

R Assignment One

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Question One

With mathematical notation, write out the statistical model you used to simulate the data for the power analysis given the assumptions listed above. Include: 1) The expression for the log-hazard function in terms of the covariates and parameters, and 2) specify the distribution of failure times given the hazard (general is fine). Clearly define all terms and parameters in the model. (15 points)

The expression for the log-hazard function is

$\log(h(t|\mathbf{x}, \boldsymbol{\beta})) = \log[h_0(t)] + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2$, where

- $\log(h(t|\mathbf{x}, \boldsymbol{\beta}))$ is the natural logarithm of the instantaneous rate (hazard) of the event at time t for a participant who has survived up to that time t , given the covariates in \mathbf{x} and coefficients in $\boldsymbol{\beta}$;
- $\log[h_0(t)]$ is the baseline instantaneous rate (hazard) of the event at time t for a participant who had neither exposure, i.e., $x_1 = 0$ and $x_2 = 0$, and survived up to time t ;
- \mathbf{x} is a vector of covariates containing
 - x_1 , an indicator variable for the first binary exposure, with $x_1 = 1$ indicating that the participant was exposed and $x_1 = 0$ indicating that the participant was not exposed; and
 - x_2 , an indicator variable for the second binary exposure, with $x_2 = 1$ indicating that the participant was exposed and $x_2 = 0$ indicating that the participant was not exposed;
- $\boldsymbol{\beta}$ is a vector of coefficients including
 - β_1 , the log hazard ratio comparing the hazard of the event for a participant who had the first exposure, i.e., $x_1 = 1$, in the numerator to the hazard of the event for a participant who did not, i.e., $x_1 = 0$, in the denominator, where neither of them had the second exposure, i.e., $x_2 = 0$ for both;
 - β_2 , the log hazard ratio comparing the hazard of the event for a participant who had the second exposure, i.e., $x_2 = 1$, in the numerator to the hazard of the event for a participant who did not, i.e., $x_2 = 0$, in the denominator, where neither of them had the first exposure, i.e., $x_1 = 0$ for both;
 - β_3 , the log of the ratio of hazard ratios, where
 - * the hazard ratio in the numerator compares the hazard of the event for a participant who had both exposures in its numerator, i.e., $x_1 = 1$ and $x_2 = 1$, to the hazard of the event for a participant who had only one of the exposures in its denominator, i.e., either $x_1 = 1$ and $x_2 = 0$ or $x_1 = 0$ and $x_2 = 1$, and

- * the hazard ratio in the denominator compares the hazard of the event for a participant who only had the other exposure, i.e., $x_1 = 0$ and $x_2 = 1$ (if both numerator and denominator above had the first exposure $x_1 = 1$) or $x_1 = 1$ and $x_2 = 0$ (if both numerator and denominator above had the second exposure $x_2 = 1$), to the hazard of the event for a participant who had neither exposure in the denominator, i.e., $x_1 = 0$ and $x_2 = 0$.

The distribution of failure times is here assumed to be exponential, i.e., $f(t) = \lambda e^{-\lambda t}$, where $\lambda = e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_1 x_2}$.

Question 2

In terms of parameter(s) from the model outlined above, specify the null (H_0) and alternative (H_A) hypotheses for a test of multiplicative interaction. (5 points)

$H_0 : \beta_3 = 0$ (or, equivalently, $e^{\beta_3} = 1$), i.e., the null hypothesis is that the ratio of the hazard ratios described above to define β_3 equals one and indicates an absence of multiplicative interaction between the exposures.

$H_1 : \beta_3 \neq 0$ (or, equivalently, $e^{\beta_3} \neq 1$), i.e., the alternative hypothesis is that the ratio of the hazard ratios described above to define β_3 is not equal to one, i.e., multiplicative interaction exists between the exposures.

Question 3

Briefly (1 sentence) interpret the *HR* for the interaction term in the above model (generally, referencing X_1 and X_2). (5 points)

The ratio of hazard ratios for the interaction term in the above model (e^{β_3}) compares

- the hazard ratio in the meta-numerator, which compares the hazard of the event for a participant who had both exposures in its numerator, i.e., $x_1 = 1$ and $x_2 = 1$, to the hazard of the event for a participant who had only one of the exposures in its denominator, i.e., either $x_1 = 1$ and $x_2 = 0$ or $x_1 = 0$ and $x_2 = 1$, and
- the hazard ratio in the meta-denominator, which compares the hazard of the event for a participant who only had the other exposure, i.e., $x_1 = 0$ and $x_2 = 1$ (if both numerator and denominator above had the first exposure $x_1 = 1$) or $x_1 = 1$ and $x_2 = 0$ (if both numerator and denominator above had the second exposure $x_2 = 1$), to the hazard of the event for a participant who had neither exposure in the denominator, i.e., $x_1 = 0$ and $x_2 = 0$;

in other words, the ratio of the interaction terms gives the change (multiplicative interaction) in the hazard for a participant who had both exposures compared to a participant who had only one, beyond the change expected from multiplying the individual exposure effects.

Question 4

Referring to the results from the simulation study, what is the estimated probability of rejecting the null if the interaction HR is equal to 1.0? *A priori* what would you expect the probability of rejecting the null to be when the true state is $HR = 1$? Why? (10 points)

The estimated probability of rejecting the null when the interaction ratio was equal to 1.0 and we set the type I error rate to be $\alpha = 0.05$ was 0.05, or 5%.

We expect the power, or the probability of rejecting the null, to equal the predetermined type I error rate α (here, 0.05 or 5%) when the hazard ratio for the interaction equals one. Why?

The type I error rate, α , is by definition the probability of rejecting the null hypothesis when it is true.

Power, essentially, is, given a particular α and a particular alternative hypothesis, the probability of rejecting the null hypothesis when the alternative hypothesis is true.

If the ratio of hazard ratios for the interaction equals one, then the null hypothesis is true. Thus calculating via simulation the power, given a particular α , to detect a ratio of one effectively sets the alternative hypothesis to be the null hypothesis. Thus the power calculation, in returning the probability of rejecting the null hypothesis when the alternative hypothesis is true as designed, will return the probability of rejecting the null hypothesis when it is true, which is definition of the *alpha* we set to estimate the power in the first place.

Question 5

What is the HR for interaction that you would need to observe in order to have at least 80% power? If you wanted to be more precise in your estimate of the minimum effect size, explain briefly how you would modify the code to find the HR that gave you an answer closer to 80% (don't provide code—just briefly describe what you would do in a few sentences). (10 points)

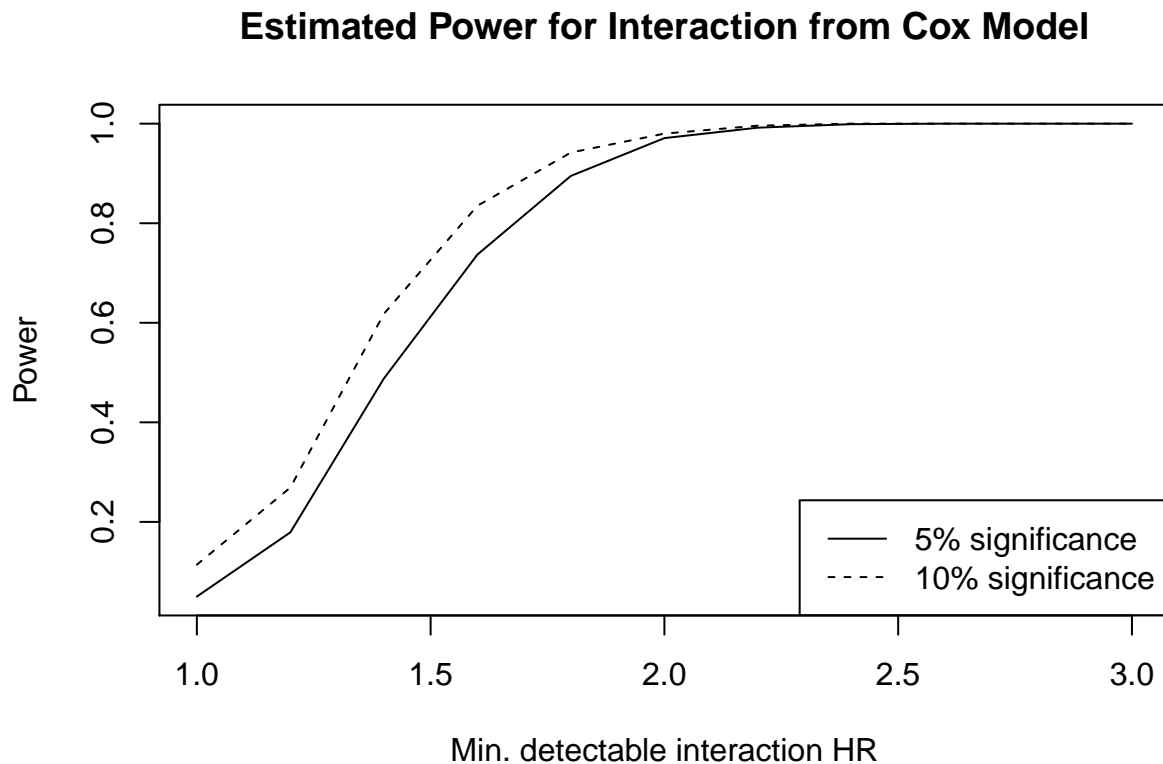
These power calculations (see the table below), done using data simulated for ratios for interaction e^{β_3} ranging from 1 to 3 at intervals of 0.2, estimate that we would need to observe a ratio for interaction of at least 1.8 at 5% significance, which would give us 89.5% power, or of at least 1.6 at 10% significance, which would give us 83.5% power. To more precisely estimate the minimum effect size, we could rewrite the code generating the vector of possible ratios for the interaction coefficient e^{β_3} to make it use intervals smaller than 0.2 between 1.6 and 1.8 for the 5% significance level (or between 1.4 and 1.6 at the 10% significance level). If we wanted a certain precision and liked coding, we could also write a loop that would keep dividing the intervals more finely and rerunning the simulation until it found a minimum ratio for the interaction that had a power above but within a pre-designated tolerance of 80%.

Table 1: Simulated power to detect interaction at 5% and 10% significance levels.

Interaction hazard ratio	Power @ 5% significance	Power at 10% significance
1.0	0.050	0.114
1.2	0.179	0.269
1.4	0.488	0.618
1.6	0.737	0.835
1.8	0.895	0.942
2.0	0.971	0.980
2.2	0.992	0.996
2.4	0.999	1.000
2.6	1.000	1.000
2.8	1.000	1.000
3.0	1.000	1.000

Question 6

For this question, present the simultaneous plot of the two power curves. Compare the pattern of power for significance tests at the 5% and 10% level and explain what you see in a few sentences. Suggest a reason why you observe what you do. (5 points)



The simulated power to detect an interaction rises and asymptotically approaches one as the minimum detectable interaction ratio rises. The power to detect the interaction appears lower at the $\alpha = 5\%$ significance level than at the $\alpha = 10\%$ significance level for all minimum detectable ratios until 2.6, when neither power is distinguishable at three decimal places from one.

The power rises as the minimum detectable interaction ratio rises because, as the ratio rises, the distribution generated by sampling from a distribution with the interaction ratio as its true mean moves away from the distribution generated by sampling from a distribution with the null interaction ratio (which equals 1) as its true mean. Thus, a smaller proportion of the values in the sampling distribution around the alternative hypothesis interaction ratio overlap “fail to reject the null” range of the sampling distribution around the hypothetical null interaction ratio, increasing the probability of rejecting the null when the alternative hypothesis is true, where that exact probability is by definition the power of the test.

The simulated power is systemically higher at the $\alpha = 10\%$ than at the $\alpha = 5\%$ significance level because setting the α essentially sets the frequency with which one rejects the null, whereas power essentially measures the frequency of rejecting the null when the alternative hypothesis is true. Per the central limit theorem, drawing repeated samples from a distribution with a true mean, as this simulation does for the simulated “true” interaction ratio, will eventually yield a normal distribution of sample values around that true mean. In that case, increasing the significance level (here, from 5% to 10%) when the alternative hypothesis is

actually true, in increasing the frequency of rejecting the null, increases the proportion of the alternative hypothesis sampling distribution that falls in the null-rejection range. As that proportion is by definition the power of the test, the power to detect the interaction ratio is increased at increased values of α .

Appendix: R code

```
knitr::opts_chunk$set(echo = FALSE,
                      warning = FALSE,
                      message = FALSE)

library(survival)
library(knitr)
library(rmarkdown)

set.seed(8765432)
N <- 500      # Number of events
              # (=sample size*(1-p[Censoring]) for uninformative censoring)
p.x <- .5     # Marginal probability of either exposure: P(X1)=P(X2)=.5

##### Generate matrix of covariates
## A matrix representing each possible exposure combination:
X.tmp <- t(matrix(c(0,0,0,
                   0,1,0,
                   1,0,0,
                   1,1,1),
                 ncol=4))

# Probability of each exposure combination: 0/0, 0/1, 1/0, 1/1:
p.x1.x2 <- c((1-p.x)^2,
            (1-p.x)*p.x,
            p.x*(1-p.x),
            p.x^2)

# Expected number of each exposure combo:
N.x1.x2 <- round(N*p.x1.x2)

# Repeat each exposure combination according to its expected number:
X <- as.data.frame(X.tmp[rep(1:dim(X.tmp)[1], N.x1.x2),])

names(X)<-c("x1", "x2", "x1.x2") # meaningful names

N.sims <- 1000 # Number of simulations

# At this point in the code, specify parameters (log-HRs, i.e. b coefficients) for a proportional hazard

# A scalar b0 corresponding to a constant baseline hazard h0(t) of 0.01.
b0 <- log(0.01)

# Scalars b1 and b2 both corresponding to main effect hazard ratios of 1.5.
b1 <- log(1.5)
b2 <- log(1.5)

# A vector b3 corresponding to hazard ratios ranging from 1 to 3
# in increments of 0.2.
b3 <- log(seq(from = 1, to = 3, by = 0.2))
```

```

# Next, complete the next block of code as follows:
# Generate a vector of exponentially distributed event times t.event stored in the data frame X. Hint:

# Generate a vector of event indicators event that have the value 1 for everyone, stored in the data fr

# Fit a Cox proportional hazards model corresponding to the analysis you wish to complete, and store th

# Initialize storage matrix for results:
p.values <- matrix(NA,N.sims,length(b3))
for (j in 1:length(b3)) {
  # Hazard function
  lambda <- exp(b0 + b1*X$x1 + b2*X$x2 + b3[j]*X$x1.x2)
  for (i in 1:N.sims){
    # Generate exponentially distributed event times (t.event)
    # and event indicator (event):

    # *****TO BE COMPLETED *****

    X$t.event <- rexp(n = N, rate = lambda)

    X$event <- 1

    # Fit corresponding Cox model and store results in fit.ph

    # *****TO BE COMPLETED *****
    fit.ph <- coxph(Surv(t.event, event) ~ x1 + x2 + x1.x2,
                    data = X,
                    ties = "efron")

    # Collect p-value from interaction term:
    p.values[i,j] <- summary(fit.ph)$coefficients[3,5]
  }
}

# Average number of times null is rejected=empirical estimate of power
p.lt.05 <- as.integer(p.values < 0.05)
est.power.05 <- apply(matrix(p.lt.05,
                             nrow=N.sims,
                             ncol=length(b3)),
                      2,
                      mean)

# Redo the above code segment, but calculate the power assuming a significance criteria of 10% rather t
p.lt.10 <- as.integer(p.values < 0.10)
est.power.10 <- apply(matrix(p.lt.10,
                             nrow=N.sims,
                             ncol=length(b3)),
                      2,
                      mean)

ratio.HR <- exp(b3) # Transform interaction coefficients to ratio scale.

```

```

# Create a table of results and output:
power.table <- t(rbind(ratio.HR, est.power.05, est.power.10))
kable(power.table,
      col.names = c("Interaction hazard ratio",
                    "Power @ 5% significance",
                    "Power at 10% significance"),
      caption = "Simulated power to detect interaction at 5% and 10% significance levels.")

# Plot results.
plot(ratio.HR,
     est.power.05,
     type="l",
     main="Estimated Power for Interaction from Cox Model",
     xlab="Min. detectable interaction HR",
     ylab="Power")

lines(ratio.HR, est.power.10, lty=2)

legend("bottomright",
      legend=c("5% significance",
              "10% significance"),
      lty=1:2)

```