## INFORMATIVE EXAMINATIONS IN LONGITUDINAL DATA: A MARKOV MODEL FORMULATION WITH APPLICATION TO HEPATITIS C DISEASE PROGRESSION

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Multi-state Markov models are frequently used to model chronic disease progression, using interval censored data from longitudinal examinations. Typically, it is assumed that the examination and disease processes are independent. However, biased estimates may be obtained if the times of examination are associated with the underlying disease process.

We propose a modified multi-state Markov model in which the probability of an examination occurring in a certain time period is assumed to be conditionally independent of the outcome of interest in that period, given some fully observed surrogate variable. Reformulating into discrete time periods allows the longitudinal data to be viewed as intermittently missing outcomes (*i.e.* missing in periods when no examination takes place).

Through simulations, we show that our modified Markov model is less biased in estimating transition rates and covariate effects when examination times are associated with the outcome. An application is presented dealing with disease progression in a cohort of hepatitis C infected patients. Liver biopsies are the gold standard for assessment of disease stage but are taken infrequently and irregularly, and hence the timings may be informative. We apply our modified model to this problem using a composite surrogate variable which includes information on age, alcohol consumption, liver function tests and previous biopsies, all of which may be associated with timing of next biopsy and the disease stage.