Contents

Glossary xii

Acronyms xiv

1 Introduction and Literature Review 1
1.1 Cancer Research in the Post-Genomic Era . . . 1
1.1.1 Cancer is a Global Health Issue . . . 2
1.1.1.1 The Genetics and Molecular Biology of Cancers . . . 3
1.1.2 The Genomics Revolution in Cancer Research . . . 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 *CDH1* 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 *CDH1* 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 *CDH1* Null Mutations . . . 37
1.4 Summary and Research Direction of Thesis . . . 37
1.4.1 Thesis Aims . . . 39

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 . . . 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

4 Synthetic Lethal Analysis of Gene Expression Data 96
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

5 Synthetic Lethal Pathway Structure **128**
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 . . . 144
5.4 Discussion . . . 145
5.5 Summary . . . 147

6 Simulation and Modelling of Synthetic Lethal Pathways **149**
6.1 Synthetic Lethal Detection Methods . . . 150
6.1.1 Performance of SLIPT and χ^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

7 Discussion **192**
7.1 Synthetic Lethality and *CDH1* Biology . . . 192
7.1.1 Established Functions of *CDH1* . . . 193
7.1.2 The Molecular Role of *CDH1* 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

References **201**

A Sample Quality **225**
A.1 Sample Correlation 225
A.2 Replicate Samples in TCGA Breast Cancer Data 228

B Software Used for Thesis **232**

C Mutation Analysis in Breast Cancer **241**
C.1 Synthetic Lethal Genes and Pathways 241
C.2 Synthetic Lethal Expression Profiles 242
C.3 Comparison to Primary Screen 245
C.3.1 Resampling Analysis 247
C.4 Compare SLIPT genes 249

D Metagene Analysis **251**
D.1 Pathway Signature Expression 251
D.2 Somatic Mutation 260
D.3 Synthetic Lethal Reactome Metagenes 261
D.4 Expression of Somatic Mutations 263

E Intrinsic Subtyping **266**

F Stomach Expression Analysis **268**
F.1 Synthetic Lethal Genes and Pathways 268
F.2 Comparison to Primary Screen 272
F.2.1 Resampling Analysis 274
F.3 Metagene Analysis 276

G Synthetic Lethal Genes in Pathways **277**

H Network Analysis for Mutation SLIPT **284**

I Pathway Structure for Mutation SLIPT **287**

J Performance of SLIPT and χ^2 **289**
J.1 Correlated Query Genes affects Specificity 295

K Simulations on Graph Structures **301**
K.0.1 Simulations from Inhibiting Graph Structures 302
K.1 Simulation across Graph Structures 305
K.2 Simulations from Complex Graph Structures 309
K.2.1 Simulations from Complex Inhibiting Graphs 312
K.3 Simulations from Pathway Graph Structures 318

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 χ^2 and SLIPT across quantiles 152
6.2 Performance of χ^2 and SLIPT across quantiles with more genes 153
6.3 Performance of χ^2 and SLIPT across quantiles with query correlation . 154
6.4 Performance of χ^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 226
A.2 Correlation analysis and sample removal 227
A.3 Replicate excluded samples 228
A.4 Replicate samples with all remaining 229
A.5 Replicate samples with some excluded 230

C.1 Synthetic lethal expression profiles of analysed samples 243
C.2 Comparison of mtSLIPT to short interfering RNA (siRNA) 245
C.3 Compare mtSLIPT and siRNA genes with correlation 249
C.4 Compare mtSLIPT and siRNA genes with correlation 249
C.5 Compare mtSLIPT and siRNA genes with siRNA viability 250

D.1 Pathway metagene expression profiles 253

D.2 Expression profiles for constituent genes of PI3K 255
D.3 Expression profiles for estrogen receptor related genes 256
D.4 Pathway metagene expression profiles 257
D.5 Expression profiles for p53 related genes 258
D.6 Expression profiles for BRCA related genes 259
D.7 Somatic mutation against the PI3K metagene 260
D.8 Somatic mutation against PIK3CA metagene 263
D.9 Somatic mutation against PI3K protein 264
D.10 Somatic mutation against AKT protein 265

F.1 Synthetic lethal expression profiles of stomach samples 270
F.2 Comparison of SLIPT in stomach to siRNA 272

G.1 Synthetic lethality in the PI3K/AKT pathway 277
G.2 Synthetic lethality in the PI3K/AKT pathway in cancer 278
G.3 Synthetic lethality in the Extracellular Matrix 279
G.4 Synthetic lethality in the GPCR Downstream 280
G.5 Synthetic lethality in the Translation Elongation 281
G.6 Synthetic lethality in the Nonsense-mediated Decay 282
G.7 Synthetic lethality in the 3′ UTR 283

H.1 Synthetic lethality and vertex degree 284
H.2 Synthetic lethality and centrality 285
H.3 Synthetic lethality and PageRank 285

I.1 Structure of synthetic lethality resampling 287

J.1 Performance of χ^2 and SLIPT across quantiles 289
J.2 Performance of χ^2 and SLIPT across quantiles 291
J.3 Performance of χ^2 and SLIPT across quantiles with more genes 293
J.4 Performance of χ^2 and SLIPT across quantiles with query correlation . 295
J.5 Performance of χ^2 and SLIPT across quantiles with query correlation . 297
J.6 Performance of χ^2 and SLIPT across quantiles with query correlation and more genes 299

K.1 Performance of simulations on a simple graph 301
K.2 Performance of simulations on an inhibiting graph 302
K.3 Performance of simulations on a constructed graph with inhibition . . . 303
K.4 Performance of simulations on a constructed graph with inhibition . . . 304
K.5 Detection of synthetic lethality within a graph structure 305
K.6 Detection of synthetic lethality within an inhibiting graph 307
K.7 Detection of synthetic lethality within an inhibiting graph 308
K.8 Performance of simulations on a branching graph 309
K.9 Performance of simulations on a complex graph 310
K.10 Performance of simulations on a large graph 311
K.11 Performance of simulations on a branching graph with inhibition 312
K.12 Performance of simulations on a branching graph with inhibition 313

K.13 Performance of simulations on a complex graph with inhibition 314
K.14 Performance of simulations on a complex graph with inhibition 315
K.15 Performance of simulations on a large constructed graph with inhibition 316
K.16 Performance of simulations on a large constructed graph with inhibition 317
K.17 Performance of simulations on the $G_{\alpha i}$ signalling pathway 318
K.18 Performance of simulations including the $G_{\alpha i}$ signalling pathway 319

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 *et al.* (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 *CDH1* from SLIPT . . . 98
4.2 Pathways for *CDH1* partners from SLIPT . . . 99
4.3 Pathways for clusters of *CDH1* partners from SLIPT . . . 104
4.4 ANOVA for synthetic lethality and correlation with *CDH1* . . . 107
4.5 Comparison of Synthetic Lethal Interaction Prediction Tool (SLIPT) genes against secondary siRNA screen . . . 111
4.6 Pathways for *CDH1* partners from SLIPT and siRNA . . . 112
4.7 Pathways for *CDH1* partners from SLIPT . . . 115
4.8 Pathways for *CDH1* partners from SLIPT and siRNA primary screen . 116
4.9 Examples of candidate metagenes synthetic lethal for *CDH1* 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 . . . 232

C.1 Candidate synthetic lethal gene partners of *CDH1* from mtSLIPT . . . 241
C.2 Pathways for *CDH1* partners from mtSLIPT . . . 242
C.3 Pathways for clusters of *CDH1* partners from mtSLIPT . . . 244
C.4 Pathways for *CDH1* partners from mtSLIPT and siRNA . . . 246
C.5 Pathways for *CDH1* partners from mtSLIPT . . . 247
C.6 Pathways for *CDH1* partners from mtSLIPT and siRNA primary screen 248

D.1 Candidate synthetic lethal metagenes against *CDH1* from mtSLIPT . . 262

E.1 Comparison of intrinsic subtypes 266

F.1 Synthetic lethal gene partners of *CDH1* from SLIPT in stomach cancer 268
F.2 Pathways for *CDH1* partners from SLIPT in stomach cancer 269
F.3 Pathways for clusters of *CDH1* partners in stomach SLIPT 271
F.4 Pathways for *CDH1* partners from SLIPT and siRNA 273
F.5 Pathways for *CDH1* partners from SLIPT in stomach cancer 274
F.6 Pathways for *CDH1* partners from SLIPT in stomach and siRNA . . . 275
F.7 Synthetic lethal metagenes against *CDH1* in stomach cancer 276

H.1 ANOVA for synthetic lethality and vertex degree 286
H.2 ANOVA for synthetic lethality and information centrality 286
H.3 ANOVA for synthetic lethality and PageRank centrality 286

I.1 Resampling for pathway structure of synthetic lethal detection methods 288

Glossary

bioinformatics	Statistical or computational approaches to biological data or research tools.
chemoprevention	The use of drugs to prevent early-stage cancers, generally applied to high-risk mutation carriers.
E-cadherin	Epithelial cadherin (calcium-dependent adhesion), a cell-adhesion protein encoded by *CDH1*.
essential	A gene which is required to be functional or expressed for a cell or organism to be viable, grow or develop.
familial	A trait recurrently occurring in families, not necessarily with a genetic cause.
functional redundancy	Genes which perform a common function, also known as genetic redundancy.
gene expression	A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells.
genome	All of the DNA sequence in the genome.
genomic	The use of data from all genes in the genome.
graph or network	A mathematical structure modelling or depicting the relationships between elements.
metagene	A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition.
mutant	A variant or dysfunctional phenotype arising from a mutation in a gene.
mutation	A change in DNA sequence that disrupts gene function.

oncogene	A gene that potentially causes cancer, typically by over-expression or mutant gene variants.
pleiotropy	When a gene has multiple biological functions.
sporadic cancer	Cancers which do occur in patients with a family history or carry a high-risk genetic variant.
synthetic lethal	Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately.
targeted therapy	Cancer treatment that specifically acts against a molecular target, in contrast to standard chemotherapy.
treatment	Medical procedures for a disease to improve patient outcomes.
tumour suppressor	A gene potentially causes cancer, typically by disruption of functions which protect the cell from cancer.

Acronyms

ANOVA	Analysis of Variance.
DNA	Deoxyribonucleic Acid.
GPCR	G Crotein Coupled Receptor.
HDGC	Hereditary Diffuse Gastric Cancer.
mtSLIPT	Synthetic Lethal Interaction Prediction Tool (against mutation).
NMD	Nonsense-Mediated Decay.
RNAi	RNA Interference.
siRNA	Short Interfering RNA.
SLIPT	Synthetic Lethal Interaction Prediction Tool.
TCGA	The Cancer Genome Atlas (genomics project).
UTR	Untranslated Region (of mRNA).

Chapter 7

Discussion

This thesis combines analysis of gene expression data from The Cancer Genome Atlas (TCGA) with experimental screening results (Telford *et al.*, 2015) to demonstrate synthetic lethal discovery for partners of *CDH1*. Together these findings further elucidate the functions of *CDH1* in the cell, functional redundancy in cancer, and represent potential targets against loss of *CDH1* function. These candidate synthetic lethal genes were further investigated for relationships within synthetic lethal pathways, developing a network-based approach to compare genes identified in genomics experiments and analyses in the process.

The synthetic lethal detection methodology, SLIPT, was applied to gene expression data throughout this thesis and was evaluated with simulated data. A simulation procedure was developed to stringently generate gene expression data from known synthetic lethal partners in simulated data. These simulations included simple and complex correlation structures and modelling synthetic lethal genes within pathways. Together, these results demonstrate SLIPT as a robust widely applicable gene expression analysis procedure (for which an R package has been released) for discovery of synthetic lethal partner genes. Performance of SLIPT on simulated data also highlights the strengths of the procedure and future directions to improve upon it.

7.1 Synthetic Lethality and *CDH1* Biology

The *CDH1* tumour suppressor gene was the focus of identifying synthetic lethal partners to demonstrate the novel SLIPT methodology. This gene is important in sporadic breast and stomach cancers, in addition to familial syndromes, such as hereditary diffuse gastric cancer (HDGC). The analysis of synthetic lethal partners of *CDH1* in breast and stomach cancers was enabled by the availability of molecular data (Bass

et al., 2014; Koboldt *et al.*, 2012) and a synthetic lethal screen conducted in MCF10A breast cells (Chen *et al.*, 2014; Telford *et al.*, 2015).

Synthetic lethal interactions arise due to functional redundancy (Boone *et al.*, 2007; Fece de la Cruz *et al.*, 2015; Kaelin, Jr, 2005) and as such the synthetic lethal partners of *CDH1* indicates the wide-ranging biological functions that E-cadherin is involved in. The diverse synthetic lethal pathways identified supports the known pleiotropic nature of the *CDH1* gene by detecting established functions of *CDH1*, replicating candidates from an experimental screen (Telford *et al.*, 2015), and identifying novel interactions with candidate genes and pathways for further investigation. The highly pleiotropic functions of E-cadherin was also consistent with *CDH1* being a tumour suppressor gene.

7.1.1 Established Functions of *CDH1*

The *CDH1* has established functions in cell-cell communication and maintaining the cytoskeleton, specifically with cell-cell adhesion by forming tight junctions and the adherens complex. More recently, additional functions of *CDH1* in the extracellular matrix and fibrin clotting have also been identified. Synthetic lethal interactions within biological pathways (i.e., partners in the same pathway as the query gene) are expected according to previous synthetic lethal experiments (Boone *et al.*, 2007; Kelley and Ideker, 2005). Synthetic lethal interactions identified in these pathways are consistent with these being functions of *CDH1*, in addition to potentially actionable targets against cancers.

7.1.2 The Molecular Role of *CDH1* in Cancer

The involvement of *CDH1* in the extracellular matrix is important in cancers as it indicates a mechanism by which *CDH1* loss may affect the tumour microenvironment, contributing to its role as a tumour and invasion suppressor. Furthermore, perturbations in the extracellular matrix and tumour microenvironment present a means by which to specifically inhibit (cancerous) *CDH1*-deficient cells, in addition to those currently being considered. These may be further supported in further investigations with 3D cell culture, "organoid", or mouse xenograft cancer models.

In contrast, many of the pathways involved in cell signalling, including G protein coupled receptors, were identified by SLIPT in addition to the experimental screen (Telford *et al.*, 2015). These support the previous results in cell line models, that these pathways are essential to the growth of *CDH1*-deficient cancers and present a potential vulnerability specific to these (cancerous) cells. Furthermore, the replication of

synthetic lethality of *CDH1* with cell signalling pathways in TCGA data across cancer types and genetic backgrounds robustly supports these pathways being clinically applicable beyond the genetic background of the model system of *CDH1*$^{-/-}$ MCF10A cells (Chen *et al.*, 2014). While the specific synthetic lethal genes were not as consistently detected between the SLIPT analyses and siRNA screen (Telford *et al.*, 2015), they were sufficient to identify synthetic lethal pathways for further experimental investigation, which are more likely to be replicated between genetic backgrounds (Dixon *et al.*, 2008). Together these results demonstrate how SLIPT can be integrated with an experimental screen to triage potential therapeutic targets for further pre-clinical investigation.

The analysis of expression data with SLIPT is also indicative of additional biological mechanisms of synthetic lethality in pathways beyond those identified in screening experiments (Telford *et al.*, 2015). In particular, translation and regulatory pathways, involving 3′ untranslated regions (UTRs) and nonsense-mediated decay (NMD), were identified as candidate synthetic lethal pathways with *CDH1* by SLIPT. These pathways represent downstream targets regulated by the putative synthetic lethal signalling pathways which cancer cells are dependent on for sustained protein expression to proliferate and evade host defense processes such as apoptosis and immune responses (Gao and Roux, 2015) .

7.2 Significance

7.2.1 Synthetic Lethality in the Genomic Era

Development of an effective synthetic lethal discovery tool for bioinformatic analysis has a wide range of applications in genetics research including functional genomics, medical and agricultural applications. The SLIPT approach demonstrated in this thesis is widely applicable to other genes and biological questions. In addition to further query of cancer genes, including other tissues, synthetic lethal gene functions are also of wider interest for their implications for genetic redundancy. Highly redundant genes, and the genetically robust systems they give rise to, are of further relevance to evolutionary, developmental, and systems biology to understand how these change over time and play a role in fundamental development of cell types, in addition to cancers (Boone *et al.*, 2007; Nowak *et al.*, 1997; Tischler *et al.*, 2008).

Developmental genes in particular, are highly evolutionary conserved and subject to high rates of redundancy (Fromental-Ramain *et al.*, 1996; Kockel *et al.*, 1997; Nowak

et al., 1997). These are often difficult to study with conventional functional genetics since individual knockouts of redundant genes do not necessarily have a mutant phenotype. Identifying genes with a common function is therefore also important to the study of developmental genes with unknown functions. Synthetic lethal discovery methods such as SLIPT provide a genomic approach to further systematic characterisation of gene function including such highly redundant developmental genes.

Similarly, variants of unknown significance and modifier loci are a major concerns in human genetics, including "monogenic" and "rare" diseases. Many of these could potentially be difficult to characterise individually due to synthetic lethal interactions where additional loci contribute to the disease (or only compensate for some variants). As such systematic identification of synthetic lethal interactions also has applications in the study of such "oligogenic" diseases along with similar applications in the study of heritability for traits including agricultural genomic selection.

Genetic redundancy is also a concern in pharmacology. Polypharmacology and network medicine are rationales to account for this by using drugs with multiple (known and specific) targets (Barabási *et al.*, 2011; Hopkins, 2008). Further characterisation of synthetic lethal genes will be valuable to the design of effective multi-target drugs or combination therapies in a range of therapeutic applications including molecular targeted therapies against cancer for which combination therapies are a popular solution for acquired resistance against individual targeted therapies. Characterisation of genetic interactions and combination therapies also has the potential to expand pharmacogenomic investigations. These may elucidate the impact of genotypes at multiple loci, which lead to adverse effects in a subset of the population due to variants in synthetic lethal genes.

Furthermore, redundant functions and synthetic lethal interactions also present a means to expand upon the concept of the "minimal" genome (Hutchison *et al.*, 2016). It is important to account for essential gene functions that are performed by redundant genes (or in combination with pleiotropic genes), rather than simply those that are perturbed by individual genes. An essential gene approach is likely to produce an underestimate that does not account for synthetic lethal interactions.

Synthetic lethal interactions are fundamentally important throughout genetics. Further understanding of them in a genomic context, facilitated by methods such as SLIPT, would contribute towards deeper understanding of gene functions and their role in traits or diseases in the post-genomic era. Genes do not function in isolation and understanding them in the context of the complexity of a cell and across genetic

backgrounds is essential to further characterise their functions and ensure that findings can be validated or applied beyond experimental systems.

7.2.2 Clinical Interventions based on Synthetic Lethality

Synthetic lethal discovery with SLIPT is of particular interest in cancer research as a complementary approach to discovery of synthetic lethal drug targets. The cancer research community relies on cell line and mouse models for screening and validation experiments (Fece de la Cruz *et al.*, 2015) which would benefit from integration with gene expression analysis as demonstrated for *CDH1* and the screen conducted by Telford *et al.* (2015). Synthetic lethal drug design against cancer mutations, including gene loss or over-expression, could lead to a revolution in cancer therapy and chemoprevention. Such therapeutics would enable personalised treatment for cancer patients and high risk individuals. Examples of the synthetic lethal strategy (Bryant *et al.*, 2005; Farmer *et al.*, 2005) for cancer treatment have been shown to be clinically effective McLachlan *et al.* (2016). Many large-scale RNA interference (RNAi) screens have been conducted recently, aiming to discover gene function and drug targets for similar application with other cancer genes, including cancers in other tissues (Fece de la Cruz *et al.*, 2015).

While SLIPT analysis and RNAi screens represent a significant step towards anti-cancer medicines, further validation is required to ensure that the synthetic lethal candidate genes and pathways identified for *CDH1* in breast and stomach cancer are applicable against *CDH1*-deficient cancers in the clinic. Validation with RNAi or pharmacological inhibitors is needed since false positives may occur in SLIPT analysis or siRNA screens. These candidates will need to be tested in pre-clinical models (cell lines and mouse xenografts) before proceeding to clinical trials. A therapeutic intervention will also require a targeted therapeutic to develop developed or repurposed against the synthetic lethal partner. Drug targets could be triaged from synthetic lethal genes by functions known to be amenable to drugs or structure with conserved specific sites that are not homologous to other genes, or those with existing drugs approved in trial for other applications. Both structure-aided drug design and compound screening are viable ways to target synthetic lethal partners.

Targeted therapeutics designed based on synthetic lethal interactions could expand the applications of "precision medicine" against molecular targets. Synthetic lethality expands the range of cancer genes which can be (indirectly) targeted to include tumour suppressor genes with loss of function, such as *CDH1*. Oncogenes with disrupted functions that are over-expressed or highly homologous to non-cancerous proto-oncogenes,

such as *MYC*, *EGFR* or *KRAS*, may also be targeted by synthetic lethality. Applications against tumour suppressor genes is particularly important, as these cannot be approached by careful dosing. Synthetic lethal drug design has the benefit of being highly specific against a particular genotype (such as CDH1$^{-/-}$) with the potential for targeted therapies with a wide therapeutic index and few adverse effects, in contrast to many current anti-cancer drug regimens (Hopkins, 2008; Kaelin, Jr, 2009). These properties are highly desirable for chemoprevention applications, such as treatment against *CDH1*-deficient in HDGC patients (Guilford *et al.*, 2010), as an alternative to monitoring or surgery.

7.3 Future Directions

While further validation and pre-clinical testing is required to translate the findings for *CDH1* to cancer therapy or prevention, there are also further avenues for research into the detection of synthetic lethality in gene expression and other genomics data. The SLIPT methodology is amenable to wider application against a range of genes for which loss of function is deleterious, including other cancer genes in breast cancer or other tissues. Synthetic lethal interactions are functionally informative, particularly for mode-of-action of known drug targets, and are also relevant for identifying functions of newly characterised genes in genomics studies and designing specific interventions against cells with loss of function in cancer and other diseases. Thus synthetic lethal detection using SLIPT in expression data could be further used for many other genes, including others relevant to human health and disease.

These investigations do not need to be limited to expression data. While expression as a measure of gene function has been the focus of this thesis, other genomics data could be used for a similar purpose for SLIPT analysis. These include DNA copy number, DNA methylation, histone activation, mutation status, protein abundance, and protein activation state. For some applications or genes, these molecular profiles may be more informative of gene function and synthetic lethal relationships. However, expression was the focus of the investigations thus far as a widely accepted measure of gene function which has widely available genomics data. SLIPT is compatible with each of these data types (if the thresholds are selected appropriately) and may perform better for some applications with these molecular profiles or a weighted combination of these. As demonstrated, SLIPT is also suitable for future investigations with pathway metagenes and other summary data as well.

It may also be possible to improve the performance of SLIPT with refinements to the statistical or computational approach. This thesis has focused on rational query-based approach which computes relatively quickly, even in R (R Core Team, 2016), and is relatively intuitive to interpret. These computations are compatible with parallel computing and the computational resources may be further reduced by using a different computing language. The `slipt` R package has been documented and released open-source (as described in Section 3.5) to facilitate further development, wider adoption, or comparison with other scientific software for similar purposes.

Alternative methods may be also improve on the statistical performance of SLIPT. In particular, the sensitivity was generally as issue with higher numbers of synthetic lethal partners in simulated data. While approaches using continuous data such as Pearson correlation and linear regression did not perform as well as SLIPT, they could be improved. A least squares regression approach in particular, enables multiple measures of relationships such as the coefficients of the fitted curve and significance of the fit (computed from the residuals). A linear modelling approach using regression is also amenable to refinement such as extending from fitting a linear relationship to a polynomial or logistic regression. Another benefit to fitting linear models is that these would enable the conditioning of known synthetic lethal partners to identify subtle signatures of further interacting partners.

This approach could also be applied iteratively on the strongest candidates from previous synthetic lethal analyses in further rounds of prediction conditioned upon them. Similarly, synthetic lethal prediction could also be approached with a Bayesian framework which is also amenable to Bayesian priors on known or previously predicted synthetic lethal partners. Either of these approaches has the potential to improve upon the synthetic lethal predictions which have been demonstrated as possible and biologically relevant by SLIPT.

7.4 Conclusions

Synthetic lethal interactions are important for understanding gene function and development of highly specific targeted anti-cancer treatments. Synthetic lethality could expand the repertoire of applications for precision cancer medicine to indirectly targeting loss of function in tumour suppressor genes. Synthetic lethal discovery with experimental screening is error prone and limited by the model systems in which it is performed. There is a need for bioinformatics tool to predict synthetic lethal interactions from gene expression data facilitates rapid identification of synthetic lethal candidates to augment functional genetic screens and cancer drug target triage. I present the original Synthetic Lethal Interaction Prediction Tool (SLIPT) methodology as a statically robust procedure which performs this analysis.

The SLIPT methodology has been demonstrated to identify biologically relevant genes and pathways. An comprehensive analysis of synthetic lethal partners of the *CDH1* was performed in TCGA breast cancer data (Koboldt *et al.*, 2012) with many of these findings replicated in stomach cancer data (Bass *et al.*, 2014). These genes clustered into several distinct groups, with distinct biological functions and elevated expression in different clinical subtypes. These analyses identified of synthetic lethal candidates in the $G_{\alpha i}$ signalling, cytoplasmic microfibres, and extracellular fibrin clotting pathways which were validated in an siRNA screen performed by Telford *et al.* (2015) and consistent with the known cytoskeletal and cell signalling roles of E-cadherin. These findings support interventions against these pathways being applicable to specific cancer therapeutics beyond the pre-clinical cell line models in which they were validated. SLIPT has also identified synthetic lethal partners in novel pathways for *CDH1* including the regulation of immune signalling and translational elongation which extend the range of pleiotropic functions of *CDH1* and present further biological mechanisms to investigate the malignancy and vulnerabilities of *CDH1*-deficient cancers.

While some of these pathways are not expected to be detected in an isolated experimental cell line model, pathway structure may have accounted for this disparity. Thus synthetic lethal candidates detected by SLIPT and siRNA were compared within graph structures of the candidate synthetic lethal pathways. However, this did not generally account for differences between detection by these approaches. Neither synthetic lethal detection methodology preferentially detected genes of more importance or connectivity in pathway structures using established network metrics. Nor could it

be generally established that SLIPT gene candidates were upstream or downstream of siRNA gene candidates in pathway structures across biological pathways.

Pathway graph structures were also included in investigations with simulated data to ascertain whether the SLIPT procedure performed desirably in data with complex correlation structures derived based on biological pathways. A simulation procedure was developed based on a statistical model of synthetic lethality which generates multivariate normal data with known synthetic lethal partners and correlation structures. The SLIPT methodology had high statistical performance, particularly when detecting few synthetic lethal genes, with large sample sizes, and a background of many non synthetic lethal genes to distinguish true partners from. This method had high specificity, performed better than Pearson correlation or the χ^2-test, and had had optimal performance across simulation parameter combinations for the thresholds used throughout this thesis. These findings were robust across correlation structures, including those derived from complex pathway structures containing strong positive and negative correlations between genes. Together, these findings support the release of the SLIPT software R packages and the application of the method to identify synthetic lethal genes within pathways and use candidate synthetic lethal genes to identify synthetic lethal pathways as demonstrated in this thesis.

Therefore, I present a widely applicable synthetic lethal procedure using gene expression data for wider use in genomics research, including the development of precision cancer medicine. This methodology is supported by the release of a software package in R, simulation results based on a statistical model of synthetic lethality, the demonstration of bioinformatics and network biology investigations into interactions with the *CDH1* gene in breast and stomach cancers.

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