

A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials

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We will illustrate a new procedure for modelling interaction between a continuous covariate Z and a categorical covariate T in a regression model, recently proposed by Royston & Sauerbrei [1]. Here T represents the two treatment arms in a parallel-group clinical trial and Z is a prognostic factor which may influence response to treatment (known as a predictive factor). Generalisation to more than two treatments is straightforward. The usual approach to analysis is to categorise Z into groups according to cutpoint(s) and to analyse the interaction in a model with main effects and multiplicative terms. The cutpoint approach raises several well-known and difficult issues for the analyst. Extending the multivariable fractional polynomial approach [2], which combines variable selection with determination of functional relationships for continuous predictors, we will investigate treatment-covariate interactions. Other prognostic variables can also be incorporated by first constructing a multivariable adjustment model which may contain binary covariates and FP transformations of continuous covariates other than Z . The main step involves FP modelling of Z within the subgroups and a test of equality of regression coefficients. If preferred, this can be done within the adjustment model. By varying the algorithm slightly we can also deal with the conceptually different cases of a predefined hypothesis of interaction or searching for interactions. We demonstrate the ability of the approach to detect and display treatment/covariate interactions in two examples from randomised controlled trials in cancer [1, 3].

References

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