

Contents

Glossary	xiii
Acronyms	xv
1 Introduction and Literature Review	1
1.1 Cancer Research in the Post-Genomic Era	1
1.1.1 Cancer is a Global Health Issue	2
1.1.1.1 The Genetics and Molecular Biology of Cancers	3
1.1.2 The Genomics Revolution in Cancer Research	3
1.1.2.1 High-Throughput Technologies	4
1.1.2.2 Bioinformatics and Genomic Data	5
1.1.3 Genomics Projects	5
1.1.3.1 The Cancer Genome Project	6
1.1.3.2 The Cancer Genome Atlas Project	6
1.1.4 Genomic Cancer Medicine	8
1.1.4.1 Cancer Genes and Driver Mutations	8
1.1.4.2 Precision Cancer Medicine	9
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine	9
1.1.4.4 Targeted Therapeutics and Pharmacogenomics	10
1.1.5 Systems and Network Biology	11
1.2 Synthetic Lethal Cancer Medicine	12
1.2.1 Synthetic Lethal Genetic Interactions	12
1.2.2 Synthetic Lethal Concepts in Genetics	13
1.2.3 Synthetic Lethality in Model Systems	15
1.2.3.1 Synthetic Lethal Pathways and Networks	15
1.2.3.2 Evolution of Synthetic Lethality	16
1.2.4 Synthetic Lethality in Cancer	17
1.2.5 Clinical Impact of Synthetic Lethality in Cancer	17
1.2.6 High-throughput Screening for Synthetic Lethality	20
1.2.6.1 Synthetic Lethal Screens	21
1.2.7 Computational Prediction of Synthetic Lethality	22
1.2.7.1 Bioinformatics Approaches to Genetic Interactions	22
1.2.7.2 Comparative Genomics	24
1.2.7.3 Analysis and Modelling of Protein Data	26
1.2.7.4 Differential Gene Expression	28
1.2.7.5 Data Mining and Machine Learning	29

1.2.7.6	Mutually Exclusive Bimodality	31
1.2.7.7	Rationale for Further Development	32
1.3	E-cadherin as a Synthetic Lethal Target	32
1.3.1	The <i>CDH1</i> gene and its Biological Functions	33
1.3.1.1	Cytoskeleton	33
1.3.1.2	Extracellular and Tumour Micro-environment	33
1.3.1.3	Cell-Cell Adhesion and Signalling	34
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor	34
1.3.2.1	Breast Cancers and Invasion	34
1.3.3	Hereditary Diffuse Gastric (and Lobular Breast) Cancer	35
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations	36
1.4	Summary and Research Direction of Thesis	37
1.4.1	Thesis Aims	38
2	Methods and Resources	40
2.1	Bioinformatics Resources for Genomics Research	40
2.1.1	Public Data and Software Packages	40
2.1.1.1	Cancer Genome Atlas Data	41
2.1.1.2	Reactome and Annotation Data	42
2.2	Data Handling	42
2.2.1	Normalisation	42
2.2.2	Sample Triage	43
2.2.3	Metagenes and the Singular Value Decomposition	43
2.2.4	Candidate Triage and Integration with Screen Data	45
2.3	Techniques	46
2.3.1	Statistical Procedures and Tests	46
2.3.2	Gene Set Over-representation Analysis	47
2.3.3	Clustering	47
2.3.4	Heatmap	47
2.3.5	Modelling and Simulations	48
2.3.5.1	Receiver Operating Characteristic Curves	49
2.3.6	Resampling Analysis	49
2.4	Pathway Structure Methods	50
2.4.1	Network and Graph Analysis	50
2.4.2	Sourcing Graph Structure Data	51
2.4.3	Constructing Pathway Subgraphs	51
2.4.4	Network Analysis Metrics	52
2.5	Implementation	53
2.5.1	Computational Resources and Linux Utilities	53
2.5.2	R Language and Packages	54
2.5.3	High Performance and Parallel Computing	57
3	Methods Developed During Thesis	59
3.1	A Synthetic Lethal Detection Methodology	59
3.2	Synthetic Lethal Simulation and Modelling	61
3.2.1	A Model of Synthetic Lethality in Expression Data	62

3.2.2	Simulation Procedure	66
3.3	Detecting Simulated Synthetic Lethal Partners	68
3.3.1	Binomial Simulation of Synthetic Lethality	69
3.3.2	Multivariate Normal Simulation of Synthetic Lethality	71
3.3.2.1	Multivariate Normal Simulation with Correlated Genes	73
3.3.2.2	Specificity with Query-Correlated Pathways	80
3.4	Graph Structure Methods	83
3.4.1	Upstream and Downstream Gene Detection	83
3.4.1.1	Permutation Analysis for Statistical Significance	84
3.4.1.2	Hierarchy Based on Biological Context	84
3.4.2	Simulating Gene Expression from Graph Structures	85
3.5	Customised Functions and Packages Developed	89
3.5.1	Synthetic Lethal Interaction Prediction Tool	90
3.5.2	Data Visualisation	90
3.5.3	Extensions to the iGraph Package	92
3.5.3.1	Sampling Simulated Data from Graph Structures	92
3.5.3.2	Plotting Directed Graph Structures	93
3.5.3.3	Computing Information Centrality	94
3.5.3.4	Testing Pathway Structure with Permutation Testing .	94
3.5.3.5	Metapackage to Install iGraph Functions	94
4	Synthetic Lethal Analysis of Gene Expression Data	95
4.1	Synthetic Lethal Genes in Breast Cancer	96
4.1.1	Synthetic Lethal Pathways in Breast Cancer	98
4.1.2	Expression Profiles of Synthetic Lethal Partners	99
4.1.2.1	Subgroup Pathway Analysis	102
4.2	Comparing Synthetic Lethal Gene Candidates	105
4.2.1	Primary siRNA Screen Candidates	105
4.2.2	Comparison with Correlation	106
4.2.3	Comparison with Primary Screen Viability	108
4.2.4	Comparison with Secondary siRNA Screen Validation	109
4.2.5	Comparison to Primary Screen at Pathway Level	111
4.2.5.1	Resampling Genes for Pathway Enrichment	113
4.2.6	Integrating Synthetic Lethal Pathways and Screens	116
4.3	Metagene Analysis	118
4.3.1	Pathway Expression	119
4.3.2	Somatic Mutation	121
4.3.3	Synthetic Lethal Pathway Metagenes	125
4.3.4	Synthetic Lethality in Breast Cancer	126
4.4	Replication in Stomach Cancer	127
4.5	Discussion	128
4.5.1	Strengths of the SLIPT Methodology	128
4.5.2	Synthetic Lethal Pathways for E-cadherin	129
4.5.3	Replication and Validation	131
4.5.3.1	Integration with short interfering RNA (siRNA) Screening	131

4.5.3.2	Replication across Tissues	132
4.6	Summary	132
5	Synthetic Lethal Pathway Structure	134
5.1	Synthetic Lethal Genes in Reactome Pathways	134
5.1.1	The PI3K/AKT Pathway	135
5.1.2	The Extracellular Matrix	137
5.1.3	G Protein Coupled Receptors	140
5.1.4	Gene Regulation and Translation	140
5.2	Network Analysis of Synthetic Lethal Genes	141
5.2.1	Gene Connectivity and Vertex Degree	142
5.2.2	Gene Importance and Centrality	143
5.2.2.1	Information Centrality	143
5.2.2.2	PageRank Centrality	145
5.3	Relationships between Synthetic Lethal Genes	147
5.3.1	Hierarchical Pathway Structure	147
5.3.1.1	Contextual Hierarchy of PI3K	147
5.3.1.2	Testing Contextual Hierarchy of Synthetic Lethal Genes	147
5.3.2	Upstream or Downstream Synthetic Lethality	151
5.3.2.1	Measuring Structure of Candidates within PI3K . . .	151
5.3.2.2	Resampling for Synthetic Lethal Pathway Structure .	153
5.4	Discussion	155
5.5	Summary	157
6	Simulation and mMdelling of Synthetic Lethal Pathways	158
6.1	Synthetic Lethal Detection Methods	159
6.1.1	Performance of SLIPT and χ^2 across Quantiles	160
6.1.1.1	Correlated Query Genes affects Specificity	163
6.1.2	Alternative Synthetic Lethal Detection Strategies	165
6.1.2.1	Correlation for Synthetic Lethal Detection	166
6.1.2.2	Testing for Bimodality with BiSEp	167
6.2	Simulations with Graph Structures	168
6.2.1	Performance over Graph Structures	169
6.2.1.1	Simple Graph Structures	169
6.2.1.2	Constructed Graph Structures	172
6.2.2	Performance with Inhibitions	174
6.2.3	Synthetic Lethality across Graph Structures	180
6.2.4	Performance within a Simulated Human Genome	183
6.3	Simulations in More Complex Graph Structures	188
6.3.1	Simulations over Pathway-based Graphs	189
6.3.2	Pathway Structures in a Simulated Human Genome	191
6.4	Discussion	194
6.4.1	Simulation Procedure	194
6.4.2	Comparing Methods with Simulated Data	195
6.4.3	Design and Performance of SLIPT	196
6.4.4	Simulations from Graph Structures	198

6.5	Summary	199
7	Discussion	201
7.1	Synthetic Lethality and <i>CDH1</i> Biology	201
7.1.1	Established Functions of <i>CDH1</i>	202
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer	202
7.2	Significance	203
7.2.1	Synthetic Lethality in the Genomic Era	203
7.2.2	Clinical Interventions based on Synthetic Lethality	205
7.3	Future Directions	206
7.4	Conclusions	208
	Bibliography	210
A	Sample Quality	234
A.1	Sample Correlation	234
A.2	Replicate Samples in The Cancer Genome Atlas (TCGA) Breast	236
B	Software Used for Thesis	240
C	Mutation Analysis in Breast Cancer	249
C.1	Synthetic Lethal Genes and Pathways	249
C.2	Synthetic Lethal Expression Profiles	250
C.3	Comparison to Primary Screen	253
C.3.1	Resampling Analysis	255
C.4	Compare Synthetic Lethal Interaction Prediction Tool (SLIPT) genes .	257
C.5	Metagene Analysis	259
C.6	Expression of Somatic Mutations	260
C.7	Metagene Expression Profiles	263
D	Intrinsic Subtyping	266
E	Stomach Expression Analysis	268
E.1	Synthetic Lethal Genes and Pathways	268
E.2	Comparison to Primary Screen	272
E.2.1	Resampling Analysis	274
E.3	Metagene Analysis	276
F	Synthetic Lethal Genes in Pathways	277
G	Pathway Connectivity for Mutation SLIPT	285
H	Information Centrality for Gene Essentiality	289
I	Pathway Structure for Mutation SLIPT	292
J	Performance of SLIPT and χ^2	297
J.1	Correlated Query Genes affects Specificity	303

K Simulations on Graph Structures	309
K.0.1 Simulations from Inhibiting Graph Structures	310
K.1 Simulation across Graph Structures	313
K.2 Simulations from Complex Graph Structures	317
K.2.1 Simulations from Complex Inhibiting Graphs	320
K.3 Simulations from Pathway Graph Structures	326

List of Figures

1.1	Synthetic genetic interactions	14
1.2	Synthetic lethality in cancer	18
2.1	Read count density	44
2.2	Read count sample mean	44
3.1	Framework for synthetic lethal prediction	60
3.2	Synthetic lethal prediction adapted for mutation	61
3.3	A model of synthetic lethal gene expression	63
3.4	Modelling synthetic lethal gene expression	64
3.5	Synthetic lethality with multiple genes	65
3.6	Simulating gene function	67
3.7	Simulating synthetic lethal gene function	67
3.8	Simulating synthetic lethal gene expression	68
3.9	Performance of binomial simulations	70
3.10	Comparison of statistical performance	70
3.11	Performance of multivariate normal simulations	72
3.12	Simulating expression with correlated gene blocks	74
3.13	Simulating expression with correlated gene blocks	75
3.14	Synthetic lethal prediction across simulations	76
3.15	Performance with correlations	77
3.16	Comparison of statistical performance with correlation structure	78
3.17	Performance with query correlations	79
3.18	Statistical evaluation of directional criteria	81
3.19	Performance of directional criteria	82
3.20	Simulated graph structures	86
3.21	Simulating expression from a graph structure	87
3.22	Simulating expression from graph structure with inhibitions	88
3.23	Demonstration of violin plots with custom features	91
3.24	Demonstration of annotated heatmap	91
3.25	Simulating graph structures	93
4.1	Synthetic lethal expression profiles of analysed samples	101
4.2	Comparison of SLIPT to siRNA	105
4.3	Compare SLIPT and siRNA genes with correlation	106
4.4	Compare SLIPT and siRNA genes with correlation	107
4.5	Compare SLIPT and siRNA genes with viability	108

4.6	Compare SLIPT genes with siRNA viability	109
4.7	Resampled intersection of SLIPT and siRNA candidates	113
4.8	Pathway metagene expression profiles	120
4.9	Expression profiles for constituent genes of PI3K	122
4.10	Expression profiles for estrogen receptor related genes	123
4.11	Somatic mutation against the PI3K metagene	124
5.1	synthetic lethality in the PI3K cascade	136
5.2	synthetic lethality in Elastic Fibre Formation	138
5.3	Synthetic lethality in Fibrin Clot Formation	139
5.4	Synthetic lethality and vertex degree	142
5.5	Synthetic lethality and centrality	145
5.6	Synthetic lethality and PageRank	146
5.7	Hierarchical structure of PI3K	148
5.8	Hierarchy score in PI3K against synthetic lethality in PI3K	149
5.9	Structure of synthetic lethality in PI3K	150
5.10	Structure of synthetic lethality resampling in PI3K	152
6.1	Performance of χ^2 and SLIPT across quantiles	161
6.2	Performance of χ^2 and SLIPT across quantiles with more genes	162
6.3	Performance of χ^2 and SLIPT across quantiles with query correlation .	163
6.4	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	164
6.5	Performance of negative correlation and SLIPT	167
6.6	Simple graph structures	170
6.7	Performance of simulations on a simple graph	171
6.8	Performance of simulations is similar in simple graphs	172
6.9	Performance of simulations on a pathway	173
6.10	Performance of simulations on a simple graph with inhibition	175
6.11	Performance is higher on a simple inhibiting graph	177
6.12	Performance of simulations on a constructed graph with inhibition . . .	178
6.13	Performance is affected by inhibition in graphs	179
6.14	Detection of synthetic lethality within a graph structure	181
6.15	Performance of simulations including a simple graph	185
6.16	Performance on a simple graph improves with more genes	186
6.17	Performance on an inhibiting graph improves with more genes	187
6.18	Performance of simulations on the PI3K cascade	190
6.19	Performance of simulations including the PI3K cascade	192
6.20	Performance on pathways improves with more genes	193
A.1	Correlation profiles of removed samples	234
A.2	Correlation analysis and sample removal	235
A.3	Replicate excluded samples	236
A.4	Replicate samples with all remaining	237
A.5	Replicate samples with some excluded	238
C.1	Synthetic lethal expression profiles of analysed samples	251

C.2	Comparison of mtSLIPT to siRNA	253
C.3	Compare mtSLIPT and siRNA genes with correlation	257
C.4	Compare mtSLIPT and siRNA genes with correlation	257
C.5	Compare mtSLIPT and siRNA genes with siRNA viability	258
C.6	Somatic mutation against PIK3CA metagene	260
C.7	Somatic mutation against PI3K protein	261
C.8	Somatic mutation against AKT protein	262
C.9	Pathway metagene expression profiles	263
C.10	Expression profiles for p53 related genes	264
C.11	Expression profiles for BRCA related genes	265
E.1	Synthetic lethal expression profiles of stomach samples	270
E.2	Comparison of SLIPT in stomach to siRNA	272
F.1	Synthetic lethality in the PI3K/AKT pathway	277
F.2	Synthetic lethality in the PI3K/AKT pathway in cancer	278
F.3	Synthetic lethality in the Extracellular Matrix	279
F.4	Synthetic lethality in the GPCRs	280
F.5	Synthetic lethality in the GPCR Downstream	281
F.6	Synthetic lethality in the Translation Elongation	282
F.7	Synthetic lethality in the Nonsense-mediated Decay	283
F.8	Synthetic lethality in the 3' UTR	284
G.1	Synthetic lethality and vertex degree	285
G.2	Synthetic lethality and centrality	286
G.3	Synthetic lethality and PageRank	287
H.1	Information centrality distribution	291
I.1	Synthetic lethality and heirarchy score in PI3K	292
I.2	Heirarchy score in PI3K against synthetic lethality in PI3K	293
I.3	Structure of synthetic lethality in PI3K	293
I.4	Structure of synthetic lethality resampling	294
J.1	Performance of χ^2 and SLIPT across quantiles	297
J.2	Performance of χ^2 and SLIPT across quantiles	299
J.3	Performance of χ^2 and SLIPT across quantiles with more genes	301
J.4	Performance of χ^2 and SLIPT across quantiles with query correlation	303
J.5	Performance of χ^2 and SLIPT across quantiles with query correlation	305
J.6	Performance of χ^2 and SLIPT across quantiles with query correlation and more genes	307
K.1	Performance of simulations on a simple graph	309
K.2	Performance of simulations on an inhibiting graph	310
K.3	Performance of simulations on a constructed graph with inhibition	311
K.4	Performance of simulations on a constructed graph with inhibition	312
K.5	Detection of synthetic lethality within a graph structure	313
K.6	Detection of synthetic lethality within an inhibiting graph	315

K.7	Detection of synthetic lethality within an inhibiting graph	316
K.8	Performance of simulations on a branching graph	317
K.9	Performance of simulations on a complex graph	318
K.10	Performance of simulations on a large graph	319
K.11	Performance of simulations on a branching graph with inhibition	320
K.12	Performance of simulations on a branching graph with inhibition	321
K.13	Performance of simulations on a complex graph with inhibition	322
K.14	Performance of simulations on a complex graph with inhibition	323
K.15	Performance of simulations on a large constructed graph with inhibition	324
K.16	Performance of simulations on a large constructed graph with inhibition	325
K.17	Performance of simulations on the $G_{\alpha i}$ signalling pathway	326
K.18	Performance of simulations including the $G_{\alpha i}$ signalling pathway	327

List of Tables

1.1	Methods for predicting genetic interactions	23
1.2	Methods for predicting synthetic lethality in cancer	23
1.3	Methods used by Wu <i>et al.</i> (2014)	25
2.1	Excluded samples by batch and clinical characteristics.	43
2.2	Computers used during thesis	53
2.3	Linux utilities and applications used during thesis	54
2.4	R installations used during thesis	55
2.5	R Packages used during thesis	55
2.6	R packages developed during thesis	57
4.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from SLIPT	97
4.2	Pathways for <i>CDH1</i> partners from SLIPT	99
4.3	Pathways for clusters of <i>CDH1</i> partners from SLIPT	103
4.4	ANOVA for synthetic lethality and correlation with <i>CDH1</i>	107
4.5	Comparing SLIPT genes against secondary siRNA screen	110
4.6	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	112
4.7	Pathways for <i>CDH1</i> partners from SLIPT	115
4.8	Pathways for <i>CDH1</i> partners from SLIPT and siRNA primary screen	117
4.9	Candidate synthetic lethal metagenes against <i>CDH1</i> from SLIPT	126
5.1	ANOVA for synthetic lethality and vertex degree	143
5.2	ANOVA for synthetic lethality and information centrality	145
5.3	ANOVA for synthetic lethality and PageRank centrality	147
5.4	ANOVA for synthetic lethality and PI3K hierarchy	150
5.5	Resampling for pathway structure of synthetic lethal detection methods	154
B.1	Complete list of R packages used during this thesis	240
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT	249
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT	250
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT	252
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA	254
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT	255
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	256
C.7	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT	259
D.1	Comparison of intrinsic subtypes	266

E.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer	268
E.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	269
E.3	Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT	271
E.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA	273
E.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer	274
E.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA	275
E.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer	276
G.1	ANOVA for synthetic lethality and vertex degree	288
G.2	ANOVA for synthetic lethality and information centrality	288
G.3	ANOVA for synthetic lethality and PageRank centrality	288
H.1	Information centrality for genes and molecules in the Reactome network	290
I.1	ANOVA for synthetic lethality and PI3K hierarchy	292
I.2	Resampling for pathway structure of synthetic lethal detection methods	294

Glossary

centrality	A network metric which identifies important <i>vertices</i> .
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
essential	A gene which is required to be functional or expressed for a cell or organism to be viable, grow or develop.
gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
information centrality	A network <i>centrality</i> metric which uses the impact of removing a <i>vertex or node</i> on connections in the network.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutation	A change in DNA sequence that disrupts gene function.
PageRank centrality	A network <i>centrality</i> metric which uses eigenvectors with a scaling factor (Brin and Page, 1998).
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.

vertex degree	A network metric of connectivity of vertices which uses the number of edges connected to each vertex or node .
vertex or node	An element of a graph structure or network.

Acronyms

ANOVA	Analysis of Variance.
GPCR	G Crotein Coupled Receptor.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NMD	Nonsense-Mediated Decay.
PI3K	Phosphoinositide 3-kinase.
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
TCGA	The Cancer Genome Atlas (genomics project).
UTR	Untranslated Region (of mRNA).

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Appendix F

Synthetic Lethal Genes in Pathways

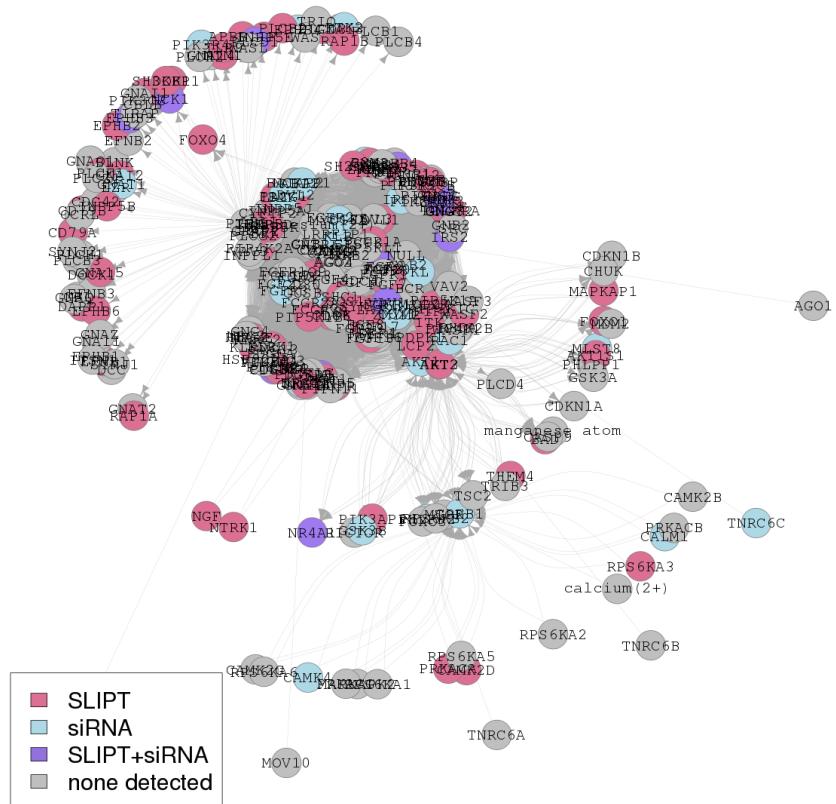


Figure F.1: **Synthetic lethality in the PI3K/AKT pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates, coloured as shown in the legend.

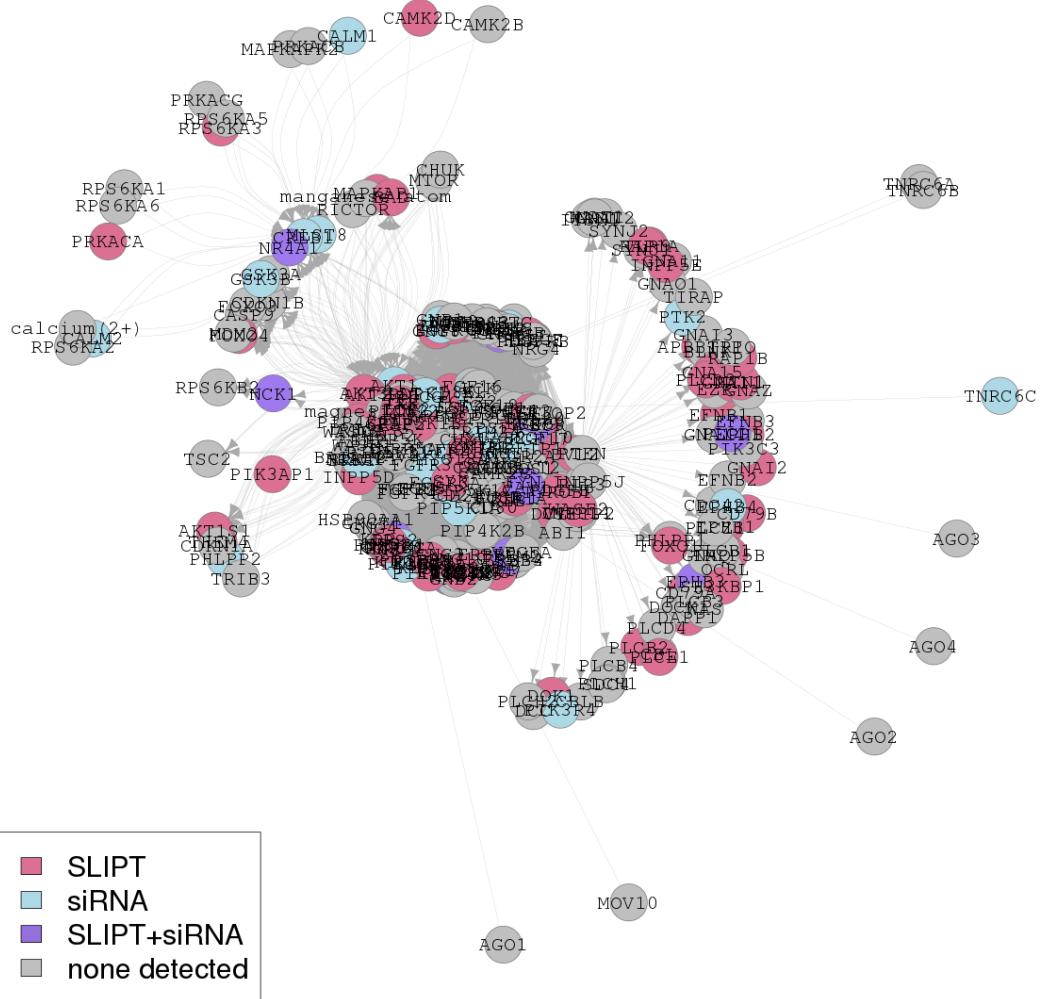


Figure F.2: Synthetic lethality in the PI3K/AKT pathway in cancer. The Reactome PI3K/AKT in cancer pathway with synthetic lethal candidates, coloured as shown in the legend.

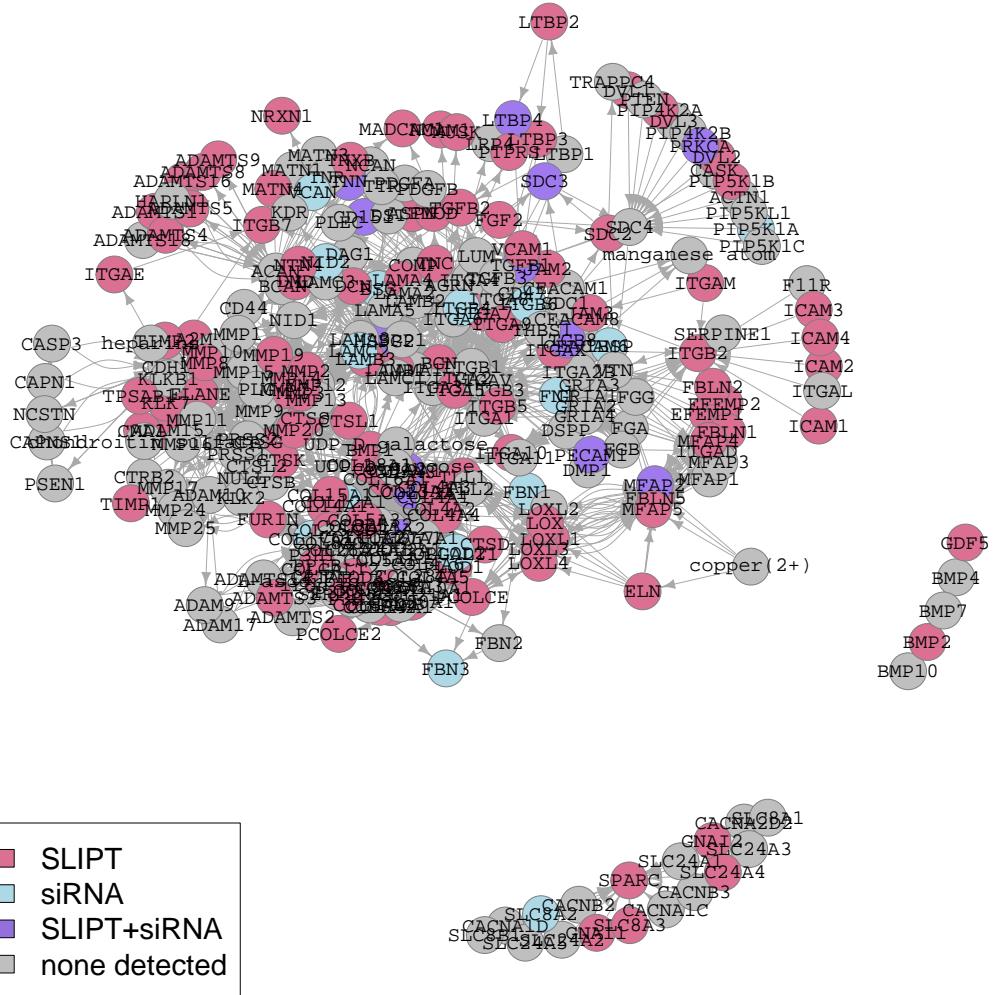


Figure F.3: Synthetic lethality in the Extracellular Matrix. The Reactome Extracellular Matrix pathway with synthetic lethal candidates, coloured as shown in the legend.

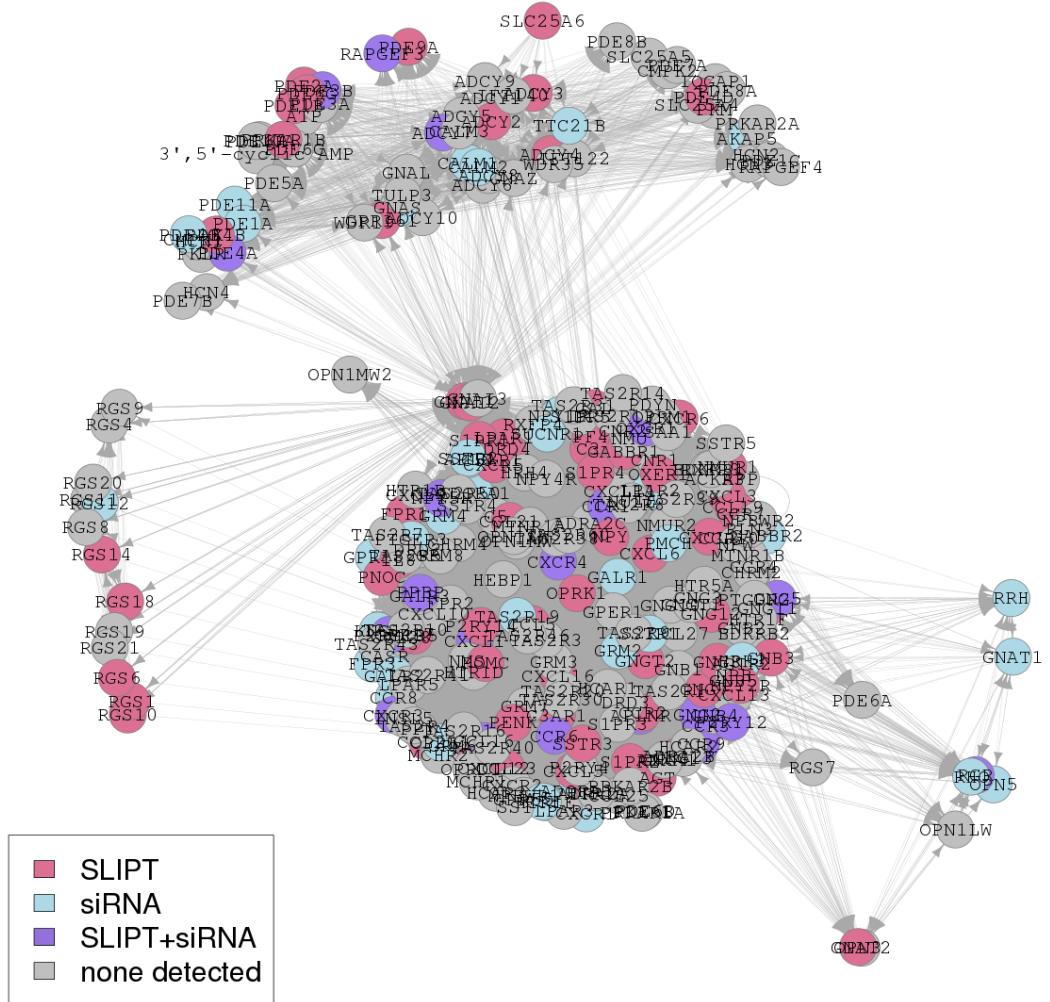


Figure F.4: **Synthetic lethality in the GPCRs.** The Reactome $G_{\alpha i}$ pathway with synthetic lethal candidates, coloured as shown in the legend.

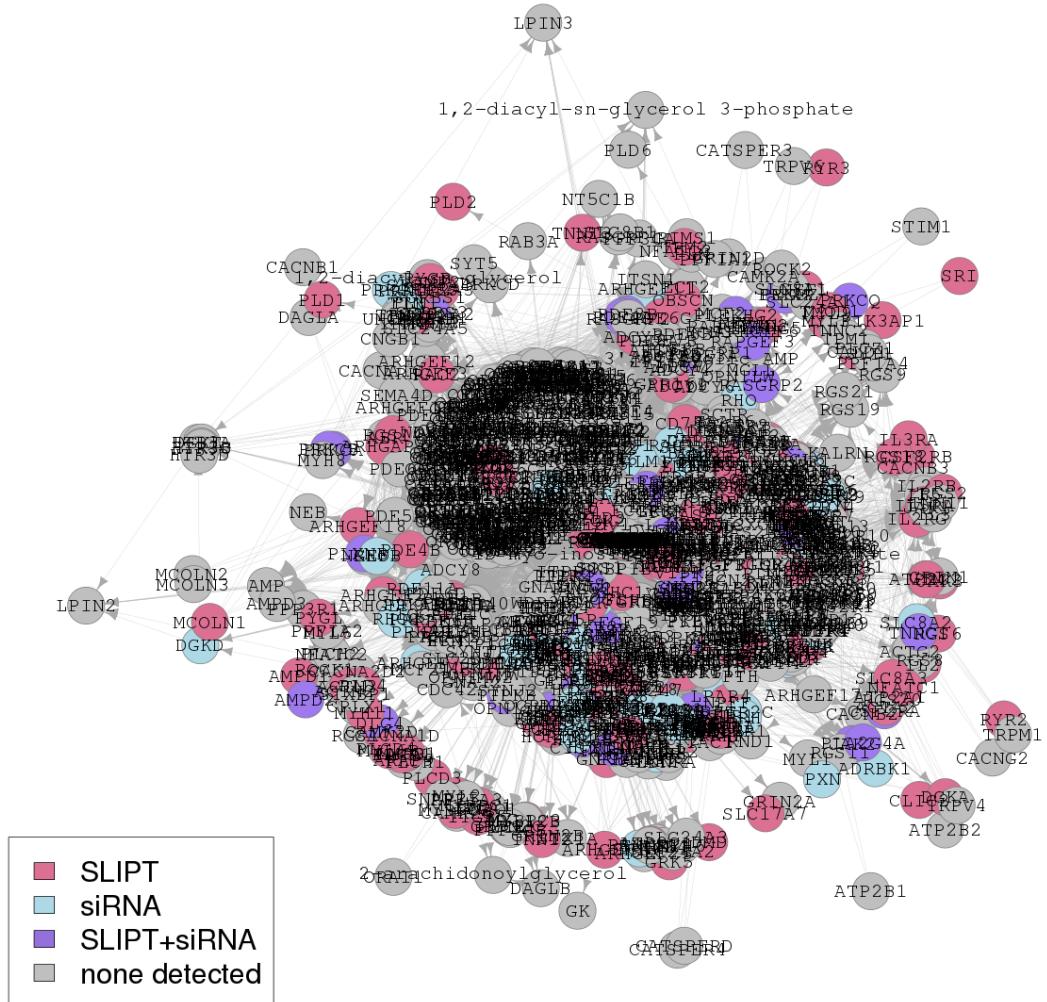


Figure F.5: **Synthetic lethality in the GPCR Downstream.** The Reactome G protein coupled receptor (GPCR) Downstream pathway with synthetic lethal candidates, coloured as shown in the legend.

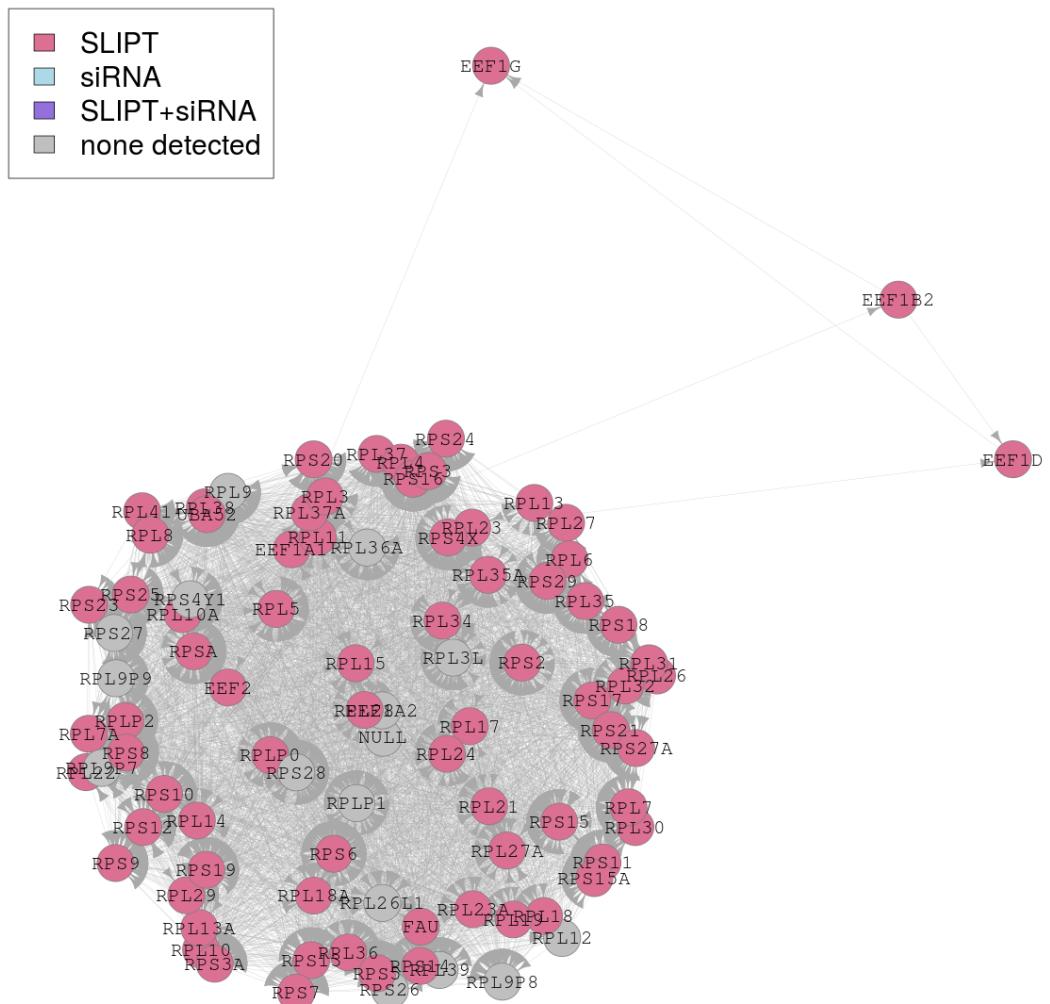


Figure F.6: **Synthetic lethality in the Translation Elongation**. The Reactome Translation Elongation pathway with synthetic lethal candidates, coloured as shown in the legend.

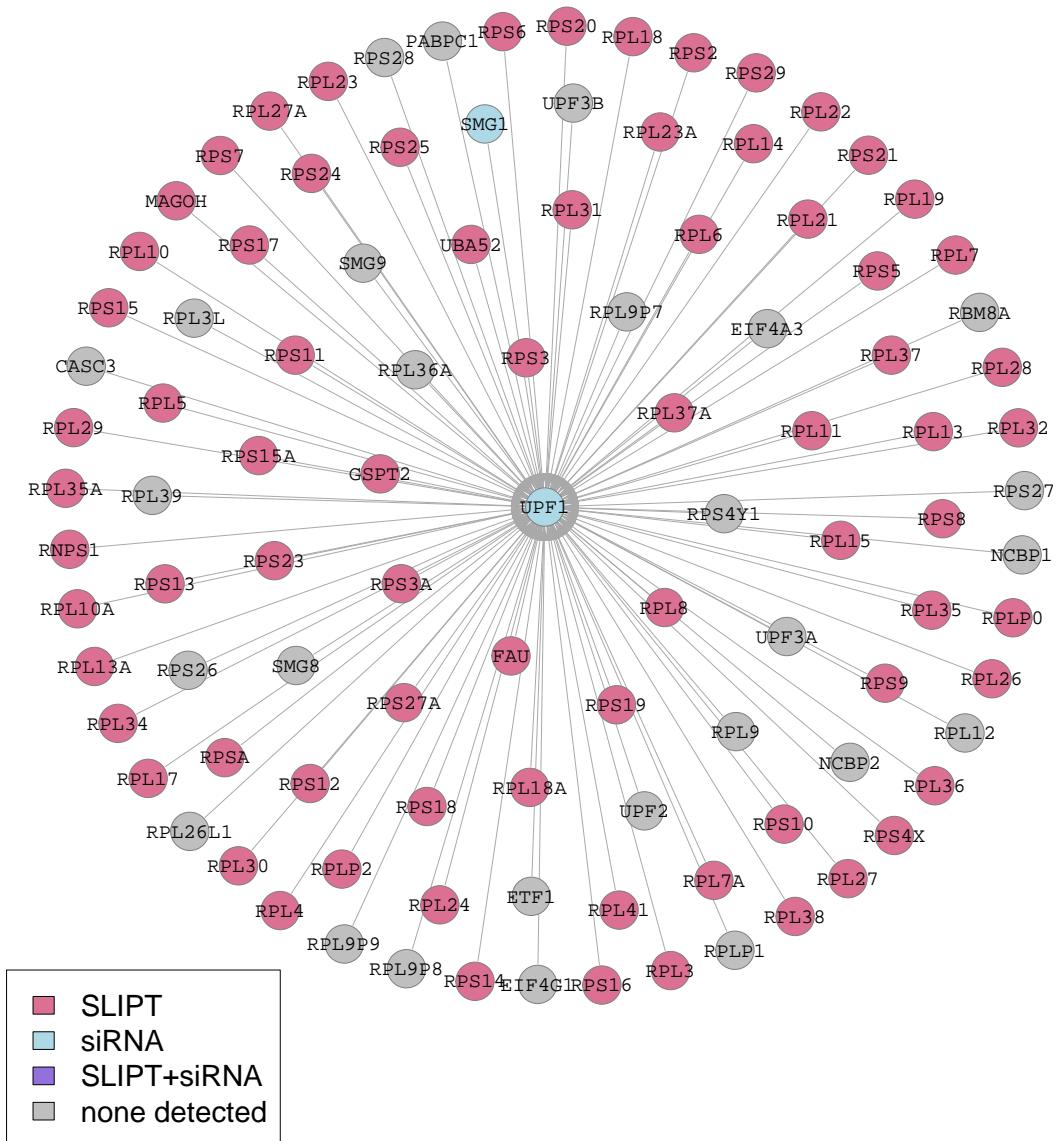


Figure F.7: Synthetic lethality in the Nonsense-mediated Decay. The Reactome nonsense-mediated decay (NMD) pathway with synthetic lethal candidates, coloured as shown in the legend.

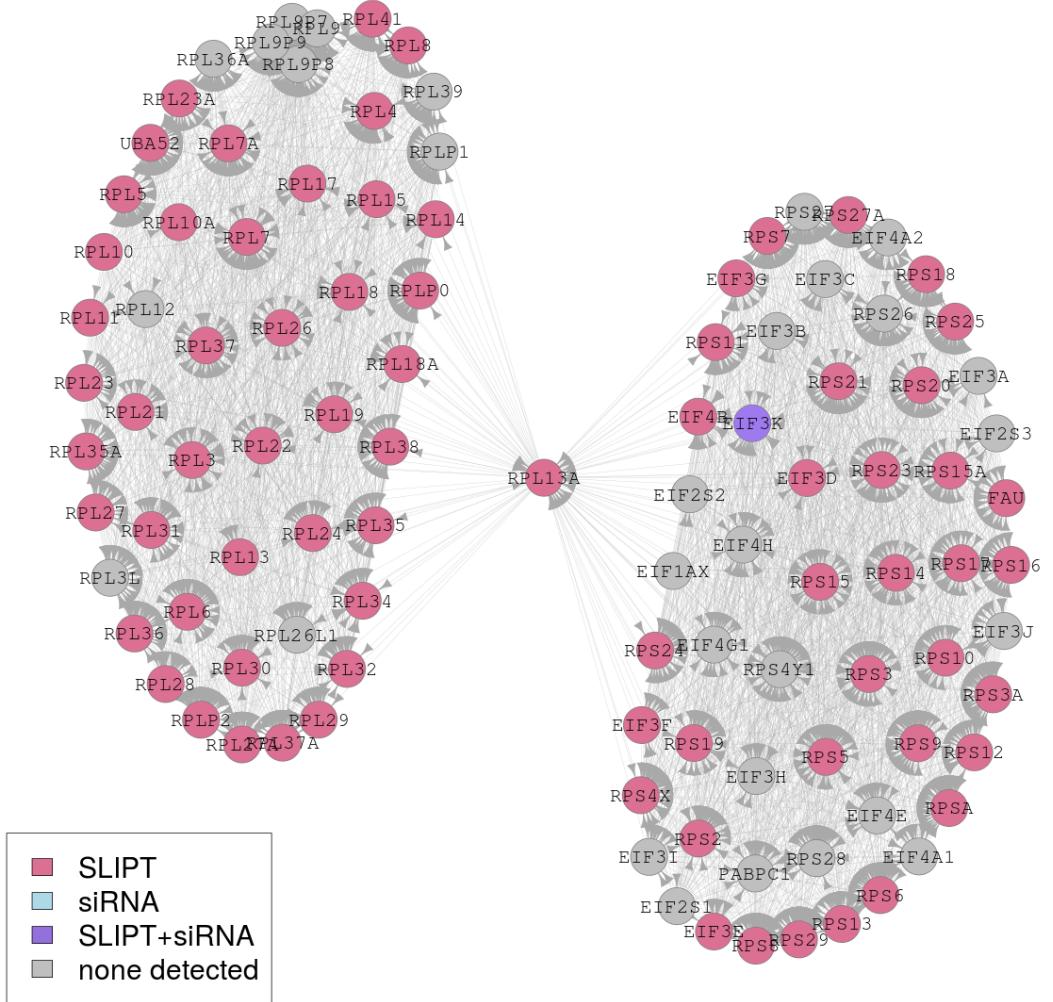


Figure F.8: **Synthetic lethality in the 3' UTR.** The Reactome 3' untranslated region (UTR) pathway with synthetic lethal candidates, coloured as shown in the legend.

Appendix G

Pathway Connectivity for Mutation SLIPT

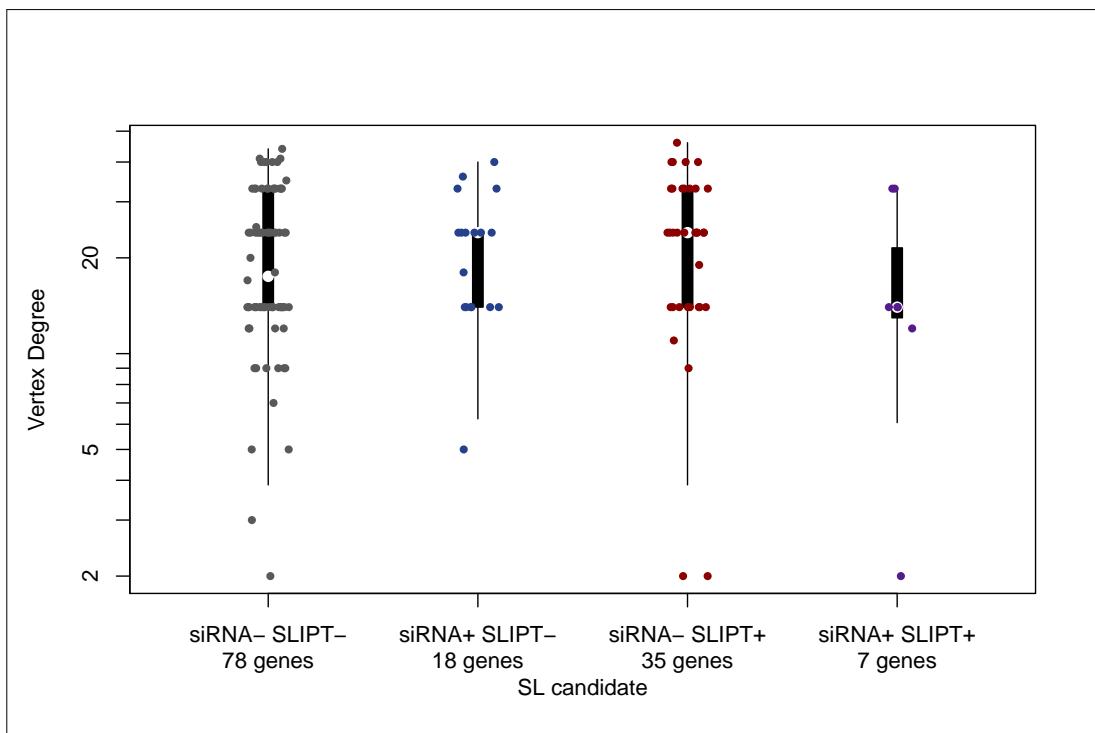


Figure G.1: **Synthetic lethality and vertex degree.** The number of connected genes (vertex degree) was compared (on a log-scale across genes detected by mtSLIPT and siRNA screening in the Reactome phosphoinositide 3-kinase (PI3K) cascade pathway. There were very few differences in vertex degree between the groups, although genes detected by siRNA included those with the fewest connections.

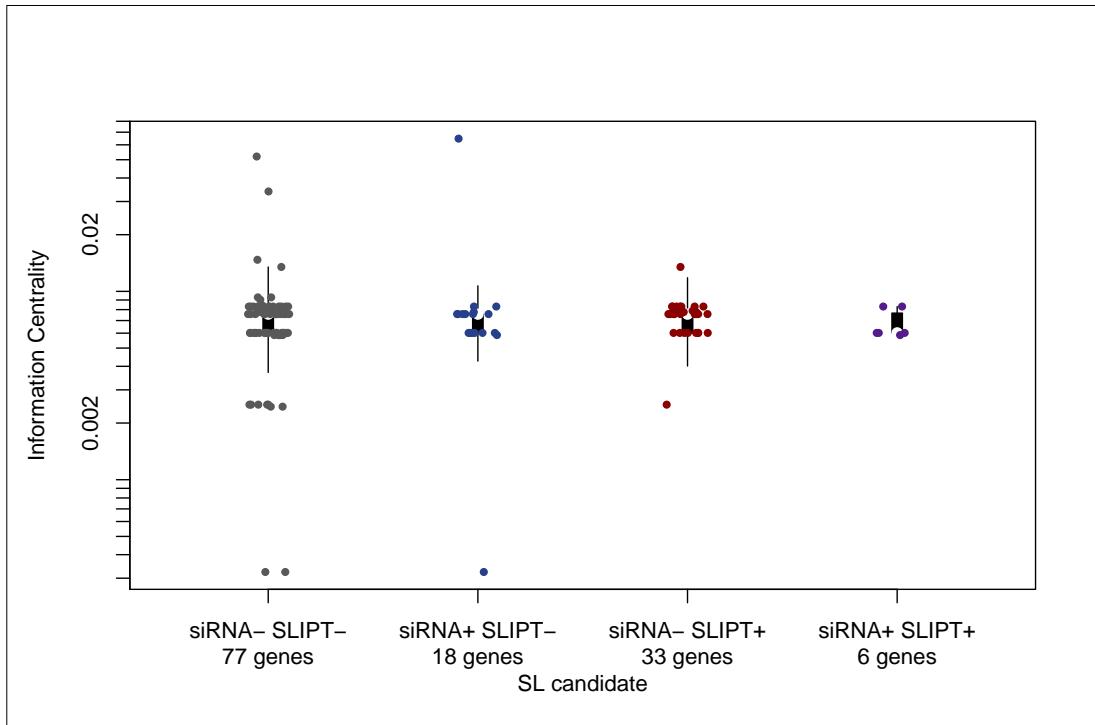


Figure G.2: **Synthetic lethality and centrality.** The information centrality was compared (on a log-scale across genes detected by [mtSLIPT](#) and [siRNA](#) screening in the Reactome PI3K cascade pathway. Genes detected by [mtSLIPT](#) or [siRNA](#) did not have higher connectivity than genes not detected by either approach. The gene with the highest centrality was detected by [siRNA](#).

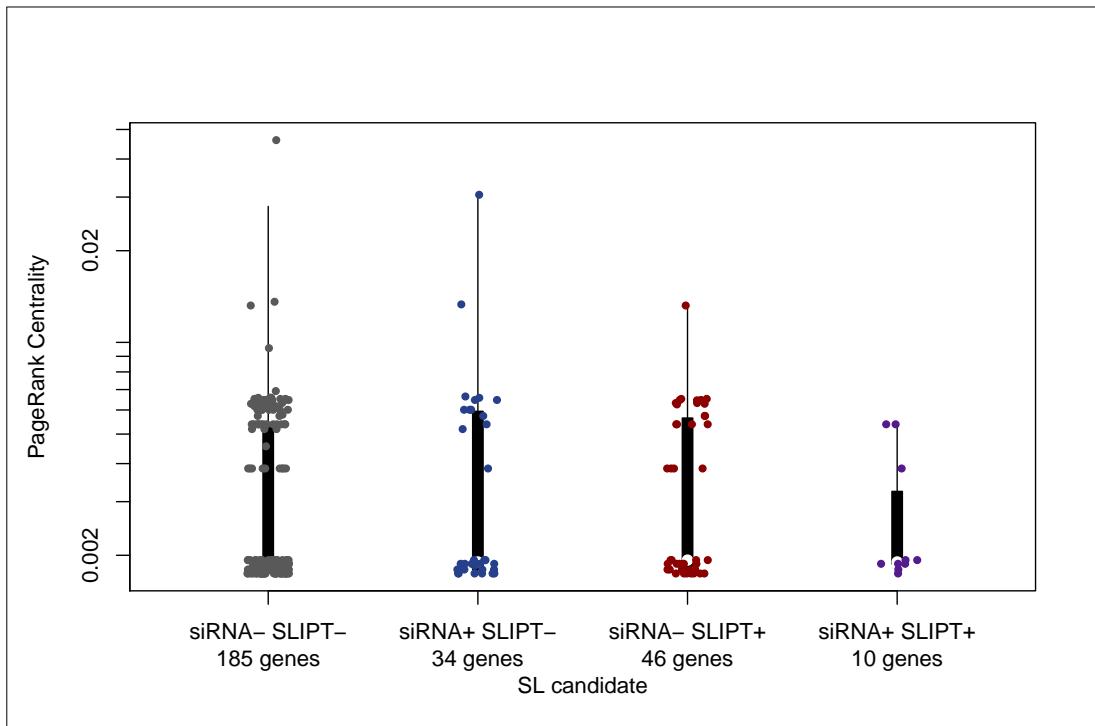


Figure G.3: Synthetic lethality and PageRank. The PageRank centrality was compared (on a log-scale across genes detected by [mtSLIPT](#) and [siRNA](#) screening in the Reactome PI3K cascade pathway. Genes detected by [siRNA](#) had a more restricted range of centrality values than other genes not detected by either approach, although these groups also had fewer genes.

Table G.1: ANOVA for synthetic lethality and vertex degree

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	15	15.50	0.0134	0.9084
mtSLIPT	1	196	195.94	0.1689	0.6825
siRNA×mtSLIPT	1	9	9.17	0.0079	0.9294

Analysis of variance for [vertex degree](#) against [synthetic lethal](#) detection approaches (with an interaction term)

Table G.2: ANOVA for synthetic lethality and information centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.000256	0.0002561	0.1851	0.6685
mtSLIPT	1	0.003225	0.0032247	2.3308	0.1318
siRNA×mtSLIPT	1	0.001238	0.0012385	0.8952	0.3476

Analysis of variance for [information centrality](#) against [synthetic lethal](#) detection approaches (with an interaction term)

Table G.3: ANOVA for synthetic lethality and PageRank centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.0002038	2.0385×10^{-4}	1.1423	0.2892
mtSLIPT	1	0.0000208	2.0752×10^{-5}	0.1163	0.7342
siRNA×mtSLIPT	1	0.0000137	1.3743×10^{-5}	0.0770	0.7823

Analysis of variance for [PageRank centrality](#) against [synthetic lethal](#) detection approaches (with an interaction term)

Appendix H

Information Centrality for Gene Essentiality

Network structure could be used to analyse gene function. This has been performed to investigate network properties of a network constructed from Reactome pathways (Croft *et al.*, 2014) imported via Pathway Commons with Paxtools (Cerami *et al.*, 2011; Demir *et al.*, 2013). Information centrality, which has been proposed as a measure of gene essentiality, was calculated as performed by Kranthi *et al.* (2013) using the efficiency and shortest path between each pair of nodes in the network before and after a node of interest is removed to test the importance of a node to network connectivity. Reactome contains substrates and cofactors in addition to genes or proteins. In support of centrality as a measure of essentiality, a number of nodes with the highest centrality (shown in Table H.1) were essential nutrients including Mg²⁺, Ca²⁺, Zn²⁺, and Fe. In addition, there were genes important in development of epithelial tissues and breast cancer such as *IL8*, *GATA3*, and *CTNNB1* detected with relatively high information centrality.

Table H.1: Information centrality for genes and molecules in the Reactome network

Node	Centrality
<i>ZNF473</i>	0.0510
Magnesium (Mg^{2+})	0.0082
<i>XBP1</i>	0.0053
Calcium (Ca^{2+})	0.0050
Zinc (Zn^{2+})	0.0048
Iron atom (Fe)	0.0041
<i>FMN</i>	0.0040
<i>AGT</i>	0.0037
<i>HSP90AA1</i>	0.0029
Phosphatidyl-L-serine	0.0029
<i>P2RX7</i>	0.0026
<i>PANX1</i>	0.0024
<i>NCAM1</i>	0.0022
<i>NUDT1</i>	0.0021
<i>PLAUR</i>	0.0020
<i>IL8</i>	0.0020
<i>HSPA8</i>	0.0019
<i>TYROBP</i>	0.0019
<i>CASP3</i>	0.0017
<i>GNAL</i>	0.0015
<i>CBLB</i>	0.0015
<i>HBB</i>	0.0014
<i>GATA4</i>	0.0013
<i>TGS1</i>	0.0013
<i>CTNNB1</i>	0.0012

Highest information centrality for genes (proteins), cofactors, and minerals in the Reactome network

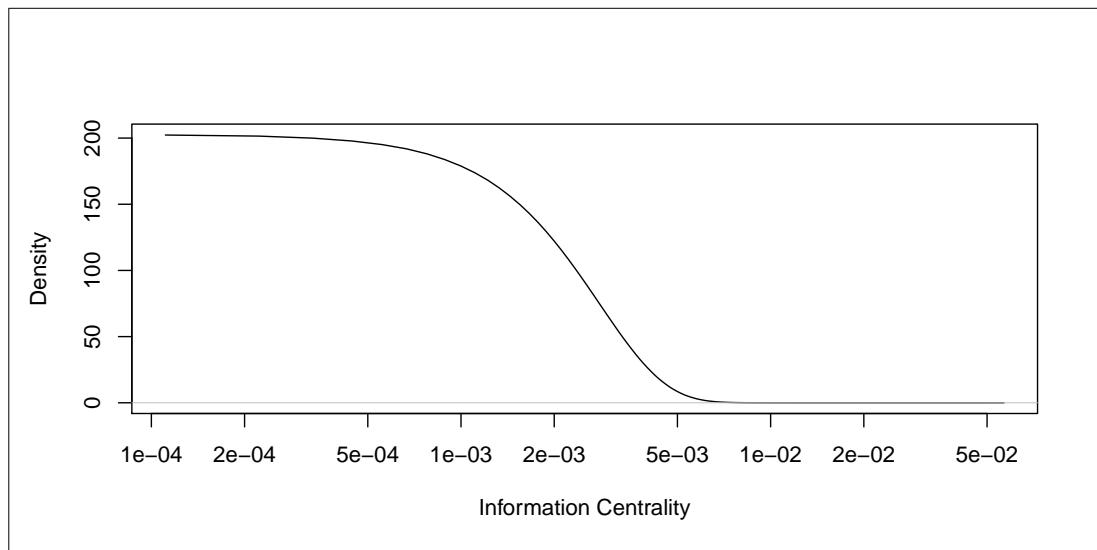


Figure H.1: **Information centrality distribution.** [Information centrality](#) in the Reactome network for nodes, including genes/proteins and other biomolecules.

Appendix I

Pathway Structure for Mutation SLIPT

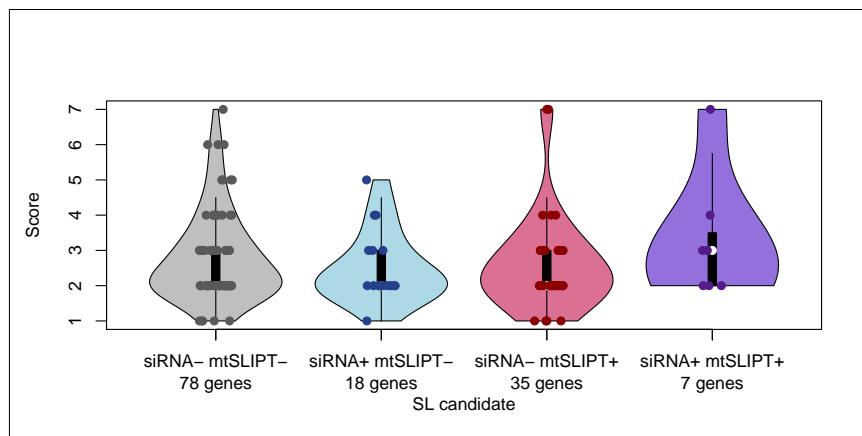


Figure I.1: **Synthetic lethality and heirarchy score in PI3K.** The hierarchical distance scores were similarly distributed across **mtSLIPT** and **siRNA** genes. Genes detected by both methods had a higher (downstream) median than either group.

Table I.1: ANOVA for synthetic lethality and PI3K hierarchy

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.001	0.00070	0.0004	0.9841
mtSLIPT	1	0.007	0.0066	0.0040	0.9496
siRNA×mtSLIPT	1	3.906	3.9056	2.3829	0.1250

Analysis of variance for **PI3K** hierarchy score against **synthetic lethal** detection approaches (with an interaction term)

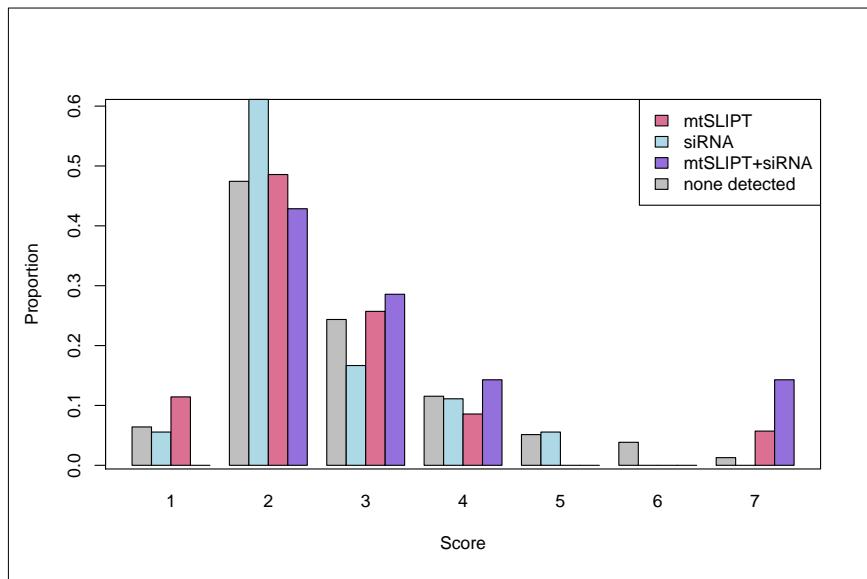


Figure I.2: Hierarchy score in PI3K against synthetic lethality in PI3K. The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.

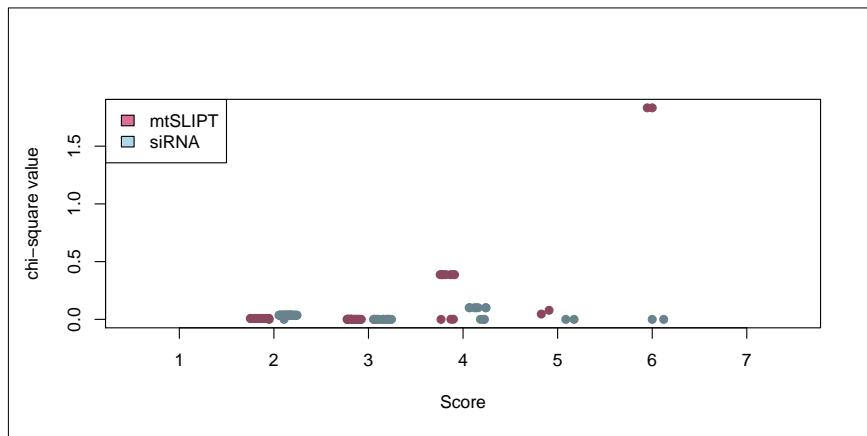


Figure I.3: Structure of synthetic lethality in PI3K. The number of mtSLIPT and siRNA genes against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities. The number of mtSLIPT and siRNA genes upstream or downstream of each gene in the Reactome PI3K pathway were tested (by the χ^2 -test). These were plotted as a split jitter stripchart against the hierarchical distance scores showing no significant tendency for either method to either of the pathway upstream or downstream extremities.

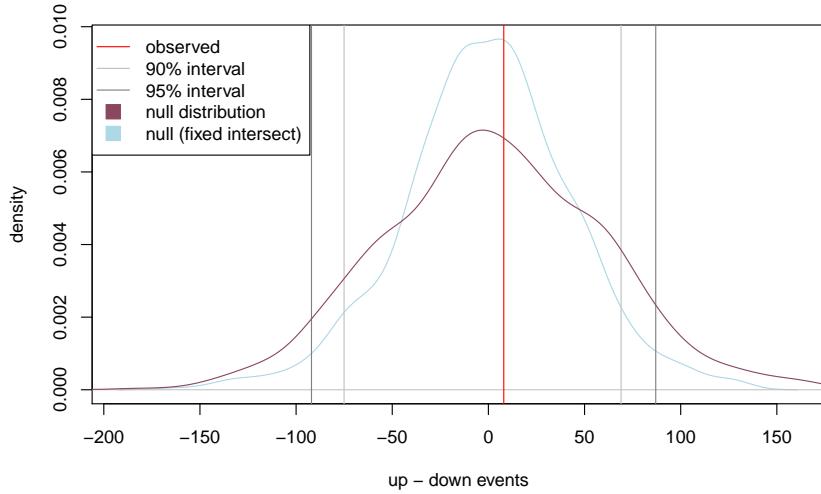


Figure I.4: Structure of synthetic lethality resampling. A null distribution (10,000 iterations) of the siRNA genes upstream or downstream of mtSLIPT genes (shown by the difference) in the PI3K pathway. The observed events (red) were compared to the the distribution (violet) and were not significant. Genes detected by both methods were fixed for the distribution (blue). The genes detected by both approaches were used.

Table I.2: Resampling for pathway structure of synthetic lethal detection methods

Pathway	Graph		States		Observed				Permutation p-value	
	Nodes	Edges	mtSL	siRNA	Up	Down	Up-Down	Up/Down	Up-Down	Down-Up
PI3K Cascade	138	1495	42	25	131	123	8	1.065	0.4473	0.5466
PI3K/AKT Signalling in Cancer	275	12882	56	44	478	440	38	1.086	0.4163	0.5810
G_{αi} Signalling	292	22003	57	58	543	866	-323	0.627	0.9507	0.0488
GPCR downstream	1270	142071	218	160	7632	6500	1132	1.174	0.1707	0.8291
Elastic fibre formation	42	175	16	7	6	7	-1	0.857	0.5512	0.3681
Extracellular matrix	299	3677	81	29	313	347	-34	0.902	0.5762	0.4215
Formation of Fibrin	52	243	11	5	8	19	-11	0.421	0.7993	0.1800
Nonsense-Mediated Decay	103	102	56	2	0	0	0		0.197	0.1373
3'-UTR-mediated translational regulation	107	2860	56	1	52	1	51	52	0.1210	0.8751
Eukaryotic Translation Elongation	92	3746	57	0	0	0	0		0.4952	0.4892

Pathways in the Reactome network tested for structural relationships between mtSLIPT and siRNA genes by resampling. The raw p-value (computed without adjusting for multiple comparisons over pathways) is given for the difference in upstream and downstream paths from mtSLIPT to siRNA gene candidate partners of CDH1 with significant pathways highlighted in bold. Sampling was performed only in the target pathway and shortest paths were computed within it. Loops or paths in either direction that could not be resolved were excluded from the analysis. The gene detected by both mtSLIPT and siRNA (or resampling for them) were included in the analysis and the number of these were fixed to the number observed.