Challenges and Strategies for Analyzing Complex Survival Data

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Outline

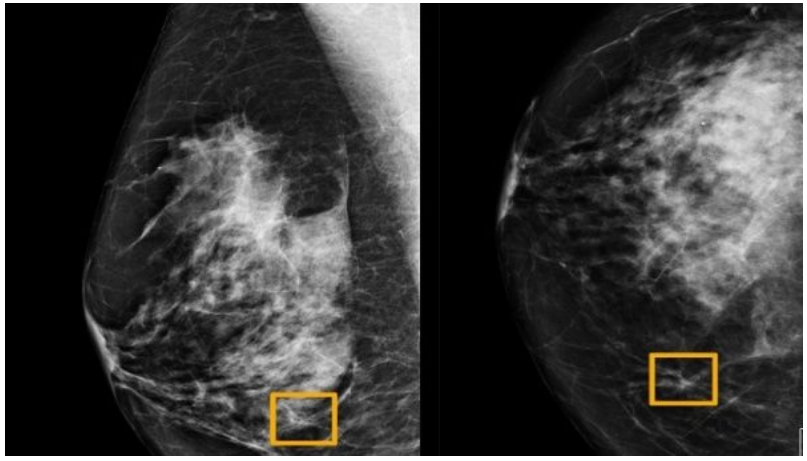
German Breast Cancer study data set*

686 patients with primary node positive breast cancer

299 patients developed recurrence and 171 died

Patients were recruited between July 1984 and December 1989 and 16 variables

Times (in days) to recurrence (`rectime`) Censoring indicator (`censrec`)



* Sauerbrei W. and Royston P. (1999).

German Breast Cancer study data set.

Patients were followed from the date of breast cancer diagnosis until censoring or death from breast cancer. Of the total of 686 women, 171 died. Of those that died, 21 had a recorded survival time equal to the recurrence time.

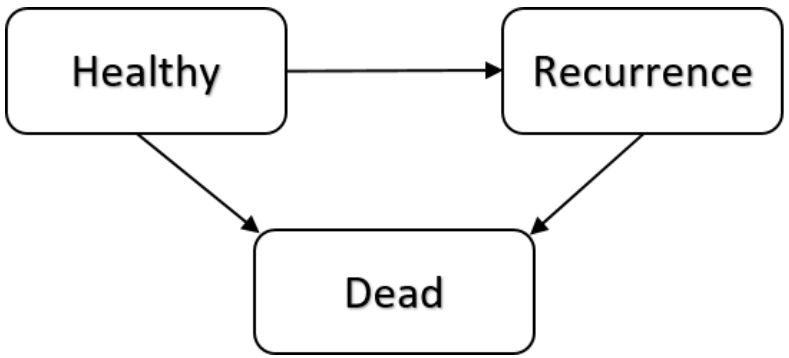


Figure: Illness-death model for breast cancer data.

The Colon Cancer study data set*.

In this study, 929 patients were followed from the date of cancer diagnosis until censoring or death.

A total of 468 patients developed a recurrence and among these 414 died; 38 patients died without recurrence. The rest of the patients (423) remained alive and disease-free up to the end of the follow-up.

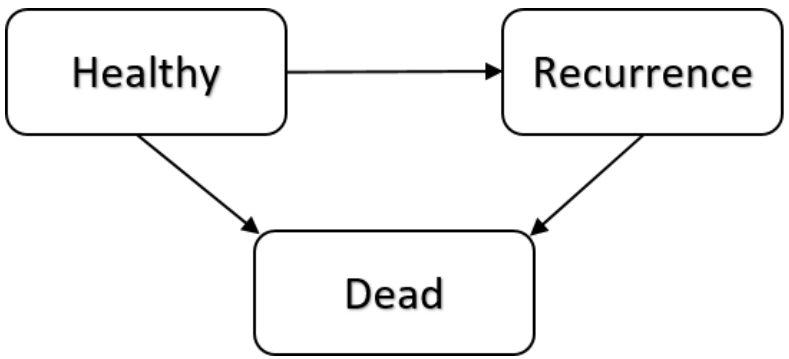


Figure: Illness-death model for colon cancer data.

* Moertel (1990).

COVID-19 data set*.

A registry of 3481 COVID-19 patients diagnosed at Centro Hospitalar Universitario de Sao Joao (CHUSJ) between March 01, 2020 and January 01, 2021 Symptoms of the disease were reported at admission, and its improvement was investigated using phone interviews.

In this study, the aim was to explore the use of survival analysis techniques for the statistical analysis of the time to the end of COVID-19 symptoms.

* Leandro et al (2023).

HIV data set.

A registry of data from the Lisbon Cohort of Men Who Have Sex With Men (MSM).

In this study, the aim was to study 'Time to infection'.

Wound healing and healing process data in patients with diabetic foot ulcers (DFU).

Patients with a chronic DFU were evaluated at fixed time points.

In these studies, the times of the events of interest (time to favorable healing process) are known only to have occurred within a time interval from the last examination without the event to the first examination after the event has occurred.

Mortality Model

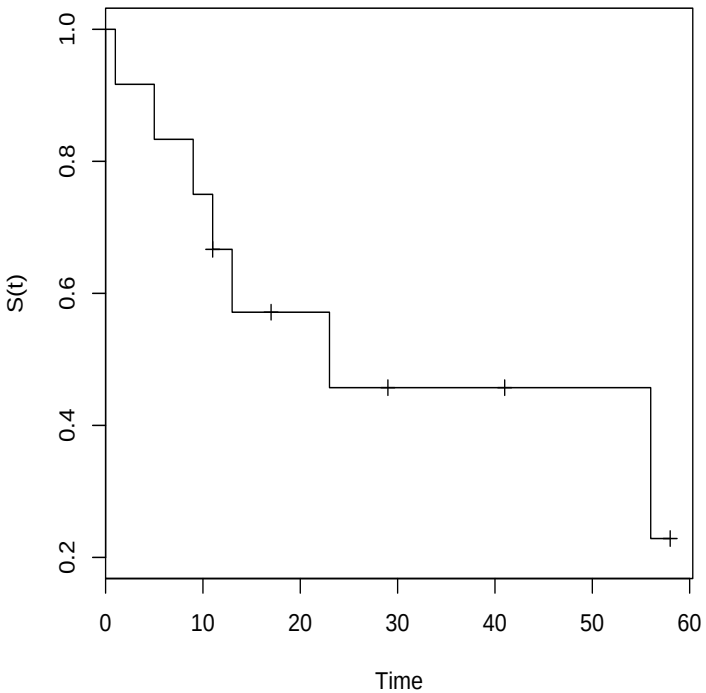
Figure: Mortality model for survival analysis.

Let T denote the survival times C a univariate right-censoring which we assume to be independent of T.

Because of censoring we only observe $(\widetilde{T}, \Delta)$ where $\widetilde{T} = \min(T, C)$, $\Delta = I(T \leq C)$.

$S(T > y)$ may be consistently estimated by the Kaplan-Meier estimator (Kaplan and Meier, 1958):

$$\widehat{S}(t) = \prod_{t_i \le t} \left(1 - \frac{d_i}{n_i}\right) \equiv \prod_{i=1}^{n} \left(1 - \frac{\Delta_{[i]}}{n - i + 1}\right)^{I(\widetilde{T}_{(i)} \le t)}$$



Kaplan-Meier survival curve

time:
1, 5, 9, 11, 11, 13, 17, 23, 29, 41, 56, 58
event:
1, 1, 1, 1, 0, 1, 0, 1, 0, 0, 1, 0

Kaplan-Meier weights

$$\widehat{S}(t) = 1 - \sum_{i=1}^{n} W_i I(\widetilde{T}_{(i)} \leq t) \equiv 1 - \widehat{F}(t),$$

where W_i is the Kaplan-Meier weight attached to $\widetilde{T}_{(i)}$:

$$W_i = \frac{\Delta_{[i]}}{n-i+1} \prod_{j=1}^{i-1} \left[1 - \frac{\Delta_{[j]}}{n-j+1} \right]$$

A presmoothed version of the Kaplan-Meier estimator:

$$\widetilde{S}(t) = 1 - \sum_{i=1}^{n} PW_i I(\widetilde{T}_{(i)} \leq t) \equiv 1 - \widetilde{F}(t),$$

where PW_i are the presmoothed Kaplan-Meier weights:

$$PW_i = \frac{m(\widetilde{T}_{(i)})}{n-i+1} \prod_{j=1}^{i-1} \left[1 - \frac{m(\widetilde{T}_{(i)})}{n-j+1} \right].$$

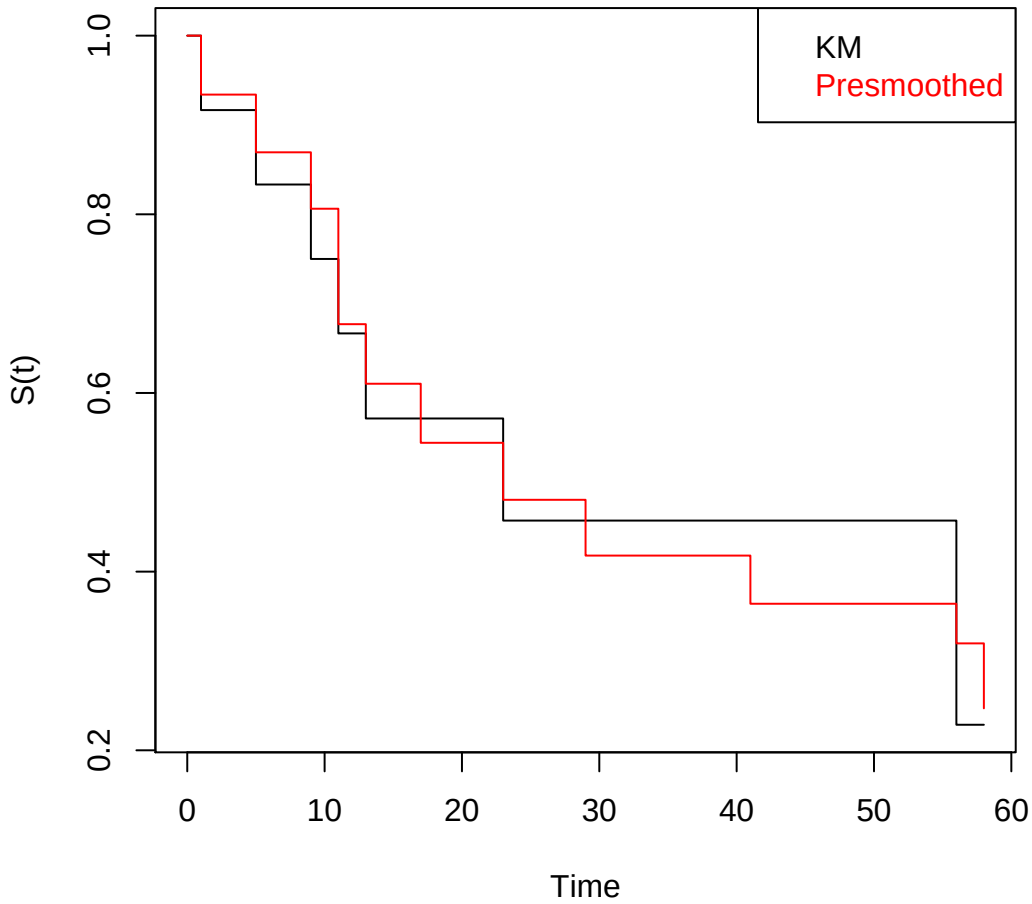


Figure: Estimated survival curve for favorable healing process.

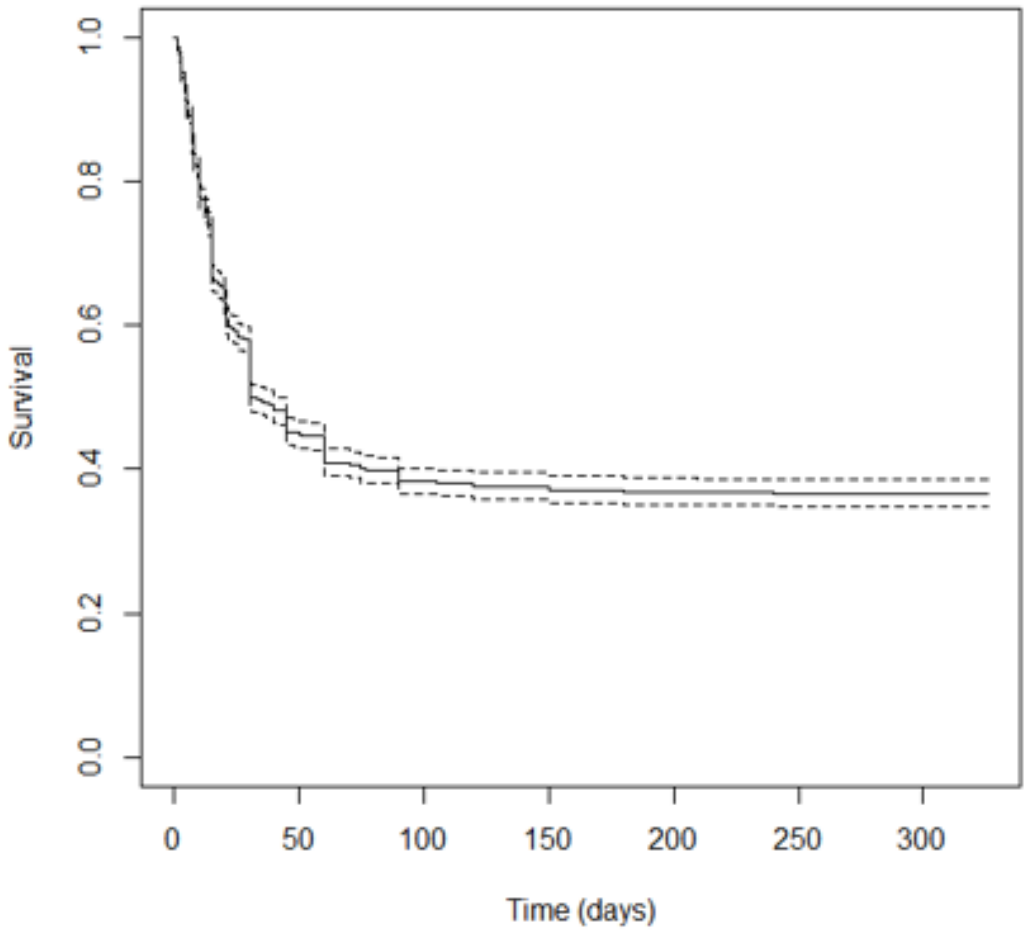
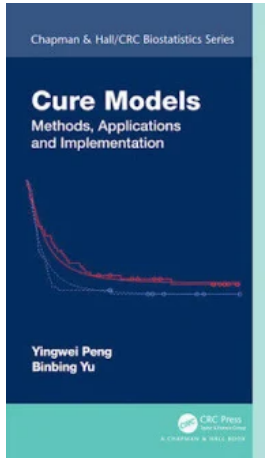


Figure: Estimated survival curve for COVID-19 study.



In many applications, the data may be interval-censored, i.e. the random variable of interest is known only to lie in an interval, instead of being observed exactly.

An analog Product-Limit estimator of the survival function for interval-censored data was introduced by Turnbull (1976).

left	right	treat	midpoint	cens
4	6	1	5	1
2	4	1	3	1
6	NA	1	6	0
4	6	1	5	1
2	NA	1	2	0
6	8	0	7	1
6	8	0	7	1
6	NA	0	6	0
2	6	0	4	1
2	8	0	5	1

Table: Lines of a possible dataset.

```
library(survival)

 left <- c(4,2, 6,4, 2,6,6, 6,2,2)
right <- c(6,4,NA,6,NA,8,8,NA,6,8)

fmla <- Surv(left, right, type="interval2")
fmla

fit <- survfit(fmla ~ 1)
summary(fit)
plot(fit)
```

```
midpoint <- c(5, 3, 6, 5, 2, 7, 7, 6, 4, 5)
    cens <- c(1, 1, 0, 1, 0, 1, 1, 0, 1, 1)
fit2 <- survfit(Surv(midpoint, cens)~1)
summary(fit2)
plot(fit)
```

```r
library(survival)

left  <- c(4,2, 6,4, 2,6,6, 6,4,6)
right <- c(6,4,NA,6,NA,8,8,NA,6,8)

fmla <- Surv(left, right, type="interval2")
fmla

fit <- survfit(fmla ~ 1)
summary(fit)
plot(fit)
```

```r
midpoint <- c(5, 3, 6, 5, 2, 7, 7, 6, 5, 7)
    cens <- c(1, 1, 0, 1, 0, 1, 1, 0, 1, 1)
fit2 <- survfit(Surv(midpoint, cens)~1)
summary(fit2)
```

```
1  treat <- c(1,1,1,1,1,0,0,0,0,0)
2  fit <- survfit(fmla ~ treat)
3  summary(fit)
4  plot(fit, col=1:2)
5
6  library(interval)
7  test <- ictest(Surv(left, right, type = "interval2") ~
       treat, scores = "logrank1")
8  test
```

```r
library(icenReg)

df <- data.frame(cbind(left, right, treat))

logist_ph_fit <- ic_par(Surv(left, right, type = "
    interval2") ~ treat, data=df, dist = "loglogistic")

summary(logist_ph_fit)

fit_ph <- ic_sp(Surv(left, right, type = "interval2") ~
    treat, model = "ph", bs_samples = 100, data = df)
summary(fit_ph)
```

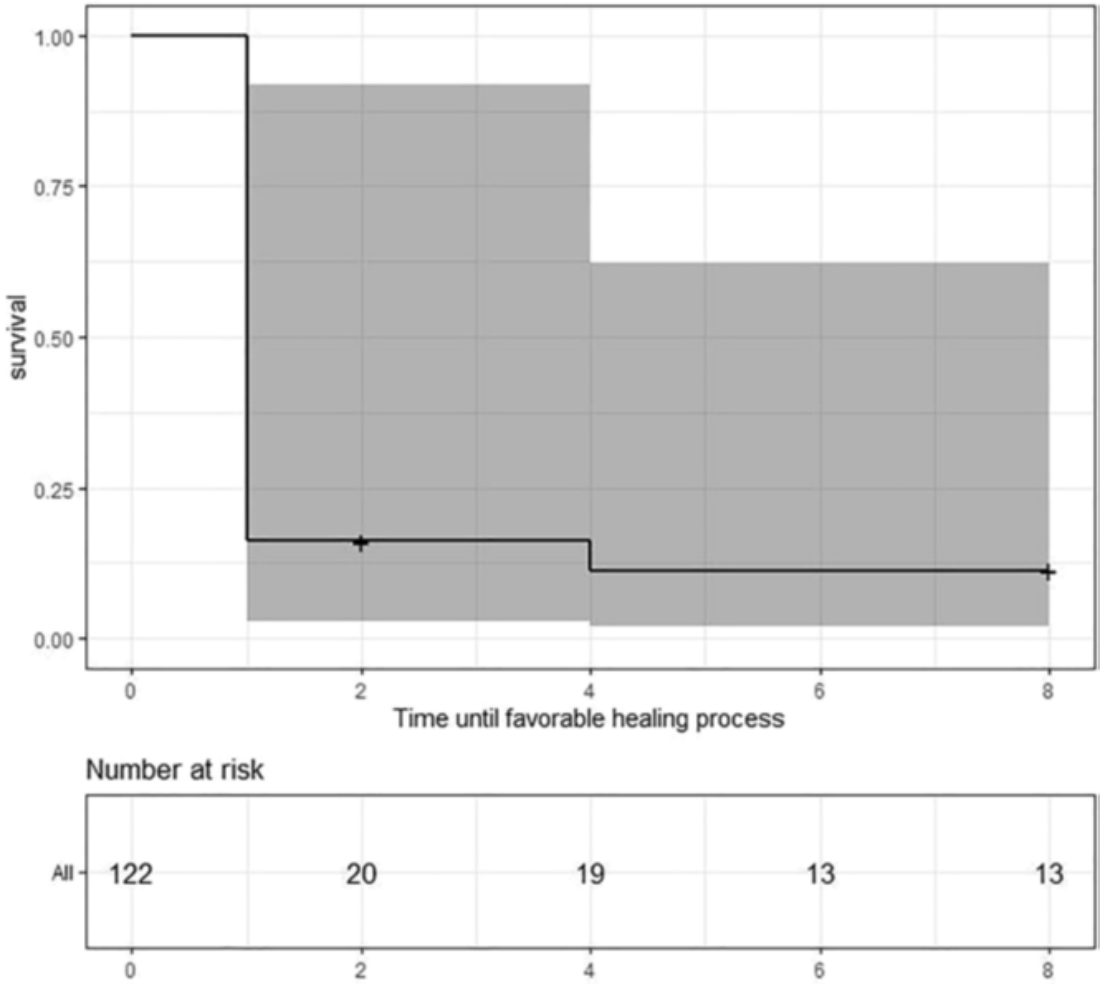


Figure: Estimated survival curve using Turnbull estimator.

Turnbull weights

The search for Turnbull weights requires the definition of a set of intervals: $I = \{(u_1, v_1], \ldots, (u_m, v_m]\}$.
The intervals are obtained from the set of all left and right interval endpoints in such a way that u_j is a left endpoint, v_j is a right endpoint and there is no other left and right endpoint between them.

```
1 left  <- c(4,2, 6,4, 2,6,6, 6,4,6)
2 right <- c(6,4,NA,6,NA,8,8,NA,6,8)
3
4 fmla <- Surv(left, right, type="interval2")
5 fmla
6
7 > fmla
8  [1] [4, 6] [2, 4] 6+      [4, 6] 2+      [6, 8]
9  [7] [6, 8] 6+      [4, 6] [6, 8]
```

Turnbull intervals: (2,4], (4,6], (6,8], (8, ∞)

Turnbull weights

The problem then reduces to estimating $p_j = P(u_j < T \leq v_j) = S(u_j) - S(v_j)$, $j = 1, \ldots, m$ that are subject to the constraints $p_j \geq 0$ and $\sum_{j=1}^{m} p_j = 1$. The likelihood can be written as

$$L(p_1, \ldots, p_m) = \prod_{i=1}^{n} \left(\sum_{j=1}^{m} \alpha_{ij} p_j \right)$$

where $\alpha_{ij} = I\{(u_j, v_j] \subseteq (L_i, R_i]\}$. Turnbull (1976) developed a procedure that involves an iterative process for which the rth iteration of p, denoted by $p^{(r)}$, is given by

$$p_j^{(r)} = \frac{1}{n} \sum_{i=1}^{n} \frac{\alpha_{ij} p_j^{(r-1)}}{\sum_{k=1}^{m} \alpha_{ik} p_k^{(r-1)}}$$

Then, the survival function can be estimated as

$$\hat{S}(t) = \begin{cases} 1 & t \leq u_1 \\ 1 - \hat{p}_1 - \ldots - \hat{p}_j & v_j < t < u_{j+1} \\ 0 & t > v_m \end{cases}$$

Available R packages that deal with interval censoring:

- survival: provides extensive support for survival analysis, including interval censoring;
- interval: functions to fit nonparametric survival curves, plot them, and perform logrank or Wilcoxon type tests;
- icenReg: parametric and semi-parametric regression;
- intccr: Semiparametric Competing Risks Regression under Interval Censoring Semiparametric regression models.

Independent censoring

Independent censoring is a key assumption: censoring process is unrelated to the underlying event times.

HIV survival study: patients are more likely to undergo an HIV test if they had a recent risk event.

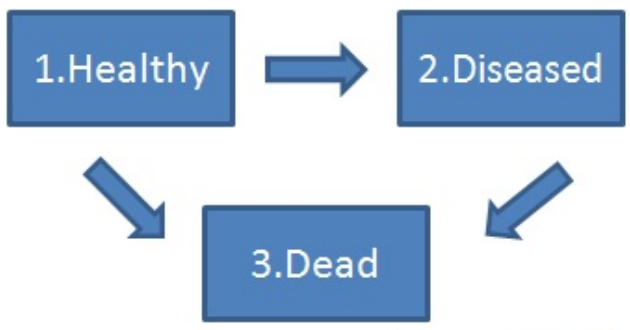
The censoring process (whether a patient is censored or not) is not independent of the event times (time to HIV infection) and is influenced by specific patient behaviors or characteristics.

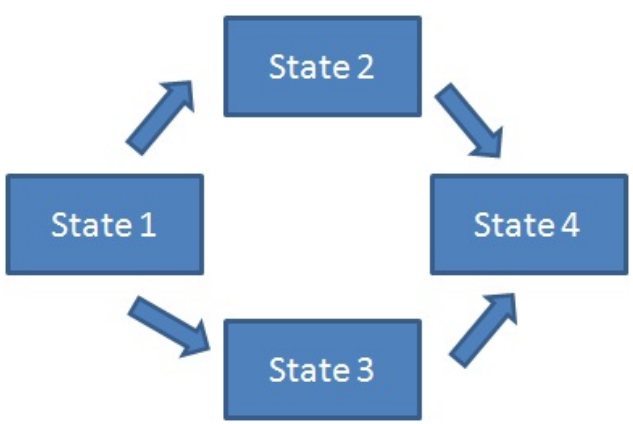
Independent censoring

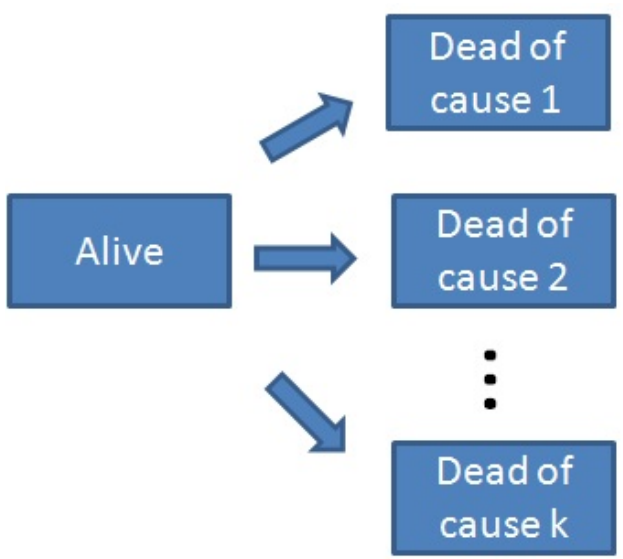
Possible strategies: Inverse Probability of Censoring Weighting (IPCW) is a technique that assigns different weights to censored observations based on the inverse of their estimated probabilities of being censored. This method adjusts for the dependent censoring by re-weighting the observations, giving more weight to censored observations that are less likely to be censored based on observed covariates.

What is a multi-state model

... is a model for a stochastic process $(Y(t), t \in \mathcal{T})$ with finite state space.



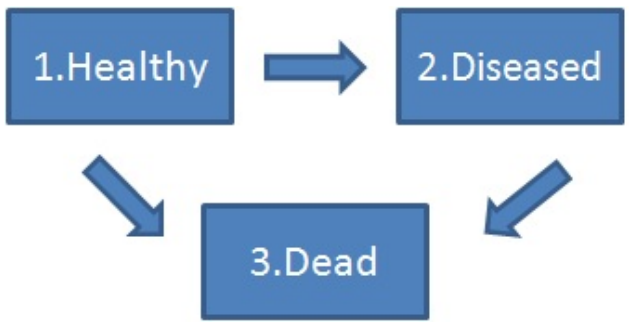




Most common goals

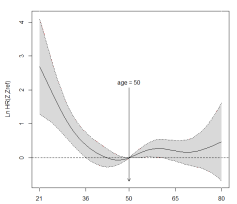
Important goals in multi-state modeling:

- Multi-state regression
  A common simplifying strategy is to decouple the whole process into various survival models, by fitting separate intensities to all permitted using semi-parametric Cox proportional hazard regression models, while making appropriate adjustments to the risk set.



	Recurrence		Death without recurrence		Death with recurrence	
Variable	HR	p-value	HR	p-value	HR	p-value
age						
linear	0.9929	0.2100	1.0527	0.0276	1.0125	0.0947
nonlin	-	1.6e-05	-	ns	-	ns
size	1.0089	0.0310	1.0189	0.1664	1.0109	0.0296
nodes	1.0472	6.9e-10	1.0515	0.0758	1.0087	0.4929
prog rec	0.9980	0.0004	0.9946	0.0711	0.9967	0.0036
hormone						
no	1	-	1	-	1	-
yes	0.6752	0.0037	0.8255	0.6774	0.9572	0.8138
grade						
I	1	-	1	-	1	-
II	1.9604	0.0100	0.9066	0.8999	1.2151	0.7096
III	2.0780	0.0037	1.6016	0.5758	1.5932	0.3921

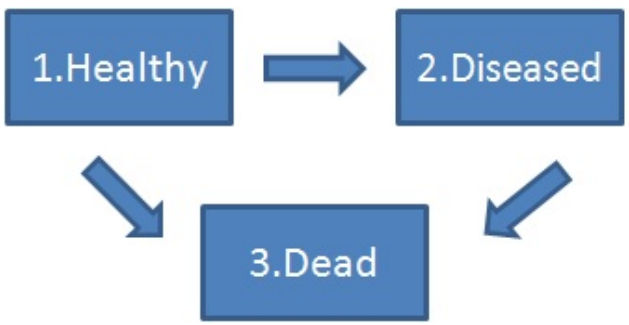
Table: Cox regression Markov models for all transitions. Breast cancer data.



Most common goals (2)

Important goals in multi-state modeling:

- Estimates of predictive probabilities:
  - Occupation Probabilities
  - Transition Probabilities
  - Cumulative Incidence Functions
  - Sojourn Distributions



Transition probabilities

Given two states i, j and $s < t$

$$p_{ij}(s,t) = P(X(t) = j | X(s) = i)$$

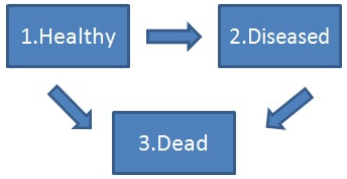
Estimating these quantities is interesting, since they allow for long-term predictions of the process.

Markov assumption

The inference in multi-state models is traditionally performed under the Markov assumption, which states that past and future are independent given the present state.

- Aalen and Johansen (SCAND. J. STAT. 1978) introduced a nonparametric estimator of $p_{ij}(s,t)$ for Markov models.
- Moreira et al (EJS 2013) propose a modification of the Aalen-Johansen estimator in the illness-death model based on presmoothing.

- dUA and Meira-Machado (Biometrics 2015) propose new estimators based on landmarking.
- Putter and Spitoni (SMMR 2016) propose a landmark Aalen-Johansen estimator.



$$p_{11}(s,t) = P(Z > t \mid Z > s) = \frac{P(Z > t)}{P(Z > s)}$$

$$p_{12}(s,t) = P(Z \leq t, T > t \mid Z > s) = \frac{P(s < Z \leq t, T > t)}{P(Z > s)}$$

$$p_{13}(s,t) = P(T \leq t \mid Z > s) = \frac{P(Z > s, T \leq t)}{P(Z > s)}$$

$$p_{22}(s,t) = P(T > t \mid Z < s, T > s) = \frac{P(Z \leq s, T > t)}{P(Z \leq s, T > s)}$$

$$p_{23}(s,t) = P(T \leq t \mid Z < s, T > s) = \frac{P(Z < s, s < T \leq t)}{P(Z \leq s, T > s)}$$

Landmark estimators

$p_{11}(s,t)$ = P(Z > t | Z > s)
$p_{12}(s,t)$ = P(Z ≤ t, T > t | Z > s)
$p_{13}(s,t)$ = P(T ≤ t | Z > s)
$p_{22}(s,t)$ = P(T > t | Z < s, T > s)

$$\widehat{p}_{11}^{\mathrm{LM}}(s,t) = \widehat{S}_Z^{(s)}(t)$$
$$\widehat{p}_{12}^{\mathrm{LM}}(s,t) = \widehat{S}_T^{(s)}(t) - \widehat{S}_Z^{(s)}(t)$$
$$\widehat{p}_{13}^{\mathrm{LM}}(s,t) = 1 - \widehat{S}_T^{(s)}(t)$$

where $S_Z^{(s)}$ and $S_T^{(s)}$ are the survival functions of the first sojourn time and total time, respectively; computed from the sample $\{i : \widetilde{Z}_i > s\}$.

$$\widehat{p}_{22}^{\mathrm{LM}}(s,t) = \widehat{S}_T^{[s]}(t) \qquad \widehat{p}_{23}^{\mathrm{LM}}(s,t) = 1 - \widehat{S}_T^{[s]}(t)$$

where $S_T^{[s]}$ is the survival functions of the total time computed from the sample $\{i : \widetilde{Z}_i \leq s, \widetilde{T}_i > s\}$.

Landmark estimators

Variance estimates:

- Greenwood estimator can be used for almost all transition probabilities.
- A simple bootstrap can be used to obtain variance estimates.

A presmoothed version of the landmark estimator - `PLM` (Meira-Machado 2016) can be used to reduce variability of the estimator when:

- Sample size is small.
- Censoring is high.
- Higher values of s.

Landmark estimators: occupation probabilities

$$P_j(t) = p_{ij}(0,t), j = 1,2,3.$$

$$\widehat{P}_1(t) = \widehat{p}_{11}(0,t) = \widehat{S}_Z(t)$$
$$\widehat{P}_2(t) = \widehat{p}_{12}(0,t) = \widehat{S}_T(t) - \widehat{S}_Z(t)$$
$$\widehat{P}_3(t) = \widehat{p}_{13}(0,t) = 1 - \widehat{S}_T(t)$$

The estimators are very simple and intuitive. They are equivalent to Pepe's estimator (Pepe 1991).

Also of interest is the estimation: $p_{hj}(s,t|X)$; $CIF_j(t|X)$; $F_j(t|X)$.

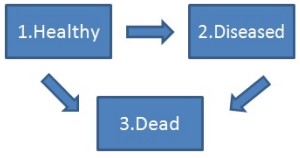
- Estimators based on a Cox's model fitted marginally to each type of transitions, with the corresponding baseline hazard function estimated by the Breslow's method.
- Nonparametric regression estimators can be introduced where local smoothing is done by introducing kernel weights that are based on Nadaraya-Watson regression.
- A single-index model is one effective tool to avoid the curse of dimensionality.

Testing the Markov Assumption

Markov assumption: future depends only on the present state and does not depend on past history.

Why is important: (i) to determine whether the AJ or a non-Markov approach is more appropriate; (ii) to choose best multi-state regression approach.

How is usually checked: by including covariates in the modelling process. This can be done by fitting a model



$$\alpha_{23}(t;Z) = \alpha_{23,0}(t)exp(\beta Z)$$

where Z is the time spent in state 1. Then we need to test $H_0 : \beta = 0$, against the general alternative, $H_1 : \beta \neq 0$.

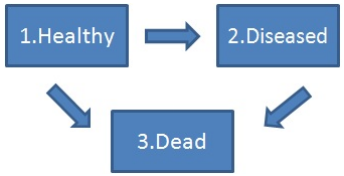
Testing the Markov Assumption

More recent methods based on the comparison of the transition probabilities were introduced:

Rodriguez-Girondo and dUA (2012, 2016): based on a local Kendall's tau, measuring the future-past association along time.

Titman and Putter (2000): introduce methods that were developed by considering summaries from families of log-rank statistics where patients are grouped by the state occupied of the process at a particular time point.

Soutinho and Meira-Machado (2022): introduce methods based on measuring the discrepancy of the non-Markov estimators of the transition probabilities to the Markovian Aalen-Johansen estimators.



State Occupation Probabilities: assuming the illness-death model where only the intermediate state may observe interval censored observations. Then,

$$\widehat{P}_1(t) = \widehat{P}(Z > t) = \widehat{S}_1^{tb}(t)$$

$$\widehat{P}_3(t) = \widehat{P}(T \leq t) = 1 - \widehat{S}^{km}(t)$$

$$\hat{P}_2(t) = \widehat{P}(Z \leq t, T > t) = 1 - \widehat{P}_1(t) - \widehat{P}_2(t)$$

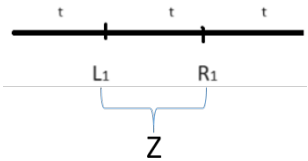
State Occupation Probabilities: an alternative estimator for $P_2(t)$:

$$\hat{P}_2(t) = \sum_{i=1}^{n} W_i I(\widetilde{T}_i > t)\hat{x}_i^t$$

$P_2(t) = P(Z \leq t, T > t)$

where W_i are the Kaplan-Meier weights; and

$$\hat{x}_i^t = 1 - \frac{\hat{S}_1(L_{1i} \vee t) - \hat{S}_1(R_{1i} \vee t)}{\hat{S}_1(L_{1i}) - \hat{S}_1(R_{1i})}$$



where $a \vee b$ stands for the maximum between a and b.

State Occupation Probabilities:

$$\hat{P}_2(t) = \sum_{j=1}^{m} p_j \times \hat{y}_j^t \times \hat{a}_j^t$$

where p_j are the Turnbull weights related to the so-called Turnbull intervals $I = \{(u_1, v_1], \ldots, (u_m, v_m]\}$; and

$$\hat{y}_j^t = \frac{\hat{S}(u_j \vee t) - \hat{S}(v_j \vee t)}{\hat{S}(u_j) - \hat{S}(v_j)}$$

and where

$$\hat{a}_j^t = \frac{1}{n} \sum_{i=1}^{n} \{1 - \frac{\hat{S}_1(L_{1i} \vee t) - \hat{S}_1(R_{1i} \vee t)}{\hat{S}_1(L_{1i}) - \hat{S}_1(R_{1i})}\} \delta_{ij}$$

where $\delta_{ij} = I\{(u_i, v_i] \subseteq (L_{2i}, R_{2i}], R_{1i} \leq s\}$

1. msm - time-homogeneous Markov models.
2. mstate - computes and displays the transition probabilities for the landmark Aalen-Johansen estimator.
3. p3state.msm - enables the user to perform inference in the illness-death model. The main feature of the package is its ability for obtaining non-Markov estimates for the transition probabilities.
4. TPmsm - computes and displays the transition probabilities for several methods.
5. markovMSM - provides methods for checking the Markov condition in multi-state survival data.
6. survidm - for inference and prediction in an illness-death model.

Can be used in 3-state models.

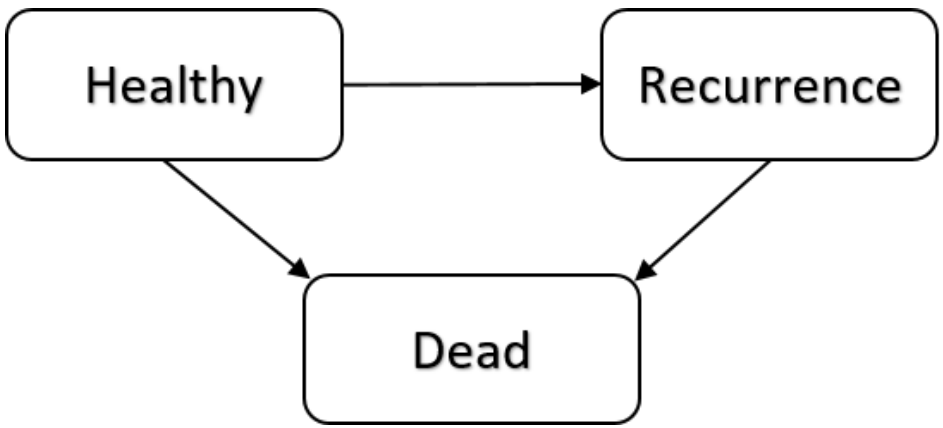
1. Can be used to:
   - Perform multi-state regression (Cox-based models)
   - Estimate the Transition Probabilities
   - Estimate the Cumulative Incidence Functions
   - Estimate the Sojourn Distributions
2. Can be estimated conditional on covariates.
3. Confidence bands are provided for all methods.
4. Numerical and graphical output is provided for all methods.

- survIDM - Create a survIDM object.
- coxidm - Fit proportional hazards regression model in each transition.
- tprob - nonparametric estimation of transition probabilities.
- CIF - nonparametric estimation of the Cumulative Incident Functions.
- sojourn - nonparametric estimation of the Sojourn time distributions.
- summary, print and plot functions.

Shiny Apps in Survival Analysis: Shiny apps simplify complex data exploration, offering real-time model fitting and visualization. With intuitive interfaces, these apps enhance insights, streamline analysis, and foster collaborative decision-making across diverse fields.

`https://emanuel-vieira.shinyapps.io/survapp/`

- Available as part of the R survival package.
- 929 patients underwent a curative surgery for colorectal cancer.
- 468 developed recurrence - 414 died; 38 died without recurrence.
- States: “Alive and Disease-Free”; “Recurrence”; “Death”.
- Covariates: Age (years)



Some numbers ...

s	State 1	$\Delta_1 = 1$	$\Delta = 1$	%*Cen*	State 2	$\Delta = 1$	%*Cen*
90	894	471	417	53.36	28	28	0
180	828	405	354	57.25	77	74	3.9
365	699	276	231	66.95	152	143	5.92
730	556	134	100	82.01	162	142	12.35
1095	502	80	54	89.24	124	96	22.58
1460	473	53	34	92.81	82	47	42.68
1825	437	28	17	96.11	74	31	58.11
2190	290	9	7	97.59	51	11	78.43

Table: Number of patients (and censoring percentages) in State 1 and 2.

Multi-state regression

```
library(survidm)
data(colonIDM)
fit.cmm <- coxidm(survIDM(time1, event1, Stime, event) ~ age
+ sex + nodes, data = colonIDM)
summary(fit.cmm)
```

`age` - important predictor on the mortality transitions (with and without recurrence) but not on the recurrence incidence;
`sex` - only revealed a significant effect on the mortality transition after recurrence.

```
res <- tprob(survIDM(time1, event1, Stime, event) ~ 1, s = 365,
method = "LM", conf = TRUE, data = colonIDM)
summary(res, time=365*1:6)
plot(res)
```

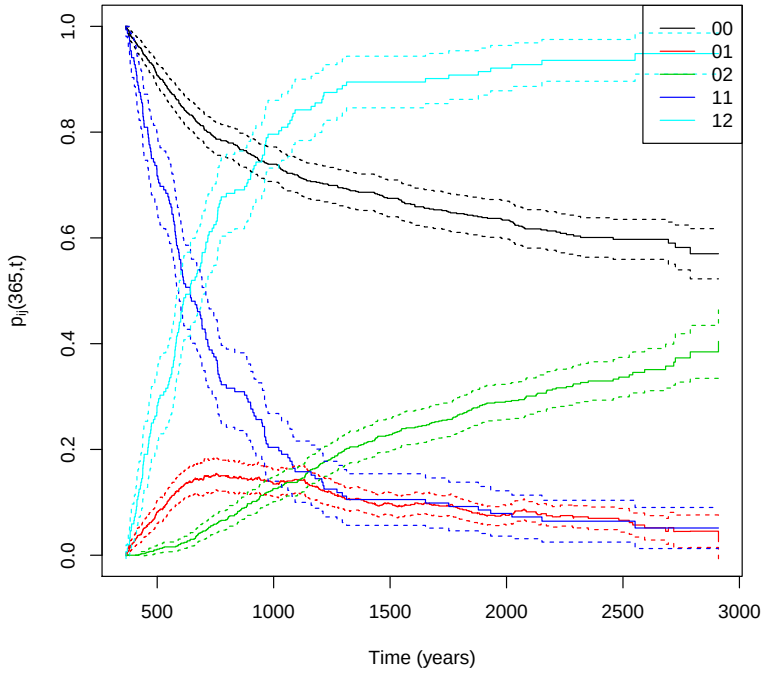


Figure: Estimates of the transition probabilities $p_{ij}(365, t)$.

Testing the Markov Assumption

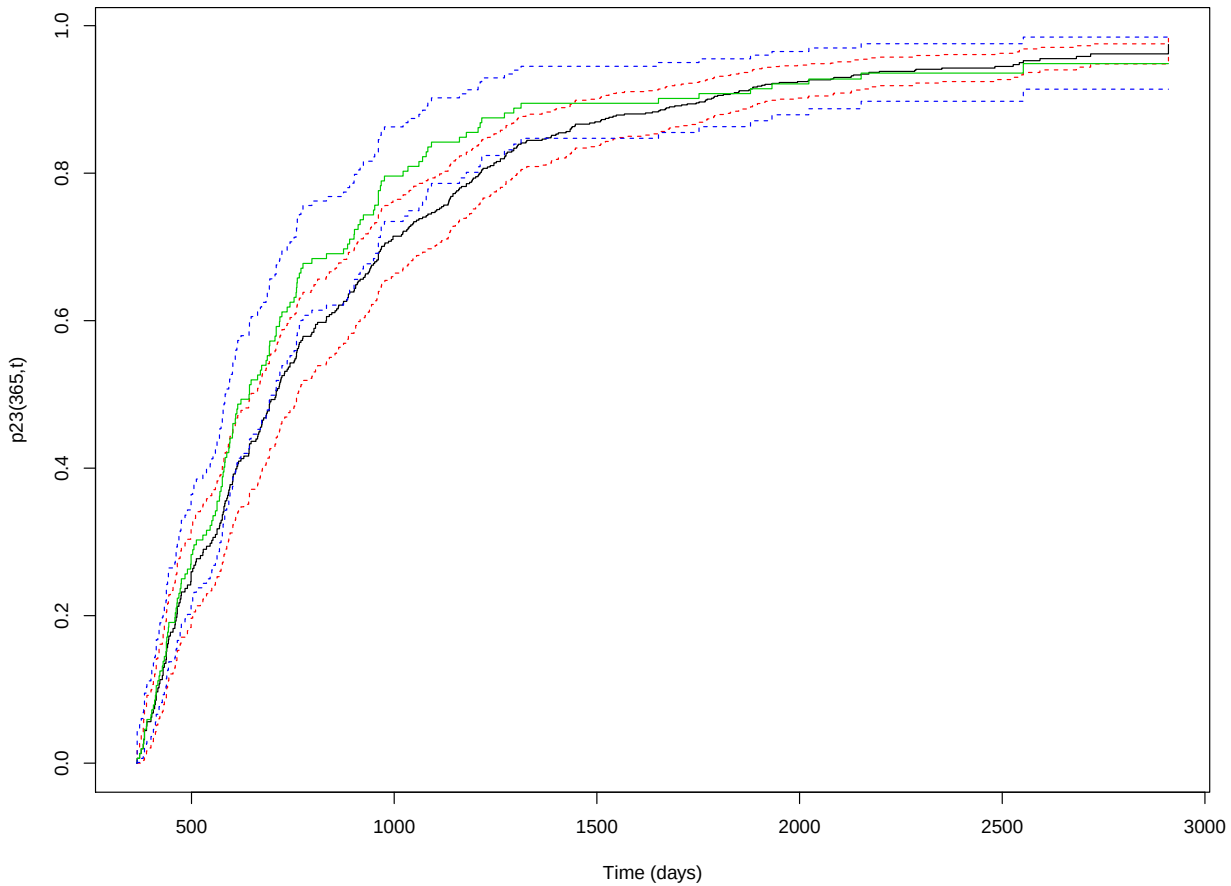
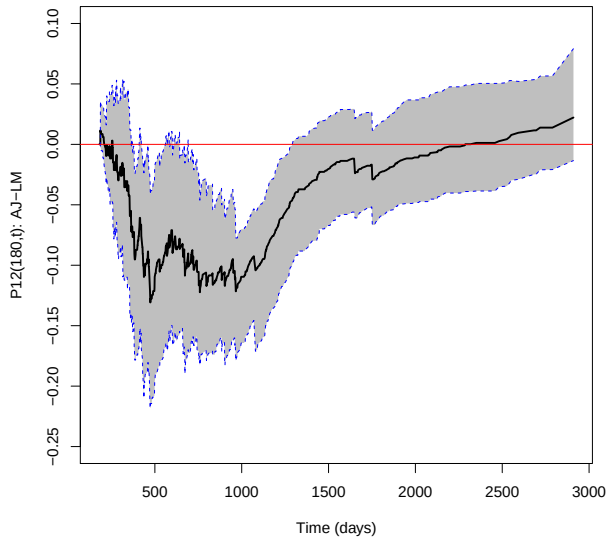
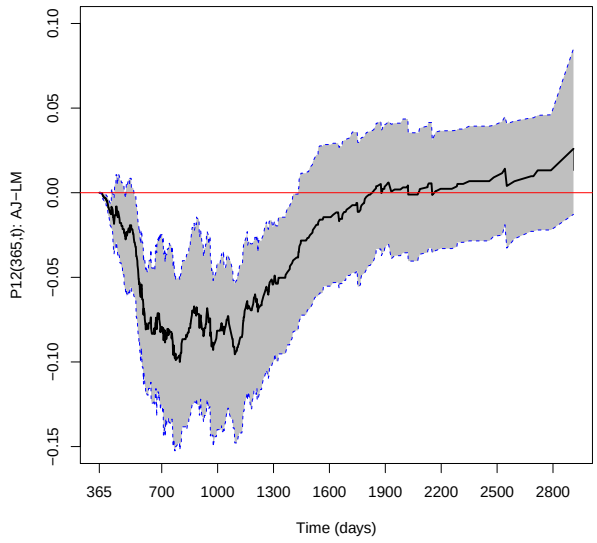
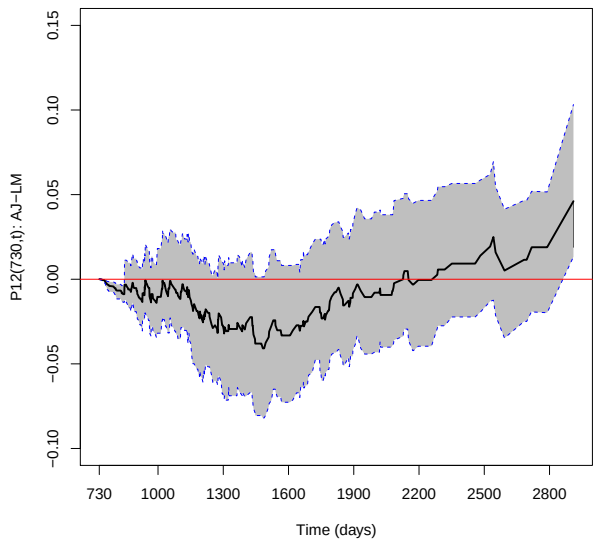


Figure: Estimates of the transition probabilities $p_{22}(365, t)$ for AJ and LMAJ. Colon cancer data.


P12(180,t): AJ−LM
0.10
0.05
0.00
−0.05
−0.10
−0.15
−0.20
−0.25
500
1000
1500
2000
2500
3000
Time (days)


P12(365,t): AJ−LM
0.10
0.05
0.00
−0.05
−0.10
−0.15
365
700
1000
1300
1600
1900
2200
2500
2800
Time (days)


P12(730,t): AJ−LM
0.15
0.10
0.05
0.00
−0.05
−0.10
730
1000
1300
1600
1900
2200
2500
2800
Time (days)

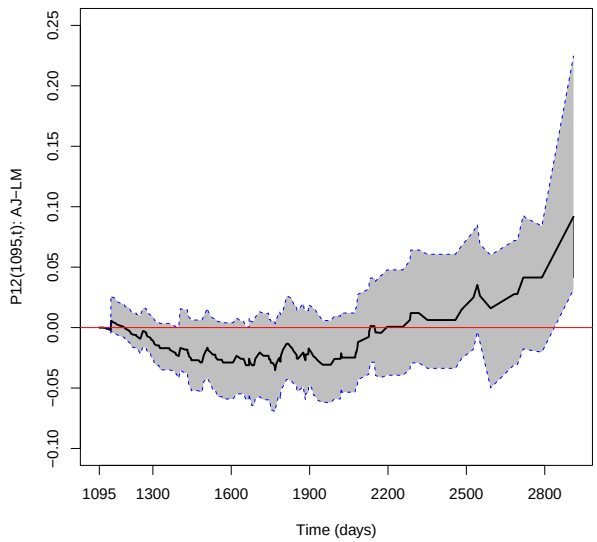

P12(1095,t): AJ−LM
0.25
0.20
0.15
0.10
0.05
0.00
−0.05
−0.10
1095
1300
1600
1900
2200
2500
2800
Time (days)

Table: Probability values of the local test for several fixed values of s (measured in days). Rejection proportions for the global tests also included. Colon cancer data.

Trans. Prob.	Method	90	180	365	730	1095	1460	Global AUC / LR	Global Cox
$\hat{p}_{12}(s,t)$	AUC(s)	0.012	0.007	0.002	0.154	0.135	0.857	0.014	0.154
$\hat{p}_{23}(s,t)$	LR(s)	0.006	0.026	0.036	0.685	0.981	0.509	0.018	0.154
	AUC(s)	0.003	0.004	0.003	0.155	0.118	0.714	0.013	0.154

LR - Tests based on the based on the log-rank statistics (Titman and Putter, 2000)
Global AUC test - achieved by combining the results obtained from local tests over different times (percentiles 5, 10, 20, 30 and 40 of the sojourn time in State 1).

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