

Contents

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	61
2.2.1	Normalisation	61
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	66
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	68
2.4	Pathway Structure Methods	69
2.4.1	Network and Graph Analysis	69
2.4.2	Sourcing Graph Structure Data	70

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	73
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
3.3.2.2.1	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	111
3.5.3.1	Sampling Simulated Data from Graph Structures	111
3.5.3.2	Plotting Directed Graph Structures	111
3.5.3.3	Computing Information Centrality	112
3.5.3.4	Testing Pathway Structure with Permutation Testing	112
3.5.3.5	Metapackage to Install iGraph Functions	113
4	Synthetic Lethal Analysis of Gene Expression Data	114
4.1	Synthetic lethal genes in breast cancer	115
4.1.1	Synthetic lethal pathways in breast cancer	117
4.1.2	Expression profiles of synthetic lethal partners	118
4.1.2.1	Subgroup pathway analysis	121
4.2	Comparison of synthetic lethal gene candidates	124
4.2.1	Comparison with siRNA screen candidates	124
4.2.1.1	Comparison with correlation	125
4.2.1.2	Comparison with viability	126
4.2.1.3	Comparison with secondary siRNA screen candidates	130
4.2.1.4	Comparison of screen at pathway level	130
4.2.1.4.1	Resampling of genes for pathway enrichment	132
4.3	Metagene Analysis	138

4.3.1	Pathway expression	138
4.3.2	Somatic mutation	141
4.3.3	Mutation locus	142
4.3.4	Synthetic lethal metagenes	144
4.4	Replication in stomach cancer	145
4.4.1	Synthetic Lethal Genes and Pathways	146
4.4.2	Synthetic Lethal Expression Profiles	148
4.4.3	Comparison to Primary Screen	150
4.4.3.1	Resampling Analysis	151
4.4.4	Metagene Analysis	151
4.5	Global Synthetic Lethality	152
4.5.1	Hub Genes	153
4.5.2	Hub Pathways	155
4.6	Replication in cell line encyclopaedia	156
4.7	Discussion	158
4.7.1	Strengths of the SLIPT Methodology	158
4.7.2	Syntheic Lethal Pathways for E-cadherin	159
4.7.3	Replication and Validation	161
4.7.3.1	Integration with siRNA Screening	161
4.7.3.2	Replication across Tissues and Cell lines	162
4.8	Summary	163
5	Synthetic Lethal Pathway Structure	166
5.1	Synthetic Lethal Genes in Reactome Pathways	167
5.1.1	The PI3K/AKT Pathway	167
5.1.2	The Extracellular Matrix	169
5.1.3	G Protein Coupled Receptors	172
5.1.4	Gene Regulation and Translation	172
5.2	Network Analysis of Synthetic Lethal Genes	173
5.2.1	Gene Connectivity and Vertex Degree	173
5.2.2	Gene Importance and Centrality	175
5.2.2.1	Information Centrality	175
5.2.2.2	PageRank Centrality	178
5.3	Testing Pathway Structure of Synthetic Lethal Genes	179
5.3.1	Hierarchical Pathway Structure	179
5.3.1.1	Contextual Hierarchy of PI3K	179
5.3.1.2	Testing Contextual Hierarchy of Synthetic Lethal Genes	179
5.3.2	Upstream or Downstream Synthetic Lethality	183
5.3.2.1	Measuring Structure of Candidates within PI3K . . .	183
5.3.2.2	Resampling for Synthetic Lethal Pathway Structure .	185
5.4	Discussion	186
5.5	Summary	188

6 Simulation and Modeling of Synthetic Lethal Pathways	191
6.1 Comparing methods	192
6.1.1 Performance of SLIPT and χ^2 across Quantiles	193
6.1.1.1 Correlated Query Genes affects Specificity	196
6.1.2 Alternative Synthetic Lethal Detection Strategies	198
6.1.2.1 Correlation for Synthetic Lethal Detection	198
6.1.2.2 Testing for Bimodality with BiSEp	200
6.2 Simulations with Graph Structures	202
6.2.1 Performance over a Graph Structure	203
6.2.1.1 Simple Graph Structures	203
6.2.1.2 Constructed Graph Structures	205
6.2.2 Performance with Inhibitions	209
6.2.3 Synthetic Lethality across Graph Structures	215
6.2.4 Performance with Feasible Gene Numbers (20,000)	218
6.2.4.1 Simple Graph Structures in a Genome	218
6.2.4.2 Constructed Graph Structures in a Genome	218
6.3 Simulations over pathway-based graphs	227
6.3.1 Pathway Structures in a Genome	229
6.4 Discussion	230
6.5 Summary	230
7 Discussion	228
7.1 Significance	228
7.2 Future Directions	229
7.3 Conclusion	230
8 Conclusion	234
References	235
A Sample Quality	260
A.1 Sample Correlation	260
A.2 Replicate Samples in TCGA Breast	263
B Software Used for Thesis	267
C Secondary Screen Data	276
D Mutation Analysis in Breast Cancer	278
D.1 Synthetic Lethal Genes and Pathways	278
D.2 Synthetic Lethal Expression Profiles	281
D.3 Comparison to Primary Screen	284
D.3.1 Resampling Analysis	286
D.4 Compare SLIPT genes	288
D.5 Metagene Analysis	290
D.6 Mutation Variation	291
D.6.1 Mutation Frequency	291

D.6.2	PI3K Mutation Expression	292
E	Metagene Expression Profiles	295
F	Stomach Expression Analysis	301
F.1	Synthetic Lethal Genes and Pathways	301
F.2	Comparison to Primary Screen	304
F.2.1	Resampling Analysis	306
F.3	Metagene Analysis	308
G	Stomach Mutation Analysis	309
G.1	Synthetic Lethal Genes and Pathways	309
G.2	Synthetic Lethal Expression Profiles	312
G.3	Comparison to Primary Screen	315
G.3.1	Resampling Analysis	317
G.4	Metagene Analysis	319
H	Global Synthetic Lethality in Stomach Cancer	320
H.1	Hub Genes	322
H.2	Hub Pathways	323
I	Replication in cell line encyclopaedia	324
J	Synthetic Lethal Genes in Pathways	329
K	Pathway Connectivity for Mutation SLIPT	337
L	Information Centrality for Gene Essentiality	341
M	Pathway Structure for Mutation SLIPT	344
N	Performance of SLIPT and χ^2	347
N.0.1	Correlated Query Genes affects Specificity	353
O	Graph Structures	359
O.1	Simulations from Graph Structures	365
O.2	Simulations from Inhibiting Graph Structures	369
O.3	Simulation across Graph Structures	378
O.4	Simulations from Graph Structures with 20K genes	382
O.5	Simulations from Inhibiting Graph Structures with 20K genes	387
O.6	Simations from Pathway Graph Structures	397

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	112
4.1	Synthetic lethal expression profiles of analysed samples	120
4.2	Comparison of SLIPT to siRNA	124
4.3	Compare SLIPT and siRNA genes with correlation	125
4.4	Compare SLIPT and siRNA genes with correlation	125
4.5	Compare SLIPT and siRNA genes with siRNA viability	127

4.6	Compare SLIPT and siRNA genes with viability	127
4.7	Compare SLIPT and siRNA genes with siRNA viability	129
4.8	Resampled intersection of SLIPT and siRNA candidates	133
4.9	Pathway metagene expression profiles	139
4.10	Somatic mutation against PI3K metagene	141
4.11	Somatic mutation locus against expression	143
4.12	Synthetic lethal expression profiles of stomach samples	149
4.13	Synthetic lethal partners across query genes	153
5.1	Synthetic Lethality in the PI3K Cascade	168
5.2	Synthetic Lethality in the Elastic Fibre Formation Pathway	170
5.3	Synthetic Lethality in the Fibrin Clot Formation	171
5.4	Synthetic Lethality and Vertex Degree	174
5.5	Synthetic Lethality and Centrality	176
5.6	Synthetic Lethality and PageRank	178
5.7	Structure of PI3K Ranking	180
5.8	Synthetic Lethality and Hierarchy Score in PI3K	181
5.9	Hierarchy Score in PI3K against Synthetic Lethality in PI3K	181
5.10	Structure of Synthetic Lethality in PI3K	182
5.11	Structure of Synthetic Lethality Resampling in PI3K	184
6.1	Performance of χ^2 and SLIPT across quantiles	194
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	195
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	196
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	197
6.5	Performance of negative correlation and SLIPT	199
6.6	Performance of simulations on a simple graph	204
6.7	Performance of simulations is similar in simple graphs	205
6.8	Performance of simulations on a constructed graph	206
6.9	Performance of simulations on a large graph	208
6.10	Performance of simulations on a simple graph with inhibition	210
6.11	Performance is higher on a simple inhibiting graph	211
6.12	Performance of simulations on a constructed graph with inhibition	213
6.13	Performance is affected by inhibition in graphs	214
6.14	Detection of Synthetic Lethality within a Graph Structure	216
6.16	Detection of Synthetic Lethality within a Graph Structure with Inhibitions	218
6.18	Performance of simulations including a simple graph	219
6.19	Performance on a simple graph improves with more genes	220
6.20	Performance of simulations including a graph structure	221
6.21	Performance of simulations including an inhibiting graph	222
6.22	Performance on an inhibiting graph improves with more genes	223
6.23	Performance of simulations including a graph structure	224
6.24	Performance of simulations including an inhibiting graph	225
6.25	Performance on an inhibiting graph improves with more genes	226
6.26	Performance of simulations on the PI3K cascade	227

6.27	Performance of simulations including the PI3K cascade	228
6.28	Performance on pathways improves with more genes	230
A.1	Correlation profiles of removed samples	261
A.2	Correlation analysis and sample removal	262
A.3	Replicate excluded samples	263
A.4	Replicate samples with all remaining	264
A.5	Replicate samples with some excluded	265
D.1	Synthetic lethal expression profiles of analysed samples	282
D.2	Comparison of mtSLIPT to siRNA	284
D.3	Compare mtSLIPT and siRNA genes with correlation	288
D.4	Compare mtSLIPT and siRNA genes with correlation	288
D.5	Compare mtSLIPT and siRNA genes with siRNA viability	289
D.6	Somatic mutation locus	291
D.7	Somatic mutation against PIK3CA metagene	292
D.8	Somatic mutation against PI3K protein	293
D.9	Somatic mutation against AKT protein	294
E.1	Pathway metagene expression profiles	296
E.2	Expression profiles for constituent genes of PI3K	297
E.3	Expression profiles for p53 related genes	298
E.4	Expression profiles for estrogen receptor related genes	299
E.5	Expression profiles for BRCA related genes	300
F.1	Comparison of SLIPT in stomach to siRNA	304
G.1	Synthetic lethal expression profiles of stomach samples	313
G.2	Comparison of mtSLIPT in stomach to siRNA	315
H.1	Synthetic lethal partners across query genes	321
J.1	Synthetic Lethality in the PI3K/AKT Pathway	329
J.2	Synthetic Lethality in the PI3K/AKT Pathway in Cancer	330
J.3	Synthetic Lethality in the Extracellular Matrix	331
J.4	Synthetic Lethality in the GPCRs	332
J.5	Synthetic Lethality in the GPCR Downstream	333
J.6	Synthetic Lethality in the Translation Elongation	334
J.7	Synthetic Lethality in the Nonsense-mediated Decay	335
J.8	Synthetic Lethality in the 3' UTR	336
K.1	Synthetic Lethality and Vertex Degree	337
K.2	Synthetic Lethality and Centrality	338
K.3	Synthetic Lethality and PageRank	339
L.1	Information centrality distribution	343
M.1	Synthetic Lethality and Heirarchy Score in PI3K	344
M.2	Heirarchy Score in PI3K against Synthetic Lethality in PI3K	345

M.3	Structure of Synthetic Lethality in PI3K	345
M.4	Structure of Synthetic Lethality Resampling	346
N.1	Performance of χ^2 and SLIPT across quantiles	347
N.2	Performance of χ^2 and SLIPT across quantiles	349
N.3	Performance of χ^2 and SLIPT across quantiles with more genes	351
N.4	Performance of χ^2 and SLIPT across quantiles with query correlation	353
N.5	Performance of χ^2 and SLIPT across quantiles with query correlation	355
N.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	357
O.1	Simple graph structures	359
O.2	Simple graph structure	360
O.3	Constructed graph structure	360
O.4	Large constructed graph structure.	361
O.5	Branching constructed graph structure	361
O.6	Complex constructed graph structure	363
O.7	Performance of simulations on a simple graph	365
O.8	Performance of simulations on a constructed graph	366
O.9	Performance of simulations on a branching graph	367
O.10	Performance of simulations on a complex graph	368
O.11	Performance of simulations on a simple graph with inhibition	369
O.12	Performance of simulations on a simple graph with inhibition	370
O.13	Performance of simulations on a constructed graph with inhibition	371
O.14	Performance of simulations on a large constructed graph with inhibition	372
O.15	Performance of simulations on a large constructed graph with inhibition	373
O.16	Performance of simulations on a branching graph with inhibition	374
O.17	Performance of simulations on a branching graph with inhibition	375
O.18	Performance of simulations on a complex graph with inhibition	376
O.19	Performance of simulations on a complex graph with inhibition	377
O.20	Detection of Synthetic Lethality within a Graph Structure	378
O.21	Detection of Synthetic Lethality within an Inhibiting Graph Structure	380
O.23	Detection of Synthetic Lethality within an Inhibiting Graph Structure	381
O.25	Performance of simulations on a simple graph with more genes	383
O.26	Performance of simulations on a simple graph with more genes	384
O.27	Performance of simulations on a simple graph with more genes	385
O.28	Performance of simulations on a simple graph with more genes	386
O.29	Performance of multivariate normal simulations	388
O.30	Performance of multivariate normal simulations	389
O.31	Performance of multivariate normal simulations	390
O.32	Performance of multivariate normal simulations	391
O.33	Performance of multivariate normal simulations	392
O.34	Performance of multivariate normal simulations	393
O.35	Performance of multivariate normal simulations	394
O.36	Performance of multivariate normal simulations	395
O.37	Performance of multivariate normal simulations	396

O.38 Performance of multivariate normal simulations	397
O.39 Performance of multivariate normal simulations	398

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	63
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	116
4.2	Pathways for <i>CDH1</i> partners from SLIPT	118
4.3	Pathway composition for clusters of <i>CDH1</i> partners from SLIPT	122
4.4	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	131
4.5	Pathways for <i>CDH1</i> partners from SLIPT	135
4.6	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen	136
4.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	145
4.8	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	147
4.9	Query synthetic lethal genes with the most SLIPT partners	154
4.10	Pathways for genes with the most SLIPT partners	155
4.11	Pathways for <i>CDH1</i> partners from SLIPT in CCLE	156
4.12	Pathways for <i>CDH1</i> partners from SLIPT in breast CCLE	158
5.1	analysis of variance (ANOVA) for Synthetic Lethality and Vertex Degree	175
5.2	ANOVA for Synthetic Lethality and Information Centrality	177
5.3	ANOVA for Synthetic Lethality and PageRank Centrality	179
5.4	ANOVA for Synthetic Lethality and PI3K Hierarchy	182
5.5	Resampling for pathway structure of synthetic lethal detection methods	186
B.1	R Packages used during Thesis	267
C.1	Comparing SLIPT genes against Secondary siRNA Screen in breast cancer	276
C.2	Comparing mtSLIPT genes against Secondary siRNA Screen in breast cancer	277
C.3	Comparing SLIPT genes against Secondary siRNA Screen in stomach cancer	277

D.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	279
D.2	Pathways for <i>CDH1</i> partners from mtSLIPT	280
D.3	Pathway composition for clusters of <i>CDH1</i> partners from mtSLIPT	283
D.4	Pathway composition for <i>CDH1</i> partners from mtSLIPT and siRNA	285
D.5	Pathways for <i>CDH1</i> partners from mtSLIPT	286
D.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	287
D.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	290
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	302
F.2	Pathway composition for clusters of <i>CDH1</i> partners in stomach SLIPT	303
F.3	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	305
F.4	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	306
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA screen	307
F.6	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT in stomach cancer	308
G.1	Synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT in stomach cancer	310
G.2	Pathways for <i>CDH1</i> partners from mtSLIPT in stomach cancer	311
G.3	Pathway composition for clusters of <i>CDH1</i> partners in stomach mtSLIPT	314
G.4	Pathway composition for <i>CDH1</i> partners from mtSLIPT and siRNA	316
G.5	Pathways for <i>CDH1</i> partners from mtSLIPT in stomach cancer	317
G.6	Pathways for <i>CDH1</i> partners from mtSLIPT in stomach and siRNA screen	318
G.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT in stomach cancer	319
H.1	Query synthetic lethal genes with the most SLIPT partners	322
H.2	Pathways for genes with the most SLIPT partners	323
I.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT in CCLE	325
I.2	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT in breast CCLE	326
I.3	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach CCLE	327
I.4	Pathways for <i>CDH1</i> partners from SLIPT in stomach CCLE	328
I.5	Pathways for <i>CDH1</i> partners from SLIPT in breast and stomach CCLE	328
K.1	ANOVA for Synthetic Lethality and Vertex Degree	340
K.2	ANOVA for Synthetic Lethality and Information Centrality	340
K.3	ANOVA for Synthetic Lethality and PageRank Centrality	340
L.1	Information centrality for genes and molecules in the Reactome network	342
M.1	ANOVA for Synthetic Lethality and PI3K Hierarchy	344
M.2	Resampling for pathway structure of synthetic lethal detection methods	346

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Appendix N

Performance of SLIPT and χ^2

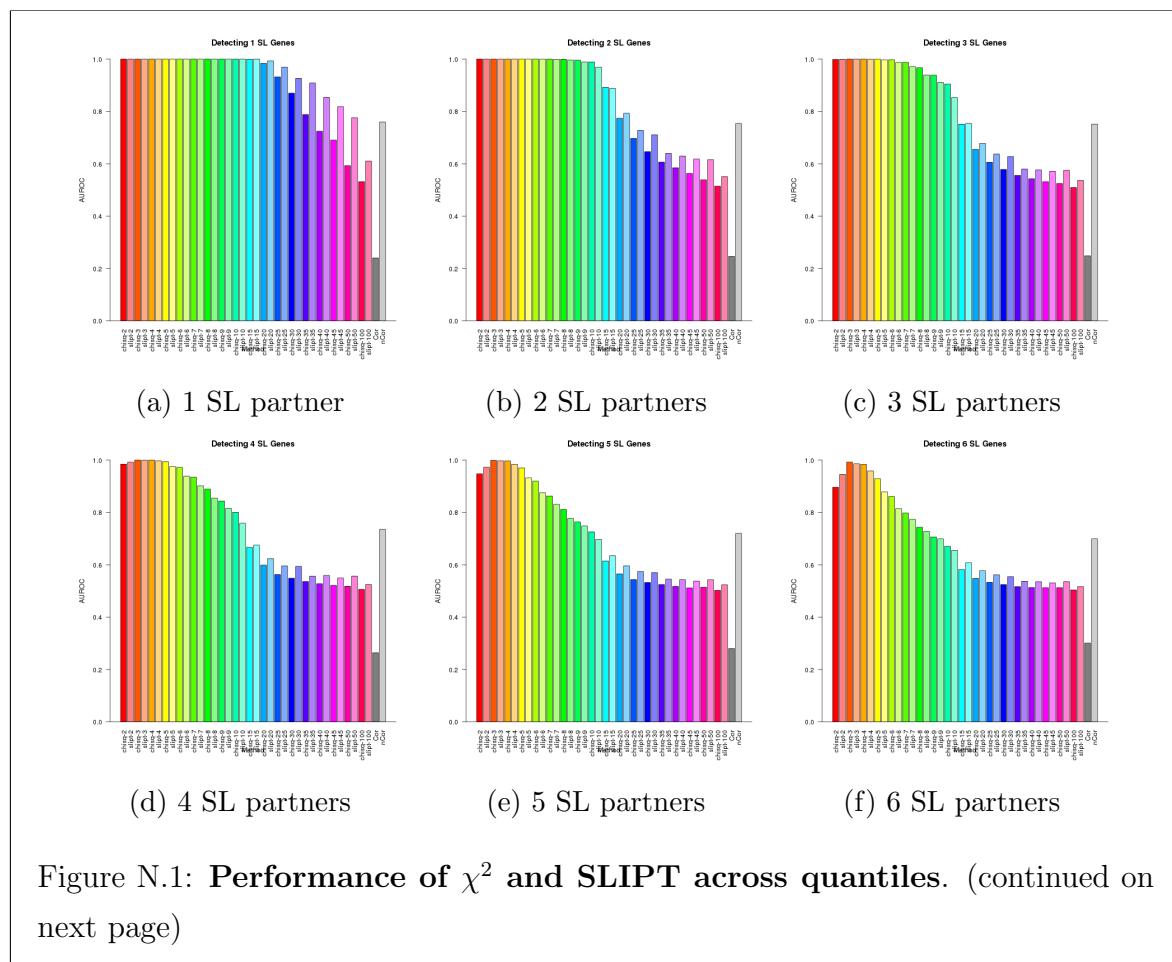


Figure N.1: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

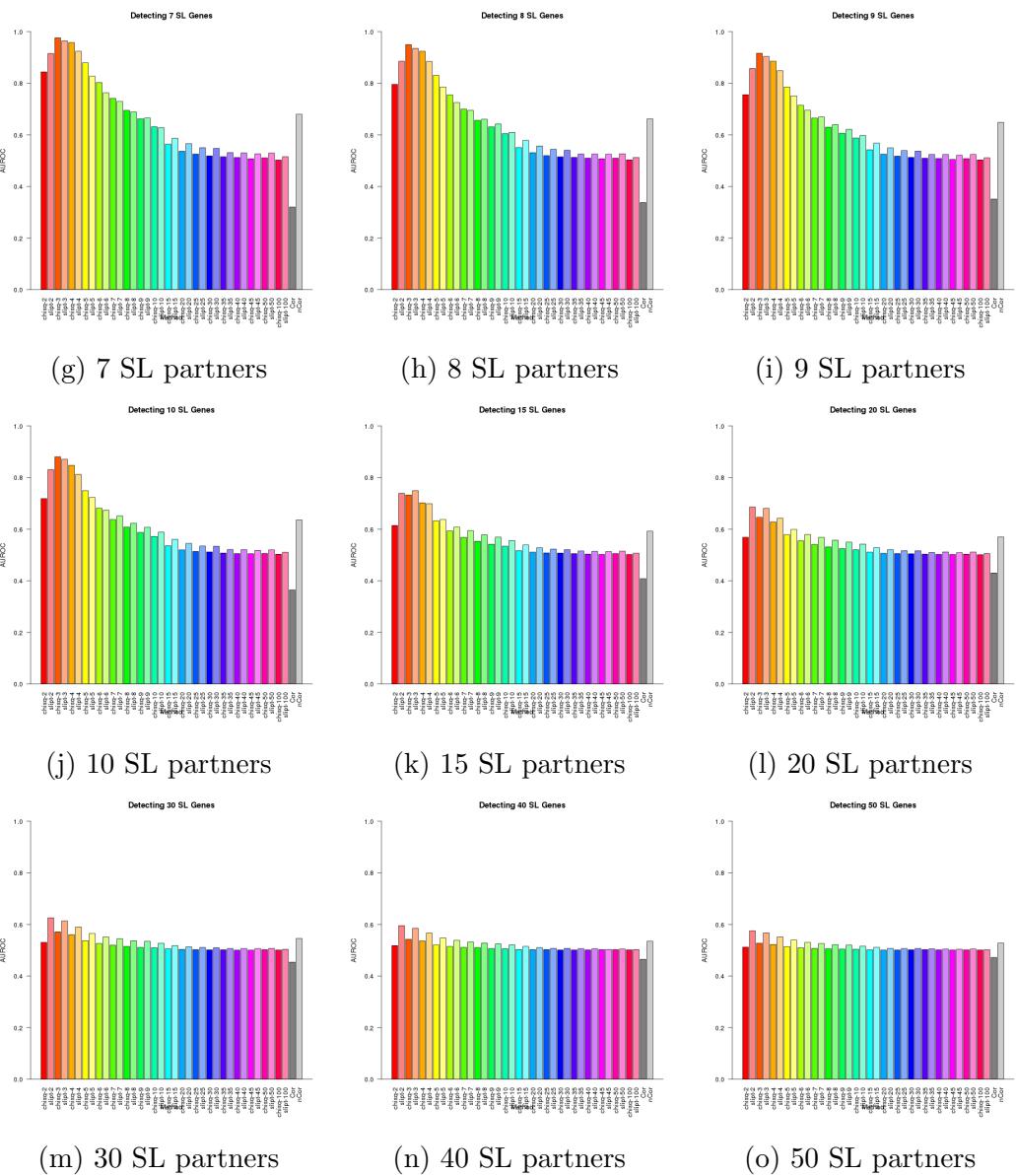


Figure N.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). Synthetic Lethal Interaction Prediction Tool (SLIPT) and χ^2 perform 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.

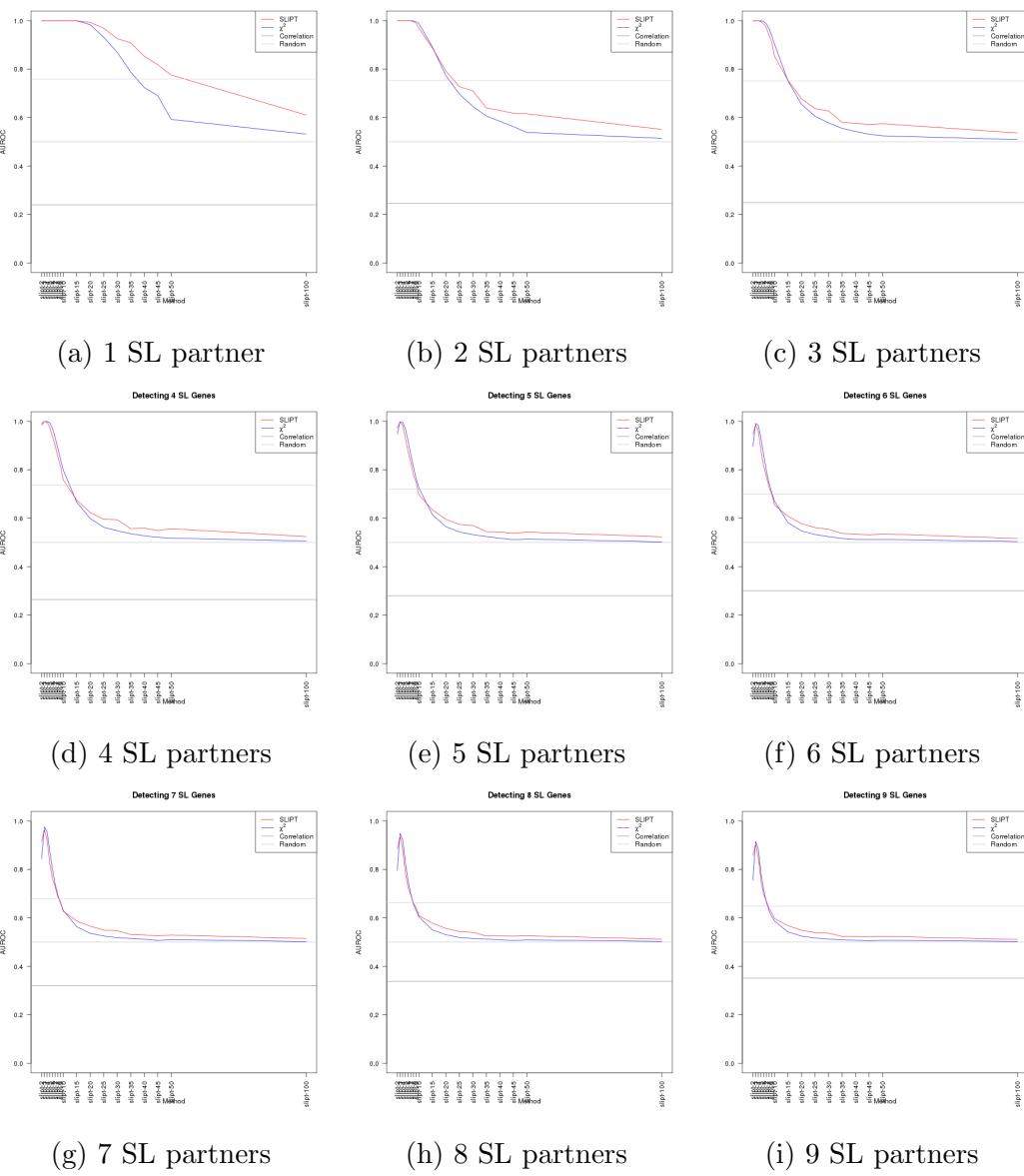


Figure N.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

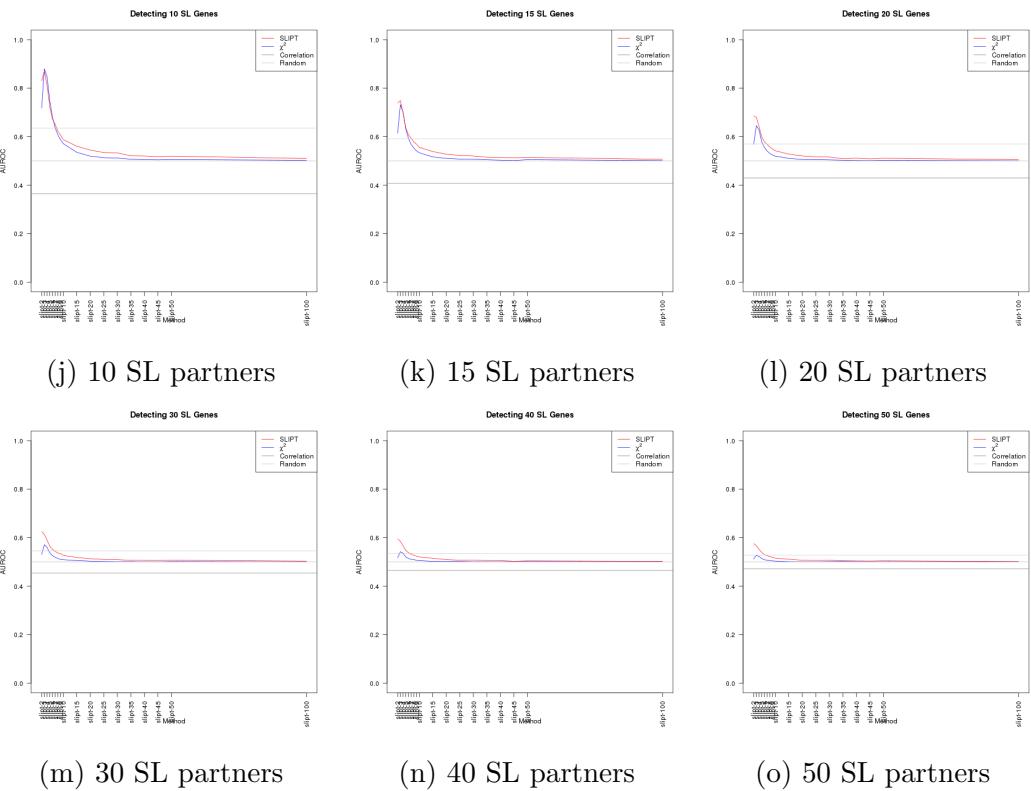


Figure N.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles and converging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

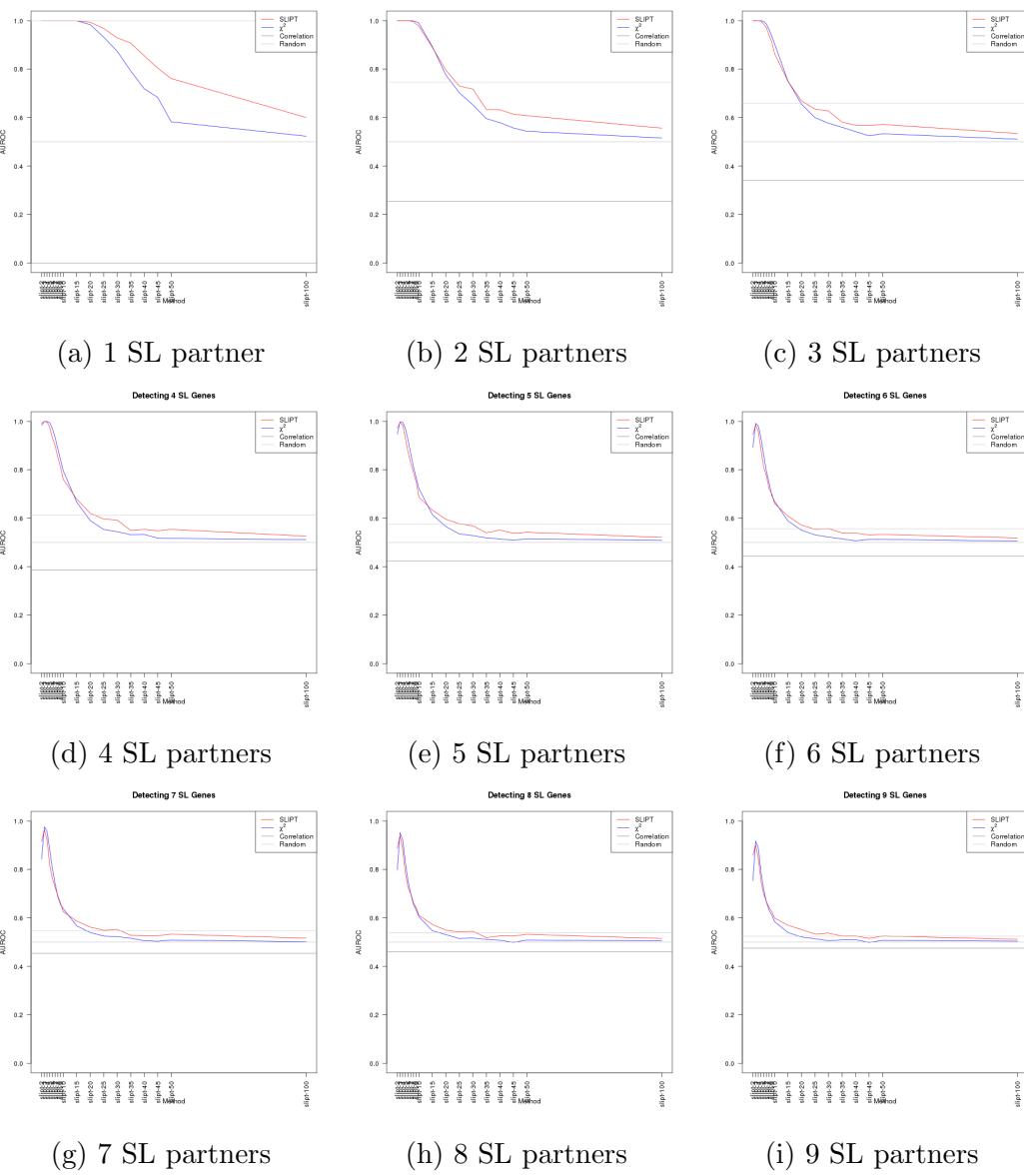


Figure N.3: Performance of χ^2 and SLIPT across quantiles with more genes. (continued on next page)

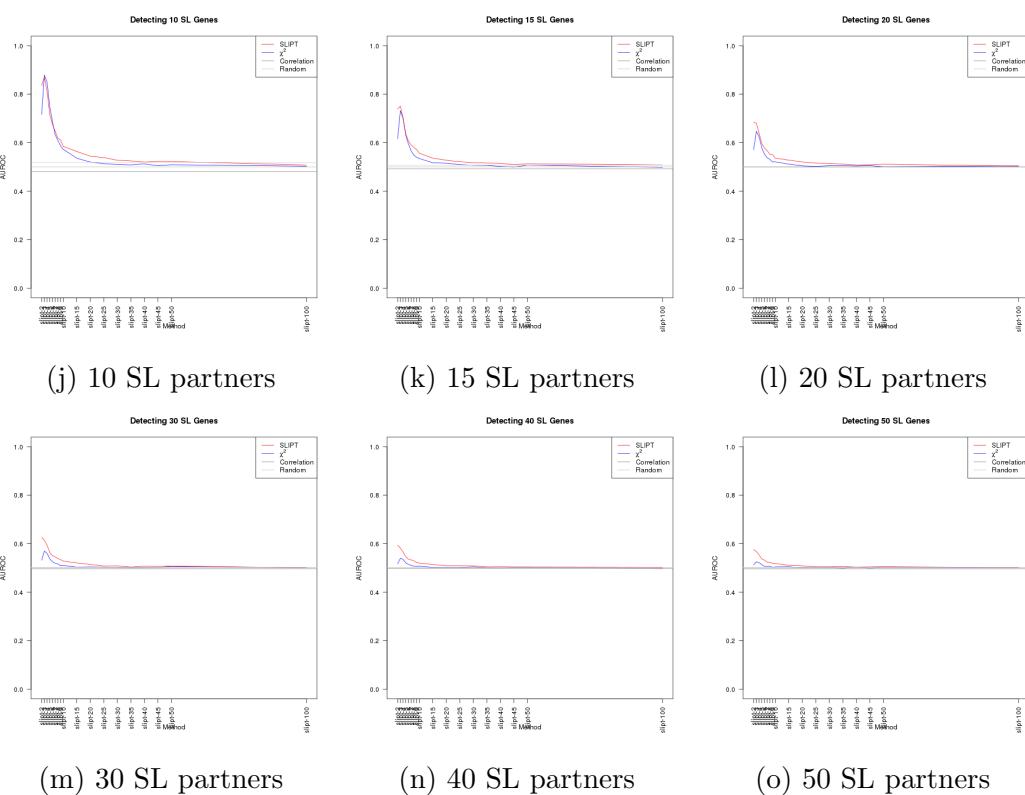


Figure N.3: Performance of χ^2 and SLIPT across quantiles with more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles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

N.0.1 Correlated Query Genes affects Specificity

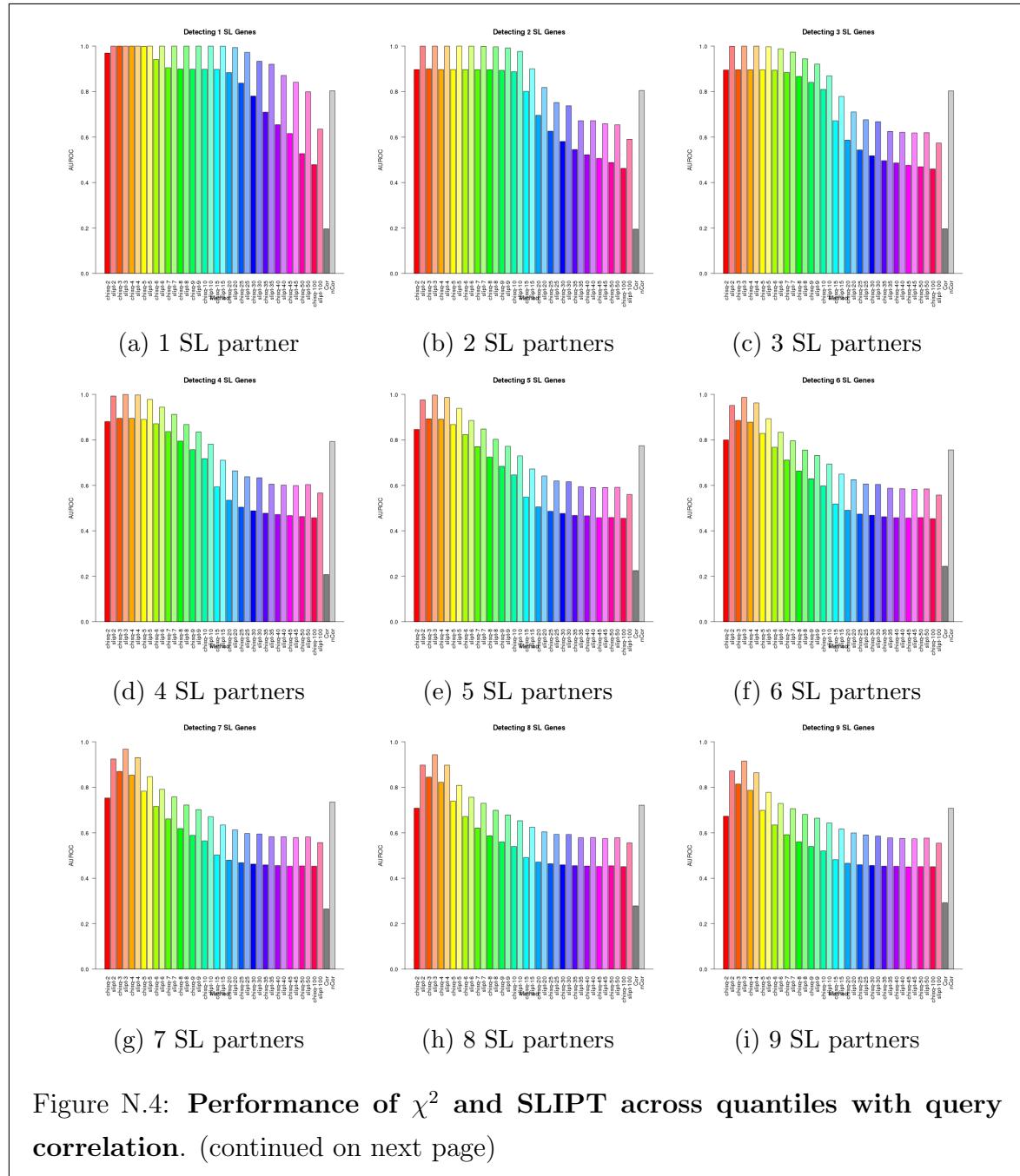


Figure N.4: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

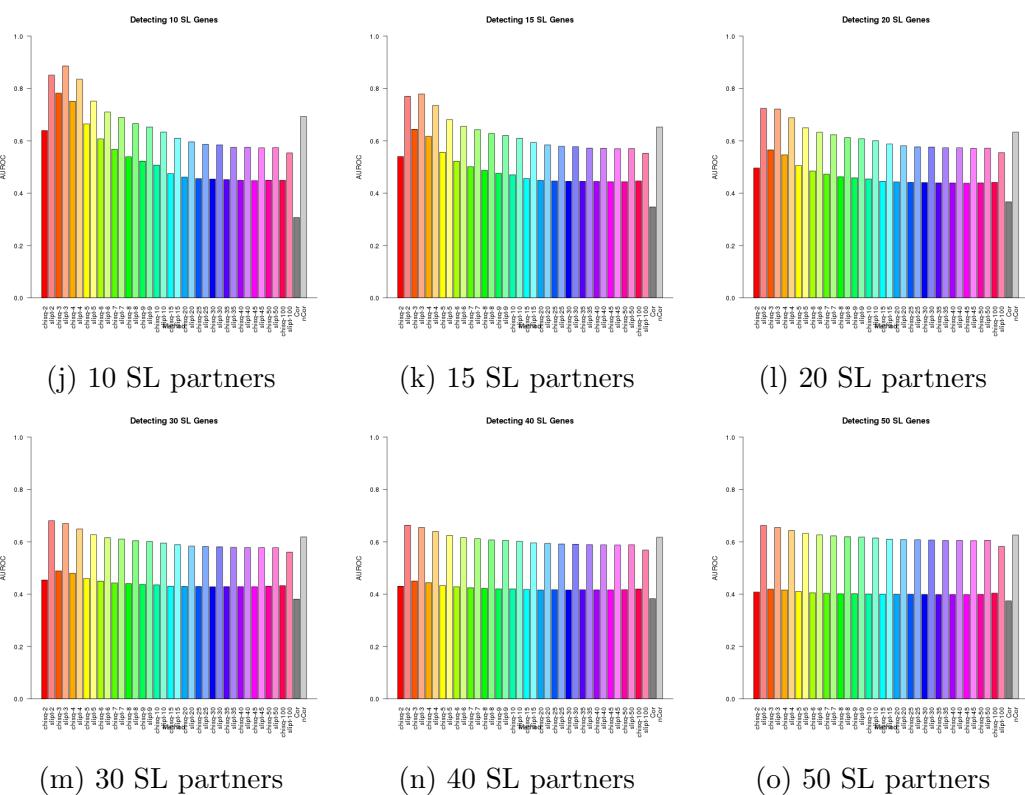


Figure N.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking 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.

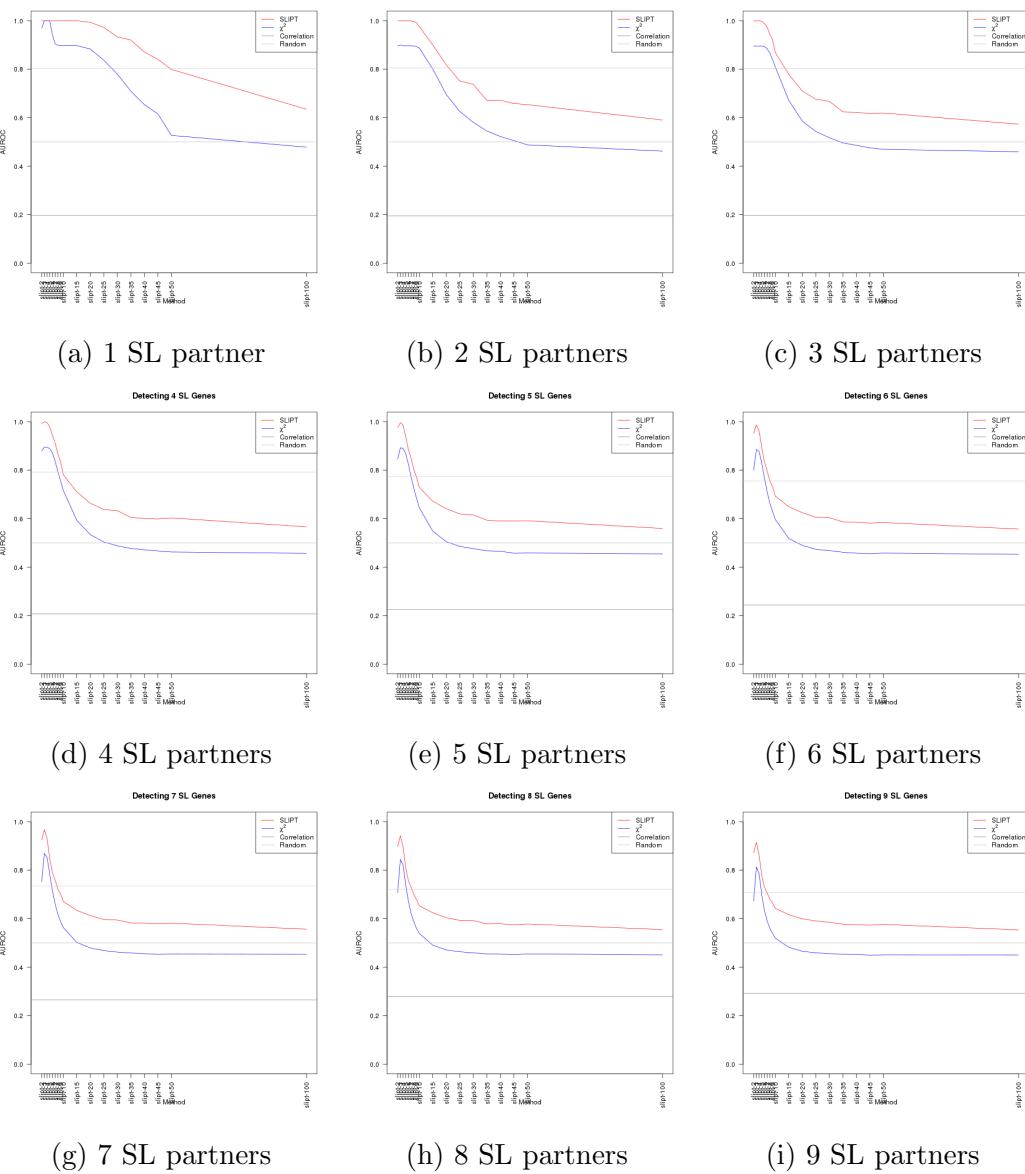


Figure N.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

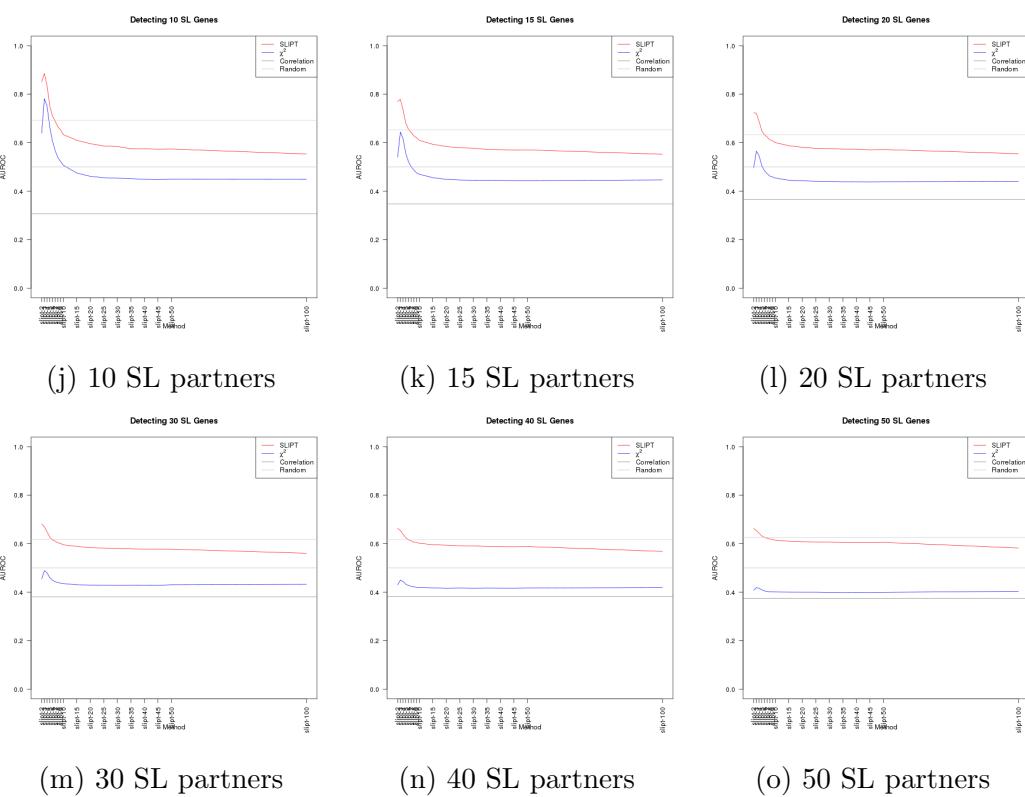


Figure N.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$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

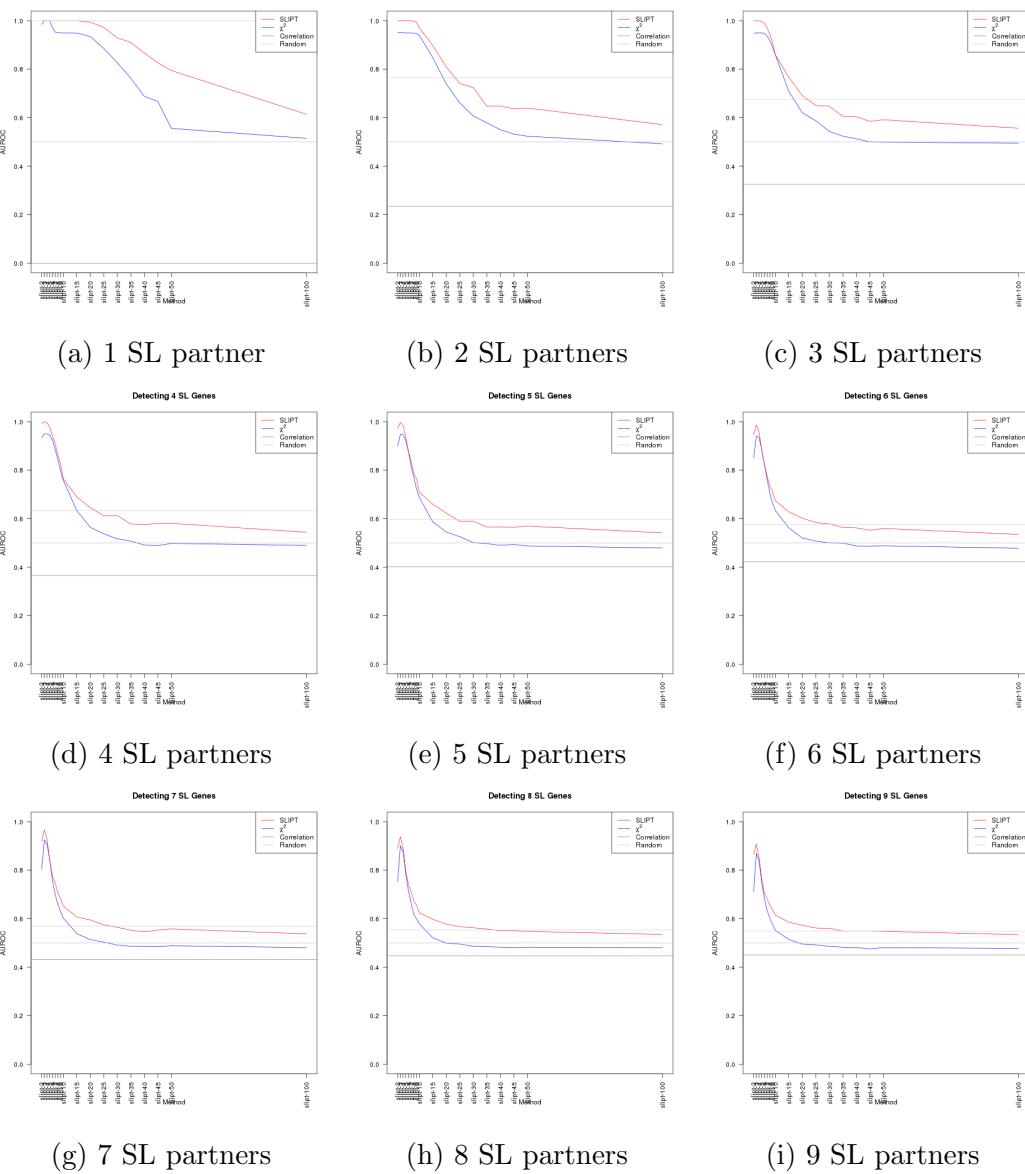


Figure N.6: **Performance of χ^2 and SLIPT across quantiles with query correlation and more genes.** (continued on next page)

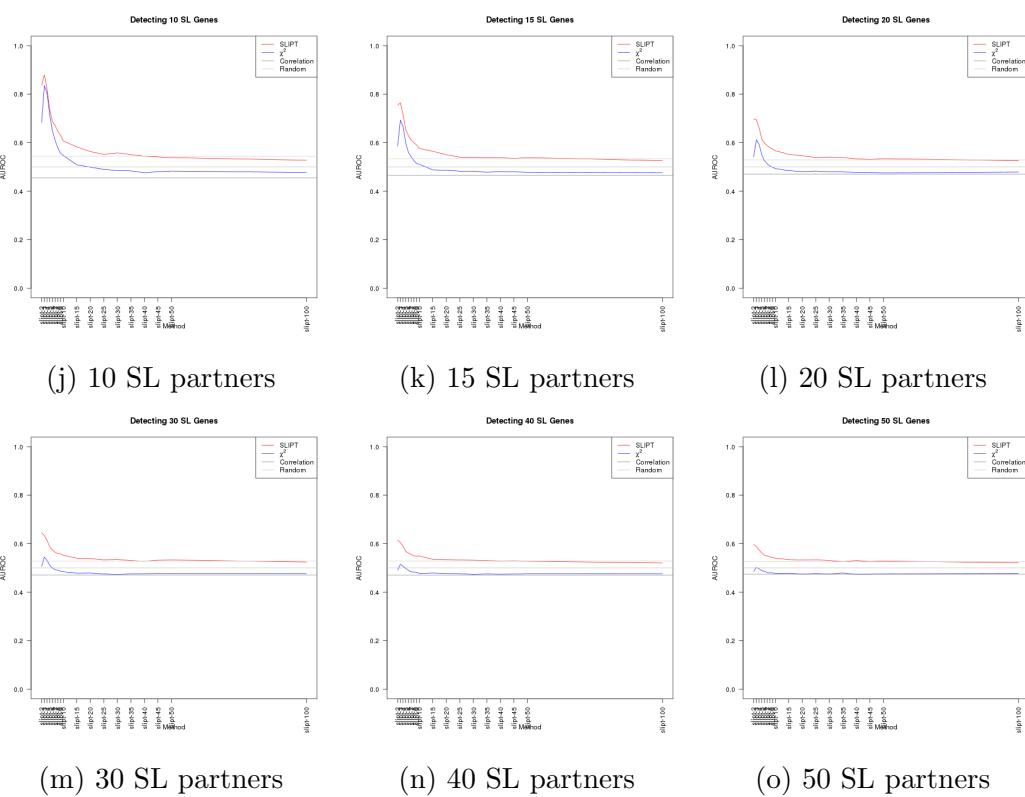
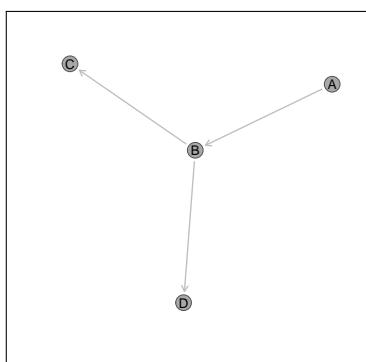


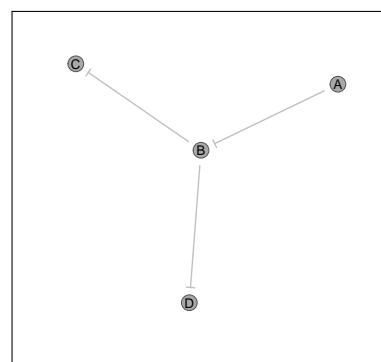
Figure N.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking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

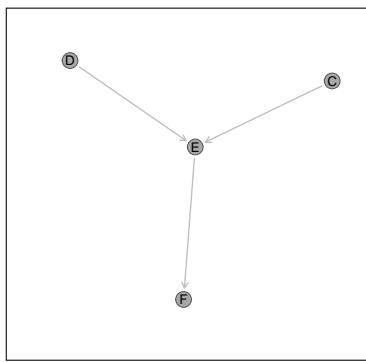
Graph Structures



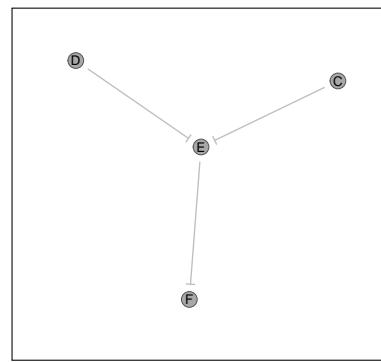
(a) Activating Graph1



(b) Inhibiting Graph1

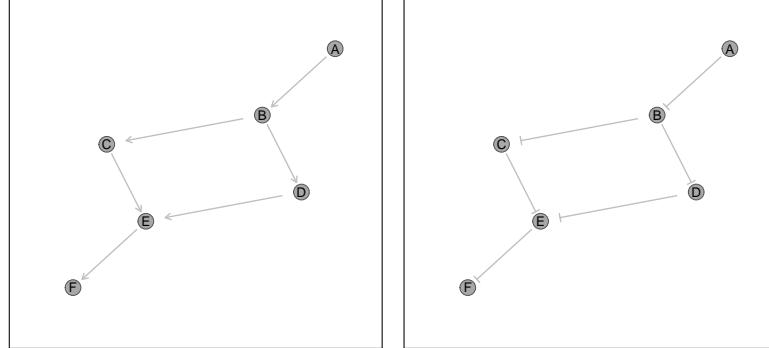


(c) Activating Graph2



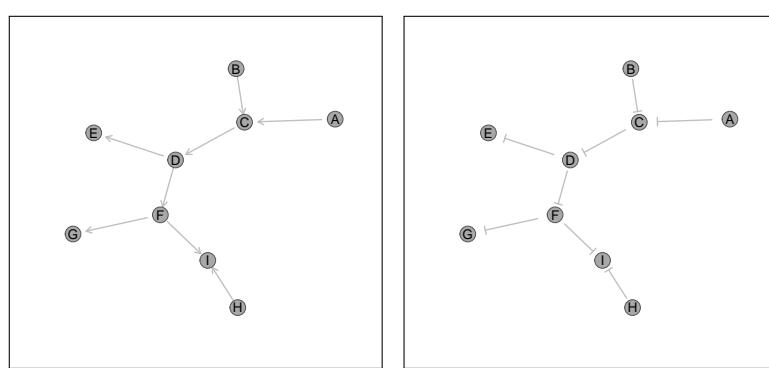
(d) Inhibiting Graph2

Figure O.1: **Simple graph structures.** A simple graph structures used to demonstrate the simulation procedure. Graph1 and Graph2 are examples of a pathway converging or diverging respectively which enables testing the importance of direction in pathway structures. These are used with both activating and inhibiting relationships as shown.

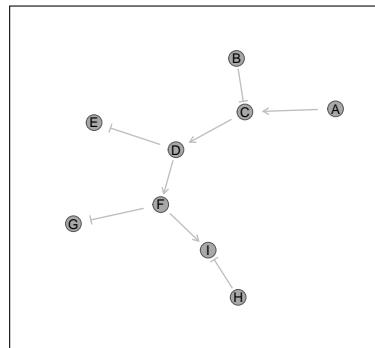


(a) Activating Graph3 (b) Inhibiting Graph3

Figure O.2: **Simple graph structure.** A constructed graph structure used for the simulation procedure. Graph3 combines the converging and diverging paths of a pathway. These are used with both activating and inhibiting relationships as shown.



(a) Activating Graph4 (b) Inhibiting Graph4



(c) Mixed Graph4

Figure O.3: **Constructed graph structure.** A constructed graph structure used for the simulation procedure. Graph4 has a core cascade with branching signals. These are used with activating, inhibiting, and a combination of these relationships as shown.

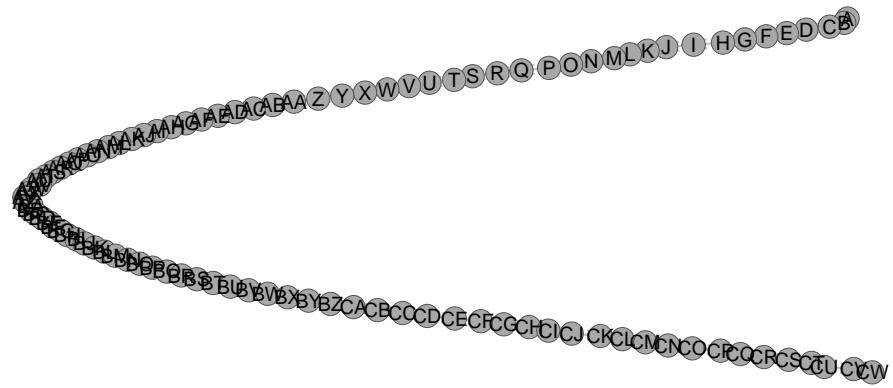
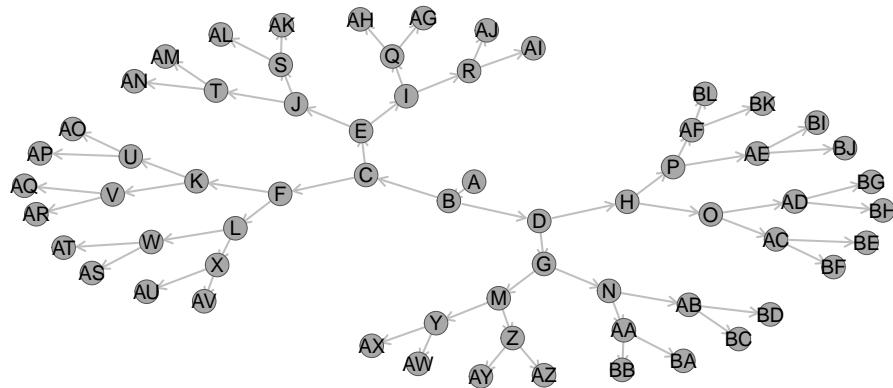
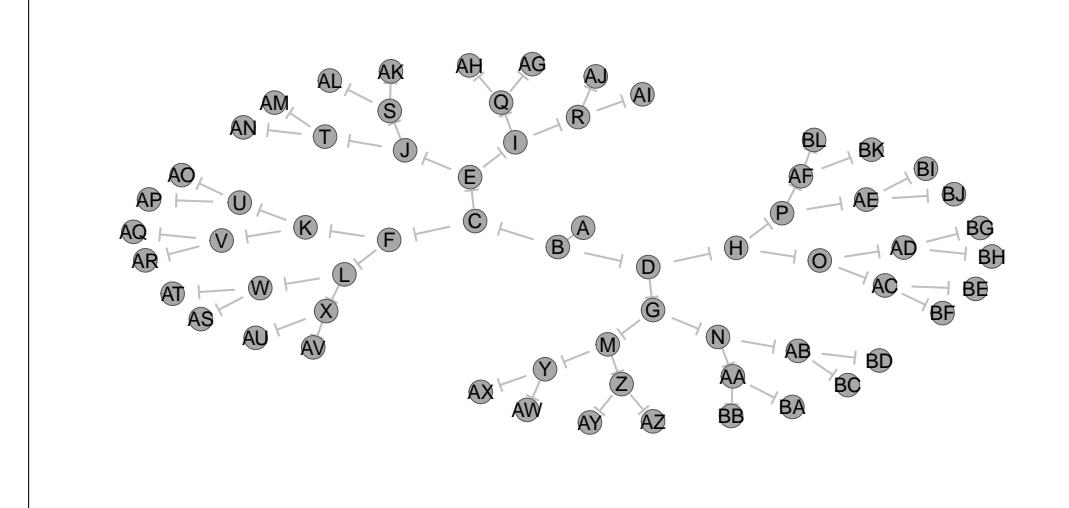


Figure O.4: Large constructed graph structure. A constructed graph structure used for the simulation procedure. Graph5 is an extended chain of 101 genes which are simulated with activating or inhibiting relations and these alternating along the chain.

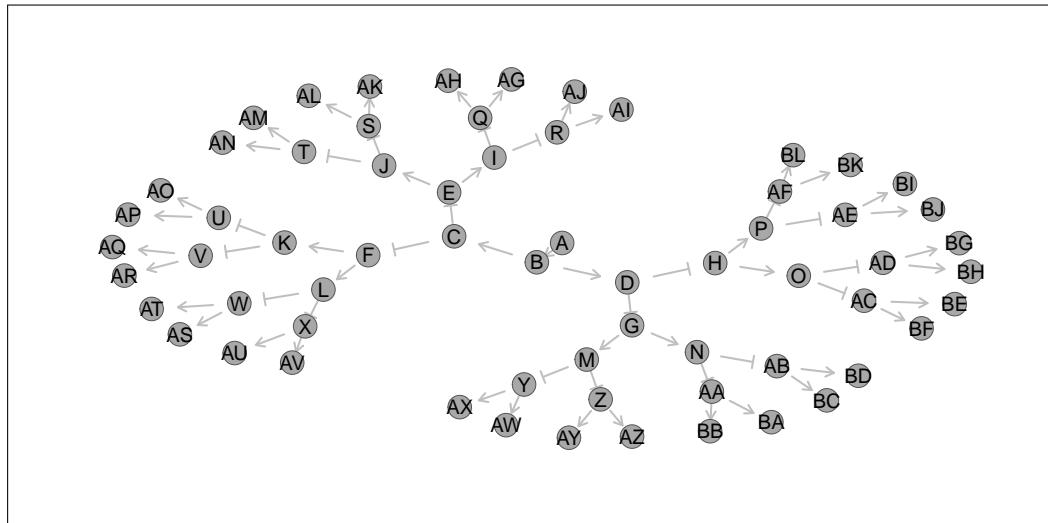


(a) Activating Graph6

Figure O.5: Branching constructed graph structure. (continued on next page)

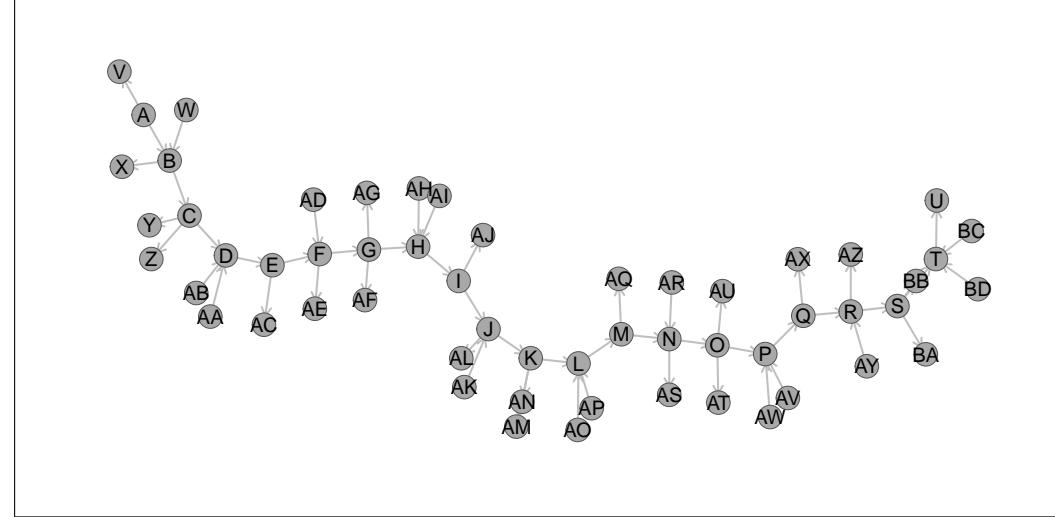


(b) Inhibiting Graph6

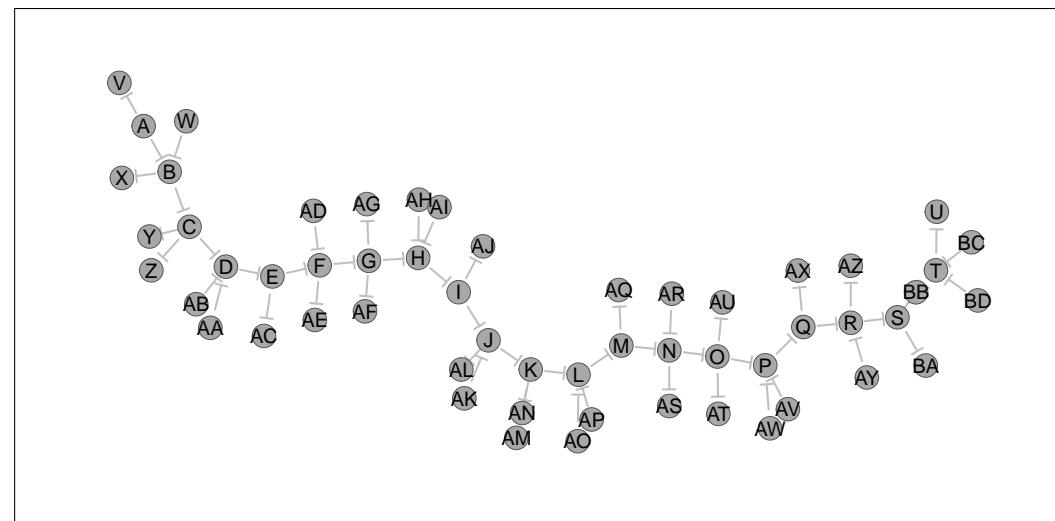


(c) Mixed Graph6

Figure O.5: Branching constructed graph structure. A constructed graph structure used for the simulation procedure. Graph6 is a branching signal cascade from a central hub. These are used with activating, inhibiting, and an alternating combination of these relationships as shown.

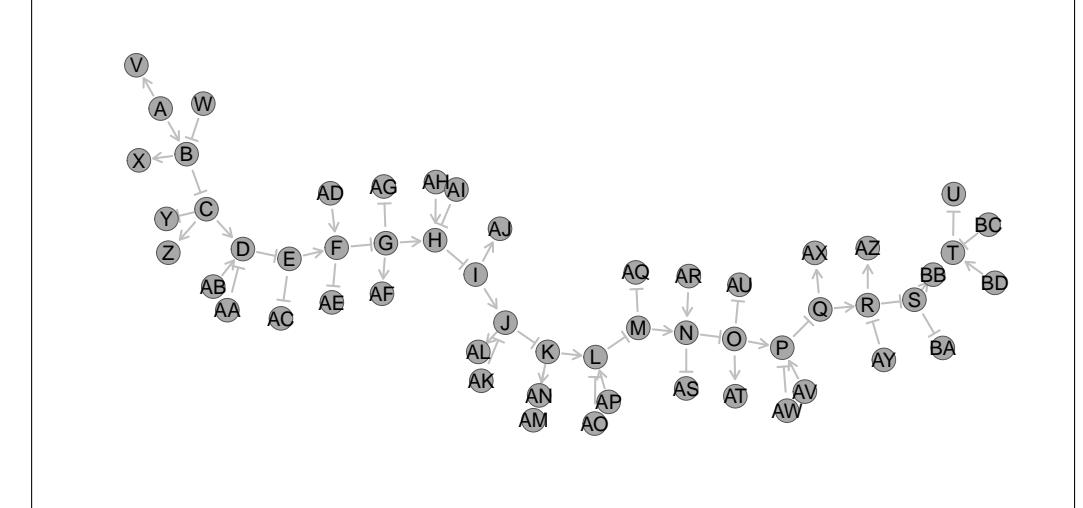


(a) Activating Graph7



(b) Inhibiting Graph7

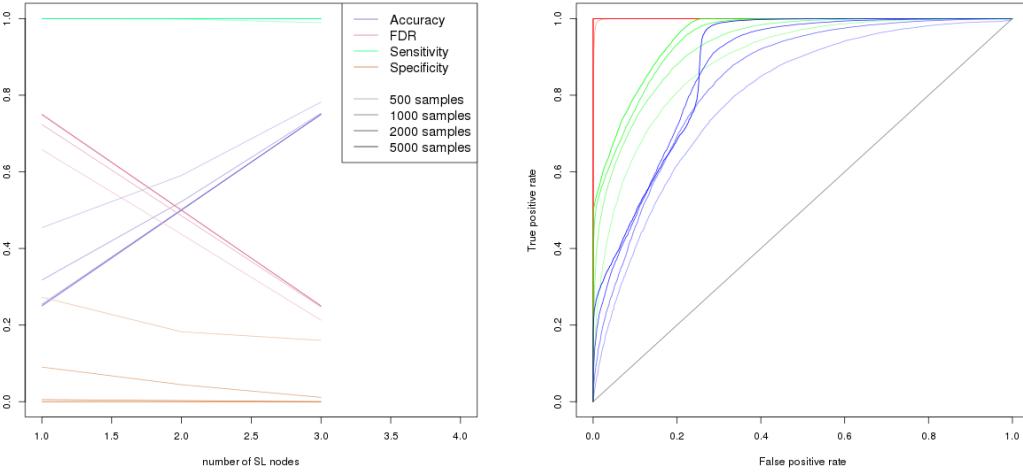
Figure O.6: **Complex constructed graph structure.** (continued on next page)



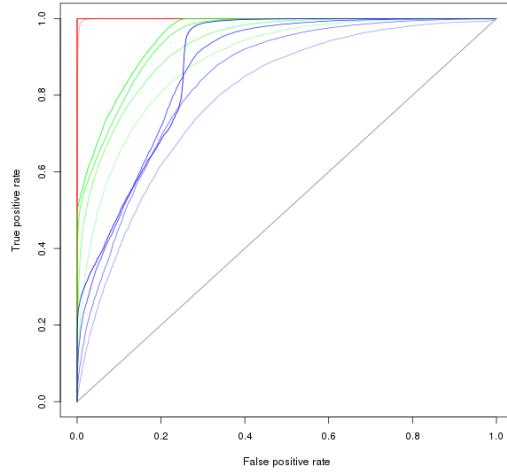
(c) Mixed Graph7

Figure O.6: Complex constructed graph structure. A constructed graph structure used for the simulation procedure. Graph7 is has a core cascade with branching signals in and out of the pathway. These are used with activating, inhibiting, and a combination of these relationships as shown.

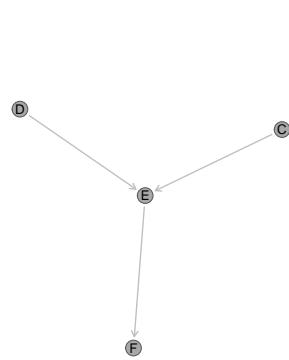
O.1 Simulations from Graph Structures



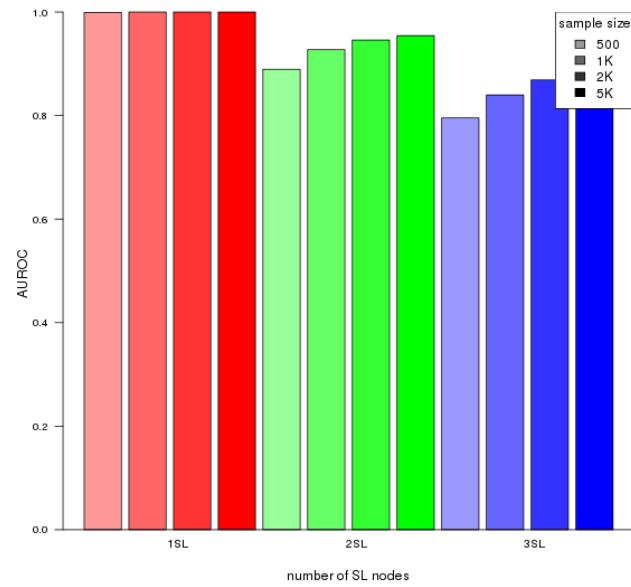
(a) Statistical evaluation



(b) Receiver operating characteristic

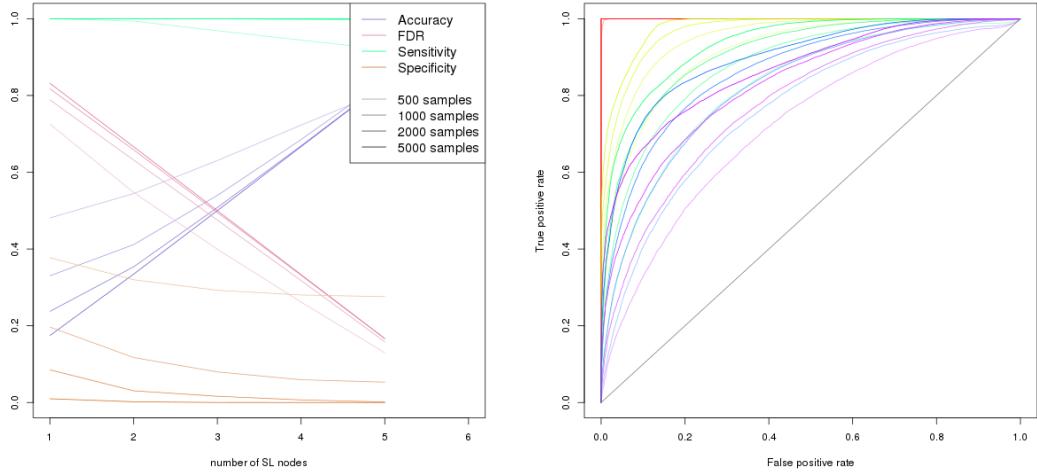


(c) Graph Structure



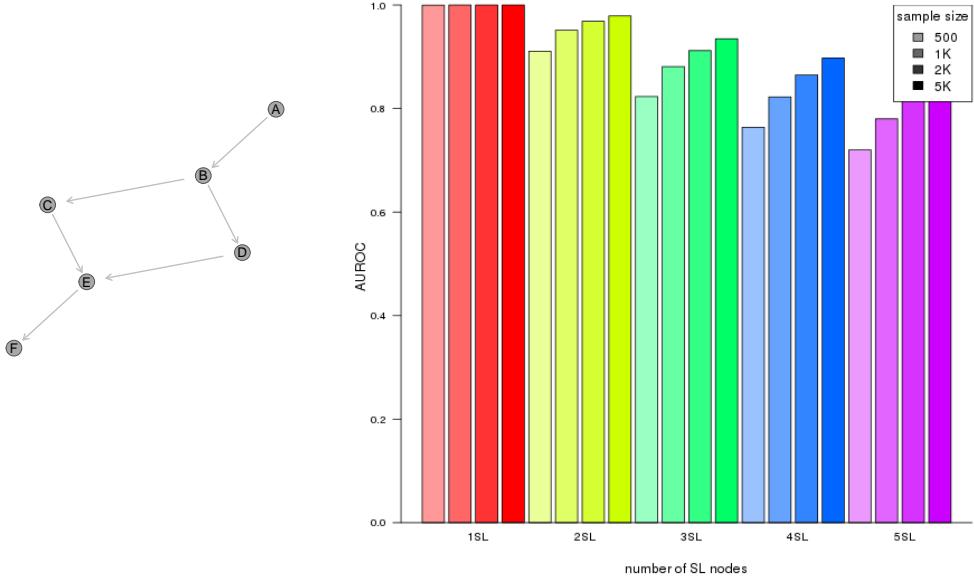
(d) Statistical performance

Figure O.7: **Performance of simulations on a simple graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph2. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation

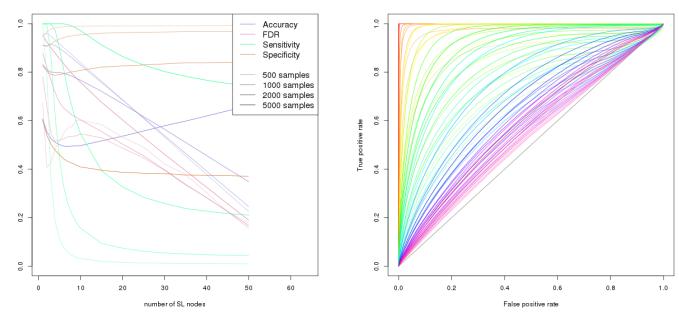
(b) Receiver operating characteristic



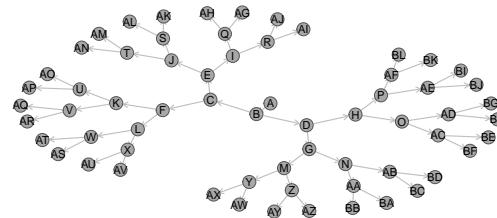
(c) Graph Structure

(d) Statistical performance

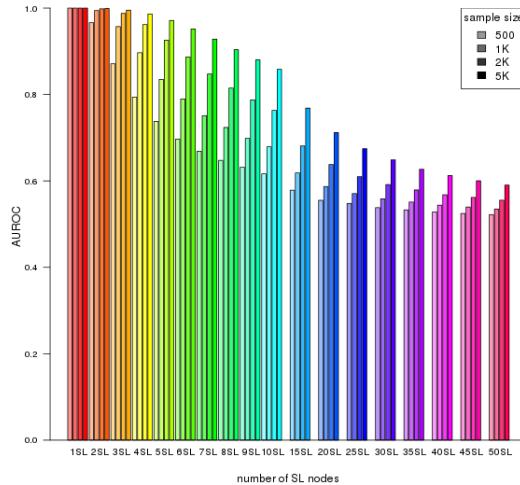
Figure O.8: Performance of simulations on a constructed graph. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph3. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

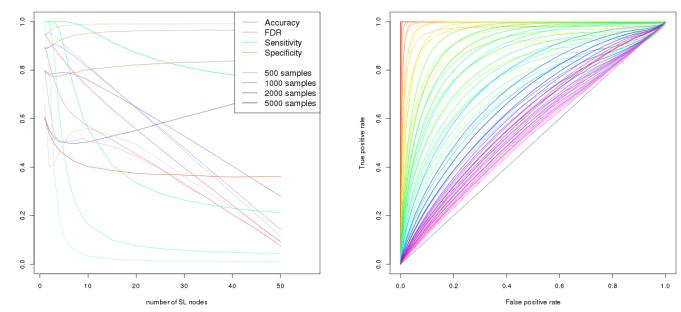


(c) Graph Structure

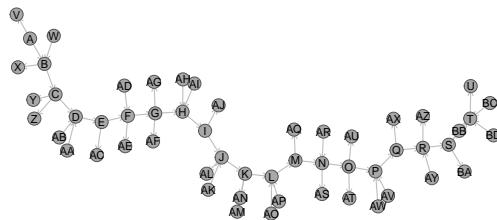


(d) Statistical performance

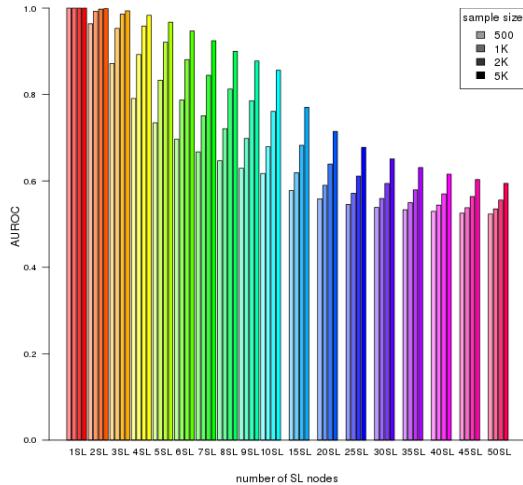
Figure O.9: Performance of simulations on a branching graph. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph6. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic



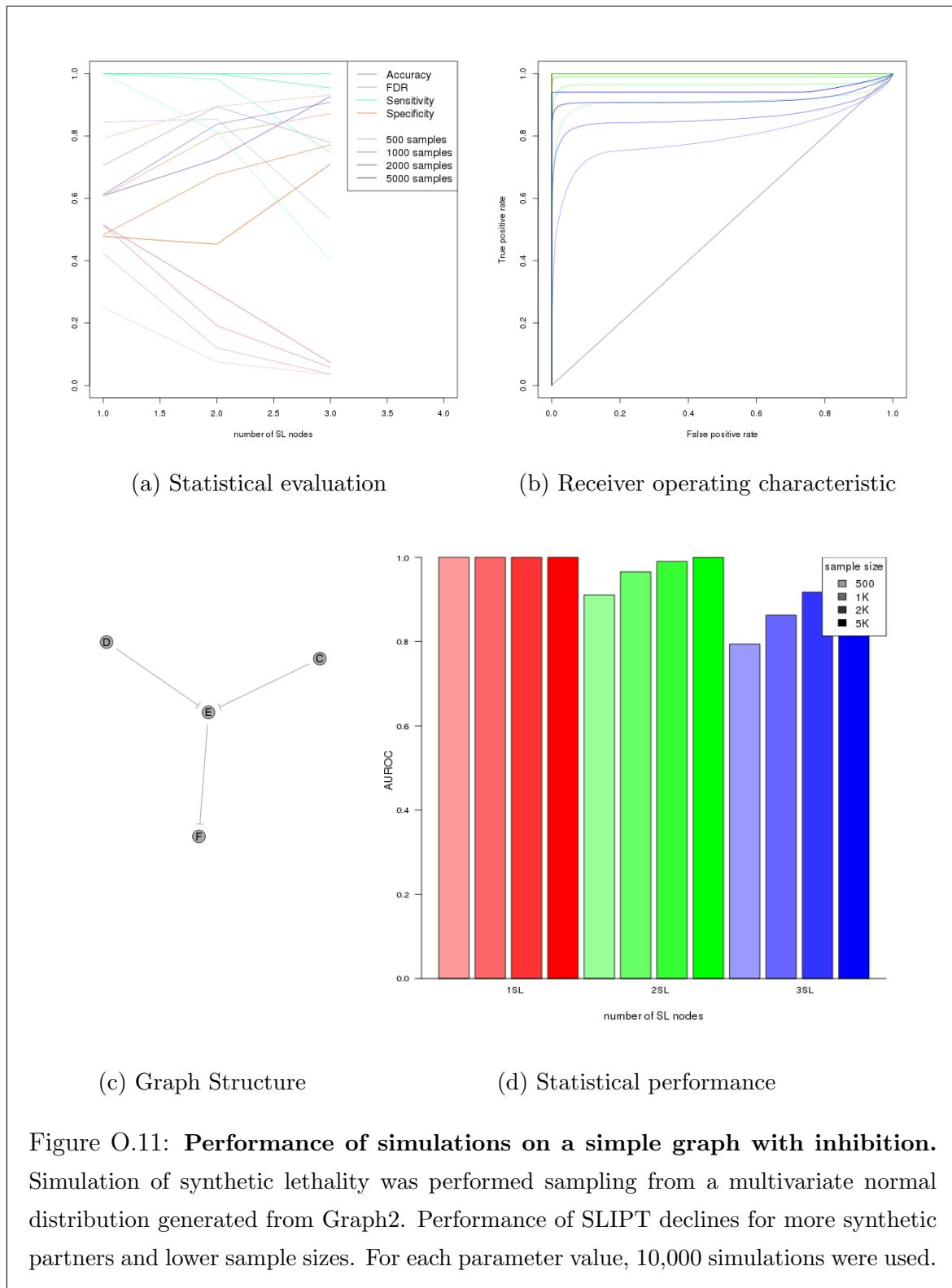
(c) Graph Structure

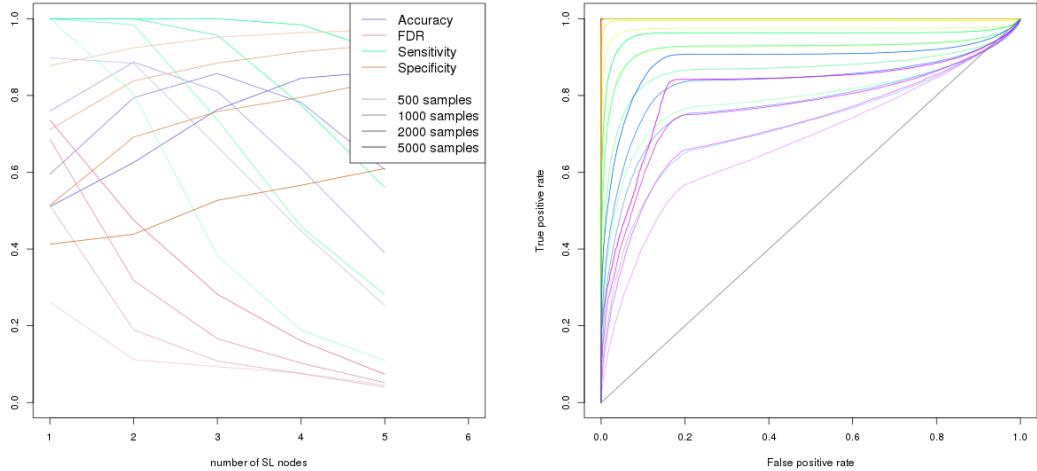


(d) Statistical performance

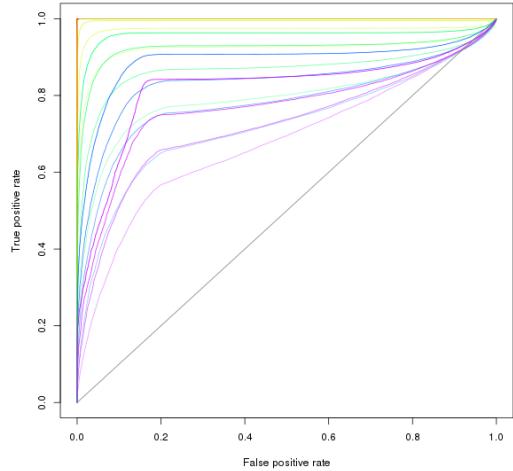
Figure O.10: **Performance of simulations on a complex graph.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph7. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.

O.2 Simulations from Inhibiting Graph Structures

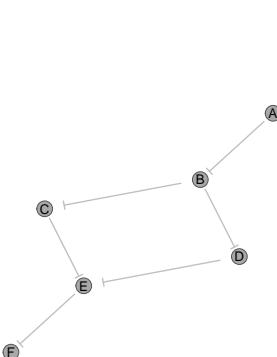




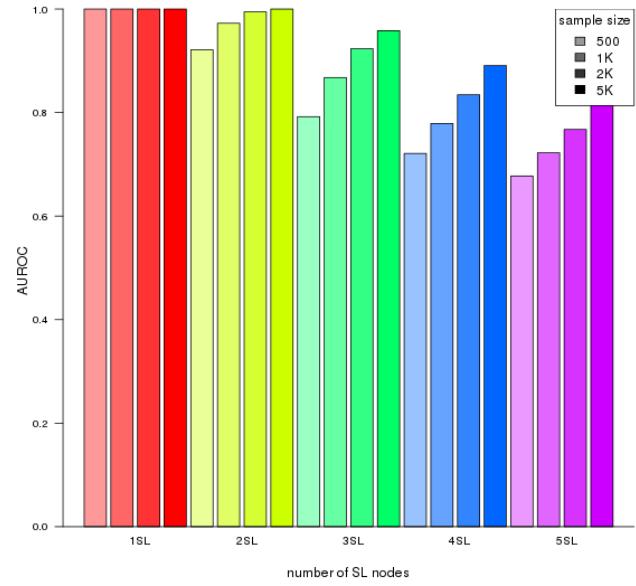
(a) Statistical evaluation



(b) Receiver operating characteristic

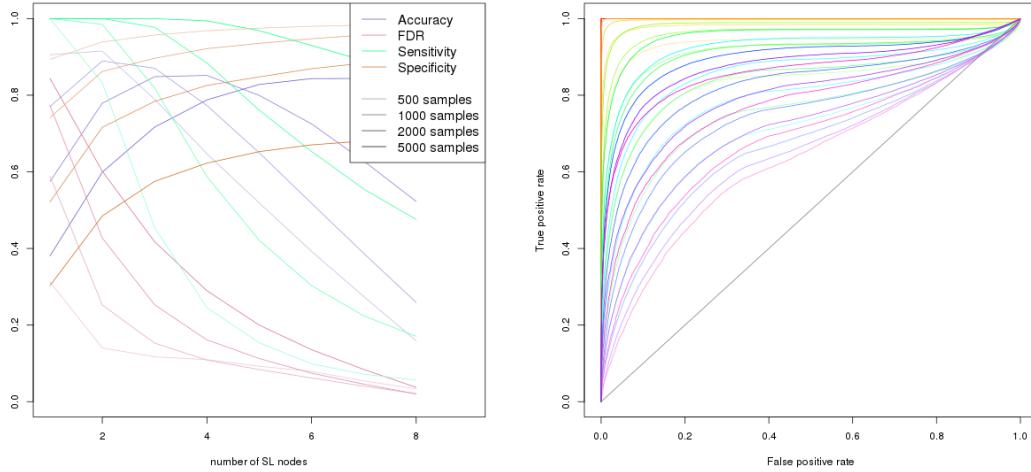


(c) Graph Structure



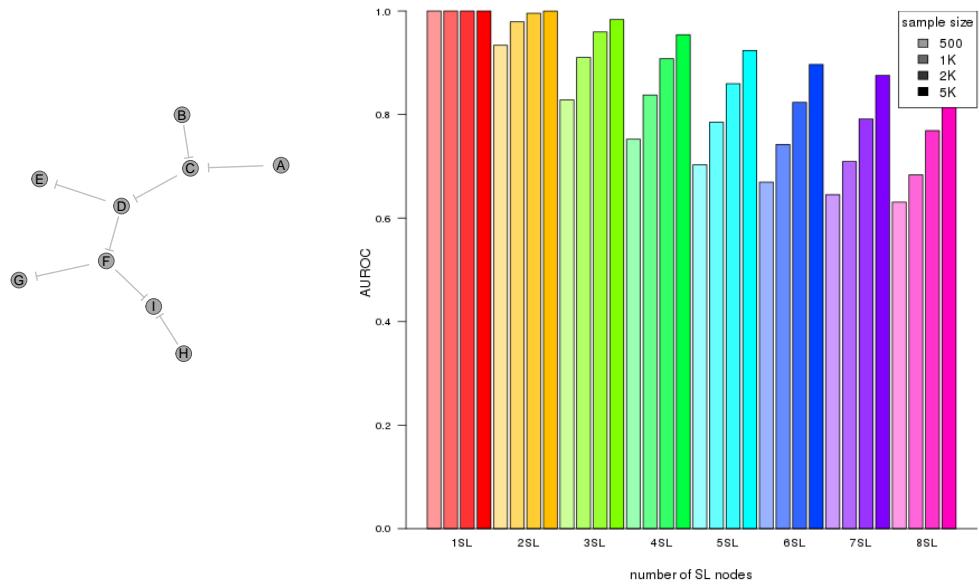
(d) Statistical performance

Figure O.12: Performance of simulations on a simple graph with inhibition.
Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph3. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation

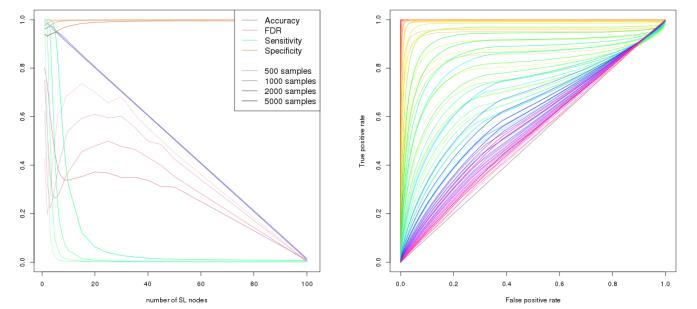
(b) Receiver operating characteristic



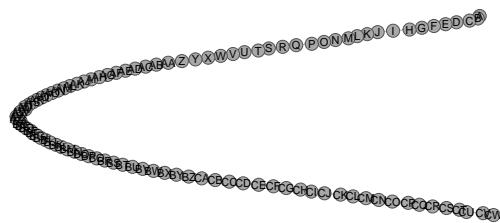
(c) Graph Structure

(d) Statistical performance

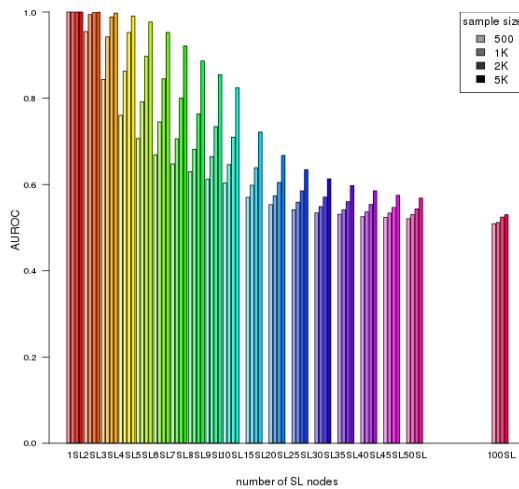
Figure O.13: Performance of simulations on a constructed graph with inhibition. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph4 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

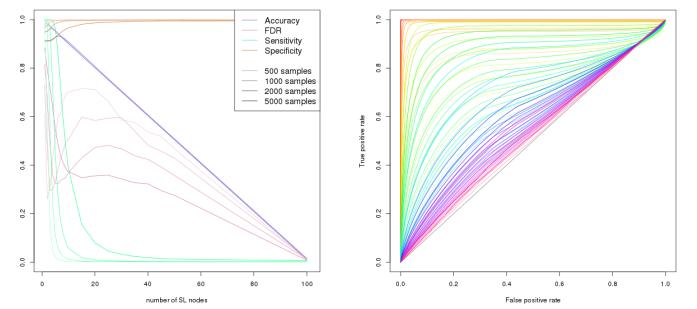


(c) Graph Structure

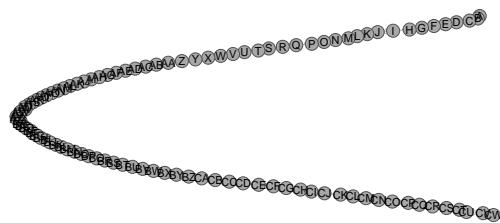


(d) Statistical performance

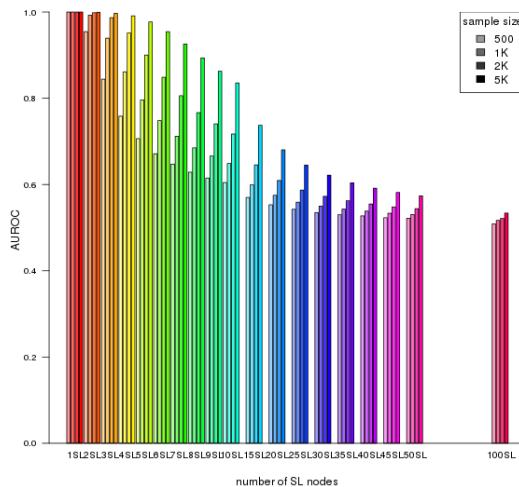
Figure O.14: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph5 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

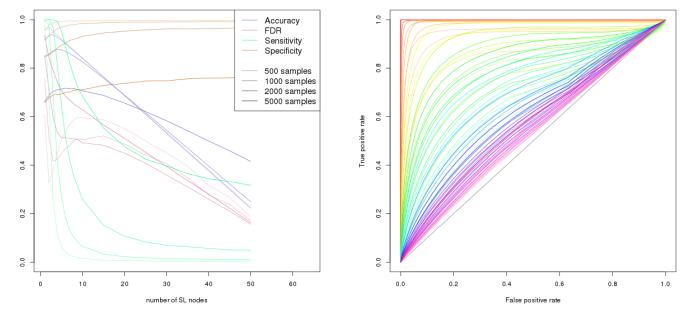


(c) Graph Structure

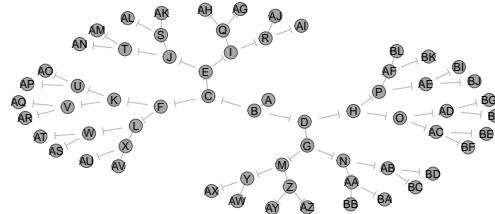


(d) Statistical performance

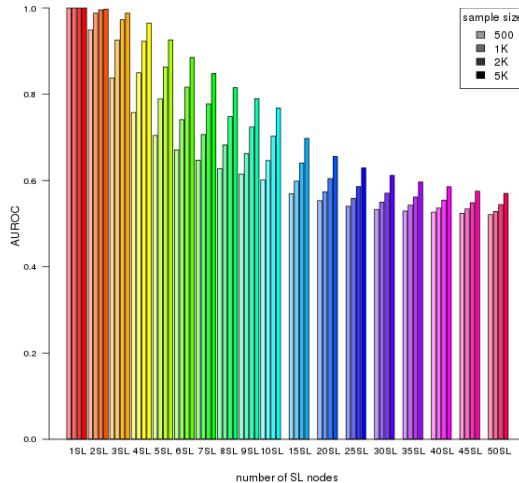
Figure O.15: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph5 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

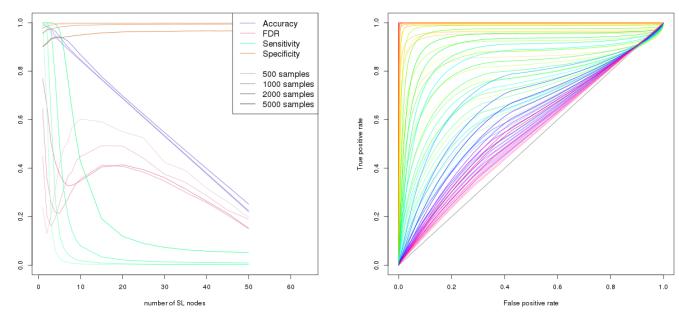


(c) Graph Structure

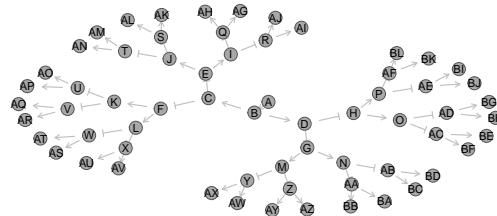


(d) Statistical performance

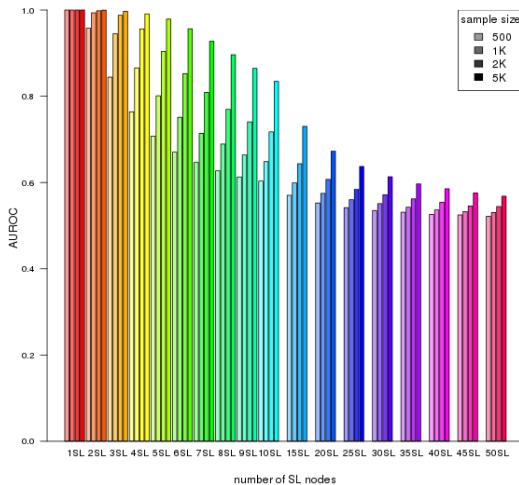
Figure O.16: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph6 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

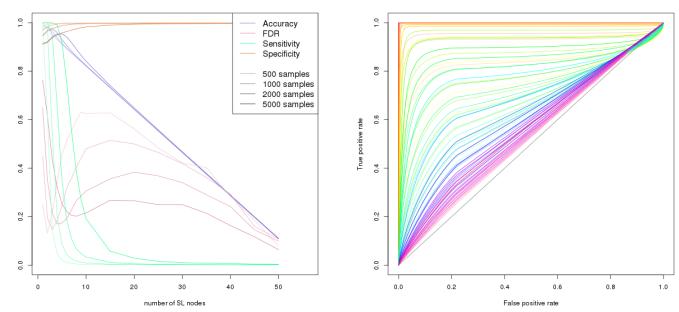


(c) Graph Structure

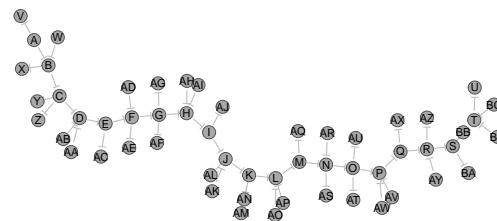


(d) Statistical performance

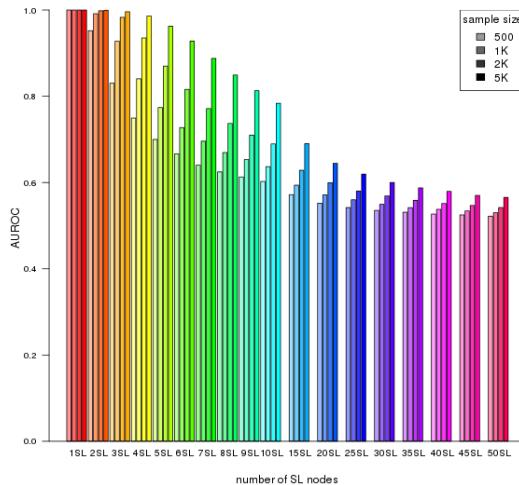
Figure O.17: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph6 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

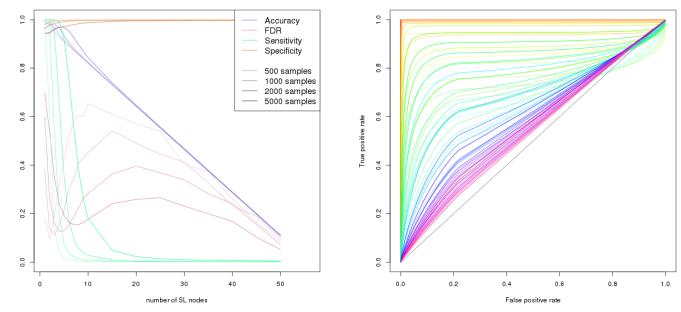


(c) Graph Structure

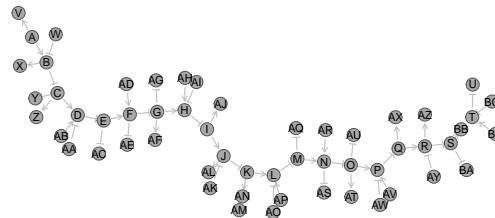


(d) Statistical performance

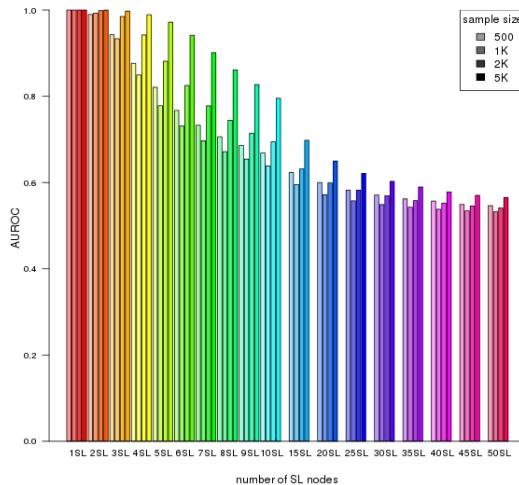
Figure O.18: Performance of simulations on a complex graph with inhibition.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph7 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic



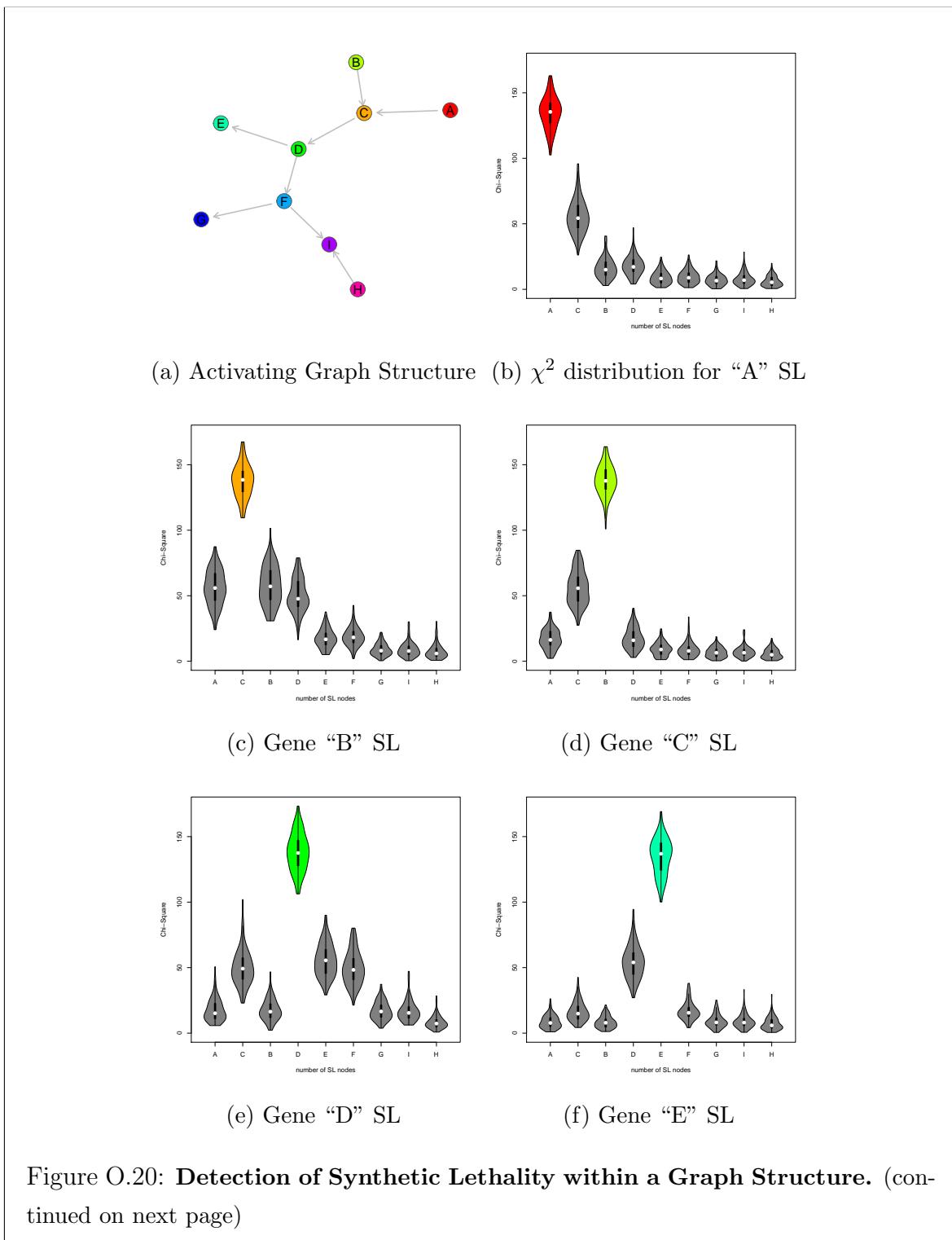
(c) Graph Structure



(d) Statistical performance

Figure O.19: Performance of simulations on a complex graph with inhibition.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph7 with a combination of relationships. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.

O.3 Simulation across Graph Structures



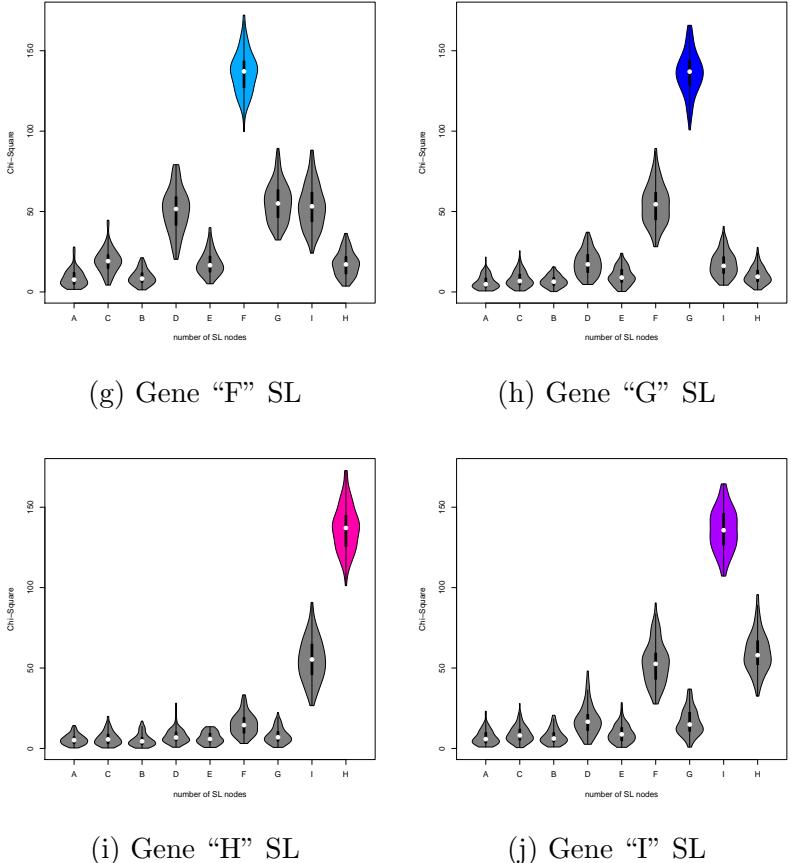
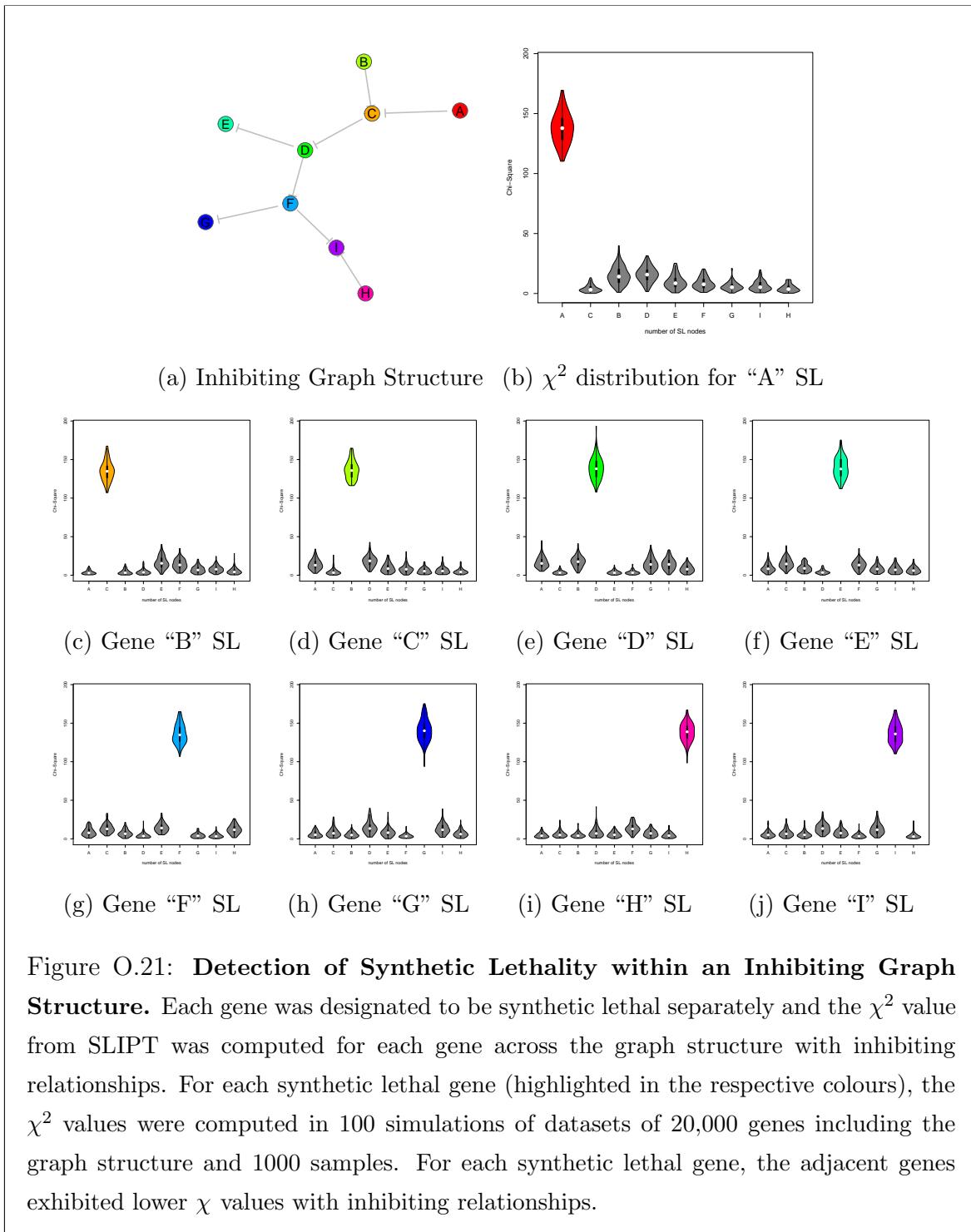
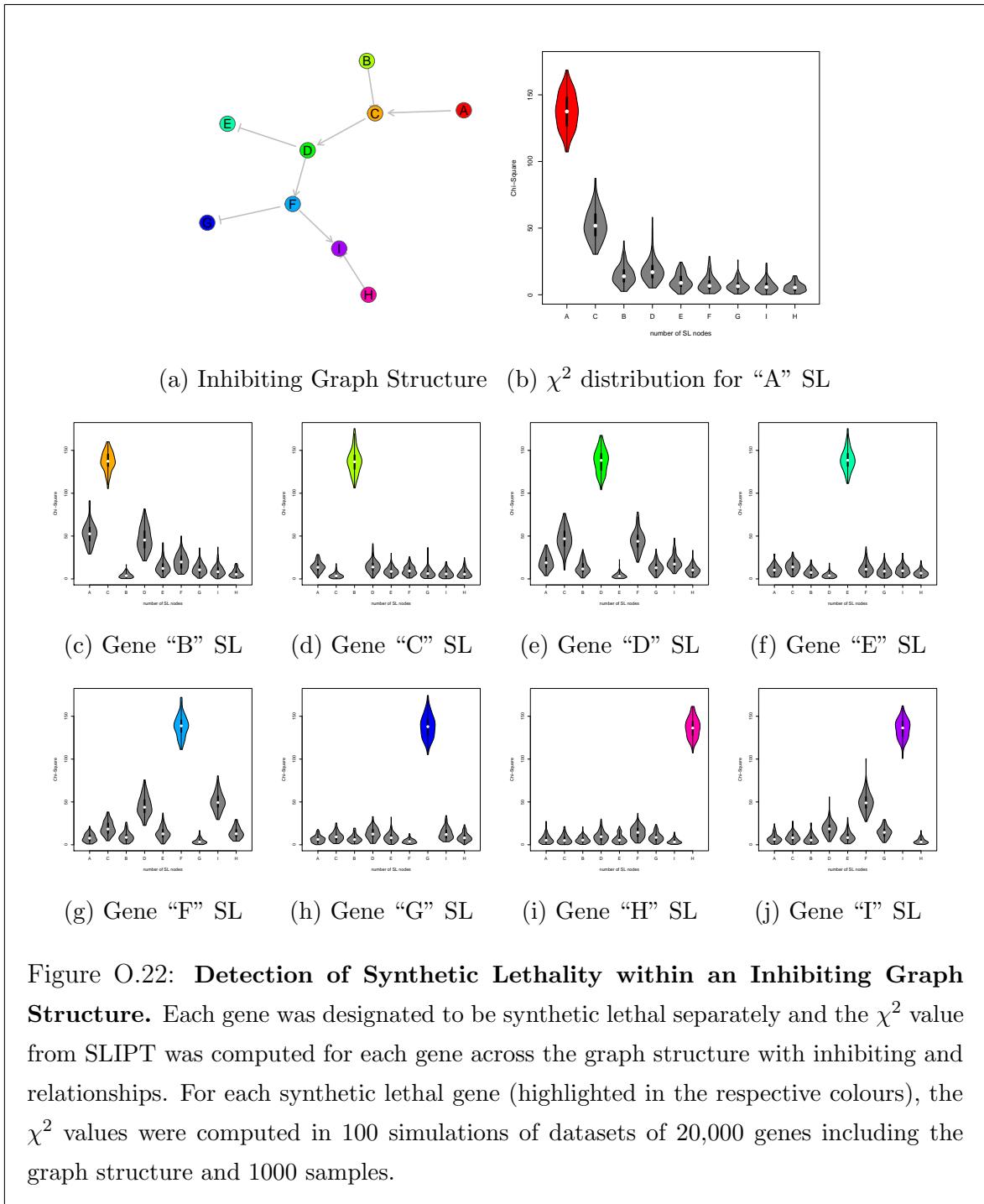
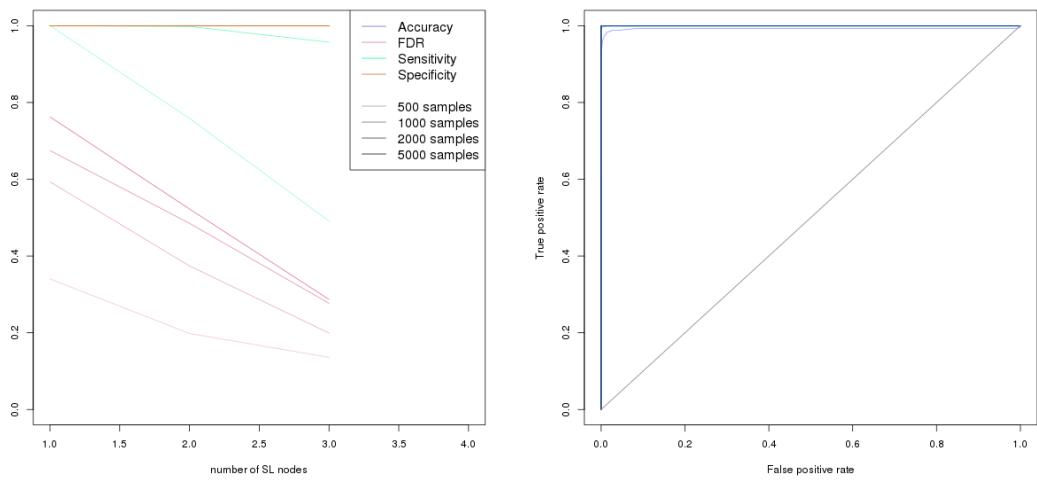


Figure O.20: Detection of Synthetic Lethality within a Graph Structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph structure. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values 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.



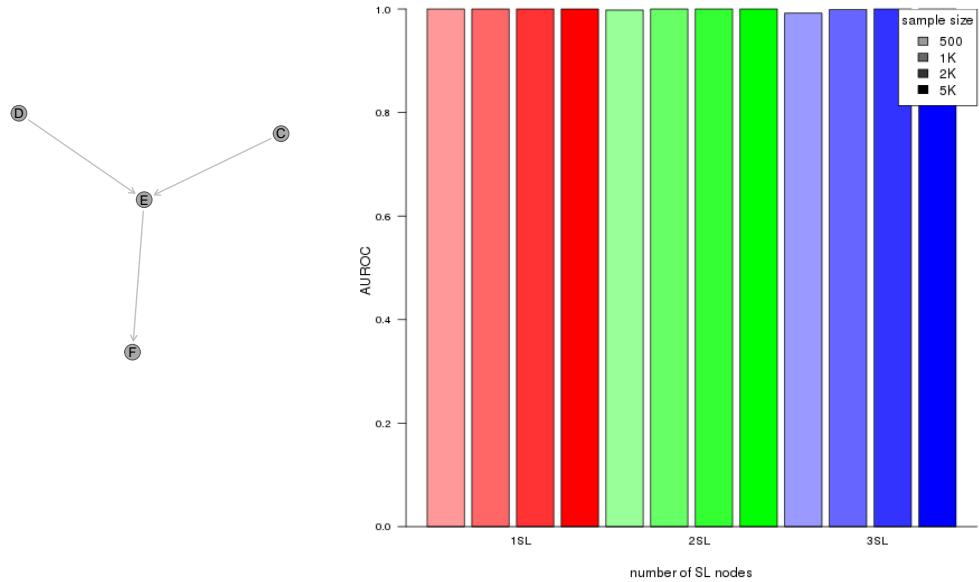


O.4 Simulations from Graph Structures with 20K genes



(a) Statistical evaluation

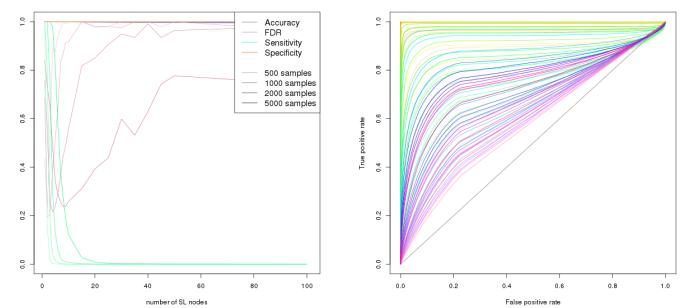
(b) Receiver operating characteristic



(c) Graph Structure

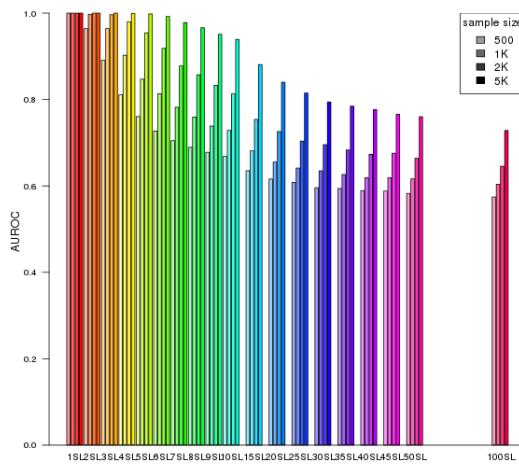
(d) Statistical performance

Figure O.23: Performance of simulations on a simple graph with more genes.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph2. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



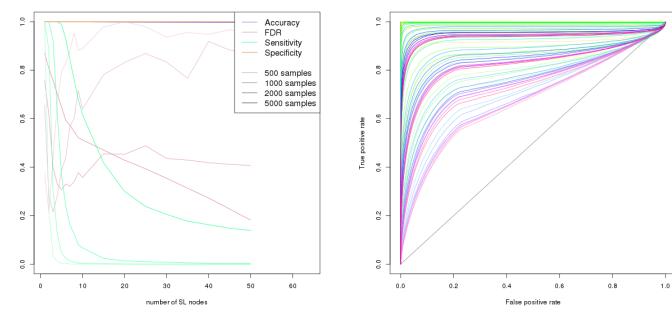
(a) Statistical evaluation (b) Receiver operating characteristic

(c) Graph Structure

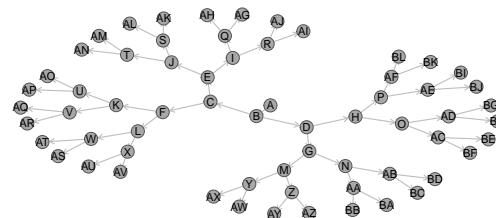


(d) Statistical performance

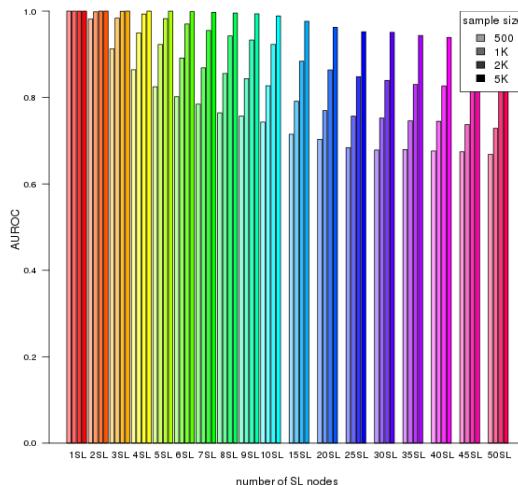
Figure O.24: Performance of simulations on a simple graph with more genes. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph2. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

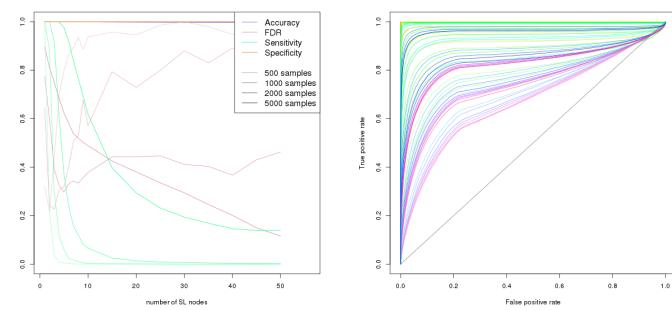


(c) Graph Structure

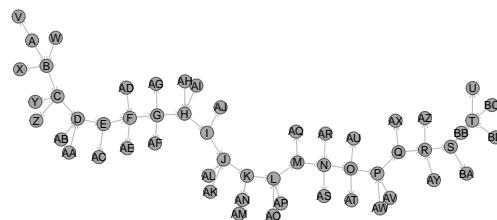


(d) Statistical performance

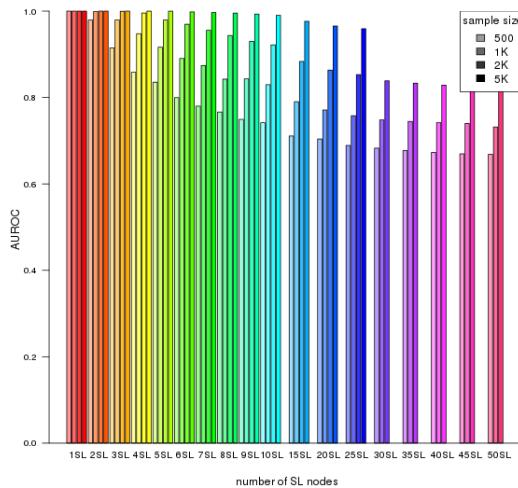
Figure O.25: Performance of simulations on a simple graph with more genes.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph2. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic



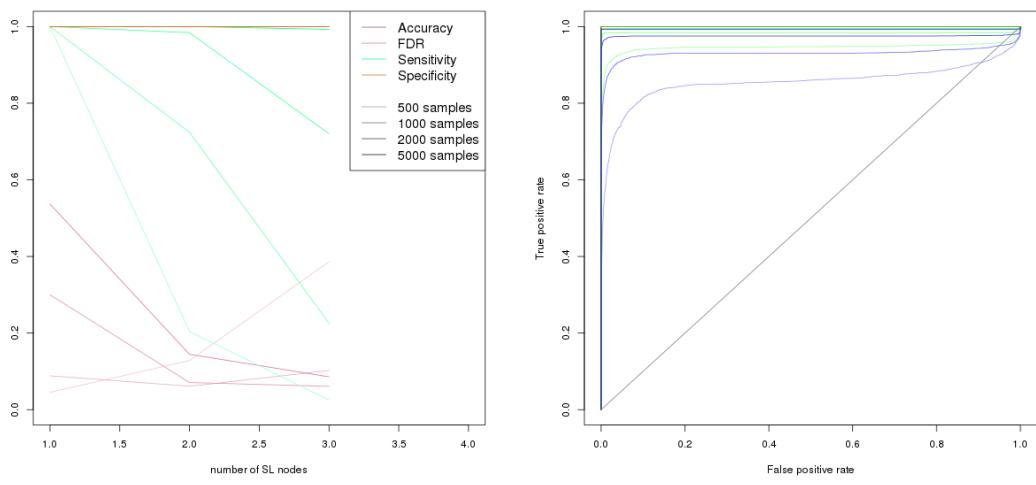
(c) Graph Structure



(d) Statistical performance

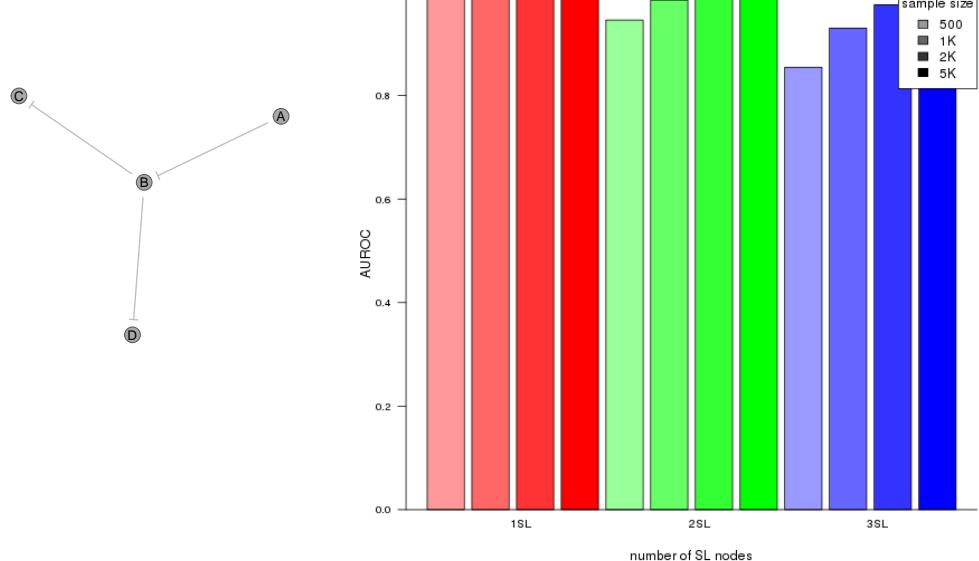
Figure O.26: Performance of simulations on a simple graph with more genes.
 Simulation of synthetic lethality was performed sampling from a multivariate normal distribution generated from Graph2. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter value, 10,000 simulations were used.

O.5 Simulations from Inhibiting Graph Structures with 20K genes



(a) Statistical evaluation

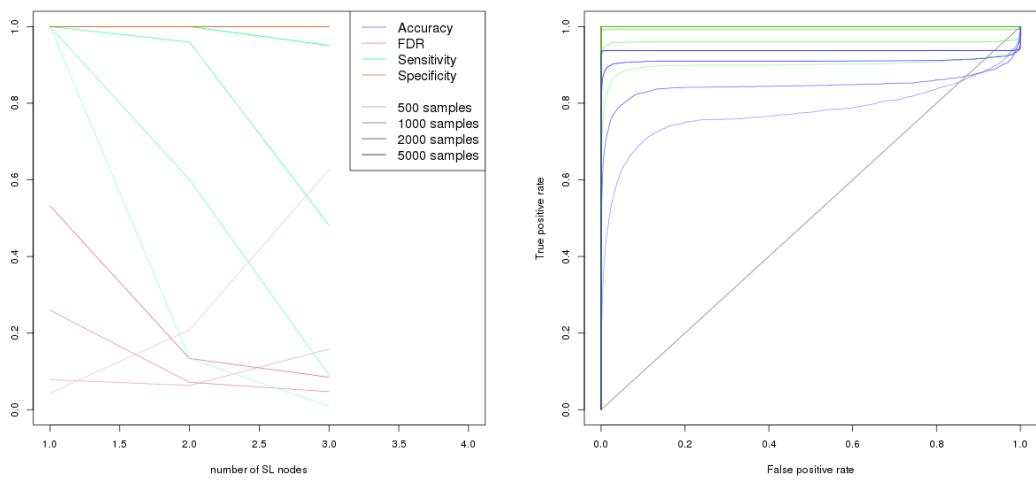
(b) Receiver operating characteristic



(c) Graph Structure

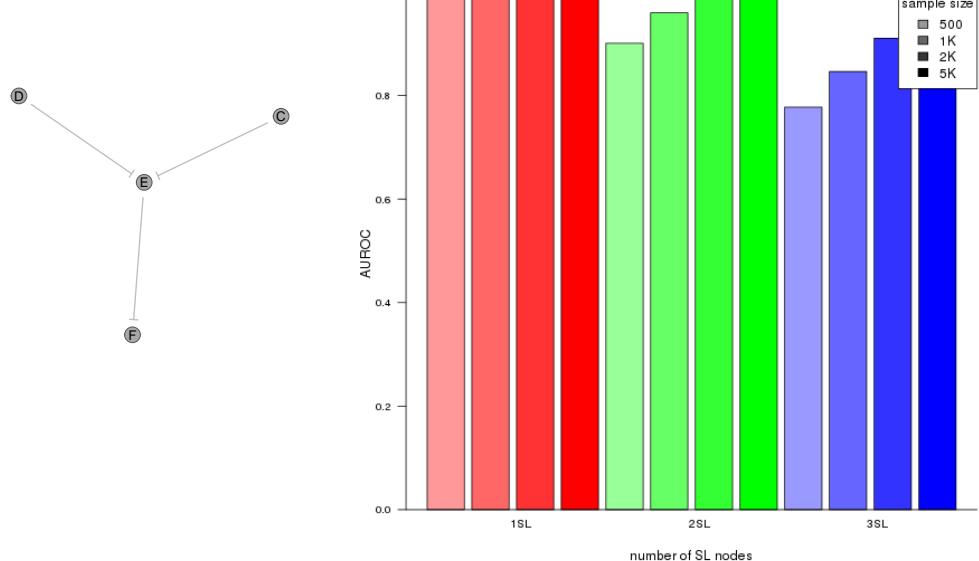
(d) Statistical performance

Figure O.27: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



(a) Statistical evaluation

(b) Receiver operating characteristic

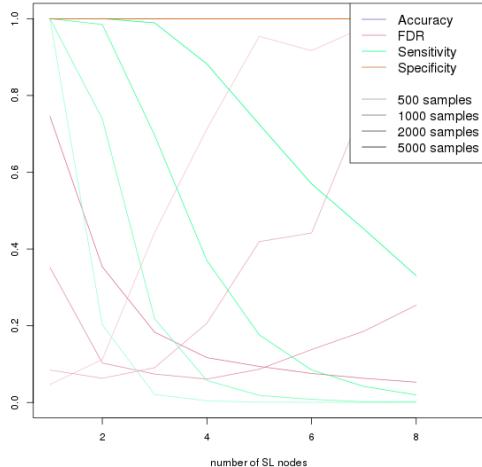


(c) Graph Structure

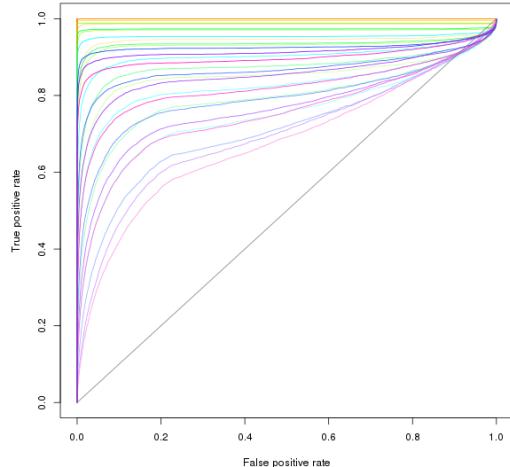
(d) Statistical performance

Figure O.28: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

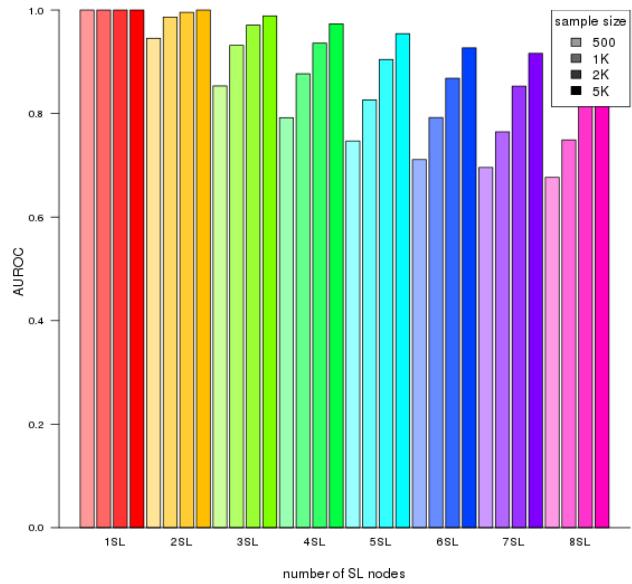
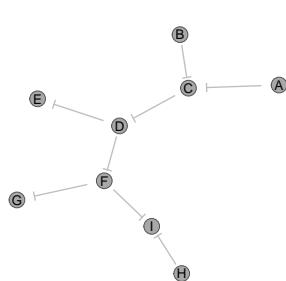
Simulations



(a) Statistical evaluation



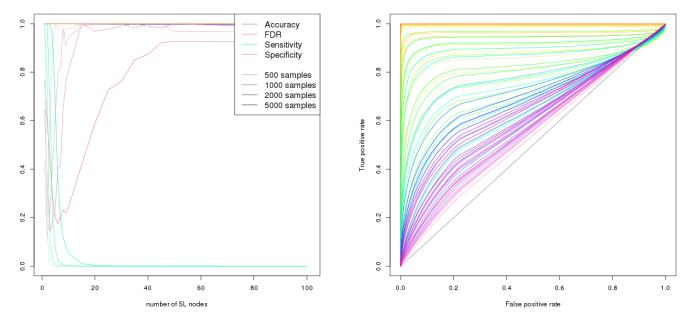
(b) Receiver operating characteristic



(c) Graph Structure

(d) Statistical performance

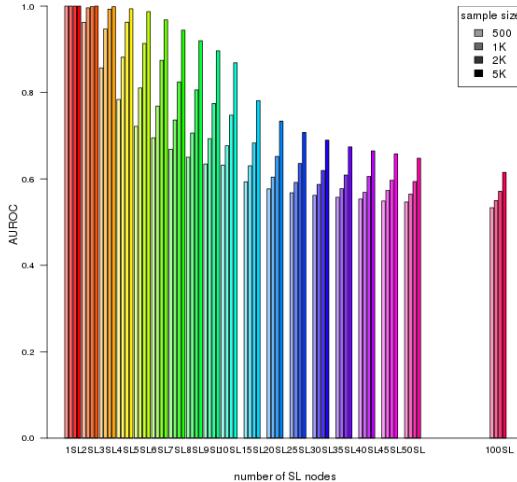
Figure O.29: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



(a) Statistical evaluation (b) Receiver operating characteristic

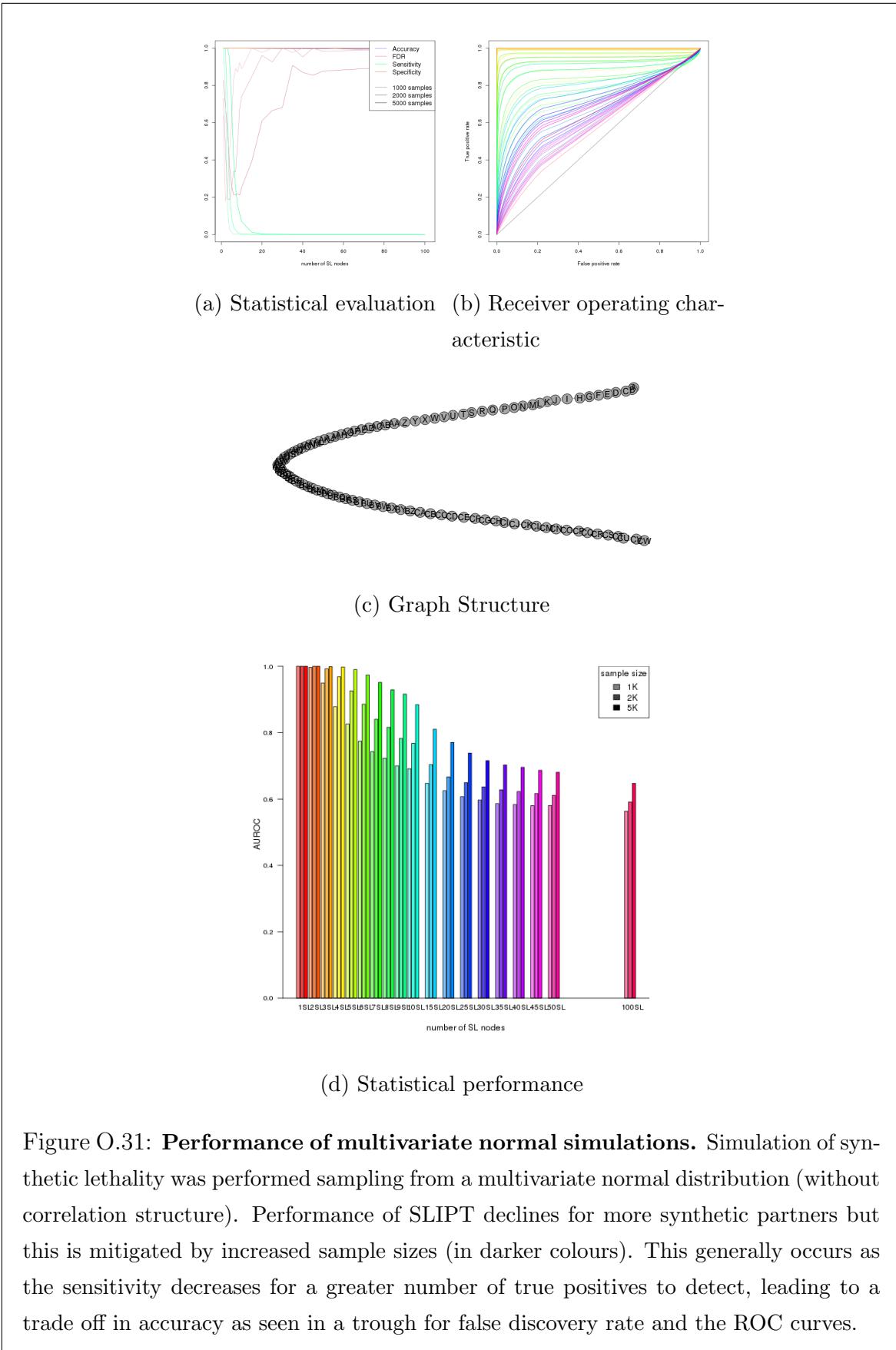


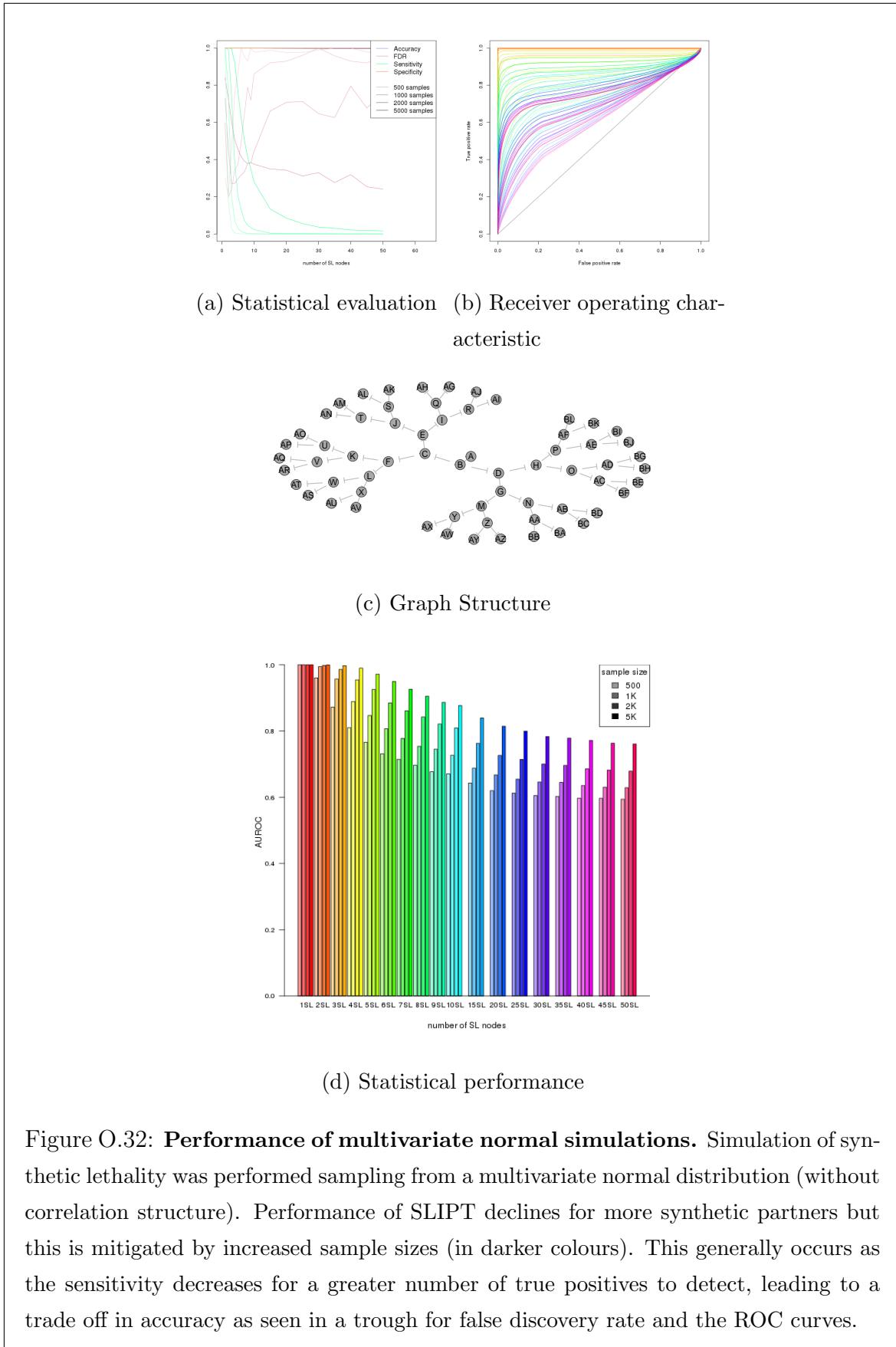
(c) Graph Structure

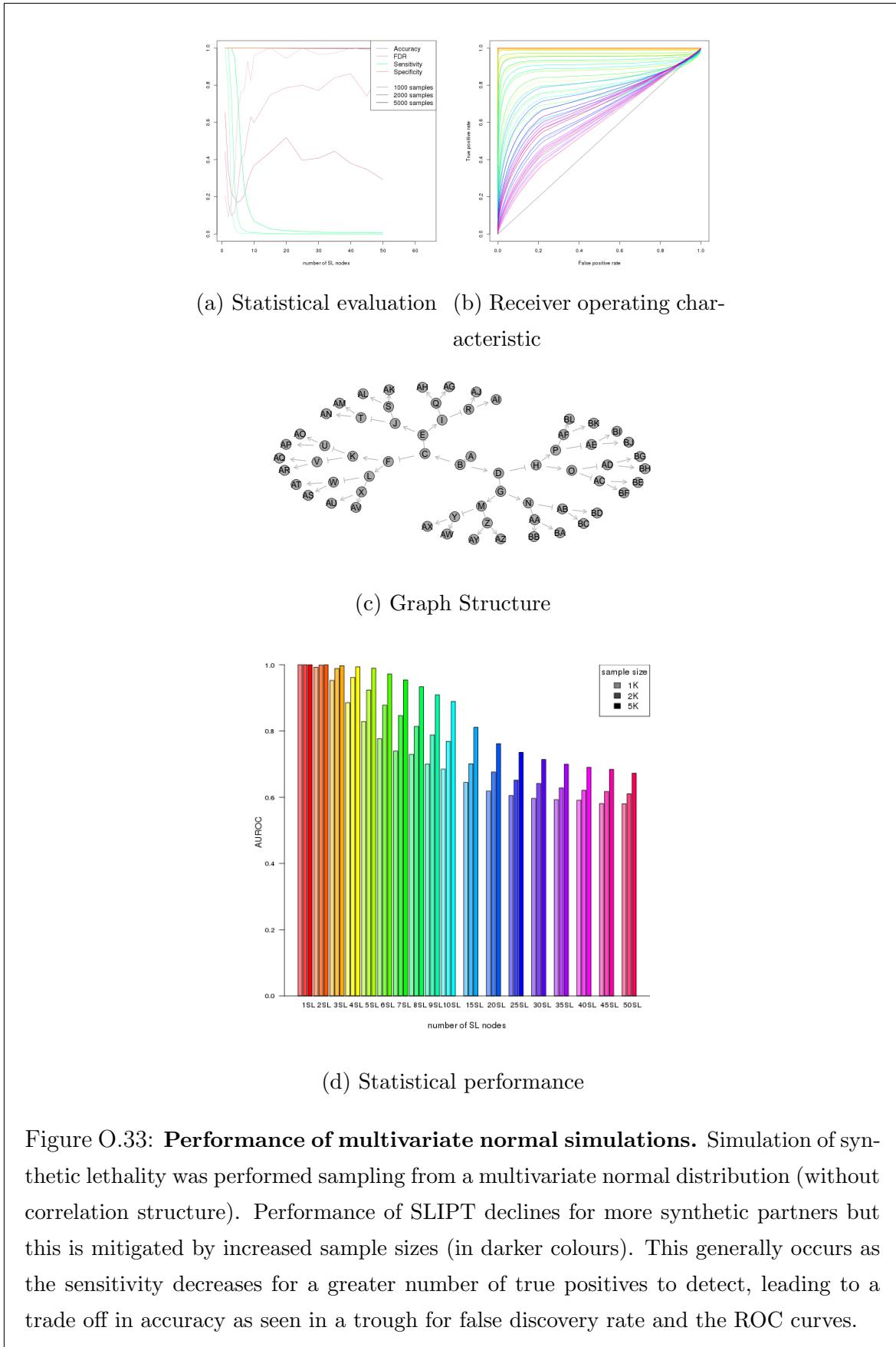


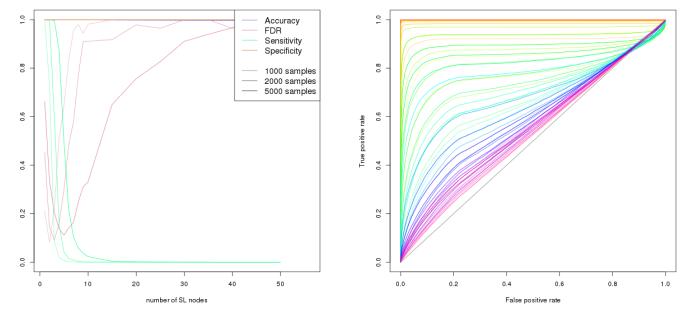
(d) Statistical performance

Figure O.30: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

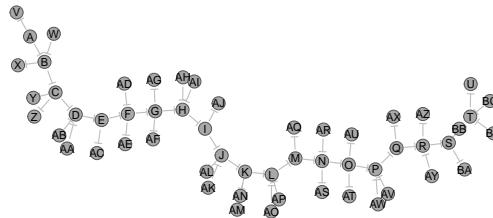




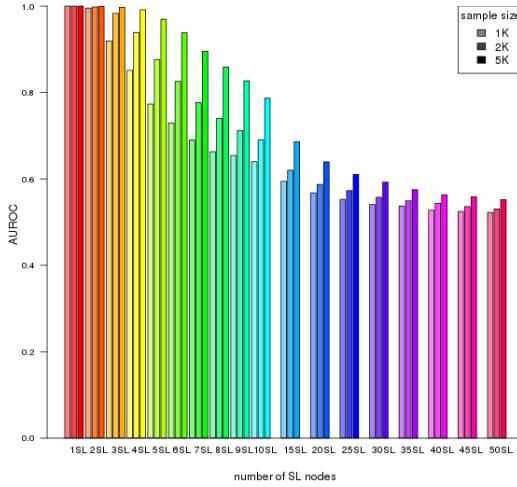




(a) Statistical evaluation (b) Receiver operating characteristic

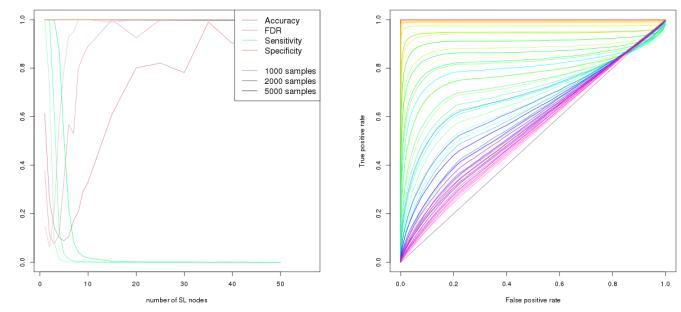


(c) Graph Structure

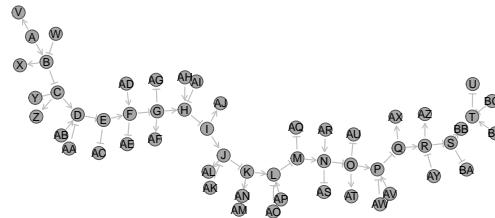


(d) Statistical performance

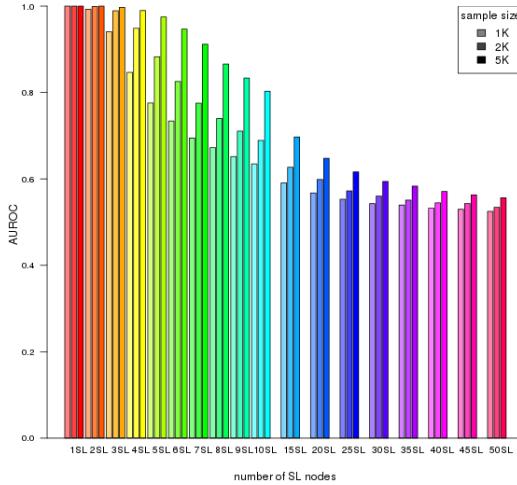
Figure O.34: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.



(a) Statistical evaluation (b) Receiver operating characteristic



(c) Graph Structure



(d) Statistical performance

Figure O.35: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

O.6 Simulations from Pathway Graph Structures

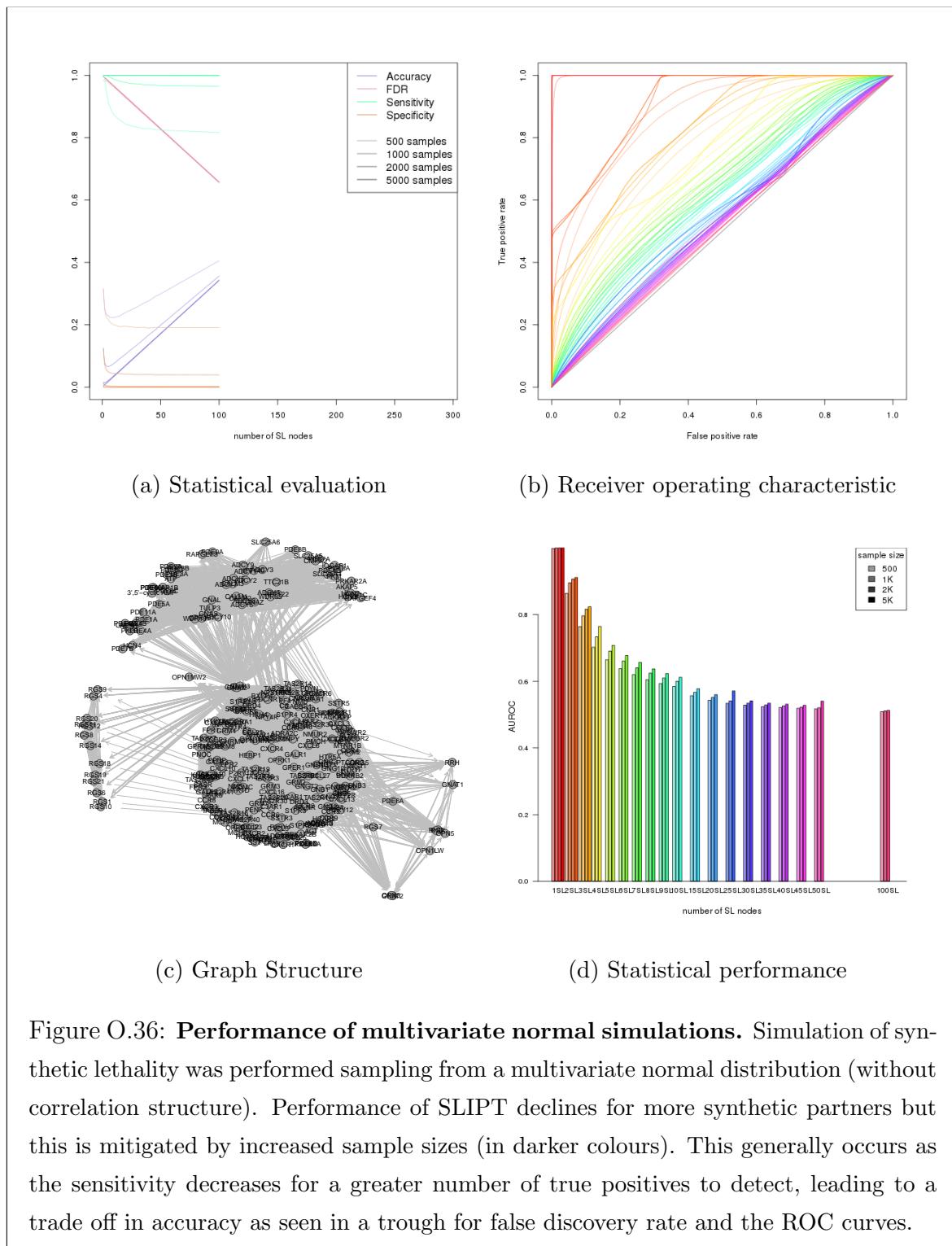
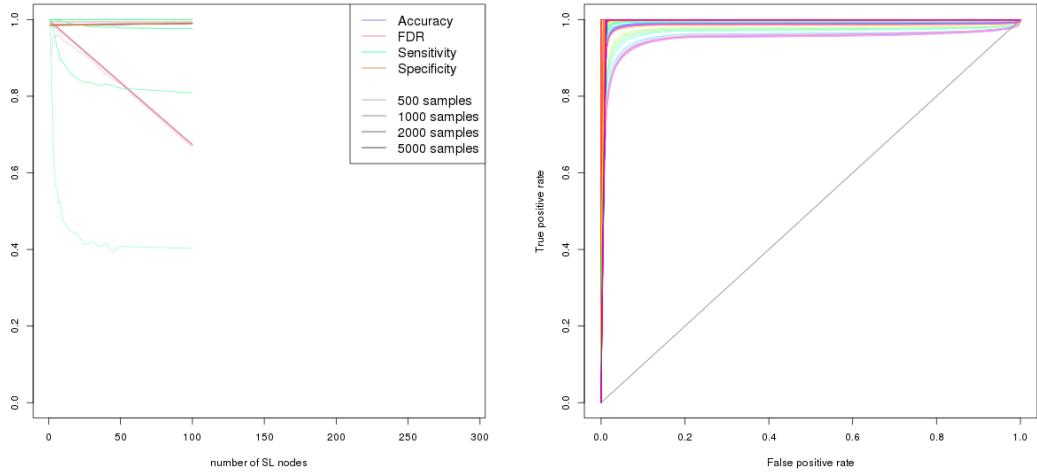
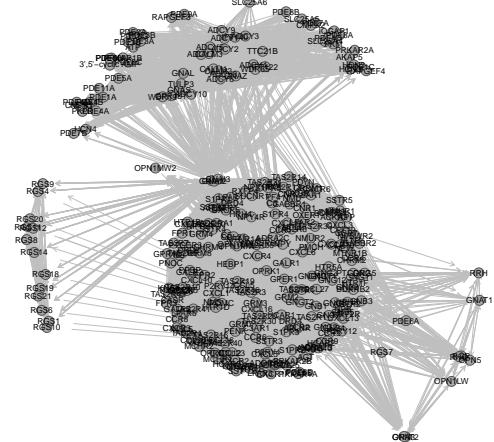


Figure O.36: **Performance of multivariate normal simulations.** Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.

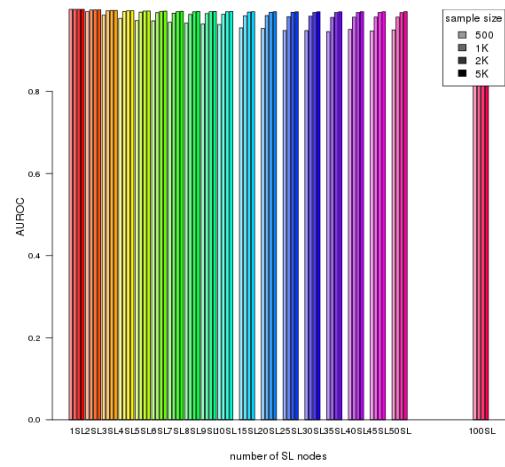


(a) Statistical evaluation

(b) Receiver operating characteristic



(c) Graph Structure



(d) Statistical performance

Figure O.37: Performance of multivariate normal simulations. Simulation of synthetic lethality was performed sampling from a multivariate normal distribution (without correlation structure). Performance of SLIPT declines for more synthetic partners but this is mitigated by increased sample sizes (in darker colours). This generally occurs as the sensitivity decreases for a greater number of true positives to detect, leading to a trade off in accuracy as seen in a trough for false discovery rate and the ROC curves.