Illustrating Marginal Structural Models by comparison of estimation methods for two different questions on breast cancer chemotherapies

Christine Gall[1,2] and Angelika Caputo[2,3]

[1] Freiburg Center for Data Analysis and Modeling, Freiburg, Germany
[2] Institute for Medical Biometry and Medical Informatics, University Medical Center Freiburg, Germany
[3] Novartis Pharma AG, Basel, Switzerland

One of the main objectives in clinical epidemiology is to detect a relation between a factor, e.g. treatment dose, and outcome. We address data where treatment is applied repeatedly in time and the respective dose rate is set according to actual measurements. If such measurements are subsequently affected by given treatment, they might act as time-dependent confounders. Marginal structural models (MSMs) proposed by Robins [1] adequately address such confounders which allows a causal interpretation of the estimated treatment effect.
In this talk, different aspects of Robins' approach are illustrated by analysing data of the GEPARDUO study [2]. This is a randomised clinical trial in breast cancer which compares two chemotherapies that are applied preoperatively. Outcome is pathohistological response measured at subsequent surgery. The chemotherapies are given in repeated cycles. Clinical values such as palpation result measured before each cycle may lead to stop chemotherapy prior to the last planned cycle.
To provide insight into Robins' approach, we address two different questions. In a first step, we investigate the difference in outcome between the two chemotherapy regimen. We account for confounding due to early stopping by inverse-probability-of-censoring weighting. In a second step, we only consider one treatment arm and look at the data as an observational study. We model the influence of the number of given cycles on outcome by an MSM. In contrast to the first step, the situation is described by means of counterfactual variables and time-dependent confounders are accounted for by estimating the parameters of the MSM via inverse-probability-of-treatment weighting. Illustrating the estimation steps by showing parallels to the first analysis and pointing out the differences, we give a different view on the concept of MSMs.

References

[1] James M. Robins, Miguel Ángel Hernán, and Babette Brumback. Marginal structural models and causal inference in epidemiology. *Epidemiology*, 11:550–560, 2000.

[2] G von Minckwitz, G Raab, A Caputo, M Schutte, J Hilfrich, JU Blohmer, B Gerber, SD Costa, E Merkle, H Eidtmann, D Lampe, C Jackisch, A du Bois, and M Kaufmann. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the geparduo study of the german breast group. *Journal of Clinical Oncology*, 23(12):2676–85, 2005.