

# Contents

<b>Glossary</b>	<b>xii</b>
<b>Acronyms</b>	<b>xiv</b>
<b>1 Introduction and Literature Review</b>	<b>1</b>
1.1 Cancer Research in the Post-Genomic Era . . . . .	1
1.1.1 Cancer is a Global Health Issue . . . . .	2
1.1.1.1 The Genetics and Molecular Biology of Cancers . . . . .	3
1.1.2 The Genomics Revolution in Cancer Research . . . . .	3
1.1.2.1 High-Throughput Technologies . . . . .	4
1.1.2.2 Bioinformatics and Genomic Data . . . . .	5
1.1.3 Genomics Projects . . . . .	5
1.1.3.1 The Cancer Genome Project . . . . .	6
1.1.3.2 The Cancer Genome Atlas Project . . . . .	6
1.1.4 Genomic Cancer Medicine . . . . .	8
1.1.4.1 Cancer Genes and Driver Mutations . . . . .	8
1.1.4.2 Precision Cancer Medicine . . . . .	9
1.1.4.3 Molecular Diagnostics and Pan-Cancer Medicine . . . . .	9
1.1.4.4 Targeted Therapeutics and Pharmacogenomics . . . . .	10
1.1.5 Systems and Network Biology . . . . .	11
1.2 Synthetic Lethal Cancer Medicine . . . . .	12
1.2.1 Synthetic Lethal Genetic Interactions . . . . .	12
1.2.2 Synthetic Lethal Concepts in Genetics . . . . .	14
1.2.3 Synthetic Lethality in Model Systems . . . . .	14
1.2.3.1 Synthetic Lethal Pathways and Networks . . . . .	15
1.2.3.2 Evolution of Synthetic Lethality . . . . .	15
1.2.4 Synthetic Lethality in Cancer . . . . .	16
1.2.5 Clinical Impact of Synthetic Lethality in Cancer . . . . .	18
1.2.6 High-throughput Screening for Synthetic Lethality . . . . .	19
1.2.6.1 Synthetic Lethal Screens . . . . .	21
1.2.7 Computational Prediction of Synthetic Lethality . . . . .	22
1.2.7.1 Bioinformatics Approaches to Genetic Interactions . . . . .	22
1.2.7.2 Comparative Genomics . . . . .	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	Mutual Exclusivity and Bimodality . . . . .	31
1.2.7.7	Rationale for Further Development . . . . .	33
1.3	E-cadherin as a Synthetic Lethal Target . . . . .	33
1.3.1	The <i>CDH1</i> gene and its Biological Functions . . . . .	33
1.3.1.1	Cytoskeleton . . . . .	34
1.3.1.2	Extracellular and Tumour Micro-environment . . . . .	34
1.3.1.3	Cell-Cell Adhesion and Signalling . . . . .	34
1.3.2	<i>CDH1</i> as a Tumour (and Invasion) Suppressor . . . . .	35
1.3.2.1	Breast Cancers and Invasion . . . . .	35
1.3.3	Hereditary Diffuse Gastric (and Lobular Breast) Cancer . . . . .	35
1.3.4	Cell Line Models of <i>CDH1</i> Null Mutations . . . . .	37
1.4	Summary and Research Direction of Thesis . . . . .	37
1.4.1	Thesis Aims . . . . .	39
<b>2</b>	<b>Methods and Resources</b>	<b>40</b>
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
<b>3</b>	<b>Methods Developed During Thesis</b>	<b>59</b>
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 . . . . .	69
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 . . . . .	81
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 . . . . .	90
3.5.1	Synthetic Lethal Interaction Prediction Tool . . . . .	90
3.5.2	Data Visualisation . . . . .	91
3.5.3	Extensions to the iGraph Package . . . . .	93
3.5.3.1	Sampling Simulated Data from Graph Structures . . . . .	93
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 . . . . .	95
<b>4</b>	<b>Synthetic Lethal Analysis of Gene Expression Data</b>	<b>96</b>
4.1	Synthetic Lethal Genes in Breast Cancer . . . . .	97
4.1.1	Synthetic Lethal Pathways in Breast Cancer . . . . .	98
4.1.2	Expression Profiles of Synthetic Lethal Partners . . . . .	100
4.1.2.1	Subgroup Pathway Analysis . . . . .	103
4.2	Comparing Synthetic Lethal Gene Candidates . . . . .	105
4.2.1	Primary siRNA Screen Candidates . . . . .	105
4.2.2	Comparison with Correlation . . . . .	105
4.2.3	Comparison with Primary Screen Viability . . . . .	108
4.2.4	Comparison with Secondary siRNA Screen Validation . . . . .	110
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 . . . . .	118
4.3	Synthetic Lethal Pathway Metagenes . . . . .	119
4.4	Replication in Stomach Cancer . . . . .	121
4.5	Discussion . . . . .	122
4.5.1	Strengths of the SLIPT Methodology . . . . .	122
4.5.2	Synthetic Lethal Pathways for E-cadherin . . . . .	123
4.5.3	Replication and Validation . . . . .	125
4.5.3.1	Integration with siRNA Screening . . . . .	125
4.5.3.2	Replication across Tissues . . . . .	126
4.6	Summary . . . . .	126

<b>5</b>	<b>Synthetic Lethal Pathway Structure</b>	<b>128</b>
5.1	Synthetic Lethal Genes in Reactome Pathways . . . . .	128
5.1.1	The PI3K/AKT Pathway . . . . .	129
5.1.2	The Extracellular Matrix . . . . .	131
5.1.3	G Protein Coupled Receptors . . . . .	134
5.1.4	Gene Regulation and Translation . . . . .	134
5.2	Network Analysis of Synthetic Lethal Genes . . . . .	136
5.2.1	Gene Connectivity and Vertex Degree . . . . .	137
5.2.2	Gene Importance and Information Centrality . . . . .	138
5.2.3	Gene Importance and PageRank Centrality . . . . .	139
5.3	Relationships between Synthetic Lethal Genes . . . . .	141
5.3.1	Detecting Upstream or Downstream Synthetic Lethality . . . . .	142
5.3.2	Resampling for Synthetic Lethal Pathway Structure . . . . .	143
5.4	Discussion . . . . .	145
5.5	Summary . . . . .	147
<b>6</b>	<b>Simulation and Modelling of Synthetic Lethal Pathways</b>	<b>149</b>
6.1	Synthetic Lethal Detection Methods . . . . .	150
6.1.1	Performance of SLIPT and $\chi^2$ across Quantiles . . . . .	151
6.1.1.1	Correlated Query Genes affects Specificity . . . . .	154
6.1.2	Alternative Synthetic Lethal Detection Strategies . . . . .	156
6.1.2.1	Correlation for Synthetic Lethal Detection . . . . .	157
6.1.2.2	Testing for Bimodality with BiSEp . . . . .	158
6.2	Simulations with Graph Structures . . . . .	159
6.2.1	Performance over Graph Structures . . . . .	160
6.2.1.1	Simple Graph Structures . . . . .	160
6.2.1.2	Constructed Graph Structures . . . . .	163
6.2.2	Performance with Inhibitions . . . . .	165
6.2.3	Synthetic Lethality across Graph Structures . . . . .	171
6.2.4	Performance within a Simulated Human Genome . . . . .	174
6.3	Simulations in More Complex Graph Structures . . . . .	179
6.3.1	Simulations over Pathway-based Graphs . . . . .	180
6.3.2	Pathway Structures in a Simulated Human Genome . . . . .	182
6.4	Discussion . . . . .	185
6.4.1	Simulation Procedure . . . . .	185
6.4.2	Comparing Methods with Simulated Data . . . . .	186
6.4.3	Design and Performance of SLIPT . . . . .	187
6.4.4	Simulations from Graph Structures . . . . .	189
6.5	Summary . . . . .	190
<b>7</b>	<b>Discussion</b>	<b>192</b>
7.1	Synthetic Lethality and <i>CDH1</i> Biology . . . . .	192
7.1.1	Established Functions of <i>CDH1</i> . . . . .	193
7.1.2	The Molecular Role of <i>CDH1</i> in Cancer . . . . .	193
7.2	Significance . . . . .	194
7.2.1	Synthetic Lethality in the Genomic Era . . . . .	194

7.2.2	Clinical Interventions based on Synthetic Lethality . . . . .	196
7.3	Future Directions . . . . .	197
7.4	Conclusions . . . . .	199
	<b>Bibliography</b>	<b>201</b>
<b>A</b>	<b>Sample Quality</b>	<b>225</b>
A.1	Sample Correlation . . . . .	225
A.2	Replicate Samples in TCGA Breast Cancer Data . . . . .	227
<b>B</b>	<b>Software Used for Thesis</b>	<b>231</b>
<b>C</b>	<b>Mutation Analysis in Breast Cancer</b>	<b>240</b>
C.1	Synthetic Lethal Genes and Pathways . . . . .	240
C.2	Synthetic Lethal Expression Profiles . . . . .	243
C.3	Comparison to Primary Screen . . . . .	246
C.3.1	Resampling Analysis . . . . .	248
C.4	Compare SLIPT genes . . . . .	250
<b>D</b>	<b>Metagene Analysis</b>	<b>252</b>
D.1	Pathway Signature Expression . . . . .	252
D.2	Somatic Mutation . . . . .	261
D.3	Synthetic Lethal Reactome Metagenes . . . . .	262
D.4	Expression of Somatic Mutations . . . . .	264
<b>E</b>	<b>Intrinsic Subtyping</b>	<b>267</b>
<b>F</b>	<b>Stomach Expression Analysis</b>	<b>269</b>
F.1	Synthetic Lethal Genes and Pathways . . . . .	269
F.2	Comparison to Primary Screen . . . . .	273
F.2.1	Resampling Analysis . . . . .	275
F.3	Metagene Analysis . . . . .	277
<b>G</b>	<b>Synthetic Lethal Genes in Pathways</b>	<b>278</b>
<b>H</b>	<b>Network Analysis for Mutation SLIPT</b>	<b>285</b>
<b>I</b>	<b>Pathway Structure for Mutation SLIPT</b>	<b>288</b>
<b>J</b>	<b>Performance of SLIPT and <math>\chi^2</math></b>	<b>290</b>
J.1	Correlated Query Genes affects Specificity . . . . .	296
<b>K</b>	<b>Simulations on Graph Structures</b>	<b>302</b>
K.0.1	Simulations from Inhibiting Graph Structures . . . . .	303
K.1	Simulation across Graph Structures . . . . .	306
K.2	Simulations from Complex Graph Structures . . . . .	310
K.2.1	Simulations from Complex Inhibiting Graphs . . . . .	313
K.3	Simulations from Pathway Graph Structures . . . . .	319

# List of Figures

1.1	Synthetic genetic interactions . . . . .	13
1.2	Synthetic lethality in cancer . . . . .	17
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 . . . . .	77
3.15	Performance with correlations . . . . .	78
3.16	Comparison of statistical performance with correlation structure . . . . .	79
3.17	Performance with query correlations . . . . .	80
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 . . . . .	92
3.24	Demonstration of annotated heatmap . . . . .	92
3.25	Simulating graph structures . . . . .	94
4.1	Synthetic lethal expression profiles of analysed samples . . . . .	101
4.2	Comparison of SLIPT with siRNA . . . . .	106
4.3	Comparison of SLIPT and siRNA genes with correlation . . . . .	106
4.4	Comparison of SLIPT and siRNA genes with correlation . . . . .	108
4.5	Comparison of SLIPT and siRNA genes with screen viability . . . . .	109

4.6	Comparison of SLIPT genes with siRNA screen viability . . . . .	109
4.7	Resampled intersection of SLIPT and siRNA candidate genes . . . . .	114
5.1	Synthetic lethality in the PI3K cascade . . . . .	130
5.2	Synthetic lethality in Elastic Fibre Formation . . . . .	132
5.3	Synthetic lethality in Fibrin Clot Formation . . . . .	133
5.4	Synthetic lethality in the GPCRs . . . . .	135
5.5	Synthetic lethality and vertex degree . . . . .	137
5.6	Synthetic lethality and centrality . . . . .	139
5.7	Synthetic lethality and PageRank . . . . .	140
5.8	Structure of synthetic lethality resampling . . . . .	142
6.1	Performance of $\chi^2$ and SLIPT across quantiles . . . . .	152
6.2	Performance of $\chi^2$ and SLIPT across quantiles with more genes . . . . .	153
6.3	Performance of $\chi^2$ and SLIPT across quantiles with query correlation . . . . .	154
6.4	Performance of $\chi^2$ and SLIPT across quantiles with query correlation and more genes . . . . .	155
6.5	Performance of negative correlation and SLIPT . . . . .	158
6.6	Simple graph structures . . . . .	161
6.7	Performance of simulations on a simple graph . . . . .	162
6.8	Performance of simulations is similar in simple graphs . . . . .	163
6.9	Performance of simulations on a pathway . . . . .	164
6.10	Performance of simulations on a simple graph with inhibition . . . . .	166
6.11	Performance is higher on a simple inhibiting graph . . . . .	168
6.12	Performance of simulations on a constructed graph with inhibition . . . . .	169
6.13	Performance is affected by inhibition in graphs . . . . .	170
6.14	Detection of synthetic lethality within a graph structure . . . . .	172
6.15	Performance of simulations including a simple graph . . . . .	176
6.16	Performance on a simple graph improves with more genes . . . . .	177
6.17	Performance on an inhibiting graph improves with more genes . . . . .	178
6.18	Performance of simulations on the PI3K cascade . . . . .	181
6.19	Performance of simulations including the PI3K cascade . . . . .	183
6.20	Performance on pathways improves with more genes . . . . .	184
A.1	Correlation profiles of removed samples . . . . .	225
A.2	Correlation analysis and sample removal . . . . .	226
A.3	Replicate excluded samples . . . . .	227
A.4	Replicate samples with all remaining . . . . .	228
A.5	Replicate samples with some excluded . . . . .	229
C.1	Synthetic lethal expression profiles of analysed samples . . . . .	244
C.2	Comparison of mtSLIPT to short interfering RNA (siRNA) . . . . .	246
C.3	Compare mtSLIPT and siRNA genes with correlation . . . . .	250
C.4	Compare mtSLIPT and siRNA genes with correlation . . . . .	250
C.5	Compare mtSLIPT and siRNA genes with siRNA viability . . . . .	251
D.1	Pathway metagene expression profiles . . . . .	254



D.2	Expression profiles for constituent genes of PI3K . . . . .	256
D.3	Expression profiles for estrogen receptor related genes . . . . .	257
D.4	Pathway metagene expression profiles . . . . .	258
D.5	Expression profiles for p53 related genes . . . . .	259
D.6	Expression profiles for BRCA related genes . . . . .	260
D.7	Somatic mutation against the PI3K metagene . . . . .	261
D.8	Somatic mutation against PIK3CA metagene . . . . .	264
D.9	Somatic mutation against PI3K protein . . . . .	265
D.10	Somatic mutation against AKT protein . . . . .	266
F.1	Synthetic lethal expression profiles of stomach samples . . . . .	271
F.2	Comparison of SLIPT in stomach to siRNA . . . . .	273
G.1	Synthetic lethality in the PI3K/AKT pathway . . . . .	278
G.2	Synthetic lethality in the PI3K/AKT pathway in cancer . . . . .	279
G.3	Synthetic lethality in the Extracellular Matrix . . . . .	280
G.4	Synthetic lethality in the GPCR Downstream . . . . .	281
G.5	Synthetic lethality in the Translation Elongation . . . . .	282
G.6	Synthetic lethality in the Nonsense-mediated Decay . . . . .	283
G.7	Synthetic lethality in the 3' UTR . . . . .	284
H.1	Synthetic lethality and vertex degree . . . . .	285
H.2	Synthetic lethality and centrality . . . . .	286
H.3	Synthetic lethality and PageRank . . . . .	286
I.1	Structure of synthetic lethality resampling . . . . .	288
J.1	Performance of $\chi^2$ and SLIPT across quantiles . . . . .	290
J.2	Performance of $\chi^2$ and SLIPT across quantiles . . . . .	292
J.3	Performance of $\chi^2$ and SLIPT across quantiles with more genes . . . . .	294
J.4	Performance of $\chi^2$ and SLIPT across quantiles with query correlation . . . . .	296
J.5	Performance of $\chi^2$ and SLIPT across quantiles with query correlation . . . . .	298
J.6	Performance of $\chi^2$ and SLIPT across quantiles with query correlation and more genes . . . . .	300
K.1	Performance of simulations on a simple graph . . . . .	302
K.2	Performance of simulations on an inhibiting graph . . . . .	303
K.3	Performance of simulations on a constructed graph with inhibition . . . . .	304
K.4	Performance of simulations on a constructed graph with inhibition . . . . .	305
K.5	Detection of synthetic lethality within a graph structure . . . . .	306
K.6	Detection of synthetic lethality within an inhibiting graph . . . . .	308
K.7	Detection of synthetic lethality within an inhibiting graph . . . . .	309
K.8	Performance of simulations on a branching graph . . . . .	310
K.9	Performance of simulations on a complex graph . . . . .	311
K.10	Performance of simulations on a large graph . . . . .	312
K.11	Performance of simulations on a branching graph with inhibition . . . . .	313
K.12	Performance of simulations on a branching graph with inhibition . . . . .	314



K.13 Performance of simulations on a complex graph with inhibition . . . . .	315
K.14 Performance of simulations on a complex graph with inhibition . . . . .	316
K.15 Performance of simulations on a large constructed graph with inhibition	317
K.16 Performance of simulations on a large constructed graph with inhibition	318
K.17 Performance of simulations on the $G_{\alpha i}$ signalling pathway . . . . .	319
K.18 Performance of simulations including the $G_{\alpha i}$ signalling pathway . . . . .	320

# 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 . . . . .	98
4.2	Pathways for <i>CDH1</i> partners from SLIPT . . . . .	99
4.3	Pathways for clusters of <i>CDH1</i> partners from SLIPT . . . . .	104
4.4	ANOVA for synthetic lethality and correlation with <i>CDH1</i> . . . . .	107
4.5	Comparison of Synthetic Lethal Interaction Prediction Tool (SLIPT) genes against secondary siRNA screen . . . . .	111
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 .	116
4.9	Examples of candidate metagenes synthetic lethal for <i>CDH1</i> from SLIPT	120
5.1	ANOVA for synthetic lethality and vertex degree . . . . .	138
5.2	ANOVA for synthetic lethality and information centrality . . . . .	139
5.3	ANOVA for synthetic lethality and PageRank centrality . . . . .	141
5.4	Resampling for pathway structure of synthetic lethal detection methods	144
B.1	Complete list of R packages used during this thesis . . . . .	231
C.1	Candidate synthetic lethal gene partners of <i>CDH1</i> from mtSLIPT . . .	241
C.2	Pathways for <i>CDH1</i> partners from mtSLIPT . . . . .	242
C.3	Pathways for clusters of <i>CDH1</i> partners from mtSLIPT . . . . .	245
C.4	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA . . . . .	247
C.5	Pathways for <i>CDH1</i> partners from mtSLIPT . . . . .	248
C.6	Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen	249
D.1	Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT . .	263

E.1	Comparison of intrinsic subtypes . . . . .	267
F.1	Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer . . . . .	269
F.2	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer . . . . .	270
F.3	Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT . . . . .	272
F.4	Pathways for <i>CDH1</i> partners from SLIPT and siRNA . . . . .	274
F.5	Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer . . . . .	275
F.6	Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA . . . . .	276
F.7	Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer . . . . .	277
H.1	ANOVA for synthetic lethality and vertex degree . . . . .	287
H.2	ANOVA for synthetic lethality and information centrality . . . . .	287
H.3	ANOVA for synthetic lethality and PageRank centrality . . . . .	287
I.1	Resampling for pathway structure of synthetic lethal detection methods . . . . .	289

# Glossary

bioinformatics	Statistical or computational approaches to biological data or research tools.
centrality	A network metric which identifies important <a href="#">vertices</a> .
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by <i>CDH1</i> .
edge or link	A relationship connecting a pair of elements of a graph structure or network, may be weighted or directional.
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.
hub	A central or highly connected component of a network.
information centrality	A network <a href="#">centrality</a> metric which uses the impact of removing a <a href="#">vertex</a> or <a href="#">node</a> 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.

non-oncogene addiction	The dependence of a cancer cell on functioning non-mutant genes.
oncogene	A gene that potentially causes cancer, typically by over-expression or mutant gene variants.
oncogene addiction	The dependence of a cancer cell on a specific oncogenic pathway.
PageRank centrality	A network <a href="#">centrality</a> metric which uses eigenvectors with a scaling factor ( <a href="#">Brin and Page, 1998</a> ).
scale-free	A property of a network which has a power law <a href="#">vertex degree</a> distribution, that is several highly connected <a href="#">hub</a> genes and many with very few connections.
shortest path	A path with the fewest possible <a href="#">edges</a> which connects two particular <a href="#">vertices</a> .
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.
tumour suppressor	A gene potentially causes cancer, typically by disruption of functions which protect the cell from cancer.
vertex degree	A network metric of connectivity of <a href="#">vertices</a> which uses the number of edges connected to each <a href="#">vertex or node</a> .
vertex or node	An element of a graph structure or network.

# Acronyms

AMP	Adenosine Monophosphate.
AMPK	<a href="#">AMP</a> -activated Protein Kinase.
ANOVA	Analysis of Variance.
BioPAX	Biological Pathway Exchange.
BMP	Bone Morphogenic Protein.
CXCR	Chemokine Receptor.
EMT	Epithelial-Mesenchymal Transition.
GPCR	G Crotein Coupled Receptor.
JAK	Janus Kinase.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NMD	Nonsense-Mediated Decay.
PDE	Phosphodiesterase.
PI3K	Phosphoinositide 3-kinase.
PIP <sub>2</sub>	Phosphatidylinositol-(4,5)-bisphosphate.
PIP <sub>3</sub>	Phosphatidylinositol-(3,4,5)-trisphosphate.
RGS	G-protein Signalling.
RHO	Ras Homolog Family.
RNA	Ribonucleic Acid.
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
TCGA	The Cancer Genome Atlas (genomics project).
TGF $\beta$	Transforming Growth Factor $\beta$ .

UTR    Untranslated Region (of mRNA).

WNT    Wingless-Related Integration Site.



## Chapter 5

# Synthetic Lethal Pathway Structure

Having identified key [pathways](#) implicated in [synthetic lethal](#) genetic interactions with *CDH1* (in Chapter 4), these were investigated for the [synthetic lethal](#) genes within them and their relationships to [pathway](#) structure in Reactome [pathways](#). This chapter will focus on the [pathway](#) structure of biological [pathways](#) detected across analyses in Chapter 4. Specifically, investigations were performed to determine whether [synthetic lethal](#) candidates, detected by [SLIPT](#) or [siRNA](#), exhibited differences with respect to metrics of [pathway](#) structure of network connectivity and importance (as described in Sections 2.4.4 and 3.5.3). The relationships between [synthetic lethal](#) candidates, detected by either approach, were also examined to determine whether [SLIPT](#) candidate genes were upstream or downstream [siRNA](#) candidate genes. These directional relationships were tested by resampling (as described in Sections 3.4.1 and 3.4.1.1) and comparisons to the [pathway](#) hierarchical score based on biological context (as derived in Section 3.4.1.2). Together these investigations into structural relationships demonstrate how a combination of network biology and statistical techniques can be performed with genes identified by a [bioinformatics](#) analysis.

## 5.1 Synthetic Lethal Genes in Reactome Pathways

The [graph](#) structure for Reactome [pathways](#) was obtained from Pathway Commons via [Biological Pathway eXchange \(BioPAX\)](#) (as described in Section 2.4.2). The [pathways](#) describe the (directional) relationships between biomolecules, including genes that encode proteins in biological [pathways](#). These relationships include cell signalling (e.g., kinase phosphorylation cascades), gene regulation (e.g., transcription factors, chromatin modifiers, [RNA](#) binding proteins), and metabolism (e.g., the product of an enzyme being the substrate of another). Together these relationships describe the

known functional [pathways](#) in a human cell with a reasonable resolution, from a curated database supported by publications documenting [pathway](#) relationships.

Pathway structures from the Reactome network (as described in Section 2.4.3) were used to derive the [graph](#) structure of each biological [pathway](#). The [synthetic lethal](#) candidate genes for notable [pathways](#) discussed in Chapter 4, including candidate [synthetic lethal pathways](#) of *CDH1*, were examined to show the [SLIPT](#) and [siRNA](#) candidates within these [pathways](#). The [synthetic lethal](#) genes considered here are those candidates detected by [SLIPT](#) (as described in Section 3.1) in The Cancer Genome Atlas (TCGA) breast cancer [expression](#) and [mutation](#) data (Koboldt *et al.*, 2012) in comparison to the candidate gene partners from the [siRNA](#) screening in breast cell lines (Telford *et al.*, 2015).

### 5.1.1 The PI3K/AKT Pathway

The [phosphoinositide 3-kinase \(PI3K\)](#) cascade signalling [pathway](#) is important in cancer because it is involved in mediating signals between the [G protein coupled receptors](#) and regulation of protein translation have both been strongly implicated to be [synthetic lethal pathways](#) with loss of *CDH1* function (in Chapter 4). These [pathways](#) have are all subject to dysregulation in cancer (Courtney *et al.*, 2010; Dorsam and Gutkind, 2007; Gao and Roux, 2015). Thus the PI3K cascade will be examined along with the most supported [synthetic lethal pathways](#) (as identified in Chapter 4). It also exhibited a relationship with *CDH1* mutations in [metagene](#) analyses (in Appendix D).

The [phosphoinositide 3-kinase \(PI3K\)](#) [pathway](#) is well characterised and has an established direction of signal transduction from extracellular stimuli (and membrane bound receptors) to the inner mechanisms of the cell, namely, the regulation of protein translation. The production of proteins is necessary for the growth of the cell so it is reasonable to suggest that these processes may be subject to (non-[oncogene](#)) addiction in some cancer cells which rely upon them for sustained protein production and cell growth. This is also supported by the [oncogenes](#) *PIK3CA* and *AKT1* being involved with the PI3K cascade and related PI3K/AKT [pathway](#) which may be subject to [oncogene addiction](#) when these proto-oncogenes are activated.

The [PI3K](#) cascade was not supported across [SLIPT](#) in TCGA breast [expression](#) data and the [siRNA](#) primary screen by over-representation (in Section 4.2.5) or resampling (in Section 4.2.5.1) but genes were detectable by either approach (as shown in Figure 5.1). While few genes were identified by both approaches, they include genes that are highly connected in the PI3K cascade and are hubs to information transmission

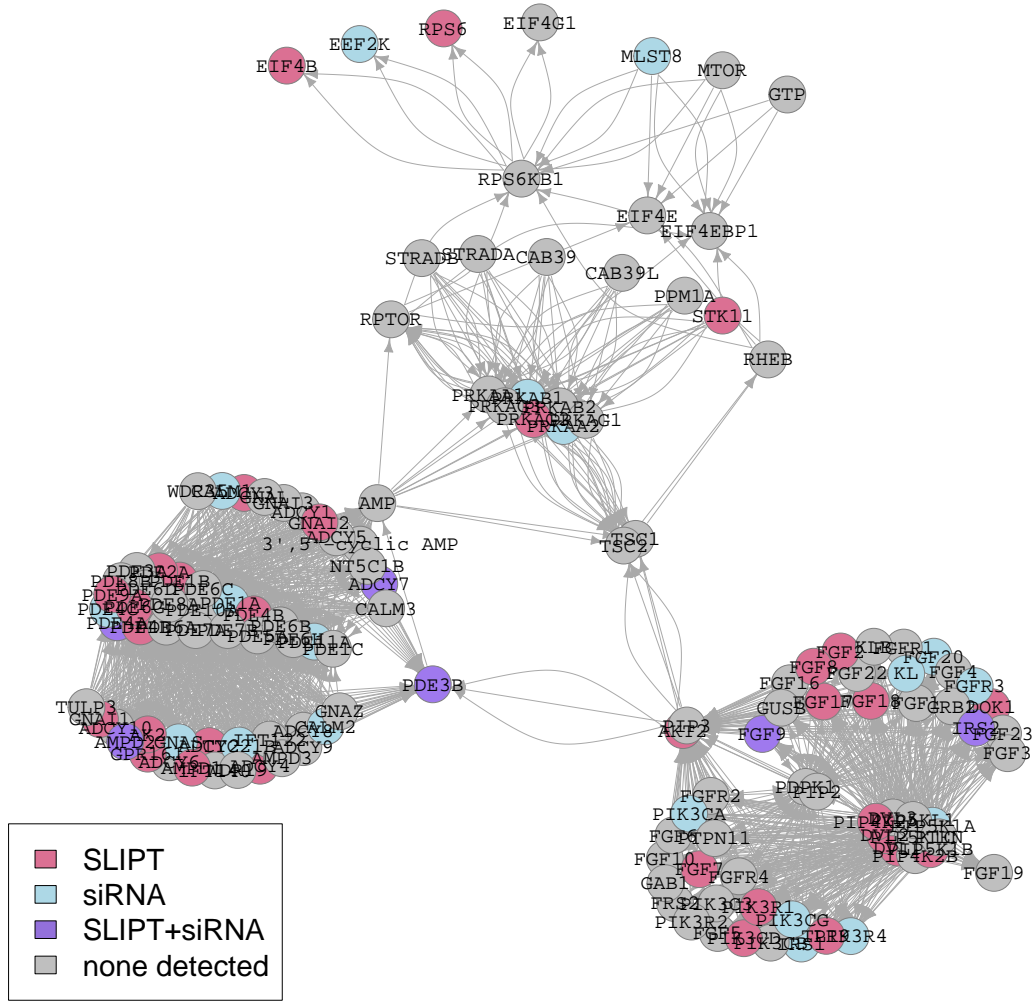


Figure 5.1: **Synthetic lethality in the PI3K cascade.** The Reactome [PI3K](#) Cascade pathway with [synthetic lethal](#) candidates coloured as shown in the legend.

such as *FGF9*, *PDE3B*, and *PDE4A*. The key upstream genes *PIK3CA* and *PIK3CG* were detected by [siRNA](#) whereas the downstream *PIK3R1* and *AKT2* genes were detected by [SLIPT](#). Gene detected by either method were also prevalent in the [PI3K](#), [phosphodiesterase \(PDE\)](#), and [AMP-activated protein kinase \(AMPK\)](#) modules, in addition to the downstream translation factors and ribosomal genes (*EIF4B*, *EEF2K*, and *RPS6*). Together these suggest that there may be further structure between the [SLIPT](#) and [siRNA](#) candidate partners of *CDH1* in [pathways](#) as illustrated by [PI3K](#). As such, [pathway](#) structure will be investigated to detect differences in the upstream and

downstream gene candidates of those detected by either method. Pathway structure may account for the disparity between SLIPT and siRNA genes, even in pathways such as PI3K where they did not significantly intersect. For instance, SLIPT gene partners may be downstream of siRNA candidates rather than replicating them directly.

This disparity between SLIPT and siRNA gene candidates synthetic lethal partners of CDH1 (i.e., a high number of genes detected by either approach with few detected by both) was replicated in the related PI3K/AKT pathway and the “PI3K/AKT in cancer” pathway (shown in Appendix Figures G.1 and G.2). Many synthetic lethal candidates were at the upstream core of these pathway networks and the downstream extremities. It is particularly notable that the many genes important in cell signalling and gene regulation were detected by either synthetic lethal detection approach. These include *AKT1*, *AKT2*, and *AKT3*, the Calmodulin signalling genes *CALM1* and *CAMK4*, and the forkhead family transcription factors *FOXO1* (a tumour suppressor) and *FOXO4* (an inhibitor of EMT).

### 5.1.2 The Extracellular Matrix

The extracellular pathways “elastic fibre formation” and “fibrin clot formation” (shown in Figures 5.2 and 5.3 respectively) were both supported across analyses (in Chapter 4). These pathways were identified by both SLIPT (for TCGA breast cancer) and siRNA gene candidates as they had significant over-representation and resampling.

Particularly for elastic fibres (Figure 5.2), the vast majority of genes were detected by either approach in addition to a significant proportion of genes detected by both approaches (as determined in Section 4.2.5). The genes detected by both approaches also appeared to have a non-random distribution in the network, with *TFGB1*, *ITGB8*, and *MFAP2* exhibiting high connectivity, and having a central role in their respective pathway modules. In addition to a structural role in the extracellular matrix and connective tissue (including the tumour microenvironment), these proteins including Furin, transforming growth factor  $\beta$  (TGF $\beta$ ), and the bone morphogenic proteins (BMPs), are also involved in responses to endocrine signals and interact with the cellular receptors for signalling pathways. Therefore it is plausible that *CDH1* deficient tumours will be subject to non-oncogene addiction to the extracellular environment and growth signals arising from this pathway. The pathway structure also indicated that the genes detected by siRNA (or by both approaches) may be downstream of those detected by SLIPT, in addition to whether connectivity or centrality is higher for synthetic lethal candidates than other genes in the pathway.

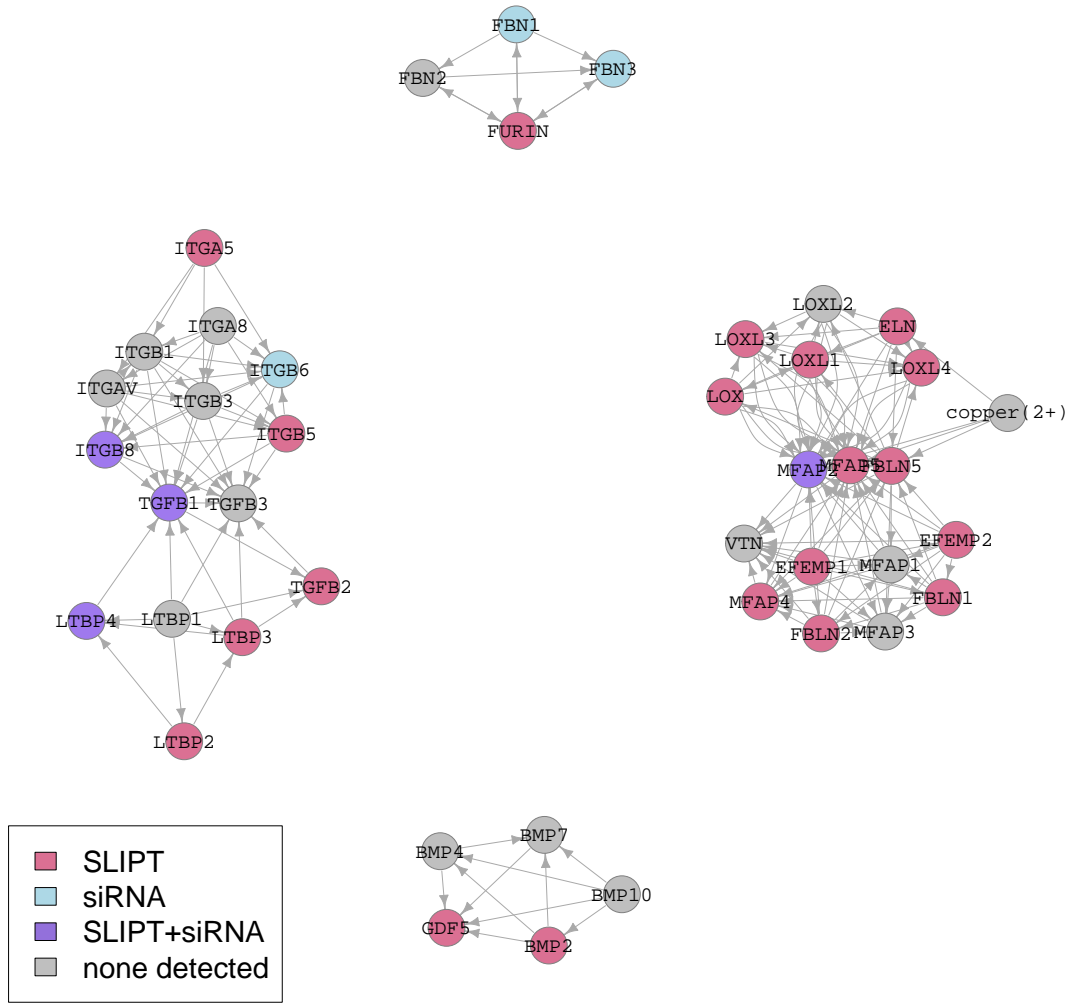


Figure 5.2: **Synthetic lethality in Elastic Fibre Formation.** The Reactome Elastic Fibre Formation [pathway](#) with [synthetic lethal](#) candidates coloured as shown in the legend.

Genes detected as [synthetic lethal](#) partners of *CDH1* by [SLIPT](#) or [siRNA](#) screening were also common in the Fibrin clot formation [pathway](#) (shown in Figure 5.3). This is consistent with the established pleiotropic role of *CDH1* in regulating fibrin clotting. It is also notable that the genes detected by either method appear to be highly connected such as *C1QBP*, *KNG1*, *F8*, *F10*, *F12*, *F13A*, and *PROC* (including many of the coagulation factors). [Synthetic lethal](#) candidates also include *SERPINE2* and *PRCP*, which only affect downstream genes, in addition to *PROCR* and *VWF*, which are only affected by upstream genes.

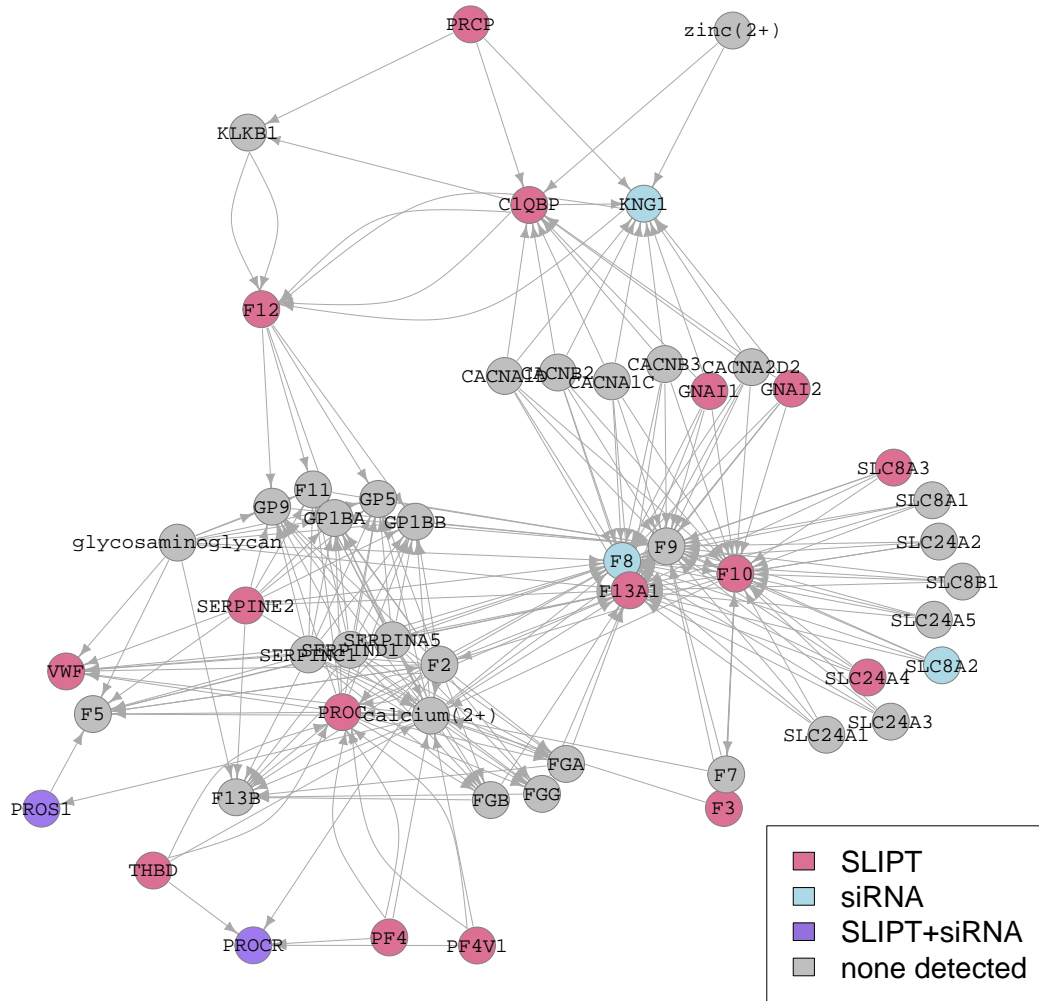


Figure 5.3: **Synthetic lethality in Fibrin Clot Formation.** The Reactome Fibrin Clot Formation [pathway](#) with [synthetic lethal](#) candidates coloured as shown in the legend.

Many of these genes are involved in the larger Extracellular Matrix [pathway](#) (shown in Appendix Figure [G.3](#)), including many of the [synthetic lethal](#) candidates discussed for elastic fibres. The number of [SLIPT](#) candidate genes outnumbers those identified by [siRNA](#), as expected from an isolated cell model. However, the endocrine response genes (e.g., *TGFB1* and *LTBP4*) which are potentially artifacts of the cell line growth process were replicated with [SLIPT](#) analysis in patient tumours (TCGA breast cancer data). There is also additional support for [synthetic lethal](#) genes (e.g., *ITGB2*, *MFAP2*, and *SPARC*) being highly connected networks hubs of the [pathway](#). The complexity of

the extracellular matrix [pathway](#) lends credence to the need for formal network analysis approaches to interpret the [pathway](#) structure of [synthetic lethal](#) candidates. Furthermore statistical approaches are needed to determine whether structural relationships are unlikely to be observed between [synthetic lethal](#) candidates by chance

### 5.1.3 G Protein Coupled Receptors

G protein coupled receptor (GPCR) [pathways](#) are highly complex (as shown in Figure 5.4 and Appendix Figure G.4). Many of genes in these [pathways](#) were [synthetic lethal](#) candidates, detected by either SLIPT or siRNA screening, including genes frequently detected with both approaches, consistent with these [pathways](#) being supported by prior analyses (in Sections 4.2.5 and 4.2.5.1). [Synthetic lethal](#) candidates include the PDE and Calmodulin genes (as discussed in Section 5.1.3) in addition to others such as the regulators of G-protein signalling (RGS), chemokine receptors (CXCR), Janus kinase (JAK), and the Ras homolog family (RHO) genes. These are important regulatory signalling [pathways](#) necessary for cellular growth and cancer proliferation. Thus the GPCR [pathways](#) (and downstream PI3K/AKT signals) are a potentially actionable vulnerability against *CDH1* deficient cancers, particularly since many existing drug targets exist among these signalling [pathways](#), some of which have been experimentally validated (Telford *et al.*, 2015). While a statistically significant number of genes in GPCR [pathways](#) was detected by both approaches (in Sections 4.2.5 and 4.2.5.1), the complexity of GPCR networks (containing hundreds of genes) further support the needs for a rational network-based approach to the relationships between SLIPT and experimental candidates.

### 5.1.4 Gene Regulation and Translation

While very few [synthetic lethal](#) genes were detected in translational [pathways](#) in an experimental screen against *CDH1* (Telford *et al.*, 2015), these were highly over-represented in translational elongation (as shown in Appendix Figure G.5). These SLIPT genes include many ribosomal proteins and the regulatory “elongation factors” which may be subject to responses in the upstream signalling [pathways](#). This observation further indicates that [pathway](#) structure may be used to identify relationships between [synthetic lethal](#) candidates detected by SLIPT and siRNA. The computational approach with SLIPT may exhibit the ability to detect downstream genes in the core translational processes, which experimental screening did not identify. The experimental screening may similarly detect upstream regulatory genes less sensitive



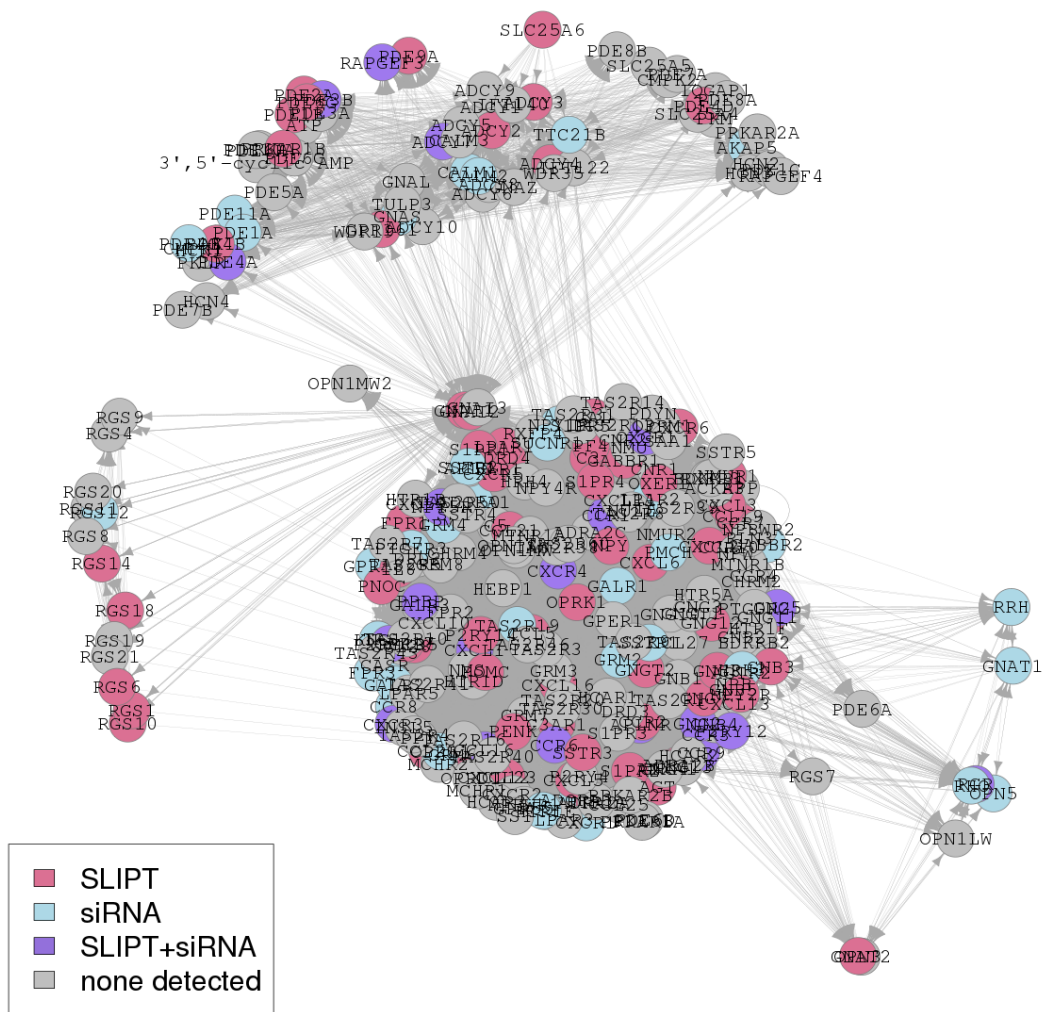


Figure 5.4: **Synthetic lethality in the GPCRs.** The Reactome  $G_{\alpha i}$  pathway with synthetic lethal candidates, coloured as shown in the legend.

to inactivation, that is, genes that are less likely to be indiscriminately lethal to both genotypes at high doses of inactivation.

Many of these SLIPT candidate genes are also among the nonsense-mediated decay (NMD) pathway (shown in Appendix Figure G.6) or 3' untranslated region (UTR) mediated translational regulation (shown in Appendix Figure G.7). While genes in these pathways were also supported by experimental screening with siRNA, there were differences in which genes were detected within the pathway structures. In particular, *UPF1* was detected in the siRNA screen and is the focal downstream gene for the entire NMD pathway showing that (in this case) siRNA genes are downstream effectors of those detected by SLIPT. 3' UTR mediated translational regulation has a similar structure with two modules connected solely by *RPL13A*, giving an example of SLIPT candidate genes with high connectivity, although there were many ribosomal proteins detected by SLIPT. However, the detection of *EIF3K*, a regulatory elongation factor (not essential to ribosomal function) was replicated across SLIPT and siRNA screening, while the majority of the elongation factors were not detected by either approach. Regulatory genes, being more amenable to experimental validation, also support further investigation into pathway structure. The SLIPT candidates may support experimental candidates in biological pathways by detecting downstream genes, which may not be detectable by experimental screening with high dose inhibitors. This difference between the approaches may explain the greater number of SLIPT candidate partners of *CDH1* than those experimentally identified.

## 5.2 Network Analysis of Synthetic Lethal Genes

Genes detected as synthetic lethal partners of *CDH1* with the SLIPT computational approach and the siRNA screen (Telford *et al.*, 2015) were compared across network metrics in the example of  $G_{\alpha i}$  signalling, a GPCR pathway. This pathway was used to demonstrate deeper network analysis approaches to synthetic lethal candidates within complex pathways it was supported across analyses (in Chapter 4), with significant over-representation in both SLIPT and siRNA screening, and the genes differed considerably between synthetic lethal detection methods (shown in Appendix Figures 5.4). These network metrics were used to measure whether the network properties differed between groups of genes detected by either or both approaches. These analyses serve to test both whether synthetic lethal gene candidates had higher connectivity or importance in a network and whether either detection approach is biased towards genes with different network properties.

### 5.2.1 Gene Connectivity and Vertex Degree

Vertex degree (the number of connections) for each gene is a fundamental property of a network. The vast majority of genes had a relatively modest number of connections, each with only a few genes in the  $G_{\alpha i}$  pathway (shown in Figure 5.5) having pathway relationships with a high number of genes, consistent with the *scale-free* property of biological networks (Barabási and Oltvai, 2004). The number of connections was similar between gene groups (by *synthetic lethal* detection). Genes detected by *siRNA* included those with the fewest connections, despite there being fewer genes that were detected by either approach. There was no statistically significant effect of either computational or experimental *synthetic lethal* detection method on vertex degree, as determined by *analysis of variance* (ANOVA) (shown by Table 5.1).

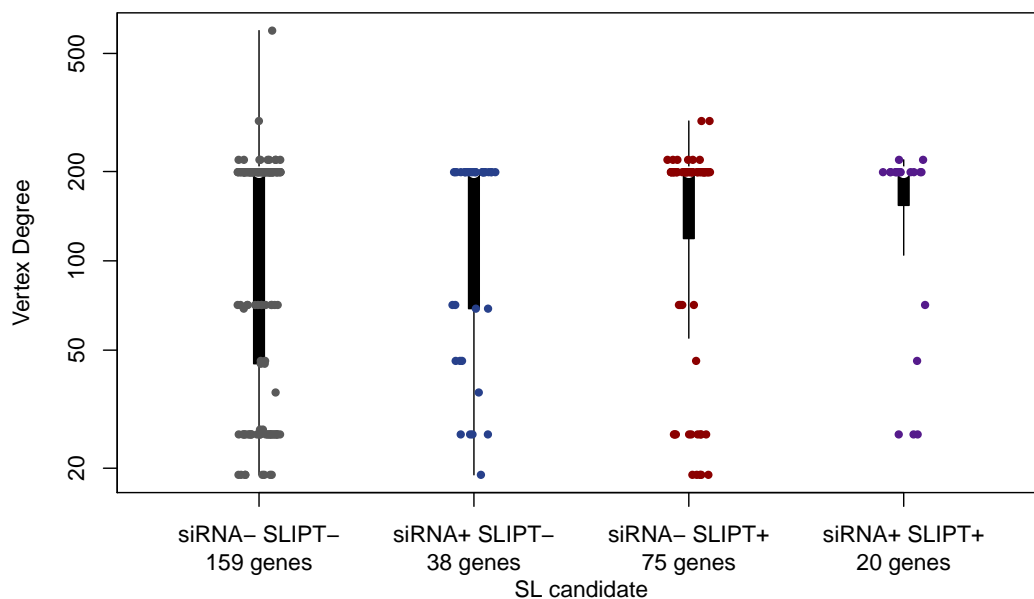


Figure 5.5: **Synthetic lethality and vertex degree.** The number of connected genes (*vertex degree*) was compared (on a log-scale) across genes detected by *SLIPT* and *siRNA* screening in the Reactome  $G_{\alpha i}$  cascade pathway. There were no differences in *vertex degree* between the groups (shown in Table 5.1), although genes detected by *siRNA* included those with the fewest connections.

Table 5.1: ANOVA for synthetic lethality and vertex degree

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	21	20.8	0.0030	0.9561
SLIPT	1	16215	16215	2.3722	0.1246
siRNA×SLIPT	1	17	17	0.0025	0.9603

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

The results for the  $G_{\alpha i}$  **pathway** were very similar when testing **synthetic lethality** against *CDH1* **mutation** (mtSLIPT). In either case, there was no significant evidence that SLIPT or mtSLIPT-specific genes had higher connectivity than those detected by siRNA screening (shown in Appendix Figure H.1 and Appendix Table H.1). Thus **synthetic lethal** detection does not discriminate among genes by their connectivity in this **pathway** network, nor is either approach constrained to detecting highly connected genes. Both approaches have been demonstrated to detect genes with many and very few connections in the  $G_{\alpha i}$  signalling **pathway**.

## 5.2.2 Gene Importance and Information Centrality

**Information centrality** is a measure of the importance of **nodes** in a network in terms of how vital they are to the transmission of information throughout the network. This applies well to biological **pathways**, particularly gene regulation and cell signalling. The **nodes** with the highest **information centrality** are not necessarily the most connected, as they may also include **nodes** that pass signals between highly connected network hubs. **Information centrality** therefore provides a distinct metric for the connectivity of a gene in a **pathway**, which has the added benefit of being directly related to the disruption of **pathway** function were it to be inactivated or removed. **Information centrality** has also been suggested to be indicative of the essentiality of genes or proteins (Kranthi *et al.*, 2013).

Within the  $G_{\alpha i}$  **pathway** (shown in Figure 5.6), the **information centrality** across gene groups detected by either **synthetic lethal** approach did not differ significantly (shown by Table 5.2). Genes detected by SLIPT span the complete range of **PageRank centrality** values for this **pathway**. These findings were replicated (shown in Appendix Figure H.2 and Appendix Table H.2). Thus neither method was unable to detect **synthetic lethal** genes in the  $G_{\alpha i}$  **pathway** with particular **centrality** constraints but they were also not detecting genes with higher **centrality** than expected by chance.

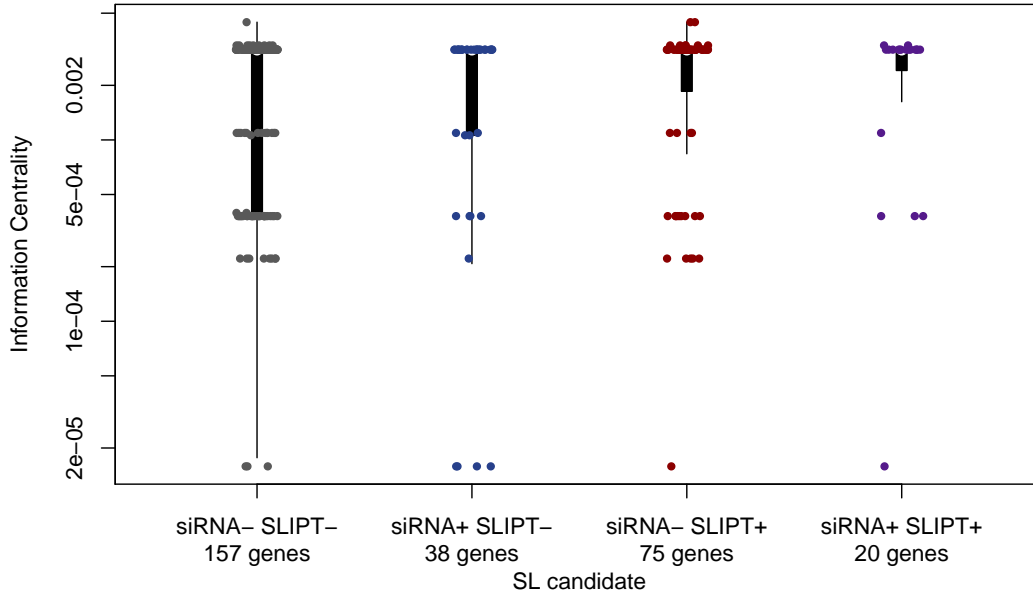


Figure 5.6: **Synthetic lethality and centrality.** The [information centrality](#) was compared (on a log-scale) across genes detected by [SLIPT](#) and [siRNA](#) screening in the Reactome  $G_{\alpha i}$  pathway. Genes detected by [SLIPT](#) or [siRNA](#) did not have higher centrality than other genes (shown in Table 5.2). Genes detected by [SLIPT](#) spanned the range of [centrality](#) values.

Table 5.2: [ANOVA](#) for synthetic lethality and information centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.00000000	$2.7000 \times 10^{-9}$	0.0016	0.96783
SLIPT	1	0.00000548	$5.4831 \times 10^{-6}$	3.3253	0.06926
siRNA $\times$ SLIPT	1	0.00000002	$1.8800 \times 10^{-8}$	0.0114	0.91511

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

### 5.2.3 Gene Importance and PageRank Centrality

[PageRank centrality](#) is another network analysis procedure to infer a hierarchy of gene importance from a network using connections and structure (Brin and Page, 1998). In contrast to the [information centrality](#) approach of removing nodes, PageRank uses the eigenvalue properties of the adjacency matrix to rank genes according to the number of connections and paths they are involved in.

This distinction is immediately clear within the  $G_{\alpha i}$  pathway (shown in Figure 5.7), which differs considerably from the information centrality scores (in Figure 5.6). Genes detected by either synthetic lethal approach did not include those with the highest PageRank centrality. There was a significant association between genes detected by SLIPT (which had a lower median) with PageRank centrality (shown by Table 5.3). The genes detected by SLIPT span the range of centrality values of siRNA showing that both approaches were capable of detecting genes of moderately high centrality (as shown for information centrality) and that the lower centrality of SLIPT candidates in  $G_{\alpha i}$  pathway may be due to synthetic lethal partners being less critical to the pathway, rather than a limitation of the methodology.

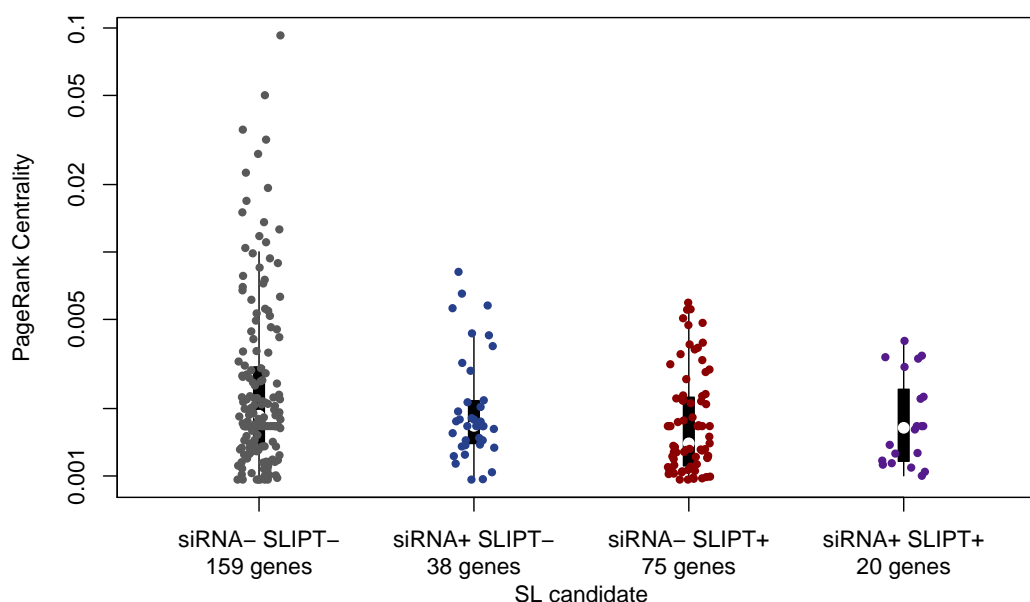


Figure 5.7: **Synthetic lethality and PageRank.** The PageRank centrality was compared (on a log-scale) across genes detected by mtSLIPT and siRNA screening in the Reactome  $G_{\alpha i}$  pathway. Genes detected by with either synthetic lethal detection approach had a more restricted range of centrality values but only SLIPT genes had a significant association with centrality (shown in Table 5.3).

There was not a significant association between siRNA candidates and PageRank centrality. The significant result for SLIPT was not replicated when testing synthetic lethality against *CDH1* mutation (shown in Appendix Figure H.3 and Appendix Ta-

ble H.3). However, this may be due to fewer genes being detected by [mtSLIPT](#) and [siRNA](#).

Table 5.3: [ANOVA](#) for synthetic lethality and PageRank centrality

	DF	Sum Squares	Mean Squares	F-value	p-value
siRNA	1	0.0001059	$1.0589 \times 10^{-4}$	2.1021	0.14818
SLIPT	1	0.0002881	$2.8808 \times 10^{-4}$	5.7188	0.01743
siRNA×SLIPT	1	0.0000477	$4.7704 \times 10^{-5}$	0.9470	0.33131

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

### 5.3 Relationships between Synthetic Lethal Genes

This network analyses so far have tested whether [synthetic lethal](#) candidate genes were more connected or important within a [pathway](#) structure, such as the  $G_{\alpha i}$  [pathway](#). However these metrics do not ascertain whether there were relationships between [SLIPT](#) and [siRNA](#) candidate partners of *CDH1*. In particular, it is plausible that they may be upstream or downstream of one and other within a [pathway](#).

The direction of a biological [pathway](#) is important, particularly those involved in cell signalling which respond to extracellular stimuli and transmit these signals via intermediary proteins to regulate core functions and responses of the cell. These [pathways](#) regulate process such as [gene expression](#) and protein translation, which are important in the proliferation of cancers ([Gao and Roux, 2015](#)). Therefore it is important to determine which [synthetic lethal](#) candidates were upstream or downstream in the context of a biological [pathway](#). In particular, [pathway](#) structure may be used to identify relationships between [SLIPT](#) and [siRNA](#) gene candidates.

A [pathway](#) structure method has been devised to use [network](#) structures to identify directional relationships between individual [SLIPT](#) and [siRNA](#) genes. This [pathway](#) structure methodology will be applied (as described in Section 3.4.1) to detect the direction of [shortest paths](#) between [SLIPT](#) and [siRNA](#) gene candidates. This will be used to demonstrate the methodology on the [PI3K](#) and  $G_{\alpha i}$  [pathways](#), to develop a statistical test for [pathway](#) structure between between [SLIPT](#) and [siRNA](#) gene candidates using resampling (as described in Section 3.4.1.1), and to apply this test for [pathway](#) structure among [synthetic lethal](#) gene candidates to the [pathways](#) identified in Chapter 4 and discussed in Section 5.1.



### 5.3.1 Detecting Upstream or Downstream Synthetic Lethality

Shortest paths in a **pathway** network were used to devise a strategy to detect **pathway** structure between **SLIPT** and **siRNA** gene candidates partners of *CDH1* (as described in Section 3.4.1). Thus we can determine whether individual **SLIPT** genes have upstream or downstream **siRNA** candidates (scored as “up” or “down” events respectively). This procedure enables the detection of directional relationships between **SLIPT** and **siRNA** gene candidates (in contrast to the hierarchical approach).

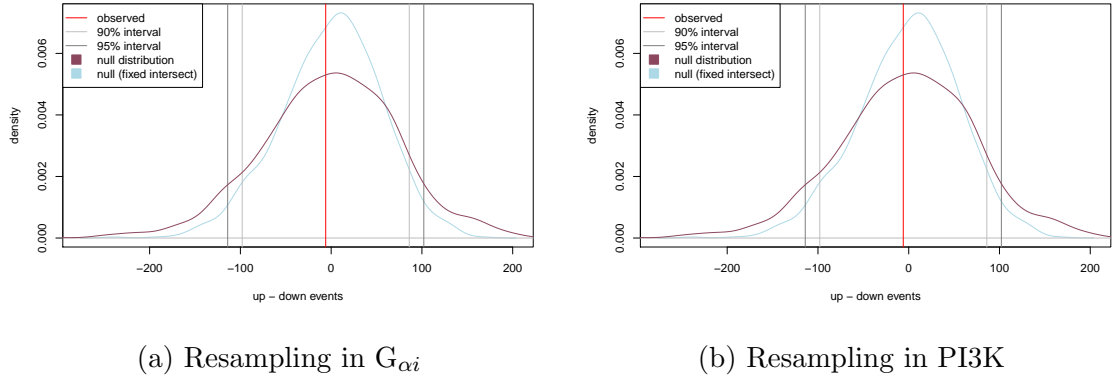


Figure 5.8: **Structure of synthetic lethality resampling.** A null distribution with 10,000 iterations of the number of **siRNA** genes upstream or downstream of **SLIPT** genes (depicted as the difference of these) in the  $G_{\alpha i}$  and **PI3K** pathways. To assess significance, the observed events (with **shortest paths**) were compared to the 90% and 95% intervals for the null distribution (shown in violet). Genes detected by both methods were fixed to the same number as observed for the alternative null distribution (shown in blue), although the observed number of events (red) was not significant in either case. In both cases, these genes detected by both approaches were included in computing the number of **shortest paths** (in either direction) between **SLIPT** and **siRNA** genes.

The total number of gene candidate pairs in either direction can be compared within a **pathway** network to assess the overall directional relationships in a **pathway**. This directionality is detectable by the difference between the number of **SLIPT** candidate genes with upstream and downstream **siRNA** gene partners. However, this measure alone is not sufficient to determine whether there is evidence of **pathway** structure between **SLIPT** and **siRNA** gene candidates partners of *CDH1* in a **pathway** network. Nevertheless, it does serve to measure the magnitude (and direction) of the consensus of directional relationships (upstream and downstream) between **SLIPT** and **siRNA**

gene candidates partners. This measure of **pathway** structure can be used for testing for statistical significance of **pathway** structure by resampling, using a permutation procedure to test whether these relationships are detectable among randomly selected gene groups rather than the detected **SLIPT** and **siRNA** gene candidates partners (as described in Sections 2.3.6 and 3.4.1.1).

This resampling procedure was performed for the **PI3K** network to generate a null distribution for the difference in the number of “up events” and “down events” for this **pathway** (as shown in Figure 5.1). Resampling yields a distribution to detect whether genes detected by **SLIPT** had significantly more upstream or downstream **siRNA** candidates. While there was modest indication that **siRNA** genes were downstream of **SLIPT** candidate genes, resampling for the **PI3K pathway** (as shown in Figure 5.8) did not detect a significant number of **siRNA** genes upstream or downstream.

In contrast, when testing **synthetic lethality** against *CDH1* mutation (**mtSLIPT**) there was modest indication that **siRNA** genes were upstream of **SLIPT** candidate genes. However, resampling (as shown in Appendix Figure ??) was also unable to detect a significant number of **siRNA** genes upstream or downstream of **mtSLIPT** candidates. Neither fixing the number of genes detected by both approaches (as shown by the blue line in Figure 5.8 and Appendix Figure ??) nor excluding these jointly detected genes altered the findings of this approach. These genes were included in the analysis because they can disproportionately count towards **siRNA** genes being upstream (or downstream) of **SLIPT** genes as they may still have different proportions of gene detected by either approach upstream (or downstream) of them. Furthermore, expanding the range of **shortest paths** to consider **links** in related **pathways** (using the “metapathways” constructed in Section 2.4.3) also had little effect on the null distribution generated, despite increasing the computational demands of the procedure.

### 5.3.2 Resampling for Synthetic Lethal Pathway Structure

The permutation procedure (as described in Section 3.4.1.1) that was performed in Section 5.3.1 for the **PI3K** cascade was also applied to other **pathways** identified in Chapter 4 and discussed in Section 5.1. These include extracellular matrix (with constituent elastic fibre and fibrin **pathways**), cell signalling (by **PI3K/AKT** and **GPCRs**), and translational **pathways** (with **NMD** and **3'UTR** regulation). The resampling results across these **pathways** (as shown in Table 5.4) had limited support for association between **pathway** structure and detection of **synthetic lethal** genes, with the majority of these being non-significant as shown for **PI3K** (in Appendix Figure ??). However,

the distribution for these [pathways](#) will differ depending on their structure, the number of genes they consist of, and the proportion of [synthetic lethal](#) candidates among them (including a higher frequency of genes detected by both methods for the [pathways](#) identified in Section 4.2.5.1). This resampling is an appropriate procedure to use to detect structural relationships across [pathways](#) as it does not assume an underlying test statistic distribution.

Pathway structure was supported for the [NMD pathway](#) (which is consistent with [siRNA](#) being downstream in Appendix Figure G.6). However, this observation rests upon a single gene and was not replicated when testing [synthetic lethality](#) ([mtSLIPT](#)) against [CDH1 mutation](#) (as shown in Appendix Table I.1) nor was it supported by the related [3'UTR regulation](#) and [translational elongation pathways](#).

Table 5.4: Resampling for [pathway](#) structure of [synthetic lethal](#) detection methods

Pathway	Graph		States		Observed				Permutation p-value	
	Nodes	Edges	SLIPT	siRNA	Up	Down	Up-Down	Up/Down	Up-Down	Down-Up
PI3K Cascade	138	1495	38	25	122	128	-6	0.953	0.5326	0.4606
PI3K/AKT Signalling in Cancer	275	12882	98	44	779	679	100	1.147	0.3255	0.6734
<b>G<sub>αi</sub> Signalling</b>	292	22003	95	58	836	1546	-710	0.541	0.9971	0.0029
GPCR downstream	1270	142071	312	160	9755	9261	494	1.053	0.3692	0.6305
Elastic fibre formation	42	175	24	7	1	2	-1	0.500	0.5461	0.3865
Extracellular matrix	299	3677	127	29	547	455	92	1.202	0.3351	0.6636
Formation of Fibrin	52	243	18	5	12	17	-5	0.706	0.6198	0.3564
<b>Nonsense-Mediated Decay</b>	103	102	74	2	0	74	-74	0	1.0000	< 0.0001
3' -UTR-mediated translational regulation	107	2860	77	1	0	0	0		0.4902	0.5027
Eukaryotic Translation Elongation	92	3746	76	0	0	0	0		0.4943	0.4933

Pathways in the Reactome network tested for structural relationships between [SLIPT](#) 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 [SLIPT](#) 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 [SLIPT](#) and [siRNA](#) (or resampling for them) were included in the analysis and the number of these were fixed to the number observed.

There does not appear to be a consensus on the directionality of [SLIPT](#) and [siRNA](#) candidates across [pathways](#) as distinct [pathways](#) showed stronger tendency for [siRNA](#) genes to be either upstream or downstream. Even related [pathways](#) such as [PI3K](#) and [PI3K/AKT](#) signalling showed directional events in opposite directions. The strongest [pathway](#) (among those tested) with support for directional [pathways](#) structure is [G<sub>αi</sub> signalling](#) which showed significant downstream [siRNA](#) genes for both [SLIPT](#) and [mt-SLIPT](#) from a large number of [shortest paths](#) (in Table 5.4 and Appendix Table I.1). This would indicate that [SLIPT](#) detects upstream regulators of genes experimentally validated by [siRNA](#). However, these results are borderline significant (with raw permutation p-values) and are unlikely to be detected after adjusting for multiple comparisons

across the 10 [pathways](#) presented here (nor in the 1652 Reactome [pathways](#) used previously in Chapter 4).

Therefore, there is insufficient evidence to determine whether there is [pathway](#) structure, gene detected upstream or downstream by either method, between the [SLIPT](#) and [siRNA](#) candidates in many of the [synthetic lethal pathways](#) (identified in Chapter 4). In particular, directional structure among [synthetic lethal](#) candidates for *CDH1* was not strongly supported in signalling [pathways](#) upon which the rationale for [pathway](#) structure hypotheses were based on. Despite the design of a robust resampling approach to test relationships between gene groups, this did not detect many structural relationships between [SLIPT](#) and [siRNA](#) gene candidates, although it may apply more broadly to gene networks. Furthermore, the [pathway](#) relationships are unlikely to be statistically supported by resampling when testing across the search space of Reactome [pathways](#) and adjusting for multiple comparisons. While there is statistically significant over-representation of many of these [pathways](#) in genes detected by both [SLIPT](#) and [siRNA](#) (as described in Chapter 4), these did not consistently show [pathway](#) structure. Furthermore, [pathway](#) structure did not account for the discrepancy between [SLIPT](#) and [siRNA](#) gene candidates which did not significantly intersect such as the [PI3K](#) cascade.

## 5.4 Discussion

These investigations used a functional [pathway](#) network that encapsulates protein complexes and functional modules. The Reactome network (Croft *et al.*, 2014) uses curated, experimentally identified [pathways](#) to determine relationships between genes and does not have the limitation of relying solely on protein binding or text-mining which are prone to false positives. While it is not documented whether these relationships are activating or inhibitory, the Reactome network (Croft *et al.*, 2014) is sufficient to test [pathway](#) relationships with directional information.

Synthetic lethal genes and [pathways](#) (for *CDH1* loss in cancer) were identified across [gene expression](#) and [mutation](#) datasets in Chapter 4. These [pathway](#) structure investigations extend those investigations into [synthetic lethal](#) gene candidates including exploring the discrepancy between [SLIPT](#) and [siRNA](#) candidate genes in a [pathway](#) such as [PI3K](#) in which they did not significantly intersect. Pathways with replicated [synthetic lethal](#) genes across these detection methods, breast and stomach cancer data, and patient and cell line data were also investigated including [pathways](#) from the extra-

cellular microenvironment to core translational [pathways](#) and the signalling [pathways](#) between them.

Synthetic lethal gene candidates in the context of [pathway](#) structures can also be interpreted to provide additional mechanisms and support for belonging to a [synthetic lethal pathway](#). Gene candidates with known mechanisms are ideal for triage of targets specific to *CDH1* deficient tumours and for further experimental validation in preclinical models. This chapter presents computational methods to use [pathway](#) structure in an attempt to detect genes with importance in a [pathway](#) and reconcile the differences between [SLIPT](#) and [siRNA](#) candidate genes with [pathway](#) relationships (e.g., one group being downstream of the other).

Many genes were detected by either method and the differences between the computational and experimental screening approaches could feasibly lead to differences in which genes within a [synthetic lethal pathway](#) are identified. Genes detected by [synthetic lethal](#) detection strategies included those of biological importance within [synthetic lethal pathways](#), those which are actionable drug targets, and those with functional implications for the biological growth mechanisms or vulnerabilities of *CDH1* deficient tumours. It appeared that genes detected by both approaches were highly connected (or of importance) in the [network](#) structure or some [pathways](#) and that there may be some structure with [SLIPT](#) and [siRNA](#) upstream or downstream of each other. However, the complexity of biological [pathways](#) meant that relationships between gene candidates were difficult to discern without formal mathematical and computational approaches and thus these were used to analyse large biological networks.

Network analysis techniques were therefore applied to formalise and quantify the connectivity and importance (centrality) of genes within [pathways](#) (using [PI3K](#) as an example). However, these network techniques were unable to identify distinct differences in the network properties of genes detected as [synthetic lethal](#) candidates by computational or experimental methods. These network metrics support the application of synthetic detection across [pathways](#) (and the findings using [pathways](#) as gene sets in Chapter 4) as neither [synthetic lethal](#) detection approach was biased towards genes of higher importance or connectivity and neither approach was insensitive to genes of lower importance or connectivity. [SLIPT](#) is therefore not biased towards genes with more crucial role in the [pathway](#) as inferred by [pathway](#) connectivity and [centrality](#) measures and detects genes irrespective of [pathway](#) structure.

Similarly, a network hierarchy based on biological context (ordered from receiving extracellular stimuli to affecting downstream [gene expression](#) and cell growth) was

devised to test whether **PI3K** genes of a particular upstream or downstream level were more frequently detected as **synthetic lethal** candidates. However, this approach was unable to ascertain whether genes detected by either method were further upstream or downstream in the **pathway** and there was no statistical evidence that either method differed in which levels of this structure were detected.

A measure of **pathway** structure between individual **SLIPT** and **siRNA** genes within a **pathway** was also devised using the direction of **shortest paths** in a directed **graph** structure. This is amenable to detecting the consensus directionality of the **pathway** across pairs of genes detected by either method. The **pathway** structure methodology developed here is generally applicable to comparison of **node** groups (allowing overlapping) including genes in biological **pathways** and their detection by different methodologies. While the **pathway** structure measure alone is not able to detect structural relationships between gene groups (e.g., **SLIPT** and **siRNA** gene candidates), it is amenable to resampling to determine whether these relationships are statistically significant.

## 5.5 Summary

Together these analyses of biological **pathways**, network metrics, and statistical procedures devised specifically for this purpose were applied to Reactome **pathway** structures to test whether structural relationships exist between **synthetic lethal** candidates. Of particular interest was whether these relationships relate to the differences between the computational (**SLIPT**) and experimental (**siRNA**) **synthetic lethal** candidate partners of *CDH1* (in the **pathways** discussed in Chapter 4).

While biologically relevant relationships were observed in specific **pathways**, there were few detectable structural relationships between **SLIPT** and **siRNA** gene candidates. These candidates did not exhibit significant differences in network connectivity or **centrality** measures. Network analyses were also unable to ascertain whether the candidates detected by either method stratified into upstream and downstream genes on the **pathway** and they likely do not.

A statistical resampling procedure was applied to **shortest path** analysis to test whether pairs of **SLIPT** and **siRNA** gene candidates were more likely to be upstream or downstream of each other. This approach detected very few structural relationships in the **synthetic lethal pathways** identified in Chapter 4. Overall, support for **pathway** structure between **SLIPT** and **siRNA** gene candidates is weak and the direction is inconsistent between **pathways**. Therefore **pathway** structure does not account for

the differences between the [SLIPT](#) and [siRNA](#) gene candidates, although this does support the validity of gene set analyses in Chapter 4 and the [synthetic lethal pathways](#) identified.

Furthermore, the resampling procedure demonstrated in this chapter is more widely applicable to gene states in [network](#) structures and may be of further utility in the analysis of biological [pathways](#) or networks. This approach was able to quantify structural relationships that were otherwise difficult to interpret and to conclusively exclude many potential relationships. In this respect, the network resampling methodology may also be applicable to triage of experimental validation.



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