

Contents

Glossary	xiii
Acronyms	xiv
1 Introduction	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer as a Global Health Concern	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Human Genome Revolution	6
1.1.2.1 The First Human Genome Sequence	6
1.1.2.2 Impact of Genomics	7
1.1.3 Technologies to Enable Genetics Research	7
1.1.3.1 DNA Sequencing and Genotyping Technologies	7
1.1.3.2 Microarrays and Quantitative Technologies	8
1.1.3.3 Massively Parallel “Next Generation” Sequencing	9
1.1.3.3.1 Molecular Profiling with Genomics Technology .	11
1.1.3.3.2 Sequencing Technologies	11
1.1.3.4 Bioinformatics as Interdisciplinary Genomic Analysis .	12
1.1.4 Follow-up Large-Scale Genomics Projects	13
1.1.5 Cancer Genomes	14
1.1.5.1 The Cancer Genome Atlas Project	15
1.1.5.1.1 Findings from Cancer Genomes	15
1.1.5.1.2 Genomic Comparisons Across Cancer Tissues .	17
1.1.5.1.3 Cancer Genomic Data Resources	18
1.1.6 Genomic Cancer Medicine	18
1.1.6.1 Cancer Genes and Driver Mutations	18
1.1.6.2 Personalised or Precision Cancer Medicine	19
1.1.6.2.1 Molecular Diagnostics and Pan-Cancer Medicine	20
1.1.6.3 Targeted Therapeutics and Pharmacogenomics	21
1.1.6.3.1 Targeting Oncogenic Driver Mutations	21
1.1.6.4 Systems and Network Biology	22
1.1.6.4.1 Network Medicine, and Polypharmacology	24
1.2 A Synthetic Lethal Approach to Cancer Medicine	25
1.2.1 Synthetic Lethal Genetic Interactions	26
1.2.2 Synthetic Lethal Concepts in Genetics	26
1.2.3 Studies of Synthetic Lethality	27

1.2.3.1	Synthetic Lethal Pathways and Networks	28
1.2.3.1.1	Evolution of Synthetic Lethality	29
1.2.4	Synthetic Lethal Concepts in Cancer	29
1.2.5	Clinical Impact of Synthetic Lethality in Cancer	31
1.2.6	High-throughput Screening for Synthetic Lethality	33
1.2.6.1	Synthetic Lethal Screens	34
1.2.7	Computational Prediction of Synthetic Lethality	37
1.2.7.1	Bioinformatics Approaches to Genetic Interactions . .	37
1.2.7.2	Comparative Genomics	38
1.2.7.3	Analysis and Modelling of Protein Data	41
1.2.7.4	Differential Gene Expression	43
1.2.7.5	Data Mining and Machine Learning	44
1.2.7.6	Bimodality	47
1.2.7.7	Rationale for Further Development	48
1.3	E-cadherin as a Synthetic Lethal Target	48
1.3.1	The <i>CDH1</i> gene and it's Biological Functions	48
1.3.1.1	Cytoskeleton	49
1.3.1.2	Extracellular and Tumour Micro-Environment	49
1.3.1.3	Cell-Cell Adhesion and Signalling	49
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	50
1.3.2.1	Breast Cancers and Invasion	50
1.3.3	Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer .	50
1.3.4	Somatic Mutations	52
1.3.4.1	Mutation Rate	52
1.3.4.2	Co-occurring Mutations	52
1.3.5	Models of <i>CDH1</i> loss in cell lines	53
1.4	Summary and Research Direction of Thesis	54
2	Methods and Resources	58
2.1	Bioinformatics Resources for Genomics Research	58
2.1.1	Public Data and Software Packages	58
2.1.1.1	Cancer Genome Atlas Data	59
2.1.1.2	Reactome and Annotation Data	60
2.2	Data Handling	60
2.2.1	Normalisation	60
2.2.2	Sample Triage	61
2.2.3	Metagenes and the Singular Value Decomposition	63
2.2.3.1	Candidate Triage and Integration with Screen Data .	63
2.3	Techniques	64
2.3.1	Statistical Procedures and Tests	64
2.3.2	Gene Set Over-representation Analysis	65
2.3.3	Clustering	65
2.3.4	Heatmap	66
2.3.5	Modeling and Simulations	66
2.3.5.1	Receiver Operating Characteristic (Performance) . .	67
2.3.6	Resampling Analysis	67

2.4	Pathway Structure Methods	68
2.4.1	Network and Graph Analysis	68
2.4.2	Sourcing Graph Structure Data	69
2.4.3	Constructing Pathway Subgraphs	70
2.4.4	Network Analysis Metrics	70
2.5	Implementation	71
2.5.1	Computational Resources and Linux Utilities	71
2.5.2	R Language and Packages	72
2.5.3	High Performance and Parallel Computing	75
3	Methods Developed During Thesis	77
3.1	A Synthetic Lethal Detection Methodology	77
3.2	Synthetic Lethal Simulation and Modelling	80
3.2.1	A Model of Synthetic Lethality in Expression Data	80
3.2.2	Simulation Procedure	84
3.3	Detecting Simulated Synthetic Lethal Partners	87
3.3.1	Binomial Simulation of Synthetic lethality	87
3.3.2	Multivariate Normal Simulation of Synthetic lethality	89
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	92
3.3.2.2	Specificity with Query-Correlated Pathways	99
3.3.2.3	Importance of Directional Testing	99
3.4	Graph Structure Methods	101
3.4.1	Upstream and Downstream Gene Detection	101
3.4.1.1	Permutation Analysis for Statistical Significance	102
3.4.1.2	Hierarchy Based on Biological Context	103
3.4.2	Simulating Gene Expression from Graph Structures	104
3.5	Customised Functions and Packages Developed	108
3.5.1	Synthetic Lethal Interaction Prediction Tool	108
3.5.2	Data Visualisation	109
3.5.3	Extensions to the iGraph Package	112
3.5.3.1	Sampling Simulated Data from Graph Structures	112
3.5.3.2	Plotting Directed Graph Structures	112
3.5.3.3	Computing Information Centrality	113
3.5.3.4	Testing Pathway Structure with Permutation Testing	113
3.5.3.5	Metapackage to Install iGraph Functions	114
4	Synthetic Lethal Analysis of Gene Expression Data	115
4.1	Synthetic Lethal Genes in Breast Cancer	116
4.1.1	Synthetic Lethal Pathways in Breast Cancer	118
4.1.2	Expression Profiles of Synthetic Lethal Partners	119
4.1.2.1	Subgroup Pathway Analysis	122
4.2	Comparing Synthetic Lethal Gene Candidates	125
4.2.1	Primary siRNA Screen Candidates	125
4.2.2	Comparison with Correlation	126
4.2.3	Comparison with Primary Screen Viability	128
4.2.4	Comparison with Secondary siRNA Screen Validation	129

4.2.5	Comparison to Primary Screen at Pathway Level	131
4.2.5.1	Resampling Genes for Pathway Enrichment	133
4.2.6	Integrating Synthetic Lethal Pathways and Screens	136
4.3	Metagene Analysis	138
4.3.1	Pathway Expression	139
4.3.2	Somatic Mutation	141
4.3.3	Synthetic Lethal Pathway Metagenes	145
4.3.4	Synthetic Lethality in Breast Cancer	146
4.4	Replication in Stomach Cancer	147
4.5	Discussion	148
4.5.1	Strengths of the SLIPT Methodology	148
4.5.2	Synthetic Lethal Pathways for E-cadherin	149
4.5.3	Replication and Validation	151
4.5.3.1	Integration with siRNA Screening	151
4.5.3.2	Replication across Tissues	152
4.6	Summary	152
5	Synthetic Lethal Pathway Structure	154
5.1	Synthetic Lethal Genes in Reactome Pathways	154
5.1.1	The PI3K/AKT Pathway	155
5.1.2	The Extracellular Matrix	157
5.1.3	G Protein Coupled Receptors	160
5.1.4	Gene Regulation and Translation	160
5.2	Network Analysis of Synthetic Lethal Genes	161
5.2.1	Gene Connectivity and Vertex Degree	162
5.2.2	Gene Importance and Centrality	163
5.2.2.1	Information Centrality	163
5.2.2.2	PageRank Centrality	165
5.3	Relationships between Synthetic Lethal Genes	167
5.3.1	Hierarchical Pathway Structure	167
5.3.1.1	Contextual Hierarchy of PI3K	167
5.3.1.2	Testing Contextual Hierarchy of Synthetic Lethal Genes	167
5.3.2	Upstream or Downstream Synthetic Lethality	171
5.3.2.1	Measuring Structure of Candidates within PI3K	171
5.3.2.2	Resampling for Synthetic Lethal Pathway Structure .	173
5.4	Discussion	175
5.5	Summary	177
6	Simulation and Modeling of Synthetic Lethal Pathways	180
6.1	Comparing Synthetic Lethal Detection Methods	181
6.1.1	Performance of SLIPT and χ^2 across Quantiles	182
6.1.1.1	Correlated Query Genes affects Specificity	185
6.1.2	Alternative Synthetic Lethal Detection Strategies	187
6.1.2.1	Correlation for Synthetic Lethal Detection	187
6.1.2.2	Testing for Bimodality with BiSEp	189
6.2	Simulations with Graph Structures	190

6.2.1	Performance over a Graph Structure	191
6.2.1.1	Simple Graph Structures	191
6.2.1.2	Constructed Graph Structures	194
6.2.2	Performance with Inhibitions	197
6.2.3	Synthetic Lethality across Graph Structures	203
6.2.4	Performance within a Simulated Human Genome	206
6.3	Simulations over pathway-based graphs	211
6.3.1	Pathway Structures in a Simulated Human Genome	214
6.4	Discussion	217
6.4.1	Simulation Procedure	217
6.4.2	Comparing Methods with Simulated Data	218
6.4.3	Design and Performance of SLIPT	219
6.4.4	Simulations from Graph Structures	221
6.5	Summary	222
7	Discussion	223
7.1	Synthetic Lethality and <i>CDH1</i> Biology	223
7.1.1	Established Functions of <i>CDH1</i>	224
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	224
7.2	Significance	225
7.2.1	Synthetic Lethality in the Genomic Era	225
7.2.2	Clinical Interventions based on Synthetic Lethality	227
7.3	Evaluating the Synthetic Lethality Prediction Tool	228
7.3.1	Strength of the Synthetic Lethality Prediction Tool	228
7.3.2	Limitations of the Synthetic Lethality Prediction Tool	228
7.3.3	Comparisons to Alternative Methods	228
7.3.3.1	Combined with Experimental Screening	228
7.3.3.2	Differences to Computational Methods	228
7.4	Future Directions	228
7.4.1	Refinements Synthetic Lethality Prediction Methods	230
7.4.1.1	Wider Use of Synthetic Lethality Prediction	230
7.4.2	Validation of Synthetic Lethal Genes and Pathways	230
7.4.2.1	Pre-clinical and Clinical Testing	230
7.4.3	Application to Further Genes and Pathways	230
8	Conclusion	231
References		235
A	Sample Quality	261
A.1	Sample Correlation	261
A.2	Replicate Samples in TCGA Breast	264
B	Software Used for Thesis	268

C Mutation Analysis in Breast Cancer	277
C.1 Synthetic Lethal Genes and Pathways	277
C.2 Synthetic Lethal Expression Profiles	280
C.3 Comparison to Primary Screen	283
C.3.1 Resampling Analysis	285
C.4 Compare SLIPT genes	287
C.5 Metagene Analysis	289
C.6 Expression of Somatic Mutations	290
C.7 Metagene Expression Profiles	293
D Intrinsic Subtyping	296
E Stomach Expression Analysis	298
E.1 Synthetic Lethal Genes and Pathways	298
E.2 Comparison to Primary Screen	302
E.2.1 Resampling Analysis	304
E.3 Metagene Analysis	306
F Synthetic Lethal Genes in Pathways	307
G Pathway Connectivity for Mutation SLIPT	315
H Information Centrality for Gene Essentiality	319
I Pathway Structure for Mutation SLIPT	322
J Performance of SLIPT and χ^2	325
J.1 Correlated Query Genes affects Specificity	331
K Graph Structures	337
K.1 Simulations from Simple Graph Structures	337
K.1.1 Simulations from Inhibiting Graph Structures	339
K.2 Simulation across Graph Structures	342
K.3 Simations from Complex Graph Structures	346
K.3.1 Simations from Complex Inhibiting Graphs	349
K.4 Simations from Pathway Graph Structures	356

List of Figures

1.1	Synthetic genetic interactions	27
1.2	Synthetic lethality in cancer	30
2.1	Read count density	62
2.2	Read count sample mean	62
3.1	Framework for synthetic lethal prediction	78
3.2	Synthetic lethal prediction adapted for mutation	79
3.3	A model of synthetic lethal gene expression	81
3.4	Modeling synthetic lethal gene expression	82
3.5	Synthetic lethality with multiple genes	83
3.6	Simulating gene function	85
3.7	Simulating synthetic lethal gene function	85
3.8	Simulating synthetic lethal gene expression	86
3.9	Performance of binomial simulations	88
3.10	Comparison of statistical performance	88
3.11	Performance of multivariate normal simulations	90
3.12	Simulating expression with correlated gene blocks	93
3.13	Simulating expression with correlated gene blocks	94
3.14	Synthetic lethal prediction across simulations	95
3.15	Performance with correlations	96
3.16	Comparison of statistical performance with correlation structure	97
3.17	Performance with query correlations	98
3.18	Statistical evaluation of directional criteria	99
3.19	Performance of directional criteria	100
3.20	Simulated graph structures	104
3.21	Simulating expression from a graph structure	106
3.22	Simulating expression from graph structure with inhibitions	107
3.23	Demonstration of violin plots with custom features	110
3.24	Demonstration of annotated heatmap	110
3.25	Simulating graph structures	113
4.1	Synthetic lethal expression profiles of analysed samples	121
4.2	Comparison of SLIPT to siRNA	125
4.3	Compare SLIPT and siRNA genes with correlation	126
4.4	Compare SLIPT and siRNA genes with correlation	127
4.5	Compare SLIPT and siRNA genes with viability	128

4.6	Compare SLIPT genes with siRNA viability	129
4.7	Resampled intersection of SLIPT and siRNA candidates	133
4.8	Pathway metagene expression profiles	140
4.9	Expression profiles for constituent genes of PI3K	142
4.10	Expression profiles for estrogen receptor related genes	143
4.11	Somatic mutation against the PI3K metagene	144
5.1	Synthetic Lethality in the PI3K Cascade	156
5.2	Synthetic Lethality in the Elastic Fibre Formation Pathway	158
5.3	Synthetic Lethality in the Fibrin Clot Formation	159
5.4	Synthetic Lethality and Vertex Degree	162
5.5	Synthetic Lethality and Centrality	165
5.6	Synthetic Lethality and PageRank	166
5.7	Hierarchical Structure of PI3K	168
5.8	Hierarchy Score in PI3K against Synthetic Lethality in PI3K	169
5.9	Structure of Synthetic Lethality in PI3K	171
5.10	Structure of Synthetic Lethality Resampling in PI3K	172
6.1	Performance of χ^2 and SLIPT across quantiles	183
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	184
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	185
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	186
6.5	Performance of negative correlation and SLIPT	188
6.6	Performance of simulations on a simple graph	192
6.7	Performance of simulations is similar in simple graphs	193
6.8	Performance of simulations on a pathway	195
6.9	Performance of simulations on a constructed graph	196
6.10	Performance of simulations on a simple graph with inhibition	198
6.11	Performance is higher on a simple inhibiting graph	200
6.12	Performance of simulations on a constructed graph with inhibition . . .	201
6.13	Performance is affected by inhibition in graphs	202
6.14	Detection of Synthetic Lethality within a Graph Structure with Inhibitions	205
6.15	Performance of simulations including a simple graph	208
6.16	Performance on a simple graph improves with more genes	209
6.17	Performance on an inhibiting graph improves with more genes	210
6.18	Performance of simulations on the PI3K cascade	213
6.19	Performance of simulations including the PI3K cascade	215
6.20	Performance on pathways improves with more genes	216
A.1	Correlation profiles of removed samples	262
A.2	Correlation analysis and sample removal	263
A.3	Replicate excluded samples	264
A.4	Replicate samples with all remaining	265
A.5	Replicate samples with some excluded	266
C.1	Synthetic lethal expression profiles of analysed samples	281

C.2	Comparison of mtSLIPT to siRNA	283
C.3	Compare mtSLIPT and siRNA genes with correlation	287
C.4	Compare mtSLIPT and siRNA genes with correlation	287
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	288
C.6	Somatic mutation against PIK3CA metagene	290
C.7	Somatic mutation against PI3K protein	291
C.8	Somatic mutation against AKT protein	292
C.9	Pathway metagene expression profiles	293
C.10	Expression profiles for p53 related genes	294
C.11	Expression profiles for BRCA related genes	295
E.1	Synthetic lethal expression profiles of stomach samples	300
E.2	Comparison of SLIPT in stomach to siRNA	302
F.1	Synthetic Lethality in the PI3K/AKT Pathway	307
F.2	Synthetic Lethality in the PI3K/AKT Pathway in Cancer	308
F.3	Synthetic Lethality in the Extracellular Matrix	309
F.4	Synthetic Lethality in the GPCRs	310
F.5	Synthetic Lethality in the GPCR Downstream	311
F.6	Synthetic Lethality in the Translation Elongation	312
F.7	Synthetic Lethality in the Nonsense-mediated Decay	313
F.8	Synthetic Lethality in the 3' UTR	314
G.1	Synthetic Lethality and Vertex Degree	315
G.2	Synthetic Lethality and Centrality	316
G.3	Synthetic Lethality and PageRank	317
H.1	Information centrality distribution	321
I.1	Synthetic Lethality and Heirarchy Score in PI3K	322
I.2	Heirarchy Score in PI3K against Synthetic Lethality in PI3K	323
I.3	Structure of Synthetic Lethality in PI3K	323
I.4	Structure of Synthetic Lethality Resampling	324
J.1	Performance of χ^2 and SLIPT across quantiles	325
J.2	Performance of χ^2 and SLIPT across quantiles	327
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	329
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation .	331
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation .	333
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	335
K.1	Performance of simulations on a simple graph	338
K.2	Performance of simulations on an inhibiting graph	339
K.3	Performance of simulations on a constructed graph with inhibition	340
K.4	Performance of simulations on a constructed graph with inhibition	341
K.5	Detection of Synthetic Lethality within a Graph Structure	342
K.6	Detection of Synthetic Lethality within an Inhibiting Graph Structure .	344

K.7	Detection of Synthetic Lethality within an Inhibiting Graph Structure	345
K.8	Performance of simulations on a large graph	346
K.9	Performance of simulations on a branching graph	347
K.10	Performance of simulations on a complex graph	348
K.11	Performance of simulations on a large constructed graph with inhibition	350
K.12	Performance of simulations on a large constructed graph with inhibition	351
K.13	Performance of simulations on a branching graph with inhibition	352
K.14	Performance of simulations on a branching graph with inhibition	353
K.15	Performance of simulations on a complex graph with inhibition	354
K.16	Performance of simulations on a complex graph with inhibition	355
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	356
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	357

List of Tables

1.1	Methods for Predicting Genetic Interactions	38
1.2	Methods for Predicting Synthetic Lethality in Cancer	39
1.3	Methods used by Wu <i>et al.</i> (2014)	40
2.1	Excluded Samples by Batch and Clinical Characteristics.	61
2.2	Computers used during Thesis	72
2.3	Linux Utilities and Applications used during Thesis	72
2.4	R Installations used during Thesis	73
2.5	R Packages used during Thesis	73
2.6	R Packages Developed during Thesis	75
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	117
4.2	Pathways for <i>CDH1</i> partners from SLIPT	119
4.3	Pathway composition for clusters of <i>CDH1</i> partners from SLIPT	123
4.4	Analysis of variance (ANOVA) for Synthetic Lethality and Correlation with <i>CDH1</i>	127
4.5	Comparing SLIPT genes against secondary siRNA screen in breast cancer	130
4.6	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	132
4.7	Pathways for <i>CDH1</i> partners from SLIPT	135
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen	137
4.9	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	146
5.1	ANOVA for Synthetic Lethality and Vertex Degree	163
5.2	ANOVA for Synthetic Lethality and Information Centrality	165
5.3	ANOVA for Synthetic Lethality and PageRank Centrality	167
5.4	ANOVA for Synthetic Lethality and PI3K Hierarchy	170
5.5	Resampling for pathway structure of synthetic lethal detection methods	174
B.1	R Packages used during Thesis	268
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	278
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	279
C.3	Pathway composition for clusters of <i>CDH1</i> partners from mtSLIPT	282
C.4	Pathway composition for <i>CDH1</i> partners from mtSLIPT and siRNA	284
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	285
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	286
C.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	289

D.1	Comparison of Intrinsic Subtypes	296
E.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	298
E.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	299
E.3	Pathway composition for clusters of <i>CDH1</i> partners in stomach SLIPT	301
E.4	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	303
E.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	304
E.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA screen	305
E.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT in stomach cancer	306
G.1	ANOVA for Synthetic Lethality and Vertex Degree	318
G.2	ANOVA for Synthetic Lethality and Information Centrality	318
G.3	ANOVA for Synthetic Lethality and PageRank Centrality	318
H.1	Information centrality for genes and molecules in the Reactome network	320
I.1	ANOVA for Synthetic Lethality and PI3K Hierarchy	322
I.2	Resampling for pathway structure of synthetic lethal detection methods	324

Glossary

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

Acronyms

ANOVA Analysis of Variance.

SLIPT Synthetic lethal interaction prediction tool.

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Appendix J

Performance of SLIPT and χ^2

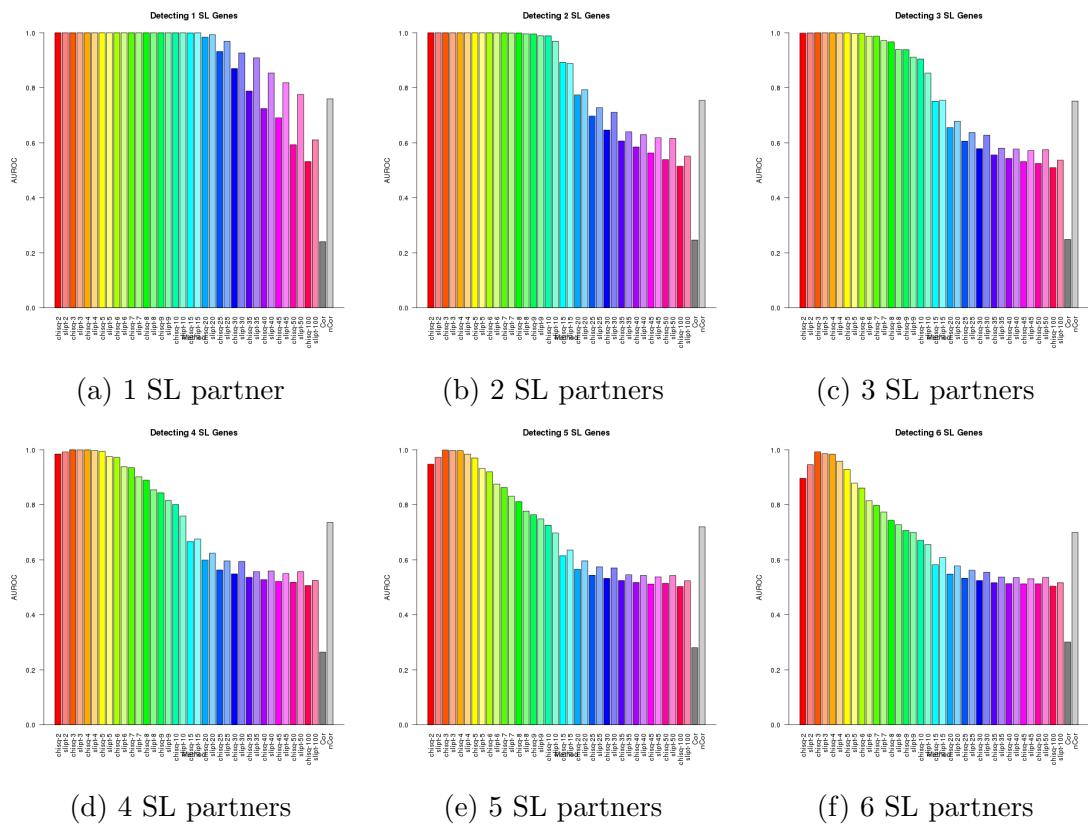


Figure J.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

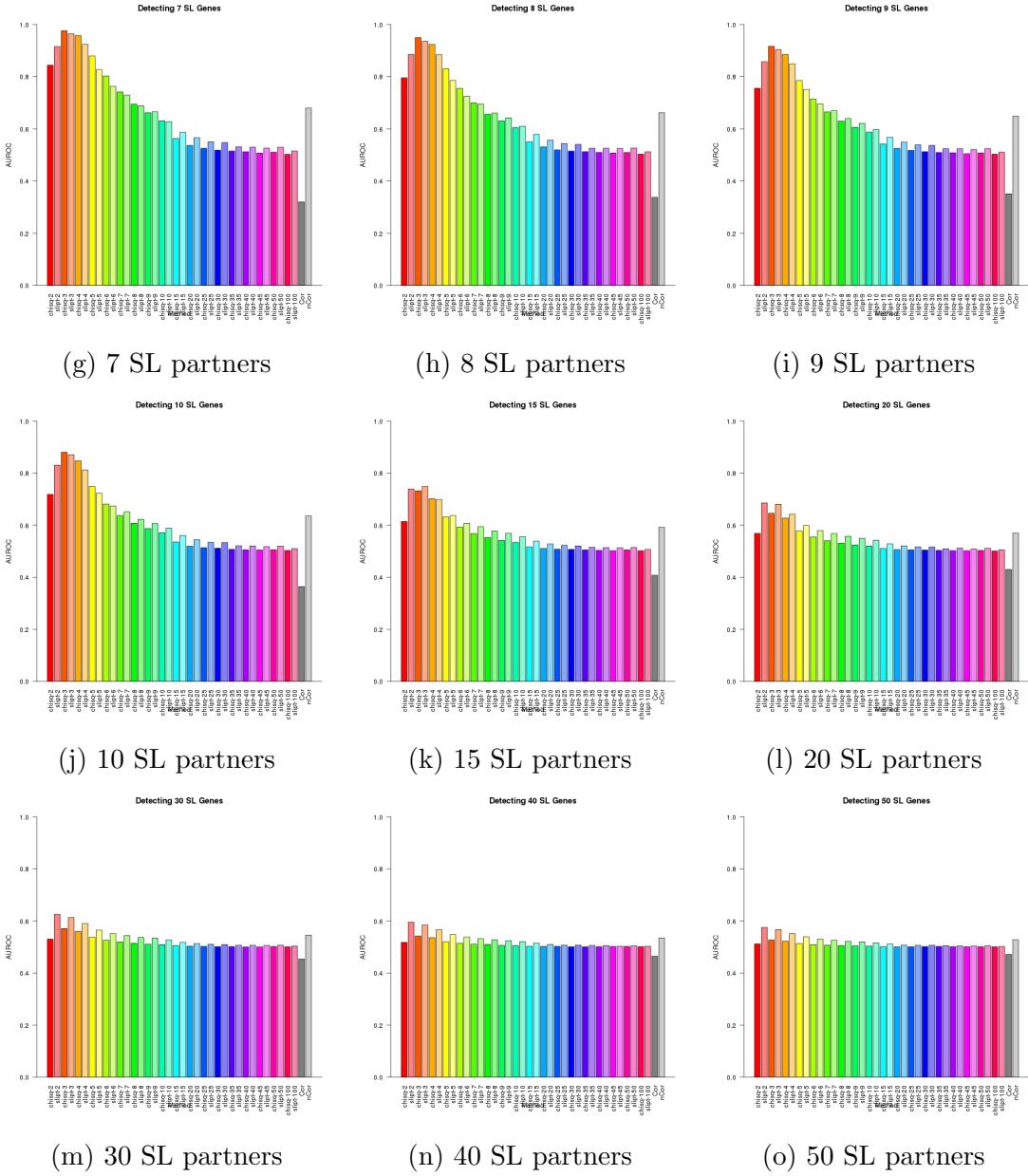


Figure J.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles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

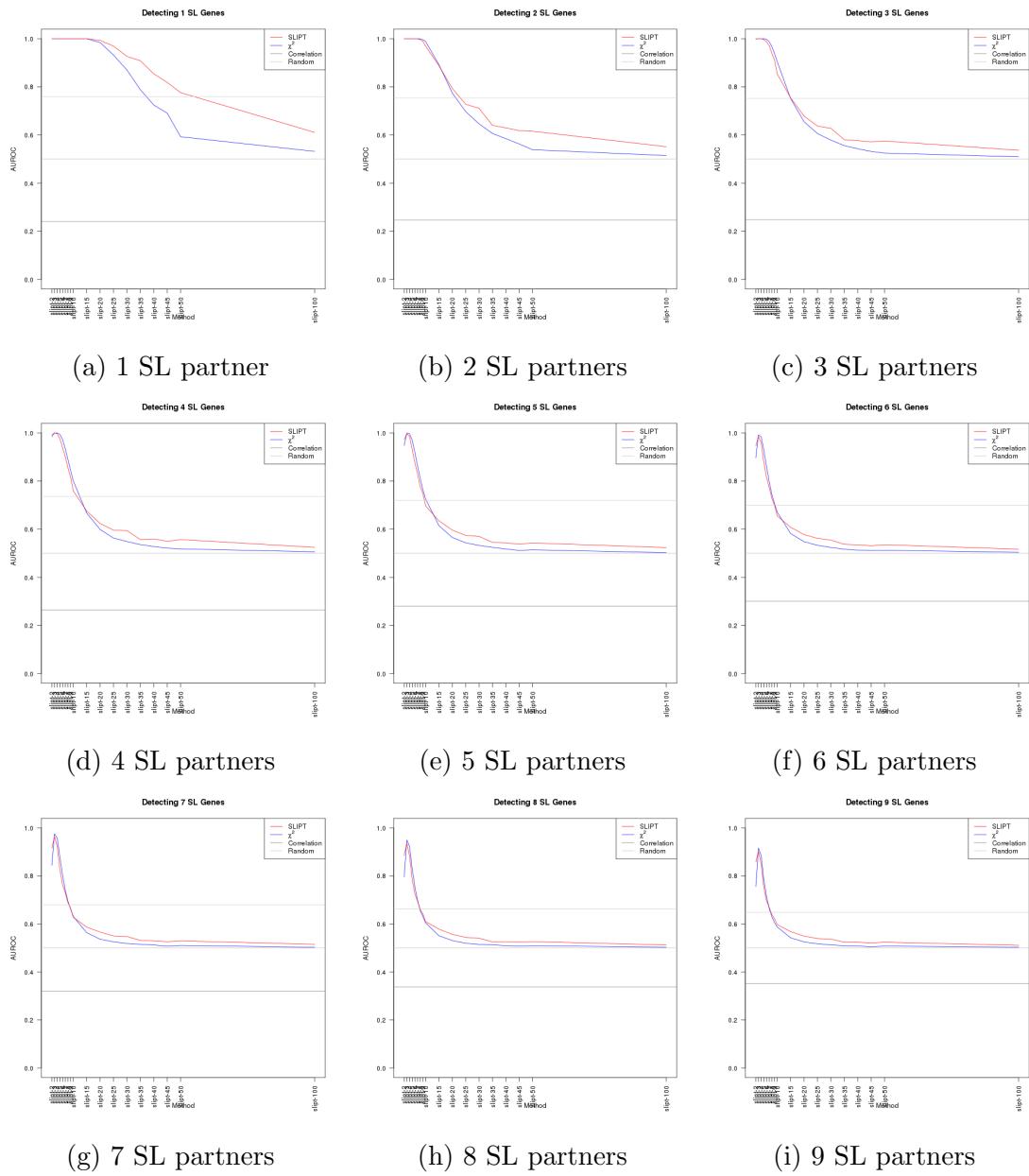


Figure J.2: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

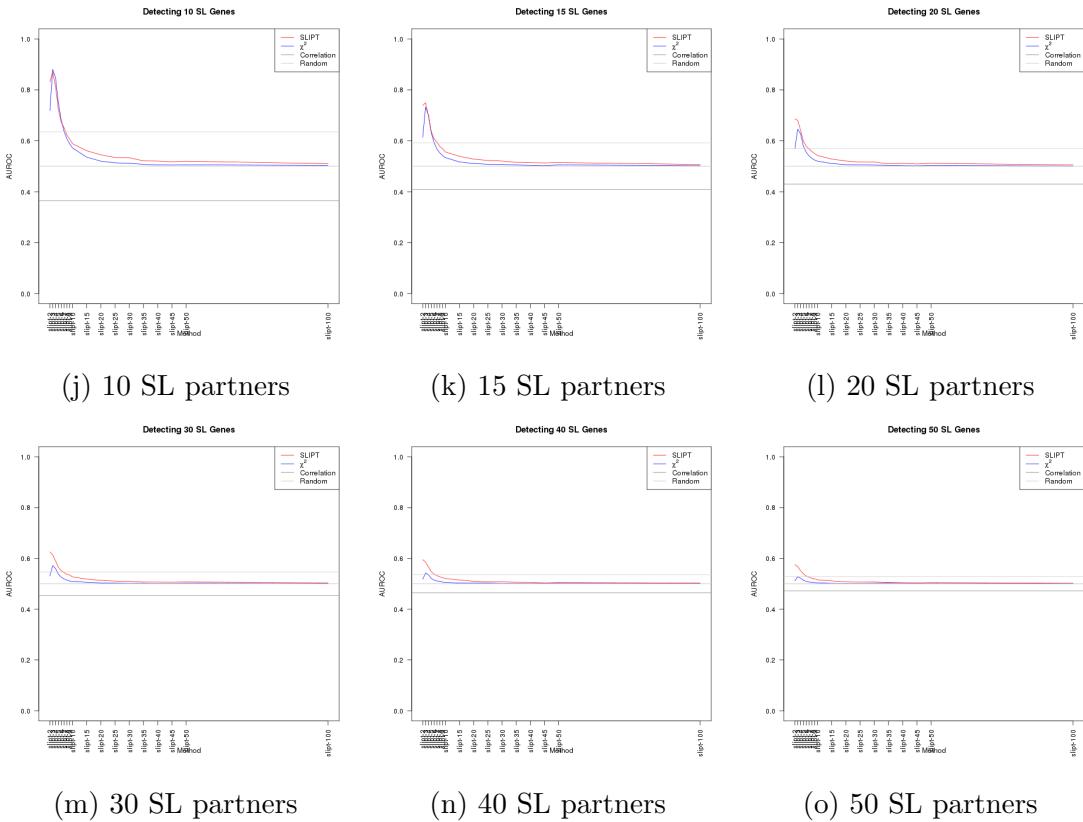


Figure J.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles and converging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

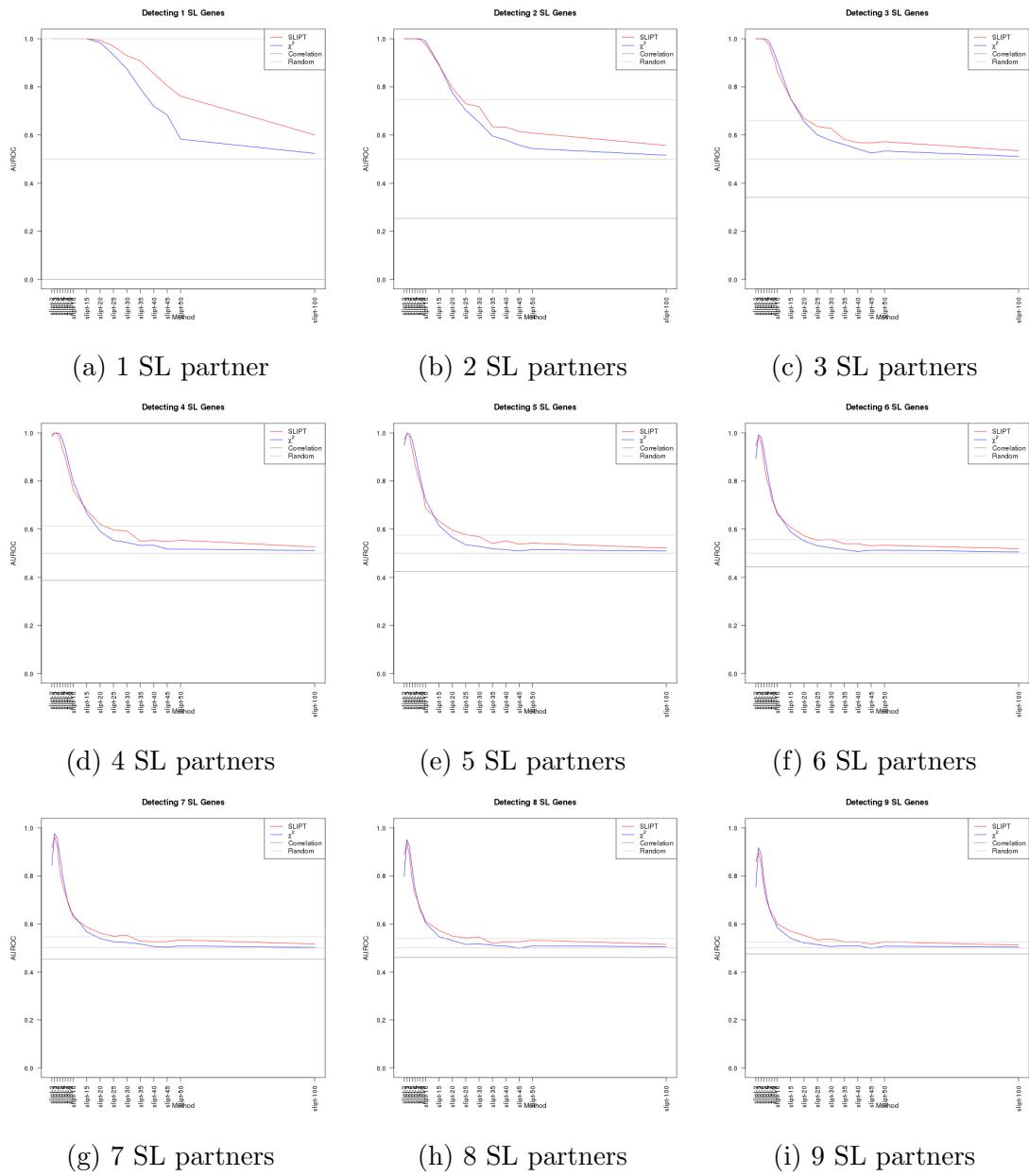


Figure J.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

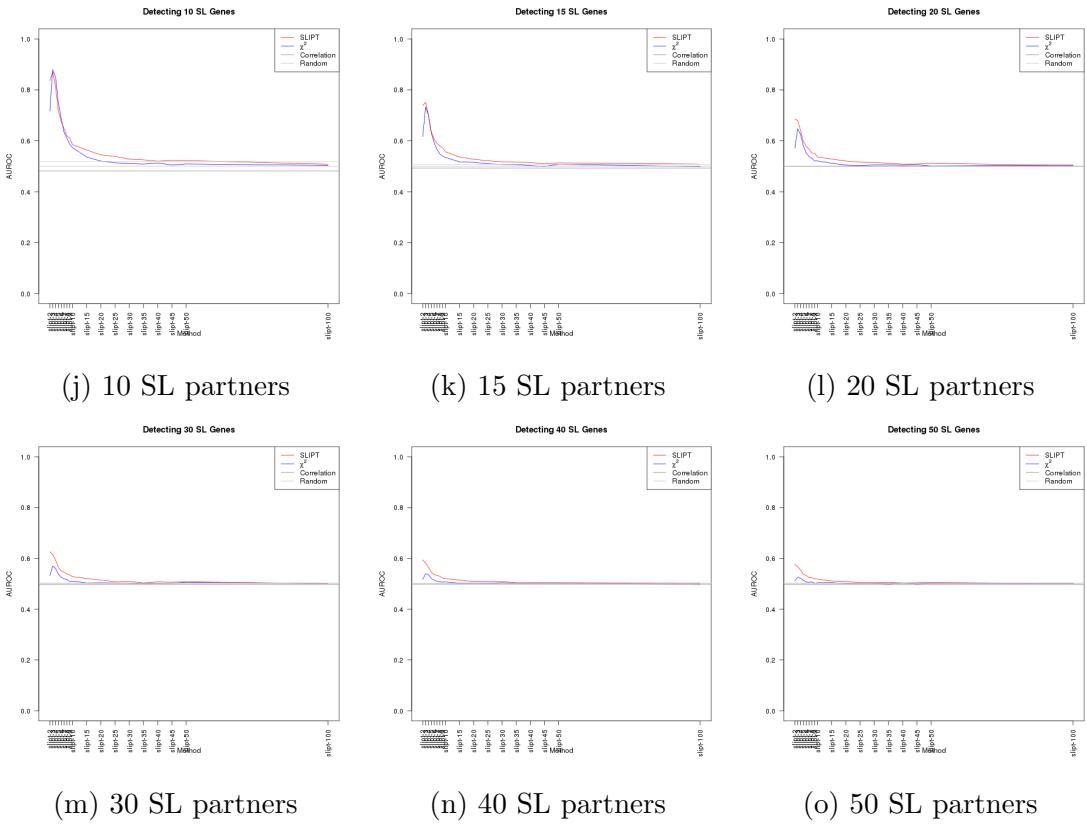


Figure J.3: Performance of χ^2 and SLIPT across quantiles with more genes.
 Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles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

J.1 Correlated Query Genes affects Specificity

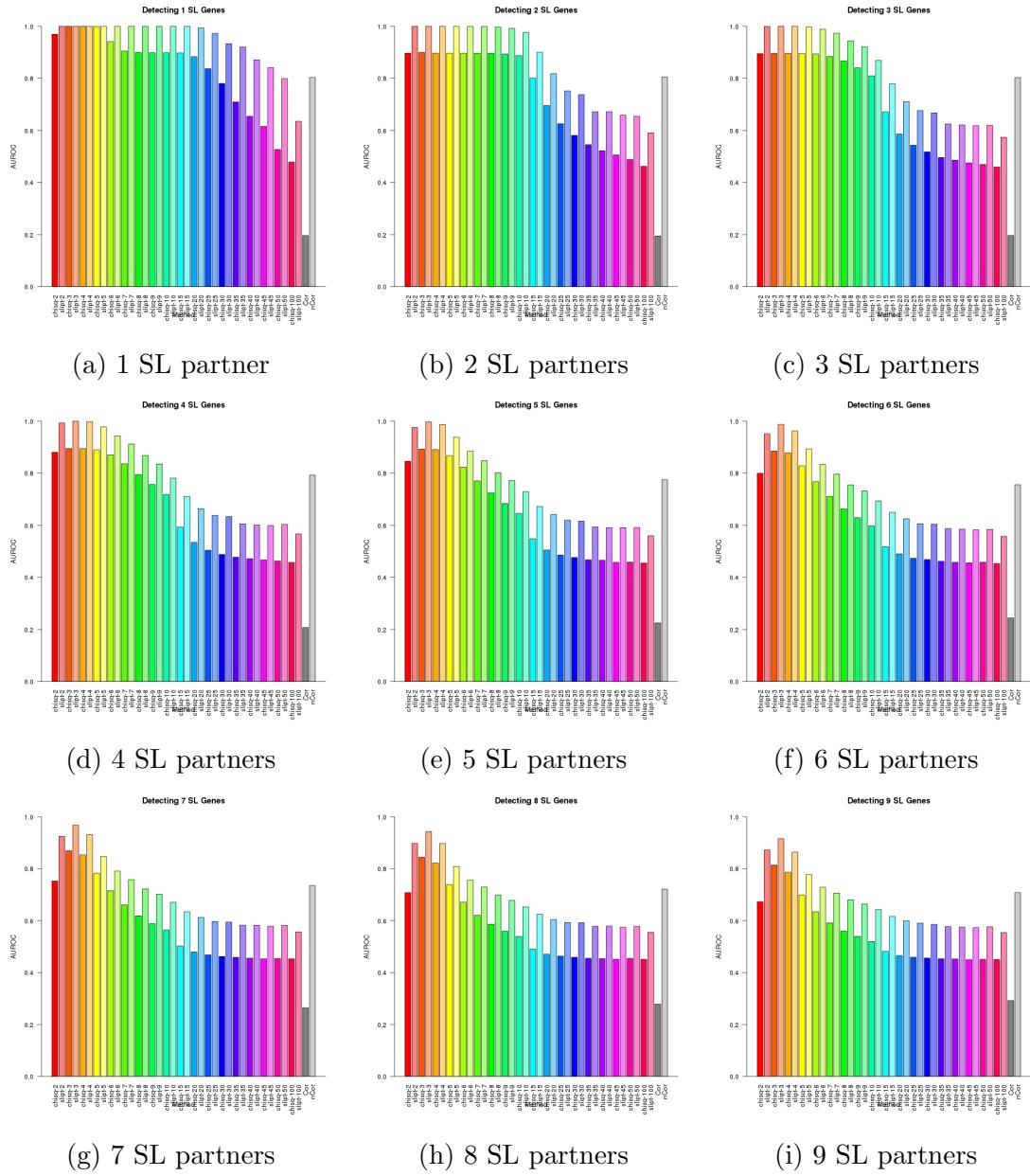


Figure J.4: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

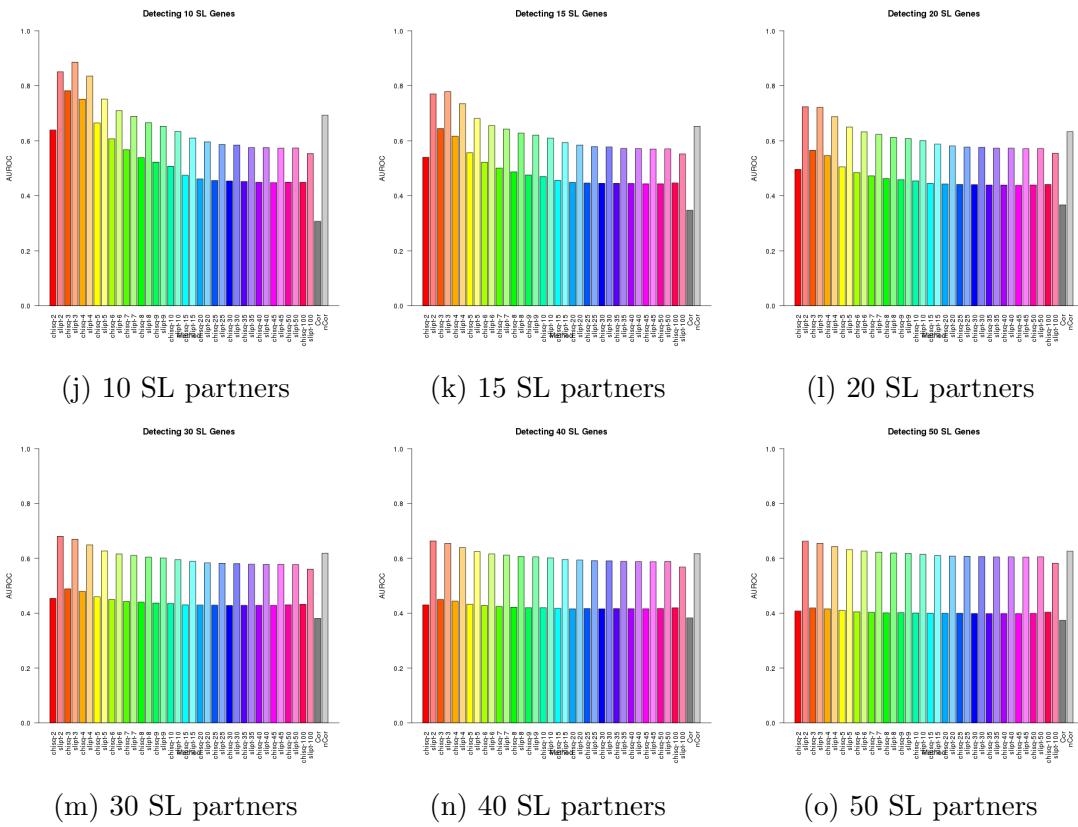


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking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

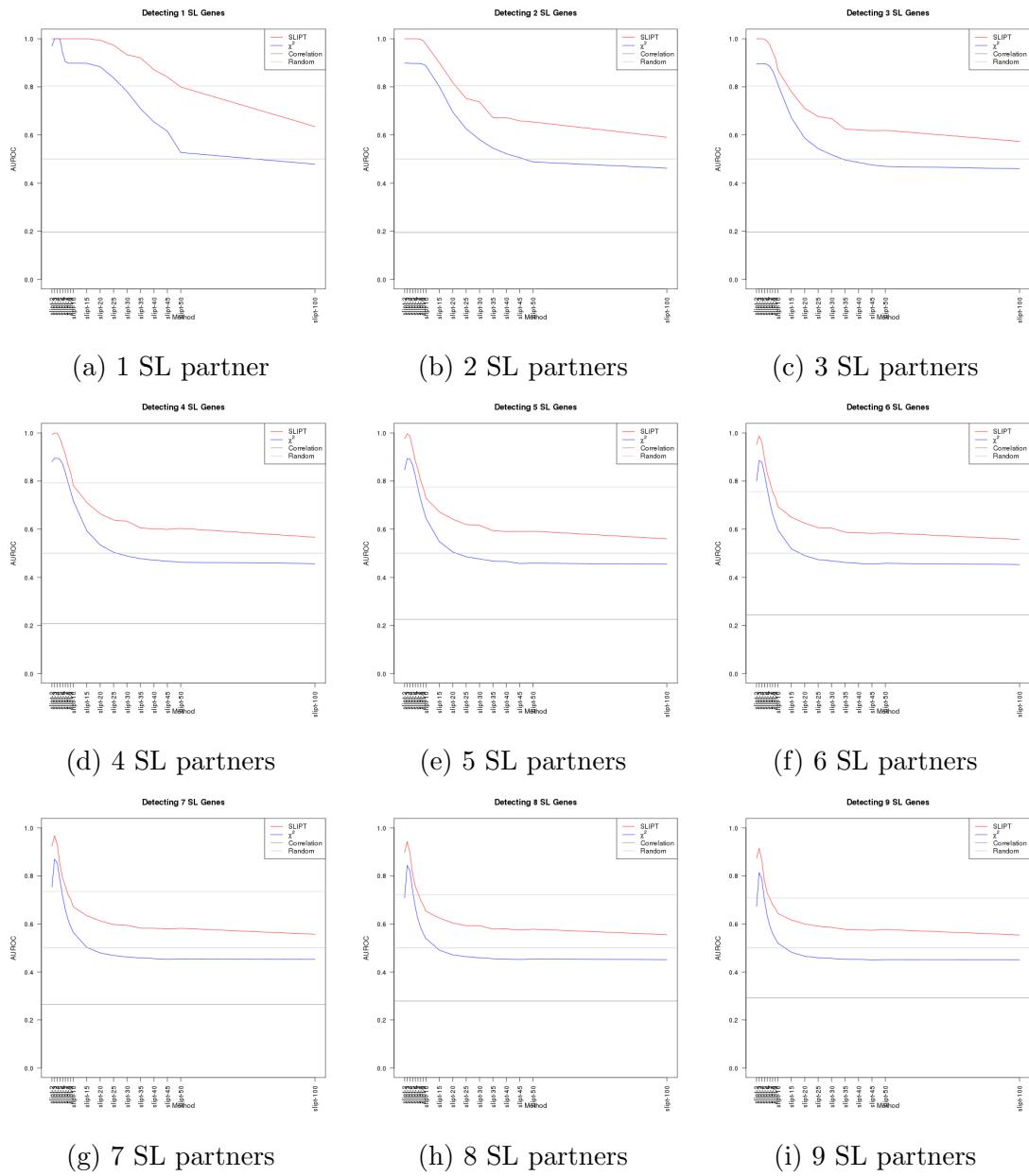


Figure J.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

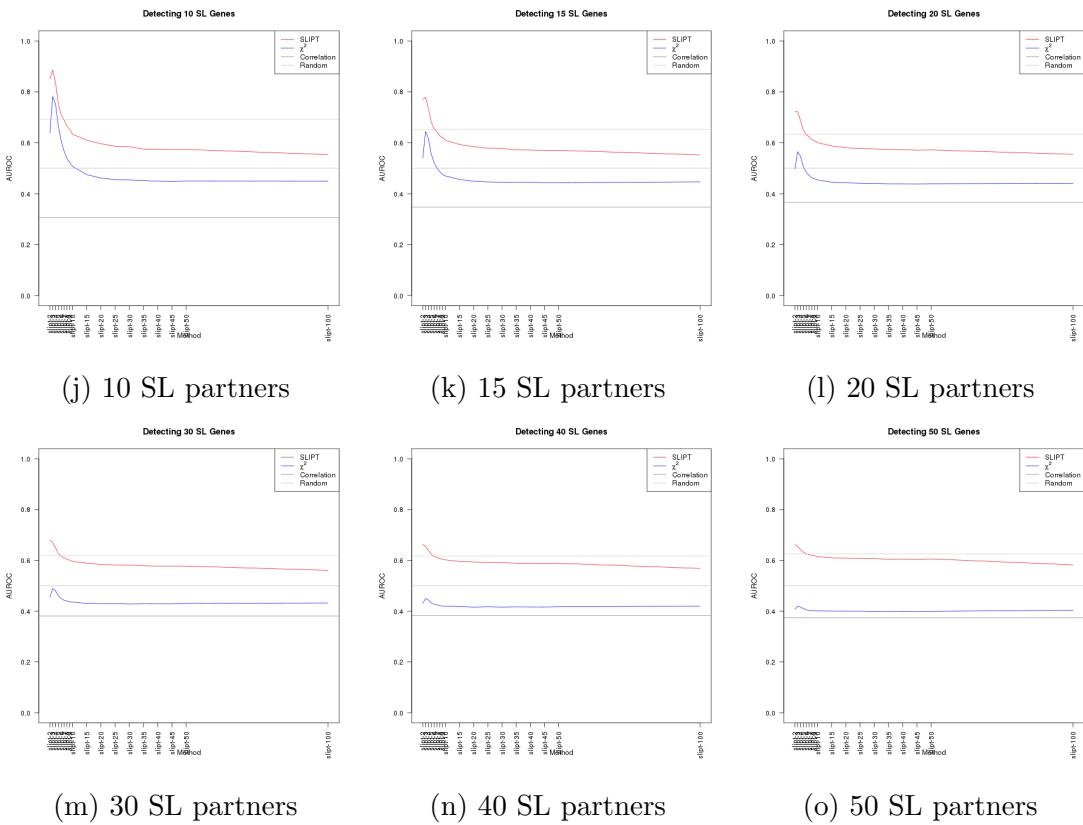


Figure J.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$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

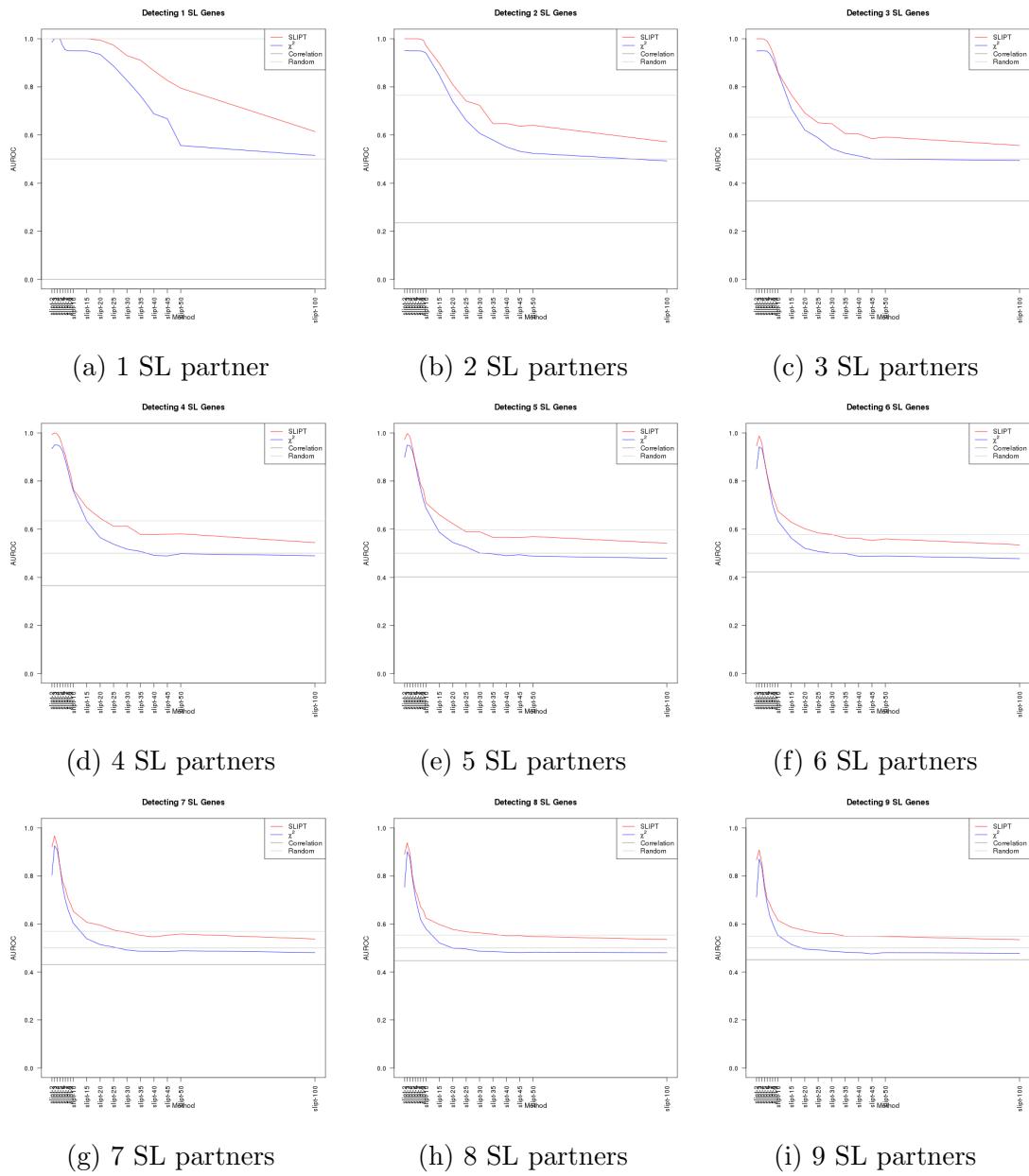


Figure J.6: **Performance of χ^2 and SLIPT across quantiles with query correlation and more genes.** (continued on next page)

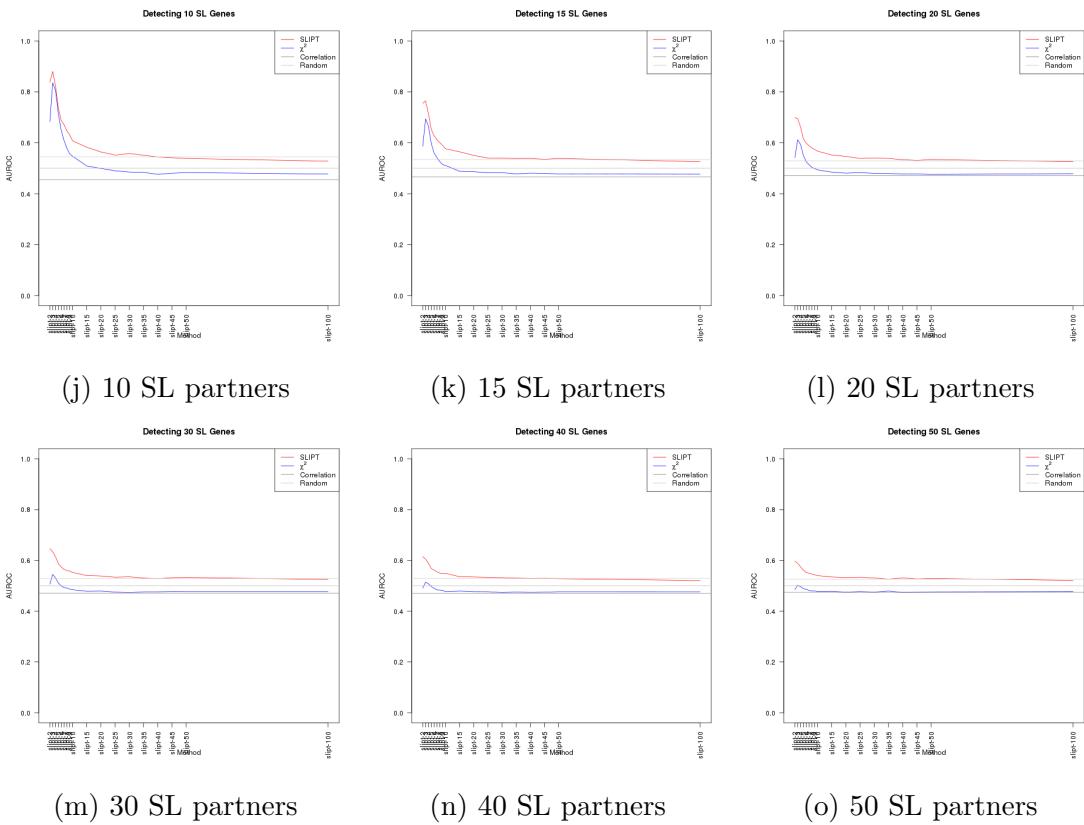
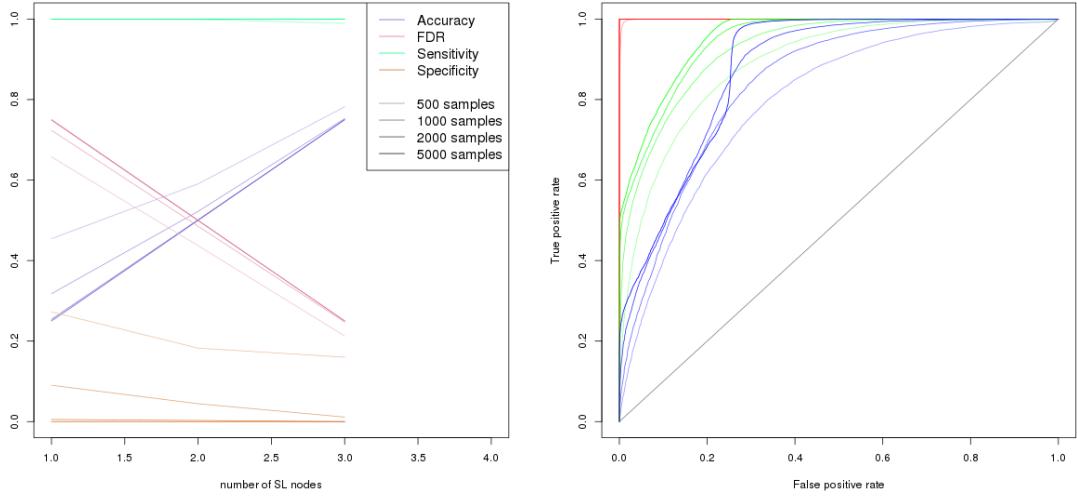


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking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

Appendix K

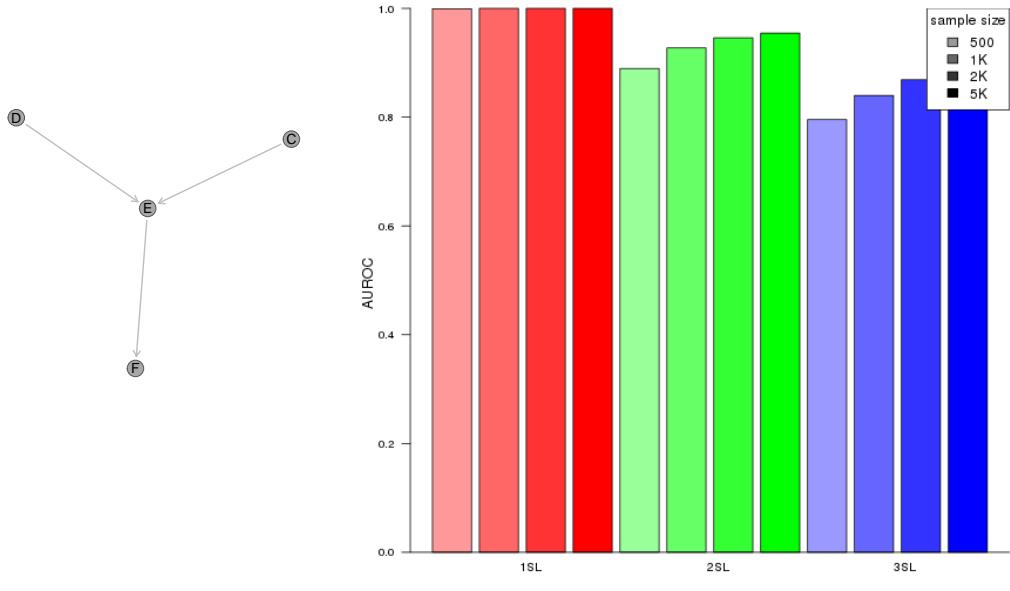
Graph Structures

K.1 Simulations from Simple Graph Structures



(a) Statistical evaluation

(b) Receiver operating characteristic



(c) Graph Structure

(d) Statistical performance

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

K.1.1 Simulations from Inhibiting Graph Structures

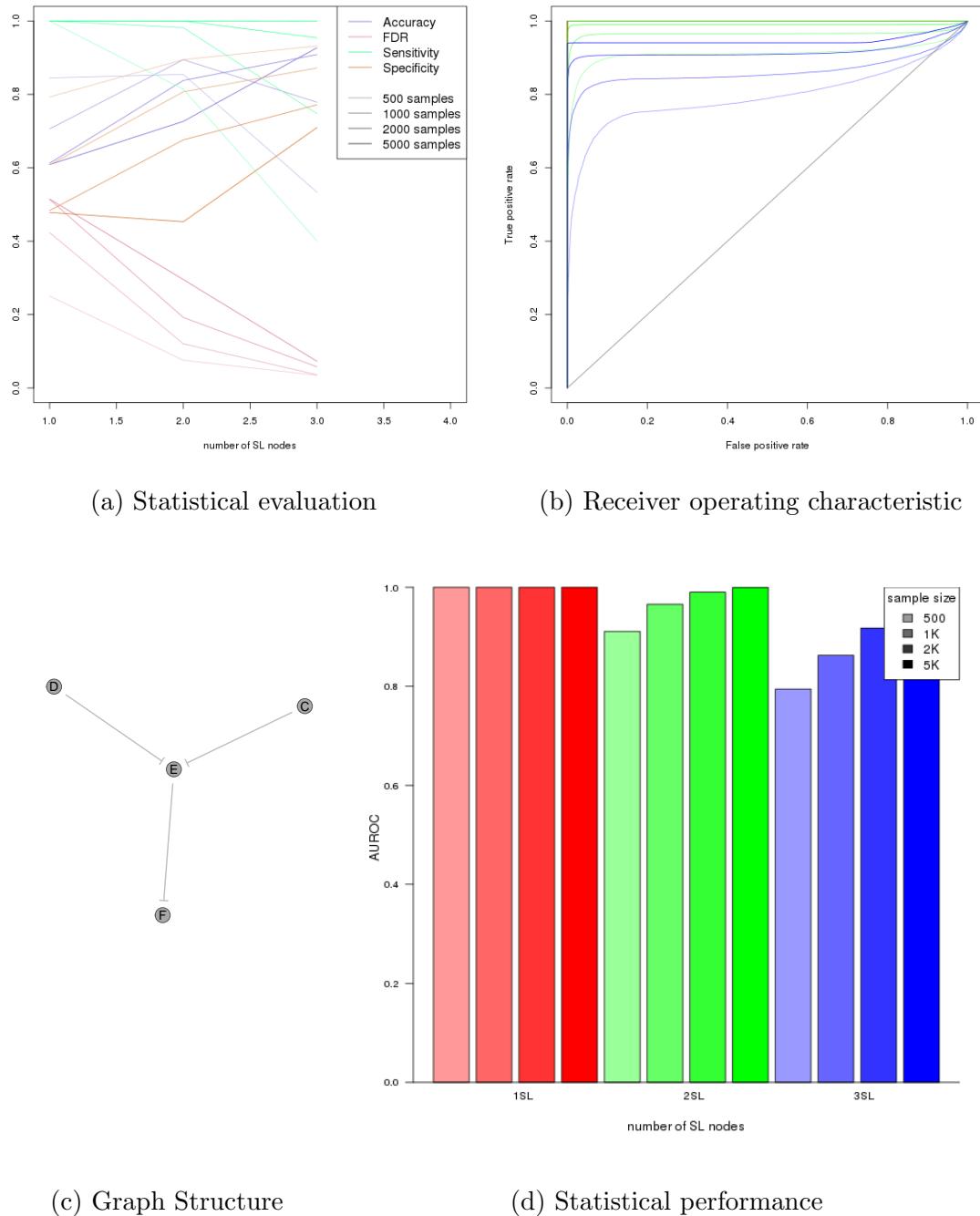


Figure K.2: Performance of simulations on an inhibiting graph. Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.

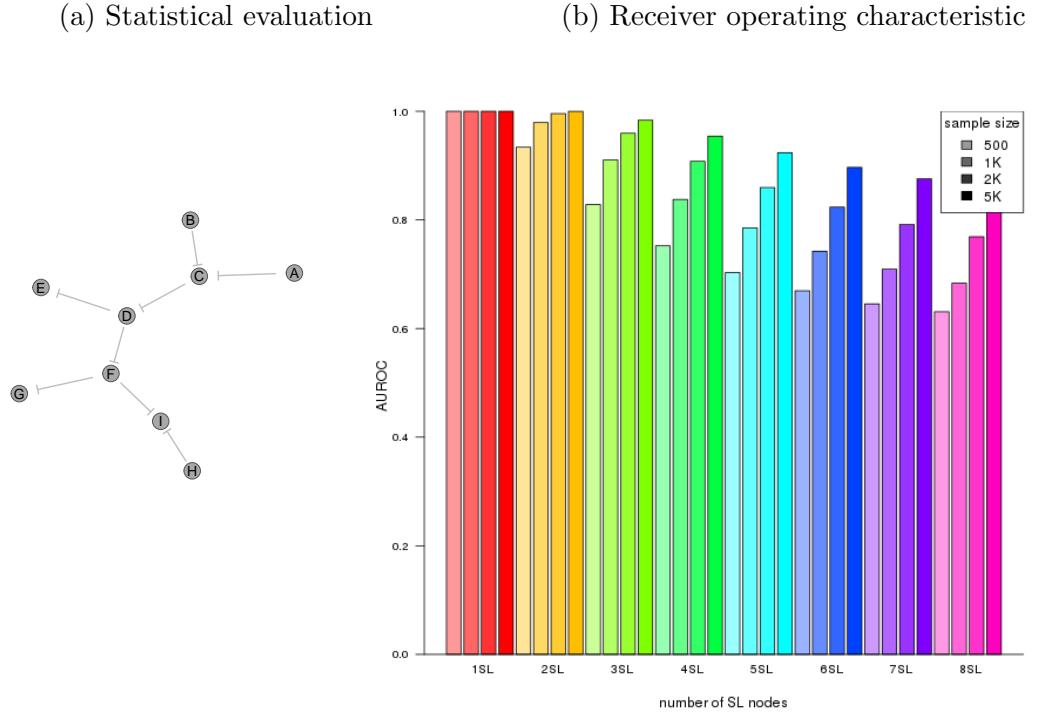
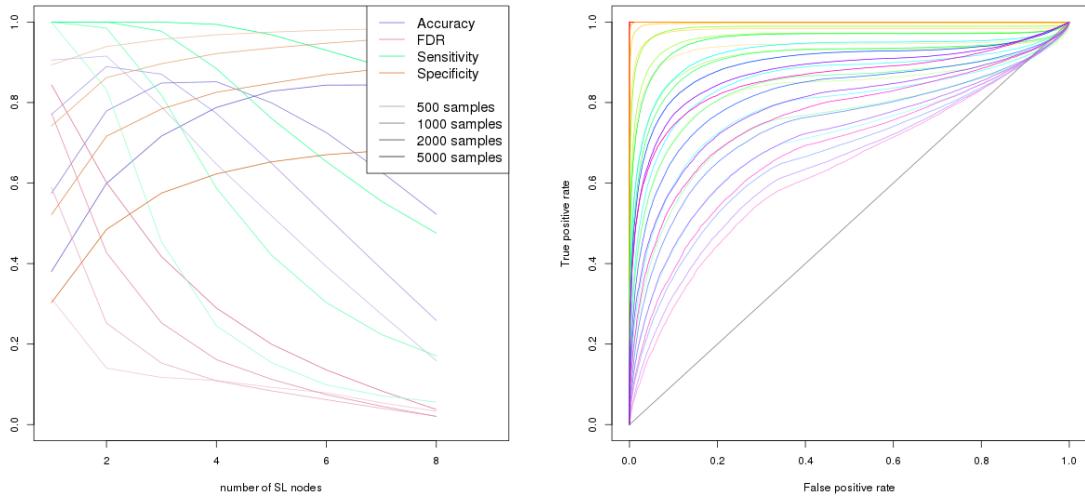
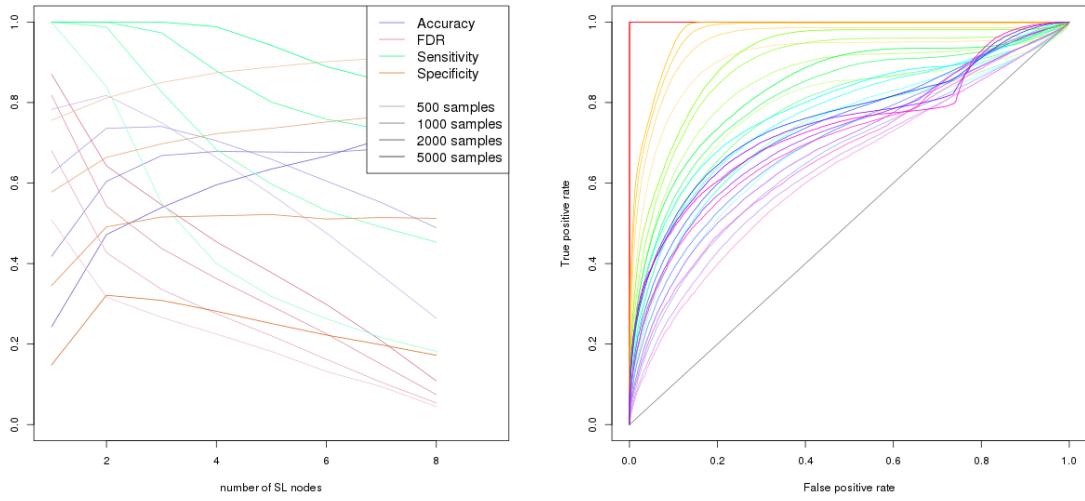
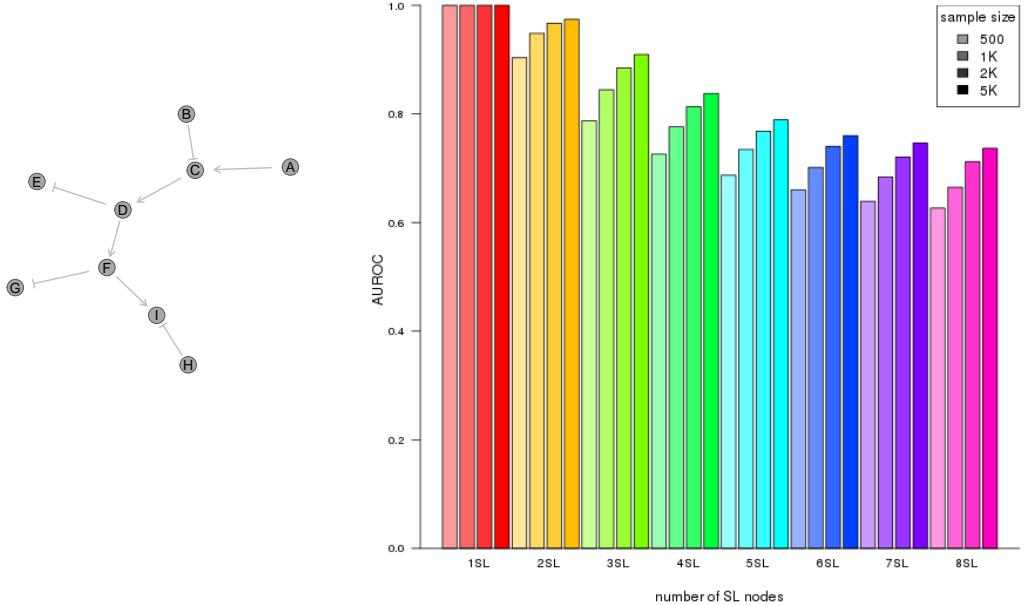


Figure K.3: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph4 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations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



(a) Statistical evaluation

(b) Receiver operating characteristic

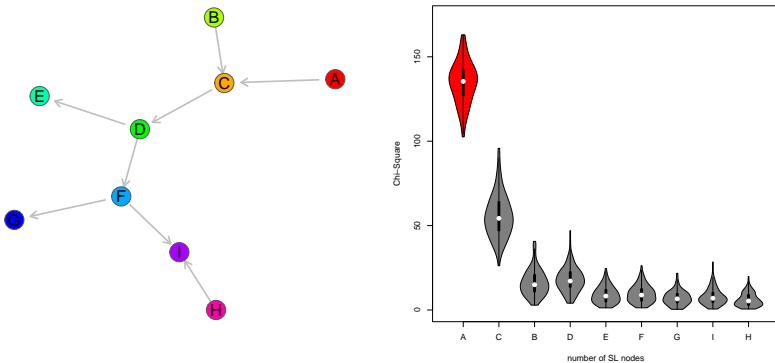


(c) Graph Structure

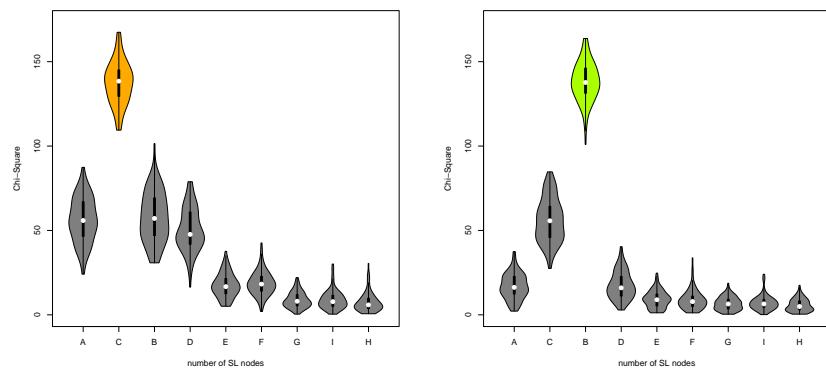
(d) Statistical performance

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

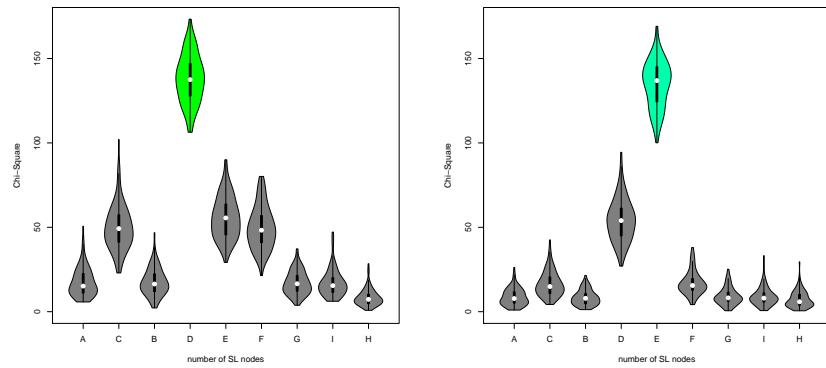
K.2 Simulation across Graph Structures



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



(c) Gene “B” SL (d) Gene “C” SL



(e) Gene “D” SL (f) Gene “E” SL

Figure K.5: **Detection of Synthetic Lethality within a Graph Structure.** (continued on next page)

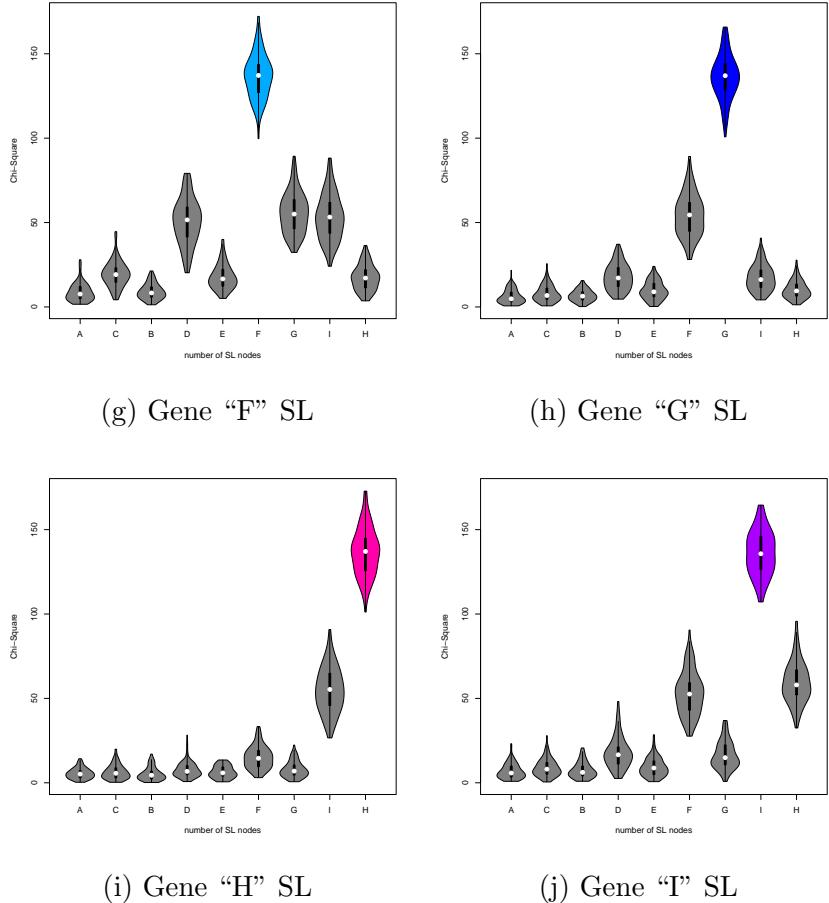
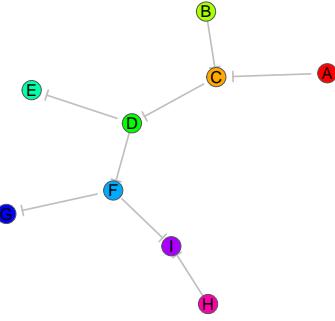
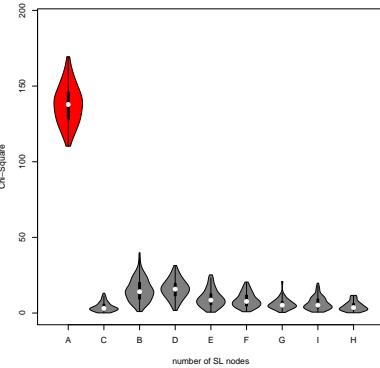


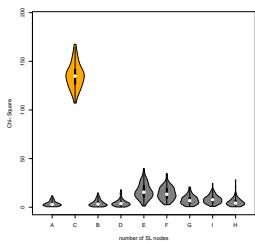
Figure K.5: Detection of Synthetic Lethality within a Graph Structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed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



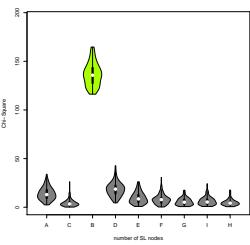
(a) Inhibiting Graph Structure



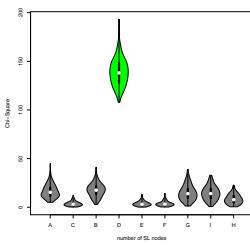
(b) χ^2 distribution for "A" SL



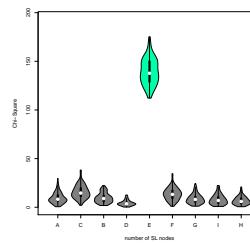
(c) Gene "B" SL



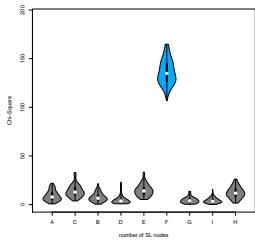
(d) Gene "C" SL



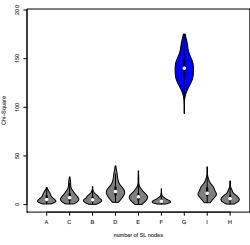
(e) Gene "D" SL



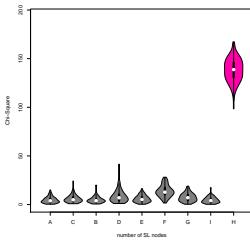
(f) Gene "E" SL



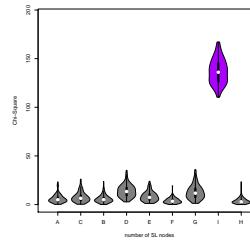
(g) Gene "F" SL



(h) Gene "G" SL

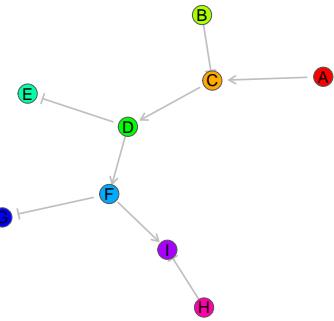


(i) Gene "H" SL

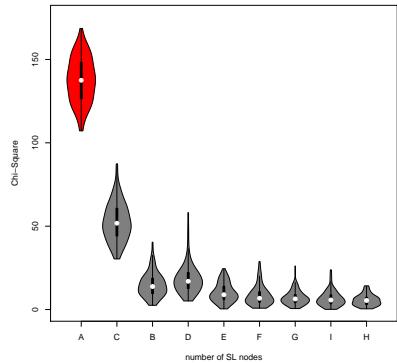


(j) Gene "I" SL

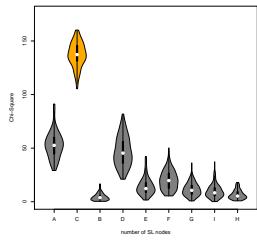
Figure K.6: Detection of Synthetic Lethality within an Inhibiting Graph Structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in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



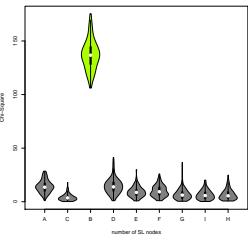
(a) Inhibiting Graph Structure



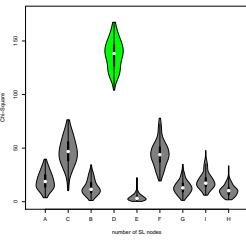
(b) χ^2 distribution for "A" SL



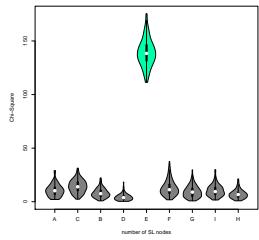
(c) Gene "B" SL



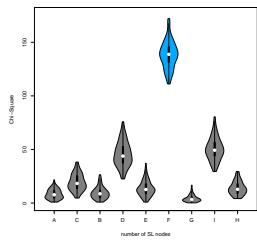
(d) Gene "C" SL



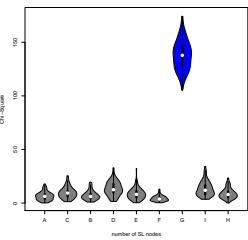
(e) Gene "D" SL



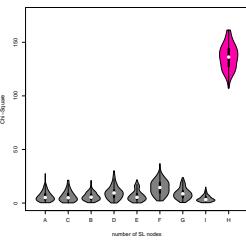
(f) Gene "E" SL



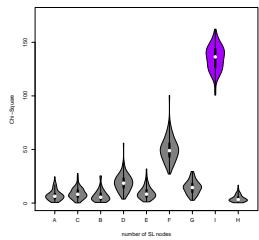
(g) Gene "F" SL



(h) Gene "G" SL



(i) Gene "H" SL



(j) Gene "I" SL

Figure K.7: Detection of Synthetic Lethality within an Inhibiting Graph 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 structure with inhibiting and relationships. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed in 100 simulations of datasets of 20,000 genes including the graph structure and 1000 samples.

K.3 Simulations from Complex Graph Structures

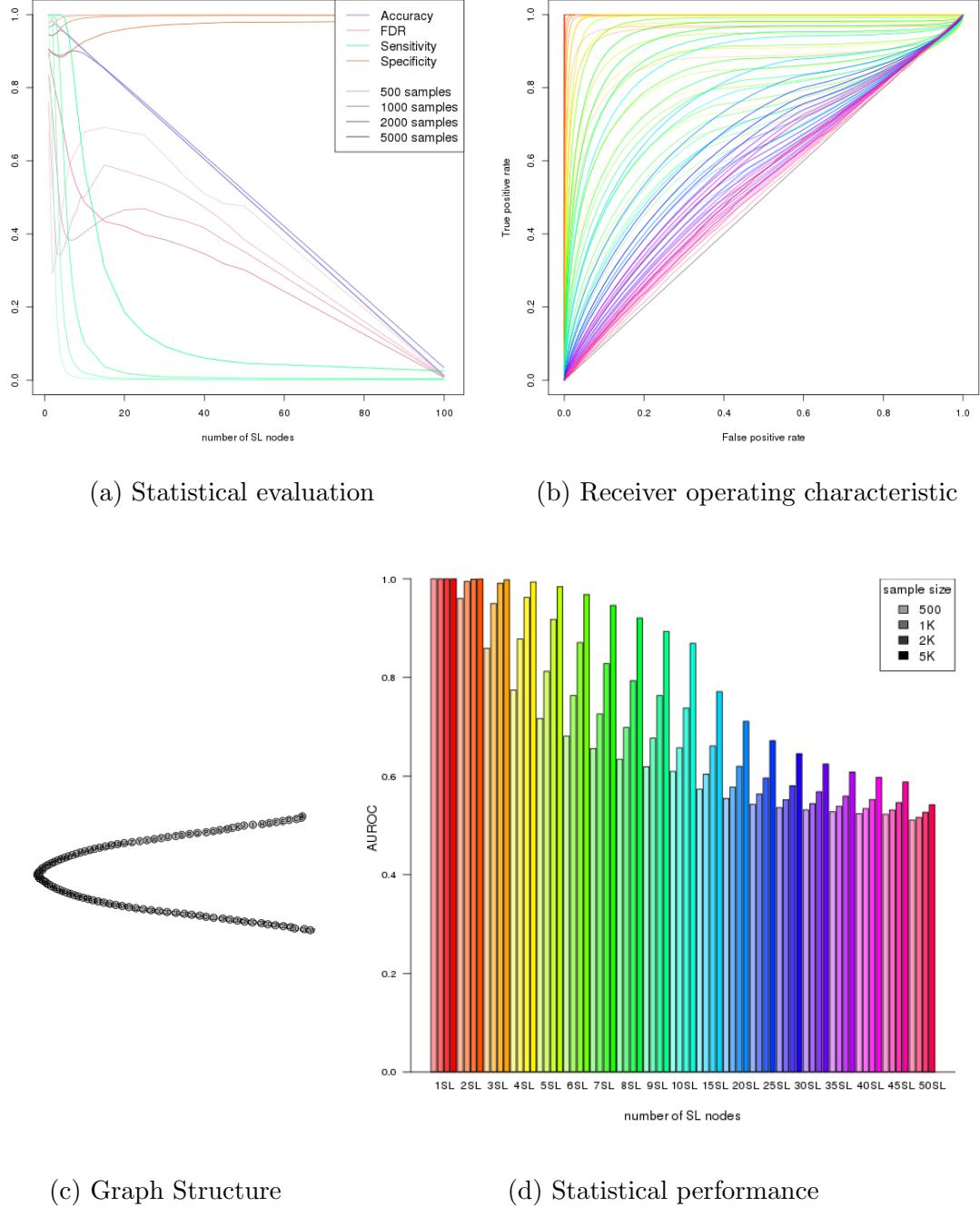
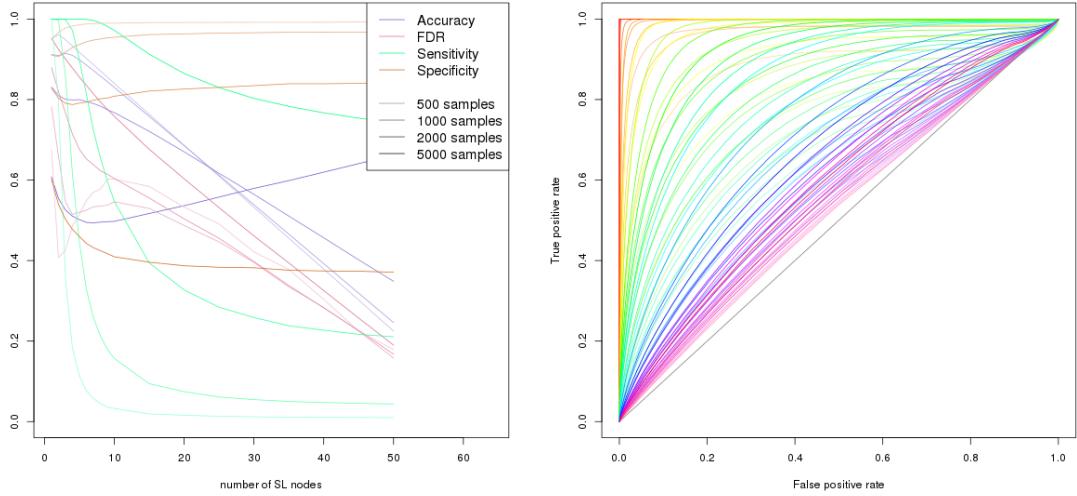
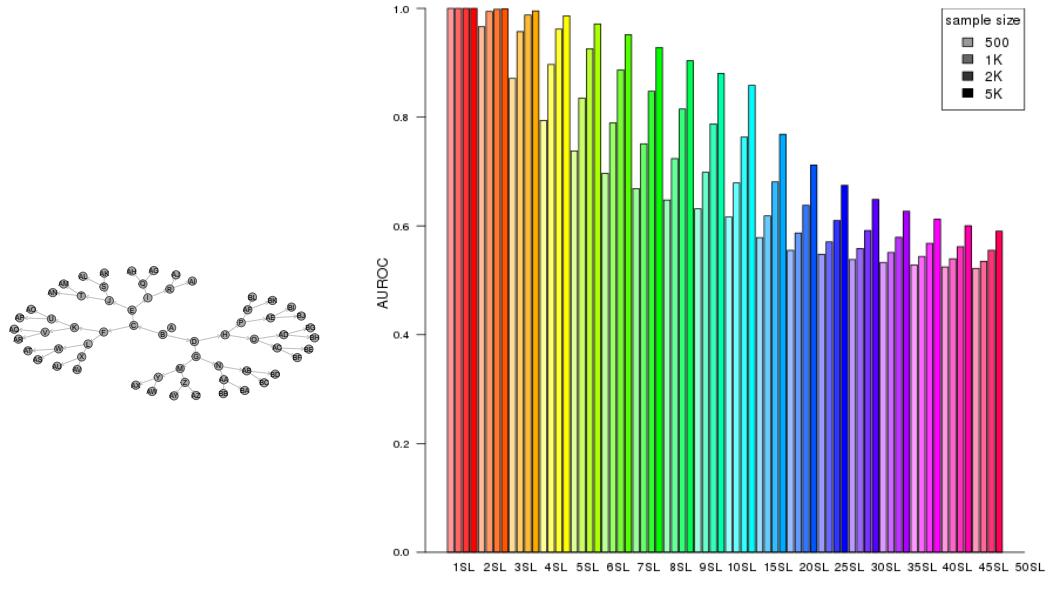


Figure K.8: **Performance of simulations on a large graph.** Simulation of synthetic lethality used a multivariate normal distribution from a large graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.



(a) Statistical evaluation

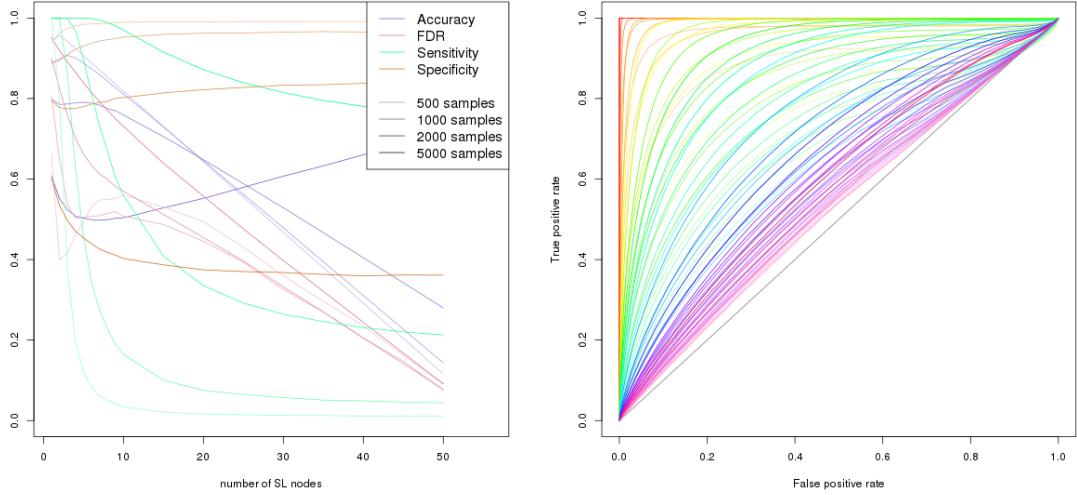
(b) Receiver operating characteristic



(c) Graph Structure

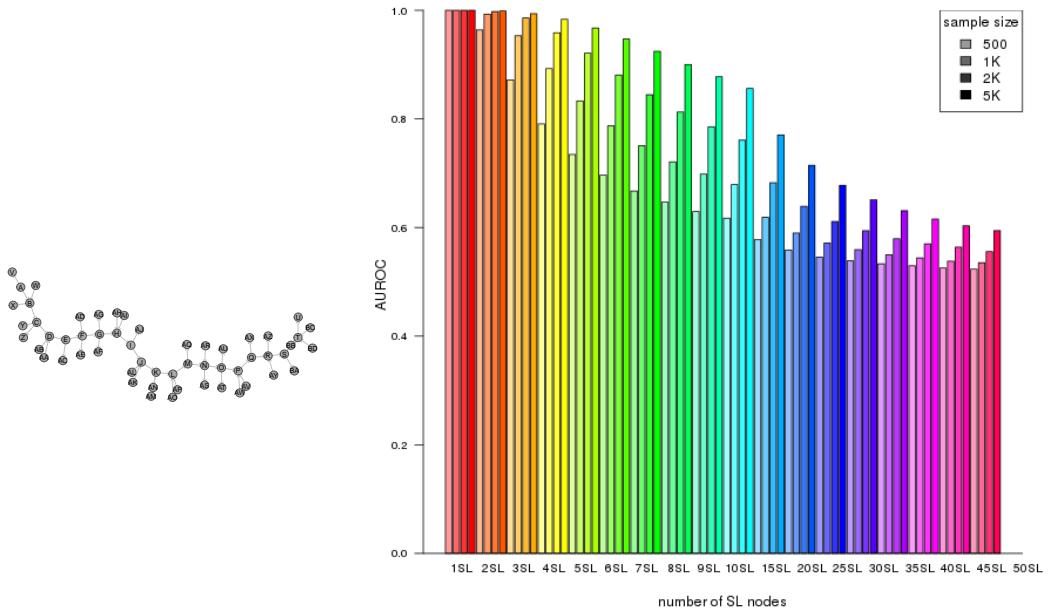
(d) Statistical performance

Figure K.9: Performance of simulations on a 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.9b match Figure K.9d.



(a) Statistical evaluation

(b) Receiver operating characteristic

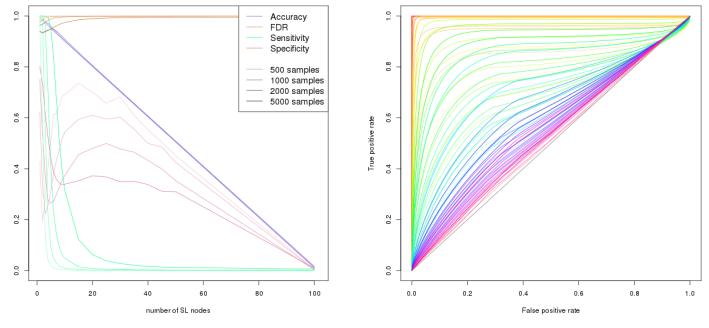


(c) Graph Structure

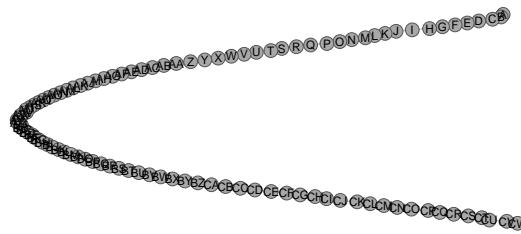
(d) Statistical performance

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

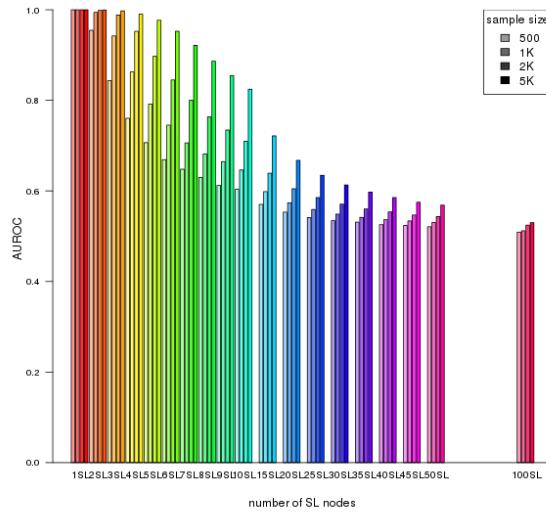
K.3.1 Simulations from Complex Inhibiting Graphs



(a) Statistical evaluation (b) Receiver operating characteristic

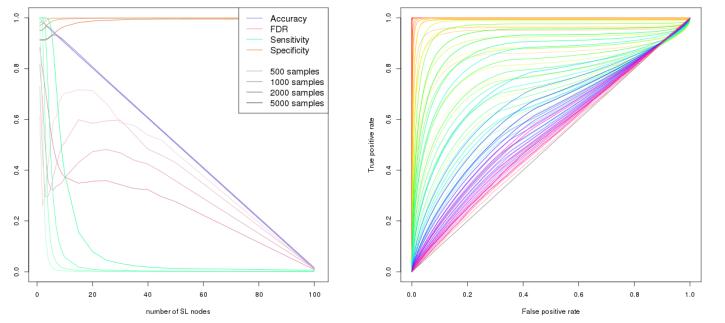


(c) Graph Structure

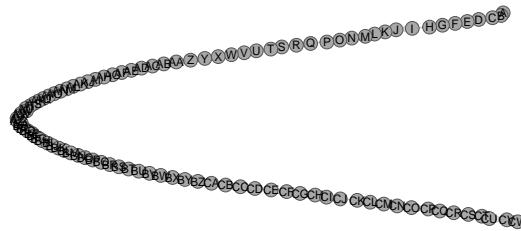


(d) Statistical performance

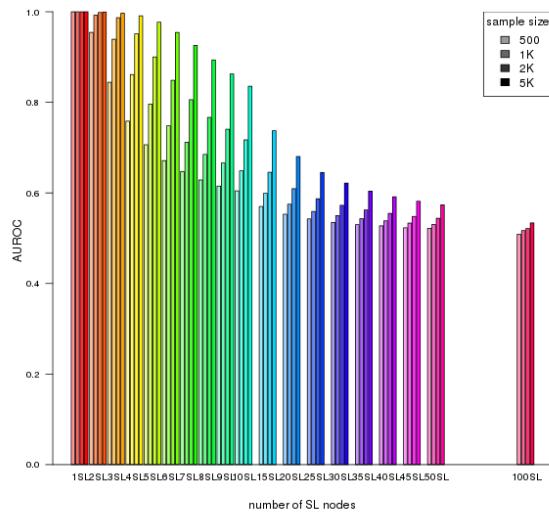
Figure K.11: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph5 with only inhibitions. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

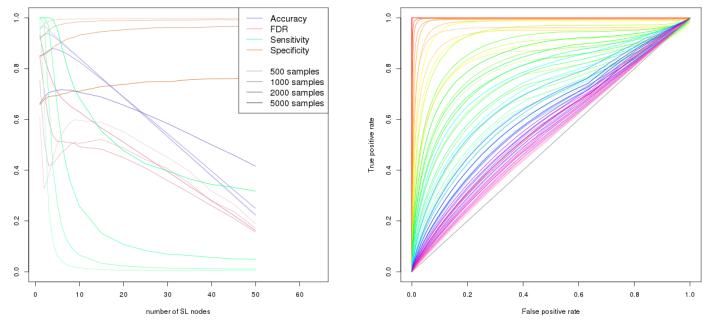


(c) Graph Structure

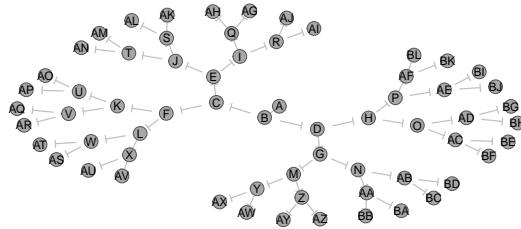


(d) Statistical performance

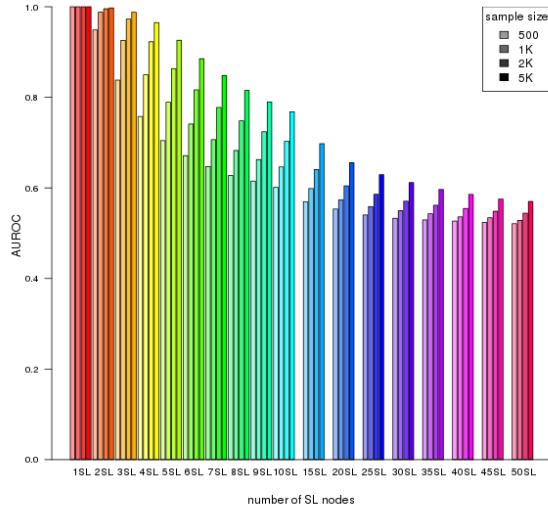
Figure K.12: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph5 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

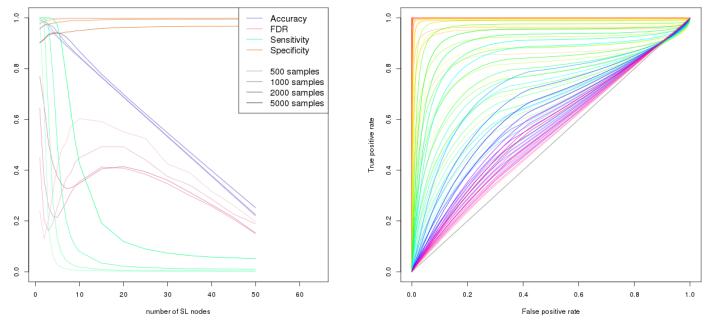


(c) Graph Structure

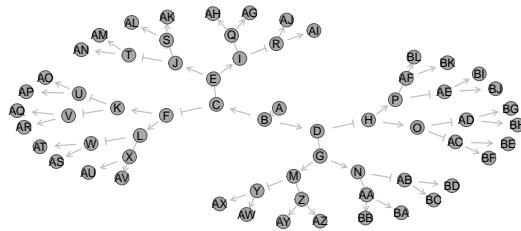


(d) Statistical performance

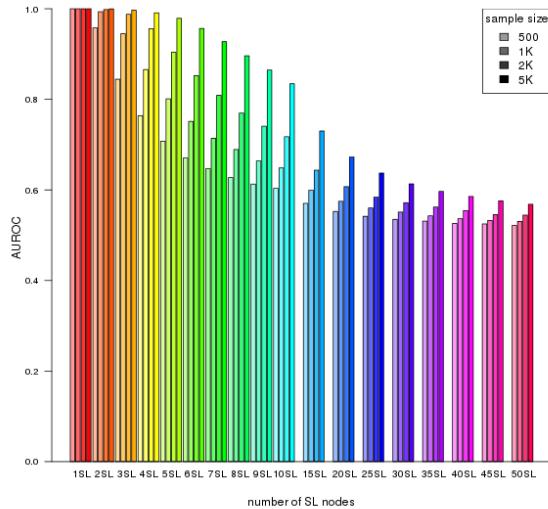
Figure K.13: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph6 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

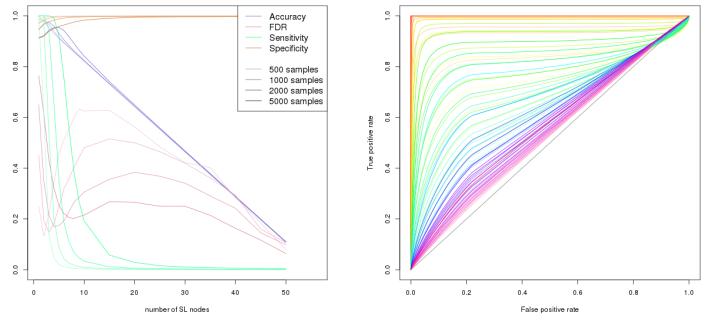


(c) Graph Structure

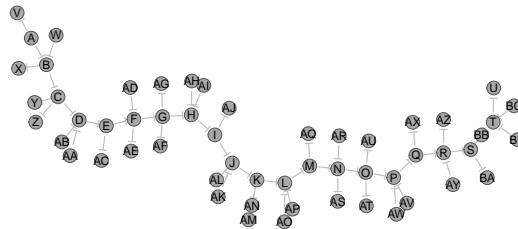


(d) Statistical performance

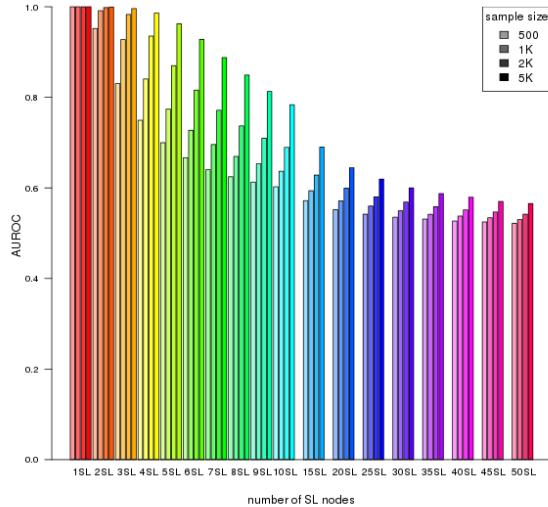
Figure K.14: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph6 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

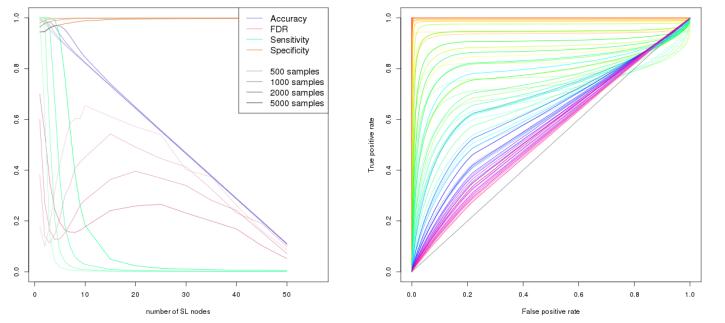


(c) Graph Structure

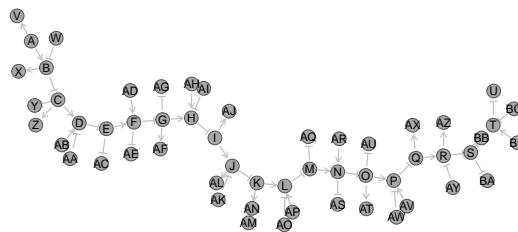


(d) Statistical performance

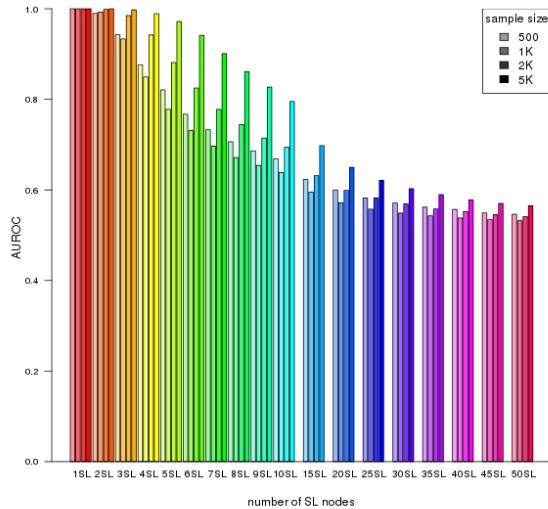
Figure K.15: Performance of simulations on a complex graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph7 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic



(c) Graph Structure



(d) Statistical performance

Figure K.16: Performance of simulations on a complex graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph7 with a combination of relationships. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations were used.

K.4 Simulations from Pathway Graph Structures

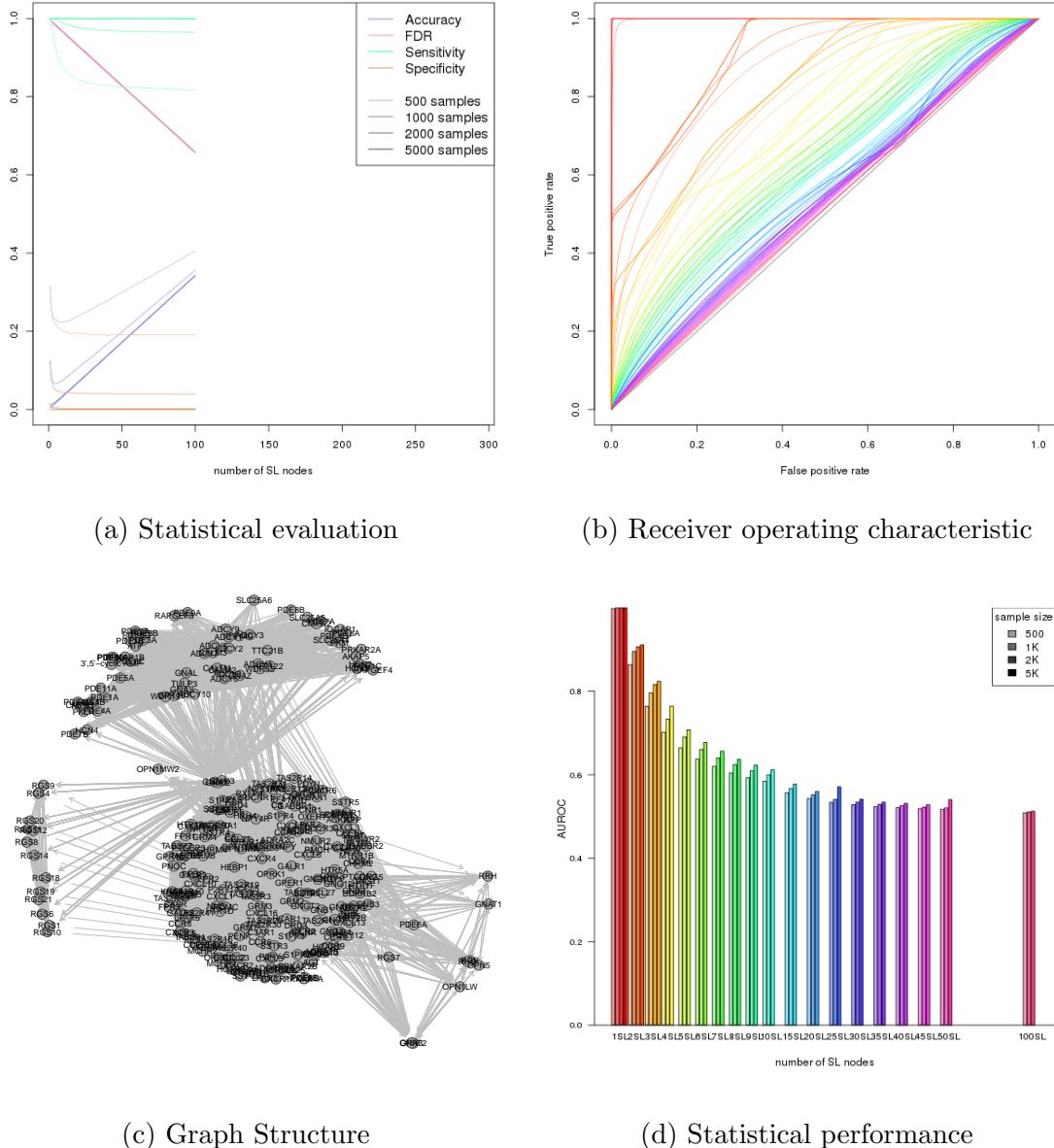
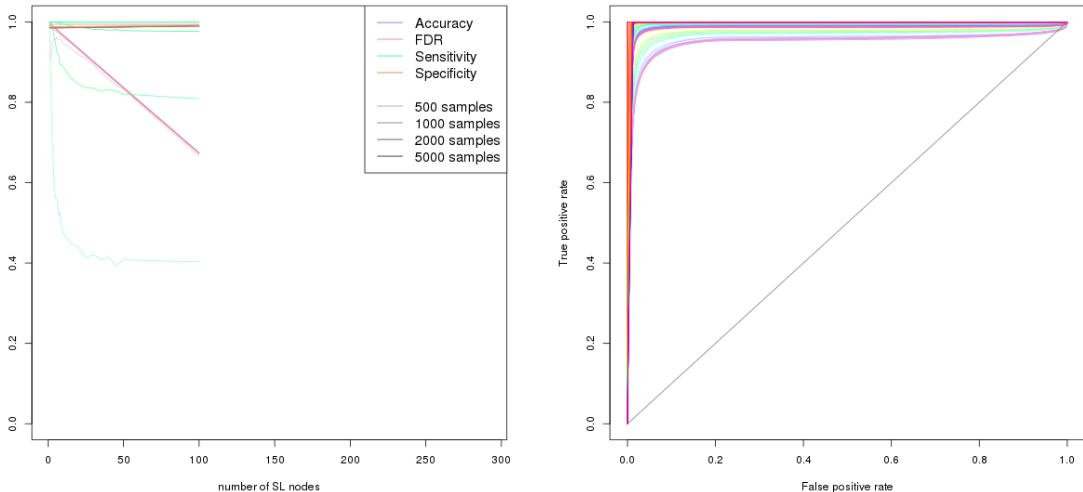
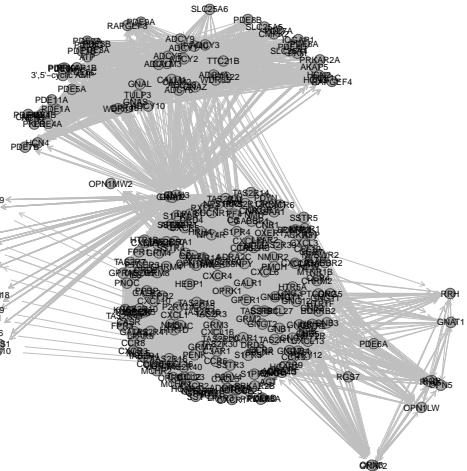


Figure K.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters for detecting synthetic lethality in the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

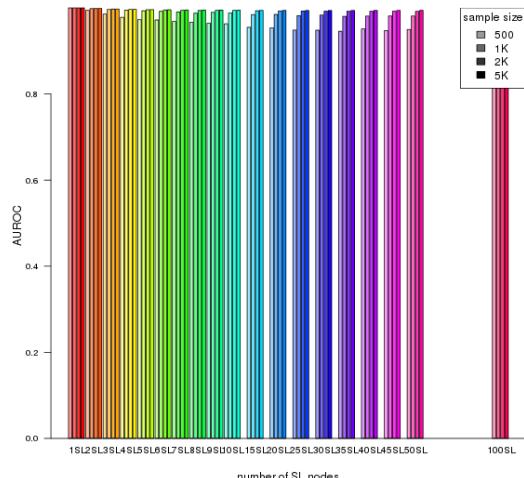


(a) Statistical evaluation

(b) Receiver operating characteristic



(c) Graph Structure



(d) Statistical performance

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