EXTENSIONS ON LONG-TERM SURVIVOR MODEL WITH RANDOM EFFECTS

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Abstract

Cured patients (or the so called long-term survivors) are increasingly being observed in clinical trial studies. As exemplified in some data sets, a considerable portion of the patients are deemed to be cured. With the presence of random hospital/centre effects, long-term survivor model has been proposed to analyze clustered survival data with a possible portion of cured patients. Under such mixture modeling setting, several extensions on random effects cure model are investigated in this thesis to accommodate the dependence among outcomes which often originate from the multi-centre research design settings.

Firstly, by taking the possible dependence of random effects into account, the long-term survivor model with bivariate random effects is proposed to assess the covariates and random effects in both recovery probability and the instantaneous failure rate. This study extends earlier work by allowing the random effects in the cure fraction and hazard function part to follow the bivariate normal distribution, which gives a generalized model with an additional correlation parameter governing the relationship between the cure probability and the hazard rate due to the hospital/clinic effects.

Secondly, a hierarchical cure model is considered for survival data obtained from multilevel research design where the nested random effects are used to model the hierarchical structure for such kind of survival data. In the modeling framework,
multilevel random effect terms are incorporated into the Cox’s proportional hazards function and the cured probability via a logistic transform, for handling the hierarchical clustering effects presented in the observed data. The proposed model is originally developed for multilevel clustered survival data. With some modifications, it is also applicable to multilevel recurrent failure time data.

Thirdly, through the Box-Cox transformation, a generalized long-term survivor model is proposed to allow flexibility in specifying the hazard function. With the general relative risk function form, the failure rate of those at-risk patients is no longer constraint to the Cox’s proportional hazard function. In particular, a family of hazard function forms are allowed, which takes exponential and linear relative risk as two special cases. The parameter governing the power transformation could be determined by means of a modified Akaike information criterion (AIC).

Adopting the GLMM method and EM algorithm, the estimation of regression parameters can be achieved by maximizing a BLUP-type log-likelihood function at the initial step, and then used to find the REML estimation for the variance component parameters. Application to some data sets, including the carcinoma data, bone marrow transplantation data, chronic granulomatous disease data and child survival study data, illustrates the usefulness of the proposed models.

Furthermore, simulation studies are conducted for each model to evaluate the
performance of the estimators, under the proposed numerical estimation scheme. In
general, unbiased estimates for both regression and variance component parameters
are observed and the estimation of standard error is also broadly satisfactory, implying
that the proposed estimation methods perform reasonably well. Some further
discussions and remarks on these proposed models and suggestions on future research
studies are provided.

**Keywords:** Cured patients; EM algorithm; GLMM; Long-term survivor; Random
effects; REML
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