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STELLINGEN

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Statistical modelling of time-varying covariates for survival data

van **Marta Spreafico**

1. The analysis of complex healthcare phenomena requires original analytical strategies and unconventional formulations to appropriately model disease evolution and describe the relationship with the time-varying processes of interest.
2. The crucial point of statistical analyses within medical contexts consists in dealing with complex data sources while taking into account the nature of the processes under study and managing the trade-off between clinical interpretability and mathematical formulation.
3. Personalized dynamic representations allow to enrich the knowledge available for modelling survival with relevant features related to the time-varying covariates of interest.
4. In a real-world setting, administrative databases can be exploited to address two delicate aspects of drug utilization studies: measuring adherence to polypharmacy and modelling drug intake as time-dependent covariate. (*Chapters 1, 2*)
5. The analysis of events of different intensity/duration occurring several times during follow-up represents a complex task that can be tackled using a marked point process for recurrent events. (*Chapter 3*)
6. Functional covariate Cox Models (FunCM) can be adopted for representing and incorporating information on the dynamics of functions over time into survival analysis starting from raw data. (*Chapter 4*)
7. Although Multiple Overall Toxicity (MOTox) score discards the categorical nature of CTCAE grades, it yields a flexible longitudinal quantification of multiple side effects that can be easily adapted to any cancer studies. (*Chapter 5*)
8. The evolution of a latent process over time can be represented through longitudinal profiles of probabilities and relative risks, by using latent Markov models and compositional data analysis. In case of Latent Overall Toxicity (LOTox), these profiles describe patient's response to therapy during treatment in terms of toxic side effects. (*Chapter 6*)
9. By moving from Intention-To-Treat analysis to Dose-Intensity models based on toxicity-treatment adjustment, the real effect of exposure modifications on survival outcomes is estimated. (*Chapter 7*)
10. A cross-sectional cooperation between statisticians and clinicians can make the patient pathway through the healthcare system more efficient, representing a significant step forward in the definition of new guidelines and personalized monitoring tools.
11. Close interdisciplinary collaboration between statisticians and clinicians should become standard practice, as it can lead to great contributions in both fields.