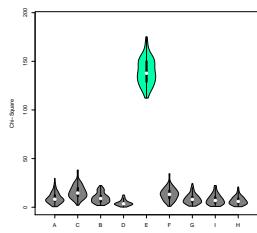
(c) Gene "B" SL



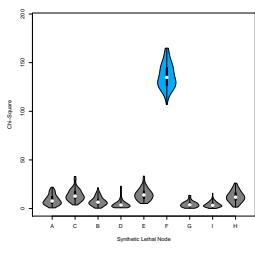
(d) Gene "C" SL



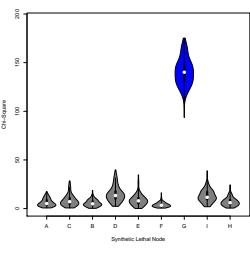
(e) Gene "D" SL



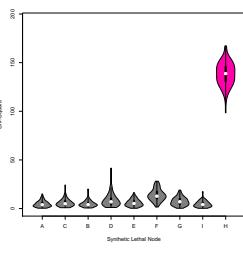
(f) Gene "E" SL



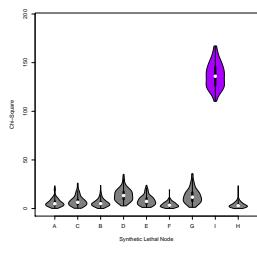
(g) Gene "F" SL



(h) Gene "G" SL

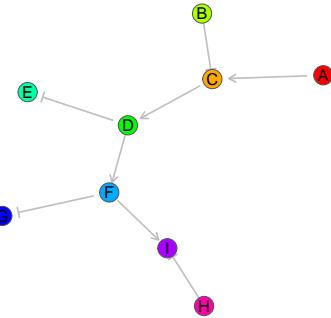


(i) Gene "H" SL

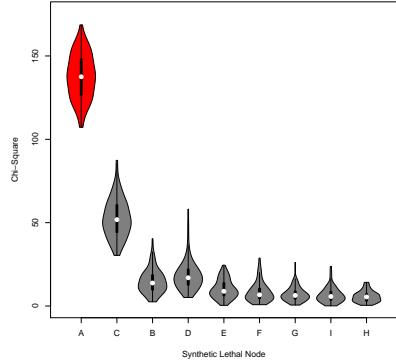


(j) Gene "I" SL

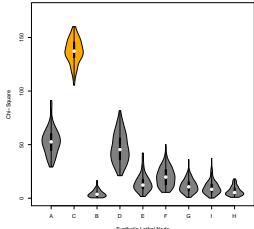
Figure K.6: Detection of synthetic lethality within an inhibiting graph. Each gene was designated to be synthetic lethal separately and the χ^2 value from [SLIPT](#) was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in the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



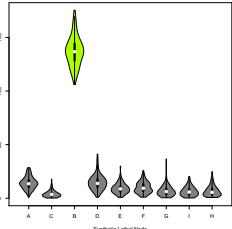
(a) Inhibiting Graph Structure



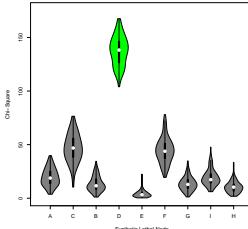
(b) χ^2 distribution for "A" SL



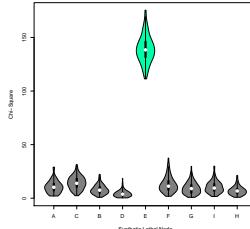
(c) Gene "B" SL



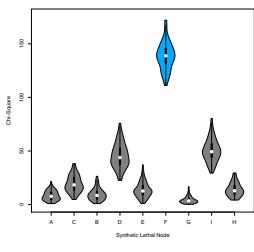
(d) Gene "C" SL



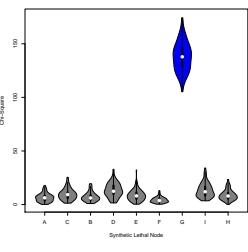
(e) Gene "D" SL



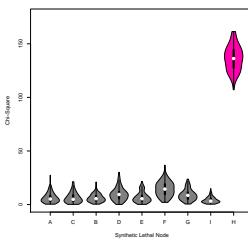
(f) Gene "E" SL



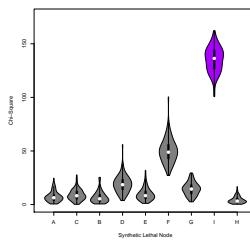
(g) Gene "F" SL



(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.2 Simulations from Complex Graph Structures

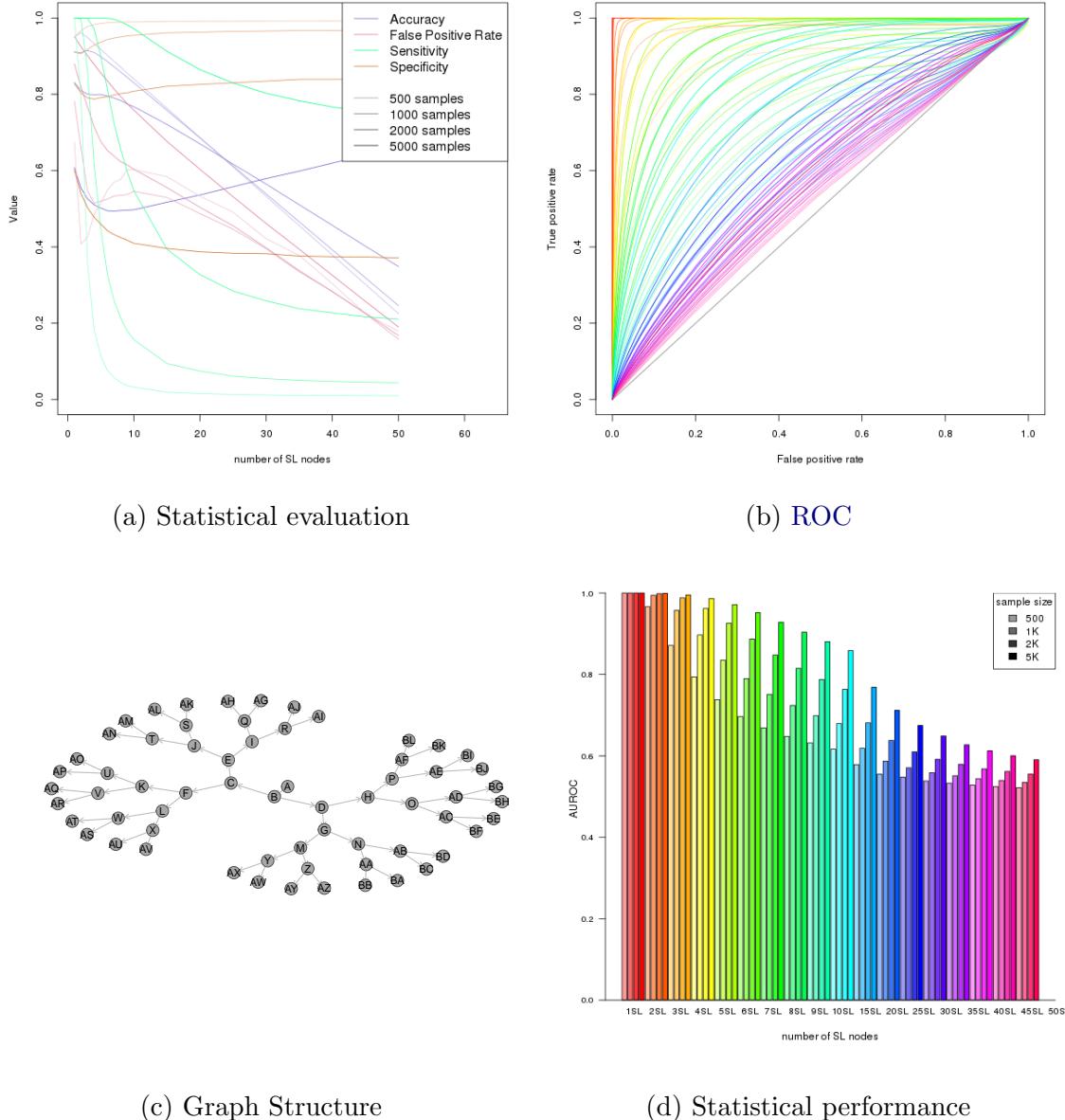
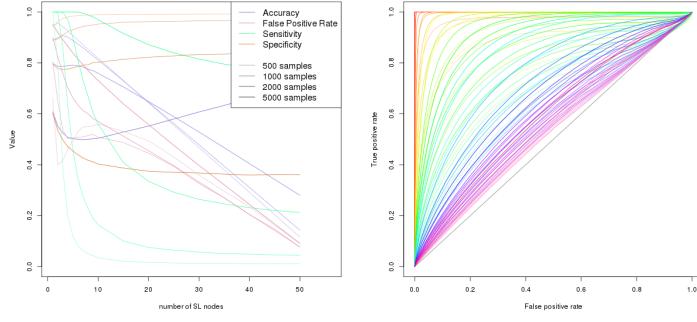
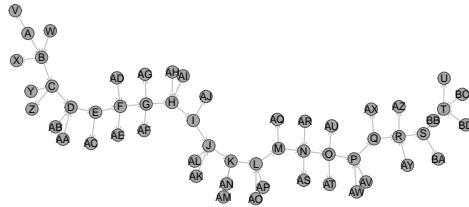


Figure K.8: **Performance of simulations on a branching graph.** Simulation of synthetic lethality used a multivariate normal distribution from a branching graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.

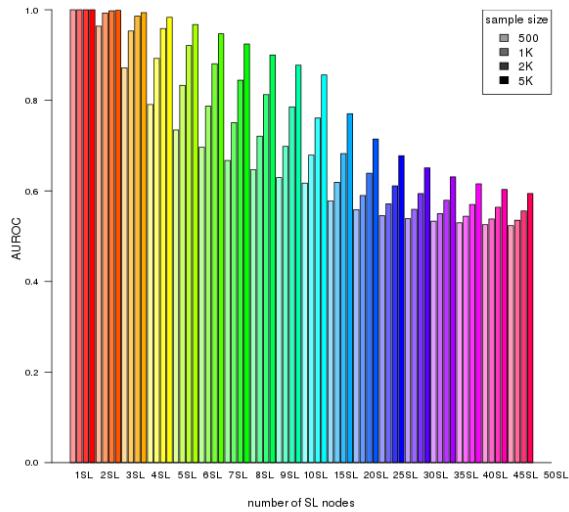


(a) Statistical evaluation

(b) ROC

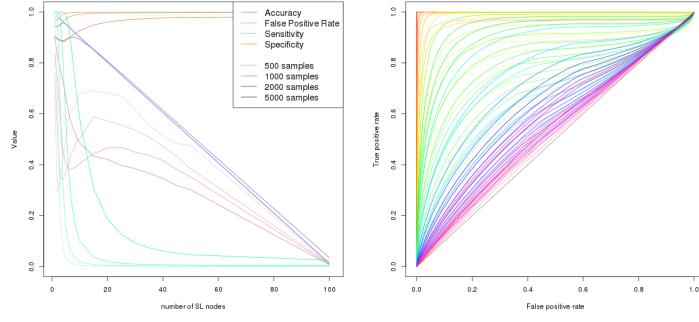


(c) Graph Structure



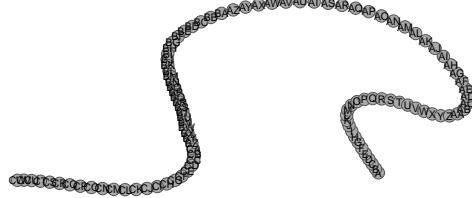
(d) Statistical performance

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

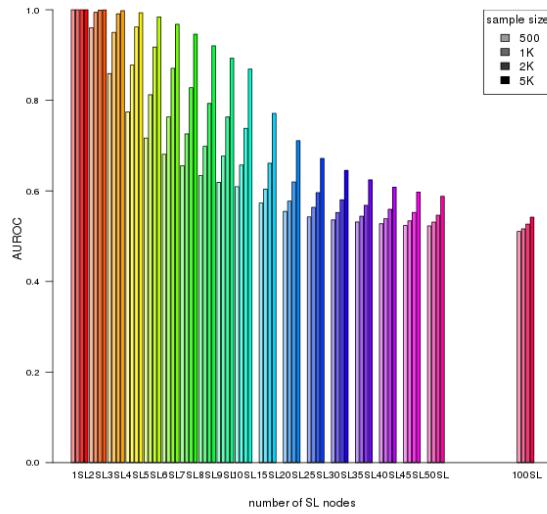


(a) Statistical evaluation

(b) ROC



(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.2.1 Simulations from Complex Inhibiting Graphs

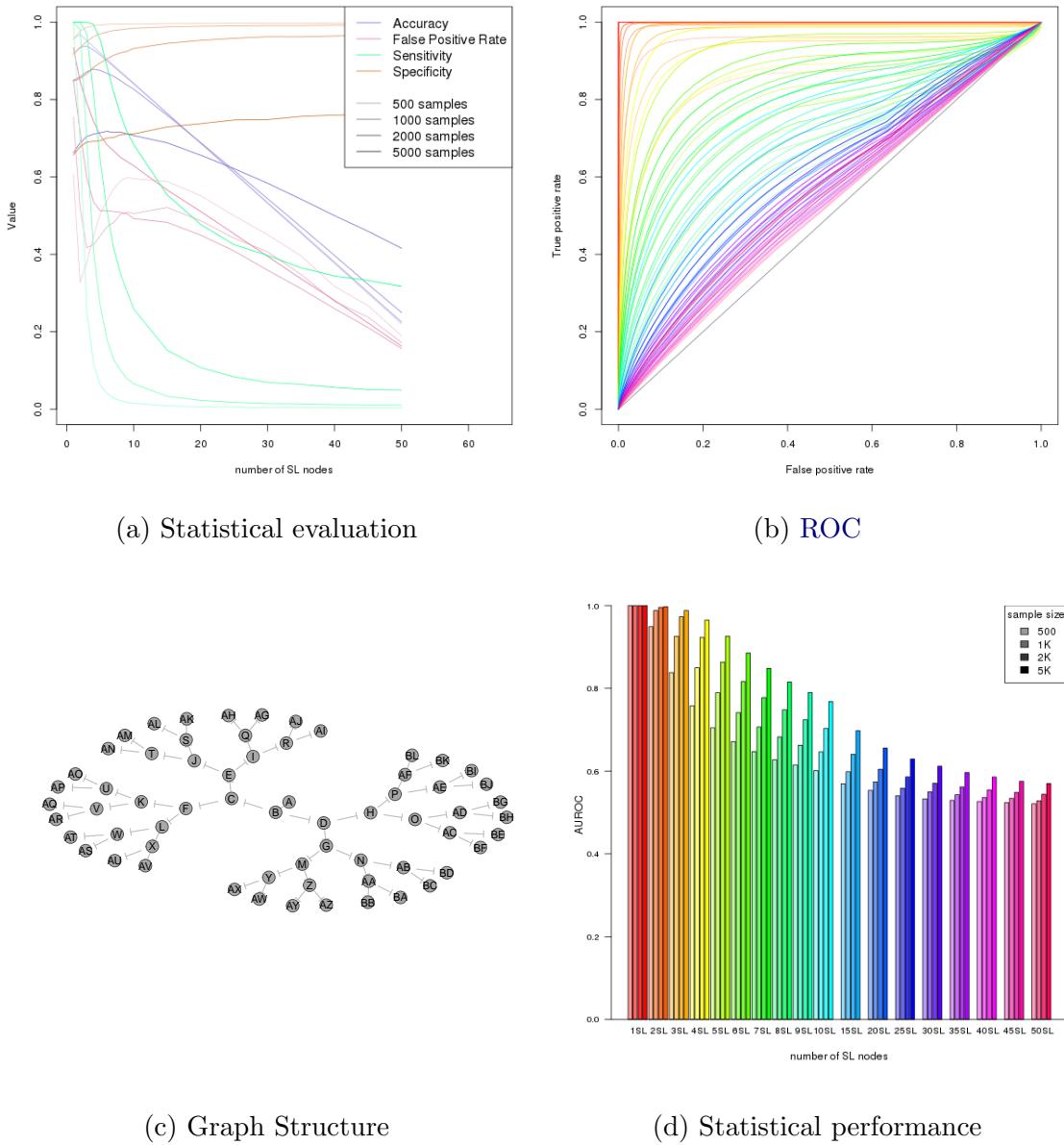
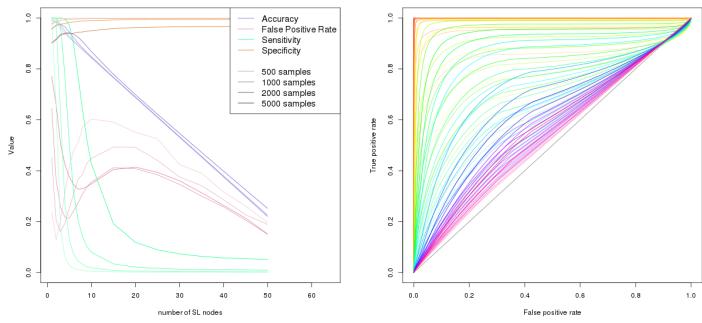
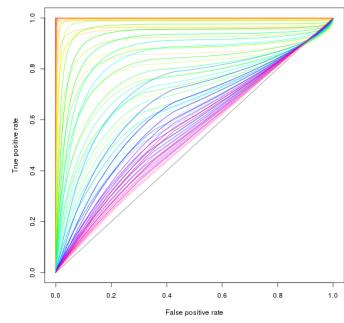


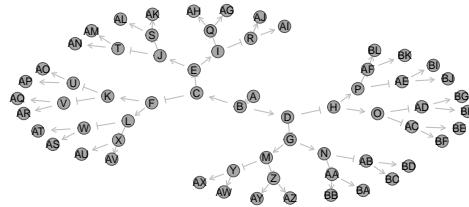
Figure K.11: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.11b match Figure K.11d.



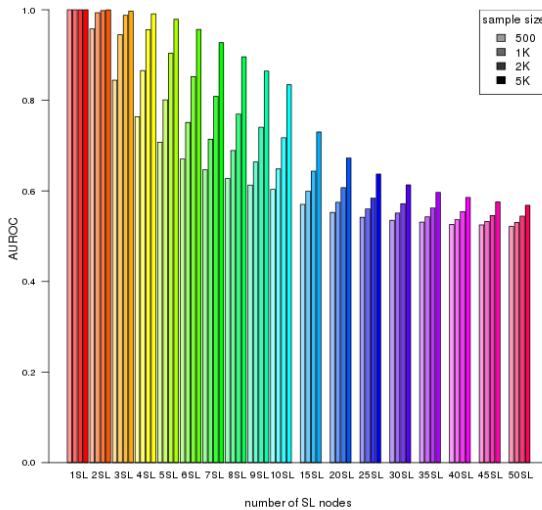
(a) Statistical evaluation



(b) ROC

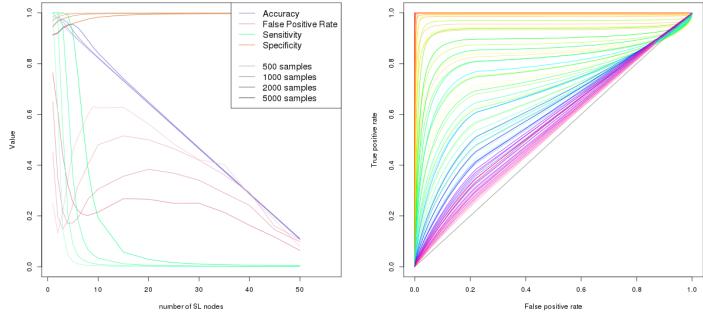


(c) Graph Structure



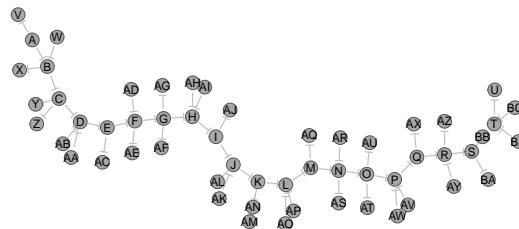
(d) Statistical performance

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

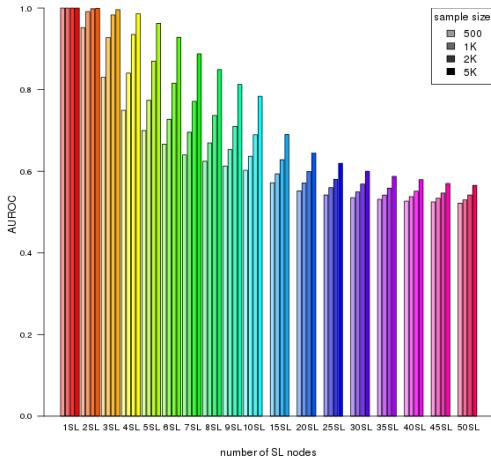


(a) Statistical evaluation

(b) ROC

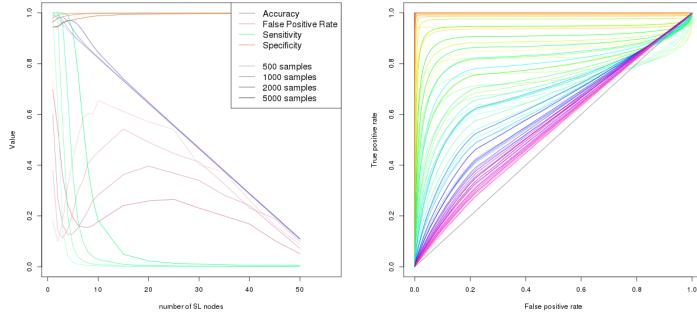


(c) Graph Structure



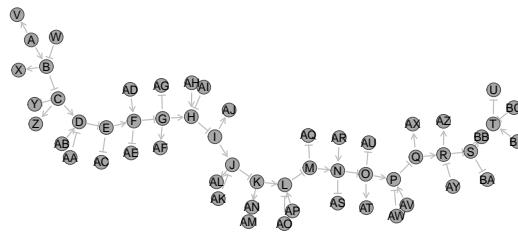
(d) Statistical performance

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

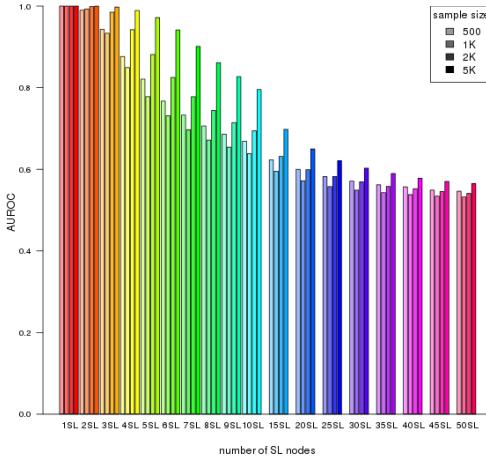


(a) Statistical evaluation

(b) ROC

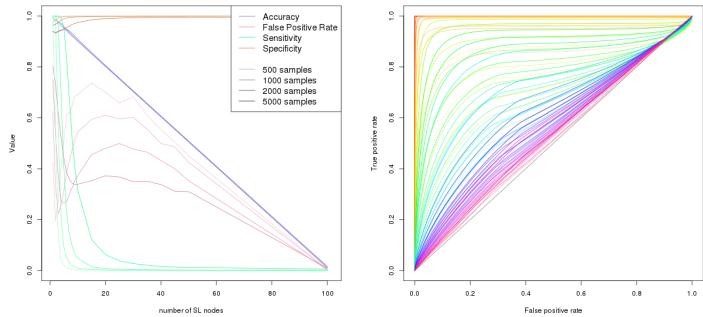


(c) Graph Structure



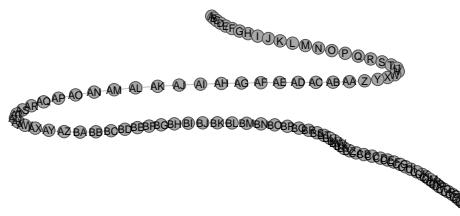
(d) Statistical performance

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

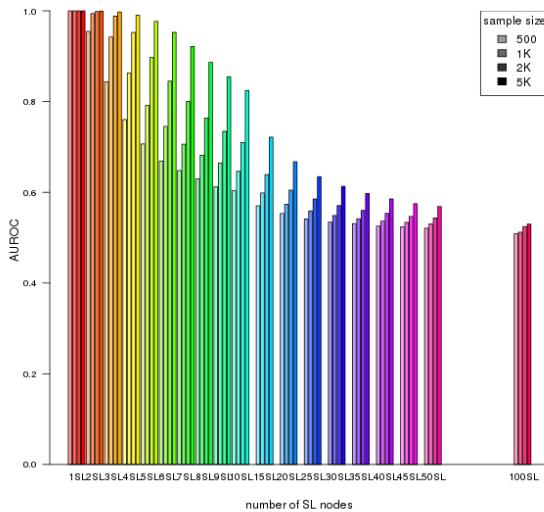


(a) Statistical evaluation

(b) ROC

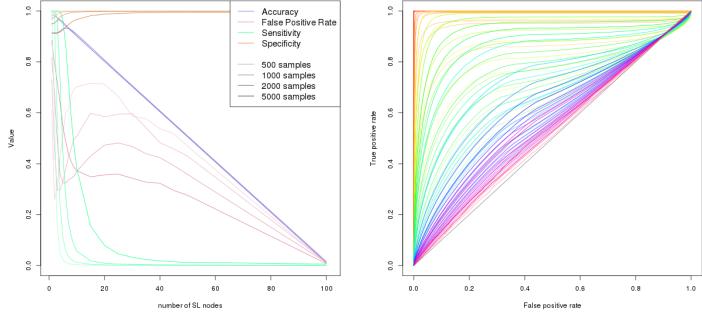


(c) Graph Structure



(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 a large graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.15b match Figure K.15d.

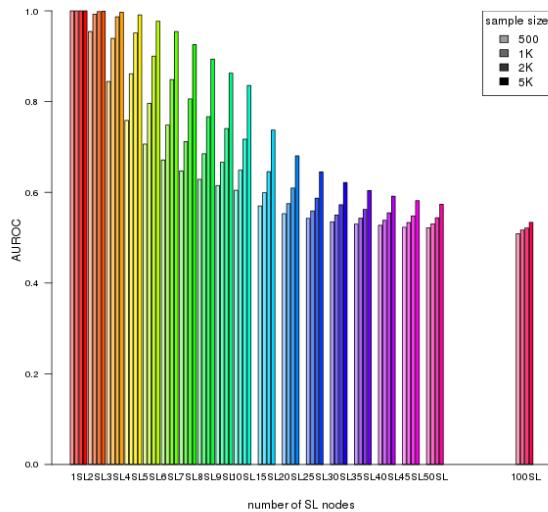


(a) Statistical evaluation

(b) ROC



(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 a large graph with alternating inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.16b match Figure K.16d.

K.3 Simulations from Pathway Graph Structures

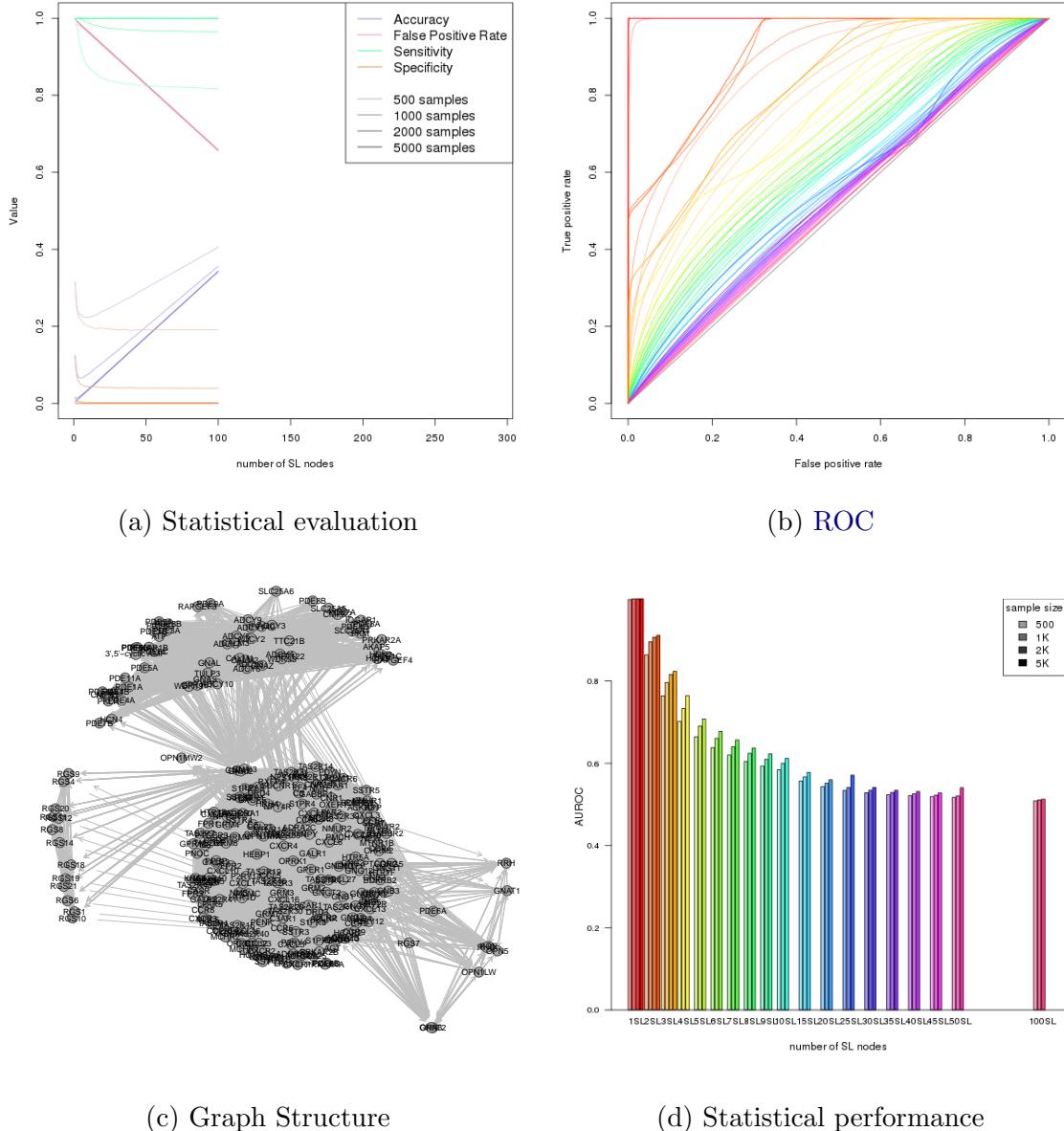


Figure K.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of **SLIPT** was high across parameters for detecting synthetic lethality in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

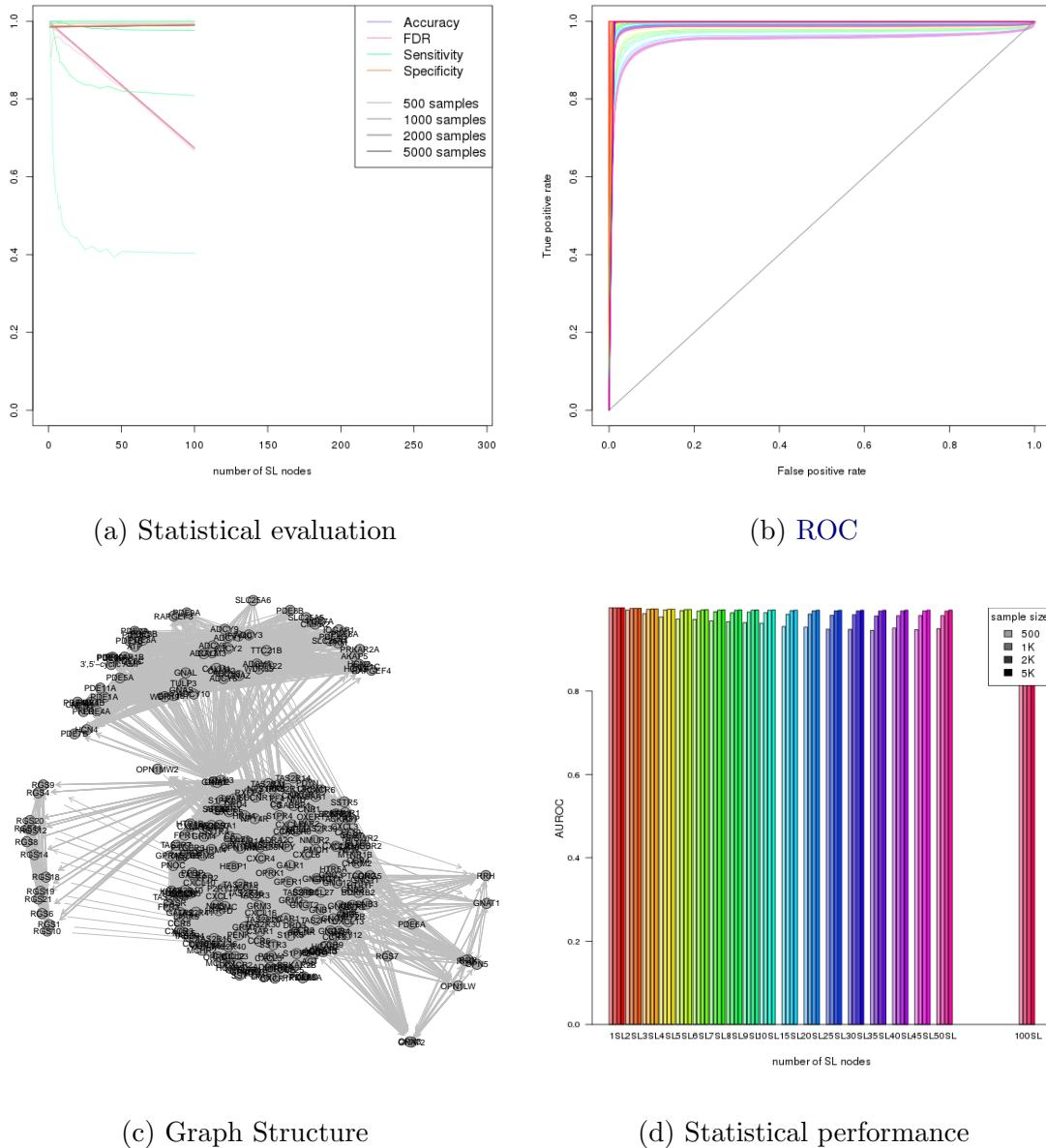


Figure K.18: Performance of simulations including the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome $G_{\alpha i}$ signalling pathway. Performance of **SLIPT** was high across parameters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