Modelling the hazard of transition into the absorbing state in the illness-death model

Elena Tassistro[1], *Davide Paolo Bernasconi*[2], *Paola Rebora*[3], *Maria Grazia Valsecchi*[4], *Laura Antolini*[5]

[1]elena.tassistro@unimib.it, Bicocca Center of Bioinformatics, Biostatistics and Bioimaging (B4 Centre), School of Medicine and Surgery, University of Milano-Bicocca

[2]davide.bernasconi@unimib.it, Bicocca Center of Bioinformatics, Biostatistics and Bioimaging (B4 Centre), School of Medicine and Surgery, University of Milano-Bicocca

[3]paola.rebora@unimib.it, Bicocca Center of Bioinformatics, Biostatistics and Bioimaging (B4 Centre), School of Medicine and Surgery, University of Milano-Bicocca

[4]grazia.valsecchi@unimib.it, Bicocca Center of Bioinformatics, Biostatistics and Bioimaging (B4 Centre), School of Medicine and Surgery, University of Milano-Bicocca

[5]laura.antolini@unimib.it, Bicocca Center of Bioinformatics, Biostatistics and Bioimaging (B4 Centre), School of Medicine and Surgery, University of Milano-Bicocca

The illness-death model is the simplest multistate model where the transition from an initial state 0 to an absorbing state 2 may involve also an intermediate state 1. The impact of the transition into 1 on the subsequent transition hazard to 2 enables to increase the knowledge about the disease evolution. The standard analysis approach is modelling the transition hazards from 0 to 2 and from 1 to 2 including time to illness as a time-varying covariate and measuring time from origin even after the transition into 1. The hazard from 1 to 2 can be also modelled only on patients in state 1, measuring time from illness and including time to illness as a fixed covariate. A recently proposed approach is a model where time after the transition into 1 is measured in both scales and time to illness is included as a time-varying covariate. Another possibility is a model where time after the transition into 1 is measured only from illness and time to illness is included as a fixed covariate. This work aims to set up a strategy a statistician can follow to fit the most suitable full-sample model on the hazards of transition to state 2.

Through theoretical reasoning and simulation protocols we developed sequential strategies a statistician can follow to: a) validate the properties of the illness-death process, from which the choice of the scale to measure time after illness depends, b) estimate the impact of time to illness on the hazard from 1 to 2, proposing also a novel modelling approach that ensures the interpretability of the coefficient of the time to illness.

In the case of Markov data, the use of the clock forward time scale is the natural way to measure the follow-up time. The clock reset scale should be considered in case of non-Markov data, since forcing to use the clock forward scale will result in a spurious effect of the time to illness, due to the time after illness and not to a different shape of the hazard function after illness.

Keywords: illness-death, Markov model, time scales.