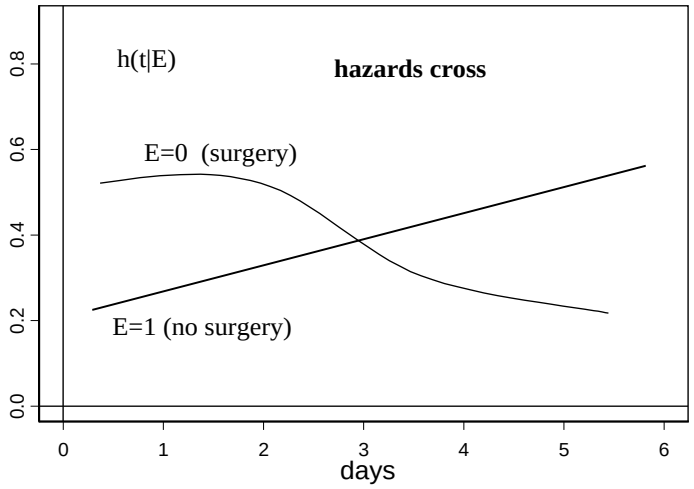
30.August 2010

Parts of Chapters 5 & 7
Stratified and Piecewise Cox Ph Models

Example 1: Recall the Kleinbaum **crossing hazards** figure:
In this study that compares surgery to no surgery, we might expect to see hazard functions for each group as follows:



Before 2 days, HR(1|0) $<$ 1, whereas later, HR(1|0) $>$ 1.
The PH assumption is violated, since HR must be constant over the follow-up time.

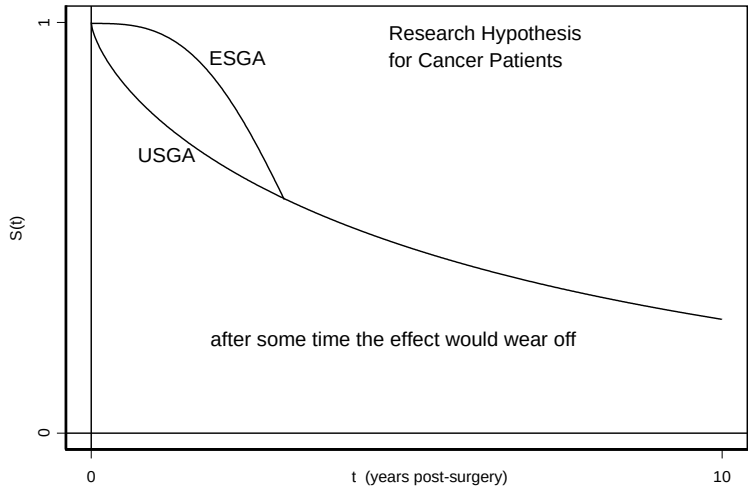
Example 2: Crossing survivor curves:
VA Cooperative Trial No. 345
This was a prospective randomized study conducted between March 1992 and August 1994. **Patients were randomly assigned** to either unsupplemented general anesthesia and postoperative analgesia (**USGA**) or epidural plus light general anesthesia and postoperative epidural morphine (**ESGA**). procedures.

A researcher began a retrospective look ca. June 2003

- It is well established that the epidural protects certain aspects of the immune function, and to block the stress response to surgical trauma.

- The epidural protocol has been common practice.

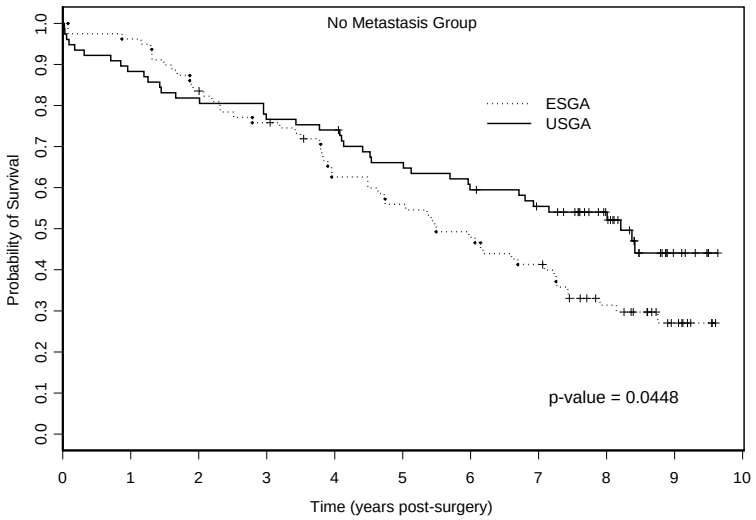
- Therefore, it was hypothesized that **cancer surgery patients** should benefit from ESGA. The research hypothesis is depicted in the following graph:



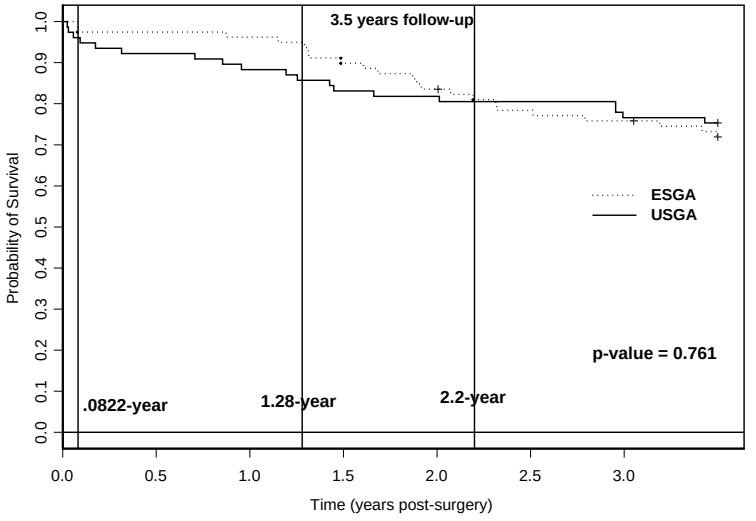
In this example we study the subset of patients in the VA trial who had had **surgery for colon cancer**. Of the 247 patients identified in that study, we have survival data on 246:

	ESGA	USGA	
METAST	42	48	90
NO MET	79	77	156
	121	125	246

What time reveals for the No MET group:



Return to the 3.5-year mark:



The Cox PH structure imposes restrictions on the behavior of survivor curves.

- With just one exposure variable $x = 0, 1$, the relationship is

$$h(t|1) = h(t|0) \cdot \exp(\beta).$$

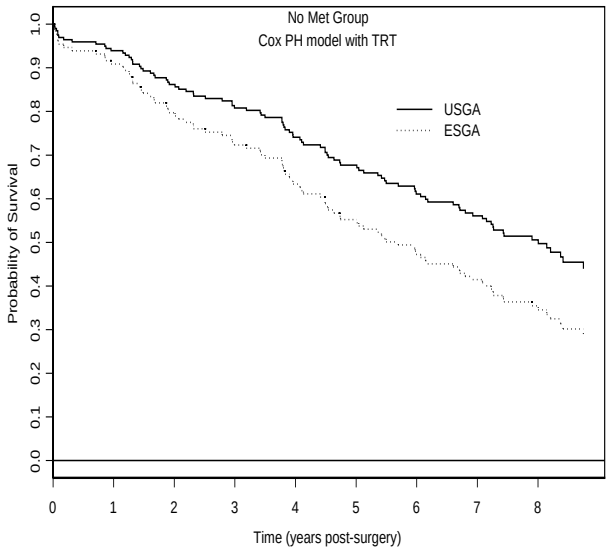
- Let TRT $= 0$ if ESGA, 1 if USGA. Then

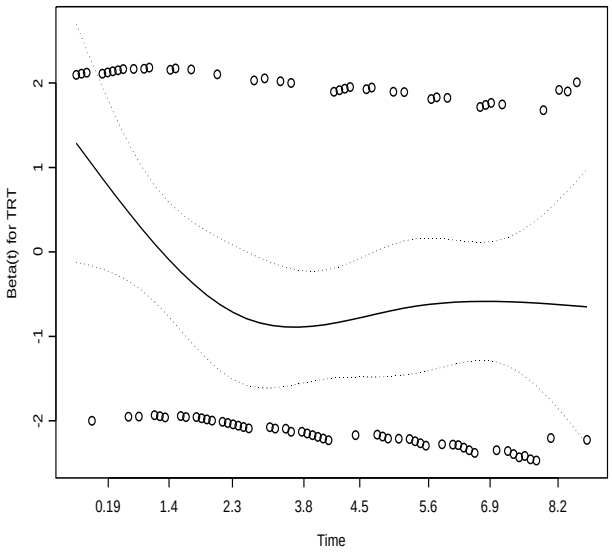
$$S(t|1) = (S(t|0))^{\exp(\beta)}.$$

  Cannot possibly model the crossing curves.

- Consider the results from the Cox PH fit to **No Met Data** only

```
> coxph(Surv(TIME,CENSOR)~TRT
        coef exp(coef) se(coef)     z     p
TRT -0.42      0.657    0.211   -1.99 0.046
Likelihood ratio test=4.03 on 1 df, p=0.0447 n=156
```





Scaled Schoenfeld residual plot, and the Grambsch-Therneau (1994) test for PH assumption. The residual plot clearly displays that TRT varies with time.

```
 > PH.test
      rho chisq      p
TRT -0.174  2.86 0.0906
```

Example 3: Divergent survivor curves
Australian study of heroin addicts, Caplehorn, et al. (1991)

- two methadone treatment clinics
- T = days remaining in treatment
  (= days until drop out of clinic)
- clinics differ in overall treatment policies
- 238 patients in the study

Description of ADDICTS data set

Data set: ADDICTS

Column 1:	Subject ID
Column 2:	Clinic (1 or 2) ← **exposure variable**
Column 3:	Survival status
	0 = censored
	1 = departed clinic
Column 4:	Survival time in days
Column 5:	Prison record ← **covariate**
	0 = none, 1 = any
Column 6:	Maximum methadone dose (mg/day)← **covariate**

Part I: The following is R code, along with modified output, that **fits two K-M curves not adjusted for any covariates** to the survival data.

```
> addict.fit <- survfit(Surv(Days.survival,Status)~Clinic,
                                    data = ADDICTS)
> addict.fit
             n  events mean se(mean) median 0.95LCL 0.95UCL
 Clinic=1  163    122  432     22.4    428     348     514
 Clinic=2   75     28  732     50.5     NA     661      NA
> survdiff(Surv(Days.survival,Status)~Clinic,data = ADDICTS)
             N     Observed Expected (O-E)^2/E (O-E)^2/V
 Clinic=1  163      122     90.9      10.6      27.9
 Clinic=2   75       28     59.1      16.4      27.9
 Chisq= 27.9  on 1 degrees of freedom, p= 1.28e-007
> plot(addict.fit, lwd = 3,col = 1,type = "l",lty=c(1, 3),
   cex=2,lab=c(10,10,7),...)
```

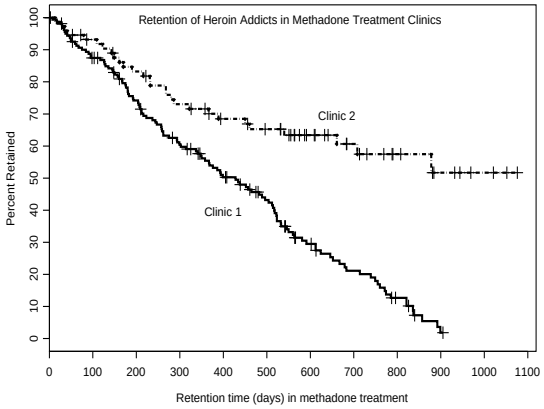


Figure 1. K-M curves for ADDICTS not adjusted for covariates.

Results:

- The log-rank test is highly significant with p-value$=$ 1.28×10^{-7}.
- The graph in Figure 1 glaringly confirms this difference.
- This graph shows curve for clinic 2 is always above curve for clinic 1.
- Curves diverge, with clinic 2 being dramatically better after about one year in retention of patients in its treatment program.
- Lastly, this suggests the PH assumption is not satisfied.

Part II: The Cox PH model We now fit a Cox PH model which adjusts for the three predictor variables. This hazard model is

$$h(t|\underline{x}) = h_0 \exp(\beta_1 \text{Clinic} + \beta_2 \text{Prison} + \beta_3 \text{Dose}).$$

A summary of the R output is:

```
> fit1 <- coxph(Surv(Days.survival,Status) ~ Clinic+Prison+
          Dose,data = ADDICTS,x = T) # Fits a  Cox PH model
> fit1
           coef    exp(coef)   se(coef)     z        p
 Clinic  -1.0098     0.364      0.21488   -4.70   2.6e-006
 Prison   0.3265     1.386      0.16722    1.95   5.1e-002
 Dose    -0.0354     0.965      0.00638   -5.54   2.9e-008

Likelihood ratio test=64.6  on 3 df, p=6.23e-014  n= 238
> testph <- cox.zph(fit1)  # Tests the proportional
                           # hazards assumption
> print(testph) # Prints the results
           rho    chisq        p
 Clinic  -0.2578  11.19    0.000824
 Prison  -0.0382  0.22     0.639324
 Dose     0.0724  0.70     0.402755
 GLOBAL     NA   12.62     0.005546
> par(mfrow = c(2, 2))
> plot(testph)  # Plots the scaled Schoenfeld residuals.
```

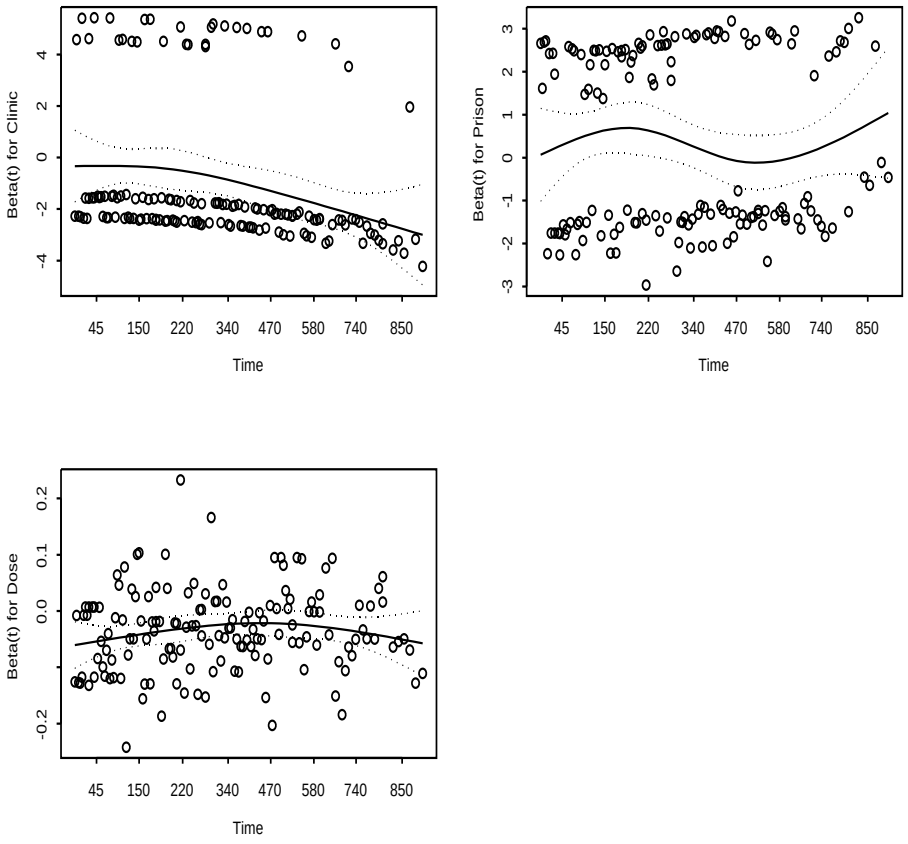


Figure 2. Diagnostic plots of the constancy of the coefficients in the fit1 model. Each plot is of a component of $\widehat{\beta}(t)$ against ordered time. A spline smoother is shown, together with ± 2 standard deviation bands.

Results:

- The `GLOBAL` test (a LRT) for non-PH is highly statistically significant with p-value = 0.005546.

- The p-values for Prison and Dose are very large, supporting that these variables are time-independent.

- The Grambsch-Therneau test has a p-value = 0.000824 for Clinic. This provides strong evidence that the variable Clinic violates the PH assumption and confirms what the graph in Figure 1 suggests.

- The plot of $\widehat{\beta}_1(t)$, the coefficient for Clinic, against ordered time in Figure 2 provides further supporting evidence of this violation.

- We recommend finding a function $g(t)$ to multiply Clinic by; that is, create a defined time-dependent variable, and then fit an extended Cox model.

Since the Cox PH model is inappropriate, the following strategies are employed:

- analyze by **stratifying** on the exposure variable; that is, do not fit any regression model, and, instead obtain the Kaplan-Meier curve for each group separately;

- to adjust for other significant factor effects, use Cox model **stratified on exposure variable** E.

  ```
  > coxph(Surv(time,status)~ X1+X2+···+strata(E))
  ```

- fit a Cox PH model that includes a time-dependent variable which measures the interaction of exposure with time. This model is called an **extended Cox model**. We try to find the point in time t_0 where the hazard rates change. Then fit a **piecewise** Cox Ph model over these two time intervals.

Part III: Stratified Cox model

Suppose we have $j = 1, 2, \ldots, s$, i.e., s strata. For each stratum we assume the Cox PH model:

$$h_j(t|\underline{x}) = h_{0j}(t) \exp(\underline{x}^{'}\underline{\beta}),\ j = 1, \ldots, s.$$

The regression coefficients are assumed to be the same in each stratum although the baseline hazard functions may ne different and completely unrelated. Then using **only the data for those subjects in the jth stratum**, we have:

Let $t_{(1j)}, \ldots, t_{(rj)}$ denote the $r \leq n_j$ ordered (uncensored) death times, so that $t_{(kj)}$ is the kth ordered death time. Let $\underline{x}_{(kj)}$ denote the vector of covariates associated with the individual who dies at $t_{(kj)}$.

Cox's partial likelihood function for the jth stratum:

$$L_{cj}(\underline{\beta}) = \prod_{kj=1}^{r} \frac{\exp(\underline{x}'_{(kj)}\underline{\beta})}{\sum_{l \in \mathcal{R}(t_{(kj)})} \exp(\underline{x}'_l\underline{\beta})}.$$

Then estimation and testing methods are as before, where the partial log likelihood to be maximized is given by

$$LL_c(\underline{\beta}) = \sum_{j=1}^{s} LL_{cj}(\underline{\beta}).$$

We now stratify on the exposure variable Clinic and fit a Cox PH model to adjust for the two time-independent covariates Prison and Dose. Modified R output and a plot of the two adjusted K-M survival curves follow.

```
> fit2 <- coxph(Surv(Days.survival,Status) ~ strata(Clinic)+
                  Prison+Dose,data=ADDICTS)
> fit2
           coef   exp(coef)   se(coef)     z        p
  Prison  0.3896     1.476     0.16893    2.31   2.1e-002
  Dose   -0.0351     0.965     0.00646   -5.43   5.6e-008

Likelihood ratio test=33.9  on 2 df, p=4.32e-008  n= 238
> survfit(fit2)
            n   events  mean  se(mean)  median  .95LCL .95UCL
  Clinic=1 162    122    434     22.0     434      358    517
  Clinic=2  74     28    624     38.1     878      661     NA
 # Note that each stratum has one less observation.
 # This tells us that the shortest observed retention
 # time in each clinic is censored.
> plot(survfit(fit2),lwd=3,col=1,type="l",lty=c(1,3),
   cex=2,lab=c(10,10,7),...)
> abline(v = 366,lty=3,lwd=2)
```

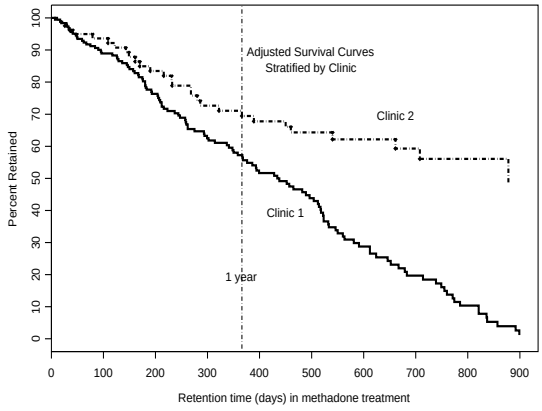


Figure 3. K-M curves adjusted for covariates Prison and Dose, stratified by Clinic.

Results:

- Figure 3 provides same pictorial evidence as Figure 1; that is, curve for clinic 2 is always above clinic 1's curve, with clinic 2 being dramatically better in retention of patients in its treatment program after about one year.

- The estimated coefficients for Prison and Dose do not change much. This gives good evidence that the stratified model does satisfy the PH assumtion; hence, this analysis is valid.

- Figure 3 provides a picture of the effect of Clinic on retention of patients. But by stratifying on Clinic, we get no estimate of its effect; i.e., no estimated

β_1 coefficient. Hence, we cannot obtain a hazard ratio for Clinic.

- The exposure variable Clinic must be in the model in order to obtain a hazard for it. For this reason, we look now to the extended Cox model.

Part IV: A Piecewise Cox PH model analysis

Here we use a model that contains two heavyside functions, $g_1(t)$ and $g_2(t)$, with t_0, **the change point**, to be determined. The hazard model is

$$\begin{aligned} h(t|\underline{x}(t)) &= h_0(t)\exp\left(\beta_1 \text{Prison} + \beta_2 \text{Dose} + \gamma_1(\text{Clinic} \times g_1(t))\right. \\ &\qquad \left. + \gamma_2(\text{Clinic} \times g_2(t))\right) \end{aligned}$$

where

$$g_1(t) = \begin{cases} 1 & \text{if } t < t_0 \\ 0 & \text{if } t \geq t_0 \end{cases} \qquad g_2(t) = \begin{cases} 1 & \text{if } t \geq t_0 \\ 0 & \text{if } t < t_0 \end{cases}$$

and

$$\text{Clinic} = \begin{cases} 1 & \text{if Clinic=1} \\ 0 & \text{if Clinic=2.} \end{cases} \tag{1}$$

The hazard ratio for the exposure variable Clinic now varies with time. It assumes two distinct values depending whether time $< t_0$ days or time $\geq t_0$ days. The form of the HR is

$$\begin{aligned} t < t_0: &\qquad \text{HR} = \exp(\gamma_1) \\ t \geq t_0: &\qquad \text{HR} = \exp(\gamma_2)\,. \end{aligned}$$

Time-dependent covariates effect the rate for upcoming events. In order to implement an extended Cox model properly in R using the `coxph` function, one must use the Anderson-Gill (1982) formulation of the proportional hazards model as a counting process. They treat

each subject as a very slow Poisson process. A censored subject is not viewed as incomplete, but as one whose event count is still zero. For a brief introduction to the counting process approach, see Appendix 2 of Hosmer & Lemeshow (1999) and the online manual S-PLUS 2000, Guide to Statistics, Vol 2, Chapter 10. Klein & Moeschberger (1997, pages 70−79) discuss this counting process formulation. They devote their Chapter 9 to the topic of modelling time-dependent covariates. For a more advanced and thorough treatment of counting processes in survival analysis, see Fleming and Harrington (1991).

The ADDICTS data set must be reformulated to match the Anderson-Gill notation. To illustrate this, consider the following cases: In both cases the t denotes the patient's recorded survival time, whether censored or not.

Case 1: For $t < t_0$, $g_1(t) = 1$ and $g_2(t) = 0$. Here a patient's data record is just one row and looks like this:

Start	Stop	Status	Dose	Prison	Clinicg1t	Clinicg2t
0	t	same	same	same	Clinic	0

Case 2: For $t \geq t_0$, $g_1(t) = 0$ and $g_2(t) = 1$. Here a patient's data record is formulated into two rows and looks like this:

Start	Stop	Status	Dose	Prison	Clinicg1t	Clinicg2t
0	t_0	0	same	same	Clinic	0
t_0	t	same	same	same	0	Clinic

The following R program puts the ADDICTS data set into the counting process form, finds the optimal change point t_0; i.e., the time which maximizes the profile log partial likelihood. We then fit the model and report results.

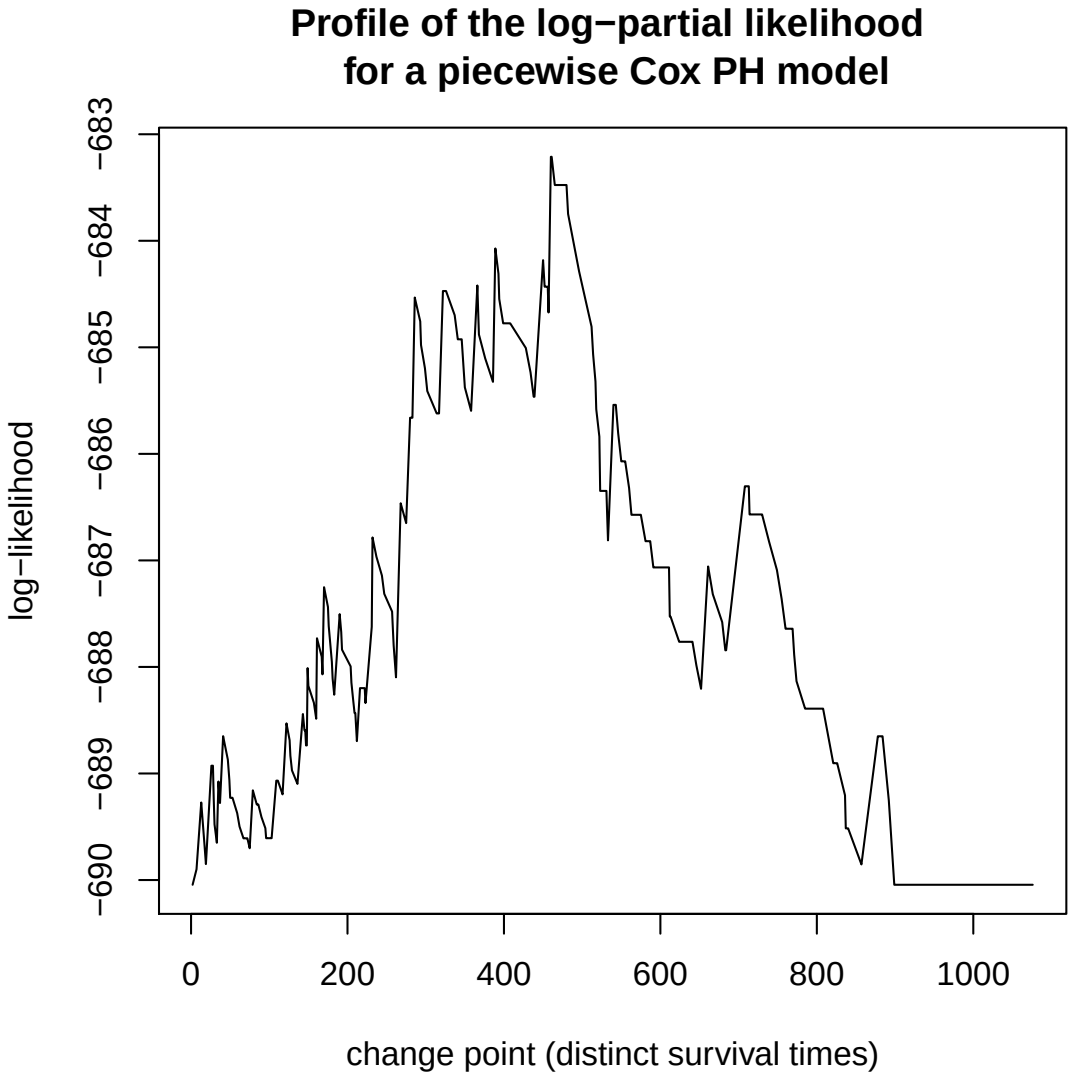
```
> ADDICTS<-read.table("C://ADDICTS.txt",header=T)
> ADDICTS$Clinic[ADDICTS$Clinic==2]<-0
> names(ADDICTS)
[1] "ID"           "Clinic"   "Status"   "Days.survival"
[5] "Prison"       "Dose"
> attach(ADDICTS)
> library(survival)
> optimal.change.point(ADDICTS,Days.survival,Status,Clinic)
    changepoint    loglik
119         461 -683.2117
> #Thus, in the survSplit function, let cut = 461.
> #Use the function extcox.1Et to obtain the dataset in the
> #Andersen-Gill counting process format
> AG<-extcox.1Et(ADDICTS,Days.survival,Status,Clinic,461)
> names(AG)
 [1] "ID"         "Clinic"     "Status"       "Days.survival"
 [5] "Prison"     "Dose"       "end"          "status"
 [9] "trt"        "start"      "ET1"          "ET2"
> fit4<-coxph(Surv(start,end,status)~Prison+Dose+ET1+ET2,
                          data=AG)
```

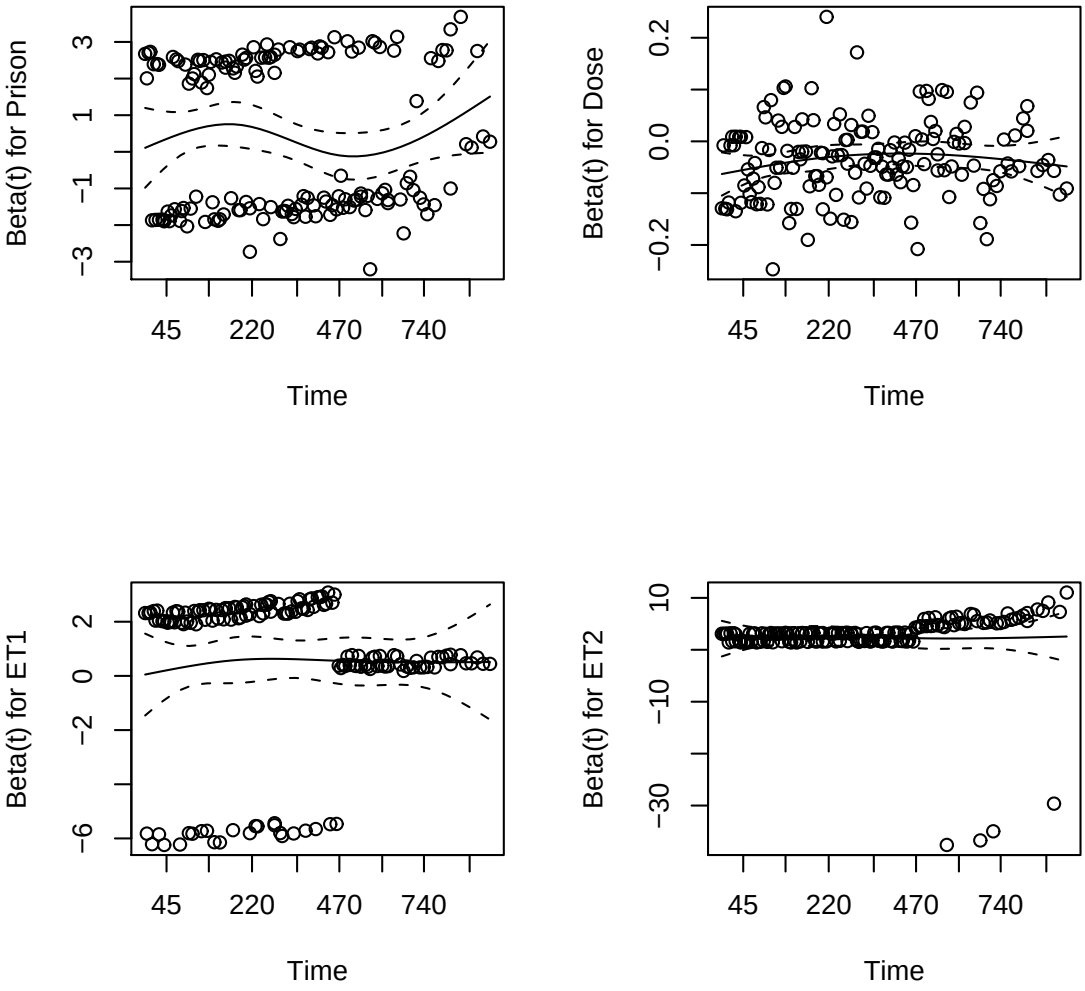
```
> fit4
Call: coxph(formula = Surv(start, end, status) ~ Prison +
        Dose + ET1 + ET2, data = AG)

          coef exp(coef) se(coef)     z       p
Prison  0.3890     1.476  0.16859  2.31 2.1e-02
Dose   -0.0354     0.965  0.00645 -5.48 4.3e-08
ET1     0.4887     1.630  0.23396  2.09  3.7e-02
ET2     2.3971    10.991  0.52998  4.52 6.1e-06

Likelihood ratio test=79  on 4 df, p=3.33e-16  n= 337
> temp<-cox.zph(fit4)
> temp
           rho  chisq     p
Prison -0.0176 0.0465 0.829
Dose    0.0829 0.9305 0.335
ET1     0.0264 0.1059 0.745
ET2    -0.0089 0.0117 0.914
GLOBAL      NA 1.0595 0.901
> windows()
> par(mfrow=c(2,2))
> plot(temp)
```

This graph is automatically outputted from the optimal.change.point function.





95% C.I.'s for the Clinic's HR's	
$t < 461$:	$[1.03, 2.58]$
$t \geq 461$:	$[3.89, 31.06]$

Results:

- The output shows a significant $\widehat{\text{HR}} = 1.63$ with p-value $= 0.037$ for the effect of Clinic when time < 461 days. For $t \geq 461$, the $\widehat{\text{HR}} = 10.99$ is highly significant with p-value $= 6.1 \times 10^{-6}$.

- The table reports confidence intervals for the two HR's. The general form of these 95% C.I.'s is $\exp(\text{coef} \pm 1.96 \times \text{se(coef)})$. The 95% C.I. for the HR when t precedes 461 is a bit above 1 and is narrow. This supports a significant effect due to clinic during the first year and has good precision. The 95% C.I. for the HR when $t \geq 461$ lies above 1 and is very wide showing a lack of precision.

- These findings support what was displayed in Figure 3. But now it is quantified. There is strong statistical evidence of a large difference in clinic survival times after 461 days in contrast to a small and but still significant difference in clinic survival times prior to 461 days, with clinic 2 always doing better in retention of patients than clinic 1. After 461 days, clinic 2 is nearly 11 times more likely to retain a patient longer than clinic 1. Also, clinic 2 has $\frac{1}{11} \approx 10\%$ the risk of clinic 1 of a patient leaving its methadone treatment program.

- See Kleinbaum (1996, Chapter 6) for further analysis of this data.

- An alternative regression quantile analysis as presented in Chapter 8 may be appropriate when the PH assumption