Computational Approaches for Pharmacogenomics: Session Introduction

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COMPUTATIONAL APPROACHES FOR PHARMACOGENOMICS

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Pharmacogenomics is an interdisciplinary field that combines genetics, classical pharmacology, and molecular biology to address individual variation in drug response. Coordinated research efforts are therefore multidisciplinary by necessity. Genetic and, maybe more importantly, genomic variation explains many differences in how people respond to medical treatments. Environmental factors including diet, age, and lifestyle influence response to medicines as well, but these also need to be placed in the context of genetics to fully understand their significance. Pharmacogenomics may ultimately lead to personalized medicine in which the most effective medicine is prescribed to individuals based on their genetic information, and adverse drug events could be virtually eliminated.

As the research emphasis on pharmacogenomics increases, there is a corresponding demand for computational and statistical methods and tools to analyze the data produced. Genome scans, gene expression arrays in the presence of drugs and large scale genotyping experiments have become common. These types of experiments yield enormous amounts of data that need to be organized, stored, analyzed and disseminated. There is an important need for computational approaches to address these issues in order to answer scientific questions such as: how do phenotypic results relate to genomic variation, and what is the significance of a particular drug on gene expression? Some of the current computational challenges in the field include database design and implementation, data sharing among pharmacogenomics centers, statistical analysis, statistical and computational method development, and real data applications.

The goal of The Pacific Symposium on Biocomputing is to explore current research in the theory and application of computational methods as they apply to problems of biological significance. The significance of pharmacogenomics is clear. Many population geneticists anticipate that this will be the first discipline wherein functional genomics translates into clinical application on a large scale. As such, PSB represents an ideal forum to further the analytical and computational approaches associated with such an endeavor. The biological and chemical technology is advancing, and a merging of pharmacogenomics with biocomputing is inevitable.

This session is dedicated to computational approaches for pharmacogenomics. The papers representing this session range from large-scale data analysis to applications of statistical methods to pharmacodynamic data models.

Micorarrays are increasingly utilized in pharmacogenomic studies. Because of the vast amount of data generated by these experiments, computational approaches are vital. Several papers in this session involve analysis of microarray data in a pharmacogenomics context. Imoto et al. describe a computational strategy for creating gene networks with regard to some chemical compound, such as a drug. They apply their approach to microarray data for human endothelial cells treated with the drug fenofibrate. The authors discovered a gene network involving a known target of fenofibrate, PPAR-α.

Borgwardt et al. developed a kernel-based approach to classify time series microarray expression data. As proof of concept, they use their method to predict drug response in Multiple Sclerosis patients from a published dataset.

As an alternative approach to microarray data analysis, Richter et al. investigate an opportunity to apply gene expression results to predict growth inhibition of human tumor cells. The authors used gene expression data to extend the classical Structure Activity Relationship (SAR) and Quantitative Structure Activity Relationship (QSAR) paradigm. They found that, in this particular case, the addition of transciptomic information worsened performance instead of enhancing it, unless the data were first aggregated in some manner.

Statistical analysis methods can also be successfully applied to pharmacogenomics data. Motsinger, et al. applied a statistical method called Multifactor Dimensionality Reduction (MDR) designed to detect gene-gene and gene-environment interactions in pharmacogenomics studies. The authors were able to identify associations between candidate genes and environmental factors and a common arrhythmia called postoperative atrial fibrillation (PoAF).

The last paper in this session focuses on a data model relating to pharmacodynamic reactions. Lin et al. applied a bivariate model created to detect the genetic determinants affecting drug response curves for systolic and

diastolic blood pressures. The authors looked at the 32AR gene and discovered a haplotype associated with the response of SBP and DBP to the drug dobutamine.