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Cancer Informatics

Array Platform Modeling and Analysis (A)

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Supplement Aims and Scope

Cancer informatics represents a hybrid discipline encompassing the fields of oncology, computer science, bioinformatics, statistics, computational biology, genomics, proteomics, metabolomics, pharmacology, and quantitative epidemiology. The common bond or challenge that unifies the various disciplines is the need to bring order to the massive amounts of data generated by researchers and clinicians attempting to find the underlying causes and effective means of treating cancer.

The future cancer informatician will need to be well-versed in each of these fields and have the appropriate background to leverage the computational, clinical, and basic science resources necessary to understand their data and separate signal from noise. Knowledge of and the communication among these specialty disciplines, acting in unison, will be the key to success as we strive to find answers underlying the complex and often puzzling diseases known as cancer.

This supplement is focused on array platform modeling and analysis, and article topics may include:

- Reverse Phase Protein Arrays (RPPA)
- Single Nucleotide Polymorphism Arrays
- RNA Arrays
- Surface Adjustment and Tissue Array Profiling
- Normalization Methodology
- Multiplicative Spatial Effects
- Multiple Small Scale Variation Tools
- Insertions, Deletions, Microsatellites and Non-Polymorphic Variants
- mRNA Transcripts
- Physical Mapping
- Functional Analysis
- Multi-Dimensional Association Studies
- Evolutionary Analysis
- RefSNP Attribubutes
- Mendelian Inheritance
- Estimating Smooth Surface from Positive Controls
- Generalized Additive Modelling of Micro-Array Data
- Analysis of Spatial Artifacts
- Quantitative Intensity Modulation
- Molecular/Proteomic Profiling
- Reproducibility Metrics
- Transcript and Protein Expression
- Analysis of Signaling Pathways
- dbSNP and JSNP Database Search Tools
- HapMap
- Promiscuous Protein in Silico
- Geometric Scoring Criteria
- Mean Signal Intensity Ratio

The year of 2015 marks the 20th anniversary of the microarray technology. Since the publication of the first microarray paper in 1995, this high-throughput technology has revolutionized our ability to study the molecular features (such as RNA expression levels, DNA copy number changes, and epigenetic regulations) of tumors, and has greatly advanced our understanding of cancer and its prevention and treatment. We take the opportunity of this special issue to celebrate the past achievements in the modeling and analysis of microarray data and to highlight some recent methodologic development in this area.

The availability of high-throughput microarray data, characterized by their large scale and complex underlying structure, has led statisticians to develop highly innovative analytic methods for detecting potential drug targets and prognostic factors for cancer. Major advances in statistical methodologies have been made on issues such as data normalization, multiple comparison adjustment, and high-dimensional variable selection and classification. Nevertheless, there still remain analytic challenges that require development of better statistical methodologies in order to more fully reap the rich information that resides in microarray data.

In this special issue, we have put together a set of articles by leading researchers in the field of microarray data analysis. These articles present novel statistical approaches to a variety of current challenges for microarray data analysis. Some of these articles are summarized below by their intended type of molecular data.

- **RNA Expression:** Normalization has been shown to be an essential preprocessing step for RNA microarray data and useful methods have been developed to normalize mRNA data. Zhou et al assess the use of quantile normalization for microRNAs, a class of small RNAs that play a regulatory role in a cell, in relation to two other data preprocessing steps – log transformation and probeset summarization. Much of the microarray data analysis has defined 'interesting' genes as those with differential expression between two groups. An alternative and less explored definition is genes with outlying expression among samples. Ghosh et al explore the use of C(α) test for detecting outlier expression and develop a bivariate extension to this test to accommodate data from two platforms on the same sample set. For data collected in a longitudinal study, analysis using multivariate adaptive splines allows flexible modeling of the trajectory. Duan et al demonstrate the use of this method using a breast cancer data to characterize genes that have age-varying expression.
- **DNA Copy Number:** Copy number changes, due to insertions, deletions, or inversions of DNA, are a major source of genomic alterations in tumors. Li et al introduce a novel method based on hidden Markov models to detect copy number variants using SNP array data and demonstrate its use in a breast cancer dataset. This method first estimates copy number for each SNP in a single array and then standardizes the estimated copy number among multiple arrays. The relationship of copy number changes to clinical outcomes can be better understood in the context of biological pathways. Huang et al propose a novel statistical method to analyze copy number alterations of a pre-defined gene set (for example, a biological pathway) and use this method to investigate how cigarette smoking may affect the expression profile of 1814 biological pathways in non-small cell lung cancer.
- **DNA Epigenetic Regulation:** The transcriptional potential of DNA molecules can be regulated by epigenetic mechanisms in a cell such as DNA methylation and histone modification, without changes to underlying DNA sequences. The role of epigenetic regulation in carcinogenesis has been increasingly appreciated. Houseman et al examine the use of DNA methylation data to build phylogenetic classification for normal breast tissues and breast tumors using three publicly available breast cancer datasets and suggest a close relationship in epigenetic states between normal breast cells and breast cancer cells.
- **Integrative Analysis of Multiple Data Types:** Data are becoming increasingly available for multiple types of molecules on the same set of samples in the private and public domains such as the Gene Expression Omnibus (GEO) and the Cancer Genome Atlas (TCGA). When multi-platform genomic data are analyzed in an integrative framework, information can be enriched across data types and the regulatory relationships between molecules can be studied. Dellinger et al develop an innovative integrative method based on gene pathways using a graph-based learning algorithm to derive a classifier for clinical outcome. They apply this method to derive classifiers of tumor stage based on RNA expression levels, DNA copy number changes, and DNA methylation profiles, using data from TCGA.

The past two decades have seen considerable improvements in our ability to molecularly characterize the cancer genome and to quantitatively understand the genetic causes of the disease. Statistical thinking and methodologies have played an important role in leveraging the wealth of genomic data collected on microarrays and other more recent profiling technologies such as next generation sequencing. They will continue to be an integral part bridging genomics data and clinical practice in the personalized medicine era.

Lead Guest Editor **Dr Li-Xuan Qin**

Dr Li-Xuan Qin is an Associate Member of Biostatistics at Memorial Sloan Kettering Cancer Center. She completed her PhD at the University of Washington. Her current work focuses on the statistical analysis of high-dimensional data for translational cancer research. Dr Qin is the author or co-author of many published papers, and holds several NIH grants as PI or co-investigator. She has been invited to give presentations in national/international conferences and academic departments.

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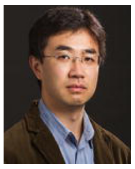

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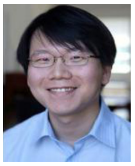

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