若手研究者インターナショナル・トレーニング・プログラム(ITP)

バイオインフォマティクスとシステムズバイオロジーの国際連携教育研究プログラム 応募書類

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Title: Network-based analysis of cancer pathways
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Partner institute of your choice : Bioinformatics Program, Boston University (Prof. Charles DeLisi)
Duration of your choice: January 24th – April 20th , 2013
Plan : *Background:* Aberration from normally functioning metabolic pathways has become one of ten hallmarks of cancer (Hanahan and Weinberg, 2011). The Cancer Genome Atlas Network studies have enriched the data repository with expression, genetic and epigenetic profiles for various cancer types (TCGA Network). Integrating such data with a priori knowledge can help clarify causal and affecting genes in the cancer cascade. Since cancer utilizes abnormal pathways, reliance upon known normal pathways solely is insufficient. Network inference from expression data have been employed to help construct cancer-specific pathways (Torkamani and Schork, 2009). Other approaches annexed literature-extracted networks with protein interactions predicted by machine learning techniques (Ciriello, et al., 2012; Wu, et al., 2010) and used this network for analysis. However, such methods reduce the current knowledge to undirected gene networks. Analysis using more detailed networks may improve the construction of causality relationships between altered genes. Another challenge for cancer pathway analysis is to identify not only the genes associated with the disease, but also the ones causing it. Several network models have been developed to discriminate between driver genes responsible for cancer initiation and metastasis, and genes downstream in the cascade. Extension of driver pathway detection methods is clearly needed. *Goals:* The purpose of the visit to Professor DeLisi's laboratory is to discuss possible improvements to current cancer pathway analysis methods. Examples of such improvements are given below: 1. Provide a network representation that enables integration of prior knowledge with predicted networks. The representation should keep information extracted from pathways databases, such as protein interaction type and direction. Also, since networks are constructed from multiple-sources with varying reliabilities, confidence in interactions should also be preserved. 2. Incorporation of novel network inference methods, such as these based on chemical

similarity. This will also allow us to detect distinctive metabolomics signatures.

3. Incorporation of knowledge provided by ENCODE project (Gerstein, et al., 2012; Khatun et al., 2012).
4. Adding protein complex information to the network. Many studies (Bandyopadhyay, et al., 2010; Dixon, et al., 2008) in yeast indicated that under different contexts protein complexes tend to preserve their composition while changing their functional relationship. Thus, rewired pathways are more expected to use the same complexes as normal known pathways.
5. Genetic mutations that affect the same pathway tend to not co-occur in the same patient, an observation called "mutual exclusivity"(Ciriello, et al., 2012). Analysis based on this assumption, incorporating pathways topology methods(Draghici, et al., 2007) hasn't been done yet.
6. Linking mutations to genetic expression,(Vaske, et al., 2009), may also clarify causal relationships.

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