BRIGHAM AND WOMEN'S HOSPITAL
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Department of Medicine
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Channing Network Science Seminar

June 19, 2015, 11am @ 5th floor conference room

Speaker: Marc Santolini, Ph.D.
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Title: **Towards a personalized approach to Heart Failure**

Abstract: Modern genetics has had a major impact in characterizing a large number of "Mendelian" single gene diseases. However, common complex diseases like Heart Failure are governed by multiple and often unknown genes. It has recently been suggested that such a complexity could be tackled by reducing the dimensionality of typically 20,000 genes to 20 to 30 modules containing tens to hundred of coexpressed genes, whose aggregate behavior can be represented by the module's "eigengene". Similarly to a GWAS approach, such eigengenes can then be associated to the phenotypes, a process referred to as Gene Module Association Study (GMAS). However, it is not clear that these topological modules represent an optimal description of the disease state. We challenge these questions using the Hybrid Mouse Diversity Panel, a model system of 100+ genetically diverse strains of mice subject to an isoproterenol (ISO) induced heart failure and on which expression data along with diverse phenotypes have been measured. First, we systematically assess the extent of the diversity of genes induced by ISO across strains. We find that the response to the stressor is very personalized, with a large number of genes being differentially expressed in only a small subset of strains. We then tackle this diversity of responses using three methods. First, we apply the GMAS methodology and exhibit a module correlated with most of the phenotypes. Then, we present a new "bottom-up" method that builds a disease module by aggregating genes associated to the phenotype. We show that the bottom-up module overlaps with the "top-down" GMAS module, while being more systematically defined, more correlated to the phenotypes, and more densely connected in the co-expression network. Even though both of these modules correlate strongly with the average ISO response, they do not give a faithful representation of the spectrum of individual phenotypes (eg the degree of hypertrophy observed). This question is finally tackled by looking at the bottom-up module of the individual responses to the stressor. We find a small number of genes that are associated to the individual response to the stressor, and are found to be significantly enriched in known hypertrophic pathways. Interestingly, these genes have a near zero average fold change and could not be found with any traditional method relying on average differential expression.

Bio: Marc Santolini is a postdoctoral researcher at the Center for Interdisciplinary Research on Complex Systems (CIRCS) and Center for Complex Network Research (CCNR) at Northeastern University under the supervision of Alain Karma, and is affiliated to the Dana Farber Cancer Institute and a collaborator at Channing Division of Network Medicine at Brigham and Women's Hospital. Prior to Northeastern University, he worked on the de novo search of transcription factor binding sites and on machine learning tools to assess the tissue specificity of enhancers in gene regulatory networks at the Statistical Physics Laboratory of École Normale Supérieure in Paris.

hosted by Yang-Yu Liu