Competing risk regression models in cohort studies with the R package CohortMethod

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Background

In survival analysis, competing risks are outcomes that preclude the main study outcome of interest, or alter the probability of experiencing the main outcome(s) [1]. The Fine and Gray model is an extension of the Cox proportional hazards model with subdistribution hazard function (Eq. 1), defined through the instantaneous rate $\lambda_k(t)$ of experiencing the event of interest $D = k$ for subjects given they have survival already to time $t$ without any competing events $K \neq k$ having occurred for observed failure time $T$ [2]:

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{\text{Prob}(t \leq T < t + \Delta t, D = k | T \geq t \cup (T < t \cap K \neq k))}{\Delta t}.$$  \hfill (1)

CohortMethod is an R package that performs comparative cohort studies in an observational database in the Observational Medical Outcomes Partnership (OMOP) common data model. CohortMethod has the capability of using a large set of covariates to fit propensity models and logistic, Poisson, and Cox regression models. In order to conduct time-to-event analyses, it is necessary to be able to conduct regression on data containing competing risks. The goal of this study is to develop functionality to include the Fine and Gray model as an outcome model to CohortMethod, while supporting the ability to trim and match on propensity scores.

Methods

Kawaguchi, Shen, Li, and Suchard (2019) have developed fast and scalable methods for the analysis of large-scale competing risks data. These methods involve using a forward-backward scan algorithm to linearize the computations for log-pseudo likelihood, gradients, and Hessian diagonals, for later use in cyclic coordinate descent. This reduces computational complexity from $O(N^2)$ to $O(N)$ in fitting Fine Gray models with $N$ subjects [3].

Previously, CohortMethod supported only (conditional) Cox regression. We have developed new function combineCompetingStudyPopulations and option riskId in createFitOutcomeModelArgs to implement Fine Gray model fitting in CohortMethod for both single and multiple analysis frameworks. combineCompetingStudyPopulations combines two study populations, one with the outcome of interest, and one with the competing event, to generate a population with information on subjects experiencing either outcome. In the event that both outcomes occur at the same time, there are options to remove these subjects, or prioritize one outcome as the event experienced by the subject. This function is implemented in a multiple analysis framework by specifying the concept ID of the competing risk outcome as the riskId in createFitOutcomeModelArgs. The regression model is then fitted using OHDSI’s Cyclops package, which implements the novel forward-backward scan algorithm to estimate the parameters for use in cyclic coordinate descent [4].
Results

We apply CohortMethod to study the relative risk of hospitalization with heart failure for new users under angiotensin-converting enzyme (ACE) inhibitors and thiazide diuretics (THZs) treatment in subjects without a prior hospitalization with heart failure or who may experience the competing event of acute myocardial infarction. From the Optum EHR data source, we identify 1,014,618 patients. After applying a large-scale propensity score model, we successfully estimate the hazard ratio under the Fine Gray model among these one-to-one matched new-users of ACE inhibitors and THZs.

To accomplish this using our new extensions, we first use CohortMethod to extract the necessary data for our analysis. We specify both our outcome of interest, and the competing risk outcome as outcomeIds in getDbCohortMethodData. We exclude all first-line hypertension drugs to prevent high correlation between covariates and our treatments.

```r
connectionDetails <- createConnectionDetails(
  dbms = "postgresql",
  server = "localhost/ohdsi",
  user = "joe",
  password = "supersecret")

excludedCovId <- c(904542, 907013, 932745, 942350, 956874, 970250,
  97466, 978555, 991382, 1305447, 1307046, 1307863,
  1308216, 1308842, 1309068, 1309799, 1310756, 1313200,
  1314002, 1314577, 1316340, 1317640, 1317967, 1318137, 1318853,
  1319880, 1319998, 1322081, 1326012, 1327978, 1328165,
  1331235, 1332418, 1334456, 1335471, 1338005, 1340128,
  1341238, 1341927, 1342439, 1344965, 1345858, 1346866,
  1346823, 1347384, 1350489, 1351557, 1353766, 1353776,
  1363053, 1363749, 1367500, 1373225, 1373928, 1386957,
  1395058, 1398937, 40226742, 40235485)

covSettings <- createDefaultCovariateSettings(
  excludedCovariateConceptIds = excludedCovId,
  addDescendantsToExclude = TRUE)

cmData <- getDbCohortMethodData(
  connectionDetails = connectionDetails,
  cdmDatabaseSchema = cdmDatabaseSchema,
  targetId = 7036,
  comparatorId = 7033,
  outcomeIds = c(7368, 7364),
  exposureDatabaseSchema = "scratch",
  exposureTable = "my_cohorts",
  outcomeDatabaseSchema = "scratch",
  outcomeTable = "my_cohorts",
  cdmVersion = "5",
  firstExposureOnly = FALSE,
  removeDuplicateSubjects = FALSE,
  restrictToCommonPeriod = FALSE,
  washoutPeriod = 0,
  covariateSettings = covSettings)
```

```r
```
Next, we define study populations for both the outcome of interest and the competing risk, and we combine
them using the new combineCompetingStudyPopulations function. We specify for subjects in the data set
who experience the outcome of interest and competing risk outcome simultaneously to be removed from the
study population. We then fit a propensity model and use the propensity score to perform matching.

```r
studyPopOutcome <- createStudyPopulation(cohortMethodData = cmData,
outcomeId = 7368,
firstExposureOnly = FALSE,
riskWindowStart = 0,
riskWindowEnd = 9999)

studyPopRisk <- createStudyPopulation(cohortMethodData = cmData,
outcomeId = 7364,
firstExposureOnly = FALSE,
riskWindowStart = 0,
riskWindowEnd = 9999)

studyPopCombined <- combineCompetingStudyPopulations(### New function
mainPopulation = studyPopOutcome,
competingRiskPopulation = studyPopRisk,
removeSubjectsWithSimultaneousEvents = TRUE)

ps <- createPs(cohortMethodData = cmData,
population = studyPopCombined)

matchedPop <- matchOnPs(population = ps,
caliper = 0.2)
```

We fit our Fine Gray outcome model on our one-to-one matched study population:

```r
outcome <- fitOutcomeModel(population = matchedPop,### Updated for multi-type events
modelType = "fgr")
```

```
## Model type: fgr
## Stratified: FALSE
## Use covariates: FALSE
## Use inverse probability of treatment weighting: FALSE
## Status: OK
##
## Estimate lower .95 upper .95 logRr seLogRr
treatment 0.942060 0.873580 1.015845 -0.059686 0.0385
```

**Conclusions**

The **CohortMethod** package now provides the ability to perform comparative cohort studies in an observa-
tional database that use the Fine Gray regression model for competing risks. Using the forward-backward
scan algorithm, **CohortMethod** calls package **Cyclops** to estimate Fine-Gray parameters in order \(O(N)\) time,
rather than \(O(N^2)\), as in other packages of the same purpose, such as **cmprsk**. Thus, its efficiency is along
the lines of previously supported survival regression models, such as the Cox proportional hazards models.
With this approach, we are able to provide a reliable estimate of Fine Gray regression coefficients in new-user
cohort studies with large numbers of observations.
References


