appropriate prior should have a probability mass at the null value. It would be quite reasonable to have a continuous prior distribution function, but nevertheless to be interested in absorption probabilities at the null, as giving a bound to those at non-null values.

I have ignored in my comments many parts of Dr. Breslow's paper which are of great interest, for instance his remarks about model selection with particular reference to risk assessment. The paper will continue to stimulate interest for many years to come.

Comment

H. Flühler

Breslow's paper is a most interesting account of the Bayesian approach to solving problems in a biological context. Although his exposition does not rely and is not supported by practical experiences of his own, he presents manifold biological and medical application problems which were preferably tackled by applied statisticians from a Bayesian point of view. I support the message of Breslow's survey that progress in the statistical sciences is achieved most efficiently by a mature integration of the Bayesian thinking in applications.

Of the many topics deserving discussion I shall concentrate on three. First, I shall make some general comments about the Bayesian impact—from the perspective of an applied statistics unit in a major chemical and pharmaceutical company—to the various stages of statistical activities. Second, I shall address the topic of longitudinal data analysis, because I feel that the Bayesian approach will offer a most dramatic progress to all types of hierarchical models—supposing the workable tools which are underway will become available to the practitioner. Third, I shall refer to the interpretational and predictional flexibility offered by the Bayesian paradigm to the scientists in making inferential assessments based on experimented evidence.

GENERAL COMMENTS

The application of statistics is the basic foodstuff for progress. In order to achieve good statistical thinking and analysis, the scientific context has to be considered and understood. The multidisciplinary collaboration stimulates novel and unconventional approaches in solving statistical problems. Four different stages in the scientific learning cycle are identified, namely (i) the informal and less structured framework; (ii) the design phase; (iii) the reporting of inferences; and (iv) the diagnostics and model criticism.

Breslow's paper mainly outlines the impact and benefits of the Bayesian approach in stages (iii) and (iv) which I fully agree. However, the practical statistician is exposed to all four stages in any sequence and repetitive cycle.

Exploratory data analysis methods combined with interactive high density dynamic graphics and classical dimension reduction techniques are the essential ingredients for the practical statistical activity of stage (i). A recent account is presented by Weihs and Schmidli (1990) in this journal. Intuition and a free mental framework in respect to modeling and searching for structure are the characteristic elements of this activity phase. The Bayesian thinking, however, which requires a more or less structured framework, does play a minor role in this context. Prior information in respect of the application background and statistical expertise are essential components applied by the practitioner in an informal way.

How does the Bayesian framework support stage (ii), the design phase? Prior knowledge should always be available at the design phase assuming the scientific investigation as an on-going learning process which involves an iterative cycle of design, experiment, analysis and interpretation. The available prior information is applied and imbedded into the design phase in a more informal, natural thinking process. A formal procedure is presented by Hedayat, Jacroux and Majunder (1988) for comparing treatments with controls.

Bayesian methodology however strongly supports the reporting inferences process, stage (iii), and the diagnostics and model criticism, stage (iv). A theoretical account of the potential power is given by Smith (1986). The Bayesian paradigm could, however, play a much stronger role in a practical context. Why do these methods not get off the ground? First, there is an obvious educational deficiency in Bayesian methods. Second, many statisticians apply a philosophical

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view against the Bayesian thinking process. Third, the lack of operational techniques and tools hardly favors the Bayesian community. To overcome these deficiencies, intellectual efforts should be devoted in these directions.

To summarize the general comment and to put it into proper perspective, the Bayesian methodology represents merely one component—although an important and hopefully growing component—of the statistical methodological repertoire of which the applied statistician should be master.

HIERARCHICAL MODELING

Repeated measures data of the same experimental unit are very common in a biological and medical context. The approaches to these types of data are given various names in the statistical literature, among them "mixed effects modeling" or "hierarchical modeling" being the more common. Important advances were achieved in the pharmaceutical sciences by Racine-Poon and Smith (1990) addressed as population models and in the biological sciences by Racine-Poon (1985) addressed as nonlinear random effects models. The technical methods of these Bayesian approaches are based on the EM-algorithm. A typical practical problem can easily have up to 100 parameters to characterize individual profile behavior and up to 10 parameters for the population relationship among individual profiles. An implementation of a fully Bayesian analysis in a practical context was not feasible due to unsurmountable integrational problems. The work of Gelfand and Smith (1990) proposes the Gibbs sampler as the technical method to calculate all required marginal densities needed for Bayesian inferences for hierarchical models. Gelfand, Hills, Racine and Smith (1990) give evidence of the practical effectiveness of the Gibbs sampler for the widely used normal linear hierarchical model structure. The achieved result of the Gibbs sampler will certainly have a most revolutionary impact to the practical application of the Bayesian framework. It definitely supports diverting considerations and efforts of the applied statistician away from technical aspects to the scientific background and conclusions given by the data, the model and the analysis. It will enable the practitioner to place more emphasis on the relationship between the data and the scientific context.

FLEXIBILITY IN INTERPRETATION AND PREDICTION

Reporting inference summaries in forms of graphical posterior densities receives universally positive responses by our biologists and pharmacists. In case of the bioequivalence problem, the posterior density of the ratio of two formulations is displayed in a histogram-like form. This operational reporting basis is easily understood by the project leader for the decision-making process in contrast to the either-or mentality of the significance testing approach (see Mandallaz and Mau, 1981).

With respect to prediction, the Bayesian framework has a lot to offer. The predictive density is a logical and natural result of the Bayesian paradigm. Remarkable applications are presented by Grieve (1988) and Gelfand, Hills, Racine and Smith (1990). The main advantages of the statistical prediction analysis are the reasoned statements about the observational space, about what is likely to happen in some future situation. It supports directly the experimental thinking process.

To conclude, I would like to characterize the ideal biostatistician of tomorrow as a scientist willing to combine statistical theory and practice and scientific background as a single unique entity. Hereby I merely support the prediction of Leonard (1983) at the conference in Madison in 1981, that the statistician of the next century will be one-third Bayesian, one-third data analyst and one-third scientist. Breslow's paper definitely provides great support to these developments.