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Ohio State - Cleveland Clinic Foundation – Case Western Reserve University

Biostatistics Joint Symposium
Thursday, May 15, 2008

240 Cockins Hall, 1958 Neil Avenue, Columbus, Ohio

(see www.stat.osu.edu/visitors/maps.html for directions to Cockins Hall)

Schedule

11:30 – 12:00	Tomas Radivoyevitch, Case Western Reserve University "Equilibrium Model Selection"
12:15 – 1:15	Buffet Lunch 724 Math Tower – 231 W. 18th Avenue
1:30 – 2:00	Haikady Nagaraja, The Ohio State University "Stochastic Modeling of Sleep-Wake Process"
2:00 – 2:30	Peter Imrey, Cleveland Clinic Foundation "Promotion Bias in Clinical Research"
2:30 – 3:00	Break
3:00 – 4:00	Frank Harrell, Vanderbilt University **"Information Allergy"**

Keynote Speaker: Frank E Harrell Jr
Chair, Department of Biostatistics
Vanderbilt University

Abstract

Information allergy is defined as (1) refusing to obtain key information needed to make a sound decision, or (2) ignoring important available information. The latter problem is epidemic in biomedical and epidemiologic research and in clinical practice. Examples include:

- ignoring some of the information in confounding variables that would explain away the effect of characteristics such as dietary habits
- ignoring probabilities and "gray zones" in genomics and proteomics research, making arbitrary classifications of patients in such a way that leads to poor validation of gene and protein patterns
- failure to grasp probabilistic diagnosis and patient-specific costs of incorrect decisions, thus making arbitrary diagnoses and placing analyst in the role of the bedside decision maker
- classifying patient risk factors and biomarkers into arbitrary "high/low" groups, ignoring the full spectrum of values
- touting the prognostic value of a new biomarker, ignoring basic clinical information that may be even more predictive
- using weak and somewhat arbitrary clinical staging systems resulting from a fear of continuous measurements
- ignoring patient spectrum in estimating the benefit of a treatment.

Examples of such problems will be discussed, concluding with an examination of how information-phobic cardiac arrhythmia research contributed to the deaths of thousands of patients.

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Further Abstracts

Equilibrium Model Selection

Tomas Radivoyevitch
Case Western Reserve University, Department of Epidemiology and Biostatistics

Ribonucleotide reductase (RNR) is precisely controlled to meet the dNTP demands of scheduled (replication driven) and unscheduled (repair driven) DNA synthesis. It has a small subunit R2 (45 kDa) that exists almost exclusively as a dimer, and a large subunit R1 (90 kDa) that dimerizes when dTTP, dGTP, dATP, or ATP binds to its specificity site, and hexamerizes when dATP or ATP binds to its activity site. In general, RNR is modeled as a pre-equilibrium of proteins, ligands, and substrates whose parameters of interest are dissociation constants K_d, and a set of turnover rate parameters k_j that map distributions of active enzyme complexes into expected k_{cat} measurements of mixtures. My research focuses on K_d estimation from protein oligomer mass measurements, rather than enzyme activity measurements, because masses are known, whereas the k_j are not, and because they allow studies of simpler mixtures of simpler, enzymatically inactive, complexes. There are 58 *a priori* plausible equilibrium models of dTTP-induced R1 dimerization. These models are all hypothesis applied derivates of a full model of two total concentration constraint quadratic equations in the two free concentrations [dTTP] and [R1]. This talk will describe this model space, the methods I used to fit it to available data, and how the top 6 models suggest subsequent experiments designed to discriminate between them.

Stochastic Modeling of Sleep-Wake Process

Haikady Nagaraja
Ohio State University, Department of Statistics

Interest in modeling the sleep process has focused lately on the binary sleep-wakefulness process. Using a dataset consisting of EEG data from 29 subjects over seven days of temporal isolation, we take a parametric approach to describe the overall sleep-wake process architecture. We show that the sleep duration times can be modeled as a random sample from a generalized gamma distribution (GGD). We consider the wake times and find that they exhibit first-order dependence. Further investigation following grouping the data into four categories finds each sample to represent realizations from a first-order Markov chain. Within the cell containing the longest wake durations, the observations from all subjects are combined to provide an excellent GGD fit. The overall sleep-wake process is considered next, and the successive sleep and wake times are found to be independent. Some modeling issues and clinical applications are also discussed. (This is a joint work with Dr. Marilisa Gibellato, US Navy.)

Promotion Bias in Clinical Research

Peter Imrey
Cleveland Clinic Foundation

Biostatisticians are central to evaluation, regulation, and clinical adoption of medical products. We frequently serve as major and even primary authors of methods and results sections of scientific and regulatory reports, study protocols, and analysis plans. A growing body of literature of which many biostatisticians are unaware, largely in medical journals, raises serious concerns about the integrity of the clinical research enterprise to which we are central.

The accumulating concerns have two themes. One is incomplete reporting of research results, either through failure to publish entire studies, or selective omission of patients and/or relevant endpoints. The other is commingling of research and marketing through orchestrated programs of climate-molding research and publication, often managed by public relations firms. These programs may include "seeding trials" -- clinical trials designed primarily for direct marketing to clinical investigators, and ghost authorships of research reports and reviews for medical opinion leaders. We define bias produced by such mechanisms, in principle, as "promotion bias." The extent of this bias is unknown, but critics claim it is substantial in some clinical areas.

These concerns have led to calls for increased transparency in research and the publication process, including clinical trial registration, more complete financial disclosure, and selective prepublication scrutiny of clinical trial planning documents and raw data. Reaction to the last among biostatisticians has been mixed.

The talk will introduce, through examples, the concerns that are gripping the medical research community. Ethical concerns will be raised about biostatistical participation in ghost-authored publications and other unlabeled intermingling of commercial advocacy with science. The speaker will argue that the public credibility of Biostatistics as a profession is threatened to the extent that promotion bias exists and is tacitly accepted, and that a more public stance against the contributing practices is warranted.

The 2008 Biostatistics Joint symposium is funded by the Statistics Department, the School of Public Health, and the Biostatistics Center of The Ohio State University