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Chapter 5

Synthetic Lethal Pathway Structure

Aims

- Synthetic Lethal Genes within a Biological Pathway Structure
- Importance and Connectivity of Synthetic Lethal Genes within Pathway Networks
- Upstream and Downstream Relationships between SLIPT and siRNA Candidates

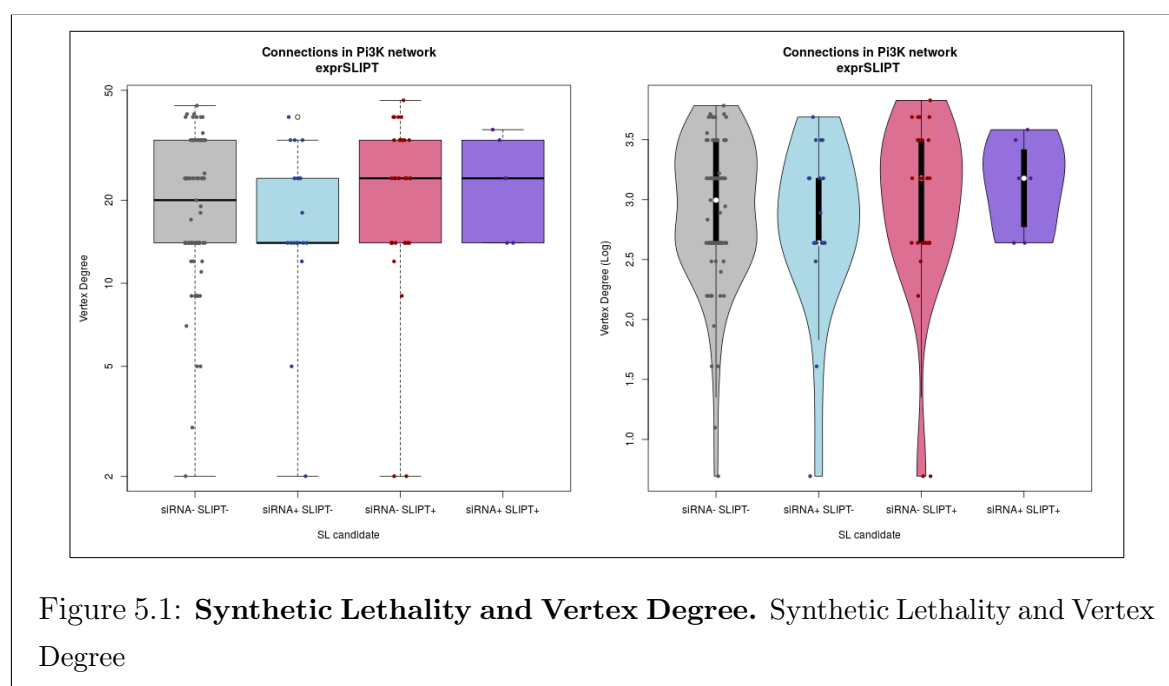
Summary

- Synthetic Lethal genes were explored within a graph structures for key pathways identified previously
- In some cases these graph structures appeared to have relationships between synthetic lethal genes
- However, no existing network metrics of importance and connectivity with the networks were elevated significantly for Synthetic Lethal genes
- Nor was there significant evidence of upstream and downstream relationships between SLIPT and siRNA Candidates in a shortest path permutation analysis

Having identified key pathways implicated in synthetic lethal genetic interactions with *CDH1*, these were investigated for the underlying 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. The synthetic lethal genes considered here are candidates those detected by SLIPT (as described in Section 3.1) in TCGA breast cancer expression and mutation data (TCGA, 2012) in comparison to the candidate gene partners from the siRNA screening in breast cell lines (Telford *et al.*, 2015).

5.1 Synthetic lethal genes in synthetic lethal pathways

5.2 Centrality and connectivity of synthetic lethal genes



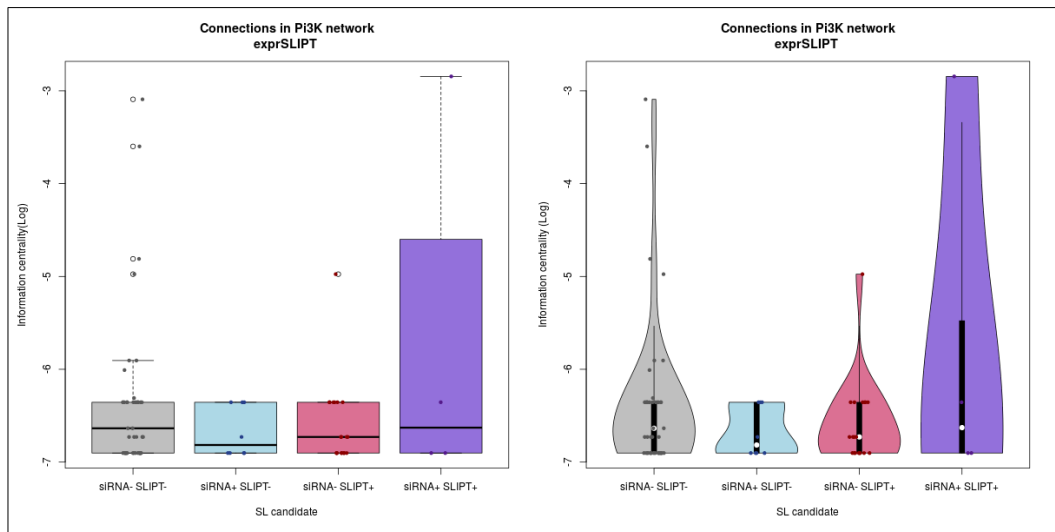


Figure 5.2: **Synthetic Lethality and Centrality.** Synthetic Lethality and Information Centrality (log-scale).

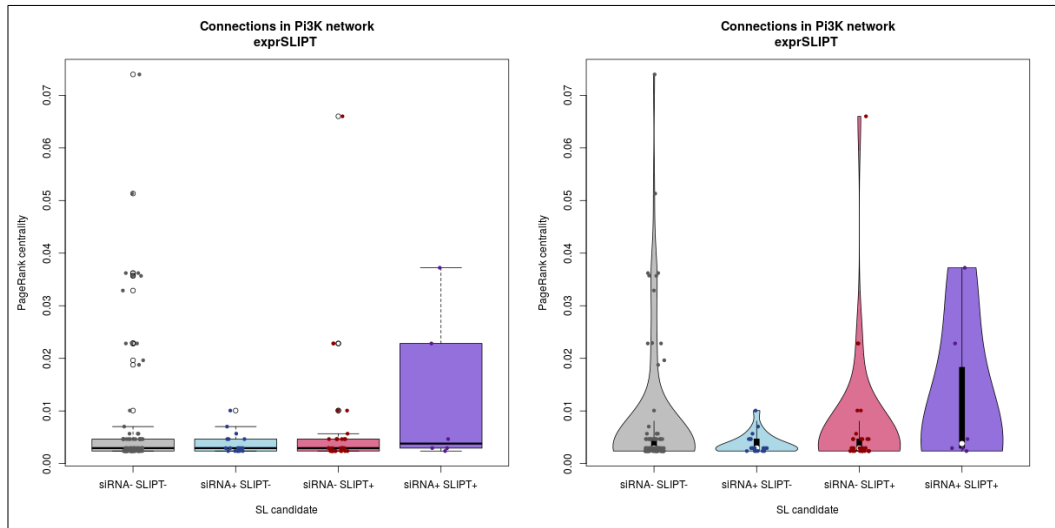


Figure 5.3: **Synthetic Lethality and PageRank.** Synthetic Lethality and PageRank.

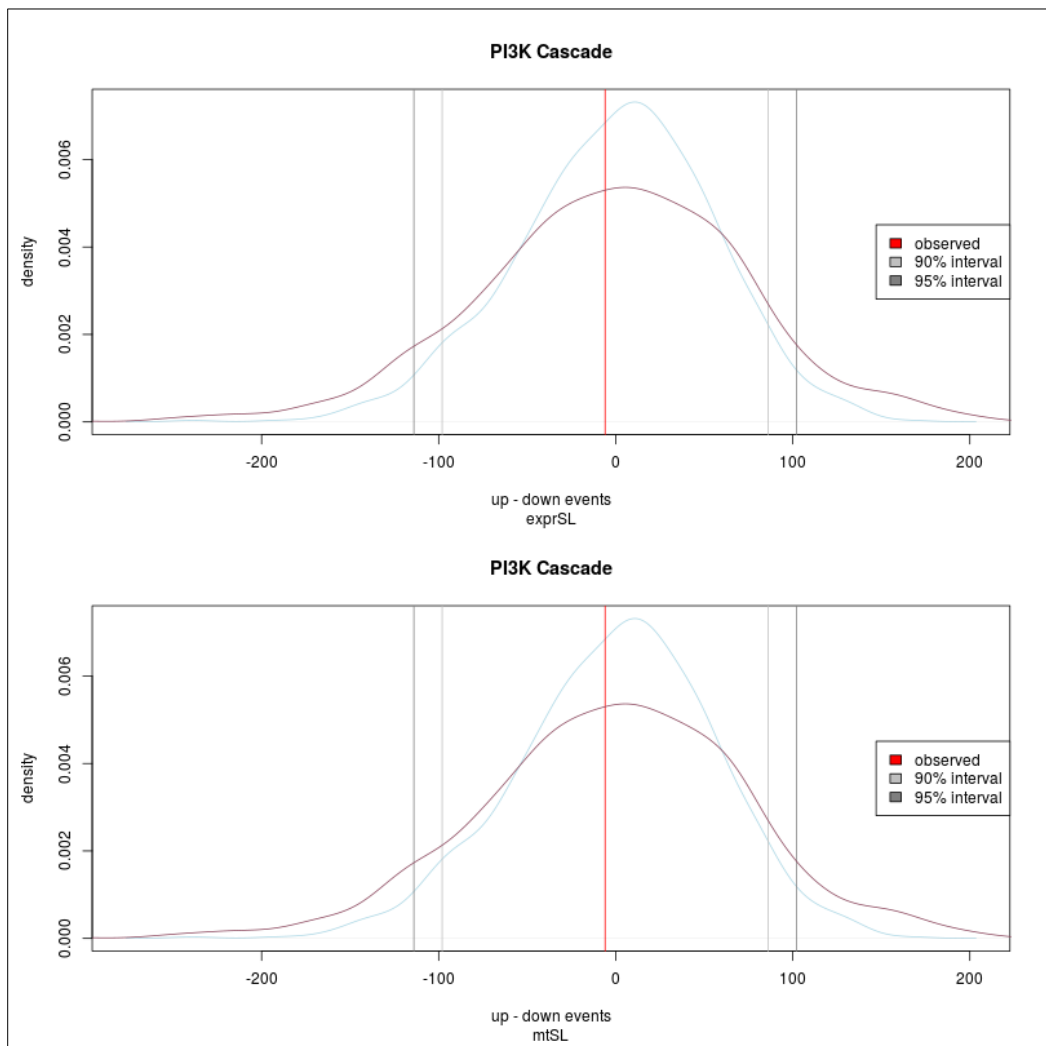


Figure 5.4: **Structure of Synthetic Lethality Resampling.** Structure of Synthetic Lethality Resampling.

5.3 Upstream or downstream synthetic lethal candidates

pathway	Graph:		States:		Observed:				Permutation p-value:	
	nodes	edges	exprSL	siRNA	up	down	up-down	up/down	up abs	down abs
PI3K Cascade	138	1495	38	25	122	128	-6	0.953125	0.5326	0.4606
PI3K/AKT Signaling in Cancer	275	12882	98	44	779	679	100	1.147275405	0.3255	0.6734
G _{αi} Signaling	292	22003	95	58	836	1546	-710	0.5407503234	0.9971	0.0029
GPCR downstream	1270	142071	312	160	9755	9261	494	1.0533419717	0.3692	0.6305
Elastic fibre formation	42	175	24	7	1	2	-1	0.5	0.5461	0.3865
Extracellular matrix	299	3677	127	29	547	455	92	1.2021978022	0.3351	0.6636
Formation of Fibrin	52	243	18	5	12	17	-5	0.7058823529	0.6198	0.3564
Nonsense-Mediated Decay	103	102	74	2	0	74	-74	0	1	0
3' -UTR-mediated translational regulation	107	2860	77	1	0	0	0	NaN	0.4902	0.5027
Eukaryotic Translation Elongation	92	3746	76	0	0	0	0	NaN	0.4943	0.4933

Sampling only within target pathway

Number of siRNA+SLIPT matched to observed

siRNA+SLIPT kept for up/down evaluation

5.4 Hierarchical approach

5.5 Discussion

5.6 Conclusion

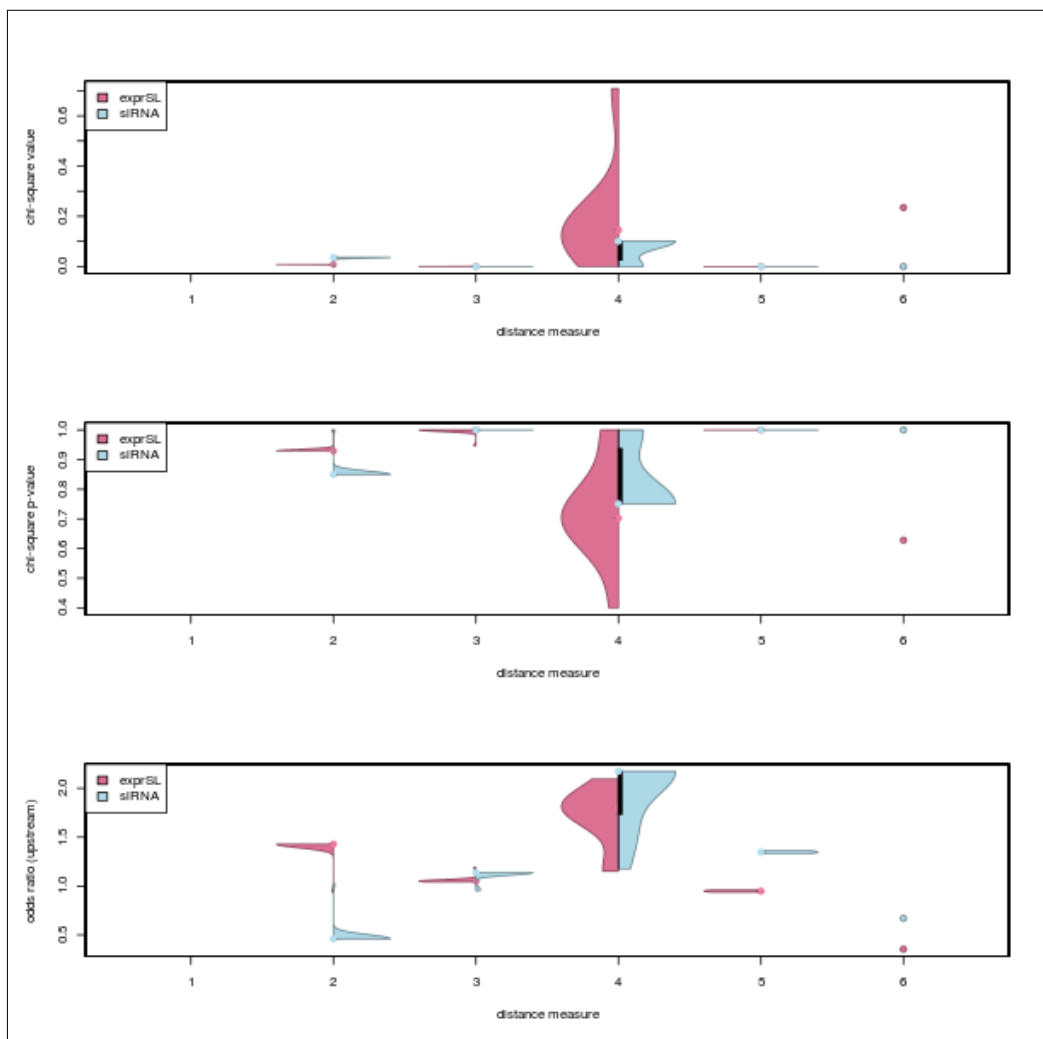


Figure 5.6: **Structure of Synthetic Lethality in PI3K.** Structure of Synthetic Lethality in PI3K.

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