

13th International Conference on

Metabolomics and Systems Biology

October 11-12, 2018 | Zurich, Switzerland



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Deciphering the mechanisms of complex diseases using network and machine learning approaches

The complex diseases, such as cancer, involves dysfunctions on multiple levels. There have been several methods to identify the dysfunctions on each level. On genomics level, GWAS (Genome-wide association study) can detect the disease phenotype associated SNPs (single nucleotide polymorphisms). But many GWAS identified SNPs locate in intergenic region and can't be annotated to specific genes. With the help of eQTL (expression quantitative trait loci) method, the downstream genes of the GWAS SNPs can be found. And based on the co-expression network, regulatory network, protein-protein interaction network, or even protein-chemical interaction network of these genes, the possible cascade of the signal transduction from the genetic perturbations can be discovered. By integrating all these omics data, we can establish a systems biology model of how the GWAS SNPs affect the expression of their direct target genes, how these direct targets affect secondary target genes, or proteins, or metabolites, and eventually cause the catastrophic pathological changes on network or pathway. With the comprehensive network, we can not only study the mechanism of one disease, but also the relationship of several traits. For example, schizophrenia and anti-tuberculosis drug-induced hepatotoxicity co-occurred frequently but they do not share common genes. We mapped their genes onto the network, the common drivers of these two diseases were revealed through two-way RWR analysis. Another example is that the lung cancer dysfunctions on several levels but how the different level dysfunctions connect are still unknown. We investigated the mutation, methylation, mRNA and microRNA expression difference between cancer and normal tissues using machine learning methods, then mapped the dysfunction of each level onto the comprehensive network. By connecting each other with shortest paths, the highly frequent shortest path genes that can cause the tumorigenesis on multiple levels were discovered. Overall, the network and machine learning approaches are effective to dissect the complex system and reveal the mechanisms of diseases.

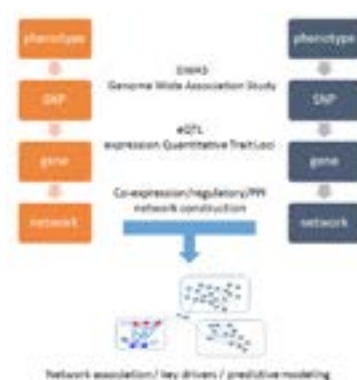


Figure 1: A generalized network based approach to study the mechanisms of complex diseases and the relationship among multiple traits.

Recent Publications

1. Cai Y D, Zhang Q, Zhang Y H, Chen L and Huang T (2017) Identification of genes associated with breast cancer metastasis to bone on a protein-protein interaction network with a shortest path algorithm. *Journal of Proteome Research*. 16(2):1027-1038.

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2. Zhang N, Wang M, Zhang P and Huang T (2016) Classification of cancers based on copy number variation landscapes. *Biochimica et Biophysica Acta*. 860(11, Part B):2750-2755.
3. Huang T et al. (2016) SNHG8 is identified as a key regulator of epstein-barr virus (EBV)-associated gastric cancer by an integrative analysis of lncRNA and mRNA expression. *Oncotarget*. 7(49):80990-81002.
4. Huang T et al. (2016) A new method for identifying causal genes of schizophrenia and anti-tuberculosis drug-induced hepatotoxicity. *Scientific Reports*. 6:32571.
5. Chen L et al. (2016) Identification of novel candidate drivers connecting different dysfunctional levels for lung adenocarcinoma using protein-protein interactions and a shortest path approach. *Scientific Reports*. 6:29849.

Biography

Tao Huang has completed his Postdoctoral Fellowship in the Department of Genetics and Genomics Sciences, Icahn School of Medicine at Mount Sinai, New York City, USA. He is currently a Professor and the Director of Bioinformatics Core Facility at the Institute of Health Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (P R China). His research interests include bioinformatics, computational biology, systems genetics and big data research. He has published over 100 articles in peer-reviewed journals. His works have been cited for 3138 times with an h-index of 26 and an i10-index of 64. He has been an Independent Reviewer for 30 journals. He is the Editor of the book: "Computational Systems Biology - Methods and Protocols" published in Springer; Guest Editor for *BBA Molecular Basis of Disease*, *BBA General Subjects*, *Artificial Intelligence in Medicine*, *BioMed Research International*, *Combinatorial Chemistry & High Throughput Screening* and *Computational and Mathematical Methods in Medicine*.

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