CONFIDENTIAL

Dose modification dose-response time varying covariate model

2023-04-10

Matthew Wiens
Metrum Research Group
Tunxis Road, Suite 112
Tariffville, CT 06081

Contents

This markdown demonstrates how a biased and incorrect conclusion of the dose-response relationship can be created through dose reductions throughout the course of a study, despite using time-varying dosing information.

We assume all patients, for simplicity, have the same QD dosing regimen, but 75% with a dose reduction, with 50 days at a full dose, and then 50 days at a half dose.

```
n_full <- 1000

n_reduction <- 3000

n <- n_full + n_reduction

dosing_data_full <- tibble(ID = seq(1:n_full),
                           START = 0,
                           STOP = 100,
                           DOSE = 1)

dosing_data_reduction <- tibble(ID = rep((n_full + 1):n, each = 2),
                                START = rep(c(0, 50), n_reduction),
                                STOP = rep(c(50, 100), n_reduction),
                                DOSE = rep(c(1, 0.5), n_reduction))

dosing_data <- bind_rows(dosing_data_full, dosing_data_reduction)
```

We also simulate TTE data, with **no** dependence on exposure (or anything else). A frailty model is used as the basis for simulation, where each patient has an expected survival time of either 25 days or 100 days (with equal probability).

```
last_time <- as.numeric(max(dosing_data$STOP))


TTEs = tibble(ID = 1:n) %>%
  mutate(mean_time = sample(c(25, 100), size = n, replace = T, prob = c(0.5, 0.5))) %>%
  mutate(actual_event_time = 1 + ceiling(rexp(n, 1/mean_time))) %>%
  mutate(EV = as.numeric(actual_event_time <= last_time),
         EVTIME = pmin(actual_event_time, last_time))
```

```
analysis_dat_raw <- dosing_data %>%
  inner_join(TTEs, by = "ID")

analysis_dat <- analysis_dat_raw %>%
  filter(EVTIME > START) %>%
  mutate(status = as.integer((EVTIME <= STOP) & EV),
         STOP = pmin(EVTIME, STOP))
```

We fit two PH survival models and one simple Cox PH fit, one with an exponential hazard function, and one with a gompertz hazard function.

```
model_exp <- flexsurvreg(Surv(START, STOP, status) ~ DOSE, dist = "exp", data = analysis_dat)


model_gompertz <- flexsurvreg(Surv(START, STOP, status) ~ DOSE, dist = "gompertz", data = analysis_dat)

model_coxph <- coxph(Surv(START, STOP, status) ~ DOSE, data = analysis_dat)
```

This analysis shows a "significant" dose-response relationship for a PH model with an exponential or Gompertz hazard. An AFT model could also be used here as well. However, note that the cox model correctly identifies the lack of dose-response relationship. While the PH models are mis-specified (because of the underlying frailty model), this sort of situation naturally arises when there are unmeasured factors that relate to survival time. It's not necessary for these unmeasured to relate to exposure

```
# Exponential Model
model_exp
```

```
## Call:
## flexsurvreg(formula = Surv(START, STOP, status) ~ DOSE, data = analysis_dat,
##     dist = "exp")
##
## Estimates:
##       data mean  est       L95%      U95%      se        exp(est)  L95%
## rate        NA   0.008171  0.006851  0.009745  0.000735        NA        NA
## DOSE  0.890320   0.849088  0.661067  1.037109  0.095931  2.337513  1.936857
##       U95%
## rate        NA
## DOSE  2.821049
##
## N = 5124,  Events: 3193,  Censored: 1931
## Total time at risk: 181547
## Log-likelihood = -16051.48, df = 2
## AIC = 32106.96
```

```
# Gompertz Model
model_gompertz
```

```
## Call:
## flexsurvreg(formula = Surv(START, STOP, status) ~ DOSE, data = analysis_dat,
##     dist = "gompertz")
##
## Estimates:
##        data mean  est        L95%       U95%       se         exp(est)
## shape         NA  -0.005310  -0.007141  -0.003479   0.000934         NA
## rate          NA   0.015366   0.011611   0.020337   0.002197         NA
## DOSE    0.890320   0.349906   0.093562   0.606251   0.130790   1.418935
##        L95%       U95%
## shape         NA         NA
## rate          NA         NA
## DOSE    1.098079   1.833544
##
## N = 5124,  Events: 3193,  Censored: 1931
## Total time at risk: 181547
```

```
## Log-likelihood = -16034.67, df = 3
## AIC = 32075.33
```

```
# Cox PH model
model_coxph
```

```
## Call:
## coxph(formula = Surv(START, STOP, status) ~ DOSE, data = analysis_dat)
##
##         coef exp(coef) se(coef)     z     p
## DOSE 0.06484   1.06698  0.17161 0.378 0.706
##
## Likelihood ratio test=0.14  on 1 df, p=0.7063
## n= 5124, number of events= 3193
```