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Mitigating bias from marker-dependent observation times for internal covariates in Cox regression

Studies of chronic disease often involve modelling the relationship between marker processes and disease onset or progression. The Cox regression model is perhaps the most common and convenient approach to analysis in this setting. In most cohort studies, however, biomarker values are only measured intermittently (e.g. at clinic visits) so Cox models often treat biomarker values as fixed at their most recently observed value until they are updated at the next visit. We consider the implications of this convention on the limiting bias of estimators when the marker values themselves impact the intensity for clinic visits. A joint multistate model is described for the marker-failure-visit process which can be fitted to mitigate this bias and an expectation-maximization algorithm is developed. An application to data from a registry of patients with psoriatic arthritis is given for illustration.