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Joint longitudinal-survival models and their application in prostate cancer.

In this talk I will illustrate the use of joint longitudinal and survival models for individual prediction of future longitudinal and event time data. The model is motivated by a prostate cancer application for patients previously treated with radiation therapy, PSA is the longitudinal variable and the event of interest is recurrence of the cancer. Features of the model include random effects, non-linear profiles for the longitudinal variable, proportional hazards model with values and derivatives of PSA as time dependent variables, dependent censoring. Estimation is via Markov chain Monte Carlo methods. I will discuss how to predict the residual time distribution for a new individual with some longitudinal data, and validation of the model using training and testing datasets. The model will be illustrated using the calculator at psacalc.sph.umich.edu . I will discuss using the model to estimate the effect of an intervention aimed to prevent prostate cancer recurrence. This is joint work with Cecile Proust-Lima, Scott Williams, Yongseok Park and Ning Liu.

Surrogate endpoints and auxiliary variables in clinical trials.

In clinical trials, the true clinical outcomes of interest often take long or cost much to collect. Hence, there is interest in identifying surrogate markers that can inform us on the treatment effects earlier and faster. The surrogate marker is a surrogate endpoint if it can replace the true endpoint and is an auxiliary variable if it can help in the estimation of the treatment effect on the true endpoint. In this talk I will review the literature on surrogate endpoints and auxiliary variables, including the landmark paper by Prentice, the work on measures of the proportion of treatment effect explained, consideration of the multiple trial setting and framing of the problem as causal models using counterfactual outcomes. This is joint work with Yun Li.

Finding subgroups of enhanced treatment effect in randomized clinical trials.

We consider the problem of subgroups of patients who may have an enhanced treatment effect in a randomized clinical trial, and it is desirable that the subgroup be defined by a limited number of covariates. The development of a standard, pre-determined strategy may help to avoid the well-known dangers of subset analysis. We present two methods developed to find subgroups of enhanced treatment effect. The first method involves the use of logistic regression and forward selection, with the largest possible model being that with all main effects, one and two-way interaction terms of the covariates and the treatment group indicator. The second method, referred to as "Virtual Twins", involves predicting response probabilities for treatment and control "twins" for each subject. The difference in these probabilities is then used as the outcome in a tree, which can potentially include any set of the covariates. Simulation studies are presented for situations in which there are and are not true subgroups of enhanced treatment effect, and the methods are compared using a variety of metrics, including area under the curve, sensitivity, specificity, positive and negative predicted values, and a cross-validation-based estimate of treatment effect. This is joint work with Jared Foster and Stephen Ruberg.

Order restricted estimation and inference in survival analysis.

In this talk I will consider order restricted inference for binomial proportions (p) and for survival curves. (S(t)). For a three group binomial problem if it is known that p1>p2>p3, then there can be substantial gain in efficiency by building these constraints into the estimation procedure. Estimation can be undertaken using isotonic regression to find the restricted MLE or by Bayesian analysis imposing the constraints through prior distributions. For survival analysis in the one and two sample case Dykstra suggested the constrained non-parametric MLE. We provide a corrected version of this constrained NPMLE. We develop efficient algorithms for finding the CNPMLE in the one sample case when the survival function is either bounded above or bounded below by a known curve, and in the two sample case when S1(t) >=S2(t). We demonstrate that a pointwise constrained NPMLE has good properties in a simulation study. This is joint work with Yongseok Park and Jack Kalbfleisch.