[BC]^2 2015 Workshop WS2 on:

Challenges and approaches in comprehensive and informative complex network analysis for precision medicine

List of abstracts (as of April 27, 2015)

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"De-novo network enrichment with multiple OMICS data types"

The emergent field of systems biology is providing life sciences with large biological networks reconstructed from data generated by recent advances in wet lab technologies. While these networks provide a static picture of the interplay of genes and their products, they fail to capture dynamic changes taking place during the development of complex diseases.

We seek to fill this gap by integrating networks with OMICS datasets (DNA microarrays, RNA sequencing, genome-wide methylation studies, etc.) to extract connected sub-networks with a high number of dysregulated genes. Efforts to tackle this challenge usually rely on setting unintuitive parameters for the underlying combined statistics and pay little attention to the interpretability of the results.

We circumvent these problems with KeyPathwayMiner, an easy-to-interpret model that performs at least as good as similar approaches when tested on real datasets. KeyPathwayMiner is publicly available as a software framework that provides interpretability, accuracy and applicability to all biological fields that can greatly benefit from systems-based analyses. We will discuss the most recent publication of the KeyPathwayMiner software [1], which introduces the latest features: support for multi-omics integration by customizable logical connectors and visualization of batch runs for parameter optimization.

We will further demonstrate the applicability of KeypathwayMiner to multi-omics studies, where epithelial-mesenchymal transition-related pathways are extracted by combining gene expression, protein expression and protein phosphorylation from cancer stem cell lines [2].

Citation:
[1] Alcaraz et al. (2014) KeyPathwayMiner 4.0: condition-specic pathway analysis by combining multiple omics studies and networks with Cytoscape, BMC Syst. Biol 8:99.
[2] Pauling et al. (2014) Elucidation of epithelial-mesenchymal transition-related pathways in a triple-negative breast cancer cell line model by multi-omics interactome analysis, Integr. Biol. 6: 1757-9694.

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"Linking genotypic features to dysregulated networks"

One of major obstacles in developing cancer treatment is cancer heterogeneity. Heterogeneity of genetic and epigenetic alterations leads to heterogeneity in gene expression, making the discovery of genetic drivers and key genes dysregulated by the corresponding genetic aberrations very challenging.

Pathway-centric approaches have emerged as methods that can empower studies of cancer. Combining the utility of algorithmic techniques with the power of network-centric approaches, we designed several approaches that allow unsupervised detection of subnetworks that are dysregulated in a subgroup of patients, important genetic features and links between phenotypic and genotypic properties.

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"Coordination of post-translational modifications in human protein interaction networks"

Post-translational modifications (PTMs) regulate protein activity, stability and protein interaction (PPI) profiles critical for cellular functioning. In combined experimental and computational approaches, we want to elucidate the role of post-translational protein modifications, such as phosphorylation, for these dynamic processes and investigate how the large number of changing PTMs is coordinated in cellular protein networks and likewise how PTMs may modulate protein-protein interaction networks.

Here we investigate whether different global post translational modifications, i.e. phosphorylation, acetylation and ubiquitination, are coordinated in human protein networks and how these PTMs are read by the cellular machinery. We identified hundreds of protein complexes that selectively accumulate different PTMs. Also protein regions of very high PTM densities, termed PTMi spots, were characterized and show domain-like features. The analysis of phosphorylation-dependent interactions provides clues on how these PPIs are dynamically and spatially constrained to separate simultaneously triggered growth signals which are often altered in oncogenic conditions. Our data indicate coordinated targeting of specific molecular functions via PTMs at different levels emphasizing a protein network approach as requisite to better understand modification impact on cellular signaling and cancer phenotypes.

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"Reconstruction of the mESC Epigenetic Network"

Mouse Embryonic Stem Cells (mESC) is the biological system for which more information about components of the epigenetic system is available. Public repositories contain results of ChIP-Seq experiments for more than 60 Chromatin Related Proteins (CRPs) and 14 for Histone modifications, as well as results for three different DNA methylation experiments, including 5-Hydroxymethylcytosine (5hmc), characteristic of Stem cells.

We have processed this information to establish a comprehensive network CRPs, histone marks and DNA modifications that tend to co-localize in the genome statistically. In this network co-localization preferences are specific of chromatin states, such as promoters and enhancers.

The analysis of the properties of the network clearly indicates the role of 5hmc in the organization of the network, i.e., 5hmc is the most crossed node. The importance of 5hmc as organizational principle was reinforced by the analysis of the concerted evolution of the protein components. In this case, 5hmc mediates the co-evolution of proteins related by their functions as writers, erasers or readers of 5hmc.

In summary, the unbiased analysis of the epigenetic network contributes to explain the functional relations of the proteins involved in the epigenetic regulation of mESC, and in particular those concerned with the stem cell specific 5hmc modification.

This work was develop in collaboration with Martin Vingron's lab (MPIMG, Berlin) in the context of the Blueprint EU consortium (Carrillo de Santa Pau, Perner, Juan et al., in preparation)