

Contents

| | |
|---------------------------------------------------------------------|-------------|
| Glossary | xi |
| Acronyms | xiii |
| 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 | 23 |
| 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 |
| 1.3.2 | Hereditary Diffuse Gastric (and Lobular Breast) Cancer | 34 |
| 1.3.3 | Cell Line Models of <i>CDH1</i> Null Mutations | 35 |
| 1.4 | Summary and Research Direction of Thesis | 36 |
| 1.4.1 | Thesis Aims | 37 |
| 2 | Methods and Resources | 41 |
| 2.1 | Bioinformatics Resources for Genomics Research | 41 |
| 2.1.1 | Public Data and Software Packages | 41 |
| 2.1.1.1 | Cancer Genome Atlas Data | 42 |
| 2.1.1.2 | Reactome and Annotation Data | 43 |
| 2.2 | Data Handling | 43 |
| 2.2.1 | Normalisation | 43 |
| 2.2.2 | Sample Triage | 43 |
| 2.2.3 | Metagenes and the Singular Value Decomposition | 44 |
| 2.2.4 | Candidate Triage and Integration with Screen Data | 46 |
| 2.3 | Techniques | 46 |
| 2.3.1 | Statistical Procedures and Tests | 47 |
| 2.3.2 | Gene Set Over-representation Analysis | 48 |
| 2.3.3 | Clustering | 48 |
| 2.3.4 | Heatmap | 48 |
| 2.3.5 | Modelling and Simulations | 49 |
| 2.3.5.1 | Receiver Operating Characteristic Curves | 50 |
| 2.3.6 | Resampling Analysis | 50 |
| 2.4 | Pathway Structure Methods | 51 |
| 2.4.1 | Network and Graph Analysis | 51 |
| 2.4.2 | Sourcing Graph Structure Data | 52 |
| 2.4.3 | Constructing Pathway Subgraphs | 52 |
| 2.4.4 | Network Analysis Metrics | 53 |
| 2.5 | Implementation | 54 |
| 2.5.1 | Computational Resources and Linux Utilities | 54 |
| 2.5.2 | R Language and Packages | 55 |
| 2.5.3 | High Performance and Parallel Computing | 58 |
| 3 | Methods Developed During Thesis | 60 |
| 3.1 | A Synthetic Lethal Detection Methodology | 60 |
| 3.2 | Synthetic Lethal Simulation and Modelling | 62 |
| 3.2.1 | A Model of Synthetic Lethality in Expression Data | 63 |
| 3.2.2 | Simulation Procedure | 67 |
| 3.3 | Detecting Simulated Synthetic Lethal Partners | 70 |
| 3.3.1 | Binomial Simulation of Synthetic Lethality | 70 |
| 3.3.2 | Multivariate Normal Simulation of Synthetic Lethality | 72 |
| 3.3.2.1 | Multivariate Normal Simulation with Correlated Genes | 74 |

| | | |
|----------|--------------------------------------------------------------|------------|
| 3.3.2.2 | Specificity with Query-Correlated Pathways | 82 |
| 3.4 | Graph Structure Methods | 84 |
| 3.4.1 | Upstream and Downstream Gene Detection | 84 |
| 3.4.1.1 | Permutation Analysis for Statistical Significance | 85 |
| 3.4.2 | Simulating Gene Expression from Graph Structures | 86 |
| 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 | 92 |
| 3.5.3.1 | Sampling Simulated Data from Graph Structures | 92 |
| 3.5.3.2 | Plotting Directed Graph Structures | 92 |
| 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 Centrality | 138 |
| 5.2.2.1 | Information Centrality | 138 |
| 5.2.2.2 | PageRank Centrality | 140 |
| 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 | 146 |
| 5.5 | Summary | 148 |
| 6 | Simulation and Modelling of Synthetic Lethal Pathways | 150 |
| 6.1 | Synthetic Lethal Detection Methods | 151 |
| 6.1.1 | Performance of SLIPT and χ^2 across Quantiles | 152 |
| 6.1.1.1 | Correlated Query Genes affects Specificity | 155 |
| 6.1.2 | Alternative Synthetic Lethal Detection Strategies | 157 |
| 6.1.2.1 | Correlation for Synthetic Lethal Detection | 158 |
| 6.1.2.2 | Testing for Bimodality with BiSEp | 159 |
| 6.2 | Simulations with Graph Structures | 160 |
| 6.2.1 | Performance over Graph Structures | 161 |
| 6.2.1.1 | Simple Graph Structures | 161 |
| 6.2.1.2 | Constructed Graph Structures | 164 |
| 6.2.2 | Performance with Inhibitions | 166 |
| 6.2.3 | Synthetic Lethality across Graph Structures | 172 |
| 6.2.4 | Performance within a Large Simulated Datasets | 175 |
| 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 Large Simulated Datasets | 183 |
| 6.4 | Discussion | 186 |
| 6.4.1 | Simulation Procedure | 186 |
| 6.4.2 | Comparing Methods with Simulated Data | 187 |
| 6.4.3 | Design and Performance of SLIPT | 188 |
| 6.4.4 | Simulations from Graph Structures | 190 |
| 6.5 | Summary | 191 |
| 7 | Discussion | 192 |
| 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 |
| | Bibliography | 201 |

| | | |
|----------|--------------------------------------------------------|------------|
| A | Sample Quality | 225 |
| A.1 | Sample Correlation | 225 |
| A.2 | Replicate Samples in TCGA Breast Cancer Data | 227 |
| B | Software Used for Thesis | 231 |
| C | Mutation Analysis in Breast Cancer | 240 |
| C.1 | Synthetic Lethal Genes and Pathways | 240 |
| C.2 | Synthetic Lethal Expression Profiles | 241 |
| C.3 | Comparison to Primary Screen | 244 |
| C.3.1 | Resampling Analysis | 246 |
| C.4 | Compare SLIPT genes | 248 |
| D | Metagene Analysis | 250 |
| D.1 | Pathway Signature Expression | 250 |
| D.2 | Synthetic Lethal Reactome Metagenes | 254 |
| E | Intrinsic Subtyping | 255 |
| F | Stomach Expression Analysis | 257 |
| F.1 | Synthetic Lethal Genes and Pathways | 257 |
| F.2 | Comparison to Primary Screen | 261 |
| F.2.1 | Resampling Analysis | 263 |
| F.3 | Metagene Analysis | 265 |
| G | Synthetic Lethal Genes in Pathways | 266 |
| H | Network Analysis for Mutation SLIPT | 273 |
| I | Pathway Structure for Mutation SLIPT | 276 |
| J | Performance of SLIPT and χ^2 | 280 |
| J.1 | Correlated Query Genes affects Specificity | 286 |
| K | Simulations on Graph Structures | 292 |
| K.0.1 | Simulations from Inhibiting Graph Structures | 293 |
| K.1 | Simulation across Graph Structures | 296 |
| K.2 | Simulations from Complex Graph Structures | 300 |
| K.2.1 | Simulations from Complex Inhibiting Graphs | 303 |
| K.3 | Simulations from Pathway Graph Structures | 309 |

List of Figures

| | | |
|------|----------------------------------------------------------------------------|-----|
| 1.1 | Synthetic genetic interactions | 13 |
| 1.2 | Synthetic lethality in cancer | 17 |
| 2.1 | Read count density | 45 |
| 2.2 | Read count sample mean | 45 |
| 3.1 | Framework for synthetic lethal prediction | 61 |
| 3.2 | Synthetic lethal prediction adapted for mutation | 62 |
| 3.3 | A model of synthetic lethal gene expression | 64 |
| 3.4 | Modelling synthetic lethal gene expression | 65 |
| 3.5 | Synthetic lethality with multiple genes | 66 |
| 3.6 | Simulating gene function | 68 |
| 3.7 | Simulating synthetic lethal gene function | 68 |
| 3.8 | Simulating synthetic lethal gene expression | 69 |
| 3.9 | Performance of binomial simulations | 71 |
| 3.10 | Comparison of statistical performance | 71 |
| 3.11 | Performance of multivariate normal simulations | 73 |
| 3.12 | Simulating expression with correlated gene blocks | 75 |
| 3.13 | Simulating expression with correlated gene blocks | 76 |
| 3.14 | Synthetic lethal prediction across simulations | 78 |
| 3.15 | Performance with correlations | 79 |
| 3.16 | Comparison of statistical performance with correlation structure | 80 |
| 3.17 | Performance with query correlations | 81 |
| 3.18 | Statistical evaluation of directional criteria | 82 |
| 3.19 | Performance of directional criteria | 83 |
| 3.20 | Simulated graph structures | 87 |
| 3.21 | Simulating expression from a graph structure | 88 |
| 3.22 | Simulating expression from graph structure with inhibitions | 89 |
| 3.23 | Demonstration of violin plots with custom features | 93 |
| 3.24 | Demonstration of annotated heatmap | 93 |
| 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 | 141 |
| 5.8 | Structure of synthetic lethality resampling | 143 |
| 6.1 | Performance of χ^2 and SLIPT across quantiles | 153 |
| 6.2 | Performance of χ^2 and SLIPT across quantiles with more genes | 154 |
| 6.3 | Performance of χ^2 and SLIPT across quantiles with query correlation | 155 |
| 6.4 | Performance of χ^2 and SLIPT across quantiles with query correlation and more genes | 156 |
| 6.5 | Performance of negative correlation and SLIPT | 159 |
| 6.6 | Simple graph structures | 162 |
| 6.7 | Performance of simulations on a simple graph | 163 |
| 6.8 | Performance of simulations is similar in simple graphs | 164 |
| 6.9 | Performance of simulations on a pathway | 165 |
| 6.10 | Performance of simulations on a simple graph with inhibition | 167 |
| 6.11 | Performance is higher on a simple inhibiting graph | 169 |
| 6.12 | Performance of simulations on a constructed graph with inhibition | 170 |
| 6.13 | Performance is affected by inhibition in graphs | 171 |
| 6.14 | Detection of synthetic lethality within a graph structure | 173 |
| 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 | 179 |
| 6.18 | Performance of simulations on the PI3K cascade | 182 |
| 6.19 | Performance of simulations including the PI3K cascade | 184 |
| 6.20 | Performance on pathways improves with more genes | 185 |
| 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 | 242 |
| C.2 | Comparison of mtSLIPT to short interfering RNA (siRNA) | 244 |
| C.3 | Compare mtSLIPT and siRNA genes with correlation | 248 |
| C.4 | Compare mtSLIPT and siRNA genes with correlation | 248 |
| C.5 | Compare mtSLIPT and siRNA genes with siRNA viability | 249 |
| D.1 | Pathway metagene expression profiles | 252 |

| | | |
|------|-------------------------------------------------------------------------------------------------------|-----|
| D.2 | Expression profiles for estrogen receptor related genes | 253 |
| F.1 | Synthetic lethal expression profiles of stomach samples | 259 |
| F.2 | Comparison of SLIPT in stomach to siRNA | 261 |
| G.1 | Synthetic lethality in the PI3K/AKT pathway | 266 |
| G.2 | Synthetic lethality in the PI3K/AKT pathway in cancer | 267 |
| G.3 | Synthetic lethality in the Extracellular Matrix | 268 |
| G.4 | Synthetic lethality in the GPCR Downstream | 269 |
| G.5 | Synthetic lethality in the Translation Elongation | 270 |
| G.6 | Synthetic lethality in the Nonsense-mediated Decay | 271 |
| G.7 | Synthetic lethality in the 3' UTR | 272 |
| H.1 | Synthetic lethality and vertex degree | 273 |
| H.2 | Synthetic lethality and centrality | 274 |
| H.3 | Synthetic lethality and PageRank | 274 |
| I.1 | Structure of synthetic lethality resampling | 276 |
| J.1 | Performance of χ^2 and SLIPT across quantiles | 280 |
| J.2 | Performance of χ^2 and SLIPT across quantiles | 282 |
| J.3 | Performance of χ^2 and SLIPT across quantiles with more genes | 284 |
| J.4 | Performance of χ^2 and SLIPT across quantiles with query correlation | 286 |
| J.5 | Performance of χ^2 and SLIPT across quantiles with query correlation | 288 |
| J.6 | Performance of χ^2 and SLIPT across quantiles with query correlation and more genes | 290 |
| K.1 | Performance of simulations on a simple graph | 292 |
| K.2 | Performance of simulations on an inhibiting graph | 293 |
| K.3 | Performance of simulations on a constructed graph with inhibition | 294 |
| K.4 | Performance of simulations on a constructed graph with inhibition | 295 |
| K.5 | Detection of synthetic lethality within a graph structure | 296 |
| K.6 | Detection of synthetic lethality within an inhibiting graph | 298 |
| K.7 | Detection of synthetic lethality within an inhibiting graph | 299 |
| K.8 | Performance of simulations on a branching graph | 300 |
| K.9 | Performance of simulations on a complex graph | 301 |
| K.10 | Performance of simulations on a large graph | 302 |
| K.11 | Performance of simulations on a branching graph with inhibition | 303 |
| K.12 | Performance of simulations on a branching graph with inhibition | 304 |
| K.13 | Performance of simulations on a complex graph with inhibition | 305 |
| K.14 | Performance of simulations on a complex graph with inhibition | 306 |
| K.15 | Performance of simulations on a large constructed graph with inhibition | 307 |
| K.16 | Performance of simulations on a large constructed graph with inhibition | 308 |
| K.17 | Performance of simulations on the $G_{\alpha i}$ signalling pathway | 309 |
| K.18 | Performance of simulations including the $G_{\alpha i}$ signalling pathway | 310 |

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. | 44 |
| 2.2 | Computers used during thesis | 54 |
| 2.3 | Linux utilities and applications used during thesis | 55 |
| 2.4 | R installations used during thesis | 56 |
| 2.5 | R Packages used during thesis | 56 |
| 2.6 | R packages developed during thesis | 58 |
| 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 | 140 |
| 5.4 | Resampling for pathway structure of synthetic lethal detection methods | 145 |
| 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 . . . | 240 |
| C.2 | Pathways for <i>CDH1</i> partners from mtSLIPT | 241 |
| C.3 | Pathways for clusters of <i>CDH1</i> partners from mtSLIPT | 243 |
| C.4 | Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA | 245 |
| C.5 | Pathways for <i>CDH1</i> partners from mtSLIPT | 246 |
| C.6 | Pathways for <i>CDH1</i> partners from mtSLIPT and siRNA primary screen | 247 |
| D.1 | Candidate synthetic lethal metagenes against <i>CDH1</i> from mtSLIPT . . | 254 |

| | | |
|-----|----------------------------------------------------------------------------|-----|
| E.1 | Comparison of intrinsic subtypes | 255 |
| F.1 | Synthetic lethal gene partners of <i>CDH1</i> from SLIPT in stomach cancer | 257 |
| F.2 | Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer | 258 |
| F.3 | Pathways for clusters of <i>CDH1</i> partners in stomach SLIPT | 260 |
| F.4 | Pathways for <i>CDH1</i> partners from SLIPT and siRNA | 262 |
| F.5 | Pathways for <i>CDH1</i> partners from SLIPT in stomach cancer | 263 |
| F.6 | Pathways for <i>CDH1</i> partners from SLIPT in stomach and siRNA | 264 |
| F.7 | Synthetic lethal metagenes against <i>CDH1</i> in stomach cancer | 265 |
| H.1 | ANOVA for synthetic lethality and vertex degree | 275 |
| H.2 | ANOVA for synthetic lethality and information centrality | 275 |
| H.3 | ANOVA for synthetic lethality and PageRank centrality | 275 |
| I.1 | Resampling for pathway structure of synthetic lethal detection methods | 277 |

Glossary

| | |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| centrality | A network metric which identifies important vertices . |
| edge or link | A relationship connecting a pair of elements of a graph structure or network, may be weighted or directional. |
| gene expression | A measure of the relative expression of each gene from the mRNA extracted from (pooled) cells. |
| graph or network | A mathematical structure modelling or depicting the relationships between elements. |
| information centrality | A network centrality metric which uses the impact of removing a vertex or node on connections in the network. |
| metagene | A consistent signal of expression for a collection of genes such as a biological pathway, derived from singular value decomposition. |
| mutation | A change in DNA sequence that disrupts gene function. |
| PageRank centrality | A network centrality metric which uses eigenvectors with a scaling factor (Brin and Page, 1998). |
| pathway | A series of biomolecules that produces a particular product or biological function. |
| shortest path | A path with the fewest possible edges which connects two particular vertices . |
| synthetic lethal | Genetic interactions where inactivation of multiple genes is inviable (or deleterious) which are viable if inactivated separately. |

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

Acronyms

| | |
|---------|---------------------------------------------------------------------|
| ANOVA | Analysis of Variance. |
| GPCR | G Protein Coupled Receptor. |
| mtSLIPT | Synthetic Lethal Interaction Prediction Tool (against mutation). |
| NMD | Nonsense-Mediated Decay. |
| PI3K | Phosphoinositide 3-kinase. |
| siRNA | Short Interfering RNA. |
| SLIPT | Synthetic Lethal Interaction Prediction Tool. |
| UTR | Untranslated Region (of mRNA). |

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Appendix G

Synthetic Lethal Genes in Pathways

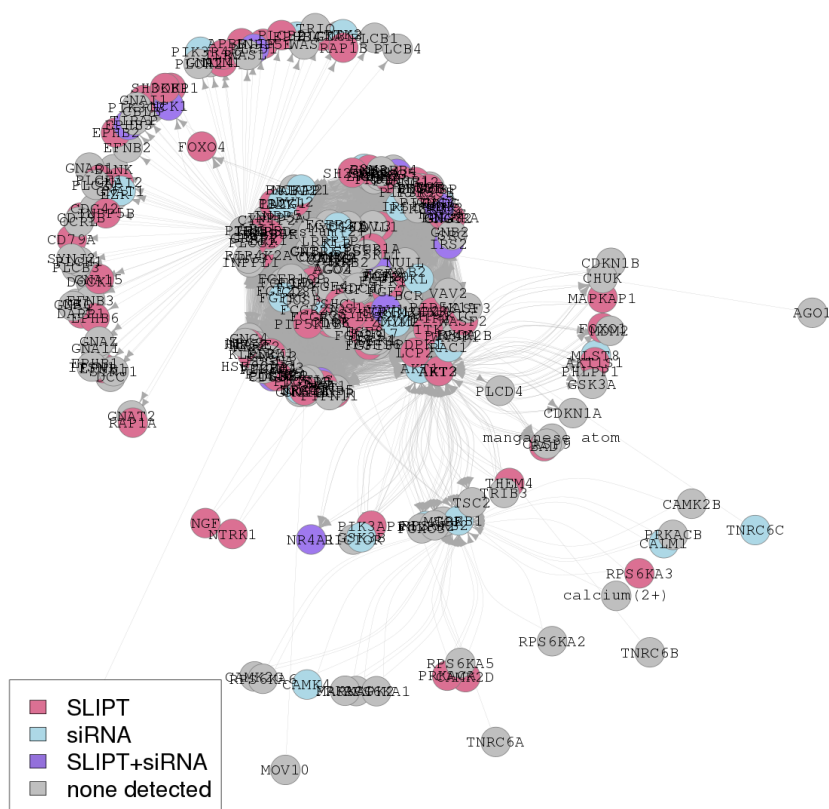


Figure G.1: **Synthetic lethality in the PI3K/AKT pathway.** The Reactome PI3K/AKT pathway with synthetic lethal candidates, coloured as shown in the legend.

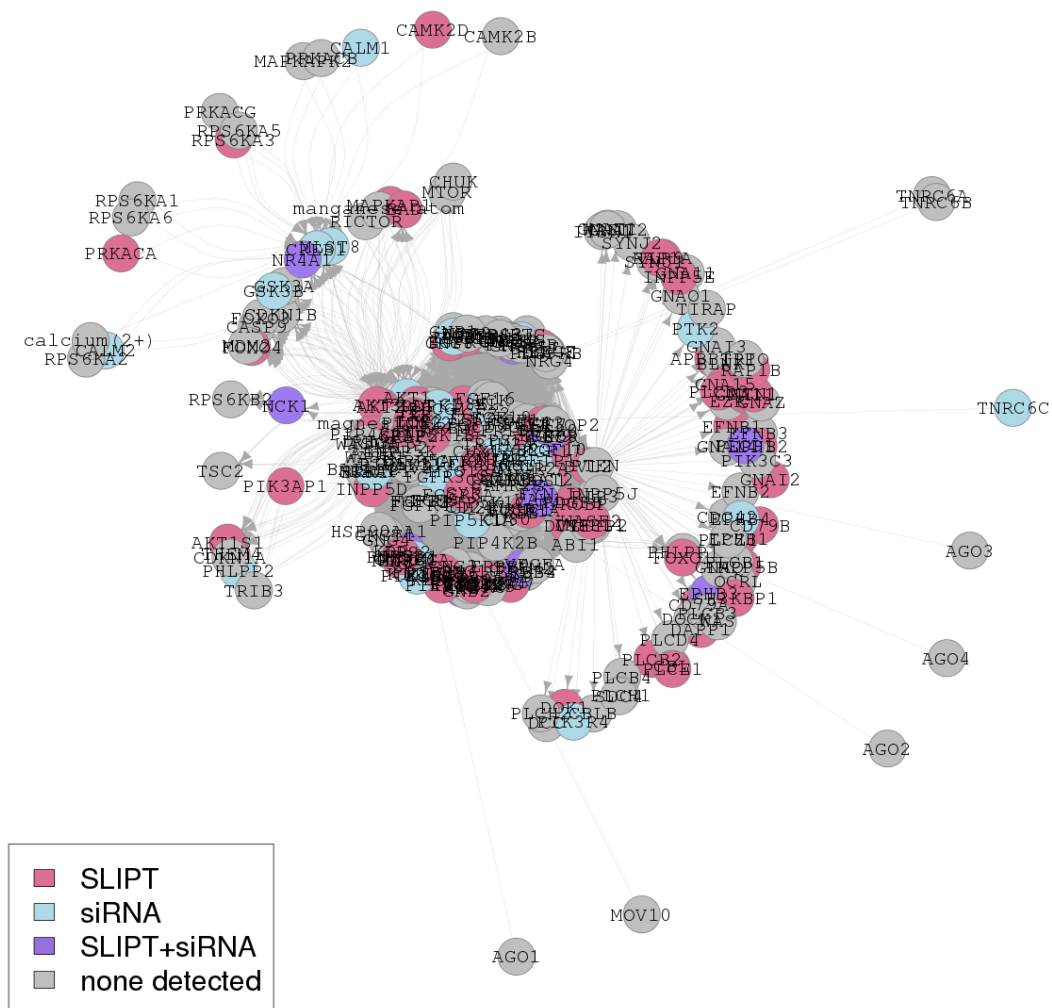


Figure G.2: **Synthetic lethality in the PI3K/AKT pathway in cancer.** The Reactome PI3K/AKT in cancer pathway with synthetic lethal candidates, coloured as shown in the legend.

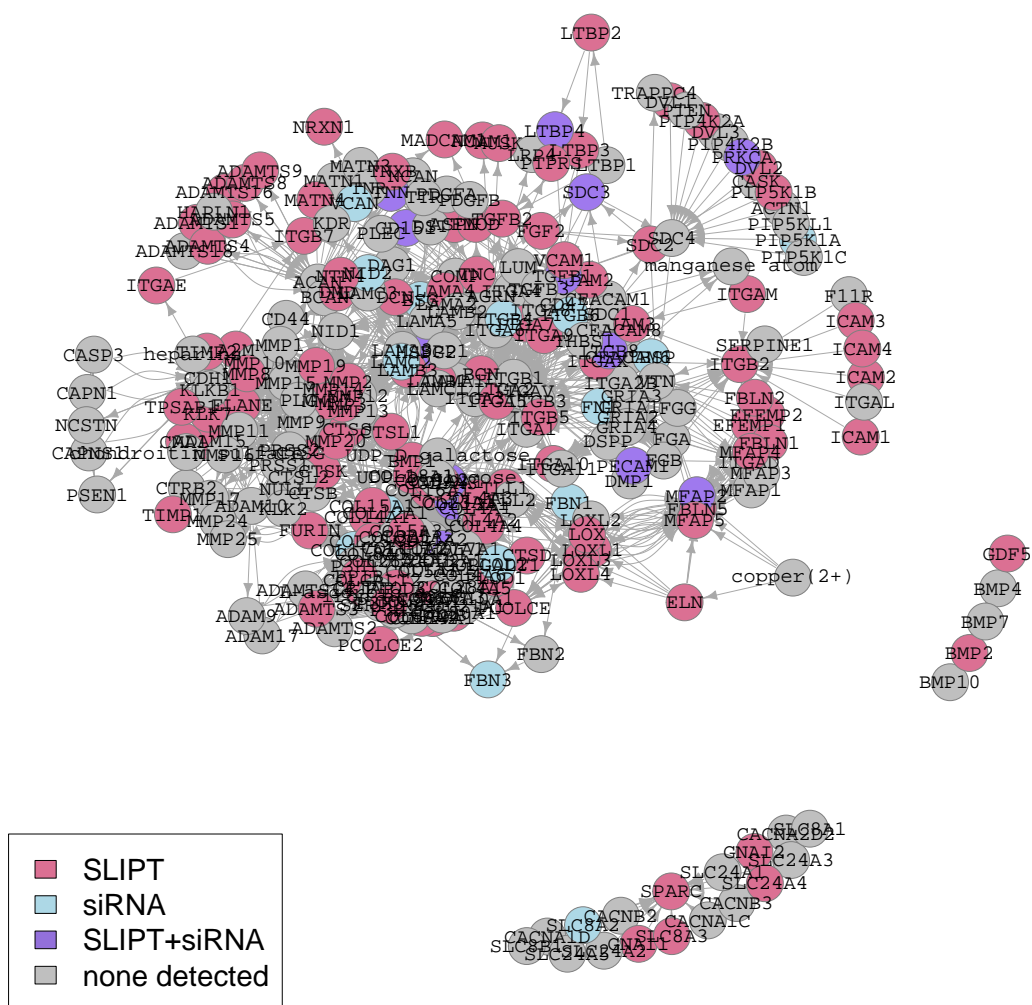


Figure G.3: **Synthetic lethality in the Extracellular Matrix.** The Reactome Extracellular Matrix pathway with synthetic lethal candidates, coloured as shown in the legend.

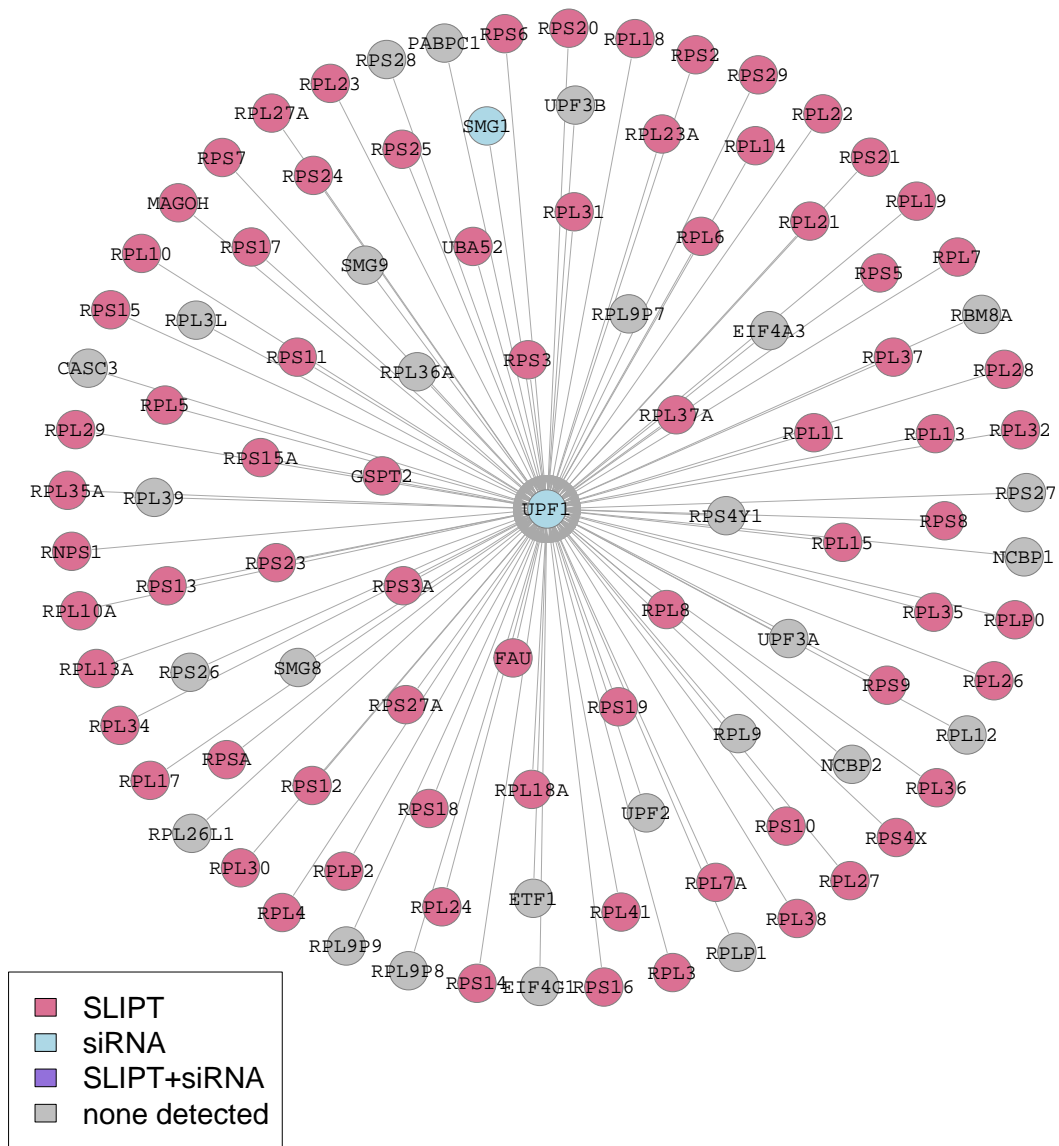


Figure G.6: **Synthetic lethality in the Nonsense-mediated Decay.** The Reactome [nonsense-mediated decay \(NMD\)](#) pathway with synthetic lethal candidates, coloured as shown in the legend.

Appendix H

Network Analysis for Mutation SLIPT

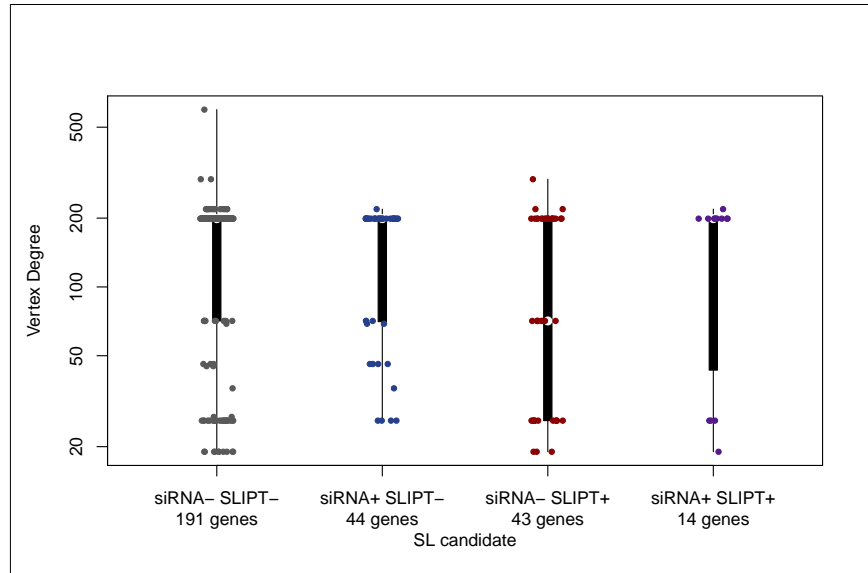


Figure H.1: **Synthetic lethality and vertex degree.** The number of connected genes (**vertex degree**) was compared (on a log-scale) across genes detected by **mtSLIPT** and **siRNA** screening in the Reactome $G_{\alpha i}$ pathway. There were no differences in **vertex degree** between the groups (shown in Table 5.1), although genes detected by **siRNA** included those with the fewest connections.

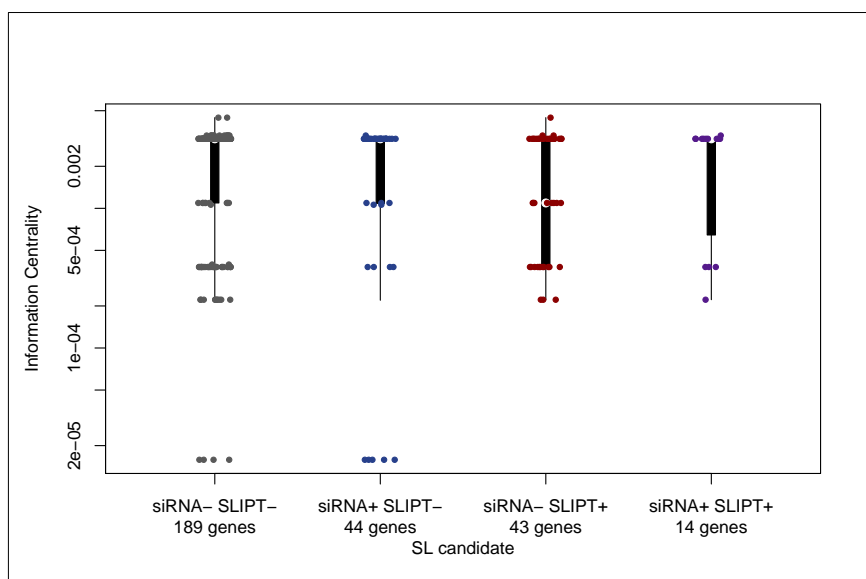


Figure H.2: **Synthetic lethality and centrality.** The [information centrality](#) was compared (on a log-scale) across genes detected by [SLIPT](#) and [siRNA](#) screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by [SLIPT](#) or [siRNA](#) did not have higher centrality than other genes (shown in Table [H.2](#)). Genes detected by [SLIPT](#) spanned the range of [centrality](#) values.

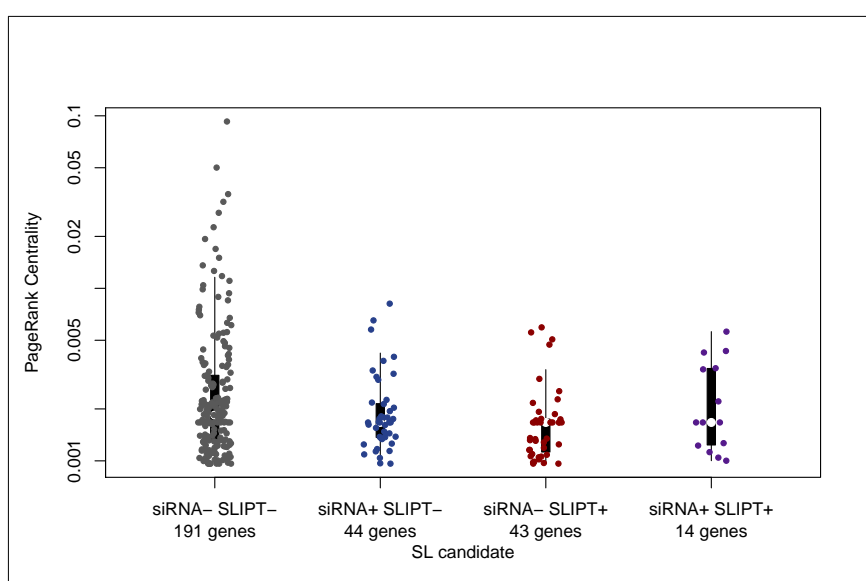


Figure H.3: **Synthetic lethality and PageRank.** The [PageRank centrality](#) was compared (on a log-scale) across genes detected by [mtSLIPT](#) and [siRNA](#) screening in the Reactome $G_{\alpha i}$ pathway. Genes detected by with either [synthetic lethal](#) detection approach had a more restricted range of [centrality](#) values neither of these had a significant association with centrality (shown in Table [H.3](#)).

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

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

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

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

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

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

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

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

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

Appendix I

Pathway Structure for Mutation SLIPT

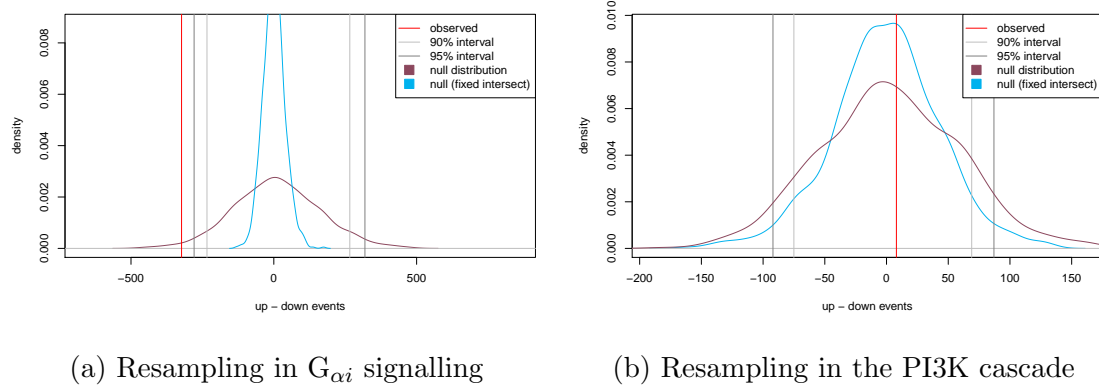


Figure I.1: **Structure of synthetic lethality resampling.** A null distribution with 10,000 iterations of the number of **siRNA** genes upstream or downstream of **mtSLIPT** genes (depicted as the difference of these) in each **pathway**. To assess significance, the observed events (with **shortest paths**) were compared to the 90% and 95% intervals for the null distribution (shown in blue). Genes detected by both methods were not fixed to the same number as observed for the alternative null distribution (shown in red), although the significance of the observed number of events (red) was changed in either case. The genes detected by both approaches were included in computing the number of **shortest paths** (in either direction) between **SLIPT** and **siRNA** genes. The permutations show (a) a significant pathway relationship for $G_{\alpha i}$ signalling and (b) and non-significant relationship for the **phosphoinositide 3-kinase (PI3K)** cascade.

Table I.1: Resampling for pathway structure of **synthetic lethal** detection methods

| PPathway | Graph | | Candidates | | Observed | | | | Permutation p-value | | p-value (FDR) |
|------------------------------------------|-------|--------|------------|-------|-----------------|-------------------|---------|---------|---------------------|---------|---------------|
| | Nodes | Edges | SLIPT | siRNA | Up ¹ | Down ² | Up–Down | Up/Down | Up–Down | Down–Up | Down–Up |
| PI3K Cascade | 138 | 1495 | 42 | 25 | 131 | 123 | 8 | 1.065 | 0.4473 | 0.5466 | 0.7263 |
| PI3K/AKT Signalling in Cancer | 275 | 12882 | 56 | 44 | 478 | 440 | 38 | 1.086 | 0.4163 | 0.5810 | 0.7263 |
| G_{ai} Signalling | 292 | 22003 | 57 | 58 | 543 | 866 | -323 | 0.627 | 0.9507 | 0.0488 | 0.488 |
| GPCR downstream | 1270 | 142071 | 218 | 160 | 7632 | 6500 | 1132 | 1.174 | 0.1707 | 0.8291 | 0.8751 |
| Elastic fibre formation | 42 | 175 | 16 | 7 | 6 | 7 | -1 | 0.857 | 0.5512 | 0.3681 | 0.7263 |
| Extracellular matrix | 299 | 3677 | 81 | 29 | 313 | 347 | -34 | 0.902 | 0.5762 | 0.4215 | 0.7263 |
| Formation of Fibrin | 52 | 243 | 11 | 5 | 8 | 19 | -11 | 0.421 | 0.7993 | 0.1800 | 0.6000 |
| Nonsense-Mediated Decay | 103 | 102 | 56 | 2 | 0 | 0 | 0 | | 0.197 | 0.1373 | 0.6000 |
| 3'-UTR-mediated translational regulation | 107 | 2860 | 56 | 1 | 52 | 1 | 51 | 52 | 0.1210 | 0.8751 | 0.8751 |
| Eukaryotic Translation Elongation | 92 | 3746 | 57 | 0 | 0 | 0 | 0 | | 0.4952 | 0.4892 | 0.7263 |

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

¹ The number of paths where the **siRNA** candidate was upstream of a **mtSLIPT** candidate

² The number of paths where the **siRNA** candidate was downstream of a **mtSLIPT** candidate