CHL 5209 Assignment 3

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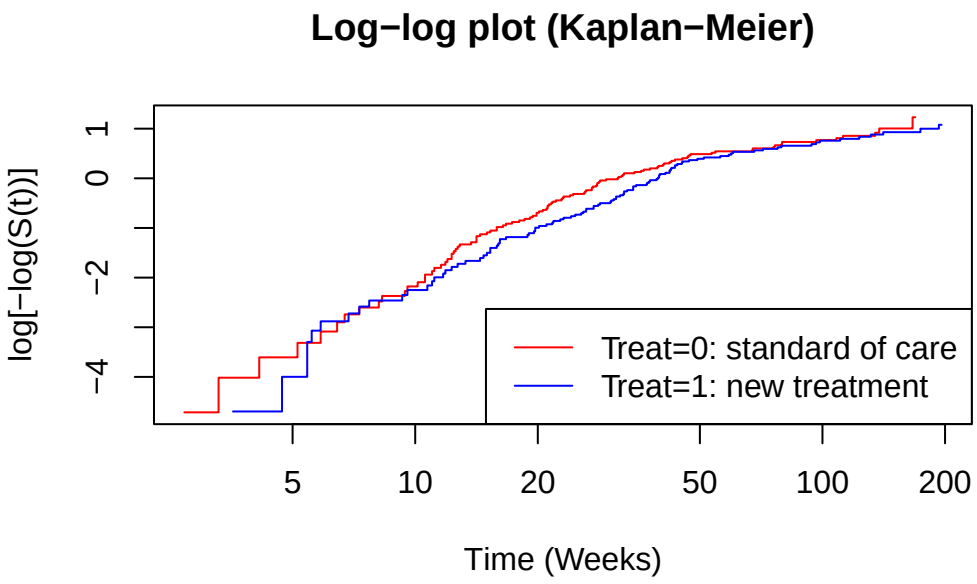
Question 1

(a)

If $log[-logS1(t)] - log[-logS0(t)] = \beta$, the lines $log[-logS1(t)]$ and $log[-logS0(t)]$ are parallel.

```
library(survival)
library(ggplot2)
library(lattice)

brain_data <- read.csv("brain.csv", header = TRUE)

fit_km <- survfit(Surv(weeks, event) ~ treat, data = brain_data)
plot(fit_km, fun = "cloglog",col = c("red", "blue"),
     xlab = "Time (Weeks)", ylab = "log[-log(S(t))]",
     main = "Log-log plot (Kaplan-Meier)")

legend("bottomright",
       legend = c("Treat=0: standard of care","Treat=1: new treatment"),
       col = c("red", "blue"), lwd=1)
```



There are few cross-over in the earlier time points, then lines are roughly parallel between 15 and 45 weeks then also between 50 and 180 weeks. This suggest that the hazard ratio between treatments may change over time. Further testing is need to check the proportionality of the treatment effect.

(b)

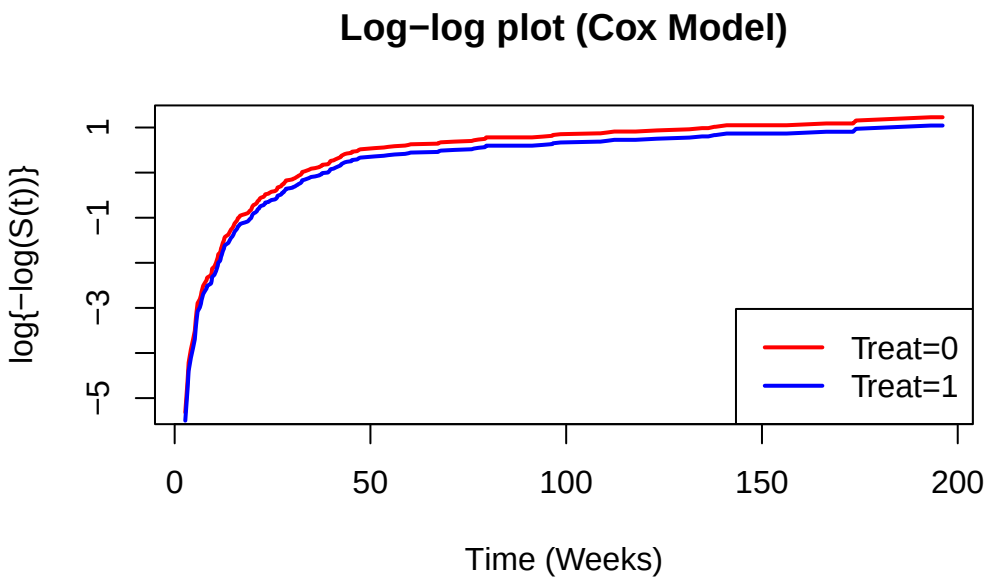
We know: $\hat{S}_0(t) = exp(-\hat{\lambda}_0(t))$ and $\hat{S}_1(t) = exp(-\hat{\lambda}_0(t)exp(\hat{\beta}))$ where $\hat{\lambda}_0(t)$ is the Breslow estimate for the cumulative baseline hazard, returned by `basehaz` funtion.

```
fit_cox <- coxph(Surv(weeks, event) ~ treat, data = brain_data)
summary(fit_cox)
```

```
Call:
coxph(formula = Surv(weeks, event) ~ treat, data = brain_data)

  n= 222, number of events= 207

         coef exp(coef) se(coef)      z Pr(>|z|)
treat -0.1839    0.8320   0.1401 -1.313    0.189

      exp(coef) exp(-coef) lower .95 upper .95
```

```
treat     0.832      1.202    0.6322     1.095

Concordance= 0.533  (se = 0.02 )
Likelihood ratio test= 1.72  on 1 df,   p=0.2
Wald test            = 1.72  on 1 df,   p=0.2
Score (logrank) test = 1.73  on 1 df,   p=0.2
```

```r
#baseline hazard using basehaz
base_haz <- basehaz(fit_cox, centered = FALSE)

#S0
S0 <- exp(-base_haz$hazard)

beta <- coef(fit_cox)[1]
#S1
S1 <- exp(-base_haz$hazard * exp(beta))

plot(log(-log(S0)) ~ base_haz$time,
     type = "l", col = "red", lwd = 2,
     xlab = "Time (Weeks)", ylab = "log{-log(S(t))}",
     main = "Log-log plot (Cox Model)")

lines(log(-log(S1)) ~ base_haz$time, col = "blue", lwd = 2)

legend("bottomright",
       legend = c("Treat=0", "Treat=1"),
       col = c("red","blue"), lwd = 2)
```



The log-log transformed survival curves are parallel, which would usually indicate that the proportional hazards assumption is met. However, this plot is not useful for checking the proportionality assumption because as you use the cox model, you are enforcing the assumption of proportional hazards.

Question 2

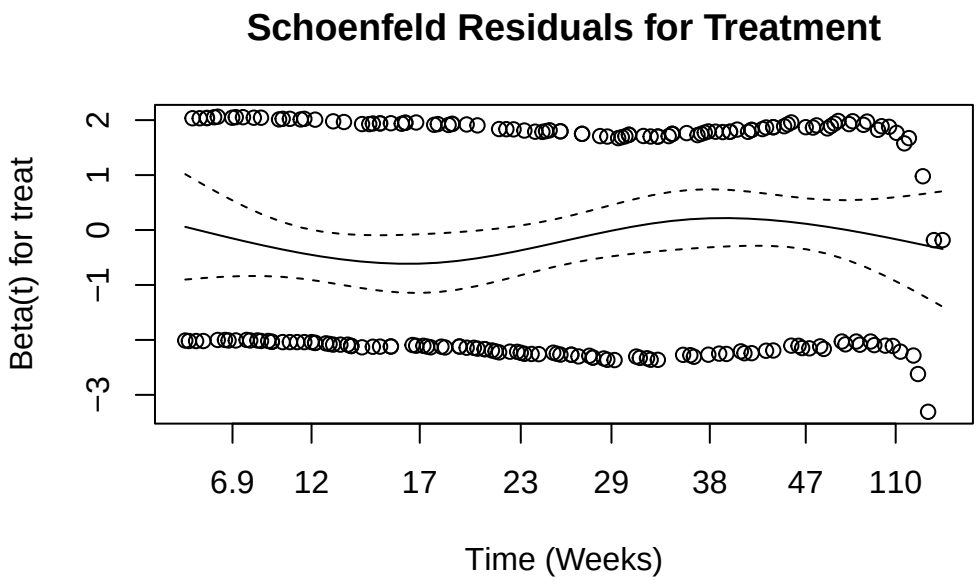
(a)

An appropriate residual check for proportionality is the Schoenfeld residuals. When you plot the scaled residuals for the variable along with estimates, if the smoothed line is reasonably smooth and horizontal, then the PH assumption is met for that variable.

```
fit_zph1 <- cox.zph(fit_cox)
fit_zph1
```

```
       chisq df    p
treat   1.26  1 0.26
GLOBAL  1.26  1 0.26
```

```
plot(fit_zph1, xlab = "Time (Weeks)", main = "Schoenfeld Residuals for
 ↪  Treatment")
```



From Schoenfeld residuals, the smoothed line do have some curvature but it stays within 1 and -1 with no strong trend of increasing or decreasing. So we need to investigate further to see if the PH assumption is met for the treatment variable.

(b)

Proportionality can be tested also by adding an interaction term (with the treatment arm indicator and time) into the model using the tt argument of the coxph. Add this to the model and interpret the result.

```
fit_time_int <- coxph(
  Surv(weeks, event) ~ treat + tt(treat),
  data = brain_data,
  tt = function(x, t, ...) x * t
)
summary(fit_time_int)
```

```
Call:
```

```
coxph(formula = Surv(weeks, event) ~ treat + tt(treat), data = brain_data,
    tt = function(x, t, ...) x * t)

  n= 222, number of events= 207

               coef exp(coef)  se(coef)      z Pr(>|z|)
treat     -0.230714  0.793966  0.217851 -1.059    0.290
tt(treat)  0.001429  1.001430  0.005094  0.280    0.779

          exp(coef) exp(-coef) lower .95 upper .95
treat         0.794     1.2595    0.5180     1.217
tt(treat)     1.001     0.9986    0.9915     1.011

Concordance= 0.533  (se = 0.02 )
Likelihood ratio test= 1.8  on 2 df,   p=0.4
Wald test            = 1.8  on 2 df,   p=0.4
Score (logrank) test = 1.81  on 2 df,   p=0.4
```

The coefficient of tt(treat) is 0.001429 with p-value of 0.779. This means that the interaction term is not significant, which indicates that the PH assumption is possibly met for the treatment variable.

Question 3

(a)

The Cox model has been adjusted for prognostic factor, age, in the dataset.

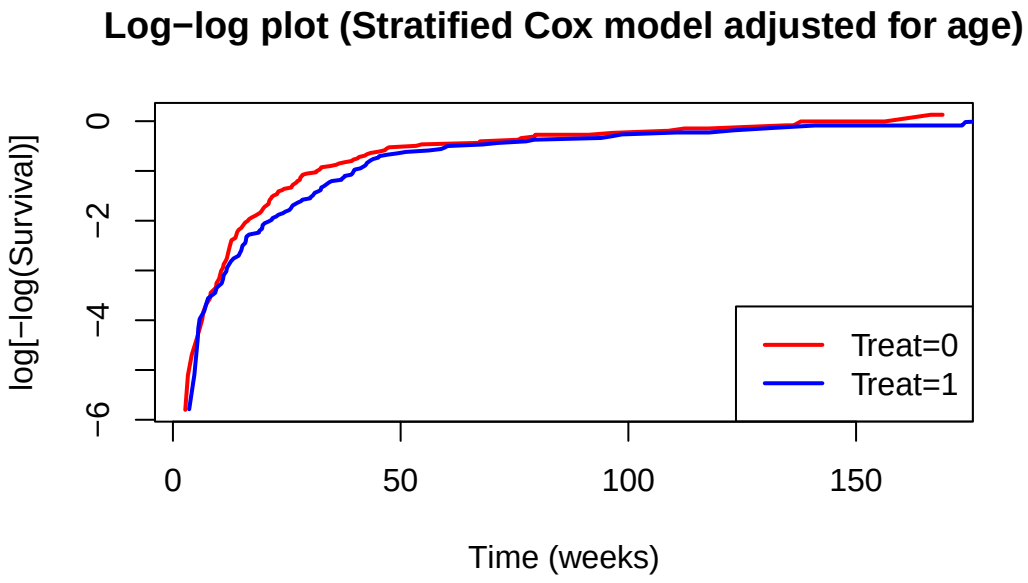
Now we will fit a stratified Cox model $\lambda_i(t) = \lambda_{zi}(t)exp(\beta' x_i)$. This can be done by not including the treatment arm indicator as a covariate, but instead entering it through a strata term.

```r
fit_strat <- coxph(Surv(weeks, event) ~ strata(treat) + age, data =
 ↪  brain_data)

#baseline hazard using basehaz
base_haz_strat <- basehaz(fit_strat, centered = FALSE)
head(base_haz_strat,5)
```

```
       hazard time  strata
1 0.003025438 2.71 treat=0
2 0.006074469 3.29 treat=0
```

```
3 0.009157599 4.14 treat=0
4 0.012279674 5.14 treat=0
5 0.015431068 5.86 treat=0
```

```r
base_haz_0 <- base_haz_strat[base_haz_strat$strata == "treat=0",]
base_haz_1 <- base_haz_strat[base_haz_strat$strata == "treat=1",]

#baseline survivals for each levels of Z
S00 <- exp(-base_haz_0$hazard)
S01 <- exp(-base_haz_1$hazard)

plot(log(-log(S00)) ~ base_haz_0$time, type = "l", col = "red", lwd = 2,
     xlab = "Time (weeks)", ylab = "log[-log(Survival)]",
     main = "Log-log plot (Stratified Cox model adjusted for age)")

lines(log(-log(S01)) ~ base_haz_1$time, col = "blue", lwd = 2)

legend("bottomright", legend=c("Treat=0","Treat=1"), col=c("red","blue"),
 ↪  lwd=2)
```



There was a slight cross-over around 10 weeks, then the difference between them gets bigger till 50 weeks, then the distance between them becomes very small then stay stable afterwards. The large change around 10 weeks and 50 weeks indicates that the treatment effect is not

constant (proportional) over time. This indicates that the PH assumption could not be met for the treatment variable.

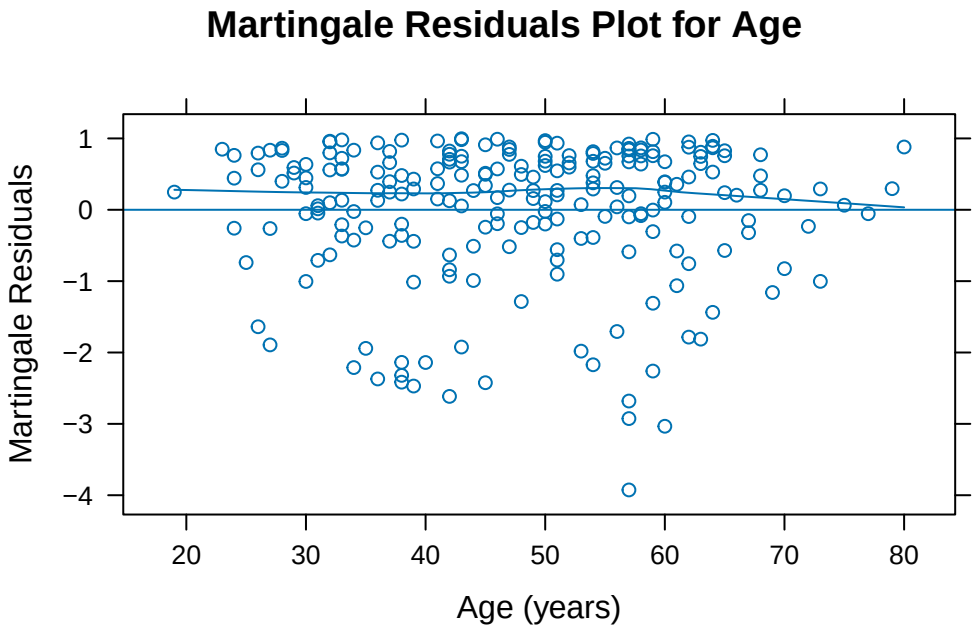
(b)

Fit a Cox model to estimate the treatment effect adjusting for age at randomization. Present and interpret an appropriate residual check for log-linearity of the age effect.

```
fit_cox_adjusted <- coxph(Surv(weeks, event) ~ treat + age, data =
 ↪  brain_data)
summary(fit_cox_adjusted)
```

```
Call:
coxph(formula = Surv(weeks, event) ~ treat + age, data = brain_data)

  n= 222, number of events= 207

           coef exp(coef)  se(coef)      z Pr(>|z|)
treat -0.216585  0.805264  0.140220 -1.545    0.122
age    0.022154  1.022401  0.005583  3.968 7.24e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
treat    0.8053     1.2418    0.6118     1.060
age      1.0224     0.9781    1.0113     1.034

Concordance= 0.592  (se = 0.022 )
Likelihood ratio test= 17.44  on 2 df,   p=2e-04
Wald test            = 17.57  on 2 df,   p=2e-04
Score (logrank) test = 17.79  on 2 df,   p=1e-04
```

```
mart_res <- residuals(fit_cox_adjusted, type = "martingale")

xyplot(mart_res ~ brain_data$age, type = c("p","r","smooth"), xlab = "Age
 ↪  (years)", ylab = "Martingale Residuals",main = "Martingale Residuals Plot
 ↪  for Age")
```



The smooth line on the martingale residuals plot is fairly linear up to around 60 years, then the line points downwards. This indicates that the log-linearity assumption of the age effect is may not be met for higher ages. Specifically, the effect of age on the log-hazard may decrease as age increases after 55 years.

(c)

Age could be added to the model also as a time-dependent covariate, to take into account that the patients are aging during the follow-up. Do this using the tt argument of the coxph function (please show your function call).

What happened to the age effect estimate compared to the model with the fixed baseline age variable? Explain why.

```
fit_age_t <- coxph(Surv(weeks, event) ~ treat + tt(age),data = brain_data,
                   tt = function(x, t, ...) x + t/52)

summary(fit_age_t)
```

```
Call:
coxph(formula = Surv(weeks, event) ~ treat + tt(age), data = brain_data,
    tt = function(x, t, ...) x + t/52)
```

```
  n= 222, number of events= 207

             coef exp(coef)  se(coef)      z Pr(>|z|)
treat   -0.216585  0.805264  0.140220 -1.545    0.122
tt(age)  0.022154  1.022401  0.005583  3.968 7.24e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

        exp(coef) exp(-coef) lower .95 upper .95
treat      0.8053     1.2418    0.6118     1.060
tt(age)    1.0224     0.9781    1.0113     1.034

Concordance= 0.592  (se = 0.023 )
Likelihood ratio test= 17.44  on 2 df,   p=2e-04
Wald test            = 17.57  on 2 df,   p=2e-04
Score (logrank) test = 17.79  on 2 df,   p=1e-04
```

From 3(b), the coefficient of age in the model with the fixed baseline age variable was 0.022154 (hazard ratio: 1.022401) with a p-value of 7.24e-05 (< 0.05). This coefficient is fixed log hazard ratio for all time points while the coefficient for tt(age) is time-varying log hazard ratio.

The coefficient of tt(age) is also 0.022154 (hazard ratio: 1.022401) with a p-value of 7.24e-05 (< 0.05). Therefore, the age effect estimate stayed the same when age was added as a time-dependent covariate compared to the model with the fixed baseline age variable. This is because of how the age was modeled in the time-dependent covariate model. Everyone ages every week by 1/52 years, therefore we modelled the time dependent age by using `tt(age)=age + t/52`. Since everyone ages uniformly at the same time by same amount, the hazard ratio will stay the same. Therefore, the age effect estimate stayed the same when age was added as a time-dependent covariate compared to the model with the fixed baseline age variable.

Question 4

(a)

Going back to the model without age or other prognostic factors, one way to avoid assuming proportionality of the treatment effect over the entire follow-up period would be to estimate separate treatment effects for early and later parts of the follow-up period. Fit a Cox model that allows for separate treatment effects before and after 30 weeks of follow-up. Construct the required time-dependent covariates by using the tt argument of the coxph function (please show your coxph function call).

```r
fit_30 <- coxph(Surv(weeks, event) ~ tt(treat),
                tt = function(x, t, ...) cbind(x*(t<30), x*(t>=30)),
                data = brain_data
)

summary(fit_30)
```

```
Call:
coxph(formula = Surv(weeks, event) ~ tt(treat), data = brain_data,
    tt = function(x, t, ...) cbind(x * (t < 30), x * (t >= 30)))

  n= 222, number of events= 207

               coef exp(coef) se(coef)      z Pr(>|z|)
tt(treat)1 -0.4409    0.6434   0.1854 -2.378   0.0174 *
tt(treat)2  0.1819    1.1995   0.2222  0.819   0.4130
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

           exp(coef) exp(-coef) lower .95 upper .95
tt(treat)1    0.6434     1.5541    0.4474    0.9254
tt(treat)2    1.1995     0.8337    0.7760    1.8540

Concordance= 0.548  (se = 0.019 )
Likelihood ratio test= 6.43  on 2 df,   p=0.04
Wald test            = 6.33  on 2 df,   p=0.04
Score (logrank) test = 6.42  on 2 df,   p=0.04
```

Comment on the results compared to the Cox model that assumed a constant treatment effect. Do you see any problems in looking for different treatment effects over the follow-up period, especially if we chose the 30-week cutoff based on seeing the non-parametric survival curves?

In the Cox model with the constant treatment effect (3b), the coefficient of `treat` was -0.216585 (hazard ratio: 0.8053) with a p-value of 0.122 (> 0.05). This means that the treatment effect was not statistically significant.

In the Cox model that allows for separate treatment effects before and after 30 weeks of follow-up, the coefficient of `tt(treat)1` (before 30 weeks) is -0.4409 (hazard ratio: 0.643457) with a p-value of 0.0174 (< 0.05) and the coefficient of `tt(treat)2` (from 30 weeks) is 0.1819 (hazard ratio: 1.199494) with a p-value of 0.4130 (> 0.05). This indicates that the treatment effect is only significant before 30 weeks but not after 30 weeks. This means that the Treat=1: new treatment had a significant protective effect (hazard ratio: 0.643457, p-value: 0.0174) before 30 weeks, but do not have enough evidence of beneficial or harmful effect after 30 weeks (p-value: 0.1819).

However, the problem with looking for different treatment effects over the follow-up period is that we decided to choose 30 weeks as a cutoff to split the time period after seeing the non-parametric survival curves, which means we chose the cutoff based on our data. This is a form of post hoc analysis, which can lead to overfitting the model to the data, and higher type I error rate, which means that we may find significant results by chance. These issues make the our results less reliable.

(b)

Specify (algebraically) the hazard model you fitted in Q4(a).

The Cox model that allows for separate treatment effects before and after 30 weeks of follow-up is:

$$\therefore \lambda_i(t) = \lambda_0(t) \cdot exp(\beta_1 \cdot treat_i \cdot I(t < 30) + \beta_2 \cdot treat_i \cdot I(t >= 30))$$

where $\lambda_0(t)$ is the baseline hazard, β_1 is the log hazard ratio for Treat=1 before 30 weeks, β_2 is the log hazard ratio for Treat=1 after 30 weeks, $treat_i$ is 1 if `treat` is 1 and 0 if `treat` is 0 for the i^{th} patient and $I(t < 30)$ is a identity function that is 1 if $t < 30$ and 0 otherwise, and $I(t >= 30)$ is a identity function that is 1 if $t >= 30$ and 0 otherwise.