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Session 7

Personalized Medicine with Dynamic Predictions

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Personalized Schedules for Invasive Diagnostic Tests With Applications in Surveillance of Chronic Diseases

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Testing for Heterogeneity in the Utility of a Surrogate Marker

Personalized Schedules for Invasive Diagnostic Tests: With Applications in Surveillance of Chronic Diseases

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Benchmark surveillance tests for diagnosing disease progression (biopsies, endoscopies, etc.) in early-stage chronic non-communicable disease patients (e.g., cancer, lung diseases) are usually invasive. For detecting progression timely, over their lifetime, patients undergo numerous invasive tests planned in a fixed one-size-fits-all manner (e.g., biannually). We present personalized test schedules based on the risk of disease progression, that aim to optimize the number of tests (burden) and time delay in detecting progression (shorter is beneficial) better than fixed schedules. Our motivation comes from the problem of scheduling biopsies in prostate cancer surveillance studies.

Using joint models for time-to-event and longitudinal data, we consolidate patients' longitudinal data (e.g., biomarkers) and results of previous tests, into an individualized future cumulative-risk of progression. To use this predicted risk profile for scheduling invasive tests we propose three different approaches. First, by minimizing loss functions motivated by Bayesian decision theory, under the predicted risk profile, to obtain the optimal time of conducting a future invasive test. Second, planning tests on those future visits where the predicted cumulative-risk of the patient is above a particular threshold (e.g., 5% risk). Third, by estimating the expected number of tests (burden) and expected time delay in detecting progression (shorter is beneficial) for all possible test schedules, and then optimizing a utility function of the expected number of tests and delay to find a mathematically optimal schedule. Since we estimate the expected number of tests and delay in a personalized manner, they can be used directly by patients and doctors to compare various test schedules for their benefit and burden and make a shared decision for a suitable schedule. In all three approaches, a common specialty of our schedules is that they automatically update on each follow-up with newly gathered data.

We compare our methodologies with currently used heuristic schedules, and schedules based on partially observable Markov decision processes. We also evaluate criteria for the selection of risk-threshold (e.g., Youden index, F1 score, net benefit) in schedules based on risk-threshold. Last, we implement our methodology in a web-application for prostate cancer patients.

Comparing risk prediction models in longitudinal context

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In this presentation, I will review our recent research on comparing risk prediction models in longitudinal cohort studies. The research was conducted under the commonly encountered clinical context where patient characteristics are measured at baseline, biomarkers and clinical history are collected over time as repeated measures until censoring or the occurrence of a terminal clinical event of predictive interest. First, in a comparison between static vs. dynamic prediction models, the latter always showed equivalent or improved prediction accuracy, and the magnitude of improvement depended critically on the concept of baseline and how the at-risk population vary over time. This result suggests that when longitudinal data are available, dynamic prediction is a useful tool that can replace the widely used static prediction approaches. Second, in a comparison between two dynamic prediction model approaches, landmark modeling vs. joint modeling, neither approach dominated the other in terms of prediction accuracy, and their performance under the simulation context depended on model misspecification. This comparison was made feasible by using a novel algorithm to simulate longitudinal data that satisfied infinitely many landmark models simultaneously. The result suggests that further research on both types of models is warranted. Third, in a comparison among various joint models for dynamic prediction, it was found that misspecification of longitudinal trajectories could decrease the prediction accuracy, which highlights the importance of future research on joint models with multivariate longitudinal data and flexible trajectories. A computational approach to facilitate the estimation of this kind of joint models will be presented.

Testing for Heterogeneity in the Utility of a Surrogate Marker

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For many clinical outcomes, randomized clinical trials to evaluate the effectiveness of a treatment or intervention require long-term follow-up of participants. In such settings, there is substantial interest in identifying and using a surrogate marker that can measured earlier and be used to evaluate the treatment effect. Several statistical methods have been proposed to evaluate potential surrogate markers; however, these methods generally do not account for or address the potential for a surrogate to vary in utility by certain patient characteristics. Such heterogeneity is important to understand, particularly if the surrogate is to be used in a future trial to potentially predict or replace the primary outcome. Here, we develop a nonparametric approach to examine and test for heterogeneity in the strength of a surrogate marker of interest. Specifically, we propose an approach and estimation procedure to measure the surrogate strength as a function of a baseline covariate, W. We then propose a testing procedure to test for evidence of heterogeneity and, if there is heterogeneity, an approach to identify a region of interest i.e., a subgroup of W where the surrogate is useful. Lastly, we extend these methods to a setting where there are multiple baseline covariates. We examine the performance of these methods using a simulation study and illustrate the methods using data from the Diabetes Prevention Program clinical trial.