Overview of Time-to-Event Analysis Theory and Concepts

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https://github.com/migariane/SVA-ULB

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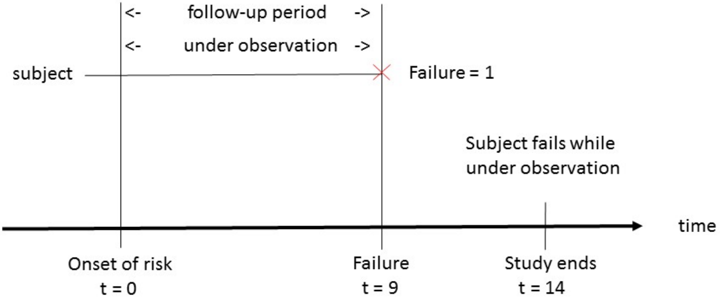
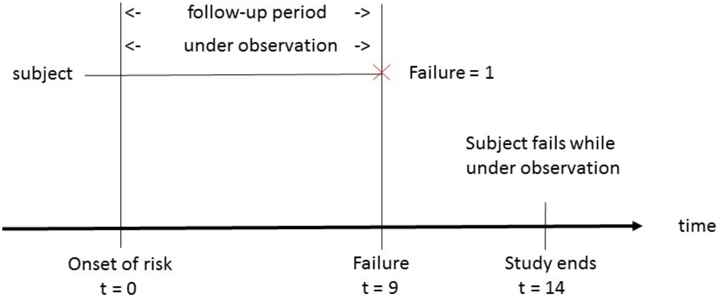
Let's practice! It is your turn!

It is censoring?



No, it is just a failure (the event of interest)



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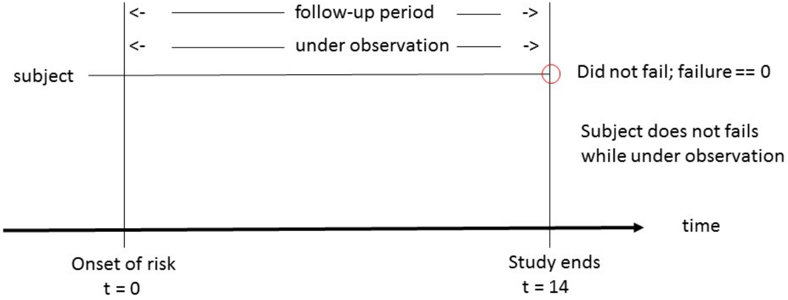

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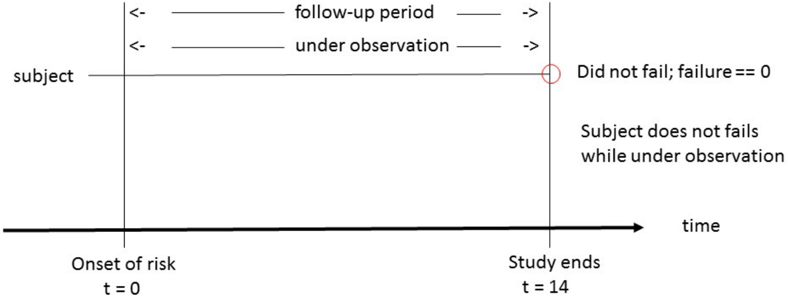

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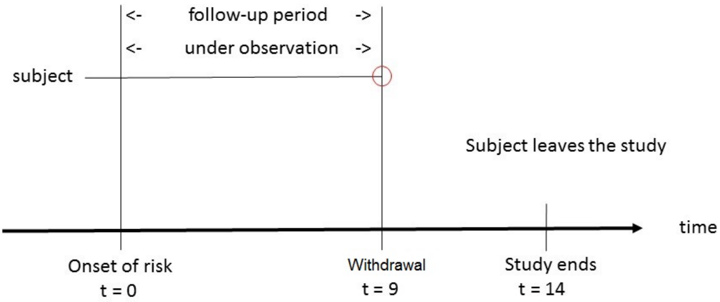
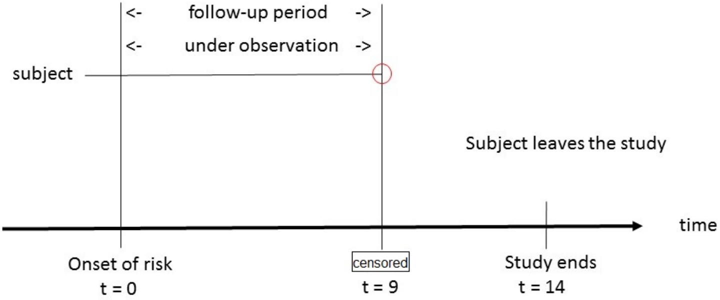


Yes, right censoring before the end of the study (LTFU)



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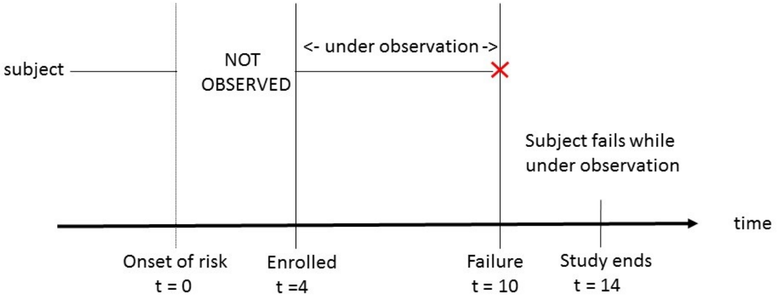

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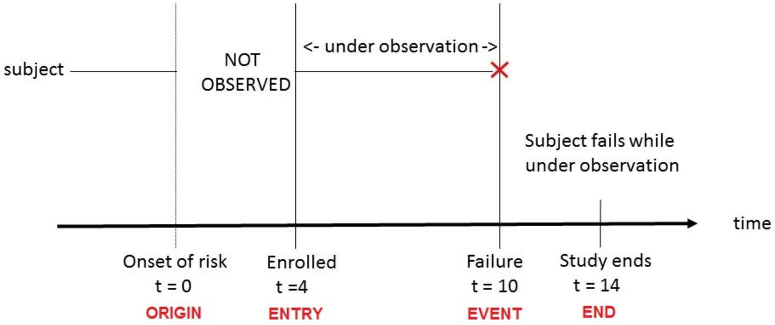
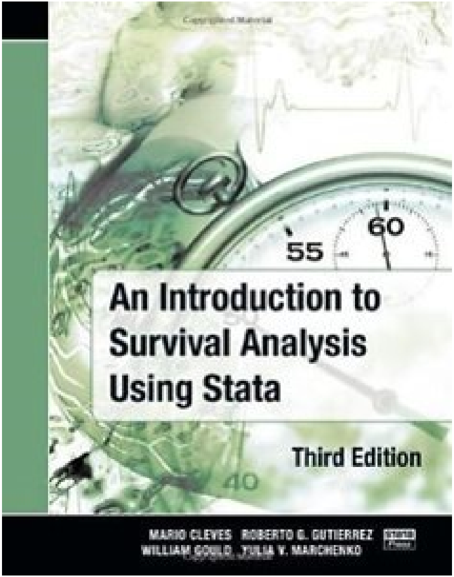


Setting TIME in Statistical Software

Setting of time: chapters 5,6,7



Stata stset command

stset finmdy, fail(dead==1) origin(time diagmdy) enter(time diagmdy)

```
     failure event:  dead == 1
obs. time interval:  (origin, finmdy]
 enter on or after:  time diagmdy
 exit on or before:  failure
    t for analysis:  (time-origin)
            origin:  time diagmdy
------------------------------------------------------------------------------
     355801  total observations
          0  exclusions
------------------------------------------------------------------------------
     355801  observations remaining, representing
     212121  failures in single-record/single-failure data
  920269050  total analysis time at risk and under observation
                                                at risk from t =         0
                                     earliest observed entry t =         0
                                          last observed exit t =     12052
```

Listing the output of the Stata stset command

list diagmdy finmdy _t0 _t _d _st in 1/10

```
     +-----------------------------------------------------+
     |   diagmdy      finmdy   _t0          _t   _d    _st |
     |-----------------------------------------------------|
  1. | 01jan2000   31dec2003     0   3.9972621    1      1 |
  2. | 29jul1998   31dec2003     0   5.4236824    0      1 |
  3. | 30jan1998   31dec2003     0   5.9164956    0      1 |
  4. | 09jul1998   31dec2003     0   5.4784394    0      1 |
  5. | 22dec1998   31dec2003     0   5.0239562    0      1 |
     |-----------------------------------------------------|
  6. | 23jan1998   31dec2003     0   5.9356605    0      1 |
  7. | 16jul1998   31dec2003     0   5.4592745    0      1 |
  8. | 07jul1999   31dec2003     0   4.4845996    0      1 |
  9. | 18aug1998   31dec2003     0   5.3689254    0      1 |
 10. | 01sep1999   01oct2003     0   4.0821355    1      1 |
     +-----------------------------------------------------+
```

Origin and Entry

Important

It is critical to distinguish between the **time** of the **STUDY ENTRY** and the **ORIGIN** of **time.**

Time

- **origin:** It defines **time 0**, that is, when we start **recording time** (date of birth, date of cancer diagnosis, etc).

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Study entry and Time Origin

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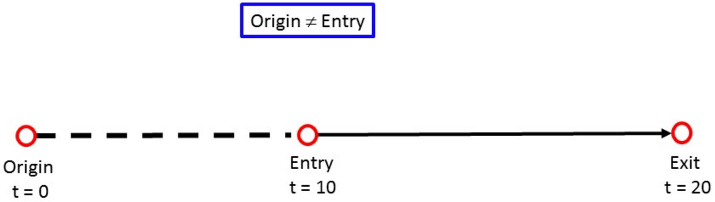

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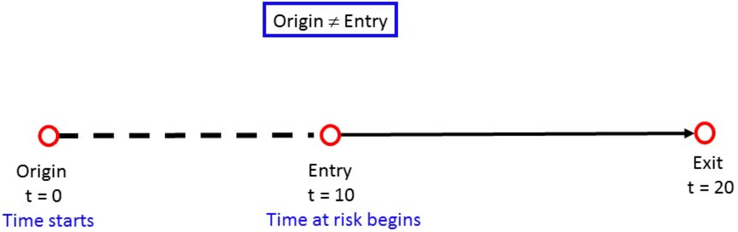

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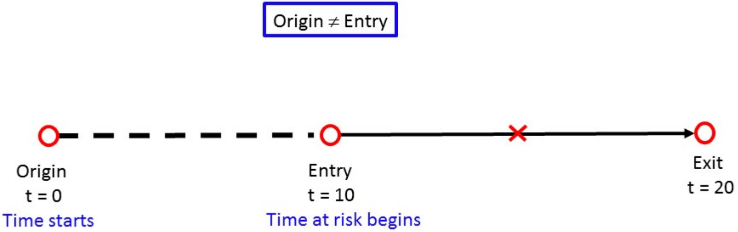

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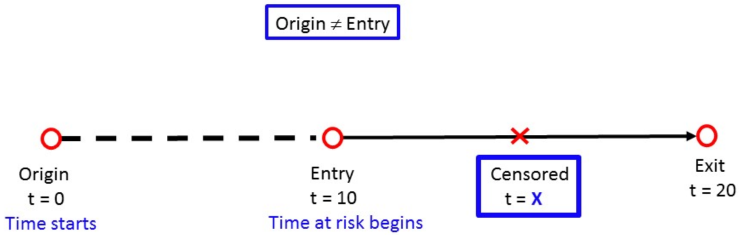

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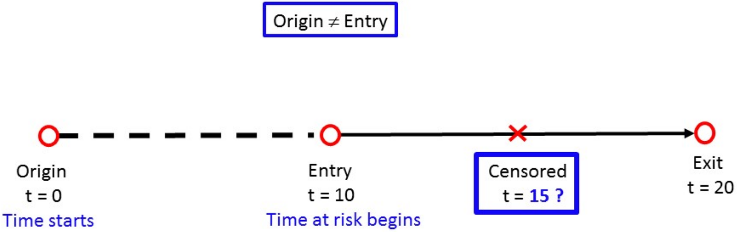

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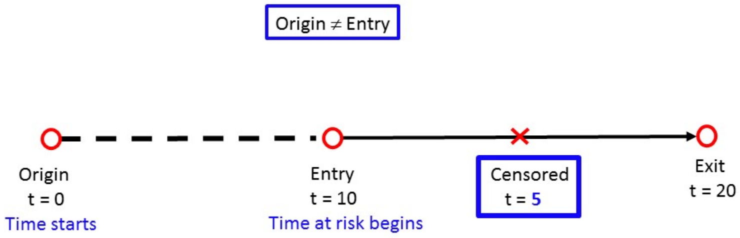

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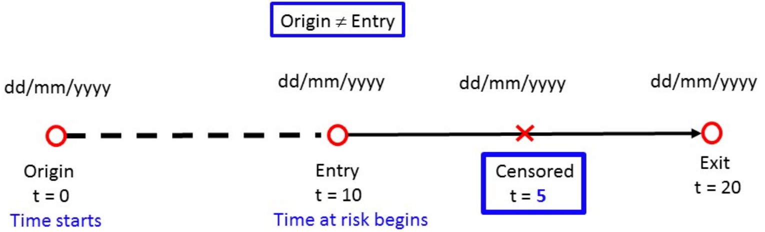
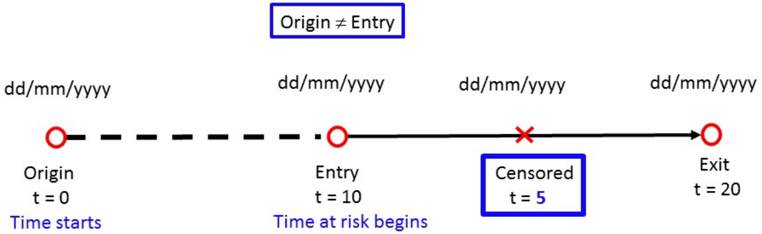


$$\text{scale} = \frac{\text{exit(dd/mm/yy)} - \text{origin(dd/mm/yy)}}{\text{scale}(365.25)}$$



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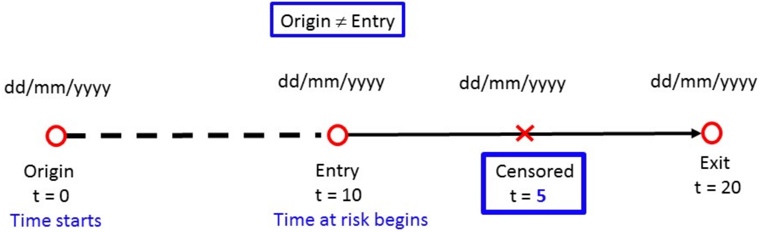
Time zero in Stata = **01.JAN.1960**



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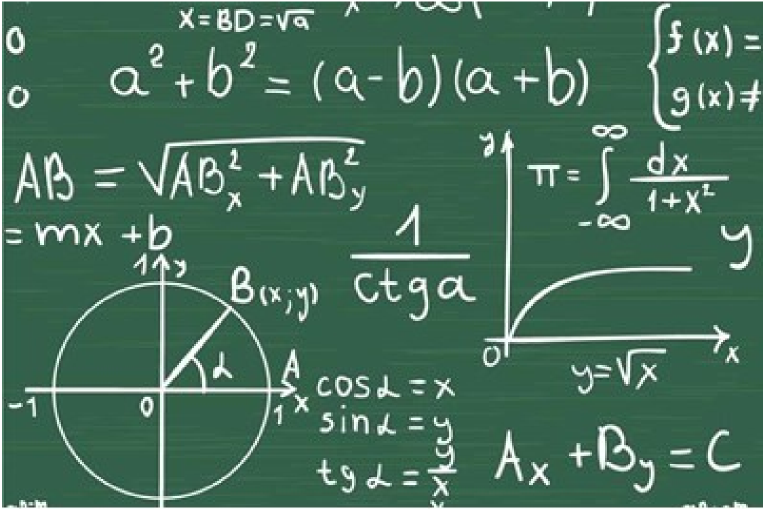
The Maths behind Survival

The anatomy of time-to-event analysis

Anatomische les door Dokter van der Meer, 1617

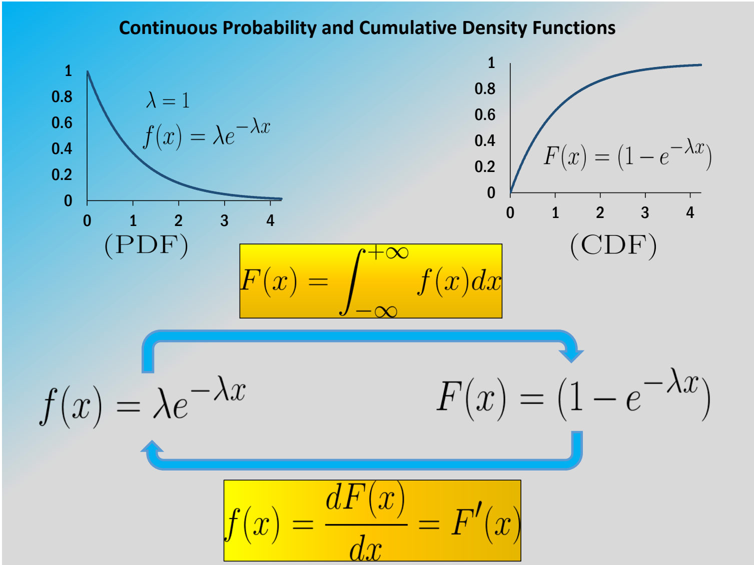
Epidemiologists



The Maths behind Survival

The Probability Density Function PDF and Cumulative Density Function CDF of a random variable

PDF and CDF



Continuous Probability and Cumulative Density Functions
1
0.8
0.6
0.4
0.2
0
0 1 2 3 4
$\lambda = 1$
$f(x) = \lambda e^{-\lambda x}$
(PDF)
$F(x) = (1 - e^{-\lambda x})$
(CDF)
$F(x) = \int_{-\infty}^{+\infty} f(x)dx$
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H(t): Cumulative hazard or Λ

$$\text{H(t)} = \int_0^t \frac{\text{f(u)}}{\text{S(u)}}\text{du} = \int_0^t \frac{1}{\text{S(u)}}\text{(F')} =$$

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$$\text{H(t)} = \int_0^t \frac{\text{f(u)}}{\text{S(u)}}\text{du} = \int_0^t \frac{1}{\text{S(u)}}\text{(F')} = \int_0^t \frac{1}{\text{S(u)}}\text{(1 - S(u))'} = \text{-log(S(t))}$$

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The soul of Survival Analysis

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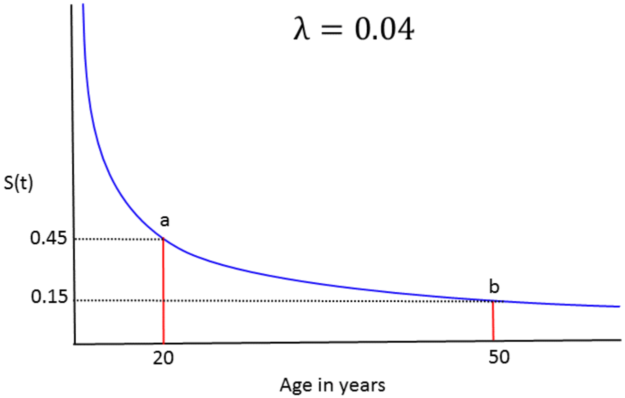
Formulae to derive h(t), H(t) and S(t): Pintilie M.(2007)

Table 2.1 Basic mathematical formulae.

	Continuous distributions		Discrete distributions	
Function	Definition	Relationship to other functions	Definition	Relationship to other functions
Cumulative distribution	$F(t) = P(T \le t)$	$F(t) = \int_0^t f(x)dx$	$F(t) = P(T \le t)$	$F(t) = \sum_{t_j \le t} p(t_j)$
Probability density	$f(t) = \frac{d}{dt}F(t)$	$f(t) = -\frac{d}{dt}S(t)$	$p(t_j) = P(T = t_j)$	$p(t_j) = S(t_{j-1}) - S(t_j)$
Survivor	$S(t) = P(T > t)$	$S(t) = 1 - F(t)$ $= \int_t^\infty f(x)dx$ $= \exp\{-H(t)\}$	$S(t) = P(T > t)^*$	$S(t) = 1 - F(t)$ $= \sum_{t_j > t} p(t_j)$ $= \exp\{-H_2(t)\}$
Hazard	$h(t) = \lim_{\delta t \to 0} \left\{ \frac{P(t \le T < t + \delta t \mid T > t)}{\delta t} \right\}$	$h(t) = f(t)/S(t)$ $= -\frac{d}{dt} \log S(t)$	$h(t_j) = P(T = t_j \mid T \ge t_j)$ $H_1(t) = \sum_{t_j \le t} h(t_j)$	$h(t_j) = p(t_j)/S(t_{j-1})$
Cumulative hazard	$H(t) = \int_0^t h(x)dx$	$H(t) = -\log S(t)$	$H_2(t) = -\sum_{t_j \le t} \log\{1 - h(t_j)\}$	$H_2(t) = -\log S(t)$

* Probability function

Deriving h(t), H(t), and S(t) from the Exponential distribution



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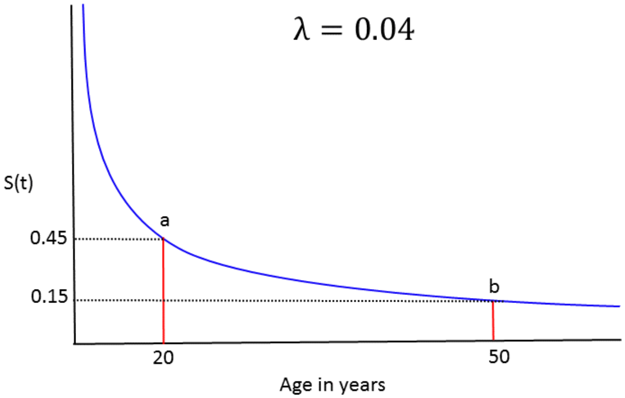

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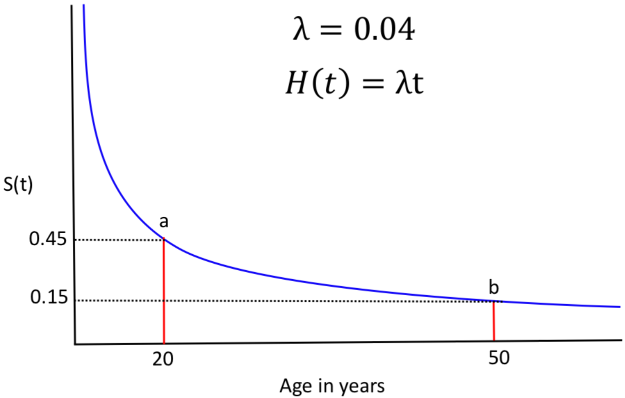

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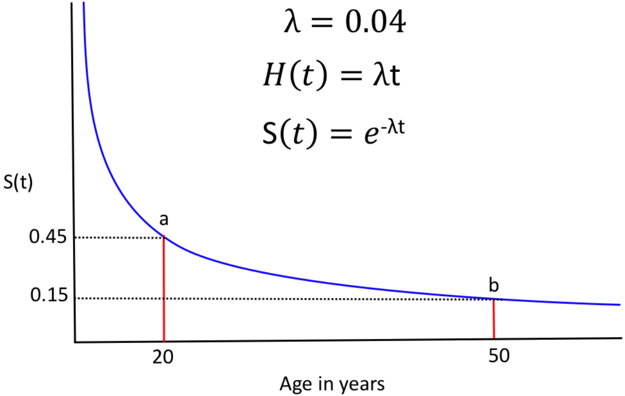

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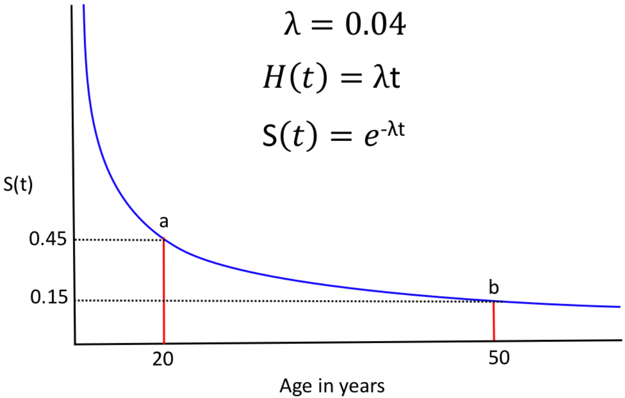

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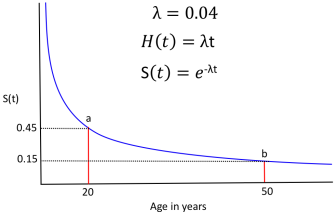

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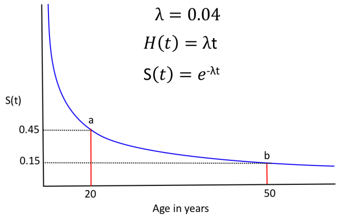

Link between hazard and velocity

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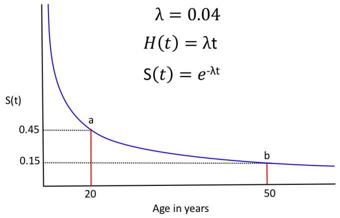

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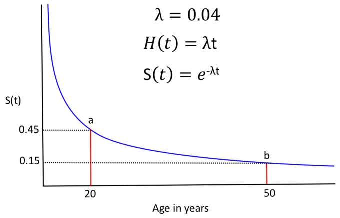

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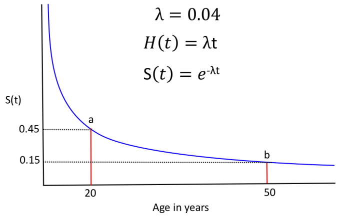

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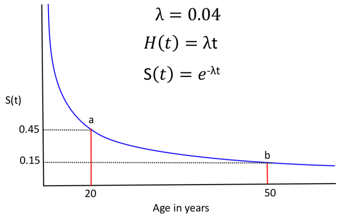

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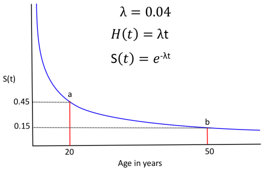

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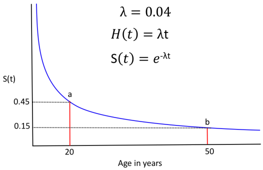

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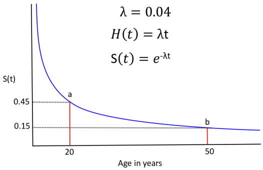

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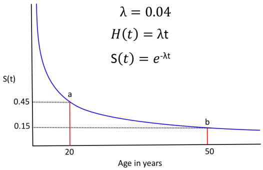

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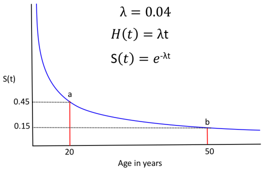

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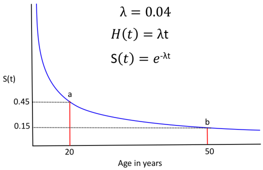

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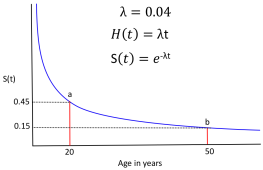

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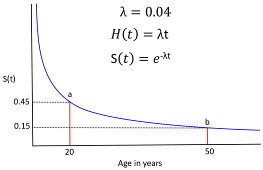

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The Statistical Methods

The Statistical Methods used in time-to-event analysis

Methods

Statistical Methods

Non-parametric

Methods

Statistical Methods

Non-parametric

- Life Tables

Methods

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						Probability	
	Total a_i	Deaths d_i	Lost c_i	N.A.R $n_i = (a_i - (c_i/2))$	Rate $r_i = d_i/n_i$	s(t)$= 1 - r_i$	S(t)=$S(i-1) \times S_i$
00-01	100	35	0	100	0.350	0.650	0.650
01-02	65	6	10	60	0.100	0.900	0.585
02-03	49	5	18	40	0.125	0.875	0.512
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Life Table in Stata

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In Stata use sts list
            Beg.              Net             Survivor      Std.
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-------------------------------------------------------------------------------
   1-6        47       8       0               0.8298     0.0548     0.6883    0.9110
  6-11        39       7       4               0.6809     0.0680     0.5275    0.7937
 11-16        28       6       2               0.5350     0.0751     0.3786    0.6684
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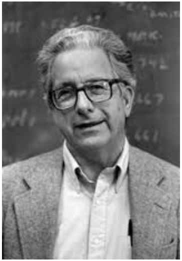

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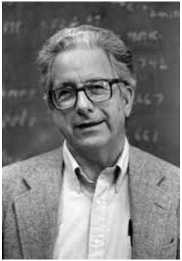

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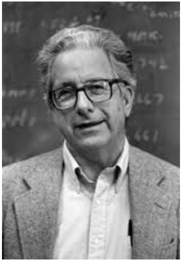

No assumptions about the functional form of the baseline hazard

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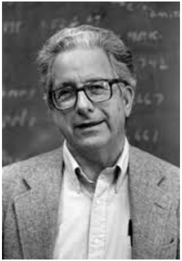

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Non-parametric

Kaplan-Meier or Product Limit Estimator

$$\widehat{S}(t) = \prod_{t_j \leq t} \left(\frac{n_j - d_j}{n_j} \right)$$

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$$\widehat{Var}\left(\hat{S}(t)\right) = \widehat{S}(t)^2 \sum_{t_j \leq t} \frac{d_j}{n_j(n_j - d_j)}$$

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$$95\% CI = \widehat{S}(t) \pm Z_{1-\frac{\alpha}{2}} \sqrt{\widehat{Var}(\widehat{S}(t))}$$

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Kaplan-Meier by group

Table 2. Kaplan-Meier survival function by treatment group

Group	time	n	d	censor	(n-d)/n	S	d/(n(n-d))	sum	ln(-ln(S))	lnln(SE)	lnln(L95%)	lnln(U95%)	L95%CI	U95%CI
Placebo	0	5	0	0	1.0000	1.0000	0.0000	0.0000						
Placebo	1	5	1	0	0.8000	0.8000	0.0500	0.0500	-1.4999	1.0021	-3.4640	0.4641	0.2038	0.9692
Placebo	2	4	1	0	0.7500	0.6000	0.0833	0.1333	-0.6717	0.7148	-2.0727	0.7293	0.1257	0.8818
Placebo	7	3	0	1	1.0000	0.6000	0.0000	0.1333	-0.6717	0.7148	-2.0727	0.7293	0.1257	0.8818
Placebo	8	2	1	0	0.5000	0.3000	0.5000	0.6333	0.1856	0.6610	-1.1099	1.4812	0.0123	0.7192
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	Placebo			Drug					Log-rank estimation		
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0	5	0	0	5	0	0	10	0	0	0	0
1	5	1	0	5	0	0	10	1	0.500	0.250	0.500
2	4	1	0	5	0	0	9	1	0.444	0.247	0.556
4	3	0	0	5	1	0	8	1	0.375	0.234	-0.375
6	3	0	0	4	0	1	7	0	0.000	0.000	0.000
7	3	0	1	3	0	0	6	0	0.000	0.000	0.000
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Log-rank test

$$\widehat{\mathbf{e}}_{\mathbf{1i}} = \frac{n_{1i} d_i}{n_i} \; ; \mathbf{U} = \sum_{i=1}^{r} \left(d_{1i} - \frac{\mathbf{n_{1i} d_i}}{\mathbf{n_i}} \right) = 1.20$$

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Inference

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$$\text{Log-rank test (Q)} = \frac{U^2}{\widehat{\text{Var}}(U)} = \frac{1.43}{1.63} = 0.88 \text{ Chi-square (1df), p-value=}\mathbf{0.348}$$

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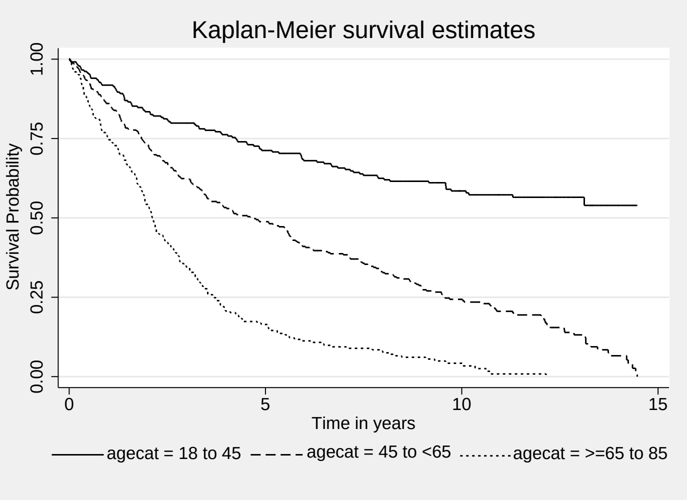

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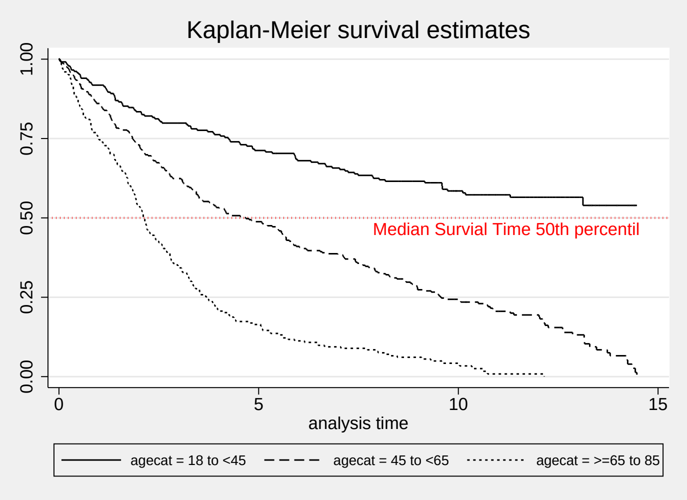

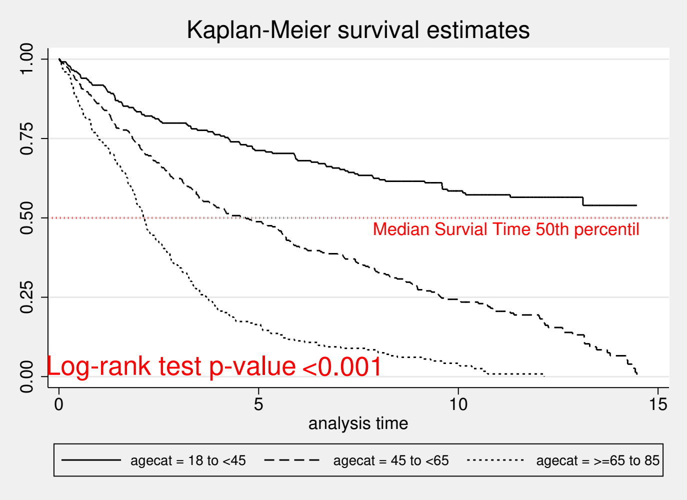
Kaplan-Meier survival estimates
1.00
0.75
0.50
0.25
0.00
0
5
10
15
analysis time
Median Survial Time 50th percentil
Log-rank test p-value <0.001
agecat = 18 to <45
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- Assumptions about the **functional form** of the $h_0(t)$ is what determines whether the model is parametric or semiparametric
- The **exponential** of the function of the covariates is needed to prevent a negative baseline hazard ($h_0(t)$)

Hazard Models

Hazard Models (HM)

The parametrization of the HM explains all:

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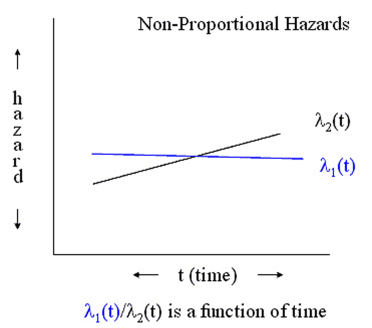
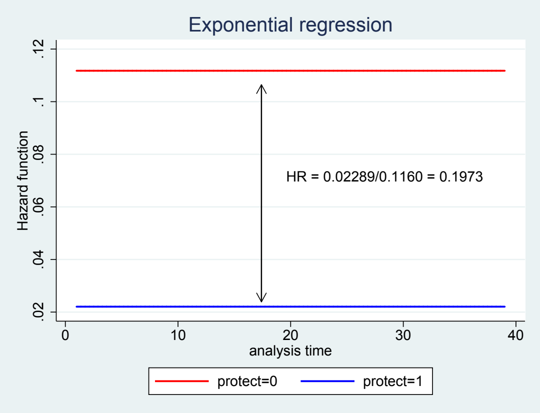


Proportionality of Hazards

Exponential model with constant Hazard



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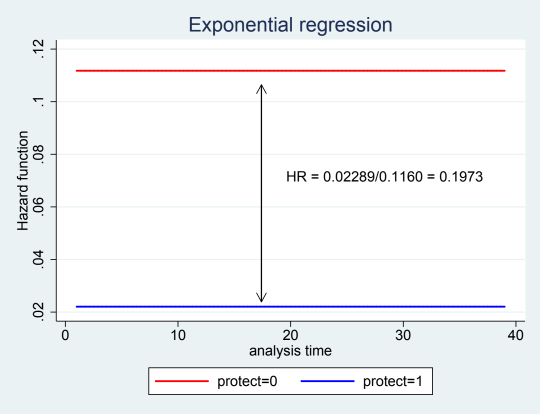


Exponential Models

```
.use http://www.stata.com/courses/nc631-13/lec4/hip2, clear
. streg protect, dist(exp) hr
         failure _d:  fracture
   analysis time _t:  time1
                 id:  id
Exponential regression -- log relative-hazard form
No. of subjects =           48                 Number of obs    =        106
No. of failures =           31
Time at risk    =          714
                                               LR chi2(1)       =      19.68
Log likelihood  =   -50.227658                 Prob > chi2      =     0.0000
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     protect |   .1973684   .0727765    -4.40   0.000     .0958099    .4065789
       _cons |   .1117647   .0256406    -9.55   0.000     .0712895      .17522
------------------------------------------------------------------------------
```

Parametric Survival Distributions: Pintilie M. (2007)

Table 2.2 Parametric models for time-to-event data.

Distribution	$f(t)$	$F(t)$	$S(t)$	$h(t)$
Exponential	$\lambda e^{-\lambda t}$	$1-e^{-\lambda t}$	$e^{-\lambda t}$	λ
Weibull	$\lambda\theta t^{\theta-1}\exp\left\{-\lambda t^{\theta}\right\}$	$1-\exp\left\{-\lambda t^{\theta}\right\}$	$\exp\left\{-\lambda t^{\theta}\right\}$	$\lambda\theta t^{\theta-1}$
Gamma	$\lambda^{\theta}t^{\theta-1}e^{-\lambda t}$	$I\Gamma(\theta,\lambda t)^{\dagger}$	$1-I\Gamma(\theta,\lambda t)$	$f(t)/S(t)$
Generalized gamma	$\dfrac{\alpha\lambda^{\theta}t^{\alpha\theta-1}\exp\left\{-\lambda t^{\alpha}\right\}}{\Gamma(\theta)}$	$I\Gamma(\theta,\lambda t^{\alpha})^{\dagger}$	$1-I\Gamma(\theta,\lambda t^{\alpha})$	$f(t)/S(t)$
Lognormal	$\dfrac{\exp\left\{-\frac{1}{2}\left(\frac{\log t-\mu}{\sigma}\right)^{2}\right\}}{\sigma t\sqrt{2\pi}}$	$\Phi\left(\dfrac{\log t-\mu}{\sigma}\right)^{\ddagger}$	$1-\Phi\left(\dfrac{\log t-\mu}{\sigma}\right)$	$f(t)/S(t)$
Log-logistic	$\dfrac{\lambda\theta t^{\theta-1}}{(1+\lambda t^{\theta})^{2}}$	$\dfrac{\lambda t^{\theta}}{1+\lambda t^{\theta}}$	$\dfrac{1}{1+\lambda t^{\theta}}$	$\dfrac{\lambda\theta t^{\theta-1}}{1+\lambda t^{\theta}}$

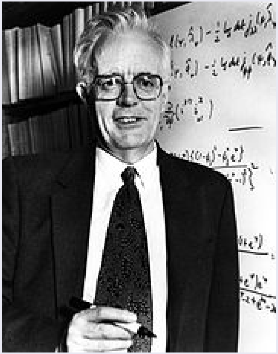
† $I\Gamma$ is the incomplete gamma function: $I\Gamma(\theta,\lambda t)=\int_0^t \lambda^{\theta}t^{\theta-1}e^{-\lambda t}dt/\Gamma(\theta)$.
‡ Φ is the cdf of the standard normal distribution.

Shiny application

http://watzilei.com/shiny

Semi-parametric Cox Proportional Hazard Model

Sir David Cox



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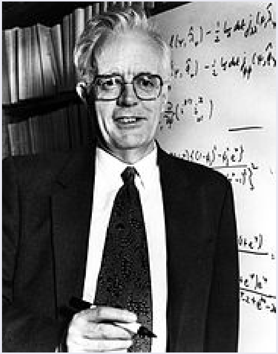

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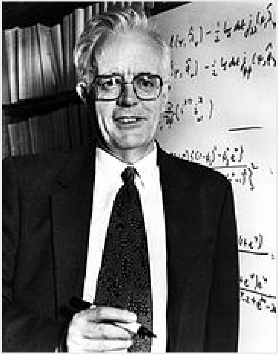

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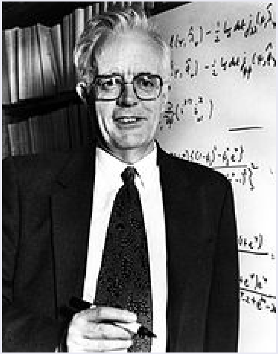

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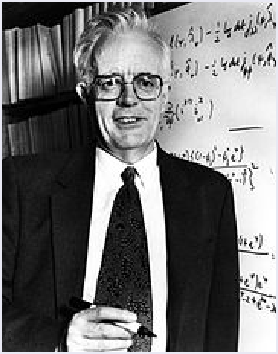

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$$\mathbf{h}(\mathbf{t}|\mathbf{x_j}) = [\mathbf{h_0}(\mathbf{t}) \times exp(\beta_0)]$$

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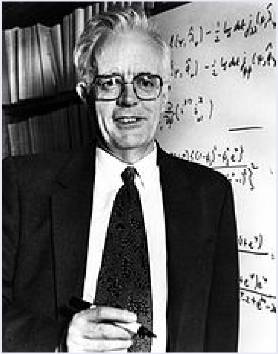

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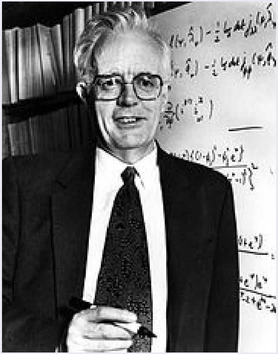

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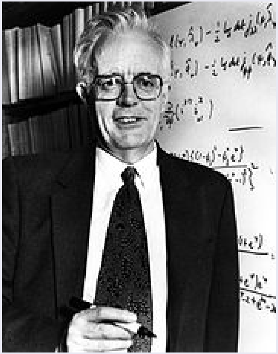

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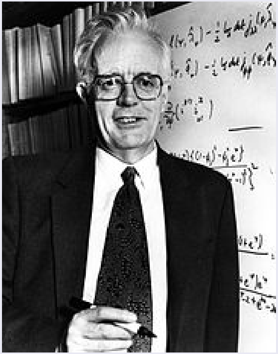

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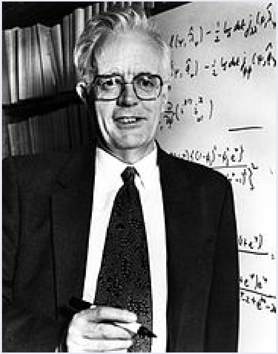

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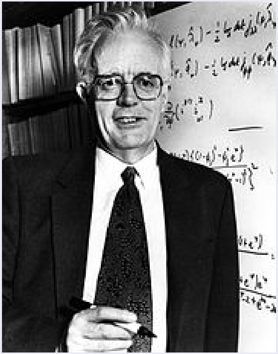

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Cox Model in Stata

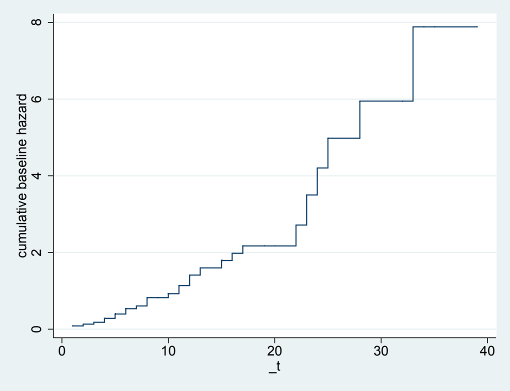
```
. use http://www.stata.com/courses/nc631-13/lec4/hip2, clear
(hip fracture study)
. stcox protect, nohr
failure _d: fracture
analysis time _t: time1
id: id
------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     protect |  -2.047599   .4404029    -4.65   0.000    -2.910773   -1.184426
------------------------------------------------------------------------------

Hazard Ratio for wearing the protect device = ? ==> exp(-2.05) = 0.129

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     protect |   .1290443   .0568315    -4.65   0.000     .0544336    .3059218
------------------------------------------------------------------------------
```

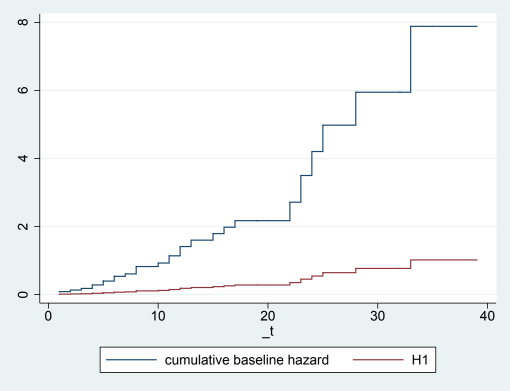
Cumulative Hazard in Stata

- predict H0, basechazard
- twoway line H0 _*t*, connect(J) sort



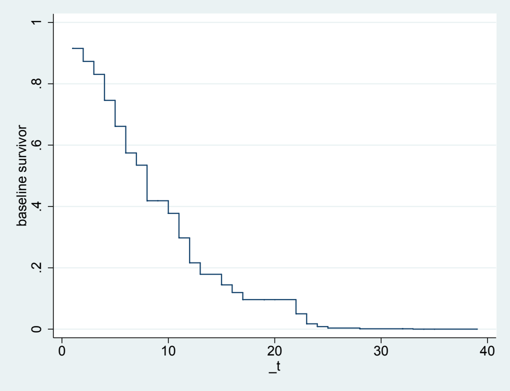
Cumulative Hazard in Stata

- generate H1 = H0*exp(_b[protect])
- twoway line H0 H1 _t, sort connect(J J)
- stcurve, cumhaz at1(protect = 0) at2(protect=1)



Baseline Survival in Stata

- predict S0, basesurv
- twoway line S0 _*t*, connect(J) sort



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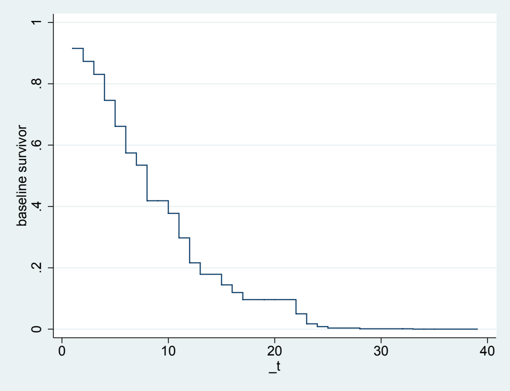

Survival by groups in Stata

- generate S1 = S0*exp(_*b*[protect])
- twoway line S0 S1 _*t*, sort connect(J J)
- stcurve, surv at1(protect = 0) at2(protect=1)

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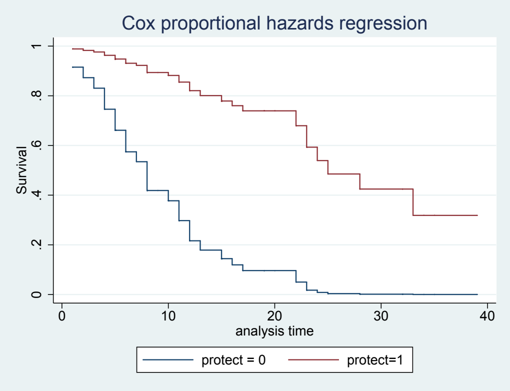

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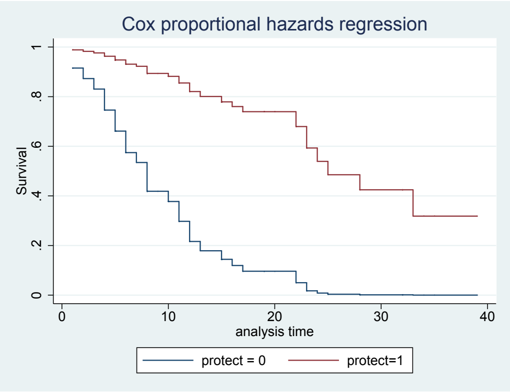

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Final overview

https://www.mailman.columbia.edu/research/population-health-methods/time-event-data-analysis

Thank you!

Muchas Gracias!