

Contents

Glossary	xiii
Acronyms	xiv
1 Introduction and Literature Review	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer is a Global Health Issue	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Genomics Revolution in Cancer Research	4
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomics Data	6
1.1.3 Genomics Projects	6
1.1.3.1 The Cancer Genome Project	6
1.1.3.2 The Cancer Genome Atlas Project	7
1.1.4 Genomic Cancer Medicine	8
1.1.4.1 Cancer Genes and Driver Mutations	9
1.1.4.2 Precision Cancer Medicine	10
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	10
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	10
1.1.5 Systems and Network Biology	11
1.1.5.1 Network Medicine and Polypharmacology	13
1.2 A Synthetic Lethal Approach to Cancer Medicine	14
1.2.1 Synthetic Lethal Genetic Interactions	14
1.2.2 Synthetic Lethal Concepts in Genetics	15
1.2.3 Synthetic Lethality in Model Systems	16
1.2.3.1 Synthetic Lethal Pathways and Networks	16
1.2.3.2 Evolution of Synthetic Lethality	17
1.2.4 Synthetic Lethality in Cancer	18
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	19
1.2.6 High-throughput Screening for Synthetic Lethality	21
1.2.6.1 Synthetic Lethal Screens	22
1.2.7 Computational Prediction of Synthetic Lethality	25
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	25
1.2.7.2 Comparative Genomics	26
1.2.7.3 Analysis and Modelling of Protein Data	29
1.2.7.4 Differential Gene Expression	31

1.2.7.5	Data Mining and Machine Learning	32
1.2.7.6	Bimodality	35
1.2.7.7	Rationale for Further Development	35
1.3	E-cadherin as a Synthetic Lethal Target	36
1.3.1	The <i>CDH1</i> gene and its Biological Functions	36
1.3.1.1	Cytoskeleton	36
1.3.1.2	Extracellular and Tumour Micro-environment	37
1.3.1.3	Cell-Cell Adhesion and Signalling	37
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	37
1.3.2.1	Breast Cancers and Invasion	38
1.3.3	Hereditary Diffuse Gastric Cancer and Lobular Breast Cancer .	38
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	39
1.4	Summary and Research Direction of Thesis	40
1.4.1	Thesis Aims	42
2	Methods and Resources	43
2.1	Bioinformatics Resources for Genomics Research	43
2.1.1	Public Data and Software Packages	43
2.1.1.1	Cancer Genome Atlas Data	44
2.1.1.2	Reactome and Annotation Data	45
2.2	Data Handling	45
2.2.1	Normalisation	45
2.2.2	Sample Triage	46
2.2.3	Metagenes and the Singular Value Decomposition	48
2.2.3.1	Candidate Triage and Integration with Screen Data .	48
2.3	Techniques	49
2.3.1	Statistical Procedures and Tests	49
2.3.2	Gene Set Over-representation Analysis	50
2.3.3	Clustering	50
2.3.4	Heatmap	51
2.3.5	Modeling and Simulations	51
2.3.5.1	Receiver Operating Characteristic (Performance) . .	52
2.3.6	Resampling Analysis	52
2.4	Pathway Structure Methods	53
2.4.1	Network and Graph Analysis	53
2.4.2	Sourcing Graph Structure Data	54
2.4.3	Constructing Pathway Subgraphs	55
2.4.4	Network Analysis Metrics	55
2.5	Implementation	56
2.5.1	Computational Resources and Linux Utilities	56
2.5.2	R Language and Packages	57
2.5.3	High Performance and Parallel Computing	60

3 Methods Developed During Thesis	62
3.1 A Synthetic Lethal Detection Methodology	62
3.2 Synthetic Lethal Simulation and Modelling	65
3.2.1 A Model of Synthetic Lethality in Expression Data	65
3.2.2 Simulation Procedure	69
3.3 Detecting Simulated Synthetic Lethal Partners	72
3.3.1 Binomial Simulation of Synthetic lethality	72
3.3.2 Multivariate Normal Simulation of Synthetic lethality	74
3.3.2.1 Multivariate Normal Simulation with Correlated Genes	77
3.3.2.2 Specificity with Query-Correlated Pathways	84
3.3.2.3 Importance of Directional Testing	84
3.4 Graph Structure Methods	86
3.4.1 Upstream and Downstream Gene Detection	86
3.4.1.1 Permutation Analysis for Statistical Significance	87
3.4.1.2 Hierarchy Based on Biological Context	88
3.4.2 Simulating Gene Expression from Graph Structures	89
3.5 Customised Functions and Packages Developed	93
3.5.1 Synthetic Lethal Interaction Prediction Tool	93
3.5.2 Data Visualisation	94
3.5.3 Extensions to the iGraph Package	97
3.5.3.1 Sampling Simulated Data from Graph Structures	97
3.5.3.2 Plotting Directed Graph Structures	97
3.5.3.3 Computing Information Centrality	98
3.5.3.4 Testing Pathway Structure with Permutation Testing .	98
3.5.3.5 Metapackage to Install iGraph Functions	99
4 Synthetic Lethal Analysis of Gene Expression Data	100
4.1 Synthetic Lethal Genes in Breast Cancer	101
4.1.1 Synthetic Lethal Pathways in Breast Cancer	103
4.1.2 Expression Profiles of Synthetic Lethal Partners	104
4.1.2.1 Subgroup Pathway Analysis	107
4.2 Comparing Synthetic Lethal Gene Candidates	110
4.2.1 Primary siRNA Screen Candidates	110
4.2.2 Comparison with Correlation	111
4.2.3 Comparison with Primary Screen Viability	113
4.2.4 Comparison with Secondary siRNA Screen Validation	114
4.2.5 Comparison to Primary Screen at Pathway Level	116
4.2.5.1 Resampling Genes for Pathway Enrichment	118
4.2.6 Integrating Synthetic Lethal Pathways and Screens	121
4.3 Metagene Analysis	123
4.3.1 Pathway Expression	124
4.3.2 Somatic Mutation	126
4.3.3 Synthetic Lethal Pathway Metagenes	130
4.3.4 Synthetic Lethality in Breast Cancer	131
4.4 Replication in Stomach Cancer	132
4.5 Discussion	133

4.5.1	Strengths of the SLIPT Methodology	133
4.5.2	Synthetic Lethal Pathways for E-cadherin	134
4.5.3	Replication and Validation	136
4.5.3.1	Integration with siRNA Screening	136
4.5.3.2	Replication across Tissues	137
4.6	Summary	137
5	Synthetic Lethal Pathway Structure	139
5.1	Synthetic Lethal Genes in Reactome Pathways	139
5.1.1	The PI3K/AKT Pathway	140
5.1.2	The Extracellular Matrix	142
5.1.3	G Protein Coupled Receptors	145
5.1.4	Gene Regulation and Translation	145
5.2	Network Analysis of Synthetic Lethal Genes	146
5.2.1	Gene Connectivity and Vertex Degree	147
5.2.2	Gene Importance and Centrality	148
5.2.2.1	Information Centrality	148
5.2.2.2	PageRank Centrality	150
5.3	Relationships between Synthetic Lethal Genes	152
5.3.1	Hierarchical Pathway Structure	152
5.3.1.1	Contextual Hierarchy of PI3K	152
5.3.1.2	Testing Contextual Hierarchy of Synthetic Lethal Genes	152
5.3.2	Upstream or Downstream Synthetic Lethality	156
5.3.2.1	Measuring Structure of Candidates within PI3K . . .	156
5.3.2.2	Resampling for Synthetic Lethal Pathway Structure .	158
5.4	Discussion	160
5.5	Summary	162
6	Simulation and Modeling of Synthetic Lethal Pathways	164
6.1	Comparing Synthetic Lethal Detection Methods	165
6.1.1	Performance of SLIPT and χ^2 across Quantiles	166
6.1.1.1	Correlated Query Genes affects Specificity	169
6.1.2	Alternative Synthetic Lethal Detection Strategies	171
6.1.2.1	Correlation for Synthetic Lethal Detection	172
6.1.2.2	Testing for Bimodality with BiSEp	173
6.2	Simulations with Graph Structures	174
6.2.1	Performance over a Graph Structure	175
6.2.1.1	Simple Graph Structures	175
6.2.1.2	Constructed Graph Structures	176
6.2.2	Performance with Inhibitions	180
6.2.3	Synthetic Lethality across Graph Structures	186
6.2.4	Performance within a Simulated Human Genome	189
6.3	Simulations in More Complex Graph Structures	194
6.3.1	Simulations over Pathway-based Graphs	195
6.3.2	Pathway Structures in a Simulated Human Genome	198
6.4	Discussion	201

6.4.1	Simulation Procedure	201
6.4.2	Comparing Methods with Simulated Data	202
6.4.3	Design and Performance of SLIPT	203
6.4.4	Simulations from Graph Structures	205
6.5	Summary	206
7	Discussion	208
7.1	Synthetic Lethality and <i>CDH1</i> Biology	208
7.1.1	Established Functions of <i>CDH1</i>	209
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	209
7.2	Significance	210
7.2.1	Synthetic Lethality in the Genomic Era	210
7.2.2	Clinical Interventions based on Synthetic Lethality	212
7.3	Future Directions	213
7.4	Conclusions	215
References		217
A	Sample Quality	243
A.1	Sample Correlation	243
A.2	Replicate Samples in TCGA Breast	246
B	Software Used for Thesis	250
C	Mutation Analysis in Breast Cancer	259
C.1	Synthetic Lethal Genes and Pathways	259
C.2	Synthetic Lethal Expression Profiles	262
C.3	Comparison to Primary Screen	265
C.3.1	Resampling Analysis	267
C.4	Compare SLIPT genes	269
C.5	Metagene Analysis	271
C.6	Expression of Somatic Mutations	272
C.7	Metagene Expression Profiles	275
D	Intrinsic Subtyping	278
E	Stomach Expression Analysis	280
E.1	Synthetic Lethal Genes and Pathways	280
E.2	Comparison to Primary Screen	284
E.2.1	Resampling Analysis	286
E.3	Metagene Analysis	288
F	Synthetic Lethal Genes in Pathways	289
G	Pathway Connectivity for Mutation SLIPT	297
H	Information Centrality for Gene Essentiality	301

I Pathway Structure for Mutation SLIPT	304
J Performance of SLIPT and χ^2	307
J.1 Correlated Query Genes affects Specificity	313
K Graph Structures	319
K.1 Simulations from Simple Graph Structures	319
K.1.1 Simulations from Inhibiting Graph Structures	321
K.2 Simulation across Graph Structures	324
K.3 Simulations from Complex Graph Structures	328
K.3.1 Simulations from Complex Inhibiting Graphs	331
K.4 Simulations from Pathway Graph Structures	338

List of Figures

1.1	Synthetic genetic interactions	15
1.2	Synthetic lethality in cancer	19
2.1	Read count density	47
2.2	Read count sample mean	47
3.1	Framework for synthetic lethal prediction	63
3.2	Synthetic lethal prediction adapted for mutation	64
3.3	A model of synthetic lethal gene expression	66
3.4	Modeling synthetic lethal gene expression	67
3.5	Synthetic lethality with multiple genes	68
3.6	Simulating gene function	70
3.7	Simulating synthetic lethal gene function	70
3.8	Simulating synthetic lethal gene expression	71
3.9	Performance of binomial simulations	73
3.10	Comparison of statistical performance	73
3.11	Performance of multivariate normal simulations	75
3.12	Simulating expression with correlated gene blocks	78
3.13	Simulating expression with correlated gene blocks	79
3.14	Synthetic lethal prediction across simulations	80
3.15	Performance with correlations	81
3.16	Comparison of statistical performance with correlation structure	82
3.17	Performance with query correlations	83
3.18	Statistical evaluation of directional criteria	84
3.19	Performance of directional criteria	85
3.20	Simulated graph structures	89
3.21	Simulating expression from a graph structure	91
3.22	Simulating expression from graph structure with inhibitions	92
3.23	Demonstration of violin plots with custom features	95
3.24	Demonstration of annotated heatmap	95
3.25	Simulating graph structures	98
4.1	Synthetic lethal expression profiles of analysed samples	106
4.2	Comparison of SLIPT to siRNA	110
4.3	Compare SLIPT and siRNA genes with correlation	111
4.4	Compare SLIPT and siRNA genes with correlation	112
4.5	Compare SLIPT and siRNA genes with viability	113

4.6	Compare SLIPT genes with siRNA viability	114
4.7	Resampled intersection of SLIPT and siRNA candidates	118
4.8	Pathway metagene expression profiles	125
4.9	Expression profiles for constituent genes of PI3K	127
4.10	Expression profiles for estrogen receptor related genes	128
4.11	Somatic mutation against the PI3K metagene	129
5.1	Synthetic Lethality in the PI3K Cascade	141
5.2	Synthetic Lethality in the Elastic Fibre Formation Pathway	143
5.3	Synthetic Lethality in the Fibrin Clot Formation	144
5.4	Synthetic Lethality and Vertex Degree	147
5.5	Synthetic Lethality and Centrality	150
5.6	Synthetic Lethality and PageRank	151
5.7	Hierarchical Structure of PI3K	153
5.8	Hierarchy Score in PI3K against Synthetic Lethality in PI3K	154
5.9	Structure of Synthetic Lethality in PI3K	156
5.10	Structure of Synthetic Lethality Resampling in PI3K	157
6.1	Performance of χ^2 and SLIPT across quantiles	167
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	168
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	169
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	171
6.5	Performance of negative correlation and SLIPT	173
6.6	Simple graph structures	176
6.7	Performance of simulations on a simple graph	177
6.8	Performance of simulations is similar in simple graphs	178
6.9	Performance of simulations on a pathway	179
6.10	Performance of simulations on a simple graph with inhibition	181
6.11	Performance is higher on a simple inhibiting graph	183
6.12	Performance of simulations on a constructed graph with inhibition . . .	184
6.13	Performance is affected by inhibition in graphs	185
6.14	Detection of Synthetic Lethality within a Graph Structure with Inhibitions	187
6.15	Performance of simulations including a simple graph	191
6.16	Performance on a simple graph improves with more genes	192
6.17	Performance on an inhibiting graph improves with more genes	193
6.18	Performance of simulations on the PI3K cascade	197
6.19	Performance of simulations including the PI3K cascade	199
6.20	Performance on pathways improves with more genes	200
A.1	Correlation profiles of removed samples	244
A.2	Correlation analysis and sample removal	245
A.3	Replicate excluded samples	246
A.4	Replicate samples with all remaining	247
A.5	Replicate samples with some excluded	248
C.1	Synthetic lethal expression profiles of analysed samples	263

C.2	Comparison of mtSLIPT to siRNA	265
C.3	Compare mtSLIPT and siRNA genes with correlation	269
C.4	Compare mtSLIPT and siRNA genes with correlation	269
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	270
C.6	Somatic mutation against PIK3CA metagene	272
C.7	Somatic mutation against PI3K protein	273
C.8	Somatic mutation against AKT protein	274
C.9	Pathway metagene expression profiles	275
C.10	Expression profiles for p53 related genes	276
C.11	Expression profiles for BRCA related genes	277
E.1	Synthetic lethal expression profiles of stomach samples	282
E.2	Comparison of SLIPT in stomach to siRNA	284
F.1	Synthetic Lethality in the PI3K/AKT Pathway	289
F.2	Synthetic Lethality in the PI3K/AKT Pathway in Cancer	290
F.3	Synthetic Lethality in the Extracellular Matrix	291
F.4	Synthetic Lethality in the GPCRs	292
F.5	Synthetic Lethality in the GPCR Downstream	293
F.6	Synthetic Lethality in the Translation Elongation	294
F.7	Synthetic Lethality in the Nonsense-mediated Decay	295
F.8	Synthetic Lethality in the 3' UTR	296
G.1	Synthetic Lethality and Vertex Degree	297
G.2	Synthetic Lethality and Centrality	298
G.3	Synthetic Lethality and PageRank	299
H.1	Information centrality distribution	303
I.1	Synthetic Lethality and Heirarchy Score in PI3K	304
I.2	Heirarchy Score in PI3K against Synthetic Lethality in PI3K	305
I.3	Structure of Synthetic Lethality in PI3K	305
I.4	Structure of Synthetic Lethality Resampling	306
J.1	Performance of χ^2 and SLIPT across quantiles	307
J.2	Performance of χ^2 and SLIPT across quantiles	309
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	311
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation .	313
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation .	315
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	317
K.1	Performance of simulations on a simple graph	320
K.2	Performance of simulations on an inhibiting graph	321
K.3	Performance of simulations on a constructed graph with inhibition	322
K.4	Performance of simulations on a constructed graph with inhibition	323
K.5	Detection of Synthetic Lethality within a Graph Structure	324
K.6	Detection of Synthetic Lethality within an Inhibiting Graph Structure .	326

K.7	Detection of Synthetic Lethality within an Inhibiting Graph Structure	327
K.8	Performance of simulations on a large graph	328
K.9	Performance of simulations on a branching graph	329
K.10	Performance of simulations on a complex graph	330
K.11	Performance of simulations on a large constructed graph with inhibition	332
K.12	Performance of simulations on a large constructed graph with inhibition	333
K.13	Performance of simulations on a branching graph with inhibition	334
K.14	Performance of simulations on a branching graph with inhibition	335
K.15	Performance of simulations on a complex graph with inhibition	336
K.16	Performance of simulations on a complex graph with inhibition	337
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	338
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	339

List of Tables

1.1	Methods for Predicting Genetic Interactions	26
1.2	Methods for Predicting Synthetic Lethality in Cancer	27
1.3	Methods used by Wu <i>et al.</i> (2014)	28
2.1	Excluded Samples by Batch and Clinical Characteristics.	46
2.2	Computers used during Thesis	57
2.3	Linux Utilities and Applications used during Thesis	57
2.4	R Installations used during Thesis	58
2.5	R Packages used during Thesis	58
2.6	R Packages Developed during Thesis	60
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	102
4.2	Pathways for <i>CDH1</i> partners from SLIPT	104
4.3	Pathway composition for clusters of <i>CDH1</i> partners from SLIPT	108
4.4	Analysis of variance (ANOVA) for Synthetic Lethality and Correlation with <i>CDH1</i>	112
4.5	Comparing SLIPT genes against secondary siRNA screen in breast cancer	115
4.6	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	117
4.7	Pathways for <i>CDH1</i> partners from SLIPT	120
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen	122
4.9	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	131
5.1	ANOVA for Synthetic Lethality and Vertex Degree	148
5.2	ANOVA for Synthetic Lethality and Information Centrality	150
5.3	ANOVA for Synthetic Lethality and PageRank Centrality	152
5.4	ANOVA for Synthetic Lethality and PI3K Hierarchy	155
5.5	Resampling for pathway structure of synthetic lethal detection methods	159
B.1	R Packages used during Thesis	250
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	260
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	261
C.3	Pathway composition for clusters of <i>CDH1</i> partners from mtSLIPT	264
C.4	Pathway composition for <i>CDH1</i> partners from mtSLIPT and siRNA	266
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	267
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	268
C.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	271

D.1	Comparison of Intrinsic Subtypes	278
E.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	280
E.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	281
E.3	Pathway composition for clusters of <i>CDH1</i> partners in stomach SLIPT	283
E.4	Pathway composition for <i>CDH1</i> partners from SLIPT and siRNA screening	285
E.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	286
E.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA screen	287
E.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT in stomach cancer	288
G.1	ANOVA for Synthetic Lethality and Vertex Degree	300
G.2	ANOVA for Synthetic Lethality and Information Centrality	300
G.3	ANOVA for Synthetic Lethality and PageRank Centrality	300
H.1	Information centrality for genes and molecules in the Reactome network	302
I.1	ANOVA for Synthetic Lethality and PI3K Hierarchy	304
I.2	Resampling for pathway structure of synthetic lethal detection methods	306

Glossary

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

Acronyms

ANOVA Analysis of Variance.

SLIPT Synthetic lethal interaction prediction tool.

References

- Aarts, M., Bajrami, I., Herrera-Abreu, M.T., Elliott, R., Brough, R., Ashworth, A., Lord, C.J., and Turner, N.C. (2015) Functional genetic screen identifies increased sensitivity to wee1 inhibition in cells with defects in fanconi anemia and hr pathways. *Mol Cancer Ther*, **14**(4): 865–76.
- Abeshouse, A., Ahn, J., Akbani, R., Ally, A., Amin, S., Andry, C.D., Annala, M., Aprikian, A., Armenia, J., Arora, A., *et al.* (2015) The Molecular Taxonomy of Primary Prostate Cancer. *Cell*, **163**(4): 1011–1025.
- Adler, D. (2005) *vioplot: Violin plot*. R package version 0.2.
- Akbani, R., Akdemir, K.C., Aksoy, B.A., Albert, M., Ally, A., Amin, S.B., Arachchi, H., Arora, A., Auman, J.T., Ayala, B., *et al.* (2015) Genomic Classification of Cutaneous Melanoma. *Cell*, **161**(7): 1681–1696.
- Akobeng, A.K. (2007) Understanding diagnostic tests 3: receiver operating characteristic curves. *Acta Pdiatrica*, **96**(5): 644–647.
- American Cancer Society (2017) Genetics and cancer. <https://www.cancer.org/cancer/cancer-causes/genetics.html>. Accessed: 22/03/2017.
- Anjomshoaa, A., Lin, Y.H., Black, M.A., McCall, J.L., Humar, B., Song, S., Fukuzawa, R., Yoon, H.S., Holzmann, B., Friederichs, J., *et al.* (2008) Reduced expression of a gene proliferation signature is associated with enhanced malignancy in colon cancer. *Br J Cancer*, **99**(6): 966–973.
- Araki, H., Knapp, C., Tsai, P., and Print, C. (2012) GeneSetDB: A comprehensive meta-database, statistical and visualisation framework for gene set analysis. *FEBS Open Bio*, **2**: 76–82.

- Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., *et al.* (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet*, **25**(1): 25–29.
- Ashworth, A. (2008) A synthetic lethal therapeutic approach: poly(adp) ribose polymerase inhibitors for the treatment of cancers deficient in dna double-strand break repair. *J Clin Oncol*, **26**(22): 3785–90.
- Audeh, M.W., Carmichael, J., Penson, R.T., Friedlander, M., Powell, B., Bell-McGuinn, K.M., Scott, C., Weitzel, J.N., Oaknin, A., Loman, N., *et al.* (2010) Oral poly(adp-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. *Lancet*, **376**(9737): 245–51.
- Babyak, M.A. (2004) What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med*, **66**(3): 411–21.
- Bamford, S., Dawson, E., Forbes, S., Clements, J., Pettett, R., Dogan, A., Flanagan, A., Teague, J., Futreal, P.A., Stratton, M.R., *et al.* (2004) The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. *Br J Cancer*, **91**(2): 355–358.
- Barabási, A.L. and Albert, R. (1999) Emergence of scaling in random networks. *Science*, **286**(5439): 509–12.
- Barabási, A.L., Gulbahce, N., and Loscalzo, J. (2011) Network medicine: a network-based approach to human disease. *Nat Rev Genet*, **12**(1): 56–68.
- Barabási, A.L. and Oltvai, Z.N. (2004) Network biology: understanding the cell's functional organization. *Nat Rev Genet*, **5**(2): 101–13.
- Barrat, A. and Weigt, M. (2000) On the properties of small-world network models. *The European Physical Journal B - Condensed Matter and Complex Systems*, **13**(3): 547–560.
- Barretina, J., Caponigro, G., Stransky, N., Venkatesan, K., Margolin, A.A., Kim, S., Wilson, C.J., Lehar, J., Kryukov, G.V., Sonkin, D., *et al.* (2012) The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature*, **483**(7391): 603–607.

Barry, W.T. (2016) *safe: Significance Analysis of Function and Expression*. R package version 3.14.0.

Baryshnikova, A., Costanzo, M., Dixon, S., Vizeacoumar, F.J., Myers, C.L., Andrews, B., and Boone, C. (2010a) Synthetic genetic array (sga) analysis in *saccharomyces cerevisiae* and *schizosaccharomyces pombe*. *Methods Enzymol*, **470**: 145–79.

Baryshnikova, A., Costanzo, M., Kim, Y., Ding, H., Koh, J., Toufighi, K., Youn, J.Y., Ou, J., San Luis, B.J., Bandyopadhyay, S., et al. (2010b) Quantitative analysis of fitness and genetic interactions in yeast on a genome scale. *Nat Meth*, **7**(12): 1017–1024.

Bass, A.J., Thorsson, V., Shmulevich, I., Reynolds, S.M., Miller, M., Bernard, B., Hinoue, T., Laird, P.W., Curtis, C., Shen, H., et al. (2014) Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*, **513**(7517): 202–209.

Bates, D. and Maechler, M. (2016) *Matrix: Sparse and Dense Matrix Classes and Methods*. R package version 1.2-7.1.

Bateson, W. and Mendel, G. (1909) *Mendel's principles of heredity, by W. Bateson*. University Press, Cambridge [Eng.].

Becker, K.F., Atkinson, M.J., Reich, U., Becker, I., Nekarda, H., Siewert, J.R., and Hfler, H. (1994) E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. *Cancer Research*, **54**(14): 3845–3852.

Bell, D., Berchuck, A., Birrer, M., Chien, J., Cramer, D., Dao, F., Dhir, R., DiSaia, P., Gabra, H., Glenn, P., et al. (2011) Integrated genomic analyses of ovarian carcinoma. *Nature*, **474**(7353): 609–615.

Benjamini, Y. and Hochberg, Y. (1995) Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological)*, **57**(1): 289–300.

Berx, G., Cleton-Jansen, A.M., Nollet, F., de Leeuw, W.J., van de Vijver, M., Cornelisse, C., and van Roy, F. (1995) E-cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. *EMBO J*, **14**(24): 6107–15.

Berx, G., Cleton-Jansen, A.M., Strumane, K., de Leeuw, W.J., Nollet, F., van Roy, F., and Cornelisse, C. (1996) E-cadherin is inactivated in a majority of invasive human

- lobular breast cancers by truncation mutations throughout its extracellular domain. *Oncogene*, **13**(9): 1919–25.
- Berx, G. and van Roy, F. (2009) Involvement of members of the cadherin superfamily in cancer. *Cold Spring Harb Perspect Biol*, **1**: a003129.
- Bitler, B.G., Aird, K.M., Garipov, A., Li, H., Amatangelo, M., Kossenkov, A.V., Schultz, D.C., Liu, Q., Shih Ie, M., Conejo-Garcia, J.R., *et al.* (2015) Synthetic lethality by targeting ezh2 methyltransferase activity in arid1a-mutated cancers. *Nat Med*, **21**(3): 231–8.
- Blake, J.A., Christie, K.R., Dolan, M.E., Drabkin, H.J., Hill, D.P., Ni, L., Sitnikov, D., Burgess, S., Buza, T., Gresham, C., *et al.* (2015) Gene Ontology Consortium: going forward. *Nucleic Acids Res*, **43**(Database issue): D1049–1056.
- Boettcher, M., Lawson, A., Ladenburger, V., Fredebohm, J., Wolf, J., Hoheisel, J.D., Frezza, C., and Shlomi, T. (2014) High throughput synthetic lethality screen reveals a tumorigenic role of adenylate cyclase in fumarate hydratase-deficient cancer cells. *BMC Genomics*, **15**: 158.
- Boone, C., Bussey, H., and Andrews, B.J. (2007) Exploring genetic interactions and networks with yeast. *Nat Rev Genet*, **8**(6): 437–49.
- Borgatti, S.P. (2005) Centrality and network flow. *Social Networks*, **27**(1): 55 – 71.
- Boucher, B. and Jenna, S. (2013) Genetic interaction networks: better understand to better predict. *Front Genet*, **4**: 290.
- Bozovic-Spasojevic, I., Azambuja, E., McCaskill-Stevens, W., Dinh, P., and Cardoso, F. (2012) Chemoprevention for breast cancer. *Cancer treatment reviews*, **38**(5): 329–339.
- Breiman, L. (2001) Random forests. *Machine Learning*, **45**(1): 5–32.
- Brin, S. and Page, L. (1998) The anatomy of a large-scale hypertextual web search engine. *Computer Networks and ISDN Systems*, **30**(1): 107 – 117.
- Broulxhon, S.M., Kyrkanides, S., Teng, X., Athar, M., Ghazizadeh, S., Simon, M., O'Banion, M.K., and Ma, L. (2014) Soluble E-cadherin: a critical oncogene modulating receptor tyrosine kinases, MAPK and PI3K/Akt/mTOR signaling. *Oncogene*, **33**(2): 225–235.

- Bryant, H.E., Schultz, N., Thomas, H.D., Parker, K.M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N.J., and Helleday, T. (2005) Specific killing of *BRCA2*-deficient tumours with inhibitors of polyadribose polymerase. *Nature*, **434**(7035): 913–7.
- Bussey, H., Andrews, B., and Boone, C. (2006) From worm genetic networks to complex human diseases. *Nat Genet*, **38**(8): 862–3.
- Butland, G., Babu, M., Diaz-Mejia, J.J., Bohdana, F., Phanse, S., Gold, B., Yang, W., Li, J., Gagarinova, A.G., Pogoutse, O., *et al.* (2008) esga: *E. coli* synthetic genetic array analysis. *Nat Methods*, **5**(9): 789–95.
- cBioPortal for Cancer Genomics (cBioPortal) (2017) cBioPortal for Cancer Genomics. <http://www.cbioportal.org/>. Accessed: 26/03/2017.
- Cerami, E.G., Gross, B.E., Demir, E., Rodchenkov, I., Babur, O., Anwar, N., Schultz, N., Bader, G.D., and Sander, C. (2011) Pathway Commons, a web resource for biological pathway data. *Nucleic Acids Res*, **39**(Database issue): D685–690.
- Chen, A., Beetham, H., Black, M.A., Priya, R., Telford, B.J., Guest, J., Wiggins, G.A.R., Godwin, T.D., Yap, A.S., and Guilford, P.J. (2014) E-cadherin loss alters cytoskeletal organization and adhesion in non-malignant breast cells but is insufficient to induce an epithelial-mesenchymal transition. *BMC Cancer*, **14**(1): 552.
- Chen, S. and Parmigiani, G. (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*, **25**(11): 1329–1333.
- Chen, X. and Tompa, M. (2010) Comparative assessment of methods for aligning multiple genome sequences. *Nat Biotechnol*, **28**(6): 567–572.
- Chipman, K. and Singh, A. (2009) Predicting genetic interactions with random walks on biological networks. *BMC Bioinformatics*, **10**(1): 17.
- Christofori, G. and Semb, H. (1999) The role of the cell-adhesion molecule E-cadherin as a tumour-suppressor gene. *Trends in Biochemical Sciences*, **24**(2): 73 – 76.
- Ciriello, G., Gatza, M.L., Beck, A.H., Wilkerson, M.D., Rhie, S.K., Pastore, A., Zhang, H., McLellan, M., Yau, C., Kandoth, C., *et al.* (2015) Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell*, **163**(2): 506–519.

- Clark, M.J. (2004) Endogenous Regulator of G Protein Signaling Proteins Suppress G_o-Dependent -Opioid Agonist-Mediated Adenylyl Cyclase Supersensitization. *Journal of Pharmacology and Experimental Therapeutics*, **310**(1): 215–222.
- Clough, E. and Barrett, T. (2016) The Gene Expression Omnibus Database. *Methods Mol Biol*, **1418**: 93–110.
- Collingridge, D.S. (2013) A primer on quantitized data analysis and permutation testing. *Journal of Mixed Methods Research*, **7**(1): 81–97.
- Collins, F.S. and Barker, A.D. (2007) Mapping the cancer genome. Pinpointing the genes involved in cancer will help chart a new course across the complex landscape of human malignancies. *Sci Am*, **296**(3): 50–57.
- Collisson, E., Campbell, J., Brooks, A., Berger, A., Lee, W., Chmielecki, J., Beer, D., Cope, L., Creighton, C., Danilova, L., et al. (2014) Comprehensive molecular profiling of lung adenocarcinoma. *Nature*, **511**(7511): 543–550.
- Corcoran, R.B., Ebi, H., Turke, A.B., Coffee, E.M., Nishino, M., Cogdill, A.P., Brown, R.D., Della Pelle, P., Dias-Santagata, D., Hung, K.E., et al. (2012) Egfr-mediated reactivation of mapk signaling contributes to insensitivity of BRAF-mutant colorectal cancers to raf inhibition with vemurafenib. *Cancer Discovery*, **2**(3): 227–235.
- Costanzo, M., Baryshnikova, A., Bellay, J., Kim, Y., Spear, E.D., Sevier, C.S., Ding, H., Koh, J.L., Toufighi, K., Mostafavi, S., et al. (2010) The genetic landscape of a cell. *Science*, **327**(5964): 425–31.
- Costanzo, M., Baryshnikova, A., Myers, C.L., Andrews, B., and Boone, C. (2011) Charting the genetic interaction map of a cell. *Curr Opin Biotechnol*, **22**(1): 66–74.
- Courtney, K.D., Corcoran, R.B., and Engelman, J.A. (2010) The PI3K pathway as drug target in human cancer. *J Clin Oncol*, **28**(6): 1075–1083.
- Creighton, C.J., Morgan, M., Gunaratne, P.H., Wheeler, D.A., Gibbs, R.A., Robertson, A., Chu, A., Beroukhim, R., Cibulskis, K., Signoretti, S., et al. (2013) Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature*, **499**(7456): 43–49.
- Croft, D., Mundo, A.F., Haw, R., Milacic, M., Weiser, J., Wu, G., Caudy, M., Garapati, P., Gillespie, M., Kamdar, M.R., et al. (2014) The Reactome pathway knowledgebase. *Nucleic Acids Res*, **42**(database issue): D472D477.

- Crunkhorn, S. (2014) Cancer: Predicting synthetic lethal interactions. *Nat Rev Drug Discov*, **13**(11): 812.
- Csardi, G. and Nepusz, T. (2006) The igraph software package for complex network research. *InterJournal, Complex Systems*: 1695.
- Dai, X., Li, T., Bai, Z., Yang, Y., Liu, X., Zhan, J., and Shi, B. (2015) Breast cancer intrinsic subtype classification, clinical use and future trends. *Am J Cancer Res*, **5**(10): 2929–2943.
- Davierwala, A.P., Haynes, J., Li, Z., Brost, R.L., Robinson, M.D., Yu, L., Mnaimneh, S., Ding, H., Zhu, H., Chen, Y., *et al.* (2005) The synthetic genetic interaction spectrum of essential genes. *Nat Genet*, **37**(10): 1147–1152.
- De Leeuw, W.J., Berx, G., Vos, C.B., Peterse, J.L., Van de Vijver, M.J., Litvinov, S., Van Roy, F., Cornelisse, C.J., and Cleton-Jansen, A.M. (1997) Simultaneous loss of E-cadherin and catenins in invasive lobular breast cancer and lobular carcinoma in situ. *J Pathol*, **183**(4): 404–11.
- De Santis, G., Miotti, S., Mazzi, M., Canevari, S., and Tomassetti, A. (2009) E-cadherin directly contributes to PI3K/AKT activation by engaging the PI3K-p85 regulatory subunit to adherens junctions of ovarian carcinoma cells. *Oncogene*, **28**(9): 1206–1217.
- Demir, E., Babur, O., Rodchenkov, I., Aksoy, B.A., Fukuda, K.I., Gross, B., Sumer, O.S., Bader, G.D., and Sander, C. (2013) Using biological pathway data with Paxtools. *PLoS Comput Biol*, **9**(9): e1003194.
- Deshpande, R., Asiedu, M.K., Klebig, M., Sutor, S., Kuzmin, E., Nelson, J., Piotrowski, J., Shin, S.H., Yoshida, M., Costanzo, M., *et al.* (2013) A comparative genomic approach for identifying synthetic lethal interactions in human cancer. *Cancer Res*, **73**(20): 6128–36.
- Dickson, D. (1999) Wellcome funds cancer database. *Nature*, **401**(6755): 729.
- Dienstmann, R. and Tabernero, J. (2011) BRAF as a target for cancer therapy. *Anti-cancer Agents Med Chem*, **11**(3): 285–95.
- Dijkstra, E.W. (1959) A note on two problems in connexion with graphs. *Numerische Mathematik*, **1**(1): 269–271.

- Dixon, S.J., Andrews, B.J., and Boone, C. (2009) Exploring the conservation of synthetic lethal genetic interaction networks. *Commun Integr Biol*, **2**(2): 78–81.
- Dixon, S.J., Fedyshyn, Y., Koh, J.L., Prasad, T.S., Chahwan, C., Chua, G., Toufighi, K., Baryshnikova, A., Hayles, J., Hoe, K.L., et al. (2008) Significant conservation of synthetic lethal genetic interaction networks between distantly related eukaryotes. *Proc Natl Acad Sci U S A*, **105**(43): 16653–8.
- Dong, L.L., Liu, L., Ma, C.H., Li, J.S., Du, C., Xu, S., Han, L.H., Li, L., and Wang, X.W. (2012) E-cadherin promotes proliferation of human ovarian cancer cells in vitro via activating MEK/ERK pathway. *Acta Pharmacol Sin*, **33**(6): 817–822.
- Dorogovtsev, S.N. and Mendes, J.F. (2003) *Evolution of networks: From biological nets to the Internet and WWW*. Oxford University Press, USA.
- Dorsam, R.T. and Gutkind, J.S. (2007) G-protein-coupled receptors and cancer. *Nat Rev Cancer*, **7**(2): 79–94.
- Erdős, P. and Rényi, A. (1959) On random graphs I. *Publ Math Debrecen*, **6**: 290–297.
- Erdős, P. and Rényi, A. (1960) On the evolution of random graphs. In *Publ. Math. Inst. Hung. Acad. Sci*, volume 5, 17–61.
- Eroles, P., Bosch, A., Perez-Fidalgo, J.A., and Lluch, A. (2012) Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. *Cancer Treat Rev*, **38**(6): 698–707.
- Farmer, H., McCabe, N., Lord, C.J., Tutt, A.N., Johnson, D.A., Richardson, T.B., Santarosa, M., Dillon, K.J., Hickson, I., Knights, C., et al. (2005) Targeting the dna repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*, **434**(7035): 917–21.
- Fawcett, T. (2006) An introduction to ROC analysis. *Pattern Recognition Letters*, **27**(8): 861 – 874. {ROC} Analysis in Pattern Recognition.
- Fece de la Cruz, F., Gapp, B.V., and Nijman, S.M. (2015) Synthetic lethal vulnerabilities of cancer. *Annu Rev Pharmacol Toxicol*, **55**: 513–531.
- Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D., and Bray, F. (2015) Cancer incidence and mortality worldwide:

sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, **136**(5): E359–386.

Fisher, R.A. (1919) Xv.the correlation between relatives on the supposition of mendelian inheritance. *Earth and Environmental Science Transactions of the Royal Society of Edinburgh*, **52**(02): 399–433.

Fong, P.C., Boss, D.S., Yap, T.A., Tutt, A., Wu, P., Mergui-Roelvink, M., Mortimer, P., Swaisland, H., Lau, A., O'Connor, M.J., et al. (2009) Inhibition of poly(adp-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*, **361**(2): 123–34.

Fong, P.C., Yap, T.A., Boss, D.S., Carden, C.P., Mergui-Roelvink, M., Gourley, C., De Greve, J., Lubinski, J., Shanley, S., Messiou, C., et al. (2010) Poly(adp)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol*, **28**(15): 2512–9.

Forbes, S.A., Beare, D., Gunasekaran, P., Leung, K., Bindal, N., Boutselakis, H., Ding, M., Bamford, S., Cole, C., Ward, S., et al. (2015) COSMIC: exploring the world's knowledge of somatic mutations in human cancer. *Nucleic Acids Res*, **43**(Database issue): D805–811.

Fraser, A. (2004) Towards full employment: using RNAi to find roles for the redundant. *Oncogene*, **23**(51): 8346–52.

Futreal, P.A., Coin, L., Marshall, M., Down, T., Hubbard, T., Wooster, R., Rahman, N., and Stratton, M.R. (2004) A census of human cancer genes. *Nat Rev Cancer*, **4**(3): 177–183.

Futreal, P.A., Kasprzyk, A., Birney, E., Mullikin, J.C., Wooster, R., and Stratton, M.R. (2001) Cancer and genomics. *Nature*, **409**(6822): 850–852.

Gao, B. and Roux, P.P. (2015) Translational control by oncogenic signaling pathways. *Biochimica et Biophysica Acta*, **1849**(7): 753–65.

Gatza, M.L., Kung, H.N., Blackwell, K.L., Dewhirst, M.W., Marks, J.R., and Chi, J.T. (2011) Analysis of tumor environmental response and oncogenic pathway activation identifies distinct basal and luminal features in HER2-related breast tumor subtypes. *Breast Cancer Res*, **13**(3): R62.

- Gatza, M.L., Lucas, J.E., Barry, W.T., Kim, J.W., Wang, Q., Crawford, M.D., Datto, M.B., Kelley, M., Mathey-Prevot, B., Potti, A., *et al.* (2010) A pathway-based classification of human breast cancer. *Proc Natl Acad Sci USA*, **107**(15): 6994–6999.
- Gatza, M.L., Silva, G.O., Parker, J.S., Fan, C., and Perou, C.M. (2014) An integrated genomics approach identifies drivers of proliferation in luminal-subtype human breast cancer. *Nat Genet*, **46**(10): 1051–1059.
- Gentleman, R.C., Carey, V.J., Bates, D.M., Bolstad, B., Dettling, M., Dudoit, S., Ellis, B., Gautier, L., Ge, Y., Gentry, J., *et al.* (2004) Bioconductor: open software development for computational biology and bioinformatics. *Genome Biol*, **5**(10): R80.
- Genz, A. and Bretz, F. (2009) Computation of multivariate normal and t probabilities. In *Lecture Notes in Statistics*, volume 195. Springer-Verlag, Heidelberg.
- Genz, A., Bretz, F., Miwa, T., Mi, X., Leisch, F., Scheipl, F., and Hothorn, T. (2016) *mvtnorm: Multivariate Normal and t Distributions*. R package version 1.0-5. URL.
- Glaire, M.A., Brown, M., Church, D.N., and Tomlinson, I. (2017) Cancer predisposition syndromes: lessons for truly precision medicine. *J Pathol*, **241**(2): 226–235.
- Globus (Globus) (2017) Research data management simplified. <https://www.globus.org/>. Accessed: 25/03/2017.
- Goodwin, S., McPherson, J.D., and McCombie, W.R. (2016) Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet*, **17**(6): 333–351.
- Grady, W.M., Willis, J., Guilford, P.J., Dunbier, A.K., Toro, T.T., Lynch, H., Wiesner, G., Ferguson, K., Eng, C., Park, J.G., *et al.* (2000) Methylation of the CDH1 promoter as the second genetic hit in hereditary diffuse gastric cancer. *Nat Genet*, **26**(1): 16–17.
- Graziano, F., Humar, B., and Guilford, P. (2003) The role of the E-cadherin gene (*CDH1*) in diffuse gastric cancer susceptibility: from the laboratory to clinical practice. *Annals of Oncology*, **14**(12): 1705–1713.
- Güell, O., Sagus, F., and Serrano, M. (2014) Essential plasticity and redundancy of metabolism unveiled by synthetic lethality analysis. *PLoS Comput Biol*, **10**(5): e1003637.

- Guilford, P. (1999) E-cadherin downregulation in cancer: fuel on the fire? *Molecular Medicine Today*, **5**(4): 172 – 177.
- Guilford, P., Hopkins, J., Harraway, J., McLeod, M., McLeod, N., Harawira, P., Taite, H., Scouler, R., Miller, A., and Reeve, A.E. (1998) E-cadherin germline mutations in familial gastric cancer. *Nature*, **392**(6674): 402–5.
- Guilford, P., Humar, B., and Blair, V. (2010) Hereditary diffuse gastric cancer: translation of *CDH1* germline mutations into clinical practice. *Gastric Cancer*, **13**(1): 1–10.
- Guilford, P.J., Hopkins, J.B., Grady, W.M., Markowitz, S.D., Willis, J., Lynch, H., Rajput, A., Wiesner, G.L., Lindor, N.M., Burgart, L.J., *et al.* (1999) E-cadherin germline mutations define an inherited cancer syndrome dominated by diffuse gastric cancer. *Hum Mutat*, **14**(3): 249–55.
- Guo, J., Liu, H., and Zheng, J. (2016) SynLethDB: synthetic lethality database toward discovery of selective and sensitive anticancer drug targets. *Nucleic Acids Res*, **44**(D1): D1011–1017.
- Hajian-Tilaki, K. (2013) Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian J Intern Med*, **4**(2): 627–635.
- Hall, M., Frank, E., Holmes, G., Pfahringer, B., Reutemann, P., and Witten, I.H. (2009) The weka data mining software: an update. *SIGKDD Explor Newsl*, **11**(1): 10–18.
- Hammerman, P.S., Lawrence, M.S., Voet, D., Jing, R., Cibulskis, K., Sivachenko, A., Stojanov, P., McKenna, A., Lander, E.S., Gabriel, S., *et al.* (2012) Comprehensive genomic characterization of squamous cell lung cancers. *Nature*, **489**(7417): 519–525.
- Hanahan, D. and Weinberg, R.A. (2000) The hallmarks of cancer. *Cell*, **100**(1): 57–70.
- Hanahan, D. and Weinberg, R.A. (2011) Hallmarks of cancer: the next generation. *Cell*, **144**(5): 646–674.
- Hanna, S. (2003) Cancer incidence in new zealand (2003-2007). In D. Forman, D. Bray F Brewster, C. Gombe Mbalawa, B. Kohler, M. Piñeros, E. Steliarova-Foucher, R. Swaminathan, and J. Ferlay (editors), *Cancer Incidence in Five Continents*,

volume X, 902–907. International Agency for Research on Cancer, Lyon, France.
Electronic version <http://ci5.iarc.fr> Accessed 22/03/2017.

Hansford, S., Kaurah, P., Li-Chang, H., Woo, M., Senz, J., Pinheiro, H., Schrader, K.A., Schaeffer, D.F., Shumansky, K., Zogopoulos, G., *et al.* (2015) Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol*, **1**(1): 23–32.

Heiskanen, M., Bian, X., Swan, D., and Basu, A. (2014) caArray microarray database in the cancer biomedical informatics grid™ (caBIG™). *Cancer Research*, **67**(9 Supplement): 3712–3712.

Heiskanen, M.A. and Aittokallio, T. (2012) Mining high-throughput screens for cancer drug targets—lessons from yeast chemical-genomic profiling and synthetic lethality. *Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery*, **2**(3): 263–272.

Hell, P. (1976) Graphs with given neighbourhoods i. problèmes combinatoires at théorie des graphes. *Proc Coll Int CNRS, Orsay*, **260**: 219–223.

Hillenmeyer, M.E. (2008) The chemical genomic portrait of yeast: uncovering a phenotype for all genes. *Science*, **320**: 362–365.

Hoadley, K.A., Yau, C., Wolf, D.M., Cherniack, A.D., Tamborero, D., Ng, S., Leiserson, M.D., Niu, B., McLellan, M.D., Uzunangelov, V., *et al.* (2014) Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. *Cell*, **158**(4): 929–944.

Hoehndorf, R., Hardy, N.W., Osumi-Sutherland, D., Tweedie, S., Schofield, P.N., and Gkoutos, G.V. (2013) Systematic analysis of experimental phenotype data reveals gene functions. *PLoS ONE*, **8**(4): e60847.

Holm, S. (1979) A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, **6**(2): 65–70.

Holme, P. and Kim, B.J. (2002) Growing scale-free networks with tunable clustering. *Physical Review E*, **65**(2): 026107.

Hopkins, A.L. (2008) Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*, **4**(11): 682–690.

- Hu, Z., Fan, C., Oh, D.S., Marron, J.S., He, X., Qaqish, B.F., Livasy, C., Carey, L.A., Reynolds, E., Dressler, L., *et al.* (2006) The molecular portraits of breast tumors are conserved across microarray platforms. *BMC Genomics*, **7**: 96.
- Huang, E., Cheng, S., Dressman, H., Pittman, J., Tsou, M., Horng, C., Bild, A., Iversen, E., Liao, M., Chen, C., *et al.* (2003) Gene expression predictors of breast cancer outcomes. *Lancet*, **361**: 1590–1596.
- International HapMap 3 Consortium (HapMap) (2003) The International HapMap Project. *Nature*, **426**(6968): 789–796.
- Jeanes, A., Gottardi, C.J., and Yap, A.S. (2008) Cadherins and cancer: how does cadherin dysfunction promote tumor progression? *Oncogene*, **27**(55): 6920–6929.
- Jerby-Arnon, L., Pfetzer, N., Waldman, Y., McGarry, L., James, D., Shanks, E., Seashore-Ludlow, B., Weinstock, A., Geiger, T., Clemons, P., *et al.* (2014) Predicting cancer-specific vulnerability via data-driven detection of synthetic lethality. *Cell*, **158**(5): 1199–1209.
- Joachims, T. (1999) Making large-scale support vector machine learning practical. In S. Bernhard, lkopf, J.C.B. Christopher, and J.S. Alexander (editors), *Advances in kernel methods*, 169–184. MIT Press.
- Ju, Z., Liu, W., Roebuck, P.L., Siwak, D.R., Zhang, N., Lu, Y., Davies, M.A., Akbani, R., Weinstein, J.N., Mills, G.B., *et al.* (2015) Development of a robust classifier for quality control of reverse-phase protein arrays. *Bioinformatics*, **31**(6): 912.
- Kaelin, Jr, W. (2005) The concept of synthetic lethality in the context of anticancer therapy. *Nat Rev Cancer*, **5**(9): 689–98.
- Kaelin, Jr, W. (2009) Synthetic lethality: a framework for the development of wiser cancer therapeutics. *Genome Med*, **1**: 99.
- Kamada, T. and Kawai, S. (1989) An algorithm for drawing general undirected graphs. *Information Processing Letters*, **31**(1): 7–15.
- Kawai, J., Shinagawa, A., Shibata, K., Yoshino, M., Itoh, M., Ishii, Y., Arakawa, T., Hara, A., Fukunishi, Y., Konno, H., *et al.* (2001) Functional annotation of a full-length mouse cDNA collection. *Nature*, **409**(6821): 685–690.

- Kelley, R. and Ideker, T. (2005) Systematic interpretation of genetic interactions using protein networks. *Nat Biotech*, **23**(5): 561–566.
- Kelly, S.T. (2013) *Statistical Predictions of Synthetic Lethal Interactions in Cancer*. Dissertation, University of Otago.
- Kelly, S.T., Single, A.B., Telford, B.J., Beetham, H.G., Godwin, T.D., Chen, A., Black, M.A., and Guilford, P.J. (unpublished) Towards HDGC chemoprevention: vulnerabilities in E-cadherin-negative cells identified by genome-wide interrogation of isogenic cell lines and whole tumors. Submitted to *Cancer Prev Res*.
- Kim, N.G., Koh, E., Chen, X., and Gumbiner, B.M. (2011) E-cadherin mediates contact inhibition of proliferation through Hippo signaling-pathway components. *Proc Natl Acad Sci USA*, **108**(29): 11930–11935.
- Kozlov, K.N., Gursky, V.V., Kulakovskiy, I.V., and Samsonova, M.G. (2015) Sequence-based model of gap gene regulation network. *BMC Genomics*, **15**(Suppl 12): S6.
- Kranthi, S., Rao, S., and Manimaran, P. (2013) Identification of synthetic lethal pairs in biological systems through network information centrality. *Mol BioSyst*, **9**(8): 2163–2167.
- Kroepil, F., Fluegen, G., Totikov, Z., Baldus, S.E., Vay, C., Schauer, M., Topp, S.A., Esch, J.S., Knoefel, W.T., and Stoecklein, N.H. (2012) Down-regulation of CDH1 is associated with expression of SNAI1 in colorectal adenomas. *PLoS ONE*, **7**(9): e46665.
- Lander, E.S. (2011) Initial impact of the sequencing of the human genome. *Nature*, **470**(7333): 187–197.
- Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., et al. (2001) Initial sequencing and analysis of the human genome. *Nature*, **409**(6822): 860–921.
- Langmead, B., Trapnell, C., Pop, M., and Salzberg, S.L. (2009) Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. *Genome Biol*, **10**(3): R25.
- Latora, V. and Marchiori, M. (2001) Efficient behavior of small-world networks. *Phys Rev Lett*, **87**: 198701.

- Laufer, C., Fischer, B., Billmann, M., Huber, W., and Boutros, M. (2013) Mapping genetic interactions in human cancer cells with RNAi and multiparametric phenotyping. *Nat Methods*, **10**(5): 427–31.
- Law, C.W., Chen, Y., Shi, W., and Smyth, G.K. (2014) voom: precision weights unlock linear model analysis tools for RNA-seq read counts. *Genome Biol*, **15**(2): R29.
- Le Meur, N. and Gentleman, R. (2008) Modeling synthetic lethality. *Genome Biol*, **9**(9): R135.
- Le Meur, N., Jiang, Z., Liu, T., Mar, J., and Gentleman, R.C. (2014) Slgi: Synthetic lethal genetic interaction. r package version 1.26.0.
- Lee, A.Y., Perreault, R., Harel, S., Boulier, E.L., Suderman, M., Hallett, M., and Jenna, S. (2010a) Searching for signaling balance through the identification of genetic interactors of the rab guanine-nucleotide dissociation inhibitor gdi-1. *PLoS ONE*, **5**(5): e10624.
- Lee, I., Lehner, B., Vavouri, T., Shin, J., Fraser, A.G., and Marcotte, E.M. (2010b) Predicting genetic modifier loci using functional gene networks. *Genome Research*, **20**(8): 1143–1153.
- Lee, I. and Marcotte, E.M. (2009) Effects of functional bias on supervised learning of a gene network model. *Methods Mol Biol*, **541**: 463–75.
- Lee, M.J., Ye, A.S., Gardino, A.K., Heijink, A.M., Sorger, P.K., MacBeath, G., and Yaffe, M.B. (2012) Sequential application of anticancer drugs enhances cell death by rewiring apoptotic signaling networks. *Cell*, **149**(4): 780–94.
- Lehner, B., Crombie, C., Tischler, J., Fortunato, A., and Fraser, A.G. (2006) Systematic mapping of genetic interactions in caenorhabditis elegans identifies common modifiers of diverse signaling pathways. *Nat Genet*, **38**(8): 896–903.
- Li, X.J., Mishra, S.K., Wu, M., Zhang, F., and Zheng, J. (2014) Syn-lethality: An integrative knowledge base of synthetic lethality towards discovery of selective anticancer therapies. *Biomed Res Int*, **2014**: 196034.
- Linehan, W.M., Spellman, P.T., Ricketts, C.J., Creighton, C.J., Fei, S.S., Davis, C., Wheeler, D.A., Murray, B.A., Schmidt, L., Vocke, C.D., *et al.* (2016) Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med*, **374**(2): 135–145.

- Lokody, I. (2014) Computational modelling: A computational crystal ball. *Nature Reviews Cancer*, **14**(10): 649–649.
- Lord, C.J., Tutt, A.N., and Ashworth, A. (2015) Synthetic lethality and cancer therapy: lessons learned from the development of PARP inhibitors. *Annu Rev Med*, **66**: 455–470.
- Lu, X., Kensche, P.R., Huynen, M.A., and Notebaart, R.A. (2013) Genome evolution predicts genetic interactions in protein complexes and reveals cancer drug targets. *Nat Commun*, **4**: 2124.
- Lu, X., Megchelenbrink, W., Notebaart, R.A., and Huynen, M.A. (2015) Predicting human genetic interactions from cancer genome evolution. *PLoS One*, **10**(5): e0125795.
- Lum, P.Y., Armour, C.D., Stepaniants, S.B., Cavet, G., Wolf, M.K., Butler, J.S., Hinchshaw, J.C., Garnier, P., Prestwich, G.D., Leonardson, A., et al. (2004) Discovering modes of action for therapeutic compounds using a genome-wide screen of yeast heterozygotes. *Cell*, **116**(1): 121–137.
- Luo, J., Solimini, N.L., and Elledge, S.J. (2009) Principles of Cancer Therapy: Oncogene and Non-oncogene Addiction. *Cell*, **136**(5): 823–837.
- Machado, J., Olivera, C., Carvalh, R., Soares, P., Berx, G., Caldas, C., Sercuca, R., Carneiro, F., and Sorbrinho-Simoes, M. (2001) E-cadherin gene (*CDH1*) promoter methylation as the second hit in sporadic diffuse gastric carcinoma. *Oncogene*, **20**: 1525–1528.
- Markowetz, F. (2017) All biology is computational biology. *PLoS Biol*, **15**(3): e2002050.
- Masciari, S., Larsson, N., Senz, J., Boyd, N., Kaurah, P., Kandel, M.J., Harris, L.N., Pinheiro, H.C., Troussard, A., Miron, P., et al. (2007) Germline E-cadherin mutations in familial lobular breast cancer. *J Med Genet*, **44**(11): 726–31.
- Mattison, J., van der Weyden, L., Hubbard, T., and Adams, D.J. (2009) Cancer gene discovery in mouse and man. *Biochim Biophys Acta*, **1796**(2): 140–161.
- McLachlan, J., George, A., and Banerjee, S. (2016) The current status of parp inhibitors in ovarian cancer. *Tumori*, **102**(5): 433–440.

- McLendon, R., Friedman, A., Bigner, D., Van Meir, E.G., Brat, D.J., Mastrogiannakis, G.M., Olson, J.J., Mikkelsen, T., Lehman, N., Aldape, K., *et al.* (2008) Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*, **455**(7216): 1061–1068.
- Miles, D.W. (2001) Update on HER-2 as a target for cancer therapy: herceptin in the clinical setting. *Breast Cancer Res*, **3**(6): 380–384.
- Mortazavi, A., Williams, B.A., McCue, K., Schaeffer, L., and Wold, B. (2008) Mapping and quantifying mammalian transcriptomes by RNA-Seq. *Nat Methods*, **5**(7): 621–628.
- Muzny, D.M., Bainbridge, M.N., Chang, K., Dinh, H.H., Drummond, J.A., Fowler, G., Kovar, C.L., Lewis, L.R., Morgan, M.B., Newsham, I.F., *et al.* (2012) Comprehensive molecular characterization of human colon and rectal cancer. *Nature*, **487**(7407): 330–337.
- Nagalla, S., Chou, J.W., Willingham, M.C., Ruiz, J., Vaughn, J.P., Dubey, P., Lash, T.L., Hamilton-Dutoit, S.J., Bergh, J., Sotiriou, C., *et al.* (2013) Interactions between immunity, proliferation and molecular subtype in breast cancer prognosis. *Genome Biol*, **14**(4): R34.
- Neeley, E.S., Kornblau, S.M., Coombes, K.R., and Baggerly, K.A. (2009) Variable slope normalization of reverse phase protein arrays. *Bioinformatics*, **25**(11): 1384.
- Novomestky, F. (2012) *matrixcalc: Collection of functions for matrix calculations*. R package version 1.0-3.
- Oliveira, C., Senz, J., Kaurah, P., Pinheiro, H., Sanges, R., Haegert, A., Corso, G., Schouten, J., Fitzgerald, R., Vogelsang, H., *et al.* (2009) Germline *CDH1* deletions in hereditary diffuse gastric cancer families. *Human Molecular Genetics*, **18**(9): 1545–1555.
- Oliveira, C., Seruca, R., Hoogerbrugge, N., Ligtenberg, M., and Carneiro, F. (2013) Clinical utility gene card for: Hereditary diffuse gastric cancer (HDGC). *Eur J Hum Genet*, **21**(8).
- Pandey, G., Zhang, B., Chang, A.N., Myers, C.L., Zhu, J., Kumar, V., and Schadt, E.E. (2010) An integrative multi-network and multi-classifier approach to predict genetic interactions. *PLoS Comput Biol*, **6**(9).

- Parker, J., Mullins, M., Cheung, M., Leung, S., Voduc, D., Vickery, T., Davies, S., Fauron, C., He, X., Hu, Z., *et al.* (2009) Supervised risk predictor of breast cancer based on intrinsic subtypes. *Journal of Clinical Oncology*, **27**(8): 1160–1167.
- Pereira, B., Chin, S.F., Rueda, O.M., Vollan, H.K., Provenzano, E., Bardwell, H.A., Pugh, M., Jones, L., Russell, R., Sammut, S.J., *et al.* (2016) Erratum: The somatic mutation profiles of 2,433 breast cancers refine their genomic and transcriptomic landscapes. *Nat Commun*, **7**: 11908.
- Perou, C.M., Sørlie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., Rees, C.A., Pollack, J.R., Ross, D.T., Johnsen, H., Akslen, L.A., *et al.* (2000) Molecular portraits of human breast tumours. *Nature*, **406**(6797): 747–752.
- Polyak, K. and Weinberg, R.A. (2009) Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. *Nat Rev Cancer*, **9**(4): 265–73.
- Prahallas, A., Sun, C., Huang, S., Di Nicolantonio, F., Salazar, R., Zecchin, D., Beijersbergen, R.L., Bardelli, A., and Bernards, R. (2012) Unresponsiveness of colon cancer to *BRAF*(v600e) inhibition through feedback activation of egfr. *Nature*, **483**(7387): 100–3.
- R Core Team (2016) *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. R version 3.3.2.
- Ravnan, M.C. and Matalka, M.S. (2012) Vemurafenib in patients with *BRAF* v600e mutation-positive advanced melanoma. *Clin Ther*, **34**(7): 1474–86.
- Ritchie, M.E., Phipson, B., Wu, D., Hu, Y., Law, C.W., Shi, W., and Smyth, G.K. (2015) limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Research*, **43**(7): e47.
- Robinson, M.D. and Oshlack, A. (2010) A scaling normalization method for differential expression analysis of RNA-seq data. *Genome Biol*, **11**(3): R25.
- Roguev, A., Bandyopadhyay, S., Zofall, M., Zhang, K., Fischer, T., Collins, S.R., Qu, H., Shales, M., Park, H.O., Hayles, J., *et al.* (2008) Conservation and rewiring of functional modules revealed by an epistasis map in fission yeast. *Science*, **322**(5900): 405–10.
- Roychowdhury, S. and Chinnaiyan, A.M. (2016) Translating cancer genomes and transcriptomes for precision oncology. *CA Cancer J Clin*, **66**(1): 75–88.

- Rung, J. and Brazma, A. (2013) Reuse of public genome-wide gene expression data. *Nat Rev Genet*, **14**(2): 89–99.
- Rustici, G., Kolesnikov, N., Brandizi, M., Burdett, T., Dylag, M., Emam, I., Farne, A., Hastings, E., Ison, J., Keays, M., et al. (2013) ArrayExpress update—trends in database growth and links to data analysis tools. *Nucleic Acids Res*, **41**(Database issue): D987–990.
- Ryan, C., Lord, C., and Ashworth, A. (2014) Daisy: Picking synthetic lethals from cancer genomes. *Cancer Cell*, **26**(3): 306–308.
- Schena, M. (1996) Genome analysis with gene expression microarrays. *Bioessays*, **18**(5): 427–431.
- Scheuer, L., Kauff, N., Robson, M., Kelly, B., Barakat, R., Satagopan, J., Ellis, N., Hensley, M., Boyd, J., Borgen, P., et al. (2002) Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol*, **20**(5): 1260–1268.
- Semb, H. and Christofori, G. (1998) The tumor-suppressor function of E-cadherin. *Am J Hum Genet*, **63**(6): 1588–93.
- Sing, T., Sander, O., Beerenwinkel, N., and Lengauer, T. (2005) Rocr: visualizing classifier performance in r. *Bioinformatics*, **21**(20): 7881.
- Slurm development team (Slurm) (2017) Slurm workload manager. <https://slurm.schedmd.com/>. Accessed: 25/03/2017.
- Sørlie, T., Perou, C.M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., Hastie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., et al. (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA*, **98**(19): 10869–10874.
- Stajich, J.E. and Lapp, H. (2006) Open source tools and toolkits for bioinformatics: significance, and where are we? *Brief Bioinformatics*, **7**(3): 287–296.
- Stratton, M.R., Campbell, P.J., and Futreal, P.A. (2009) The cancer genome. *Nature*, **458**(7239): 719–724.
- Ström, C. and Helleday, T. (2012) Strategies for the use of poly(adenosine diphosphate ribose) polymerase (parp) inhibitors in cancer therapy. *Biomolecules*, **2**(4): 635–649.

- Sun, C., Wang, L., Huang, S., Heynen, G.J.J.E., Prahallad, A., Robert, C., Haanen, J., Blank, C., Wesseling, J., Willems, S.M., *et al.* (2014) Reversible and adaptive resistance to *BRAF*(v600e) inhibition in melanoma. *Nature*, **508**(7494): 118–122.
- Telford, B.J., Chen, A., Beetham, H., Frick, J., Brew, T.P., Gould, C.M., Single, A., Godwin, T., Simpson, K.J., and Guilford, P. (2015) Synthetic lethal screens identify vulnerabilities in gpcr signalling and cytoskeletal organization in E-cadherin-deficient cells. *Mol Cancer Ther*, **14**(5): 1213–1223.
- The 1000 Genomes Project Consortium (1000 Genomes) (2010) A map of human genome variation from population-scale sequencing. *Nature*, **467**(7319): 1061–1073.
- The Cancer Genome Atlas Research Network (TCGA) (2012) Comprehensive molecular portraits of human breast tumours. *Nature*, **490**(7418): 61–70.
- The Cancer Genome Atlas Research Network (TCGA) (2017) The Cancer Genome Atlas Project. <https://cancergenome.nih.gov/>. Accessed: 26/03/2017.
- The Catalogue Of Somatic Mutations In Cancer (COSMIC) (2016) Cosmic: The catalogue of somatic mutations in cancer. <http://cancer.sanger.ac.uk/cosmic>. Release 79 (23/08/2016), Accessed: 05/02/2017.
- The Comprehensive R Archive Network (CRAN) (2017) Cran. <https://cran.r-project.org/>. Accessed: 24/03/2017.
- The ENCODE Project Consortium (ENCODE) (2004) The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science*, **306**(5696): 636–640.
- The National Cancer Institute (NCI) (2015) The genetics of cancer. <https://www.cancer.gov/about-cancer/causes-prevention/genetics>. Published: 22/04/2015, Accessed: 22/03/2017.
- The New Zealand eScience Infrastructure (NeSI) (2017) NeSI. <https://www.nesi.org.nz/>. Accessed: 25/03/2017.
- Tierney, L., Rossini, A.J., Li, N., and Sevcikova, H. (2015) *snow: Simple Network of Workstations*. R package version 0.4-2.
- Tiong, K.L., Chang, K.C., Yeh, K.T., Liu, T.Y., Wu, J.H., Hsieh, P.H., Lin, S.H., Lai, W.Y., Hsu, Y.C., Chen, J.Y., *et al.* (2014) Csnk1e/ctnnb1 are synthetic lethal to tp53 in colorectal cancer and are markers for prognosis. *Neoplasia*, **16**(5): 441–50.

- Tischler, J., Lehner, B., and Fraser, A.G. (2008) Evolutionary plasticity of genetic interaction networks. *Nat Genet*, **40**(4): 390–391.
- Tomasetti, C. and Vogelstein, B. (2015) Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*, **347**(6217): 78–81.
- Tong, A.H., Evangelista, M., Parsons, A.B., Xu, H., Bader, G.D., Page, N., Robinson, M., Raghibizadeh, S., Hogue, C.W., Bussey, H., *et al.* (2001) Systematic genetic analysis with ordered arrays of yeast deletion mutants. *Science*, **294**(5550): 2364–8.
- Tong, A.H., Lesage, G., Bader, G.D., Ding, H., Xu, H., Xin, X., Young, J., Berriz, G.F., Brost, R.L., Chang, M., *et al.* (2004) Global mapping of the yeast genetic interaction network. *Science*, **303**(5659): 808–13.
- Tran, B., Dancey, J.E., Kamel-Reid, S., McPherson, J.D., Bedard, P.L., Brown, A.M., Zhang, T., Shaw, P., Onetto, N., Stein, L., *et al.* (2012) Cancer genomics: technology, discovery, and translation. *J Clin Oncol*, **30**(6): 647–660.
- Travers, J. and Milgram, S. (1969) An experimental study of the small world problem. *Sociometry*, **32**(4): 425–443.
- Tsai, H.C., Li, H., Van Neste, L., Cai, Y., Robert, C., Rassool, F.V., Shin, J.J., Harbom, K.M., Beaty, R., Pappou, E., *et al.* (2012) Transient low doses of dna-demethylating agents exert durable antitumor effects on hematological and epithelial tumor cells. *Cancer Cell*, **21**(3): 430–46.
- Tunggal, J.A., Helfrich, I., Schmitz, A., Schwarz, H., Gunzel, D., Fromm, M., Kemler, R., Krieg, T., and Niessen, C.M. (2005) E-cadherin is essential for in vivo epidermal barrier function by regulating tight junctions. *EMBO J*, **24**(6): 1146–1156.
- Tutt, A., Robson, M., Garber, J.E., Domchek, S.M., Audeh, M.W., Weitzel, J.N., Friedlander, M., Arun, B., Loman, N., Schmutzler, R.K., *et al.* (2010) Oral poly(adp-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet*, **376**(9737): 235–44.
- van der Meer, R., Song, H.Y., Park, S.H., Abdulkadir, S.A., and Roh, M. (2014) RNAi screen identifies a synthetic lethal interaction between PIM1 overexpression and PLK1 inhibition. *Clinical Cancer Research*, **20**(12): 3211–3221.

- van der Post, R.S., Vogelaar, I.P., Carneiro, F., Guilford, P., Huntsman, D., Hoogerbrugge, N., Caldas, C., Schreiber, K.E., Hardwick, R.H., Ausems, M.G., *et al.* (2015) Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *J Med Genet*, **52**(6): 361–374.
- van Steen, K. (2012) Travelling the world of gene-gene interactions. *Briefings in Bioinformatics*, **13**(1): 1–19.
- van Steen, M. (2010) *Graph Theory and Complex Networks: An Introduction*. Maarten van Steen, VU Amsterdam.
- Vapnik, V.N. (1995) *The nature of statistical learning theory*. Springer-Verlag New York, Inc.
- Vizeacoumar, F.J., Arnold, R., Vizeacoumar, F.S., Chandrashekhar, M., Buzina, A., Young, J.T., Kwan, J.H., Sayad, A., Mero, P., Lawo, S., *et al.* (2013) A negative genetic interaction map in isogenic cancer cell lines reveals cancer cell vulnerabilities. *Mol Syst Biol*, **9**: 696.
- Vogelstein, B., Papadopoulos, N., Velculescu, V.E., Zhou, S., Diaz, L.A., and Kinzler, K.W. (2013) Cancer genome landscapes. *Science*, **339**(6127): 1546–1558.
- Vos, C.B., Cleton-Jansen, A.M., Berx, G., de Leeuw, W.J., ter Haar, N.T., van Roy, F., Cornelisse, C.J., Peterse, J.L., and van de Vijver, M.J. (1997) E-cadherin inactivation in lobular carcinoma in situ of the breast: an early event in tumorigenesis. *Br J Cancer*, **76**(9): 1131–3.
- Waldron, D. (2016) Cancer genomics: A multi-layer omics approach to cancer. *Nat Rev Genet*, **17**(8): 436–437.
- Wang, K., Singh, D., Zeng, Z., Coleman, S.J., Huang, Y., Savich, G.L., He, X., Mieczkowski, P., Grimm, S.A., Perou, C.M., *et al.* (2010) MapSplice: accurate mapping of RNA-seq reads for splice junction discovery. *Nucleic Acids Res*, **38**(18): e178.
- Wang, X. and Simon, R. (2013) Identification of potential synthetic lethal genes to p53 using a computational biology approach. *BMC Medical Genomics*, **6**(1): 30.
- Wappett, M. (2014) Bisep: Toolkit to identify candidate synthetic lethality. r package version 2.0.

- Wappett, M., Dulak, A., Yang, Z.R., Al-Watban, A., Bradford, J.R., and Dry, J.R. (2016) Multi-omic measurement of mutually exclusive loss-of-function enriches for candidate synthetic lethal gene pairs. *BMC Genomics*, **17**: 65.
- Warnes, G.R., Bolker, B., Bonebakker, L., Gentleman, R., Liaw, W.H.A., Lumley, T., Maechler, M., Magnusson, A., Moeller, S., Schwartz, M., *et al.* (2015) *gplots: Various R Programming Tools for Plotting Data*. R package version 2.17.0.
- Watts, D.J. and Strogatz, S.H. (1998) Collective dynamics of 'small-world' networks. *Nature*, **393**(6684): 440–2.
- Weinstein, I.B. (2000) Disorders in cell circuitry during multistage carcinogenesis: the role of homeostasis. *Carcinogenesis*, **21**(5): 857–864.
- Weinstein, J.N., Akbani, R., Broom, B.M., Wang, W., Verhaak, R.G., McConkey, D., Lerner, S., Morgan, M., Creighton, C.J., Smith, C., *et al.* (2014) Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*, **507**(7492): 315–322.
- Weinstein, J.N., Collisson, E.A., Mills, G.B., Shaw, K.R., Ozenberger, B.A., Ellrott, K., Shmulevich, I., Sander, C., Stuart, J.M., Chang, K., *et al.* (2013) The Cancer Genome Atlas Pan-Cancer analysis project. *Nat Genet*, **45**(10): 1113–1120.
- Wickham, H. and Chang, W. (2016) *devtools: Tools to Make Developing R Packages Easier*. R package version 1.12.0.
- Wickham, H., Danenberg, P., and Eugster, M. (2017) *roxygen2: In-Line Documentation for R*. R package version 6.0.1.
- Wong, S.L., Zhang, L.V., Tong, A.H.Y., Li, Z., Goldberg, D.S., King, O.D., Lesage, G., Vidal, M., Andrews, B., Bussey, H., *et al.* (2004) Combining biological networks to predict genetic interactions. *Proceedings of the National Academy of Sciences of the United States of America*, **101**(44): 15682–15687.
- World Health Organization (WHO) (2017) Fact sheet: Cancer. <http://www.who.int/mediacentre/factsheets/fs297/en/>. Updated February 2017, Accessed: 22/03/2017.
- Wu, M., Li, X., Zhang, F., Li, X., Kwoh, C.K., and Zheng, J. (2014) In silico prediction of synthetic lethality by meta-analysis of genetic interactions, functions, and pathways in yeast and human cancer. *Cancer Inform*, **13**(Suppl 3): 71–80.

- Yu, H. (2002) Rmpi: Parallel statistical computing in r. *R News*, **2**(2): 10–14.
- Zhang, F., Wu, M., Li, X.J., Li, X.L., Kwoh, C.K., and Zheng, J. (2015) Predicting essential genes and synthetic lethality via influence propagation in signaling pathways of cancer cell fates. *J Bioinform Comput Biol*, **13**(3): 1541002.
- Zhang, J., Baran, J., Cros, A., Guberman, J.M., Haider, S., Hsu, J., Liang, Y., Rivkin, E., Wang, J., Whitty, B., et al. (2011) International cancer genome consortium data portal a one-stop shop for cancer genomics data. *Database: The Journal of Biological Databases and Curation*, **2011**: bar026.
- Zhong, W. and Sternberg, P.W. (2006) Genome-wide prediction of c. elegans genetic interactions. *Science*, **311**(5766): 1481–1484.
- Zweig, M.H. and Campbell, G. (1993) Receiver-operating characteristic (roc) plots: a fundamental evaluation tool in clinical medicine. *Clinical Chemistry*, **39**(4): 561–577.

Appendix J

Performance of SLIPT and χ^2

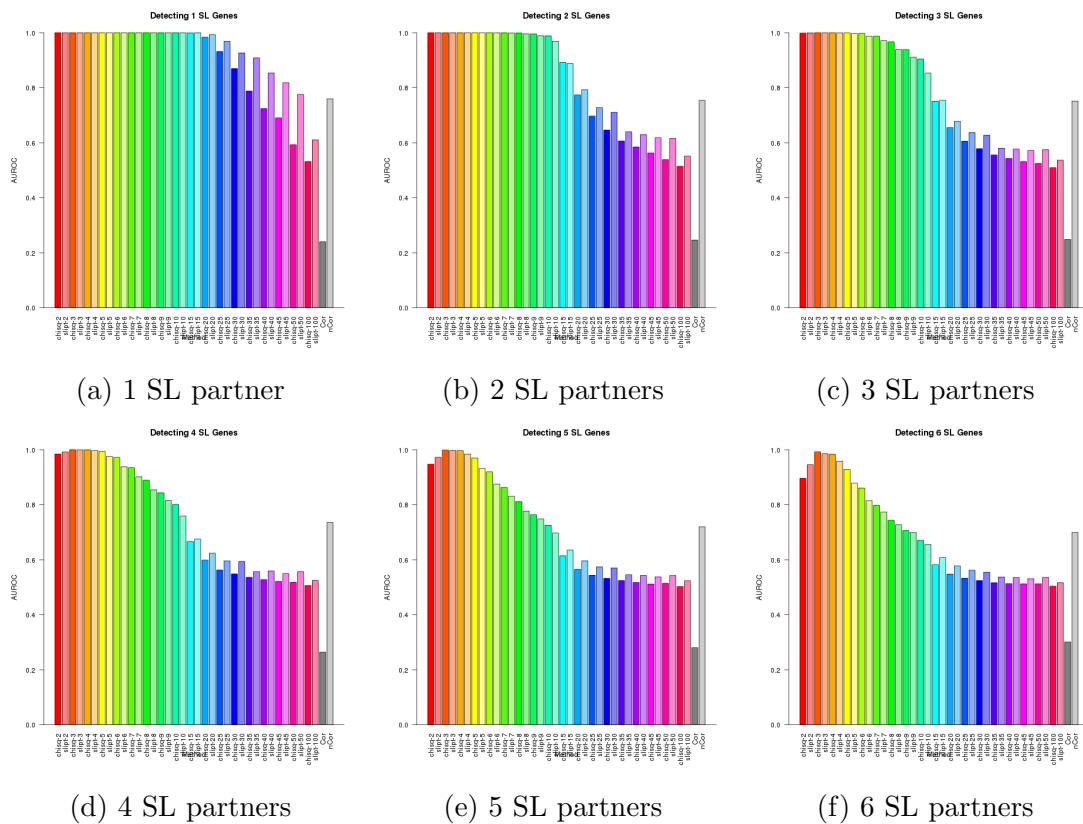


Figure J.1: Performance of χ^2 and SLIPT across quantiles. (continued on next page)

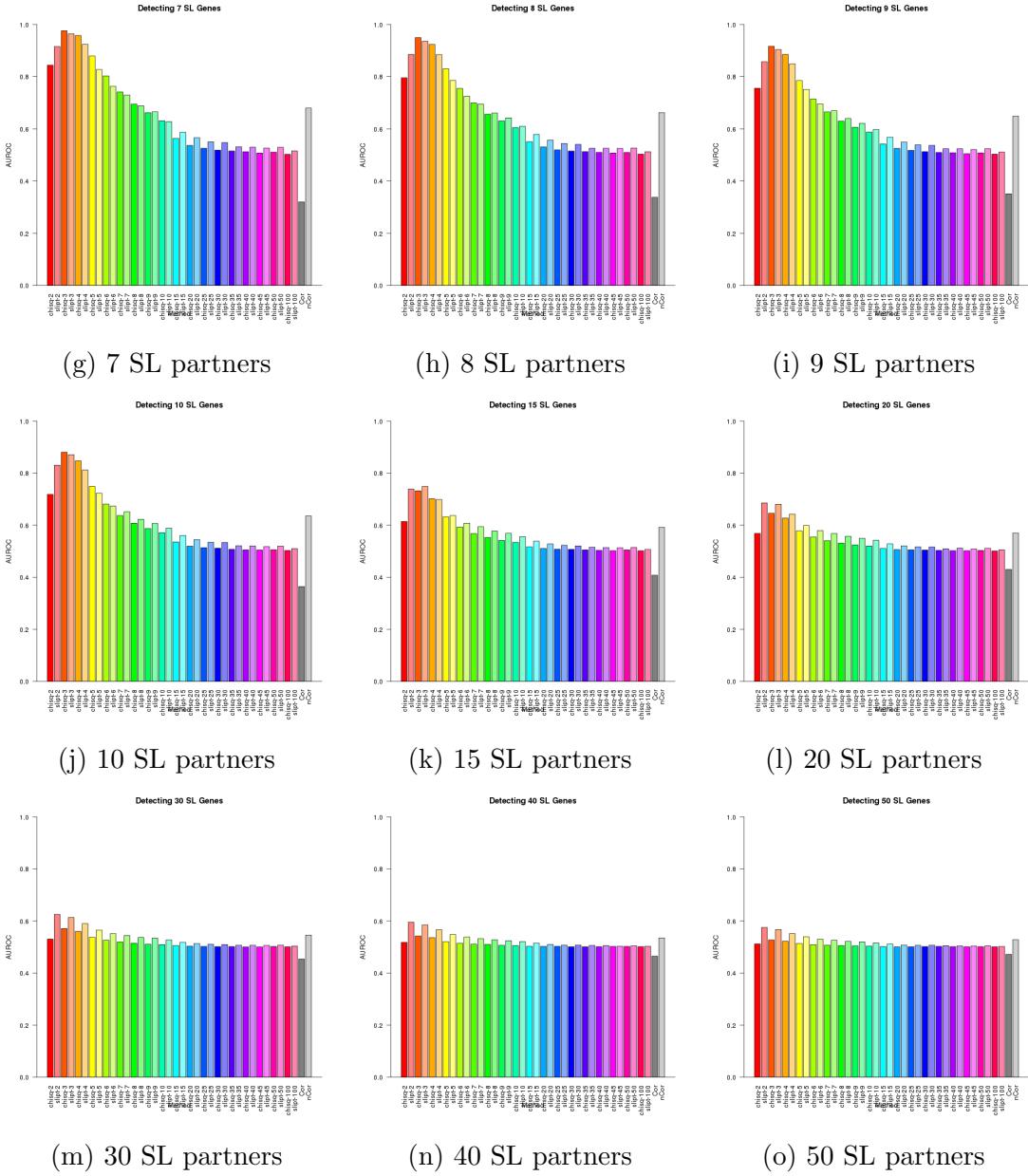


Figure J.1: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles 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.

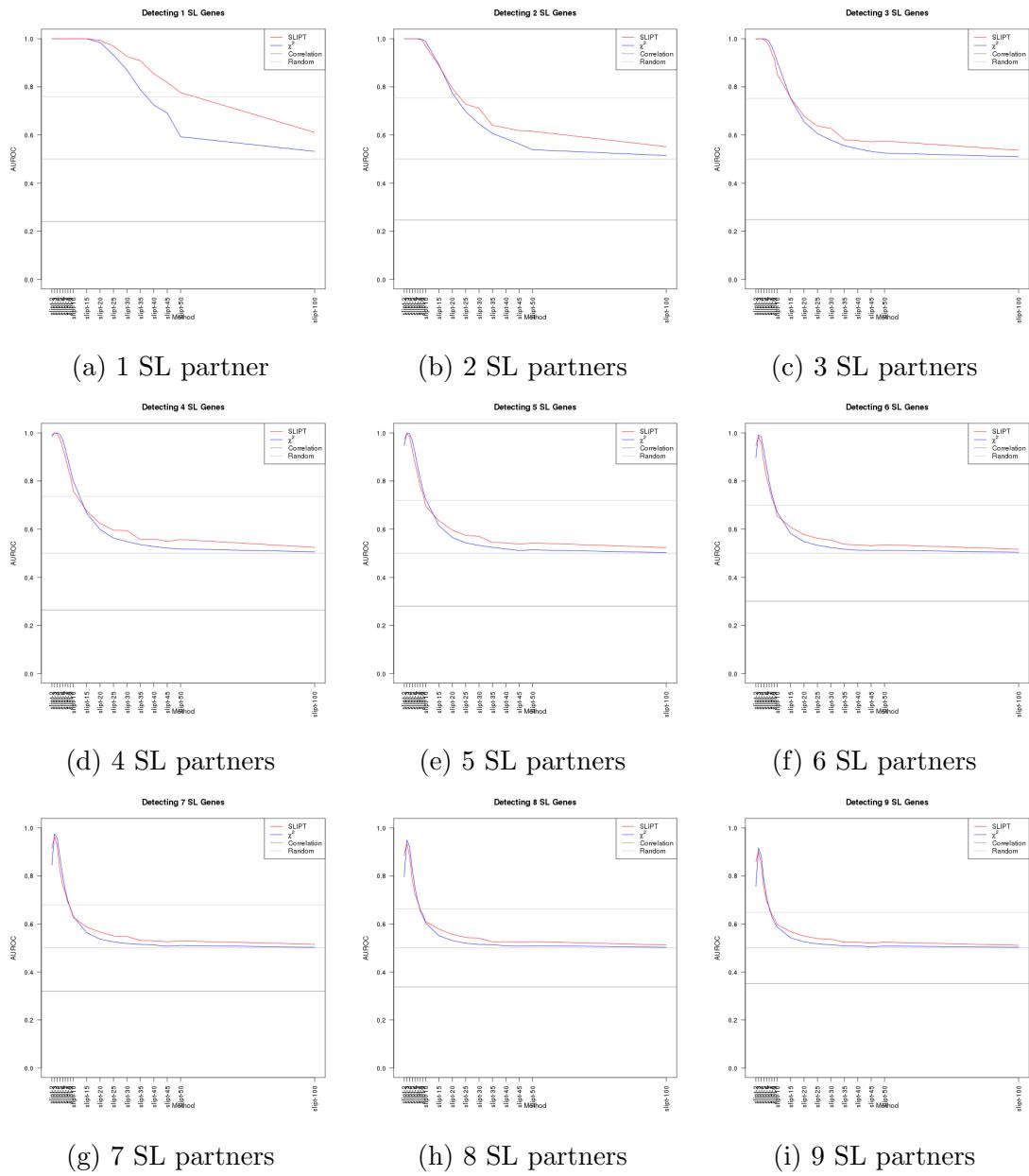


Figure J.2: **Performance of χ^2 and SLIPT across quantiles.** (continued on next page)

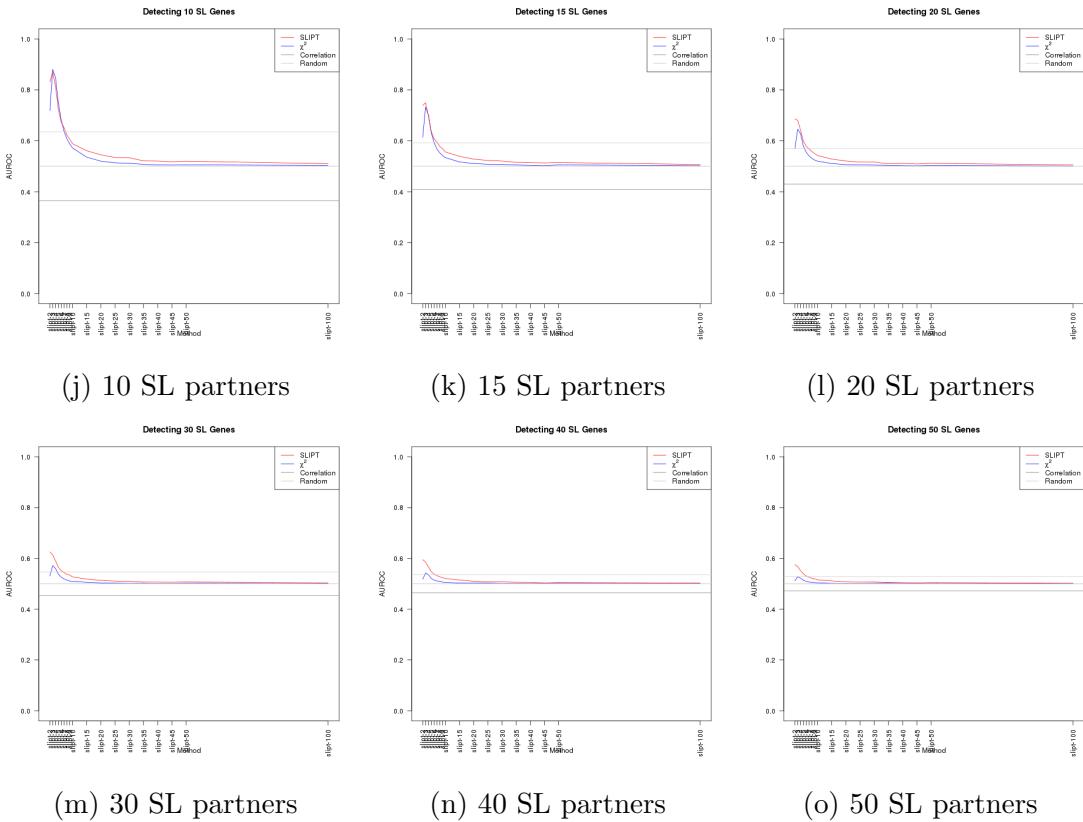


Figure J.2: Performance of χ^2 and SLIPT across quantiles. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles and converging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

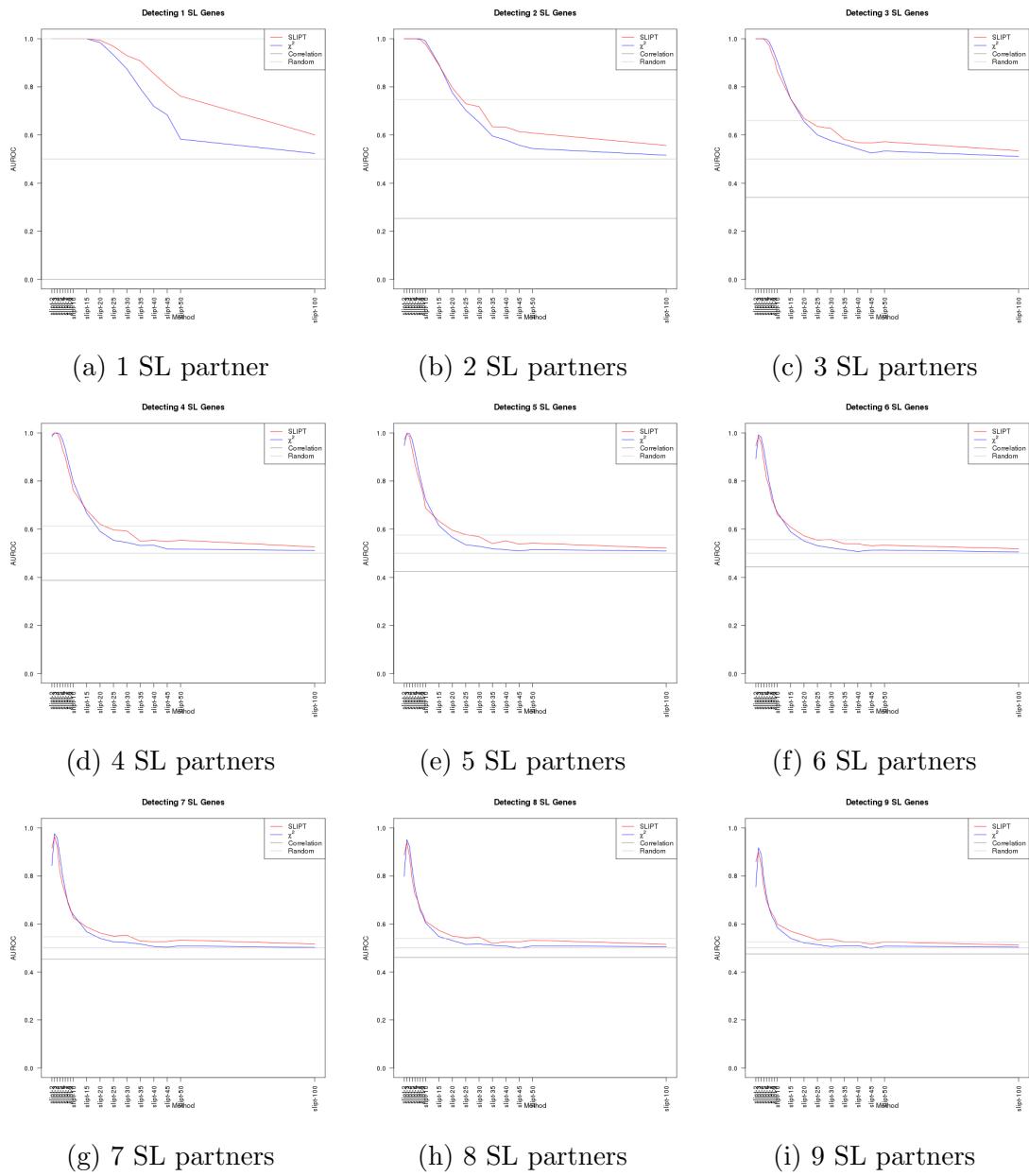


Figure J.3: **Performance of χ^2 and SLIPT across quantiles with more genes.**
 (continued on next page)

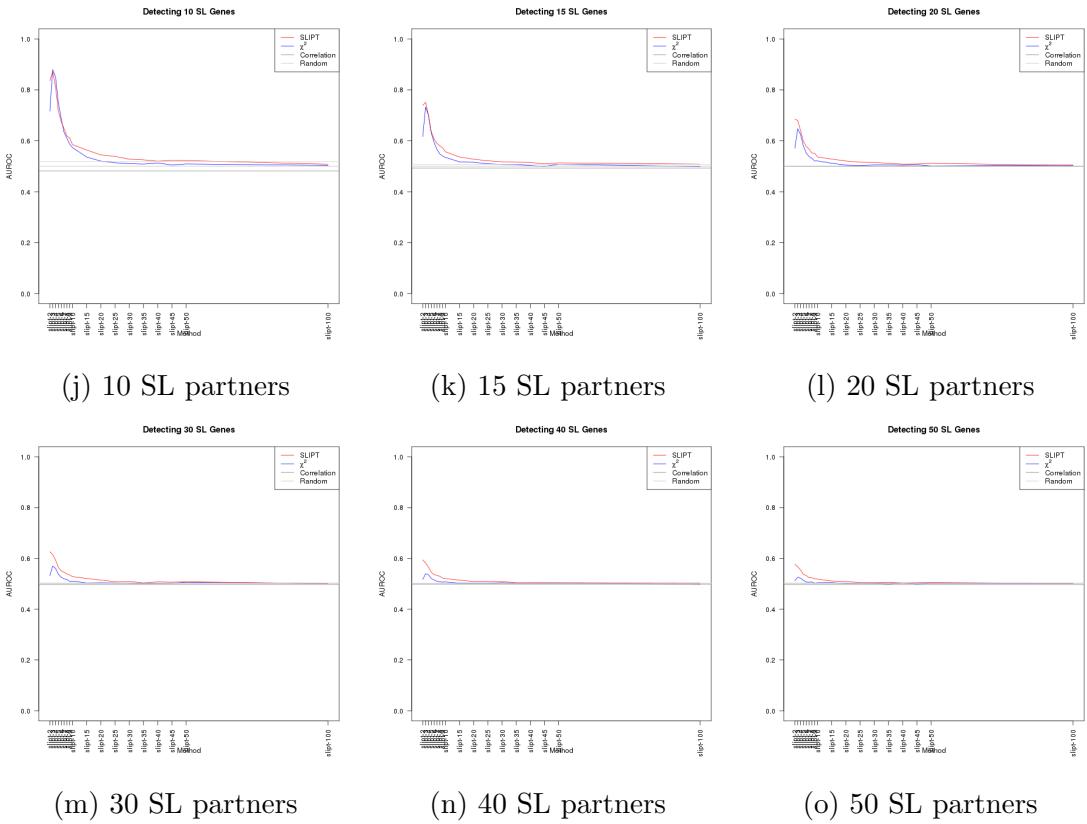


Figure J.3: Performance of χ^2 and SLIPT across quantiles with more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$ -quantiles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

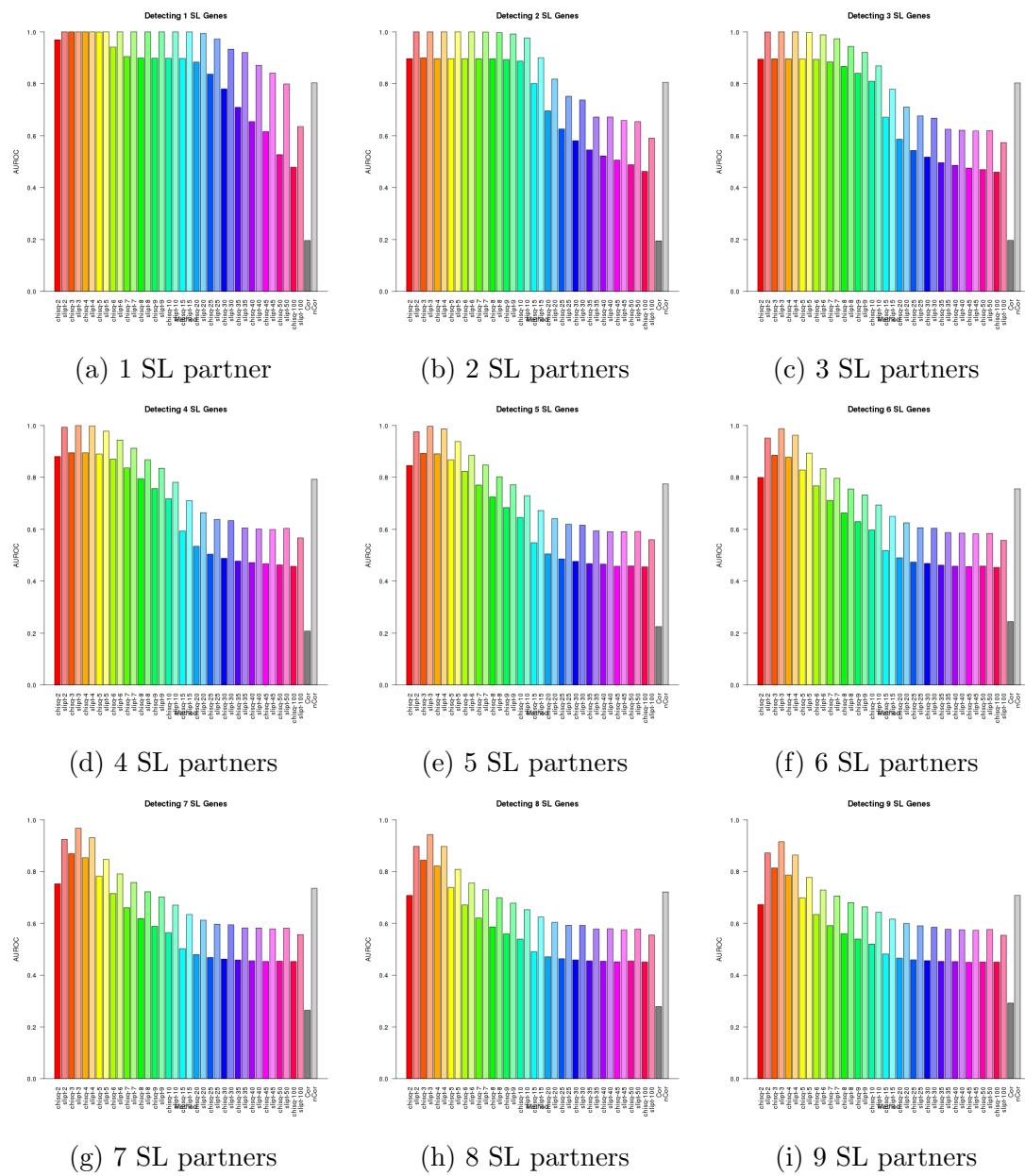


Figure J.4: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

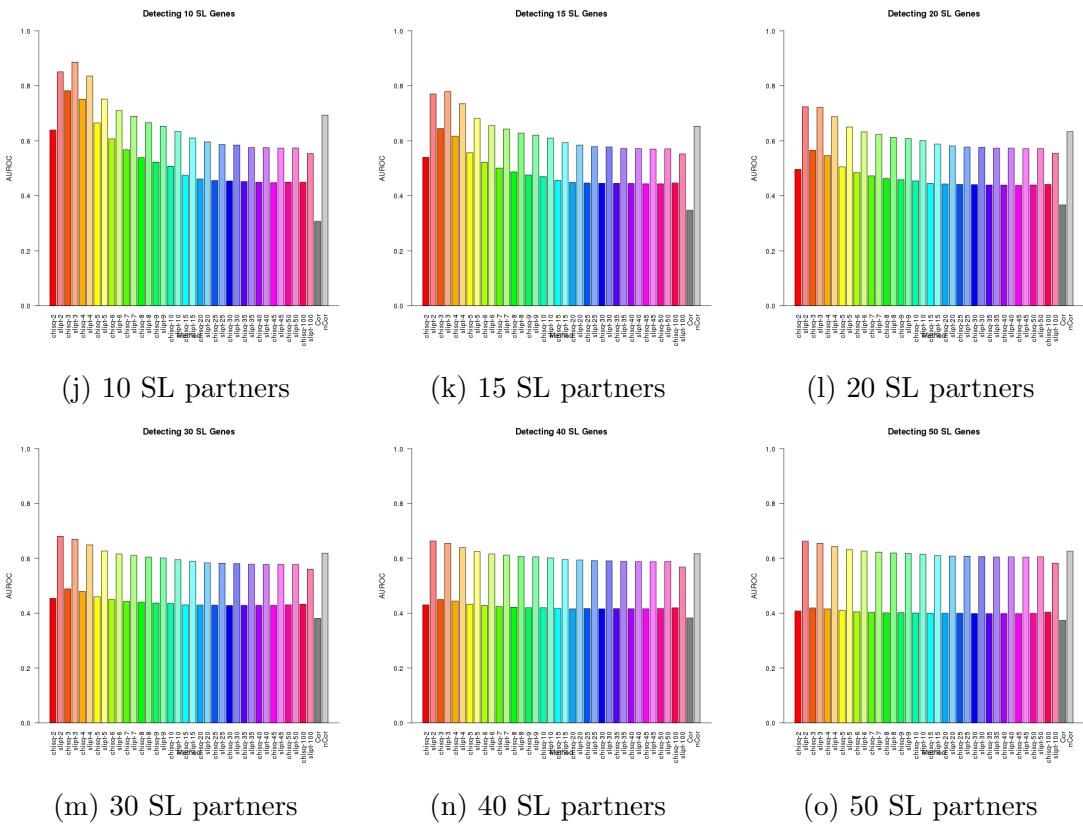


Figure J.4: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The barplot uses the same hues for each quantile (grey for correlation) and darker for χ^2 (and positive correlation). SLIPT and χ^2 perform similarly, peaking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

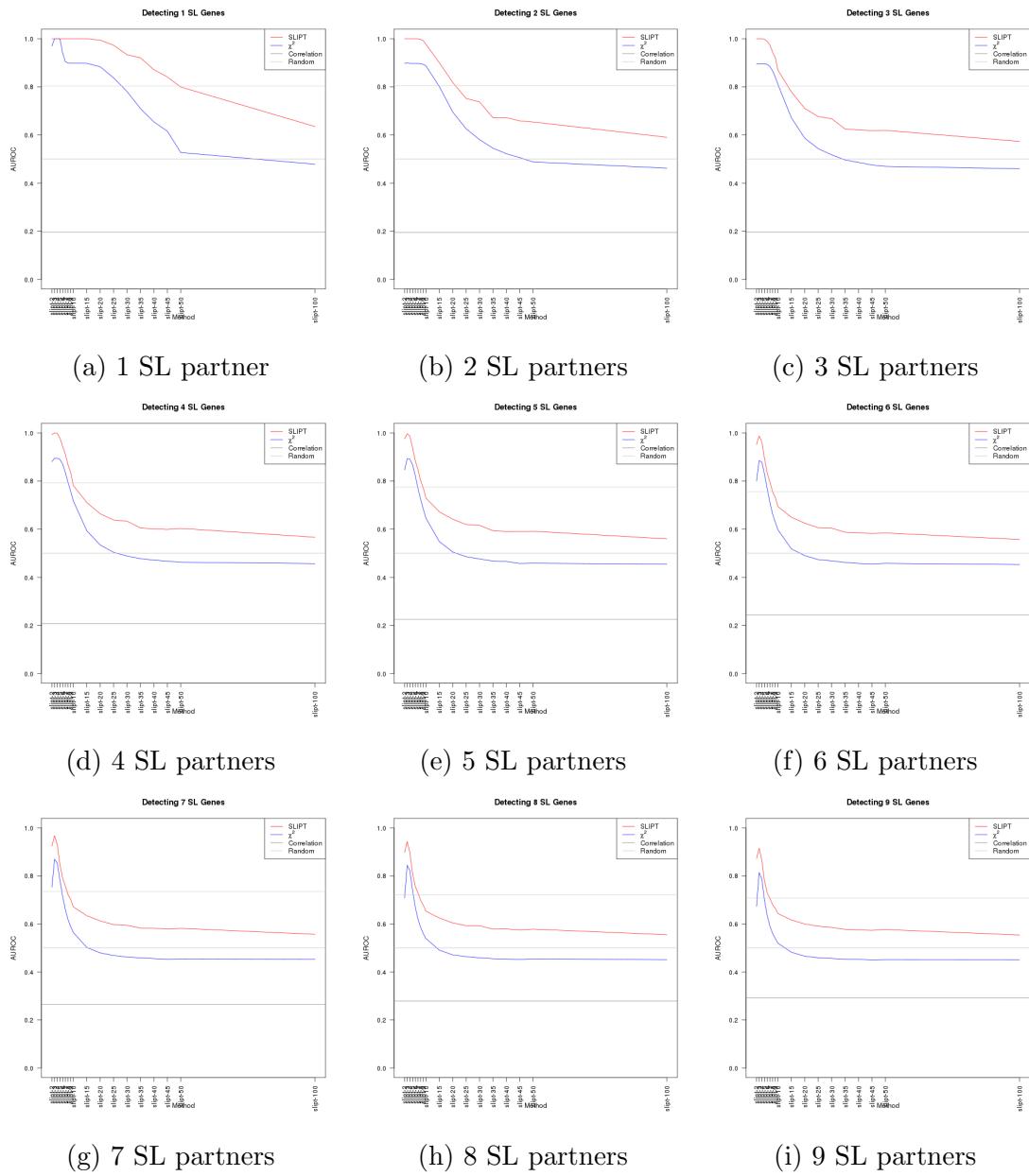


Figure J.5: **Performance of χ^2 and SLIPT across quantiles with query correlation.** (continued on next page)

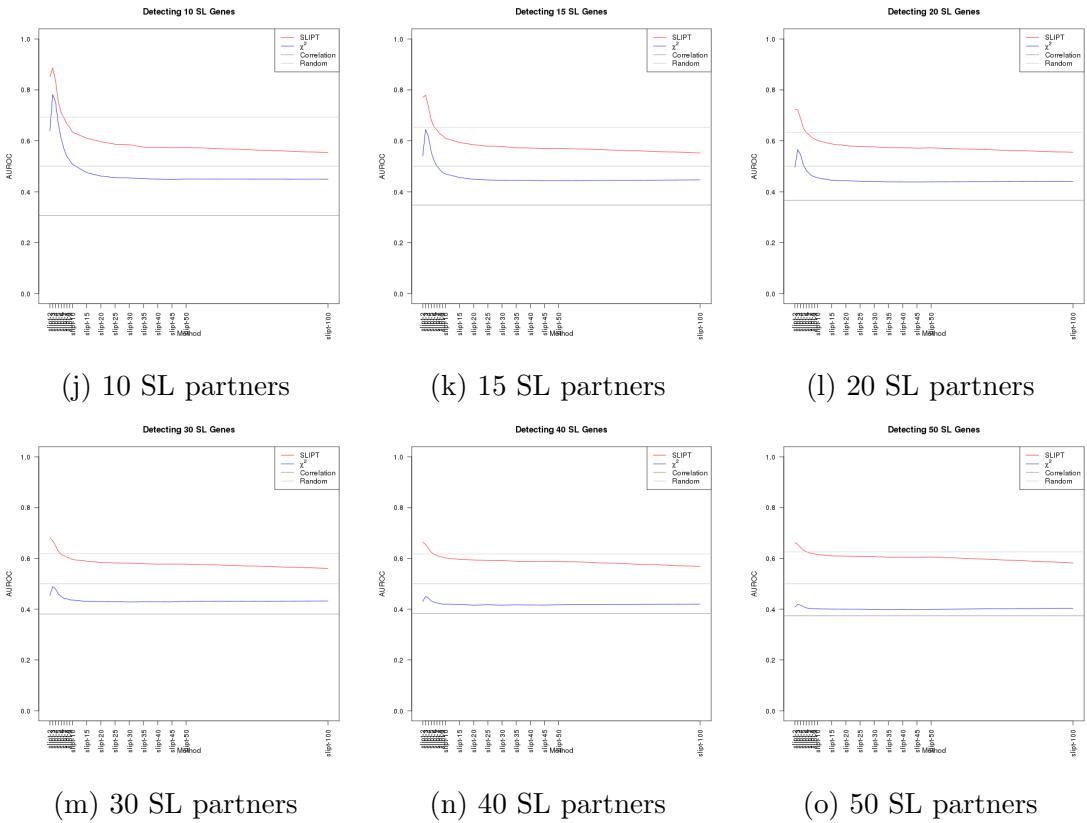


Figure J.5: Performance of χ^2 and SLIPT across quantiles with query correlation. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking at $\frac{1}{3}$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

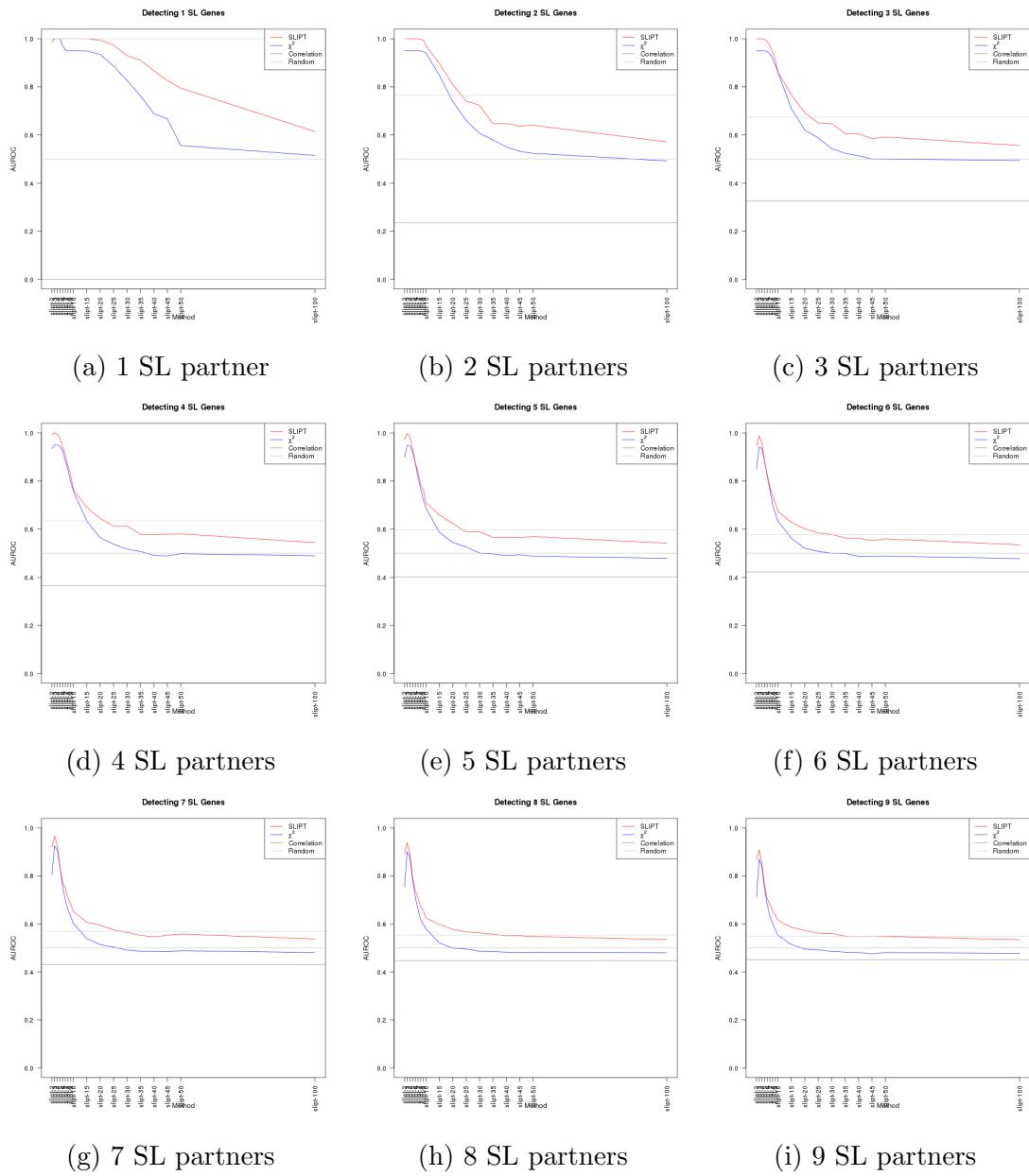


Figure J.6: **Performance of χ^2 and SLIPT across quantiles with query correlation and more genes.** (continued on next page)

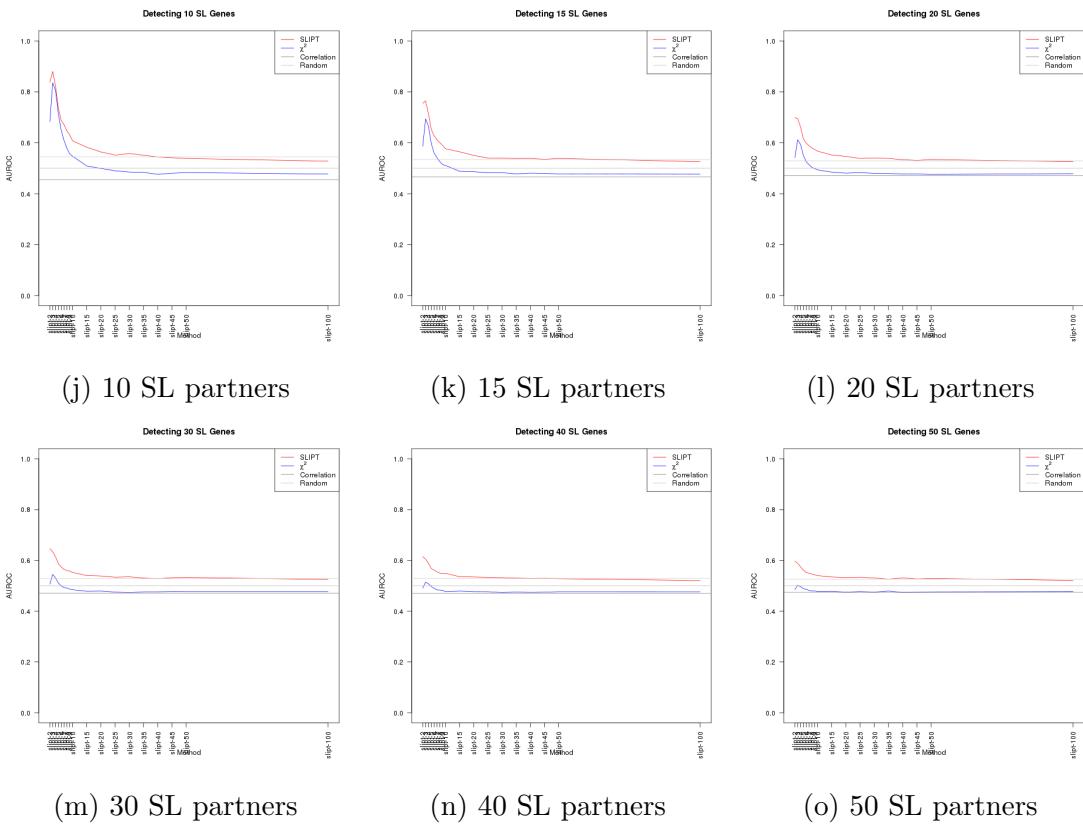
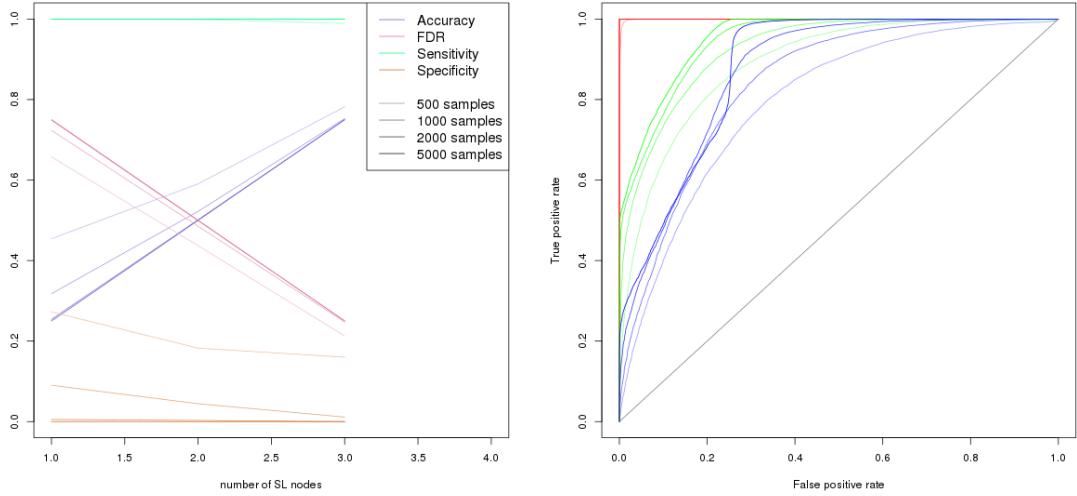


Figure J.6: Performance of χ^2 and SLIPT across quantiles with query correlation and more genes. Synthetic lethal detection with quantiles as in axis labels. The line plots are coloured for SLIPT (red), χ^2 (blue) and correlation (grey) according to the legend. SLIPT and χ^2 perform similarly, peaking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

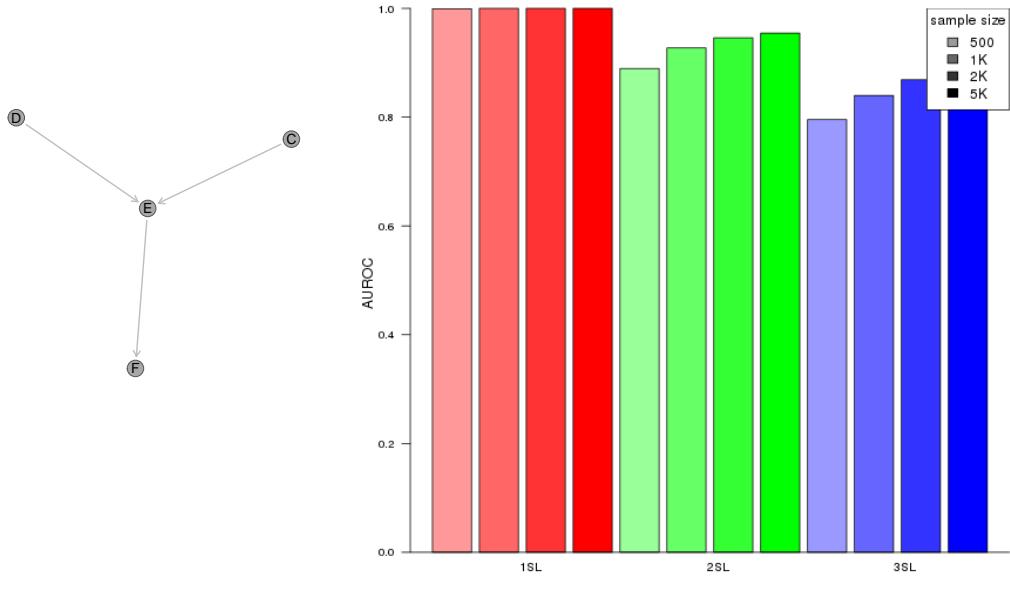
Graph Structures

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

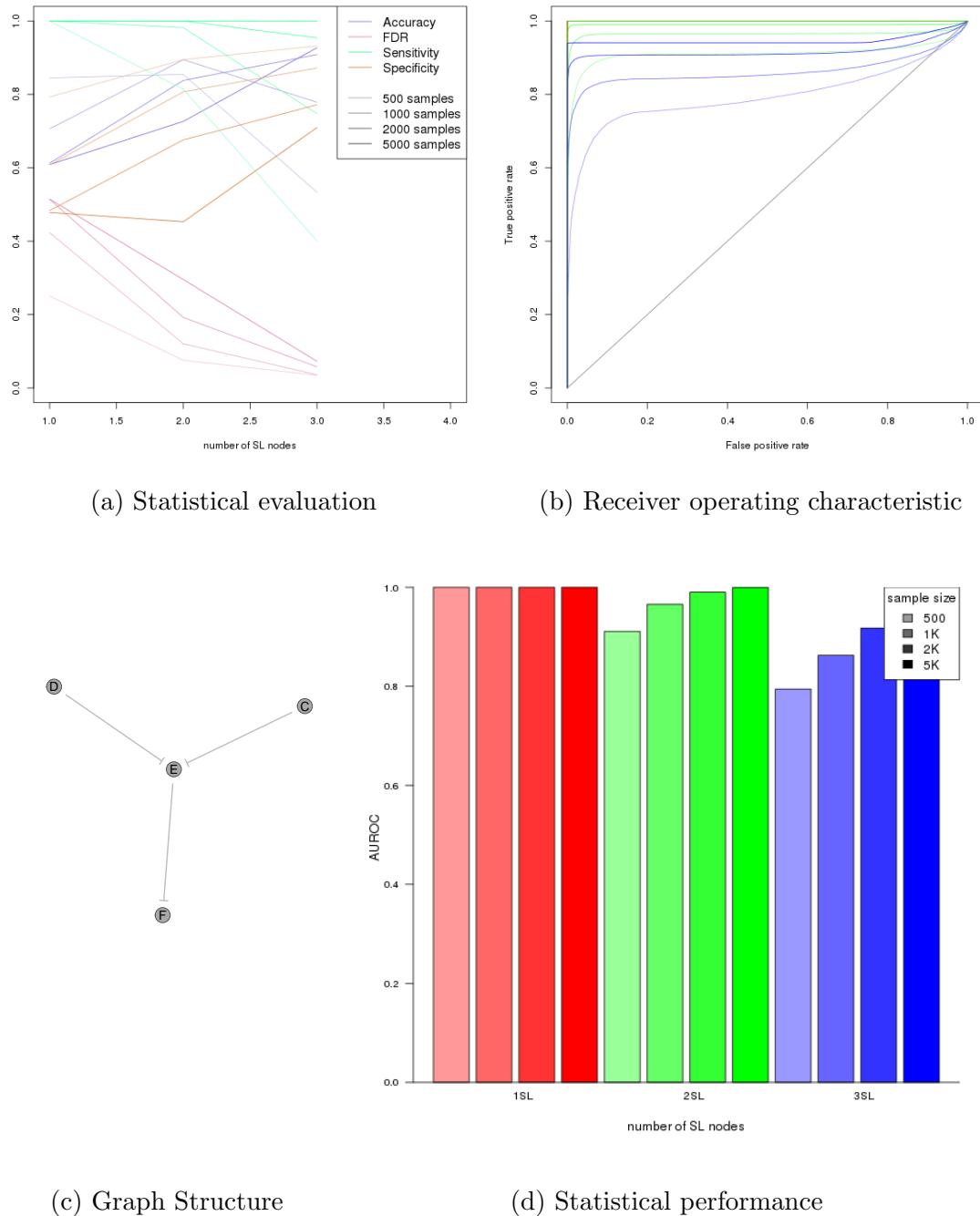


Figure K.2: Performance of simulations on an inhibiting graph. Simulation of synthetic lethality used a multivariate normal distribution from a converging graph. For each parameter, 10,000 simulations were used. Colours in Figure K.2b match Figure K.2d.

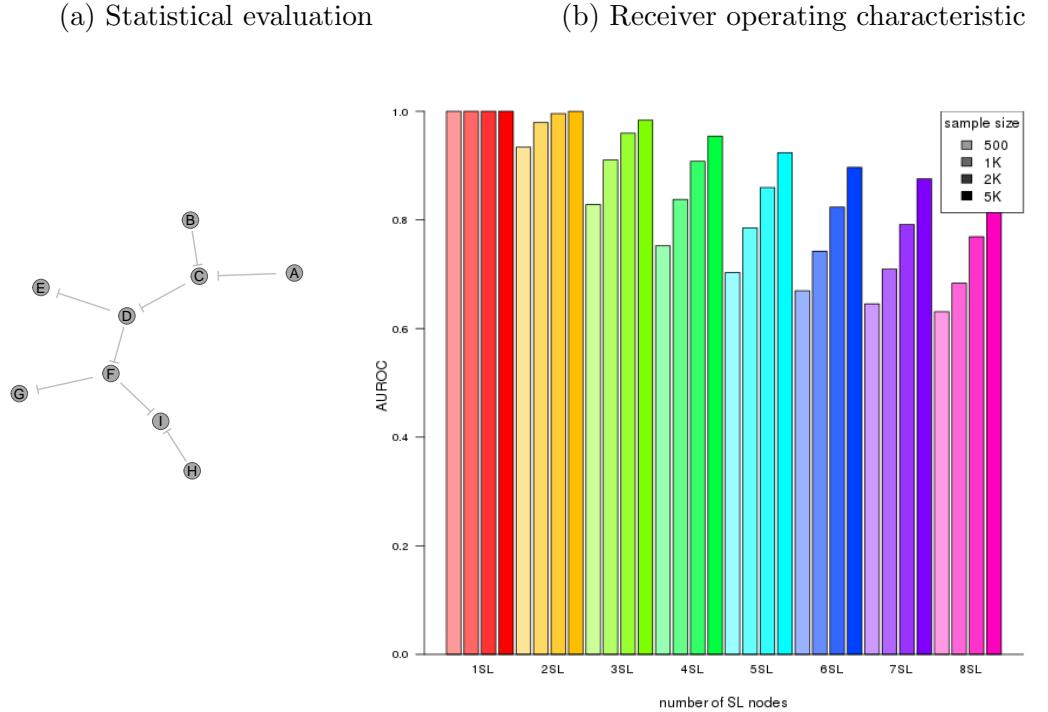
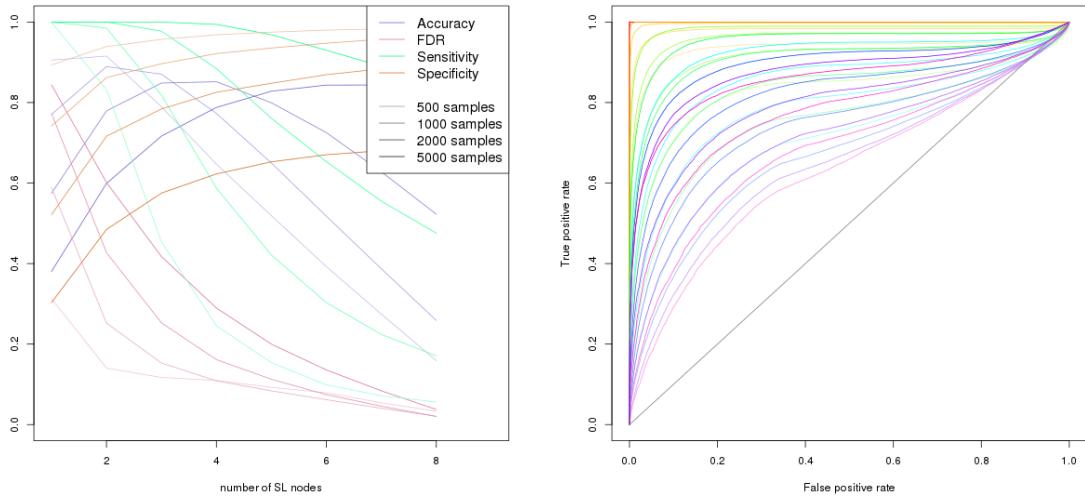
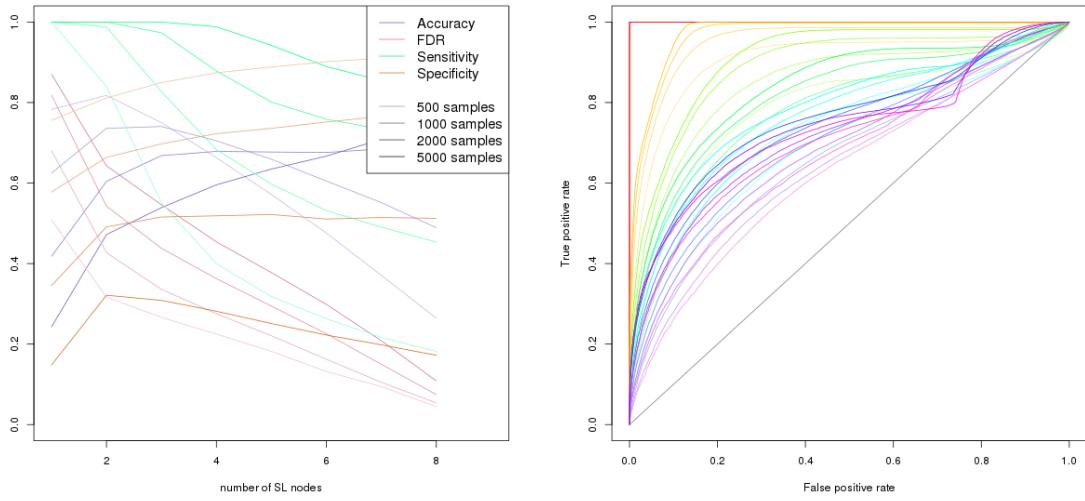
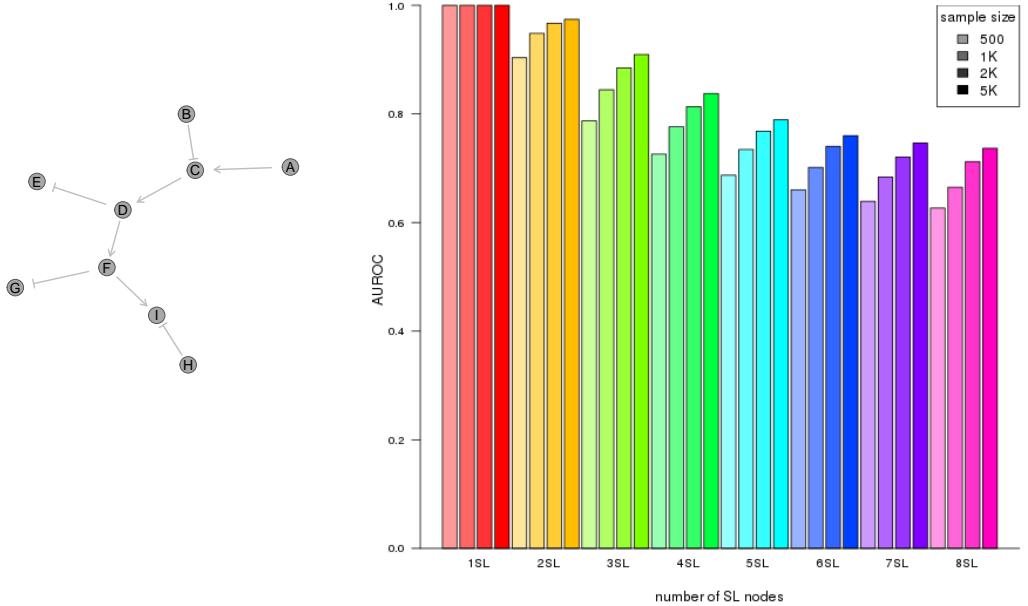


Figure K.3: Performance of simulations on a constructed graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph4 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations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



(a) Statistical evaluation

(b) Receiver operating characteristic

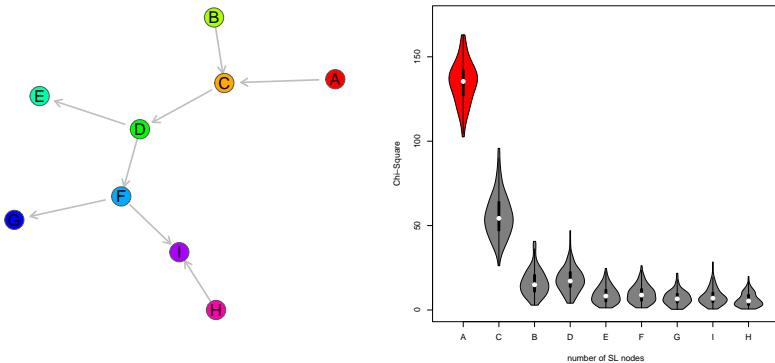


(c) Graph Structure

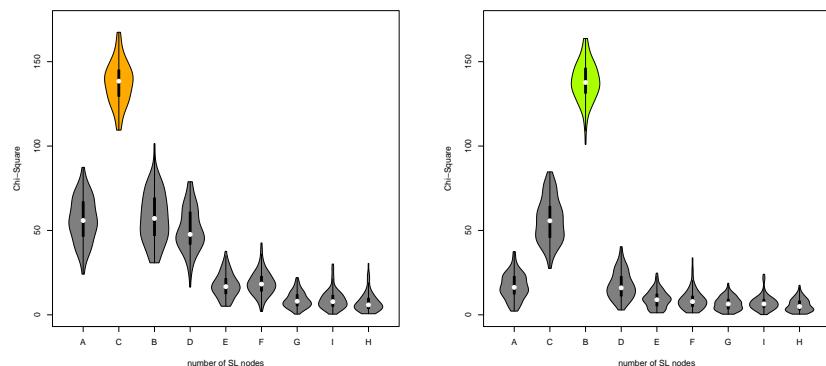
(d) Statistical performance

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.

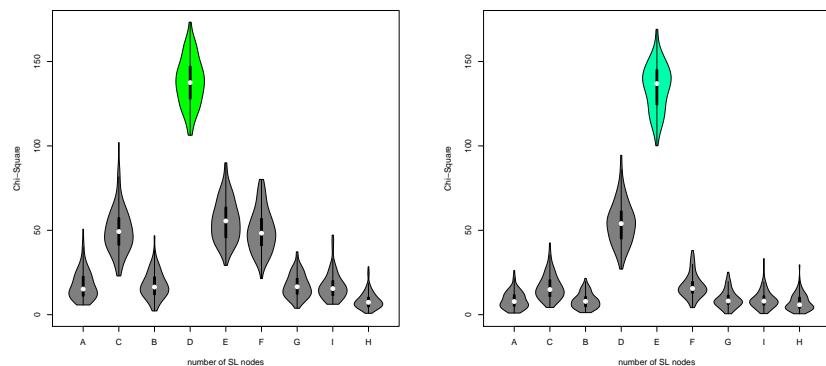
K.2 Simulation across Graph Structures



(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)

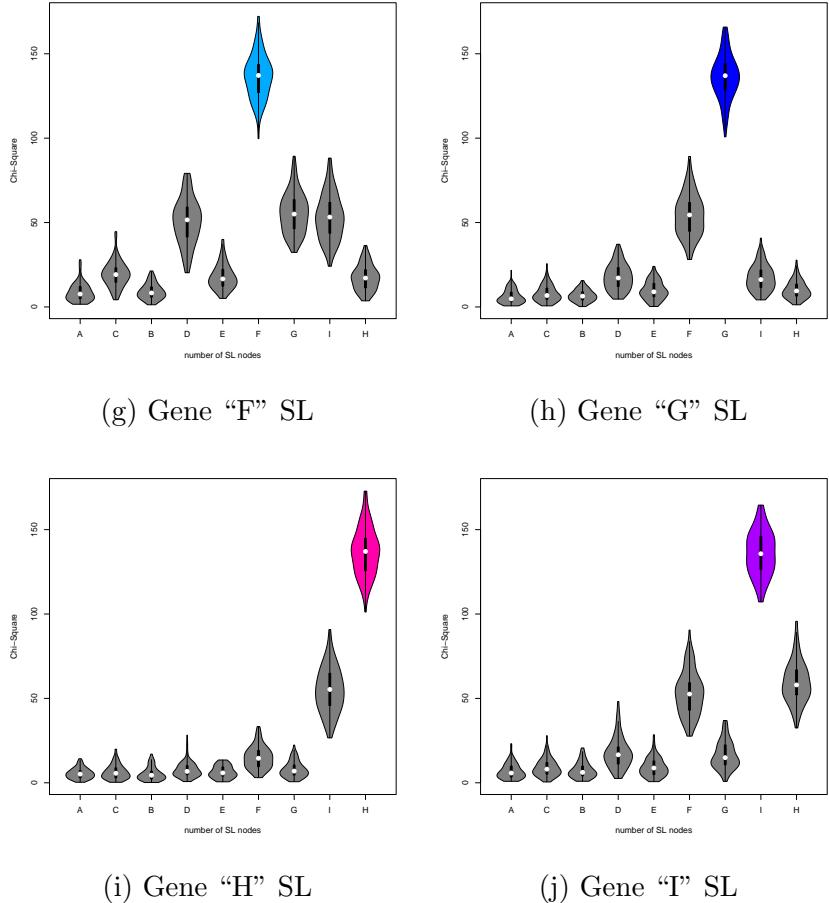
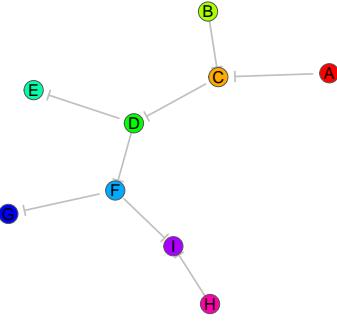
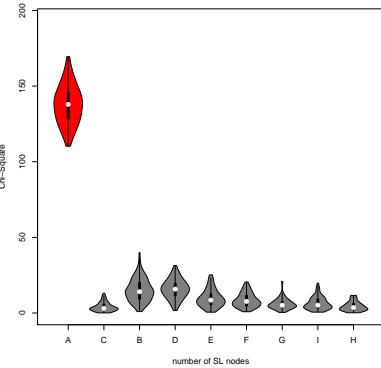


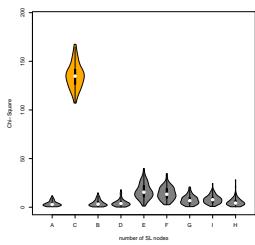
Figure K.5: Detection of Synthetic Lethality within a Graph Structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph. For each synthetic lethal gene (highlighted in the respective colours), the χ^2 values were computed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



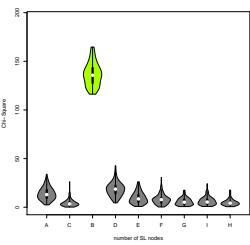
(a) Inhibiting Graph Structure



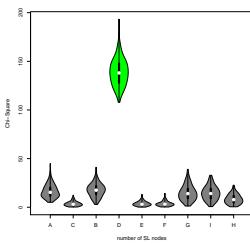
(b) χ^2 distribution for "A" SL



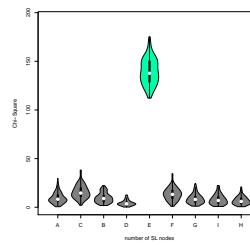
(c) Gene "B" SL



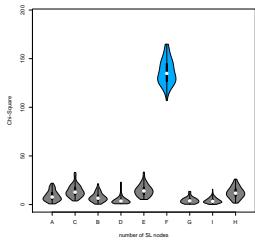
(d) Gene "C" SL



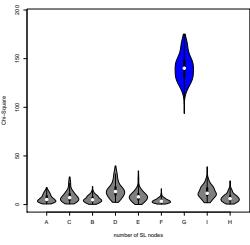
(e) Gene "D" SL



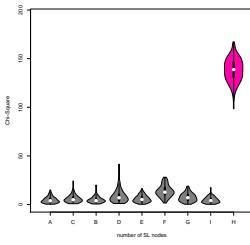
(f) Gene "E" SL



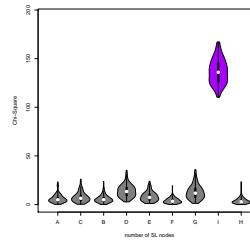
(g) Gene "F" SL



(h) Gene "G" SL

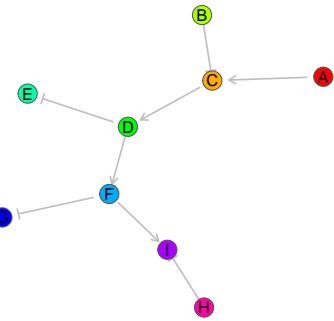


(i) Gene "H" SL

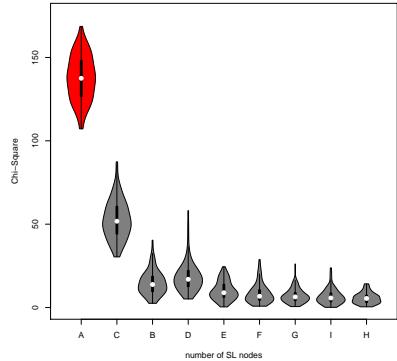


(j) Gene "I" SL

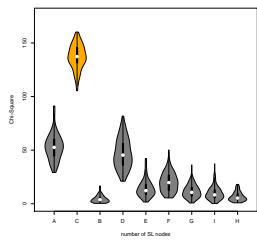
Figure K.6: Detection of Synthetic Lethality within an Inhibiting Graph Structure. Each gene was designated to be synthetic lethal separately and the χ^2 value from SLIPT was computed for each gene across the graph structure with inhibiting relationships. For each synthetic lethal gene (highlighted in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



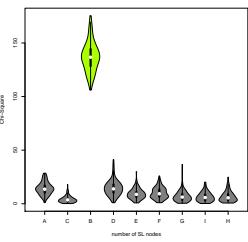
(a) Inhibiting Graph Structure



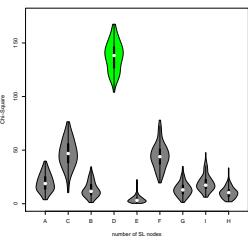
(b) χ^2 distribution for "A" SL



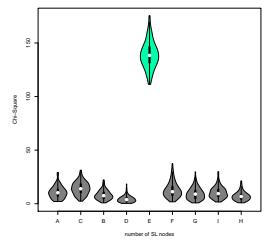
(c) Gene "B" SL



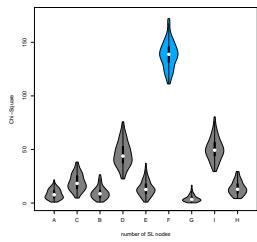
(d) Gene "C" SL



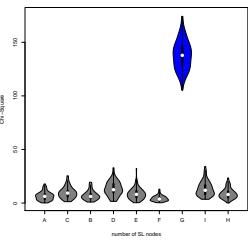
(e) Gene "D" SL



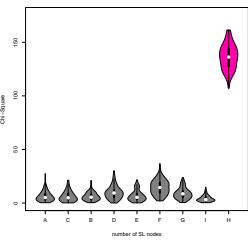
(f) Gene "E" SL



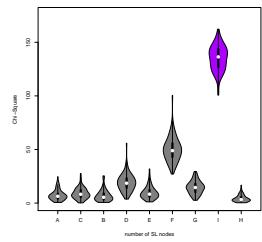
(g) Gene "F" SL



(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

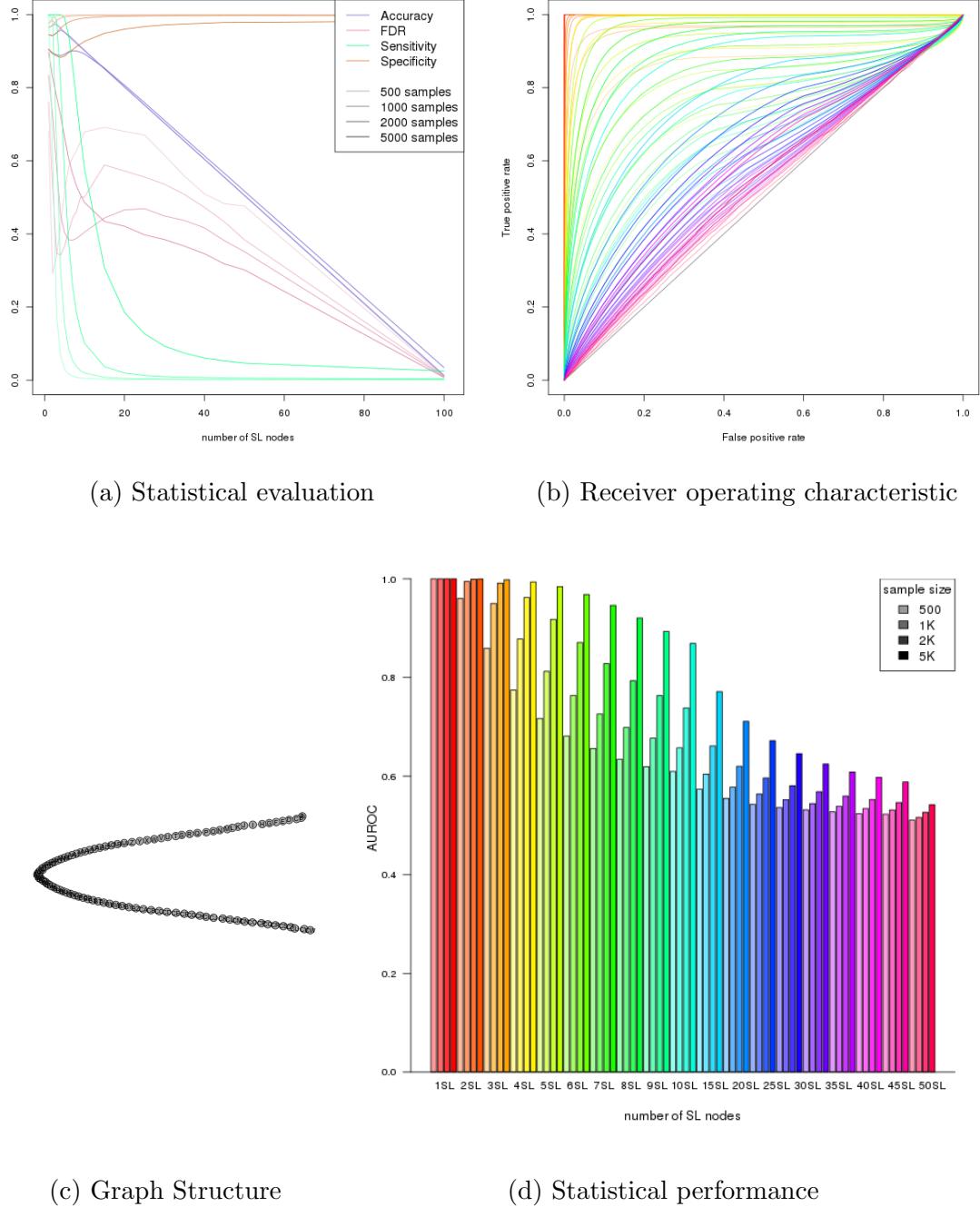
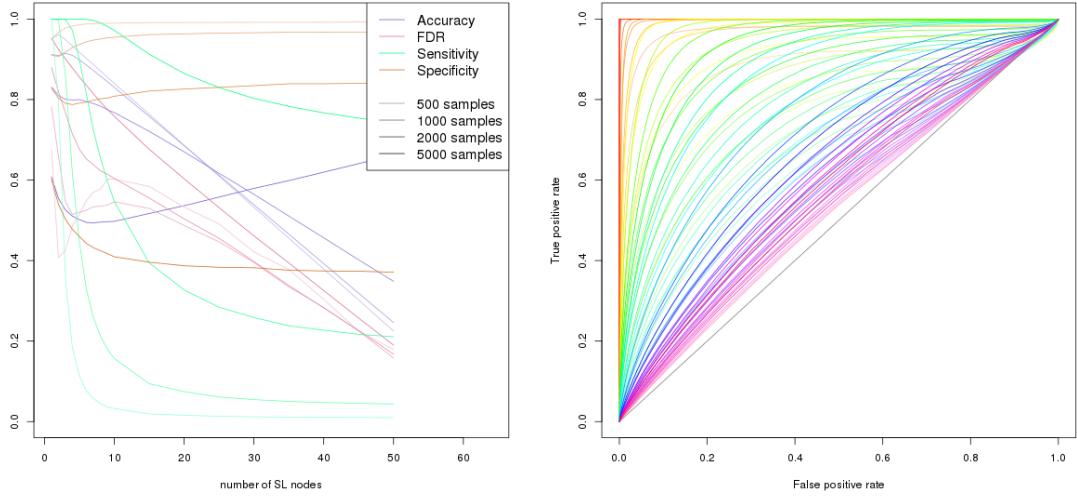
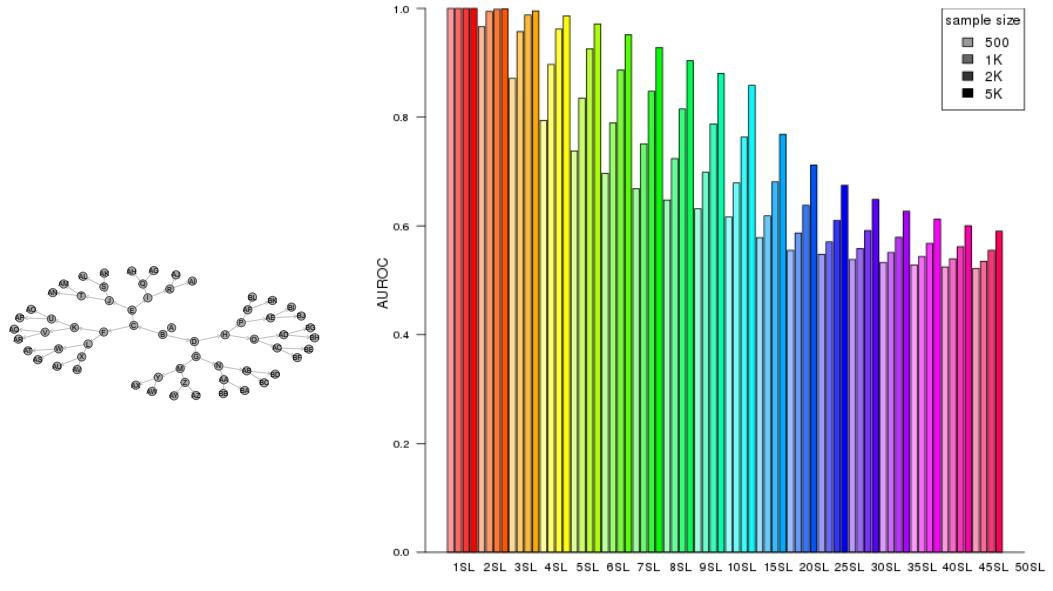


Figure K.8: **Performance of simulations on a large graph.** Simulation of synthetic lethality used a multivariate normal distribution from a large graph. For each parameter, 10,000 simulations were used. Colours in Figure K.8b match Figure K.8d.



(a) Statistical evaluation

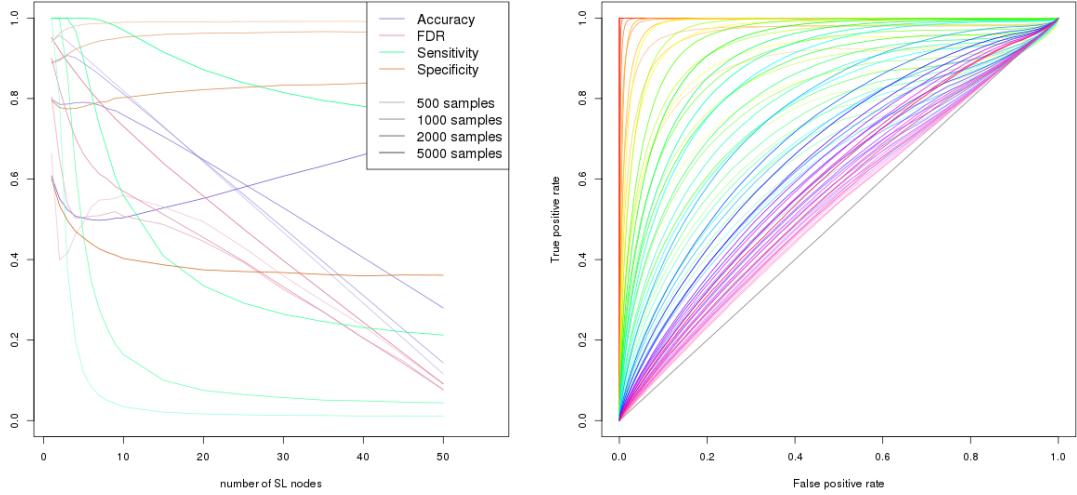
(b) Receiver operating characteristic



(c) Graph Structure

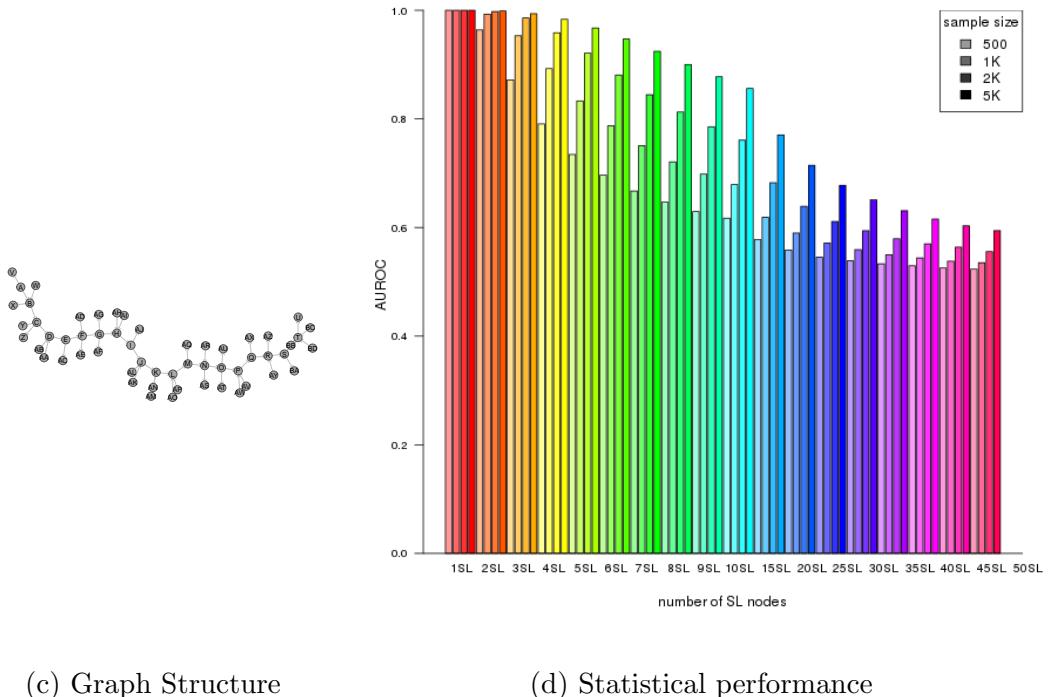
(d) Statistical performance

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

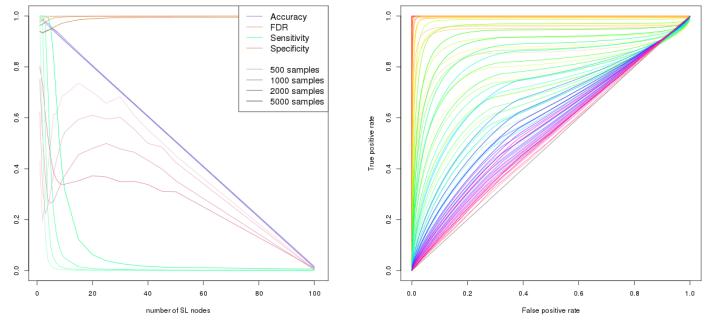


(c) Graph Structure

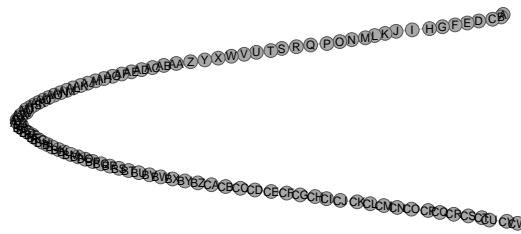
(d) Statistical performance

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.

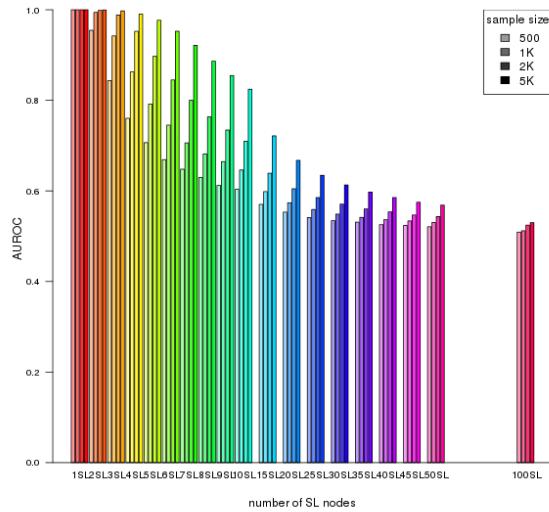
K.3.1 Simulations from Complex Inhibiting Graphs



(a) Statistical evaluation (b) Receiver operating characteristic

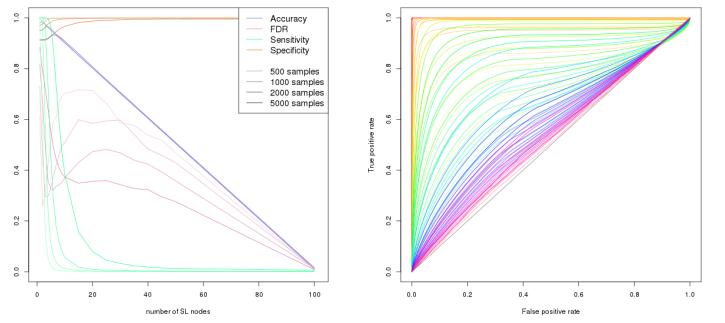


(c) Graph Structure

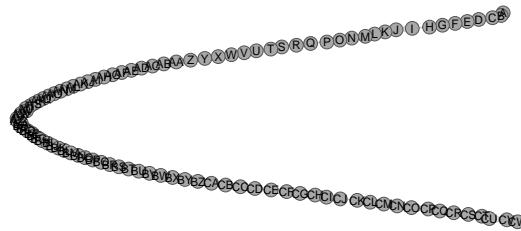


(d) Statistical performance

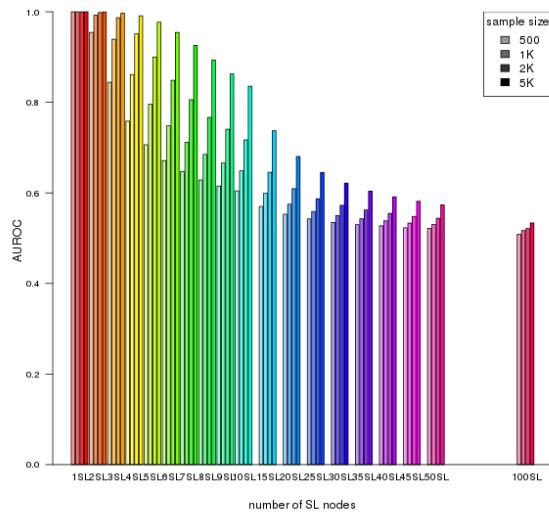
Figure K.11: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph5 with only inhibitions. For each parameter, 10,000 simulations were used.



(a) Statistical evaluation (b) Receiver operating characteristic

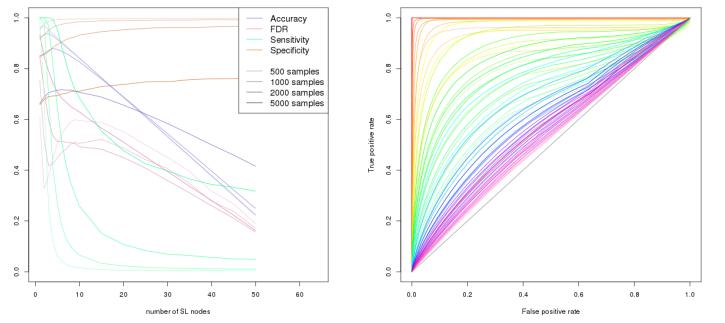


(c) Graph Structure

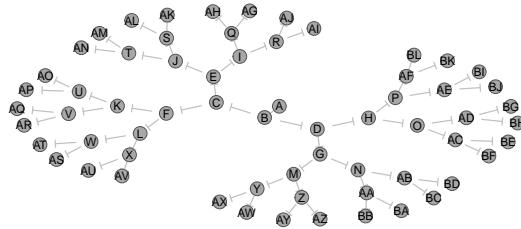


(d) Statistical performance

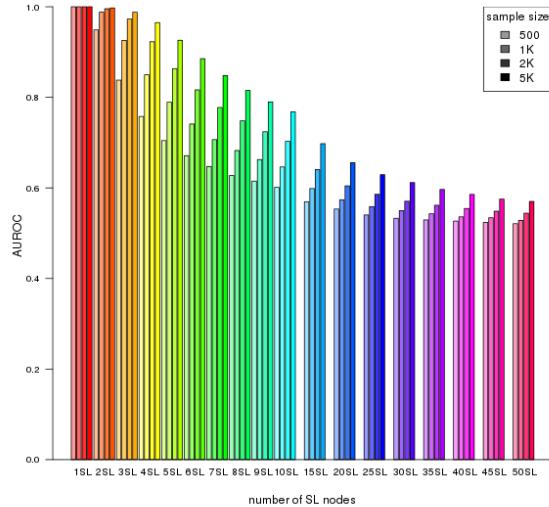
Figure K.12: Performance of simulations on a large constructed graph with inhibition. Simulation of synthetic lethality used a multivariate normal distribution from Graph5 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter,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



(a) Statistical evaluation (b) Receiver operating characteristic

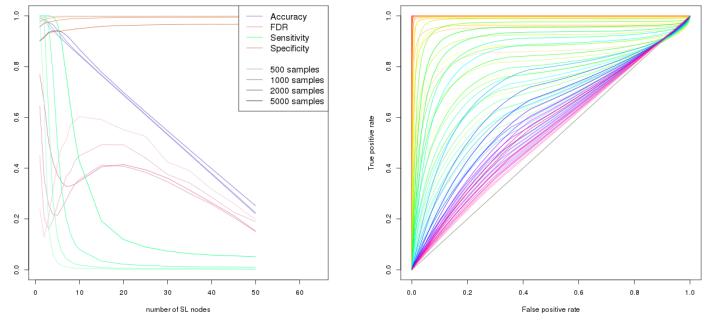


(c) Graph Structure

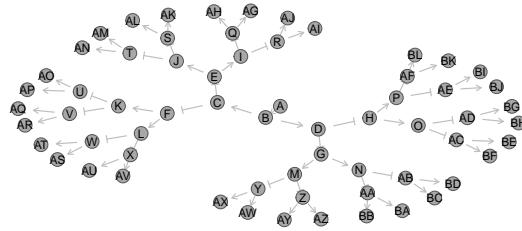


(d) Statistical performance

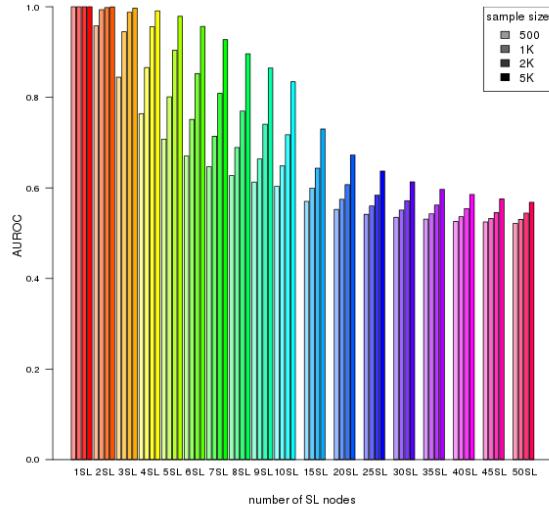
Figure K.13: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph6 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations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



(a) Statistical evaluation (b) Receiver operating characteristic

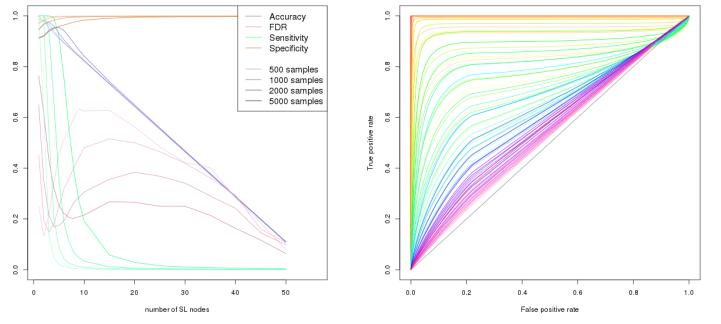


(c) Graph Structure

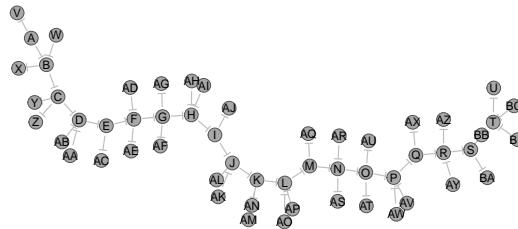


(d) Statistical performance

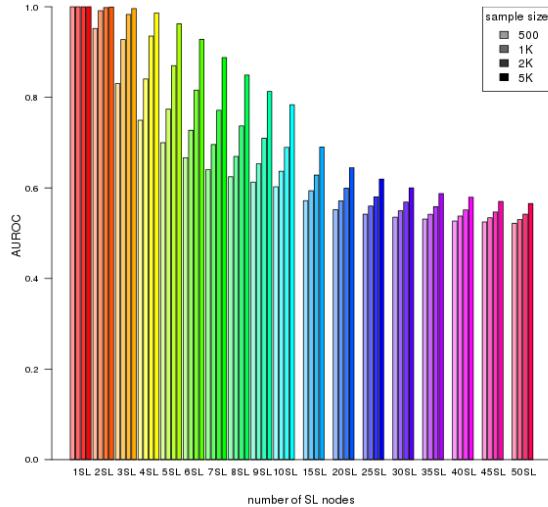
Figure K.14: Performance of simulations on a branching graph with inhibition.
 Simulation of synthetic lethality used a multivariate normal distribution from Graph6 with alternating inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000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



(a) Statistical evaluation (b) Receiver operating characteristic

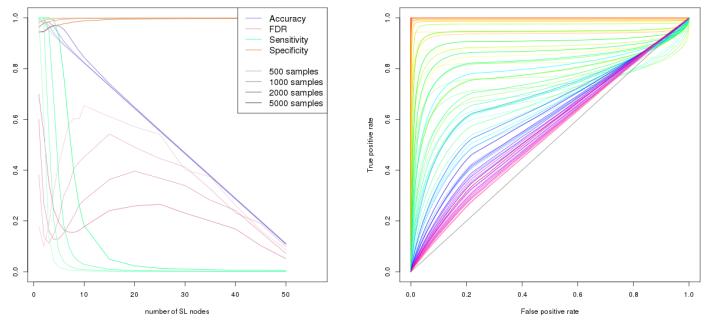


(c) Graph Structure

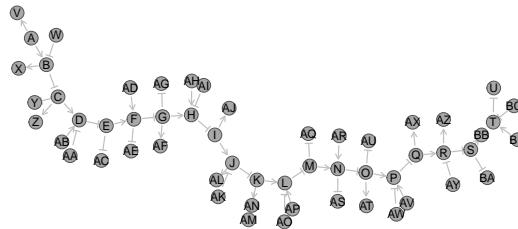


(d) Statistical performance

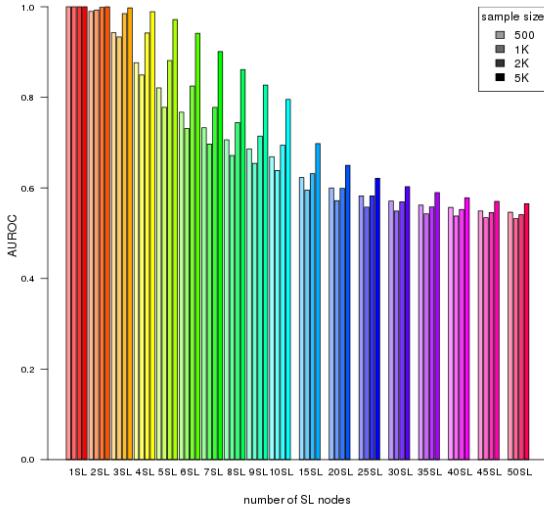
Figure K.15: Performance of simulations on a complex graph with inhibition.
Simulation of synthetic lethality used a multivariate normal distribution from Graph7 with only inhibitions. Performance of SLIPT declines for more synthetic partners and lower sample sizes. For each parameter, 10,000 simulations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

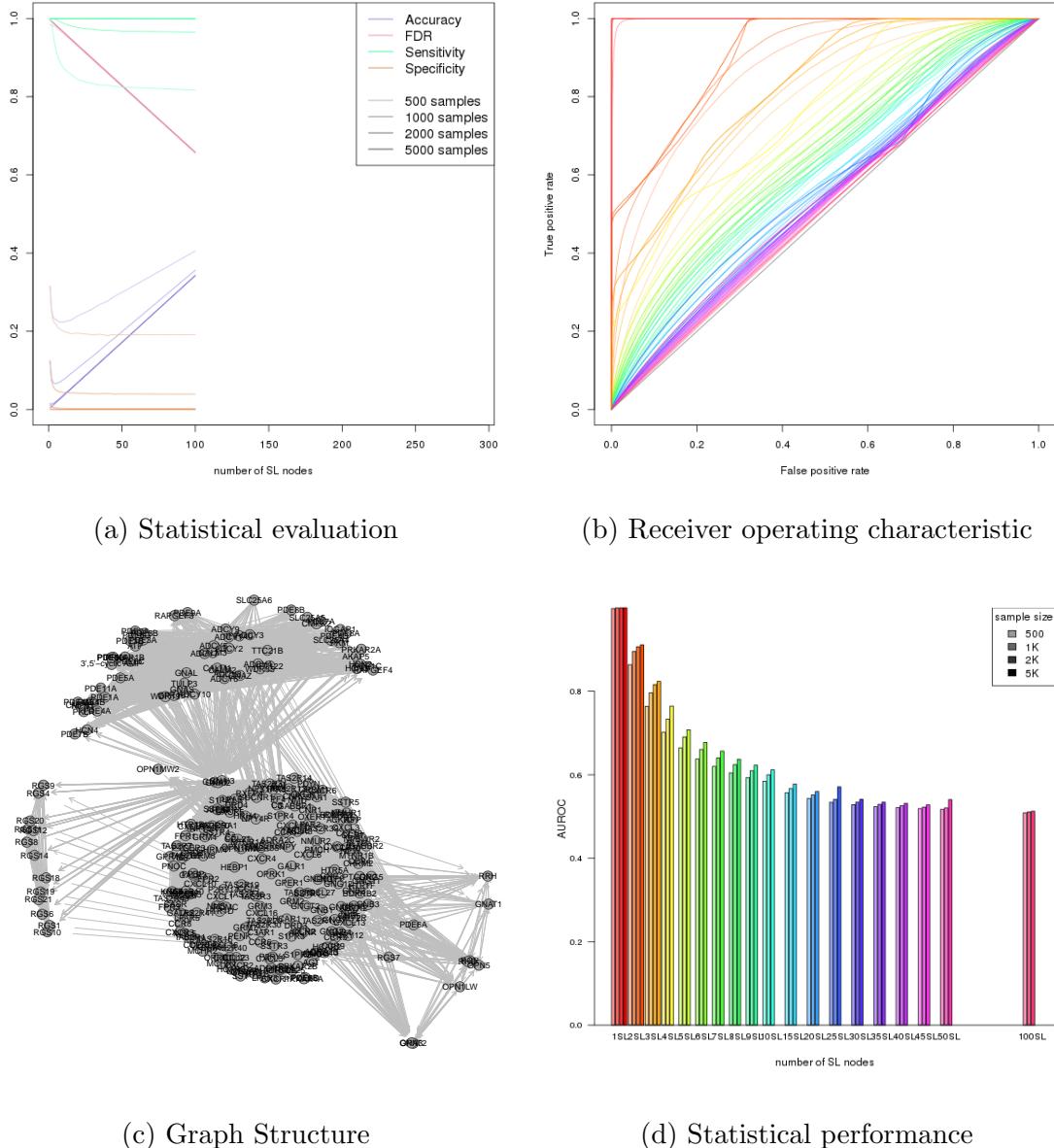


Figure K.17: Performance of simulations on the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution based on the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters for detecting synthetic lethality in the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

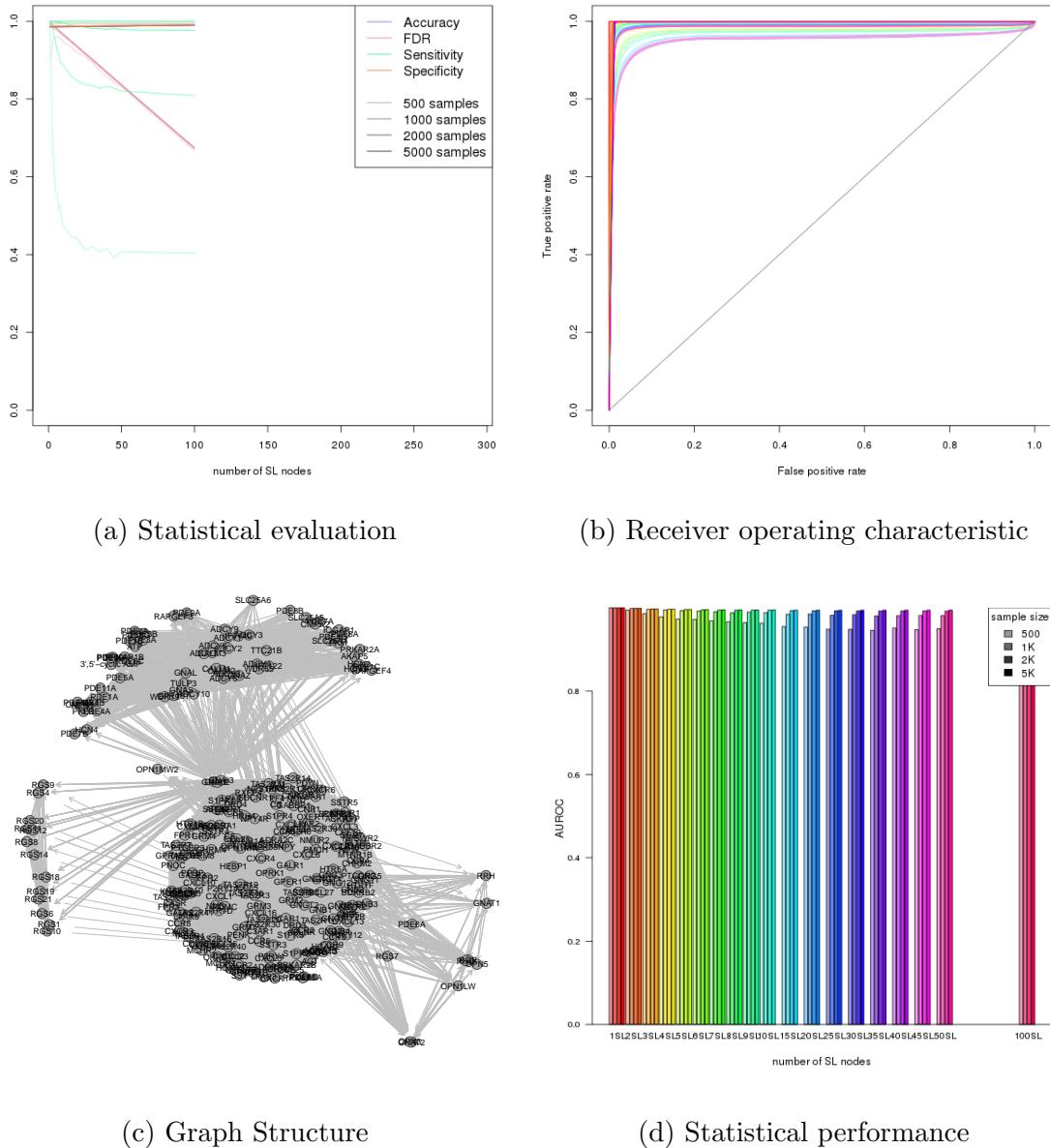


Figure K.18: Performance of simulations including the $G_{\alpha i}$ signalling pathway. Simulation of synthetic lethality used a multivariate normal distribution (without correlation structure apart from the Reactome $G_{\alpha i}$ signalling pathway. Performance of SLIPT was high across parameters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