

Contents

Glossary	xi
Acronyms	xii
1 Introduction and Literature Review	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer is a Global Health Issue	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Genomics Revolution in Cancer Research	3
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomic Data	5
1.1.3 Genomics Projects	5
1.1.3.1 The Cancer Genome Project	6
1.1.3.2 The Cancer Genome Atlas Project	6
1.1.4 Genomic Cancer Medicine	8
1.1.4.1 Cancer Genes and Driver Mutations	8
1.1.4.2 Precision Cancer Medicine	9
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	9
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	10
1.1.5 Systems and Network Biology	11
1.2 Synthetic Lethal Cancer Medicine	12
1.2.1 Synthetic Lethal Genetic Interactions	12
1.2.2 Synthetic Lethal Concepts in Genetics	14
1.2.3 Synthetic Lethality in Model Systems	14
1.2.3.1 Synthetic Lethal Pathways and Networks	15
1.2.3.2 Evolution of Synthetic Lethality	15
1.2.4 Synthetic Lethality in Cancer	16
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	18
1.2.6 High-throughput Screening for Synthetic Lethality	19
1.2.6.1 Synthetic Lethal Screens	21
1.2.7 Computational Prediction of Synthetic Lethality	22
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	22
1.2.7.2 Comparative Genomics	23
1.2.7.3 Analysis and Modelling of Protein Data	26
1.2.7.4 Differential Gene Expression	28
1.2.7.5 Data Mining and Machine Learning	29

1.2.7.6	Mutual Exclusivity and Bimodality	31
1.2.7.7	Rationale for Further Development	33
1.3	E-cadherin as a Synthetic Lethal Target	33
1.3.1	The <i>CDH1</i> gene and its Biological Functions	33
1.3.2	Hereditary Diffuse Gastric (and Lobular Breast) Cancer	34
1.3.3	Cell Line Models of <i>CDH1</i> Null Mutations	35
1.4	Summary and Research Direction of Thesis	36
1.4.1	Thesis Aims	37
2	Methods and Resources	38
2.1	Bioinformatics Resources for Genomics Research	38
2.1.1	Public Data and Software Packages	38
2.1.1.1	Cancer Genome Atlas Data	39
2.1.1.2	Reactome and Annotation Data	40
2.2	Data Handling	40
2.2.1	Normalisation	40
2.2.2	Sample Triage	40
2.2.3	Metagenes and the Singular Value Decomposition	41
2.2.4	Candidate Triage and Integration with Screen Data	43
2.3	Techniques	43
2.3.1	Statistical Procedures and Tests	44
2.3.2	Gene Set Over-representation Analysis	45
2.3.3	Clustering	45
2.3.4	Heatmap	45
2.3.5	Modelling and Simulations	46
2.3.5.1	Receiver Operating Characteristic Curves	47
2.3.6	Resampling Analysis	47
2.4	Pathway Structure Methods	48
2.4.1	Network and Graph Analysis	48
2.4.2	Sourcing Graph Structure Data	49
2.4.3	Constructing Pathway Subgraphs	49
2.4.4	Network Analysis Metrics	50
2.5	Implementation	51
2.5.1	Computational Resources and Linux Utilities	51
2.5.2	R Language and Packages	52
2.5.3	High Performance and Parallel Computing	55
3	Methods Developed During Thesis	57
3.1	A Synthetic Lethal Detection Methodology	57
3.2	Synthetic Lethal Simulation and Modelling	59
3.2.1	A Model of Synthetic Lethality in Expression Data	60
3.2.2	Simulation Procedure	64
3.3	Detecting Simulated Synthetic Lethal Partners	67
3.3.1	Binomial Simulation of Synthetic Lethality	67
3.3.2	Multivariate Normal Simulation of Synthetic Lethality	69
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	71

3.3.2.2	Specificity with Query-Correlated Pathways	79
3.4	Graph Structure Methods	81
3.4.1	Upstream and Downstream Gene Detection	81
3.4.1.1	Permutation Analysis for Statistical Significance	82
3.4.2	Simulating Gene Expression from Graph Structures	83
3.5	Customised Functions and Packages Developed	87
3.5.1	Synthetic Lethal Interaction Prediction Tool	87
3.5.2	Data Visualisation	88
3.5.3	Extensions to the iGraph Package	89
3.5.3.1	Sampling Simulated Data from Graph Structures	89
3.5.3.2	Plotting Directed Graph Structures	89
3.5.3.3	Computing Information Centrality	91
3.5.3.4	Testing Pathway Structure with Permutation Testing .	91
3.5.3.5	Metapackage to Install iGraph Functions	92
4	Synthetic Lethal Analysis of Gene Expression Data	93
4.1	Synthetic Lethal Genes in Breast Cancer	94
4.1.1	Synthetic Lethal Pathways in Breast Cancer	95
4.1.2	Expression Profiles of Synthetic Lethal Partners	97
4.1.2.1	Subgroup Pathway Analysis	100
4.2	Comparing Synthetic Lethal Gene Candidates	102
4.2.1	Primary siRNA Screen Candidates	102
4.2.2	Comparison with Correlation	102
4.2.3	Comparison with Primary Screen Viability	105
4.2.4	Comparison with Secondary siRNA Screen Validation	107
4.2.5	Comparison to Primary Screen at Pathway Level	108
4.2.5.1	Resampling Genes for Pathway Enrichment	110
4.2.6	Integrating Synthetic Lethal Pathways and Screens	115
4.3	Synthetic Lethal Pathway Metagenes	116
4.4	Replication in Stomach Cancer	118
4.5	Discussion	119
4.5.1	Strengths of the SLIPT Methodology	119
4.5.2	Synthetic Lethal Pathways for E-cadherin	120
4.5.3	Replication and Validation	122
4.5.3.1	Integration with siRNA Screening	122
4.5.3.2	Replication across Tissues	123
4.6	Summary	123
5	Synthetic Lethal Pathway Structure	125
5.1	Synthetic Lethal Genes in Reactome Pathways	125
5.1.1	The PI3K/AKT Pathway	126
5.1.2	The Extracellular Matrix	128
5.1.3	G Protein Coupled Receptors	131
5.1.4	Gene Regulation and Translation	131
5.2	Network Analysis of Synthetic Lethal Genes	133
5.2.1	Gene Connectivity and Vertex Degree	134

5.2.2	Gene Importance and Centrality	135
5.2.2.1	Information Centrality	135
5.2.2.2	PageRank Centrality	137
5.3	Relationships between Synthetic Lethal Genes	138
5.3.1	Detecting Upstream or Downstream Synthetic Lethality	139
5.3.2	Resampling for Synthetic Lethal Pathway Structure	141
5.4	Discussion	143
5.5	Summary	145
6	Simulation and Modelling of Synthetic Lethal Pathways	147
6.1	Synthetic Lethal Detection Methods	148
6.1.1	Performance of SLIPT and χ^2 across Quantiles	149
6.1.1.1	Correlated Query Genes affects Specificity	152
6.1.2	Alternative Synthetic Lethal Detection Strategies	154
6.1.2.1	Correlation for Synthetic Lethal Detection	155
6.1.2.2	Testing for Bimodality with BiSEp	156
6.2	Simulations with Graph Structures	157
6.2.1	Performance over Graph Structures	158
6.2.1.1	Simple Graph Structures	158
6.2.1.2	Constructed Graph Structures	161
6.2.2	Performance with Inhibitions	163
6.2.3	Synthetic Lethality across Graph Structures	169
6.2.4	Performance within a Large Simulated Datasets	172
6.3	Simulations in More Complex Graph Structures	176
6.3.1	Simulations over Pathway-based Graphs	177
6.3.2	Pathway Structures in a Large Simulated Datasets	180
6.4	Discussion	183
6.4.1	Simulation Procedure	183
6.4.2	Comparing Methods with Simulated Data	184
6.4.3	Design and Performance of SLIPT	185
6.4.4	Simulations from Graph Structures	187
6.5	Summary	188
7	Discussion	189
7.1	Synthetic Lethality and <i>CDH1</i> Biology	189
7.1.1	Established Functions of <i>CDH1</i>	190
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	190
7.2	Significance	191
7.2.1	Synthetic Lethality in the Genomic Era	191
7.2.2	Clinical Interventions based on Synthetic Lethality	193
7.3	Future Directions	194
7.4	Conclusions	196
Bibliography		198

A Sample Quality	222
A.1 Sample Correlation	222
A.2 Replicate Samples in TCGA Breast Cancer Data	224
B Software Used for Thesis	228
C Mutation Analysis in Breast Cancer	237
C.1 Synthetic Lethal Genes and Pathways	237
C.2 Synthetic Lethal Expression Profiles	238
C.3 Comparison to Primary Screen	241
C.3.1 Resampling Analysis	243
C.4 Compare SLIPT genes	245
D Metagene Analysis	247
D.1 Pathway Signature Expression	247
D.2 Synthetic Lethal Reactome Metagenes	251
E Intrinsic Subtyping	252
F Stomach Expression Analysis	254
F.1 Synthetic Lethal Genes and Pathways	254
F.2 Comparison to Primary Screen	258
F.2.1 Resampling Analysis	260
F.3 Metagene Analysis	262
G Synthetic Lethal Genes in Pathways	263
H Network Analysis for Mutation SLIPT	270
I Pathway Structure for Mutation SLIPT	273
J Performance of SLIPT and χ^2	275
J.1 Correlated Query Genes affects Specificity	281
K Simulations on Graph Structures	287
K.0.1 Simulations from Inhibiting Graph Structures	288
K.1 Simulation across Graph Structures	291
K.2 Simulations from Complex Graph Structures	295
K.2.1 Simulations from Complex Inhibiting Graphs	298
K.3 Simulations from Pathway Graph Structures	304

List of Figures

1.1	Synthetic genetic interactions	13
1.2	Synthetic lethality in cancer	17
2.1	Read count density	42
2.2	Read count sample mean	42
3.1	Framework for synthetic lethal prediction	58
3.2	Synthetic lethal prediction adapted for mutation	59
3.3	A model of synthetic lethal gene expression	61
3.4	Modelling synthetic lethal gene expression	62
3.5	Synthetic lethality with multiple genes	63
3.6	Simulating gene function	65
3.7	Simulating synthetic lethal gene function	65
3.8	Simulating synthetic lethal gene expression	66
3.9	Performance of binomial simulations	68
3.10	Comparison of statistical performance	68
3.11	Performance of multivariate normal simulations	70
3.12	Simulating expression with correlated gene blocks	72
3.13	Simulating expression with correlated gene blocks	73
3.14	Synthetic lethal prediction across simulations	75
3.15	Performance with correlations	76
3.16	Comparison of statistical performance with correlation structure	77
3.17	Performance with query correlations	78
3.18	Statistical evaluation of directional criteria	79
3.19	Performance of directional criteria	80
3.20	Simulated graph structures	84
3.21	Simulating expression from a graph structure	85
3.22	Simulating expression from graph structure with inhibitions	86
3.23	Demonstration of violin plots with custom features	90
3.24	Demonstration of annotated heatmap	90
3.25	Simulating graph structures	91
4.1	Synthetic lethal expression profiles of analysed samples	98
4.2	Comparison of SLIPT with siRNA	103
4.3	Comparison of SLIPT and siRNA genes with correlation	103
4.4	Comparison of SLIPT and siRNA genes with correlation	105
4.5	Comparison of SLIPT and siRNA genes with screen viability	106

4.6	Comparison of SLIPT genes with siRNA screen viability	106
4.7	Resampled intersection of SLIPT and siRNA candidate genes	111
5.1	Synthetic lethality in the PI3K cascade	127
5.2	Synthetic lethality in Elastic Fibre Formation	129
5.3	Synthetic lethality in Fibrin Clot Formation	130
5.4	Synthetic lethality in the GPCRs	132
5.5	Synthetic lethality and vertex degree	134
5.6	Synthetic lethality and centrality	136
5.7	Synthetic lethality and PageRank	138
5.8	Structure of synthetic lethality resampling	140
6.1	Performance of χ^2 and SLIPT across quantiles	150
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	151
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	152
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	153
6.5	Performance of negative correlation and SLIPT	156
6.6	Simple graph structures	159
6.7	Performance of simulations on a simple graph	160
6.8	Performance of simulations is similar in simple graphs	161
6.9	Performance of simulations on a pathway	162
6.10	Performance of simulations on a simple graph with inhibition	164
6.11	Performance is higher on a simple inhibiting graph	166
6.12	Performance of simulations on a constructed graph with inhibition . .	167
6.13	Performance is affected by inhibition in graphs	168
6.14	Detection of synthetic lethality within a graph structure	170
6.15	Performance of simulations including a simple graph	173
6.16	Performance on a simple graph improves with more genes	174
6.17	Performance on an inhibiting graph improves with more genes	176
6.18	Performance of simulations on the PI3K cascade	179
6.19	Performance of simulations including the PI3K cascade	181
6.20	Performance on pathways improves with more genes	182
A.1	Correlation profiles of removed samples	222
A.2	Correlation analysis and sample removal	223
A.3	Replicate excluded samples	224
A.4	Replicate samples with all remaining	225
A.5	Replicate samples with some excluded	226
C.1	Synthetic lethal expression profiles of analysed samples	239
C.2	Comparison of mtSLIPT to short interfering RNA (siRNA)	241
C.3	Compare mtSLIPT and siRNA genes with correlation	245
C.4	Compare mtSLIPT and siRNA genes with correlation	245
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	246
D.1	Pathway metagene expression profiles	249

D.2	Expression profiles for estrogen receptor related genes	250
F.1	Synthetic lethal expression profiles of stomach samples	256
F.2	Comparison of SLIPT in stomach to siRNA	258
G.1	Synthetic lethality in the PI3K/AKT pathway	263
G.2	Synthetic lethality in the PI3K/AKT pathway in cancer	264
G.3	Synthetic lethality in the Extracellular Matrix	265
G.4	Synthetic lethality in the GPCR Downstream	266
G.5	Synthetic lethality in the Translation Elongation	267
G.6	Synthetic lethality in the Nonsense-mediated Decay	268
G.7	Synthetic lethality in the 3' UTR	269
H.1	Synthetic lethality and vertex degree	270
H.2	Synthetic lethality and centrality	271
H.3	Synthetic lethality and PageRank	271
I.1	Structure of synthetic lethality resampling	273
J.1	Performance of χ^2 and SLIPT across quantiles	275
J.2	Performance of χ^2 and SLIPT across quantiles	277
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	279
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation	281
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation	283
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	285
K.1	Performance of simulations on a simple graph	287
K.2	Performance of simulations on an inhibiting graph	288
K.3	Performance of simulations on a constructed graph with inhibition	289
K.4	Performance of simulations on a constructed graph with inhibition	290
K.5	Detection of synthetic lethality within a graph structure	291
K.6	Detection of synthetic lethality within an inhibiting graph	293
K.7	Detection of synthetic lethality within an inhibiting graph	294
K.8	Performance of simulations on a branching graph	295
K.9	Performance of simulations on a complex graph	296
K.10	Performance of simulations on a large graph	297
K.11	Performance of simulations on a branching graph with inhibition	298
K.12	Performance of simulations on a branching graph with inhibition	299
K.13	Performance of simulations on a complex graph with inhibition	300
K.14	Performance of simulations on a complex graph with inhibition	301
K.15	Performance of simulations on a large constructed graph with inhibition	302
K.16	Performance of simulations on a large constructed graph with inhibition	303
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	304
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	305

List of Tables

1.1	Methods for predicting genetic interactions	23
1.2	Methods for predicting synthetic lethality in cancer	23
1.3	Methods used by Wu <i>et al.</i> (2014)	25
2.1	Excluded samples by batch and clinical characteristics.	41
2.2	Computers used during thesis	51
2.3	Linux utilities and applications used during thesis	52
2.4	R installations used during thesis	53
2.5	R Packages used during thesis	53
2.6	R packages developed during thesis	55
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	95
4.2	Pathways for <i>CDH1</i> partners from SLIPT	96
4.3	Pathways for clusters of <i>CDH1</i> partners from SLIPT	101
4.4	ANOVA for synthetic lethality and correlation with <i>CDH1</i>	104
4.5	Comparison of Synthetic Lethal Interaction Prediction Tool (SLIPT) genes against secondary siRNA screen	108
4.6	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	109
4.7	Pathways for <i>CDH1</i> partners from SLIPT	112
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen .	113
4.9	Examples of candidate metagenes synthetic lethal for <i>CDH1</i> from SLIPT	117
5.1	ANOVA for synthetic lethality and vertex degree	135
5.2	ANOVA for synthetic lethality and information centrality	136
5.3	ANOVA for synthetic lethality and PageRank centrality	137
5.4	Resampling for pathway structure of synthetic lethal detection methods	142
B.1	Complete list of R packages used during this thesis	228
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT . . .	237
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	238
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT	240
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA	242
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	243
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	244
D.1	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT . .	251

E.1	Comparison of intrinsic subtypes	252
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	254
F.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	255
F.3	Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT	257
F.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	259
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	260
F.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA	261
F.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer	262
H.1	ANOVA for synthetic lethality and vertex degree	272
H.2	ANOVA for synthetic lethality and information centrality	272
H.3	ANOVA for synthetic lethality and PageRank centrality	272
I.1	Resampling for pathway structure of synthetic lethal detection methods	274

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

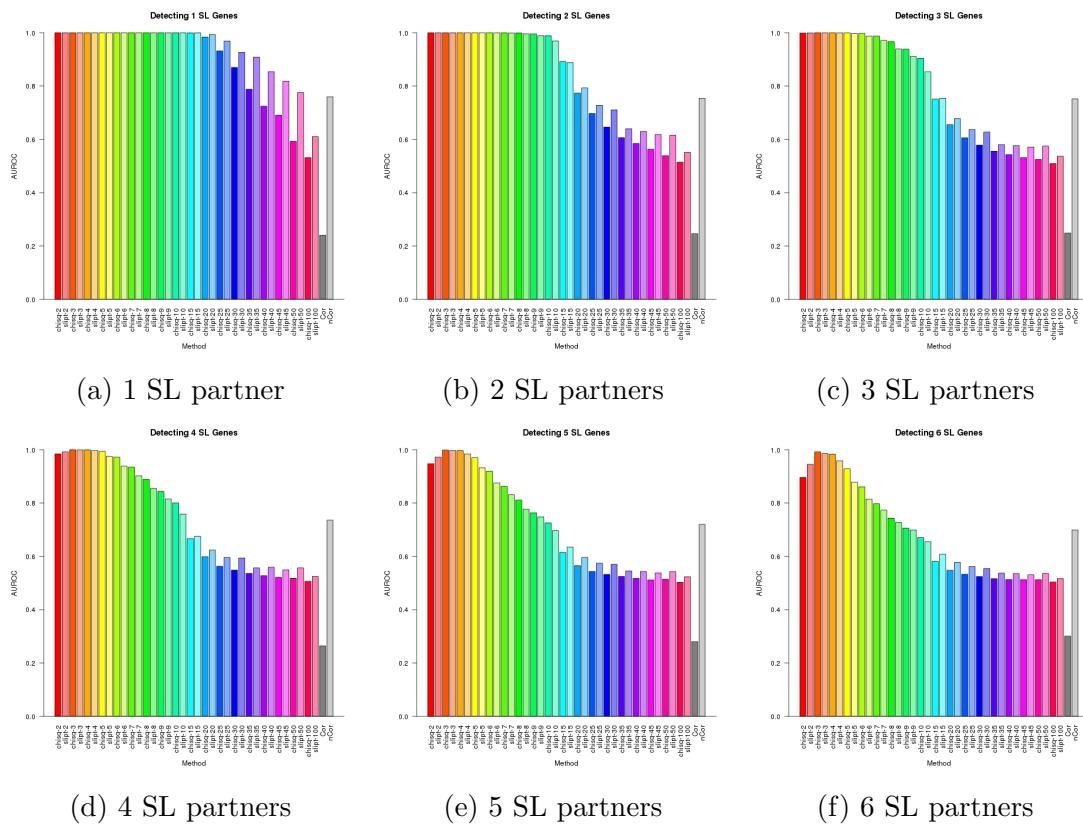


Figure J.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

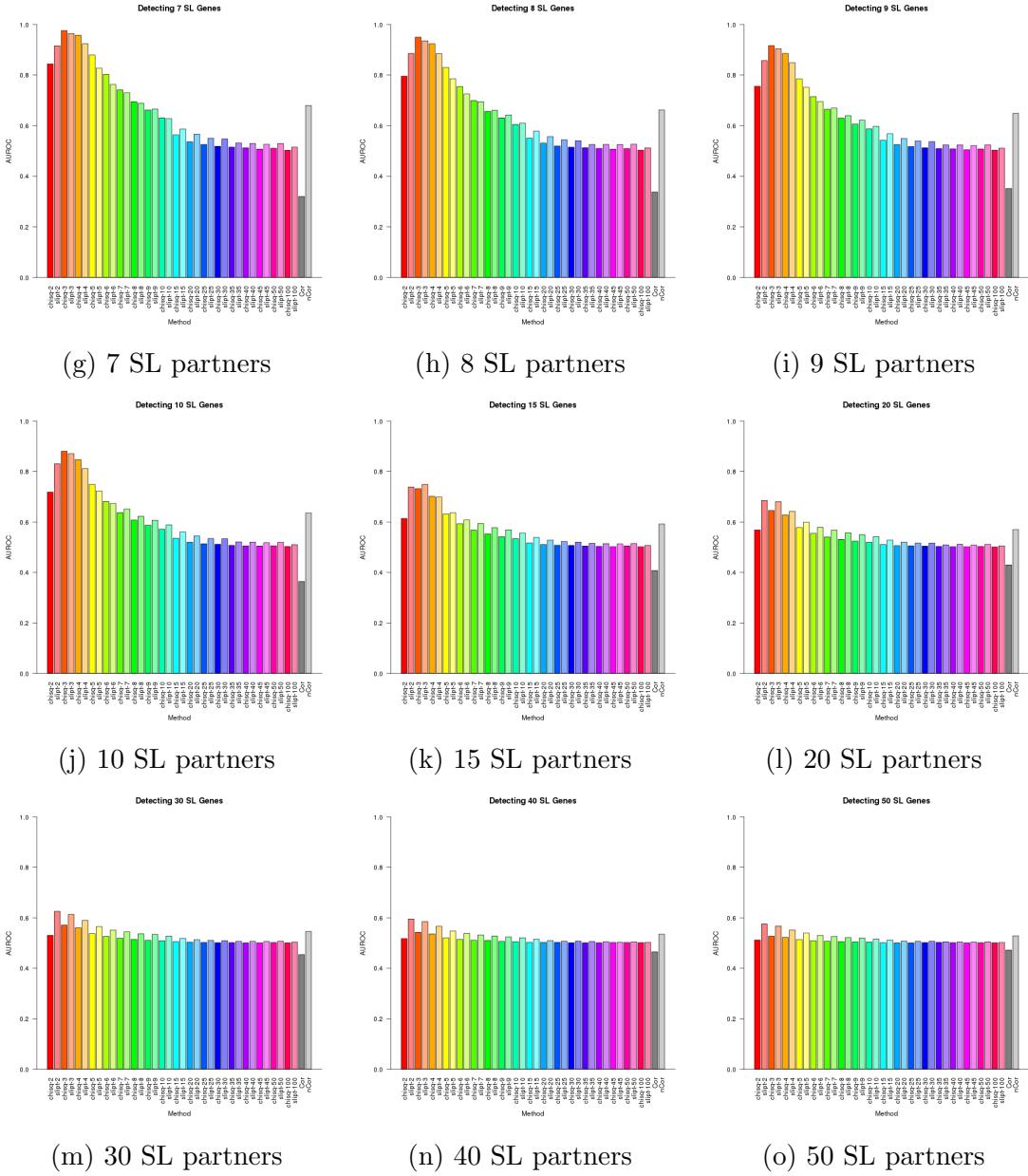


Figure J.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles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

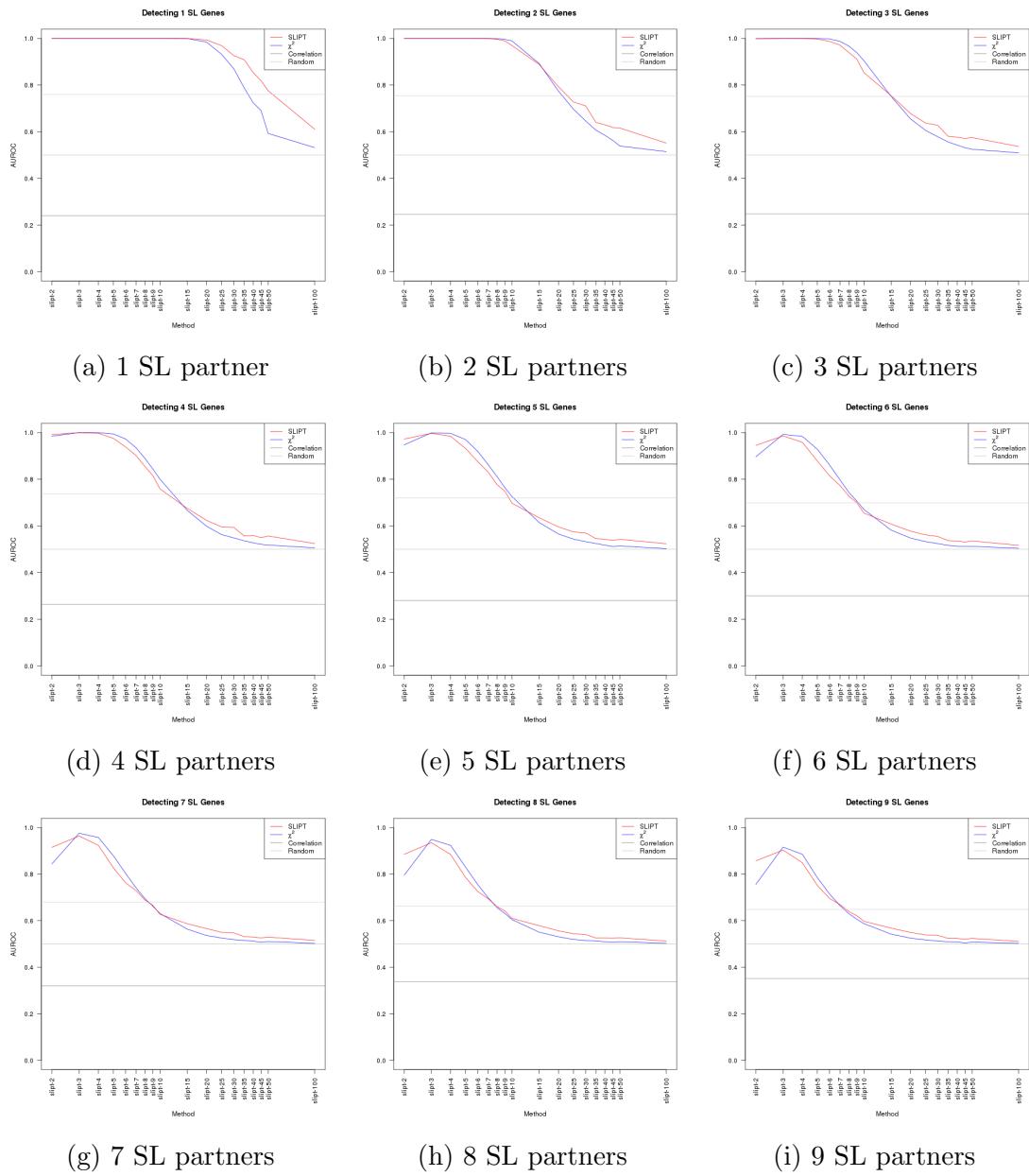


Figure J.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

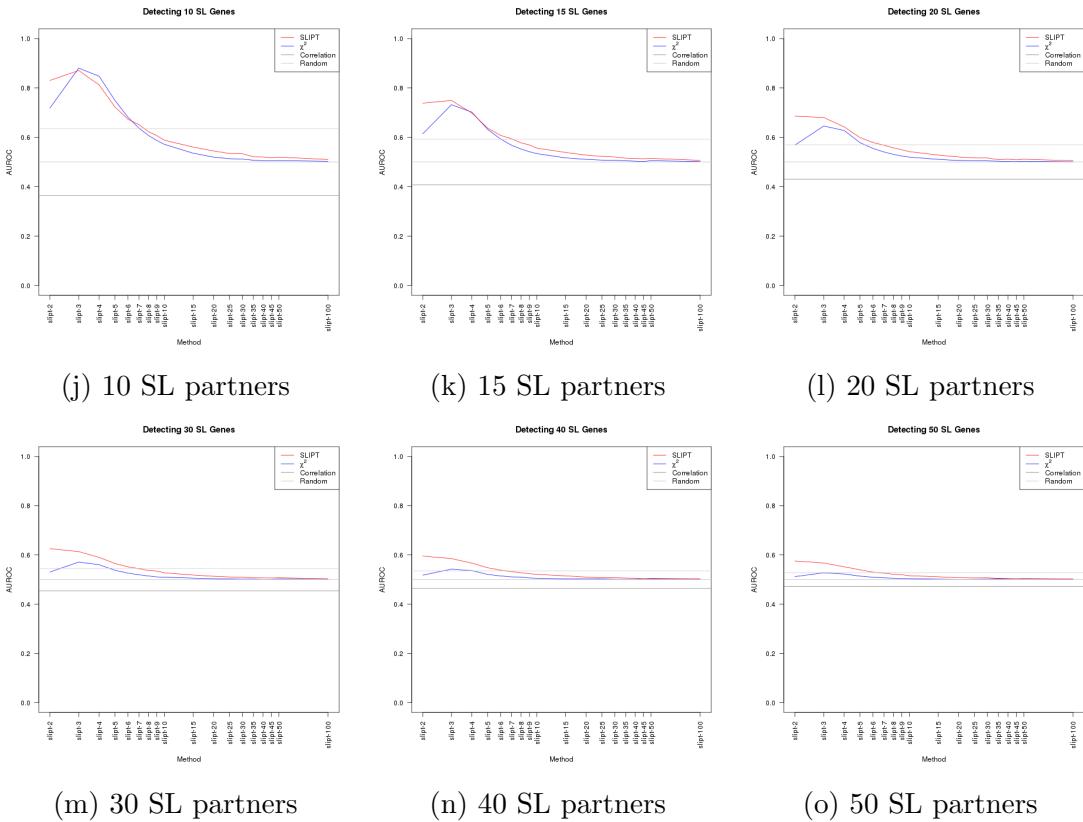


Figure J.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles and converging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

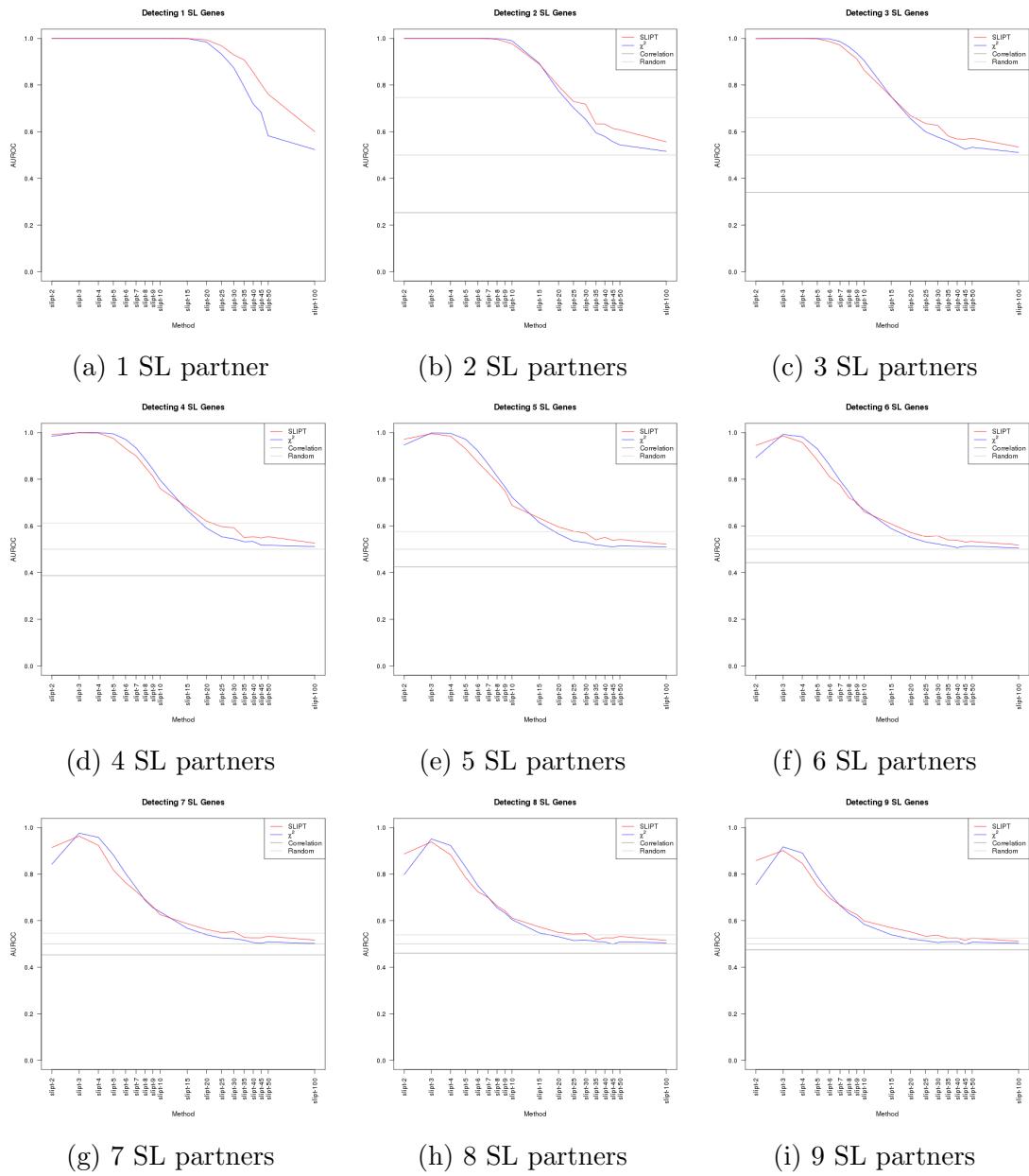


Figure J.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

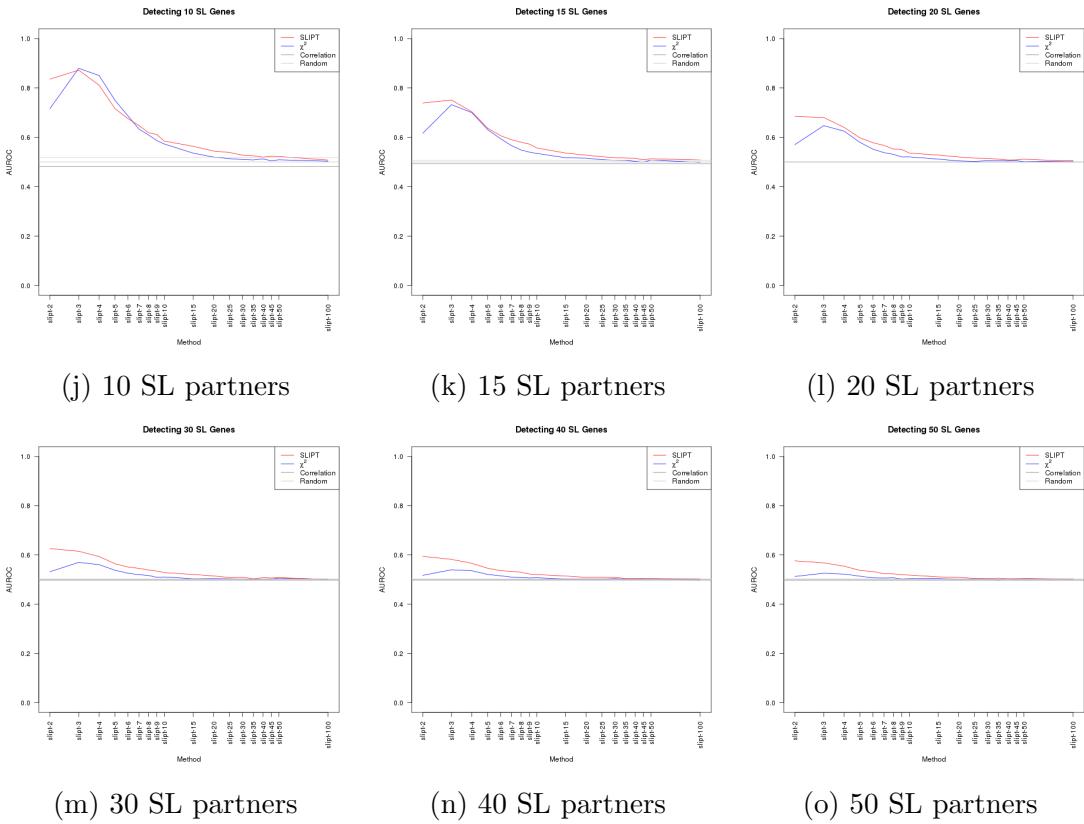


Figure J.3: Performance of χ^2 and SLIPT across quantiles with more genes.
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles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

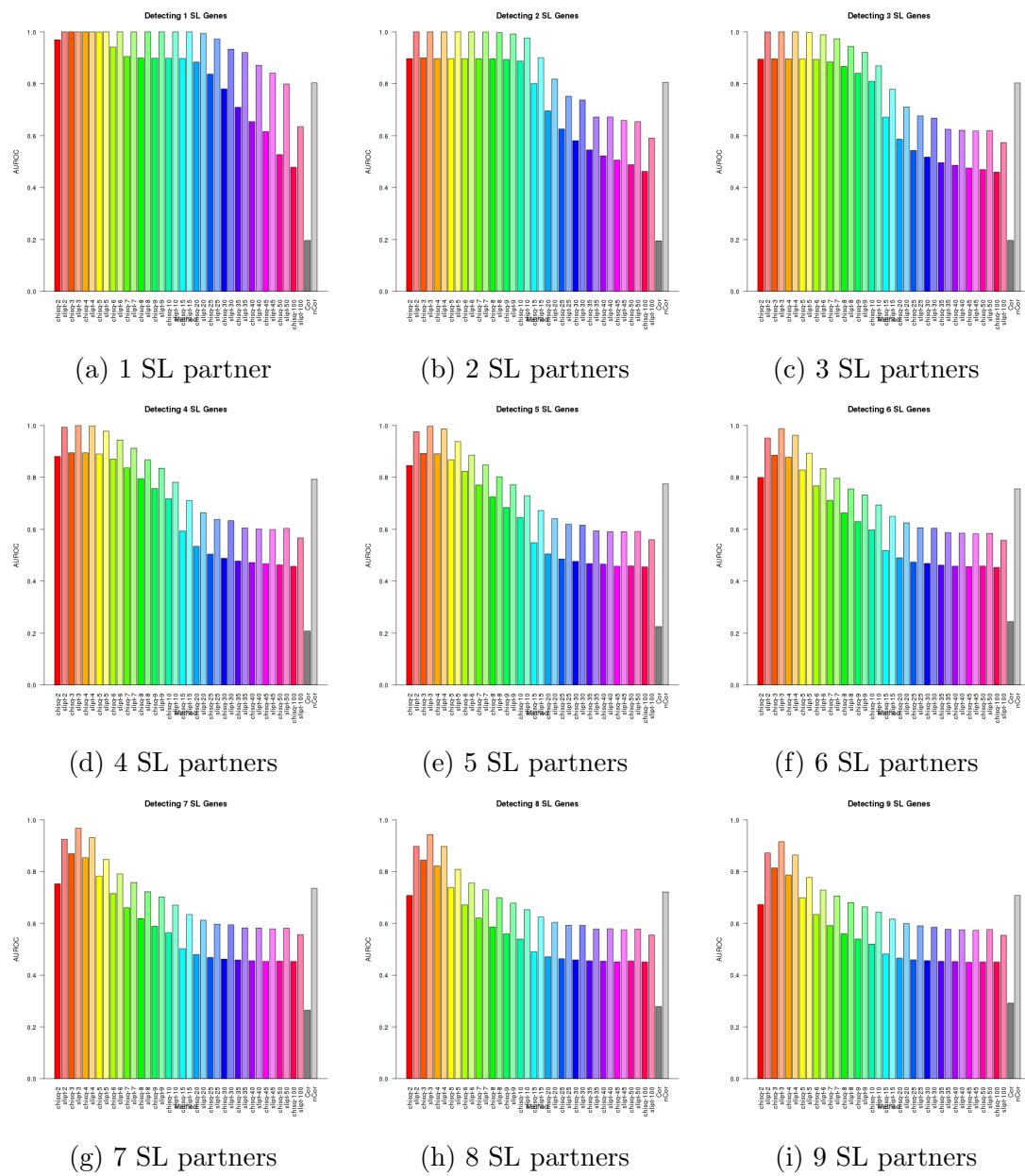


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. (continued on next page)

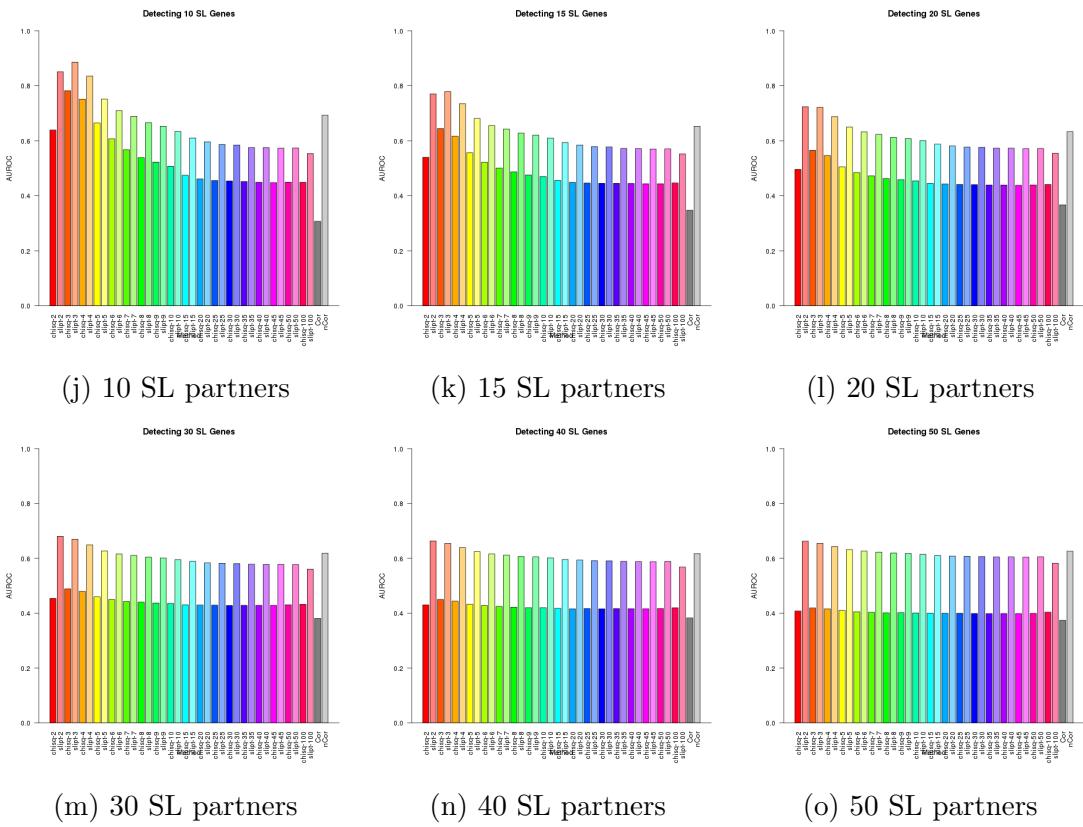


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplots have the same hue for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 performed similarly, peaking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

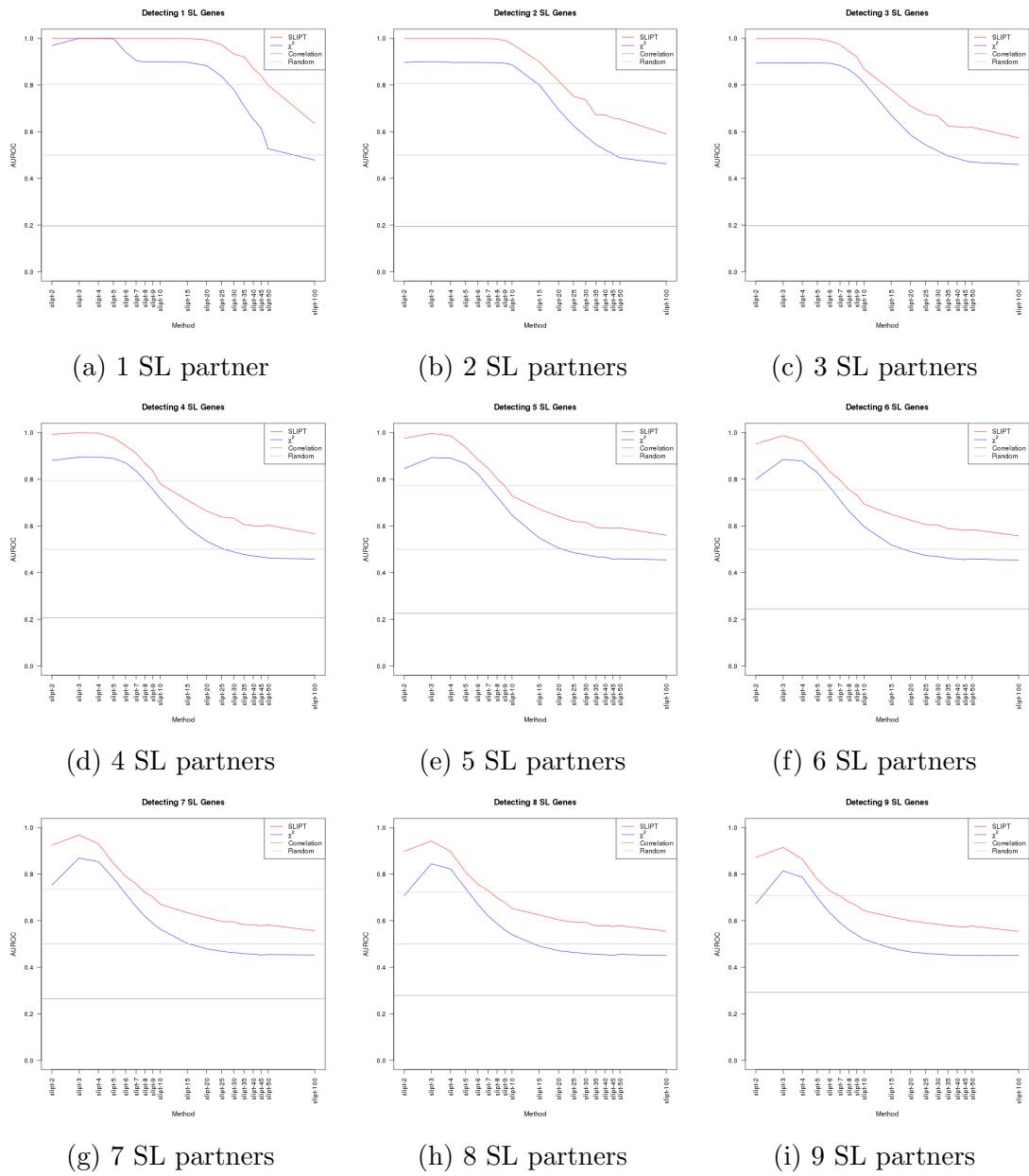


Figure J.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

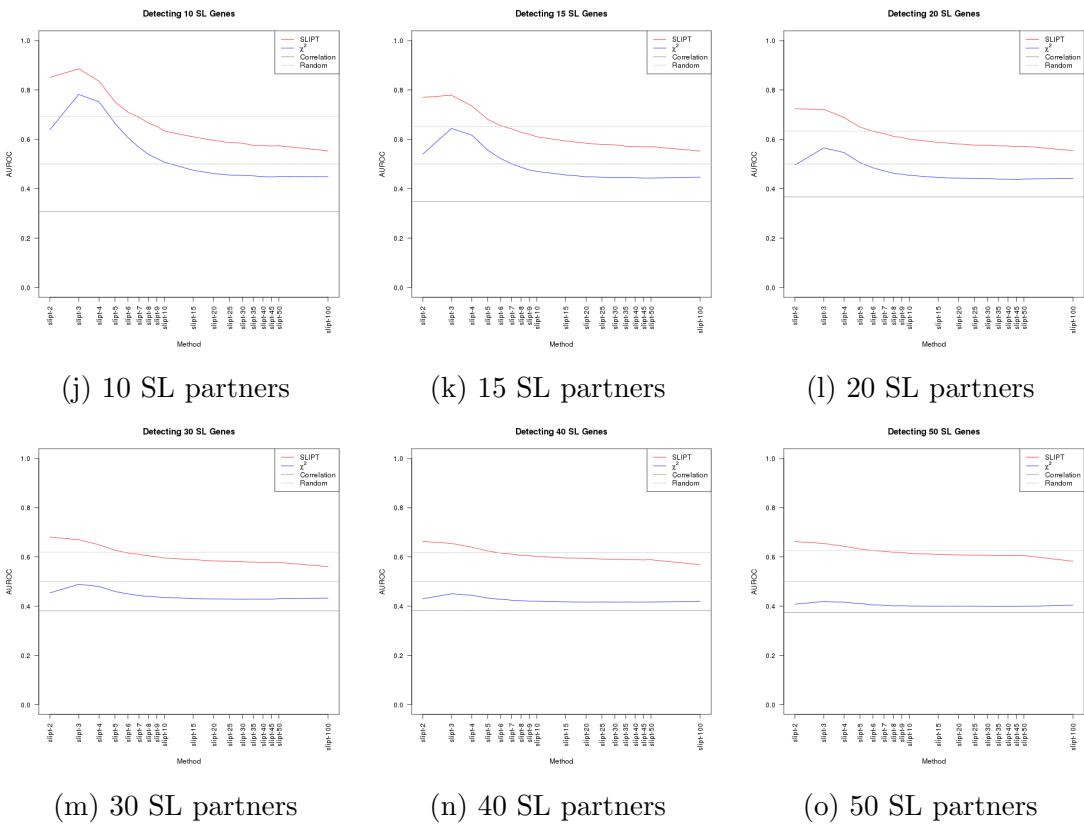


Figure J.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking at $1/3$ -quantiles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

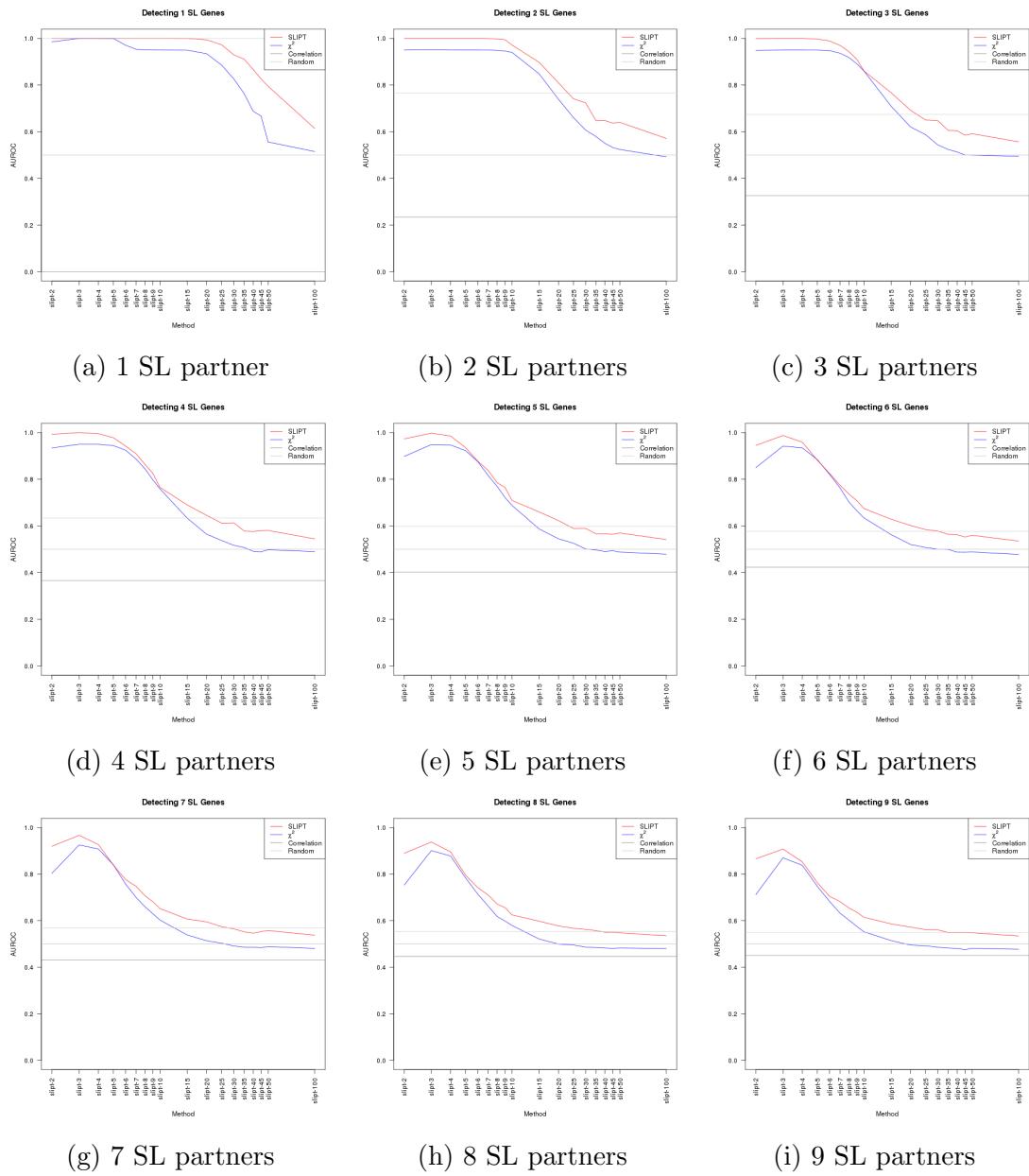


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. (continued on next page)

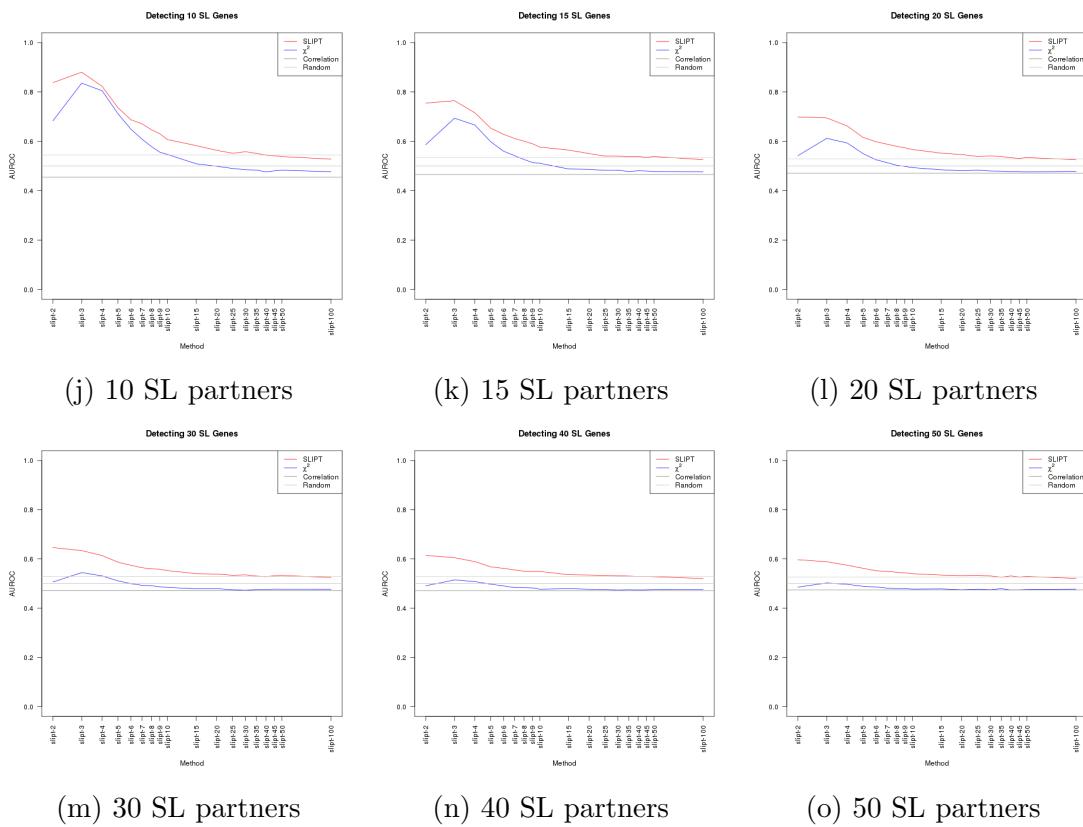


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey), according to the legend. SLIPT and χ^2 performed similarly, peaking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

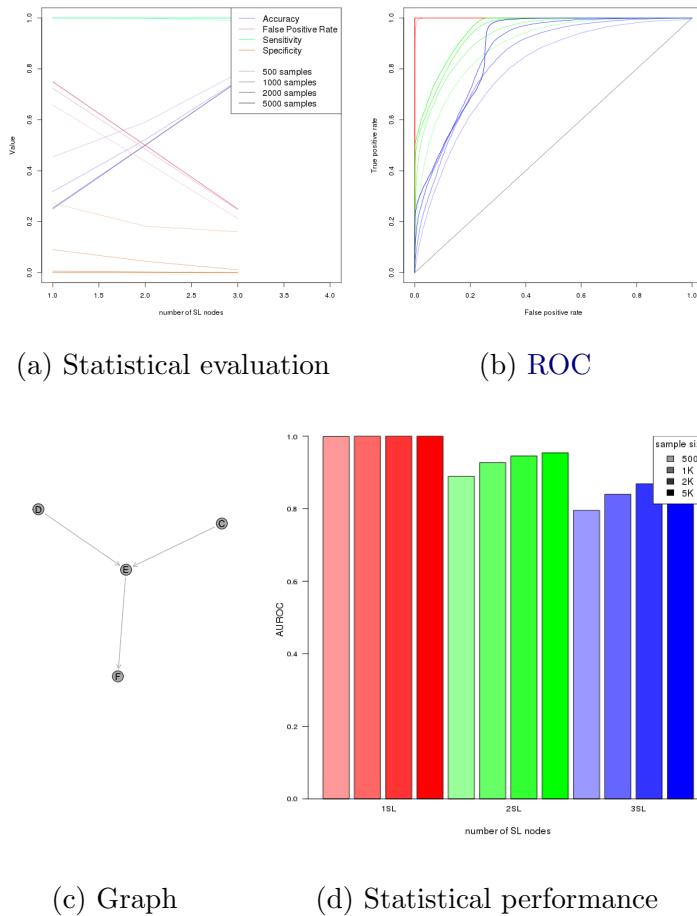


Figure K.1: **Performance of simulations on a simple graph.** Simulation of synthetic lethality was performed using a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.1b match Figure K.1d.

K.0.1 Simulations from Inhibiting Graph Structures

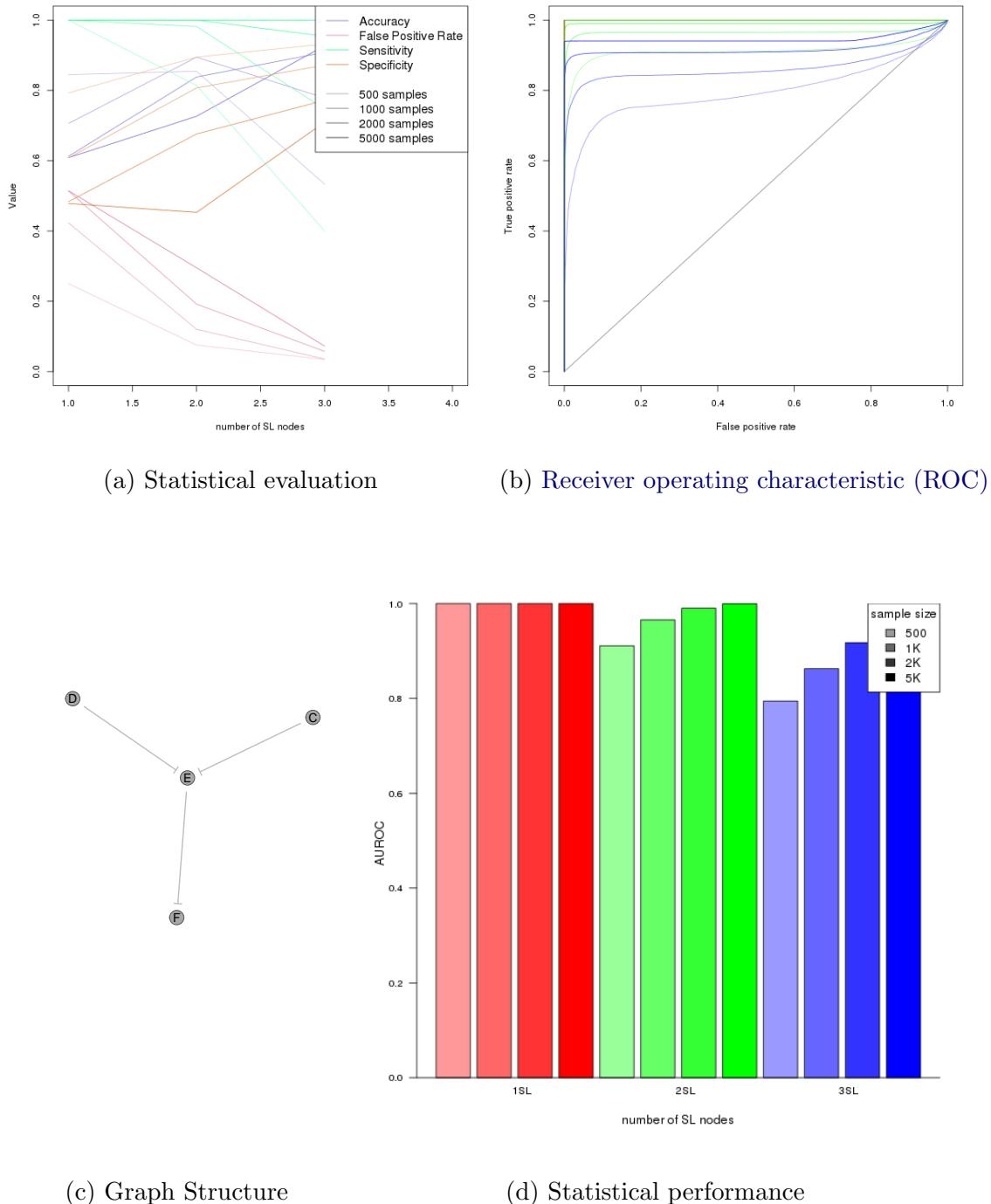


Figure K.2: **Performance of simulations on an inhibiting graph.** Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.

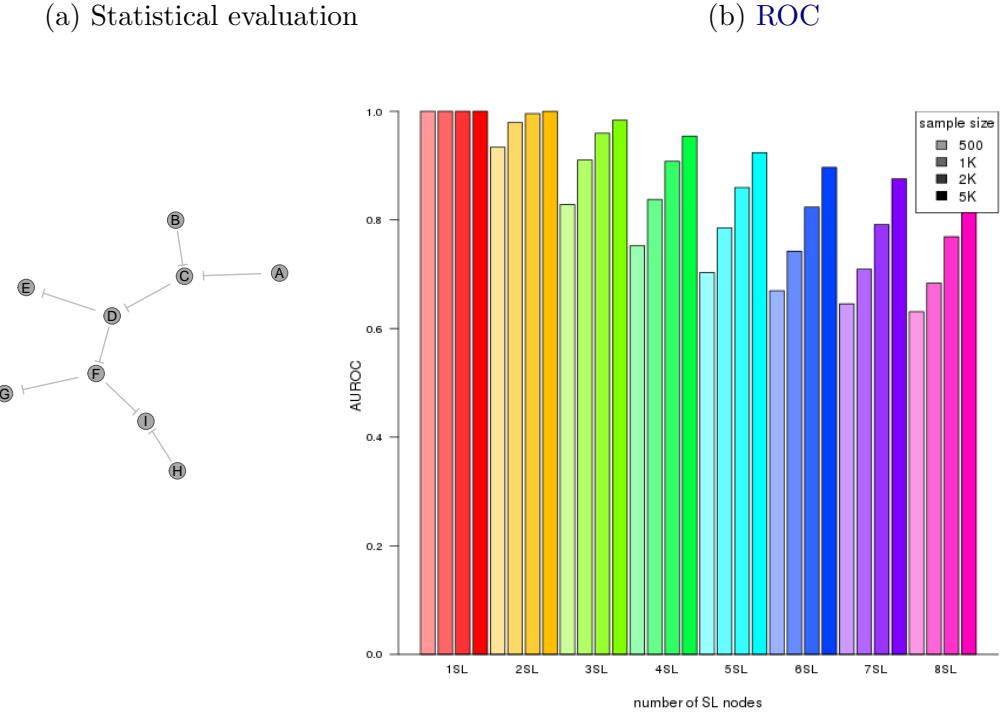
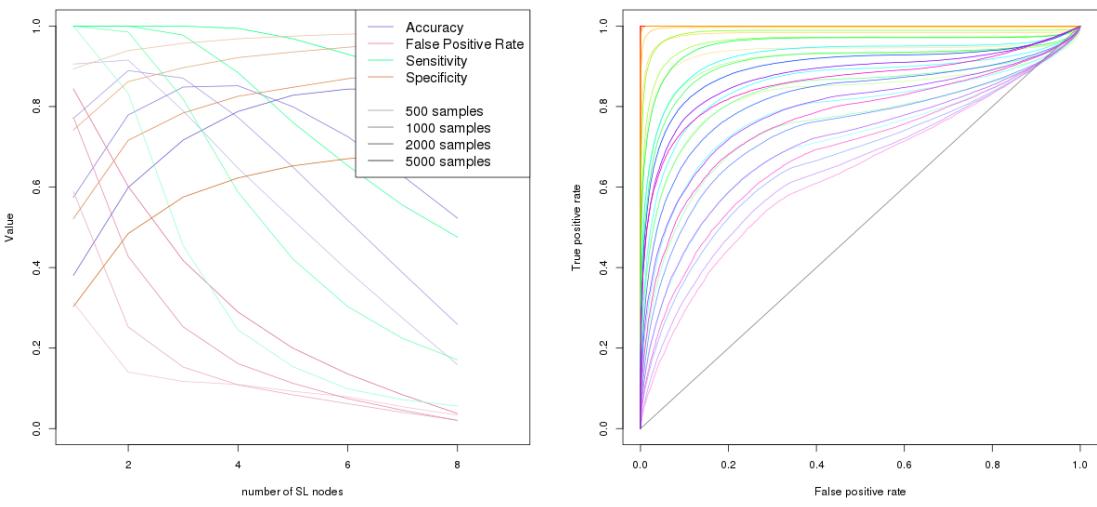
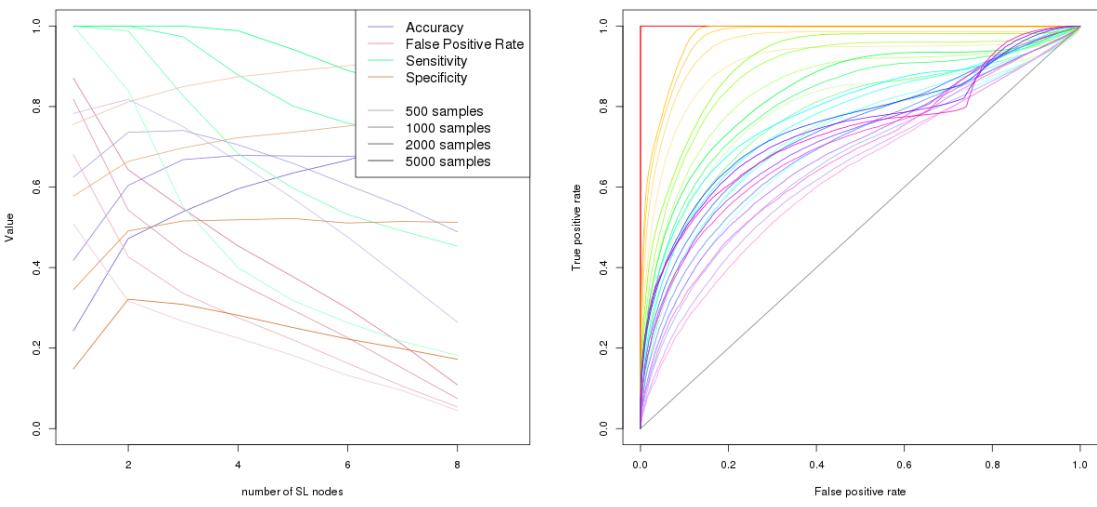
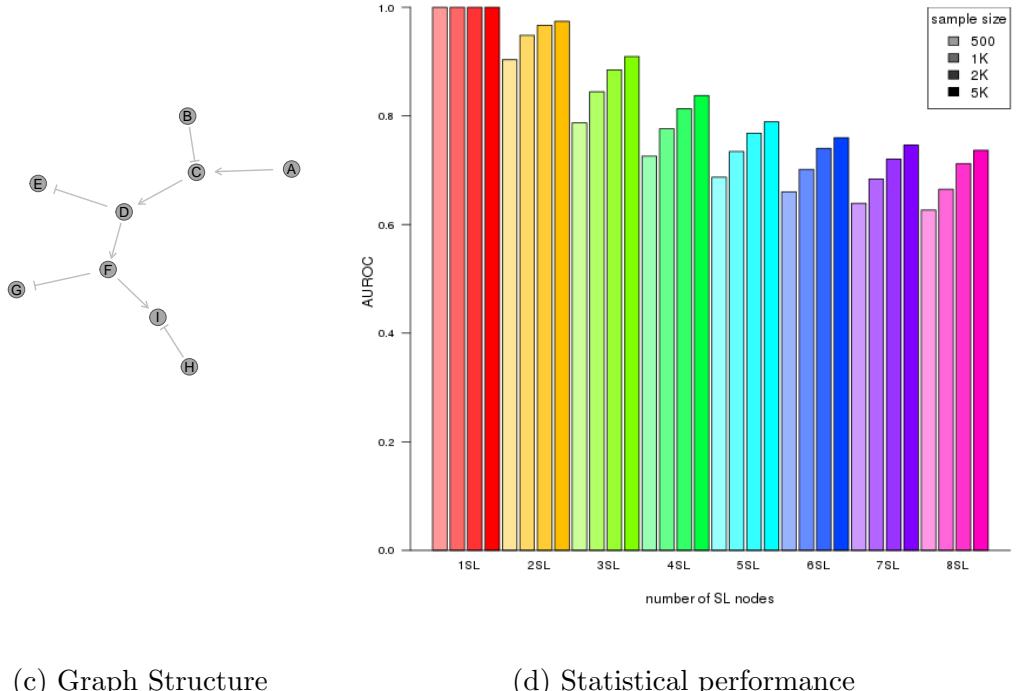


Figure K.3: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a pathway with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.3b match Figure K.3d.



(a) Statistical evaluation

(b) ROC

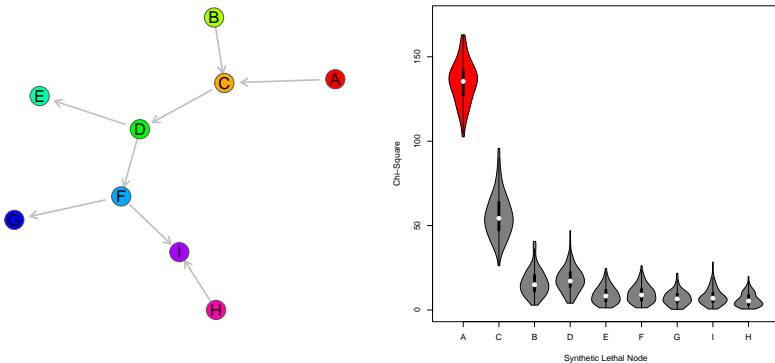


(c) Graph Structure

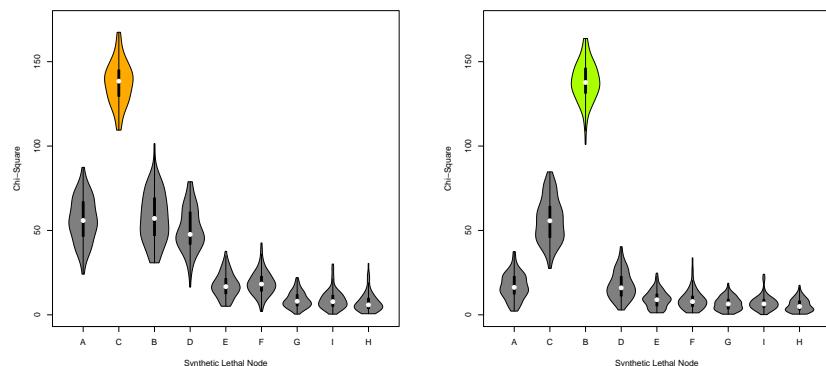
(d) Statistical performance

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.

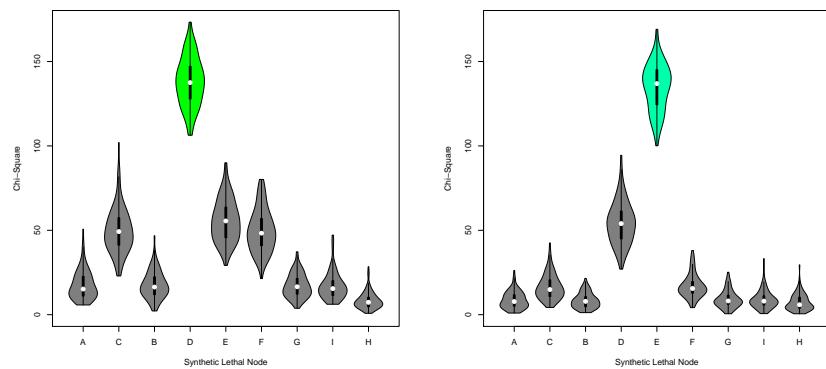
K.1 Simulation across Graph Structures



(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)

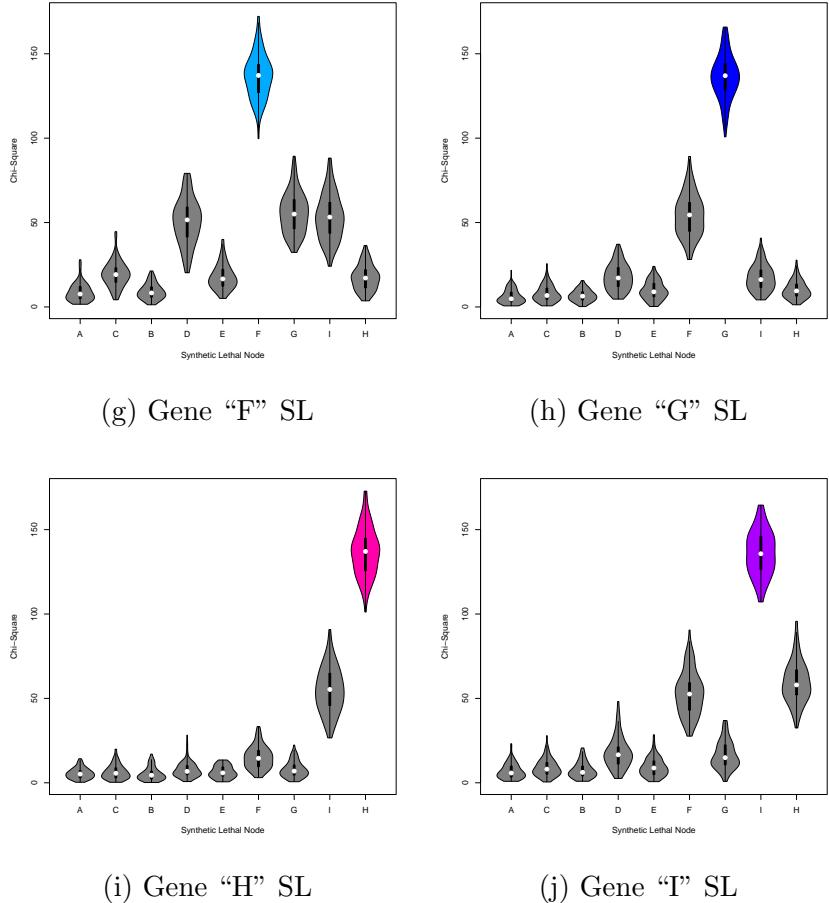
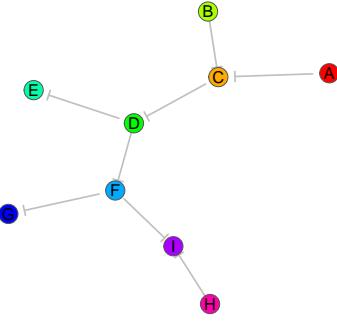
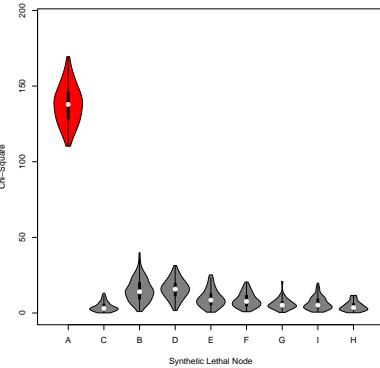


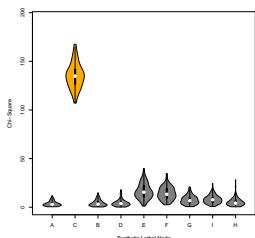
Figure K.5: Detection of synthetic lethality within a graph structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from [SLIPT](#) was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were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



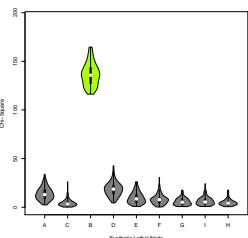
(a) Inhibiting Graph Structure



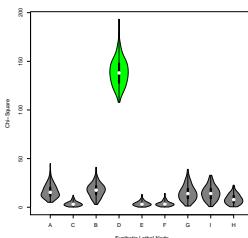
(b) χ^2 distribution for "A" SL



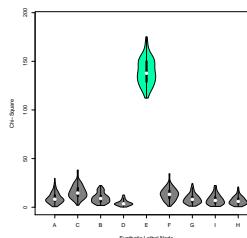
(c) Gene "B" SL



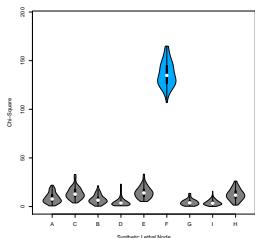
(d) Gene "C" SL



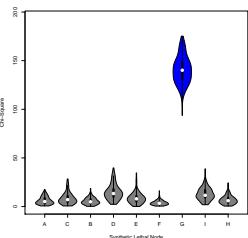
(e) Gene "D" SL



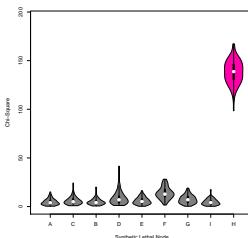
(f) Gene "E" SL



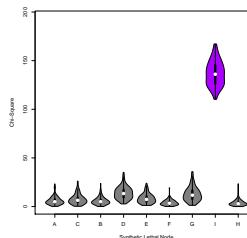
(g) Gene "F" SL



(h) Gene "G" SL

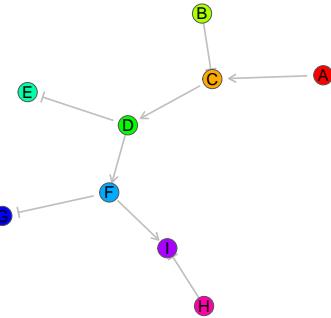


(i) Gene "H" SL

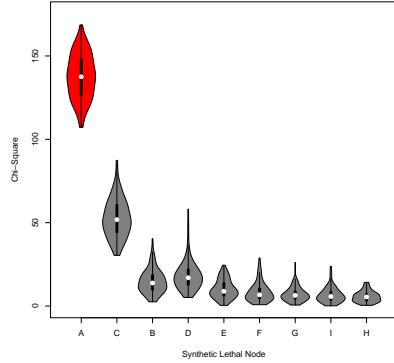


(j) Gene "I" SL

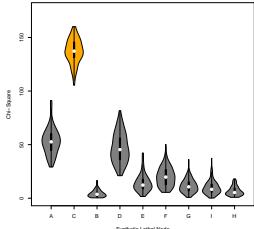
Figure K.6: Detection of synthetic lethality within an inhibiting graph. Each gene was designated to be synthetic lethal separately and the χ^2 value from **SLIPT** was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in the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



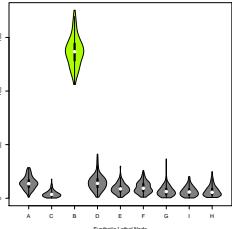
(a) Inhibiting Graph Structure



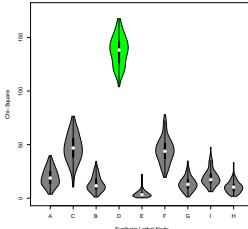
(b) χ^2 distribution for "A" SL



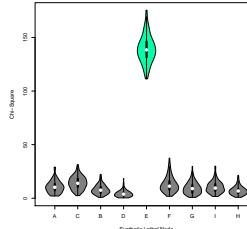
(c) Gene "B" SL



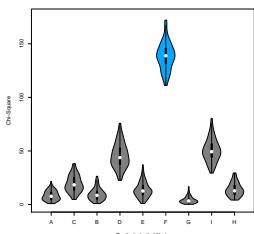
(d) Gene "C" SL



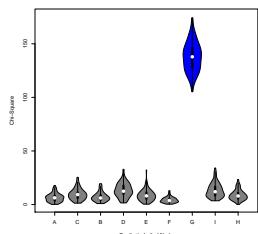
(e) Gene "D" SL



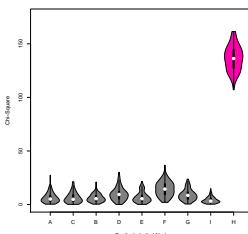
(f) Gene "E" SL



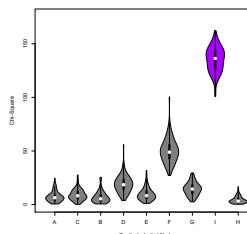
(g) Gene "F" SL



(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

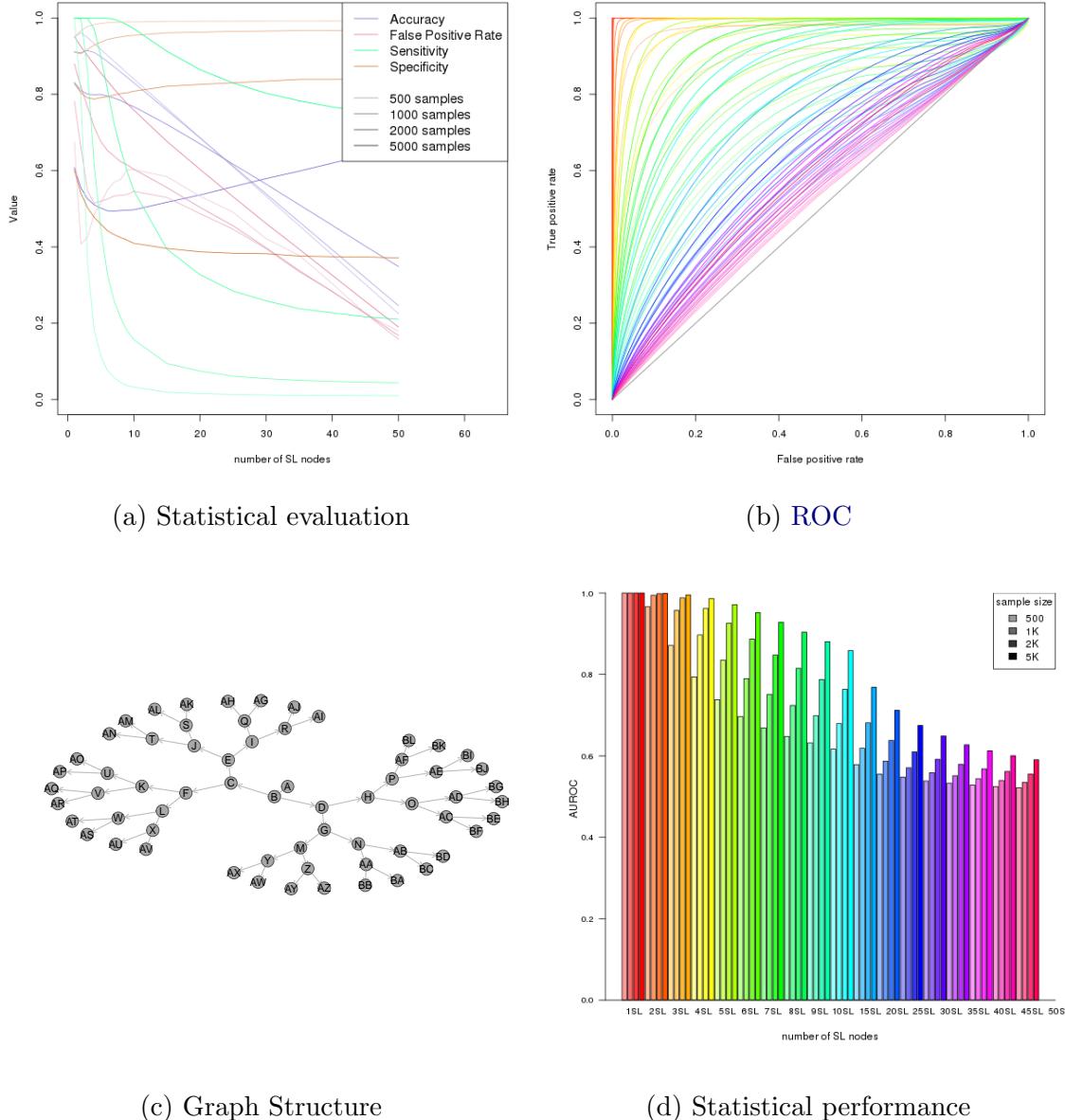
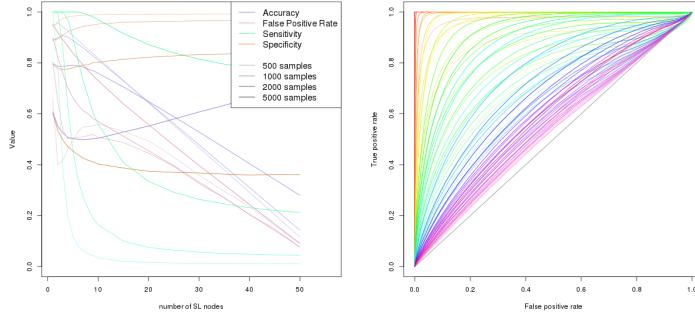
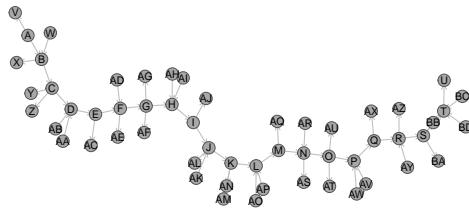


Figure K.8: **Performance of simulations on a branching graph.** Simulation of synthetic lethality used a multivariate normal distribution from a branching graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.

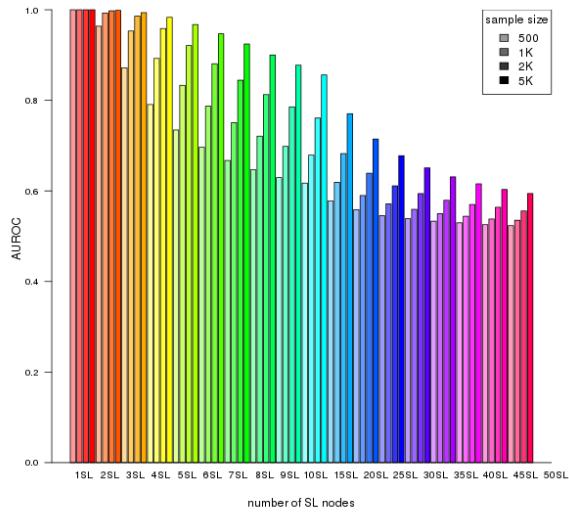


(a) Statistical evaluation

(b) ROC

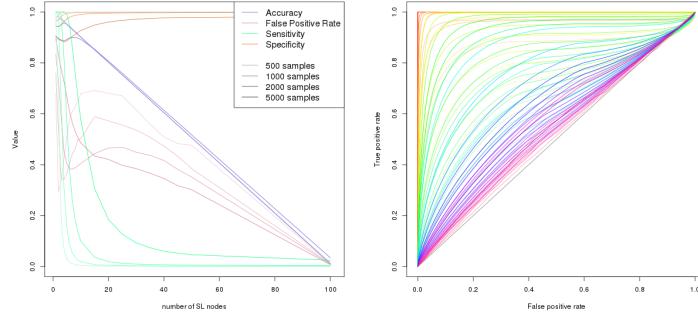


(c) Graph Structure



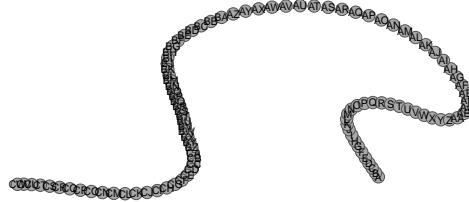
(d) Statistical performance

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.

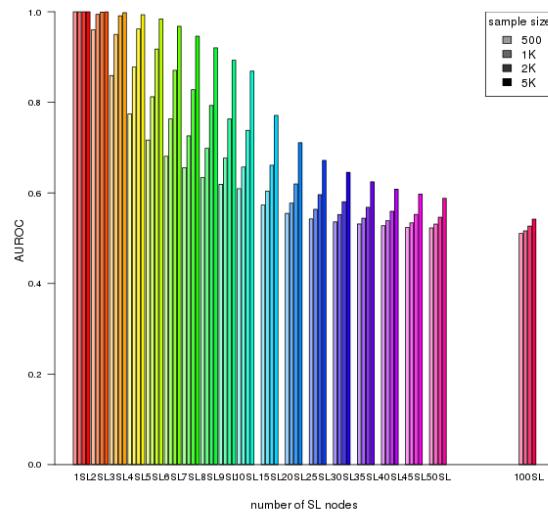


(a) Statistical evaluation

(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

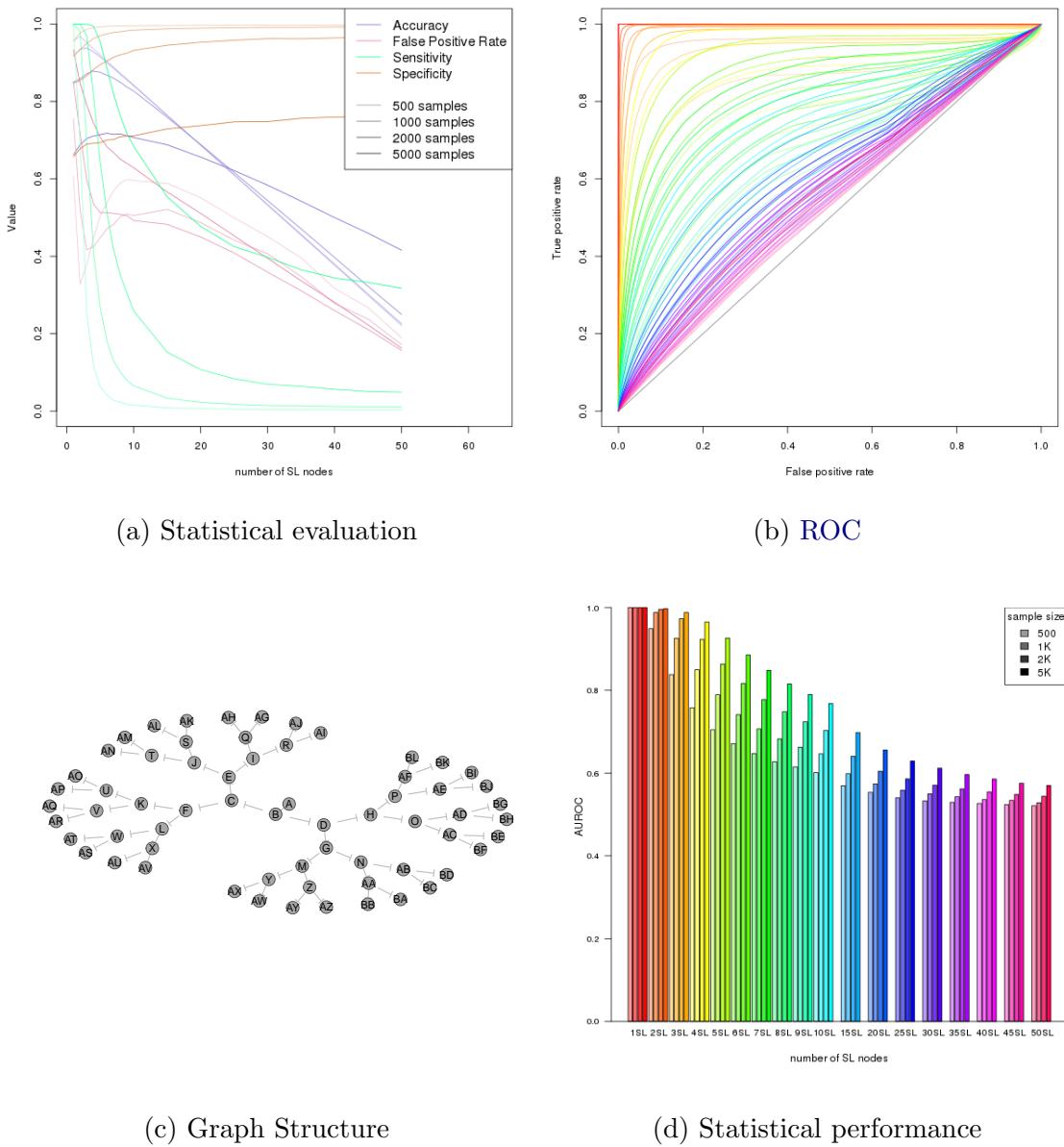
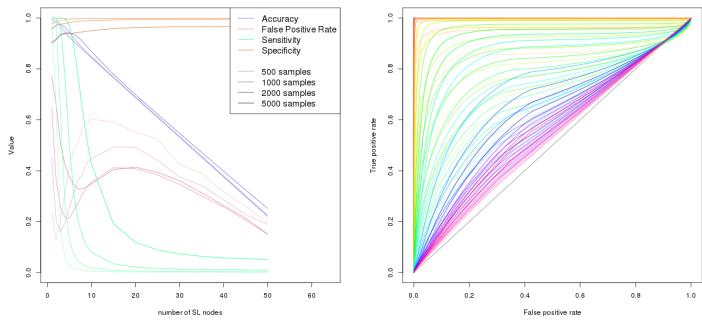
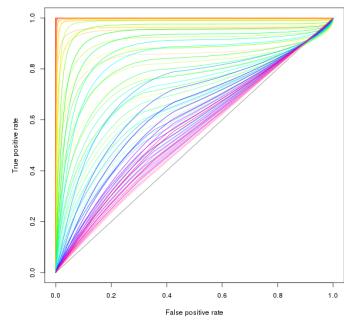


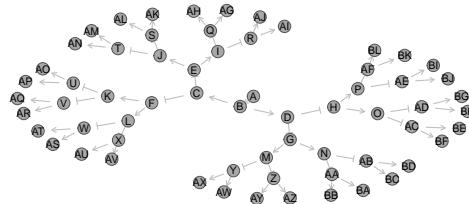
Figure K.11: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from a branching graph with only inhibitions. For each parameter, 10,000 simulations were used. Colours in Figure K.11b match Figure K.11d.



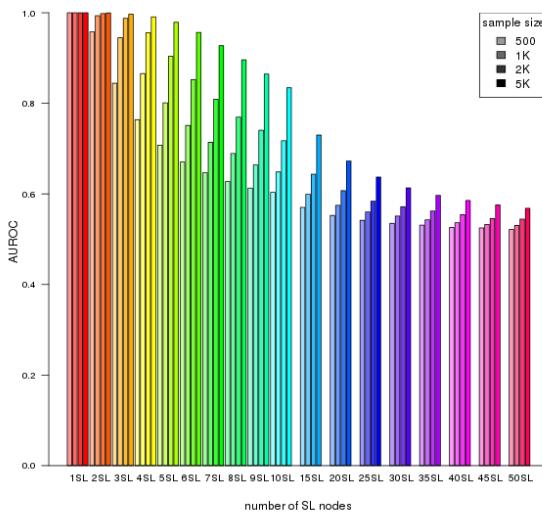
(a) Statistical evaluation



(b) ROC

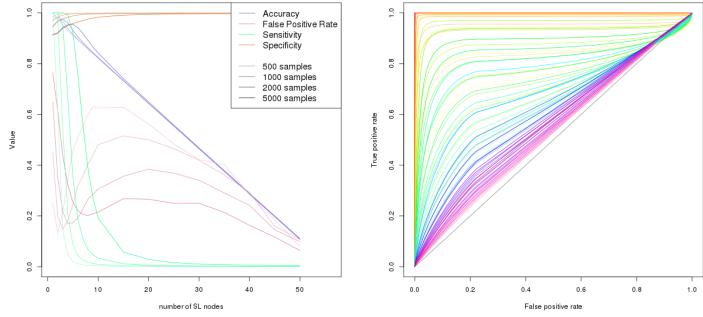


(c) Graph Structure



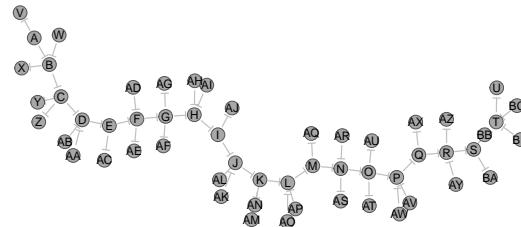
(d) Statistical performance

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.

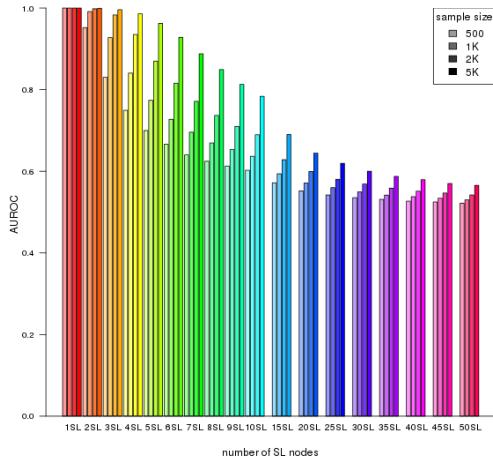


(a) Statistical evaluation

(b) ROC

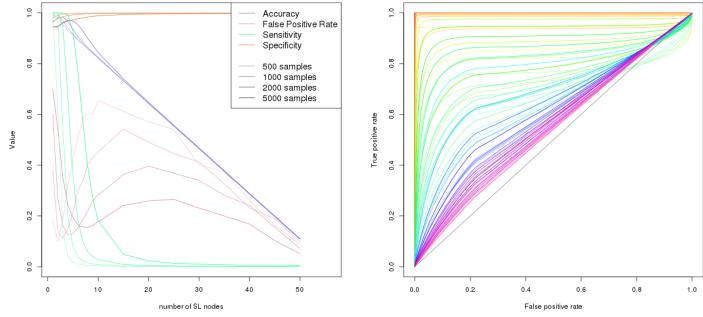


(c) Graph Structure



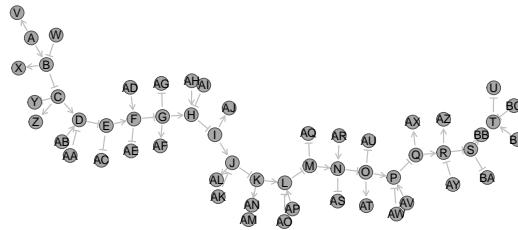
(d) Statistical performance

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.

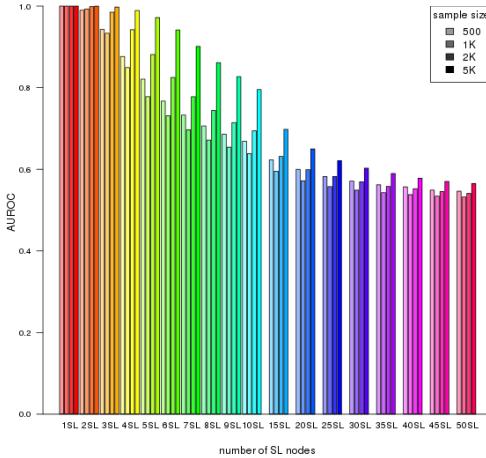


(a) Statistical evaluation

(b) ROC

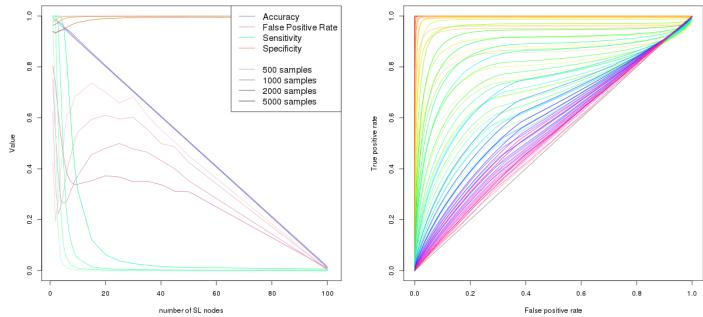


(c) Graph Structure



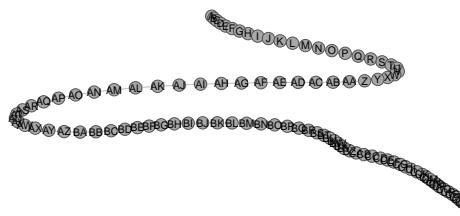
(d) Statistical performance

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.

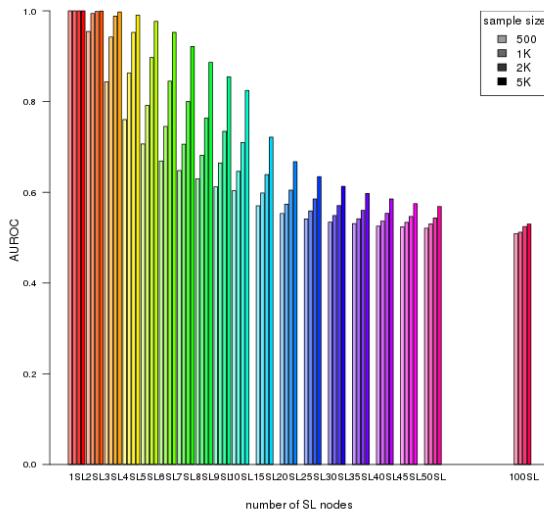


(a) Statistical evaluation

(b) ROC

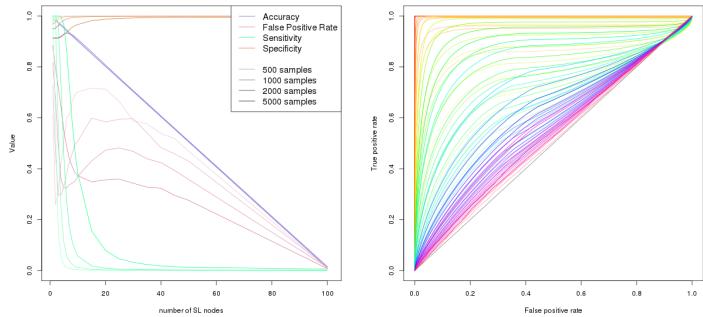


(c) Graph Structure



(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.

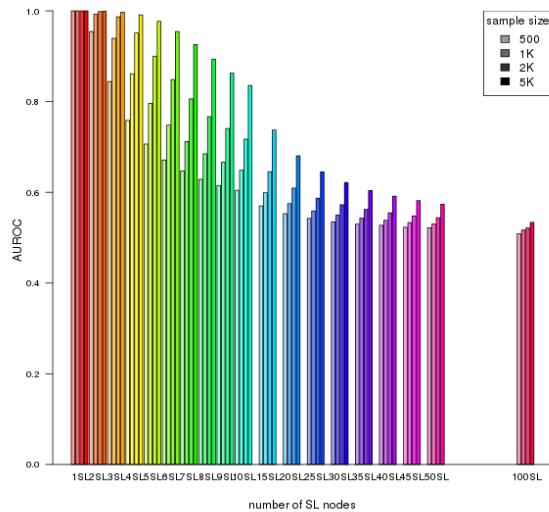


(a) Statistical evaluation

(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

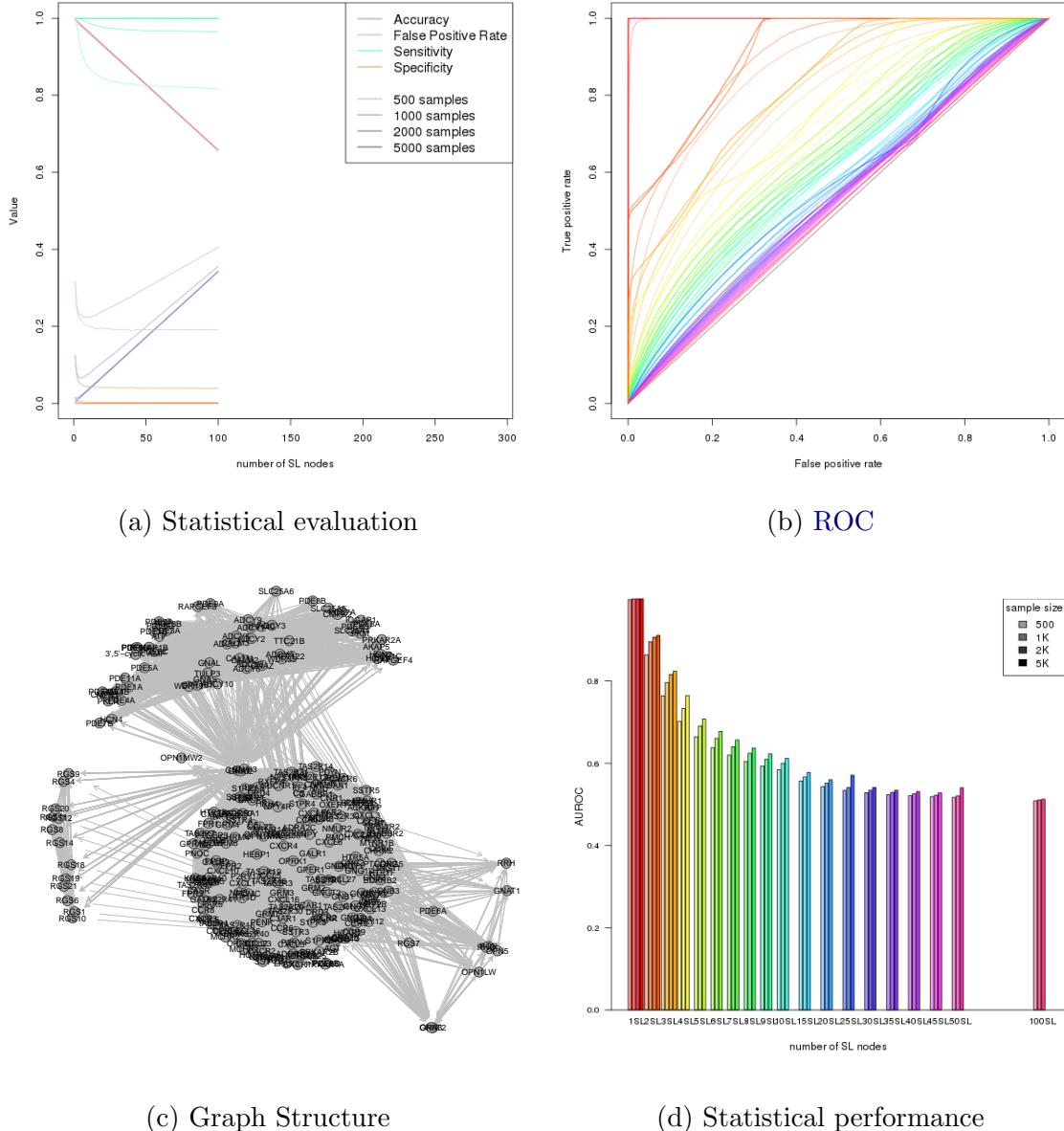


Figure K.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of [SLIPT](#) was high across parameters for detecting synthetic lethality in 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.

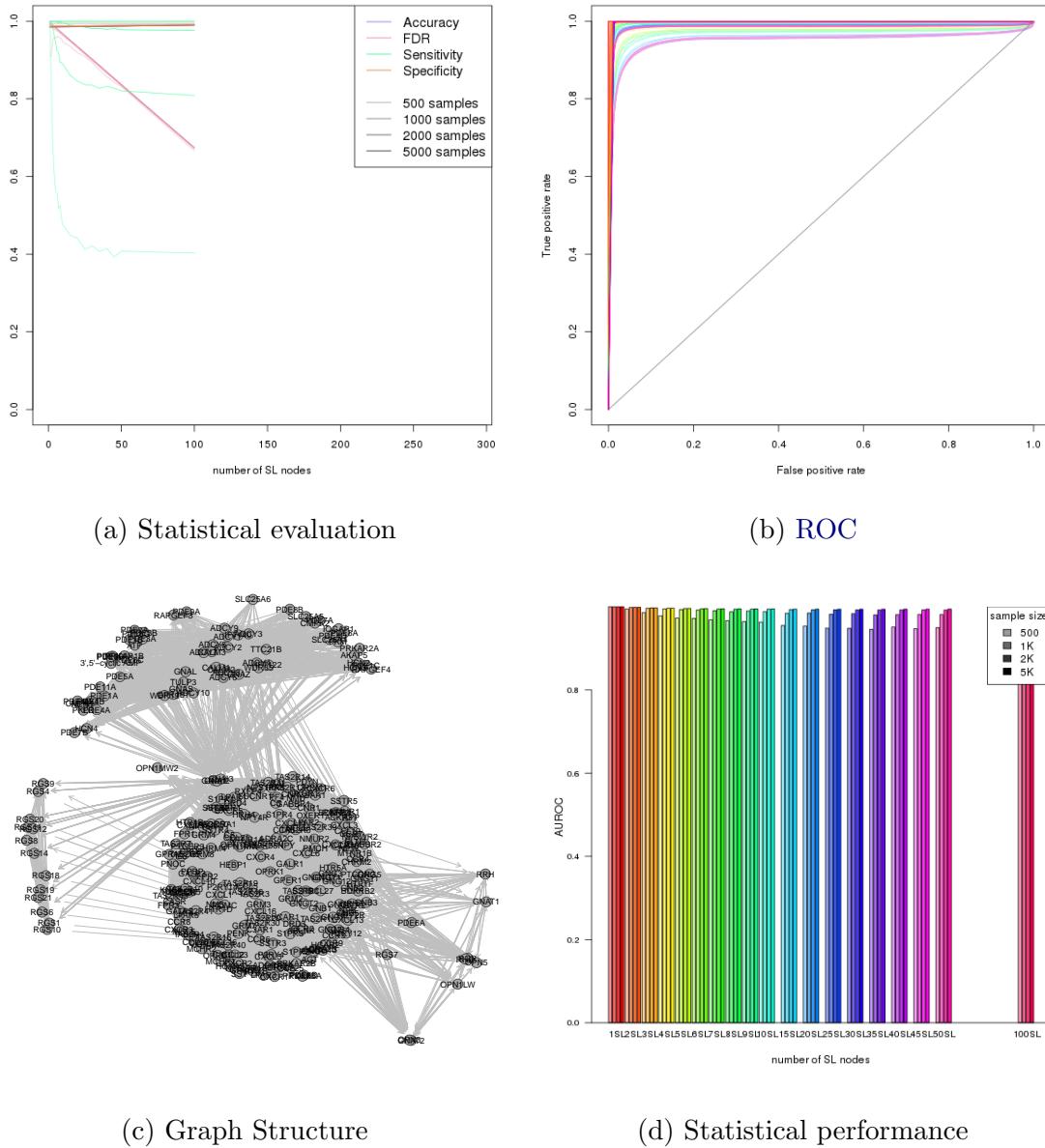


Figure K.18: Performance of simulations including the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome $G_{\alpha i}$ signalling pathway. Performance of **SLIPT** was high across parameters 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.