DADOS MELANOMA

Sobrevida de 205 pacientes após cirurgia de melanoma cutâneo maligno em estágio clínico I.

Resposta: Tempo até o óbito ou final do estudo, em dias/365 -> anos
Censuras: à direita tipo I (status = 1 óbito e 0 = censura)
Covariáveis: ulc = ulceração (1 = presente, 2 = ausente)
thich = espessura do tumor (1/100 mm)
sexo = sexo do paciente (0 = feminino e 1 = masculino)

Obs: log(thick) foi centrada em seu valor médio

Fonte: Drzewiecki, K.T., Ladefoged, C., and Christensen, H.E. (1980), Biopsy and prognosis for cutaneous malignant melanoma in clinical stage I. Scand. J. Plast. Reconstru. Surg. 14, 141-144.

```
library(survival)
library(timereg)
library(survivalROC)

data(melanoma)
attach(melanoma)

Status<-ifelse(status==1, 1, 0)
espessura<- log(thick) - mean(log(thick))
tempo<-days/365
esp <- ifelse(espessura > 0.05,1,0)

data1 <- as.data.frame(cbind(ulc, espessura, sex, tempo, Status, esp))
attach(data1)

set.seed(157)
n1<-dim(melanoma)[1]
ei<-rnorm(n1,0,0.001)
tempos <- data1$tempo + ei

data2 <- as.data.frame(cbind(ulc, espessura, sex, tempos, Status, esp))
detach(data1);
attach(data2)
```

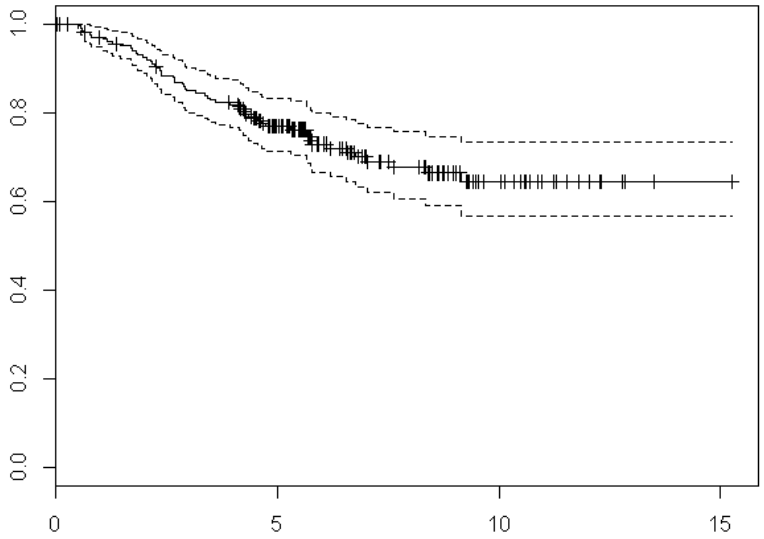
Descritiva

```
> table(Status)
  0   1
148  57           # 72% CENSURAS - TIPO I

> table(ulc)
  0   1
115  90

> table(sex,Status)
   Status
sex  0  1
  0 98 28
  1 50 29

> table(ulc,Status)
   Status
ulc  0  1
  0 99 16
  1 49 41
```

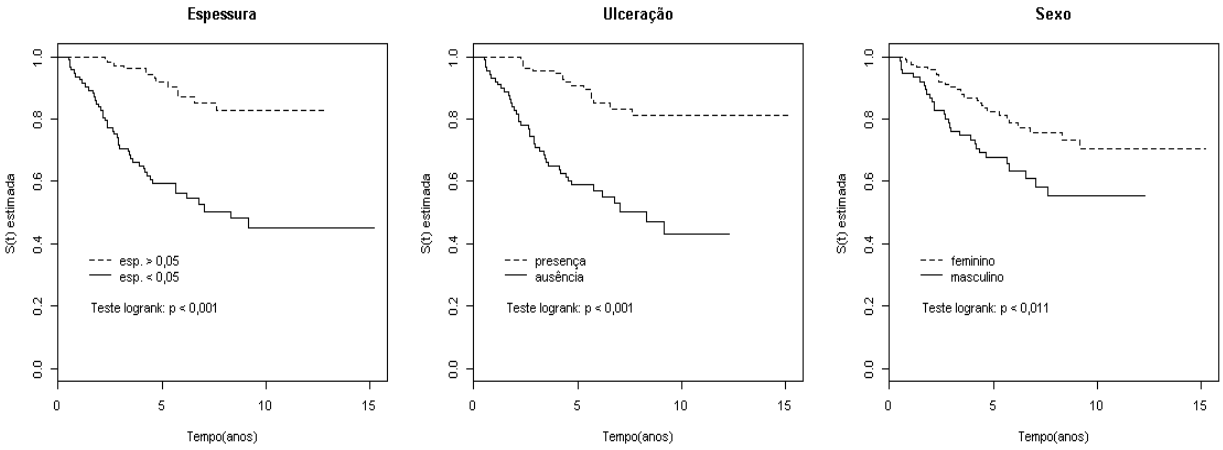
```
> esp<- ifelse(espessura > 0.05,1,0)
> table(esp,Status)
   Status
esp  0  1
  0 96 13
  1 52 44

> summary(melanoma$thick)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
     10      97     194     292     356    1742
> summary(espessura)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
-2.92100 -0.64860  0.04452  0.00000  0.65160  2.23900

> summary(tempos)
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
 0.02742  4.17500  5.49100  5.89800  8.33500 15.25000

> summary(tempos[Status==1])
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
 0.5102  1.9670  2.9080  3.4330  4.5640  9.1440

> summary(tempos[Status==0])
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
 0.02741  4.95900  6.10100  6.84800  8.99400 15.25000
```

Kaplan-Meier Geral

```
ekm <- survfit(Surv(tempos,Status) ~ 1, data=data2)
plot(ekm, mark.time=T)
```



Kaplan-Meier e teste logrank para as 3 covariáveis



AJUSTE MODELO DE COX

```
mod1<-coxph(Surv(tempo,Status) ~ ulc + espessura + sex, method="breslow",
data=data2)
```

	coef	exp(coef)	se(coef)	z	p
ulc	0.939	2.56	0.324	2.89	0.0038
espessura	0.576	1.78	0.179	3.21	0.0013
sex	0.381	1.46	0.271	1.41	0.1588

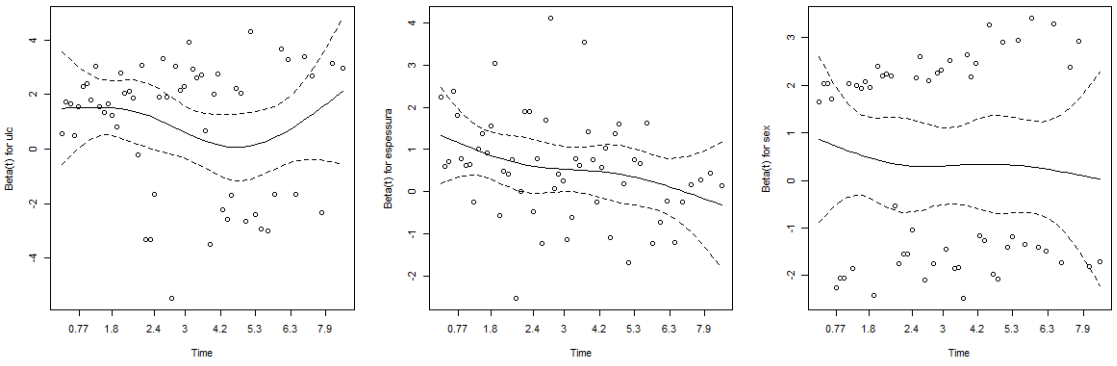
Avaliação da suposição de taxas de falha proporcionais

$H_0: \beta_j(t) = \beta$, para j = 1,..., p

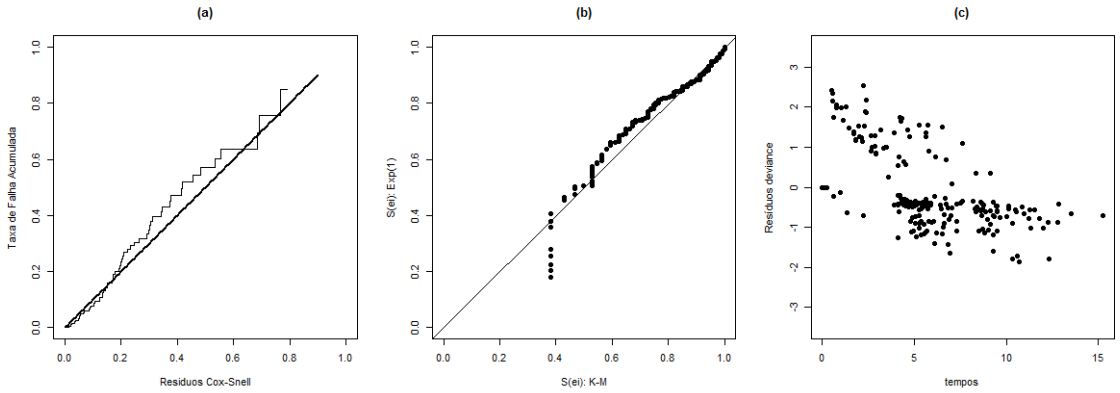
```
cox.zph(mod1)
```

	rho	chisq	p
ulc	-0.1158	0.719	0.3964
espessura	-0.2906	3.924	0.0476
sex	-0.0725	0.308	0.5792
GLOBAL	NA	8.231	0.0415

```
par(mfrow=c(1,3))
plot(cox.zph(mod1))
```



Análise dos Resíduos de Cox-Snell e Resíduos deviance



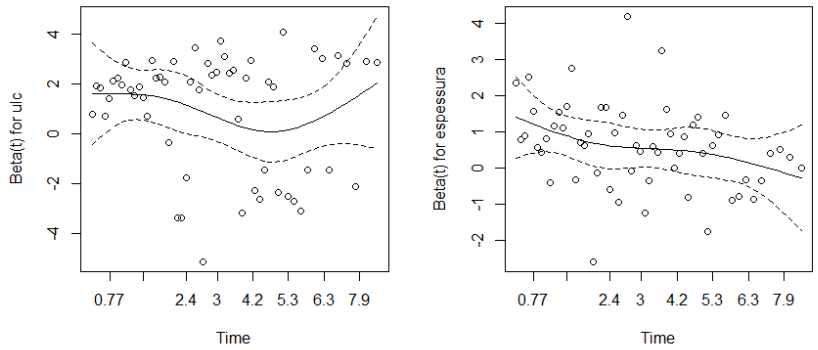
Modelo de Cox excluindo a covariável SEXO

```
mod1.1<-coxph(Surv(tempo,Status) ~ ulc + espessura, method="breslow", data=data2)
summary(mod1.1)
             coef exp(coef) se(coef)     z Pr(>|z|)
ulc        0.9712    2.6412   0.3209 3.027  0.00247 **
espessura 0.6104    1.8411   0.1759 3.470  0.00052 ***
```

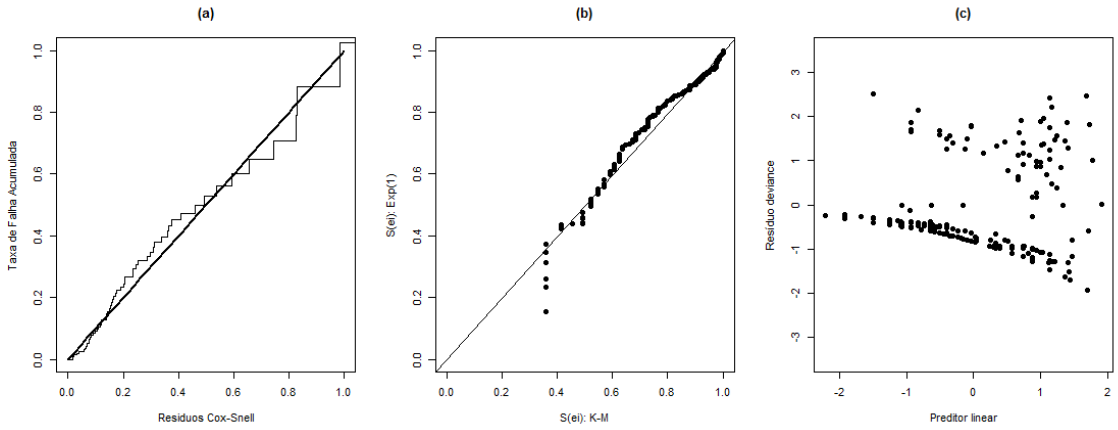
Avaliação da suposição de taxas de falha proporcionais

H_0: $\beta_j(t) = \beta$, para j = 1,..., p

```
cox.zph(mod1.1)
             rho chisq      p
ulc       -0.135 0.953 0.3289
espessura -0.304 4.142 0.0418
GLOBAL         NA 7.826 0.0200
```

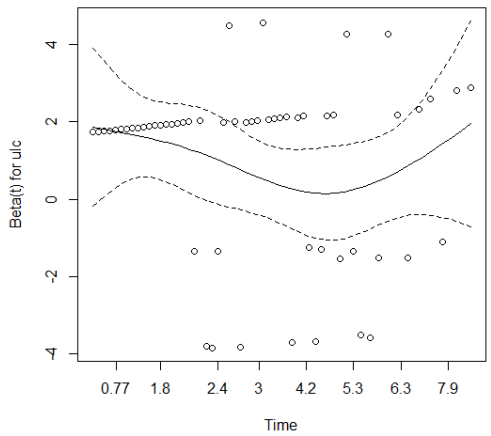


Análise dos resíduos de Cox-Snell e deviance



Modelo de Cox estratificado: espessura ~ mediana

```
esp<- ifelse(espessura > 0.05,1,0)
mod4<-coxph(Surv(tempo,Status) ~ ulc + sex + strata(esp), method="breslow",
data=data2)
     coef exp(coef) se(coef)    z      p
ulc 0.931     2.536    0.324 2.87 0.0041
sex 0.336     1.400    0.271 1.24 0.2140

Likelihood ratio test=11.4  on 2 df, p=0.00327
n= 205, number of events= 57

mod4.1<-coxph(Surv(tempo,Status) ~ ulc + strata(esp), method="breslow",
data=data2)
     coef exp(coef) se(coef) z      p
ulc 0.961     2.615    0.321 3 0.0027

Likelihood ratio test=9.91  on 1 df, p=0.00165
n= 205, number of events= 57

cox.zph(mod4.1)
      rho chisq     p
ulc -0.141     1 0.316
```

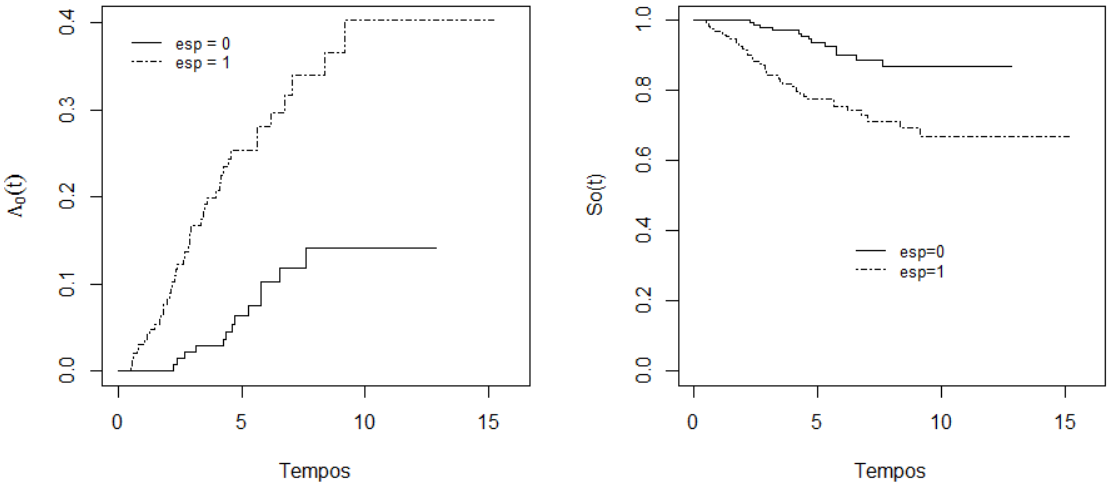


Teste da Razão de verossimilhanças – betas comuns

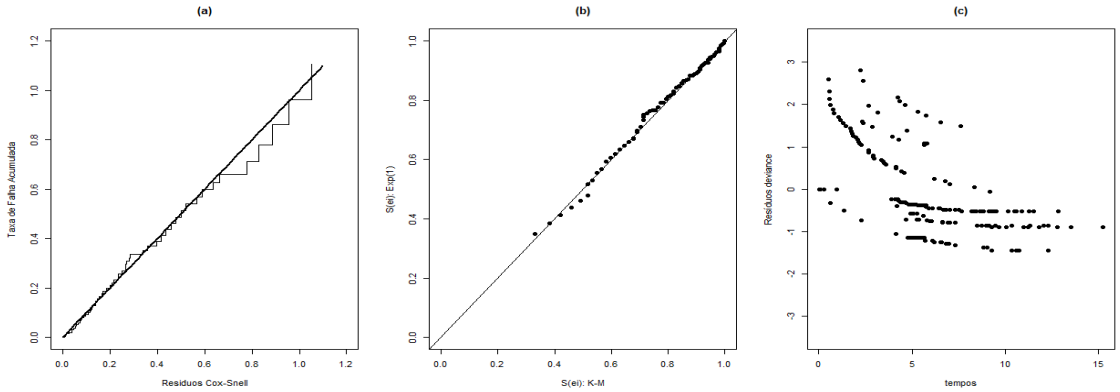
```
dat1<-subset(data2,esp==0)
dat2<-subset(data2,esp==1)
mod4<-coxph(Surv(tempos,Status) ~ ulc + strata(esp), method="breslow", data=data2)
mod4.2<-coxph(Surv(tempos,Status) ~ ulc, method="breslow", data=dat1)
mod4.3<-coxph(Surv(tempos,Status) ~ ulc, method="breslow", data=dat2)
trv<- 2*(-mod4$loglik[2]+mod4.2$loglik[2]+mod4.3$loglik[2])
cbind(trv, 1-pchisq(trv,2))
```

```
        trv
[1,] 0.7278751 0.6949346
```

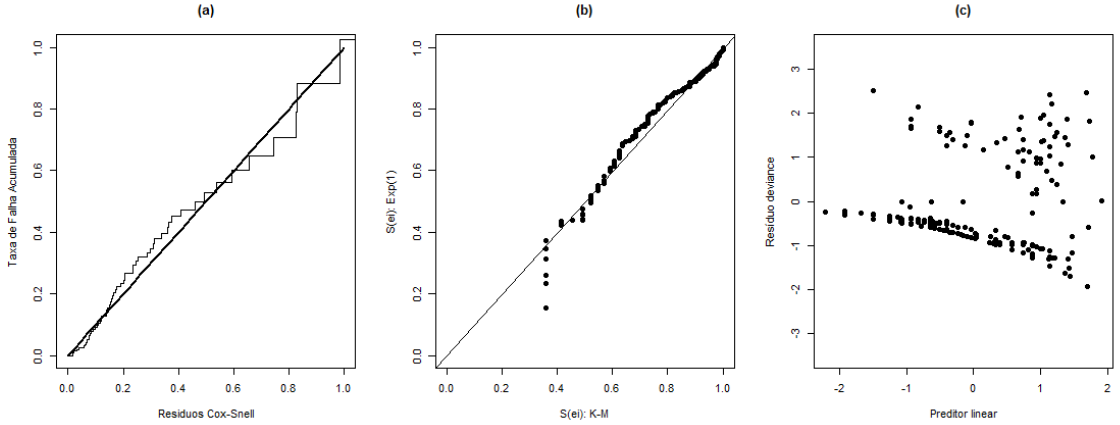
```
H0<-basehaz(mod4,centered=F) # risco acumulado de base
H01<-as.matrix(H0[1:109,1])    # estrato 1 (esp=0)
H02<-as.matrix(H0[110:205,1])  # estrato 2 (esp=1)
tempo1<- H0$time[1:109]        # tempos do estrato 1
S01<-exp(-H01)                 # sobrevivência de base estrato 1
round(cbind(tempo1,S01,H01),digits=5) # funções de base estrato 1
tempo2<- H0$time[110:205]             # tempos do estrato 2
S02<-exp(-H02)                        # sobrevivência de base estrato 2
round(cbind(tempo2,S02,H02),digits=5) # funções de base estrato 2
par(mfrow=c(1,2))
plot(tempo2,H02,lty=4,type="s",xlab="Tempos",xlim=range(c(0,16)),
                               ylab=expression(Lambda[0]* (t)))
lines(tempo1,H01,type="s",lty=1)
legend(0.0,0.4,lty=c(1,4),c("esp = 0","esp = 1"),lwd=1,bty="n",cex=0.8)
plot(c(0,tempo1),c(1,S01),lty=1,type="s",xlab="Tempos",xlim=range(c(0,16)),
                                                       ylim=c(0,1),ylab="So(t)")
lines(c(0,tempo2),c(1,S02),lty=4,type="s")
legend(6,0.4,lty=c(1,4),c("esp=0","esp=1"),lwd=1,bty="n",cex=0.8)
```



Análise dos Resíduos de Cox-Snell e deviance (Cox Estratificado)



Análise dos Resíduos de Cox-Snell e deviance (Cox Padrão)



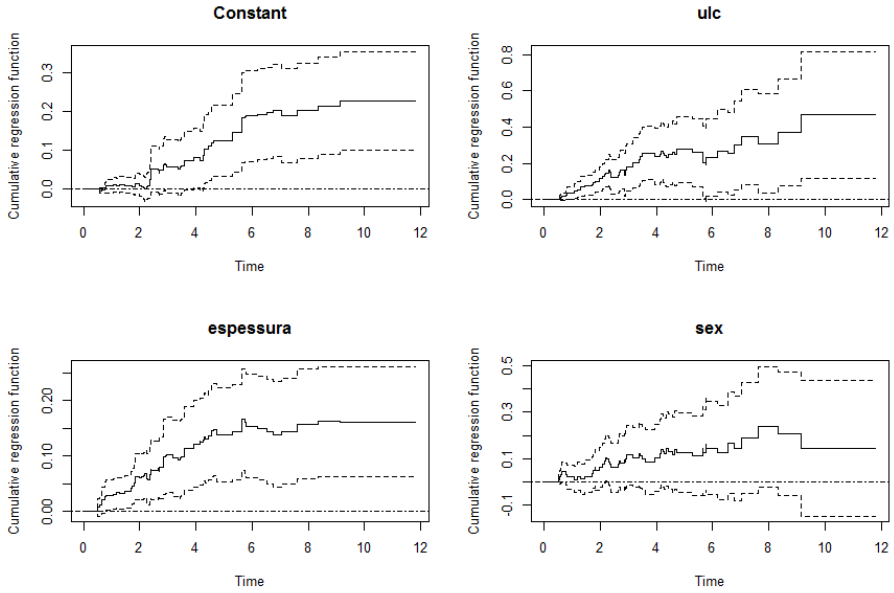
Ajuste do Modelo Aditivo de Aalen

ADDREG

```
source("https://docs.ufpr.br/~giolo/Livro/ApendiceA/Addreg.r")
mod2 <- addreg(Surv(tempos,Status)~ ulc + espessura + sex, data=data2)
```

```
Remark: Stopped at time 12.30547 because of too low rank.
        (Last estimate at time 12.27183)
```

```
  Estimates at time 12.27183:
           Coef. Std. Error     95% C.I.    Test statistic P-vaule
Constant  0.226      0.065  0.099  0.354           3.283   0.001
ulc       0.466      0.179  0.115  0.817           3.117   0.002
espessura 0.162      0.050  0.063  0.261           3.427   0.001
sex       0.145      0.149 -0.147  0.438           1.590   0.112
```

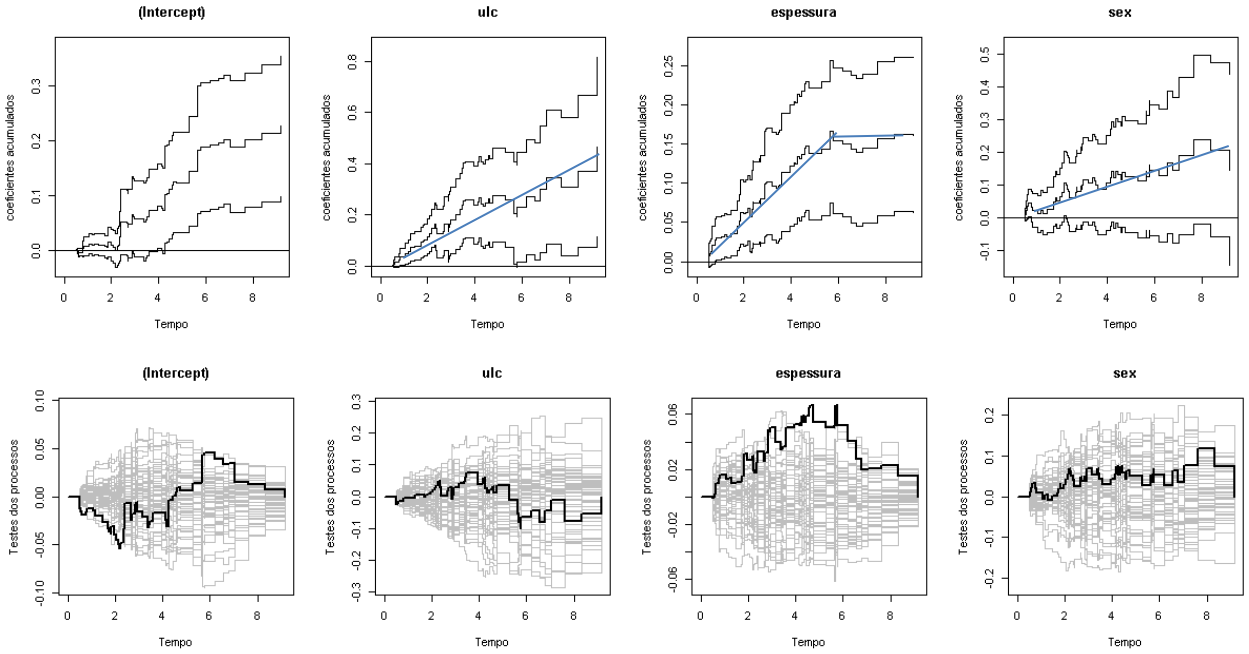


TIMEREG

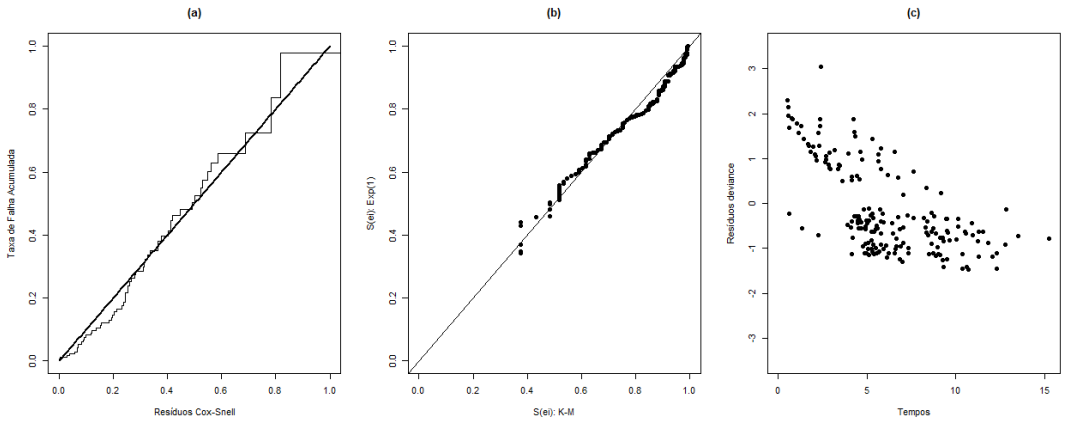
```
mod3 <- aalen(Surv(tempos,Status)~ ulc + espessura + sex, residuals=1,data=data2)
summary(mod3)
```

```
Test for non-significant effects
             Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                           3.33                0.014
ulc                                   3.68                0.008
espessura                             3.53                0.009
sex                                   2.08                0.318

Test for time invariant effects
                 Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                       0.0538                      0.332
ulc                               0.0990                      0.754
espessura                         0.0662                      0.049
sex                               0.1170                      0.428
                  Cramer von Mises test p-value H_0:constant effect
(Intercept)                      0.00465                      0.359
ulc                              0.01590                      0.791
espessura                        0.01050                      0.040
sex                              0.02550                      0.433
```

```
mod3$cum
          time   (Intercept)         ulc   espessura         sex
 [1,] 0.0000000  0.000000e+00 0.000000000 0.000000000 0.000000000
 [2,] 0.5085433  6.503850e-04 0.001322698 0.007914416 0.009926853
 ...
[57,] 8.3346068  2.133328e-01 0.370026174 0.162641044 0.206156079
[58,] 9.1447507  2.263496e-01 0.466213618 0.161846932 0.145171177
```



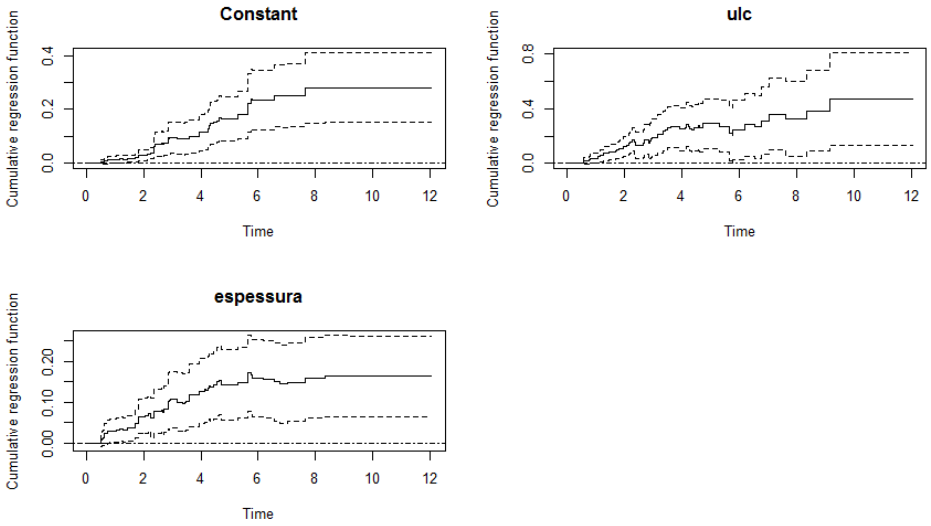
Análise dos Resíduos de Cox-Snell e deviance



Modelo Aditivo de Aalen sem a covarável sexo

```
source("http://www.ufpr.br/~giolo/Livro/ApendiceA/Addreg.r")
mod2.1 <- addreg(Surv(tempos,Status)~ ulc + espessura, data=data2)
```

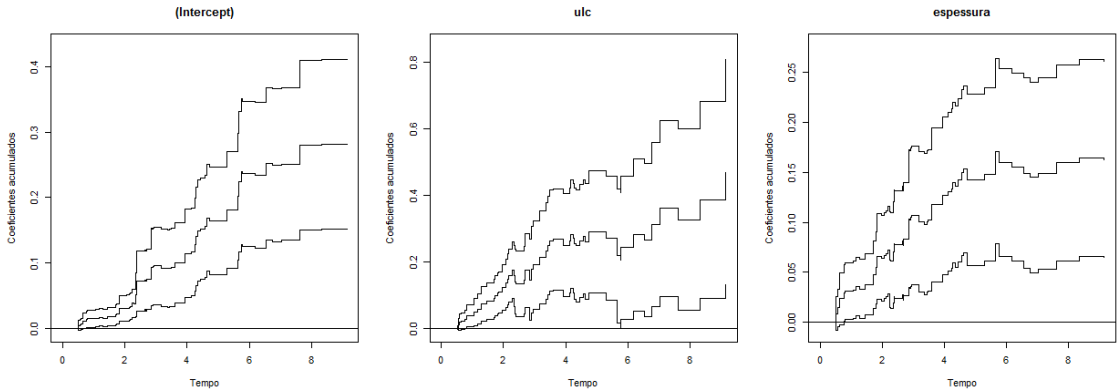
```
Remark: Stopped at time 12.78813 because of too low rank.
        (Last estimate at time 12.30547)

Estimates at time 12.30547:
           Coef. Std. Error   95% C.I.   Test statistic P-vaule
Constant  0.281      0.066 0.151  0.411          4.579   0.000
ulc       0.470      0.173 0.130  0.809          3.224   0.001
espessura 0.163      0.050 0.064  0.261          3.474   0.001
```

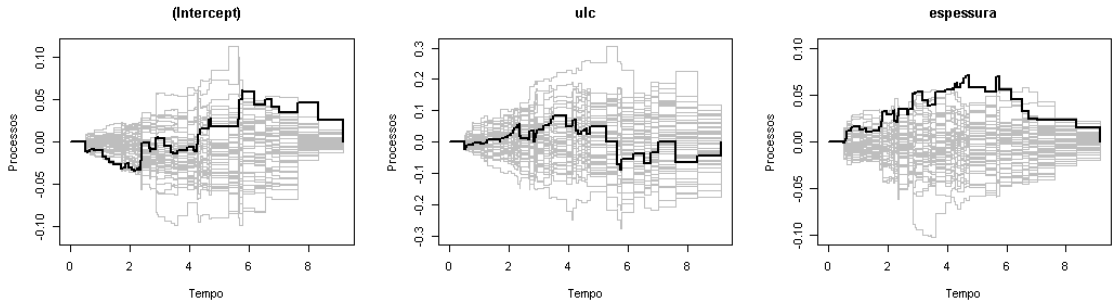


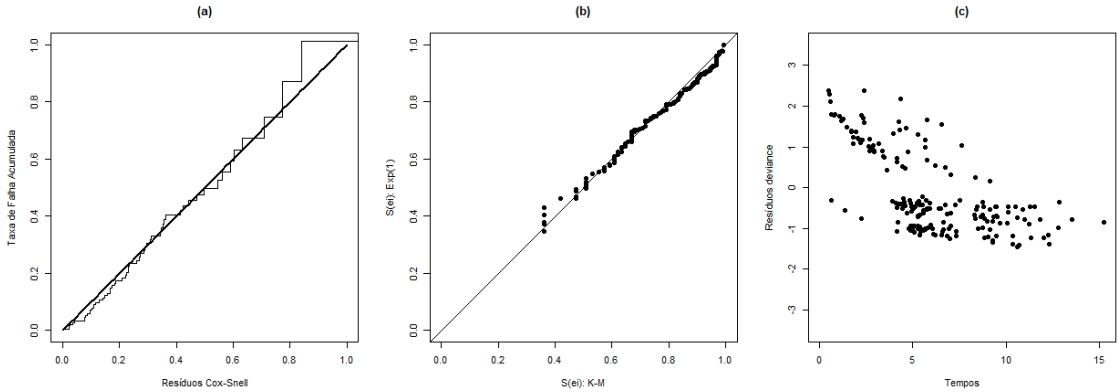

```
mod3.1 <- aalen(Surv(tempos,Status)~ ulc + espessura, residuals=1,data=data2)
summary(mod3.1)
```

```
Test for non-significant effects
             Supremum-test of significance p-value H_0: B(t)=0
(Intercept)                           4.21                0.000
ulc                                   3.79                0.004
espessura                             3.57                0.002

Test for time invariant effects
                  Kolmogorov-Smirnov test p-value H_0:constant effect
(Intercept)                        0.0621                       0.211
ulc                                0.0907                       0.800
espessura                          0.0707                       0.028
                   Cramer von Mises test p-value H_0:constant effect
(Intercept)                        0.0066                       0.203
ulc                                0.0144                       0.786
espessura                          0.0124                       0.024
```

```
mod3.1$cum
           time (Intercept)         ulc   espessura
 [1,] 0.0000000 0.000000000 0.000000000 0.000000000
 [2,] 0.5085433 0.003942107 0.002367912 0.008515386
...
[57,] 8.3346068 0.281644226 0.385255695 0.164305642
[58,] 9.1447507 0.281228405 0.469800162 0.162934266
```


(Intercept)
ulc
espessura
Coeficientes acumulados
Tempo


(Intercept)
ulc
espessura
Processos
Tempo


(a)
(b)
(c)
Taxa de Falha Acumulada
Resíduos Cox-Snell
S(ei): Exp(1)
S(ei): K-M
Resíduos deviance
Tempos

Comparando o ajuste global dos modelos