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Estimating causal effects in non-Markov multi-state models

Multi-state models, as a generalization of traditional time-to-event models, is a convenient framework for analysing transitions between a possible large number of states. In the interest of causal inference, some or all of these states might represent a joint outcome of interest. Based on traditional outcome measures from multi-state models, various causal estimands of interest can be formulated, for example the average treatment effect (ATE) or the treatment effect on the treated (ATT). Estimation can in principal be based on any type of traditional hazard model, for each transition intensity at a time, before overall outcome measures are derived using the Aalen-Johansen estimator.

First, we show that some of these outcome measures, such as state transition probabilities, can be very sensitive to violation of the Markov assumption. Others, like state occupation probabilities, are proven not to be. We look at two general estimation procedures for transition probabilities in non-Markov models based on landmark subsampling. Then, we discuss the use of hazard regression models versus inverse probability weighted Nelson-Aalen estimators for the purpose of causal inference in such multi-state models and it’s relation to more traditional inverse probability weighting and g-computation of marginal structural models. For time-fixed interventions, estimation of both ATE and ATT is a rather straight forward extension of traditional approaches, while for time-varying treatments, we arge that ATT is both easiest to interpret and to estimate.

The motivating examples are based on a study on the effects of national workplace initiatives on long-term sick leave and work participation, analysing a large scale dataset linked from numerous Norwegian population-wide registries.