Theoretical Biology Seminar

Integrative Analytics Connecting Genotype and Phenotype for Precision Oncology

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Understanding the molecular mechanisms that control the biology of health and disease requires multiscale models that map relationships between genes and phenotypes. Measuring, parameterising and simulating molecular systems in exhaustive detail is typically impossible due to biological complexity, our limited knowledge and limited available data. Therefore, simplifying abstractions in concert with empirical analysis of matched genome-scale and descriptive data are valuable strategies. We developed the Gabi algorithm to connect clinical variables with molecular measurements; including a novel relevance thresholding procedure and information-theoretic directionality inference. Gabi outperformed existing state-of-the-art approaches on blind test data. We applied Gabi to derive a causal information-flow network for invasive hormone-driven breast tumours. Findings include a switch involving the estrogen receptor (ERα) and its phosphorylated form, which had opposing regulatory effects on many common targets. Gabi predicted proteins that influence important clinical parameters (e.g. tumour stage) and Feedback Vertex Set (FVS) analysis revealed key network control nodes. Analysis of our causal network identified patient risk groups that have prognostic value in multivariate modeling controlling for clinical variables. I will also discuss the NetNC algorithm [Cancers 2020;12:2823] and SynLeGG resource [Nucleic Acids Research 2021;49:W613-8]. NetNC recovers the network-defined signal in noisy data, for example defining biologically coherent modules in matched drug-sensitive vs drug-resistant n=1 patient samples. SynLeGG and the MultiSEp algorithm interrogate mutually exclusive loss signatures in multiomics data, towards context-specific synthetic lethal drug targets and companion diagnostic biomarkers. Application of MultiSEp to Multiple Myeloma (MM) patients and cytogenetic subtypes revealed context-specific synthetic lethal networks that inform fundamental biology, including for poorly characterised and noncoding genes. Almost all MM patients relapse and succumb to therapy-resistant disease; accordingly, more effective treatments are urgently needed. Analysis of our predicted MM patient synthetic lethal networks reveals individual 'nexus' genes where the network neighbourhood genes are collectively mutated in a relatively high proportion of MM cohorts, representing attractive drug targets. Laboratory follow-up further validates our computational approaches.

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