

## **Saddlepoint Approximation for Semi-Markov Process with Application to a Cardiovascular Randomised Study (LIPID)**

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Semi-Markov processes are gaining popularity as models of disease progression in survival analysis. In this paper we extend the approach of Butler and Bronson (2002) to account for censoring and apply it to a cardiovascular trial (LIPID). The technique we propose combines both the likelihood and saddlepoint techniques to fit a semi-Markov model specified through transition probabilities and moment-generating functions (MGF). This approach is computationally simple, can model a patient's history of events represented as a flowgraph (or multistage model) and allows accurate estimation of clinically important quantities, e.g. the overall survival, hazard ratio or excess risk. As a simple illustration, we consider a illness-death model (randomization, recovered stroke, death) for our data. Each individual passage time from one stage to another is fitted by a suitable parametric distribution and the results are then combined to provide i) a likelihood function for the network, ii) a transmittance matrix describing the process, iii) estimation of the relevant parameters. Moreover inference to test the treatment effect is available either by bootstrapping or by a direct derivation of a likelihood ratio test. Extensions to more complex flowgraphs including loops – returns to a previous state – can also be envisaged. The technique is obviously flexible enough to be applied to many applications in clinical trials.

### **References**

- [1] Butler R, Bronson D (2002) Bootstrapping survival times in stochastic systems by using saddlepoint approximations. *J.R. Statist. Soc. B* 64:31-49
- [2] LIPID Study Group (1998) Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 339:1349-1357