Parallel Session - Methodological Developments for Systems Biology

1PS2-03 Information-theoretic causality predicts proteomic control of clinical parameters and reveals cancer network biomarkers

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We developed an algorithm for causal network inference (Gabi) to connect genotype with phenotype, tailored for Systems Medicine applications – where available datasets typically contain tens to hundreds of observational variables. Indeed, systematic perturbation approaches are not applicable in a clinical setting. Gabi successfully integrates clinical observations with Reverse Phase Protein Array (RPPA) or Tissue Microarray (TMA) datasets. The algorithm includes a novel relevance thresholding procedure, facility to incorporate prior knowledge, and information-theoretic directionality inference that employs conditional mutual information. Evaluation on blind test data found that Gabi outperformed existing state-of-the-art approaches in terms of both network connectivity and directionality inference. Available as an easy to install R package, Gabi also offers a novel strategy to obtain directed, signed networks for downstream systems biology applications.
We applied Gabi to derive a causal information-flow network for invasive hormone-driven breast tumours (n=284) with 137 nodes and 2101 edges; nodes represent eleven clinical parameters, 106 proteins and twenty phospho-forms. Proteomic measurements, including post-translational modifications, are key for molecular dissection of cancer mechanisms. Findings include a switch involving the estrogen receptor (ERalpha) and its phosphorylated form, which had opposing regulatory effects on many common targets. For example, ERalpha drove growth and increased adhesion, whereas phospho-ERalpha activated Epithelial to Mesenchymal Transition. Gabi predicted proteins that control important clinical parameters (e.g. tumour stage). Analysis of our causal network identified patient risk groups that clearly stratified by overall survival. Multivariate modeling controlling for clinical variables demonstrates that the network-based risk groups have significant prognostic value.

1PS2-04 Understanding the System Dynamics of Mitochondrial Retrograde Signaling from a Differential Equation-based Framework

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Keywords Mitochondrial retrograde signaling, Differential equation-based network, Multiple-input single-output System (MISO)

Mitochondrial quality control is essential to maintain cell viability. Retrograde signaling is the process in which mitochondria send quality information to regulate the nuclear genome. Moreover, mitochondria communicate with nuclear genome via biochemical networks; the nucleus responds properly depending on the signal sent by multiple mitochondrial agents, making retrograde signaling a multiple-input-single-output (MISO) problem in communication theory. However, it is unclear how the cell extracts multidimensional mitochondrial information from dynamical concentration patterns of signaling molecules. To address this issue, we used budding yeast, Saccharomyces cerevisiae, as a model organism to investigate the communication between the mitochondrial network and nucleus. Mitochondrial membrane potential and translocation of Rtg3p/Rtg1p are considered to be the input and output of the communication system. The mathematical model of yeast retrograde signaling was constructed by a differential equation-based framework; the parameters of the model were generated by Monte Carlo Method and fitting with the translocation data of Rtg proteins. In this study, we have provided a control theory view of mitochondrial retrograde signaling that may lead to a better understanding of the intracellular communication between the mitochondrial network and the nucleus genome.