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"Parameter Estimation for the Exponential-Normal Convolution Model for Background Correction of Affymetrix GeneChip Data"

Monnie McGee, PhD
Department of Statistical Science
Southern Methodist University
Dallas, Texas

Abstract:

There are many methods of correcting microarray data for non-biological sources of error. Authors routinely supply software or code so that interested analysts can implement their methods. Even with a thorough reading of associated references, it is not always clear how requisite parts of the method are calculated in the software packages. However, it is important to have an understanding of such details, as this understanding is necessary for proper use of the output, or for implementing extensions to the model.

In this paper, the calculation of parameter estimates used in Robust Multichip Average (RMA), a popular preprocessing algorithm for Affymetrix GeneChip brand microarrays, is elucidated. The background correction method for RMA assumes that the perfect match (PM) intensities observed result from a convolution of the true signal, assumed to be exponentially distributed, and a background noise component, assumed to have a normal distribution. A conditional expectation is calculated to estimate signal. Estimates of the mean and variance of the normal distribution and the rate parameter of the exponential distribution are needed to calculate this expectation. Simulation studies show that the current estimates are flawed; therefore, new ones are suggested. We examine the performance of preprocessing under the exponential-normal convolution model using several different methods to estimate the parameters.

Friday, January 12, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

Refreshments will be provided at 9:45am

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"Considerations in Adapting Clinical Trial Design for Drug Development"

H.M. James Hung, Ph.D.
Division of Biometrics I, OB/OTS/CDER
Food and Drug Administration

Abstract:

Enhancing flexibility of clinical trial designs is one of the hot topics nowadays. Proper adaptation of clinical trial design is one of the ways for achieving this goal and has drawn much attention from clinical trialists. In past decades, the classical design has been improved to allow the flexibility for terminating the trial early if the experimental treatment is proven effective or deemed harmful or futile, based on the data accumulating during the course of the trial. Statistical validity of such an enhanced design in terms of type I error is maintained. The operational aspects of this design can still be an issue but, by and large, there have been many good models for how to deal with these aspects. As the flexibility of trial design is enhanced further, the potential risk that the resulting trial may not be interpretable increases. In this presentation we shall share our review experience, discuss the many issues arising from use of more flexible designs and hopefully stimulate further research in this area.

Friday, January 19, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

Refreshments will be provided at 9:45am

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"Adaptive 'Simon' Designs for Heterogeneous Patient Populations in Phase II Cancer Trials"

Karen Messer, PhD
Director of Biostatistics
Moores UCSD Cancer Center
Univeristy of California
San Diego, CA

Abstract:

In a Phase II cancer trial it may be advantageous to open enrollment to several patient populations, each with a very different null probability of response. For example in a trial of a novel therapeutic agent for relapsed Acute Myelogenous Leukemia (AML), patients in a first relapse may have a 30% probability of response under standard treatment, while patients in second relapse or higher may have only a 10% probability of response. These Phase II trials are generally uncontrolled (they often use "historical controls"), and the experimental agent may be expected to induce certain Grade 3 toxicities which would not be considered dose limiting. Furthermore, historically most of these Phase II trials can be expected to prove no better than standard-of-care. Phase II trials with these characteristics are usually designed with an early stopping rule which checks for initial evidence of efficacy after a first stage enrollment target is met. If there is insufficient evidence, the trial stops for futility. We discuss the standard two-stage optimal designs in this situation, and describe their operating characteristics under heterogeneous patient enrollment. These are compared to other approaches in the literature. Simple, approximately optimal designs which account for heterogeneity are presented. We recommend a practical adaptive design strategy which we have implemented at Moores UCSD Cancer Center.

Friday, February 2, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

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"Statistical Analysis of Reverse-Phase Protein Arrays"

Kevin Coombes, PhD
Department of Biostatistics &
Applied Mathematics
University of Texas
M. D. Anderson Cancer Center

Abstract:

Reverse-Phase Protein Arrays (RPPAs, aka protein lysate arrays, tissue lysate arrays, or lysate arrays) are recently developed tools for measuring protein expression levels in large numbers of samples. These assays are for the most part massively parallelized versions of enzyme-linked immunosorbent assays (ELISAs). In their massive parallelization, these assays are similar to cDNA microarrays (for mRNA) and CGH assays (for DNA). However, while those assays make thousands of measurements on a single sample ("forward-phase"), RPPAs measure one thing on hundreds of samples ("reverse-phase").

In this talk, we will attempt to place RPPAs in the broader context of other protein assays. Given this background, we will then describe issues we have encountered in modeling this data, and describe some of the tools we have developed for this purpose. Open questions will be identified.

Friday, February 16, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

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"Sequential Monitoring of Randomization Tests"

William F. Rosenberger, PhD
Professor and Chairman of Statistics
George Mason University

Abstract:

Randomization provides a basis for inference, but it is rarely taken advantage of. We discuss randomization tests based on the family of linear rank tests in the context of sequential monitoring of clinical trials. Such tests are applicable for categorical, continuous, and survival time outcomes. We prove the asymptotic joint normality of sequentially monitored test statistics, which allows the computation of sequential monitoring critical values under the Lan-DeMets procedure. Since randomization tests are not based on likelihoods, the concept of information is murky. We give an alternate definition of randomization and show how to compute it for different randomization procedures. The randomization procedures we discuss are the permuted block design, stratified block design, and stratified urn design. We illustrate these results by reanalyzing a clinical trial in retinopathy.

Thursday, March 1, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

Refreshments will be provided at 9:45am

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"Use of a Visual Programming Environment for Creating and Optimizing Mass Spectrometry Diagnostic Workflows"

Maciek Sasinowski, Ph.D.
Founder and CEO of INCOGEN, Inc.
Williamsburg, VA

Abstract:

The use of mass spectrometry for clinical applications has extraordinary potential for accurate, early, and minimally invasive diagnoses of complex diseases, such as cancer, which require sensitive diagnostic tools for prognosis and development of flexible treatment strategies. Unfortunately, current mass spectrometry data analysis options available to researchers often require improvised combinations of tools provided by instrument manufacturers, third-parties, and in-house development. The lack of unified interfaces to access existing resources presents a significant bottleneck in the research and discovery process.

In this seminar, we present a modular software tool for the analysis of mass spectrometry profiling data that aims to address this bottleneck. The modules that comprise the analysis workflows can be broadly classified into three categories: signal processing tools, variable selection algorithms, and classification utilities. The software tool provides a platform that allows researchers to construct, validate, and optimize classification workflows of serum samples analyzed with time-of-flight mass spectrometry. Our work suggests that this type of flexible and interactive architecture is highly useful for 1) the development of mass spectrometry workflows and 2) biomarker discovery and validation in clinical environments.

Friday, March 16, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

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"The Assessment of Multivariate Bioequivalence"

Thomas Mathew, Ph.D.
Department of Mathematics & Statistics, UMBC
Baltimore, MD

Abstract:

The purpose of bioequivalence testing is to compare the bioavailabilities of two drug products: a brand name drug and a generic copy, for the purpose of establishing the equivalence between the two. The primary data for bioequivalence testing consist of the concentration of the active ingredient in the blood measured at several time points, after administering the drug. The concentration is plotted against time, and three responses are obtained: the area under the plasma concentration-time curve, simply referred to as area under the curve or AUC, the maximum concentration that shows up in the blood, and the time to reach the maximum concentration. Univariate bioequivalence consists of the separate modeling and analysis of the data based on the three univariate responses. Multivariate bioequivalence consists of the joint modeling and analysis of the data on the three variables, or any two of them. It is standard practice to use mixed effects models. Very extensive literature is available on the topic of univariate bioequivalence testing; a brief review will be given in my talk, addressing the concepts of average bioequivalence, and variance bioequivalence. In the univariate case, statistical procedures have been developed to address these. The literature in the multivariate case is very limited, dealing only with average bioequivalence. In my talk, I will address various aspects of multivariate bioequivalence testing, and will describe test procedures, along with some data analysis.

Friday, April 20, 2007 10:00-11:00 am

New Research Building, E501 Conference Room

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"Systems pharmacology of type 2 diabetes: a case study for pharmaceutical development"

Terence E. Ryan, PhD
Senior Director, Systems Biology
Biological Technologies
Wyeth Research
Collegeville, PA

Abstract:

A key issue in drug discovery is the appropriate use of animal models to study human disease and therapeutic drug response. Animal models have, in general, been used to mimic human disease based upon relatively few points of analogy. The richness of open discovery "omics" platforms allows a comprehensive measurement of disease and drug response across a range of analyte classes, allowing investigators to better understand the predictive value of animal models for human disease. In a study conducted by GlaxoSmithKline, we compared disease effects and treatment response in two mouse models of type 2 diabetes and in a parallel human study. Three registered medicines for diabetes (rosglitazone, metformin, and glyburide) were studied, and detailed measurements of transcripts, lipids, metabolites, and proteins were obtained in tissues and biofluids. Integrated data analysis using various multivariate techniques allowed for the generation of predictive fingerprints which shorten the time required to demonstrate treatment efficacy in diabetes trials, as well as allowing the identification of patients most likely to respond to a particular therapy form baseline measurements. In addition, analysis uncovered a previously unsuspected mechanism for rosiglitazone activity in diabetic adipose. The use of Systems Biology approaches with large "omic" datasets holds great promise for deeper understandings of disease biology and pharmacology

Friday, May 4, 2007 10:00-11:00 am

Lombardi Comprehensive Cancer Center, Room 131 (LL Lombardi)

Refreshments will be provided at 9:45am

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"Repetitive DNA and the evolution of eukaryotic gene regulation"

King Jordan, PhD
Associate Professor
School of Biology
Georgia Institute of Technology
Atlanta, GA

Abstract:

At least 50% of the human genome is made up of repetitive DNA, while only 1.5% is dedicated to protein coding sequences. The functional and evolutionary significance of this repetitive DNA fraction is very much an open question. We use computational methods to explore the ways that repetitive DNA, transposable elements in particular, has influenced the structure, function and evolution of eukaryotic genomes. I will discuss recent results related to the effects of repetitive DNA on nucleosome binding affinities along vertebrate proximal promoter regions and demonstrate how this relates to the regulation of gene expression. I will also provide evidence detailing the evolution of a number of distinct classes of gene regulatory sequences from transposable elements. Taken together these results suggest a model for the evolution of eukaryotic genomes and gene regulation. This model holds that the challenges posed by transposable elements have led repeatedly to the emergence of genome defense mechanisms. These emergent regulatory mechanisms, including methylation, chromatin and RNA interference, were subsequently co-opted to serve as global regulatory systems, which in turn have provided for the regulatory complexity characteristic of the eukaryotic evolutionary lineage.

Friday, May 18, 2007 10:00-11:00 am

Lombardi Comprehensive Cancer Center, E501 New Research Bldg.

Refreshments will be provided at 9:45am

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