

# **GSERM - St. Gallen 2019**

## Parametric Survival Models

June 20, 2019 (morning session)

# A General Parametric Model

$$f(t) = \lim_{\Delta t \rightarrow 0} \frac{\Pr(t \leq T < t + \Delta t)}{\Delta t}$$

$$\begin{aligned} S(t) &= \Pr(T \geq t) \\ &= 1 - \int_0^t f(t) dt \\ &= 1 - F(t) \end{aligned}$$

$$\begin{aligned} h(t) &= \frac{f(t)}{S(t)} \\ &= \lim_{\Delta t \rightarrow 0} \frac{\Pr(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \end{aligned}$$

$$L = \prod_{i=1}^N [f(T_i)]^{C_i} [S(T_i)]^{1-C_i}$$

$$\ln L = \sum_{i=1}^N \{C_i \ln [f(T_i)] + (1 - C_i) \ln [S(T_i)]\}$$

$$\ln L | \mathbf{X}, \boldsymbol{\beta} = \sum_{i=1}^N \{C_i \ln [f(T_i | \mathbf{X}, \boldsymbol{\beta})] + (1 - C_i) \ln [S(T_i | \mathbf{X}, \boldsymbol{\beta})]\}$$

# The Exponential Model

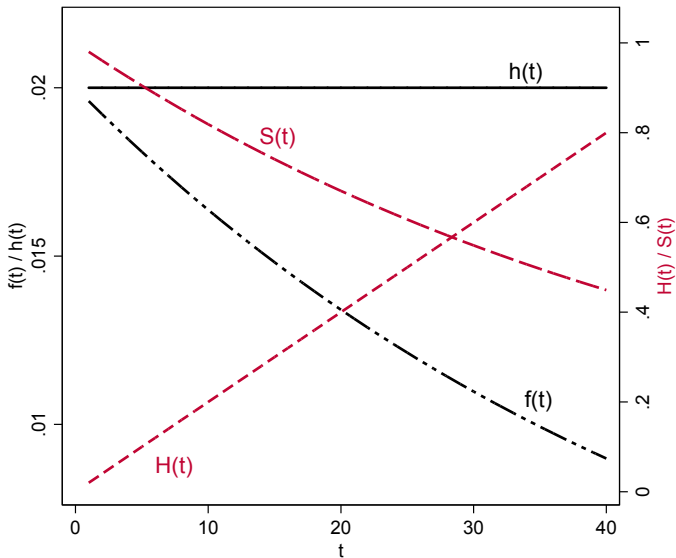
$$h(t) = \lambda$$

$$\begin{aligned} H(t) &= \int_0^t h(t) dt \\ &= \lambda t \end{aligned}$$

$$\begin{aligned} S(t) &= \exp[-H(t)] \\ &= \exp(-\lambda t) \end{aligned}$$

$$\begin{aligned} f(t) &= h(t)S(t) \\ &= \lambda \exp(-\lambda t) \end{aligned}$$

# The Exponential Model, Illustrated



$$\lambda_i = \exp(\mathbf{X}_i\beta).$$

$$S_i(t) = \exp(-e^{\mathbf{X}_i\beta} t).$$

# Exponential (log-)Likelihood

$$\begin{aligned}\ln L &= \sum_{i=1}^N \left\{ C_i \ln \left[ \exp(\mathbf{X}_i \beta) \exp(-e^{\mathbf{X}_i \beta} t) \right] + \right. \\ &\quad \left. (1 - C_i) \ln \left[ \exp(-e^{\mathbf{X}_i \beta} t) \right] \right\} \\ &= \sum_{i=1}^N \left\{ C_i \left[ (\mathbf{X}_i \beta) (-e^{\mathbf{X}_i \beta} t) \right] + (1 - C_i) (-e^{\mathbf{X}_i \beta} t) \right\}\end{aligned}$$

## Exponential: “AFT”

For:

$$\ln T_i = \mathbf{X}_i \gamma + \epsilon_i$$

Means:

$$T_i = \exp(\mathbf{X}_i \gamma) \times u_i$$

$$\epsilon_i = \ln T_i - \mathbf{X}_i \gamma$$

$u_i \sim \text{exponential} \rightarrow \epsilon_i \sim \text{extreme value}$



## Interpretation: Hazard Ratios

$$\text{HR}_k = \frac{\widehat{h(t)|X_k = 1}}{\widehat{h(t)|X_k = 0}}$$

$$h_i(t) = \exp(\beta_0)\exp(\mathbf{X}_i\beta)$$

$$\begin{aligned}\text{HR}_k &= \frac{\widehat{h(t)|X_k = 1}}{\widehat{h(t)|X_k = 0}} \\&= \frac{\exp(\hat{\beta}_0 + X_1\hat{\beta}_1 + \dots + \hat{\beta}_k(1) + \dots)}{\exp(\hat{\beta}_0 + X_1\hat{\beta}_1 + \dots + \hat{\beta}_k(0) + \dots)} \\&= \frac{\exp(\hat{\beta}_k \times 1)}{\exp(\hat{\beta}_k \times 0)} \\&= \exp(\hat{\beta}_k)\end{aligned}$$

$$\begin{aligned}\text{HR}_k &= \frac{\hat{h}(t)|X_k + \delta}{\hat{h}(t)|X_k} \\ &= \exp(\delta \hat{\beta}_k)\end{aligned}$$

$$\text{HR}_{\frac{i}{j}} = \frac{\exp(\mathbf{X}_i \hat{\beta})}{\exp(\mathbf{X}_j \hat{\beta})}$$

# AFT Interpretation: Survival Effects

In:

$$T_i = \exp(\mathbf{X}_i\gamma) \times u_i$$

Note that:

$$E[S(T_i)] = \exp(\mathbf{X}_i\gamma)$$

This means that:

$$\Delta X_k = 1 \longrightarrow 100 \times [1 - \exp(\gamma_k)] \text{ percent change in } E[S(t)]$$

# Example: King et al. (1990) Data

```
> summary(KABL)
```

id	country	durat	ciep12
Min. : 1.00	Min. : 1.000	Min. : 0.50	Min. :0.0000
1st Qu.: 79.25	1st Qu.: 4.000	1st Qu.: 6.00	1st Qu.:1.0000
Median :157.50	Median : 7.000	Median :14.00	Median :1.0000
Mean :157.50	Mean : 7.182	Mean :18.44	Mean :0.8631
3rd Qu.:235.75	3rd Qu.:10.000	3rd Qu.:28.00	3rd Qu.:1.0000
Max. :314.00	Max. :15.000	Max. :59.00	Max. :1.0000

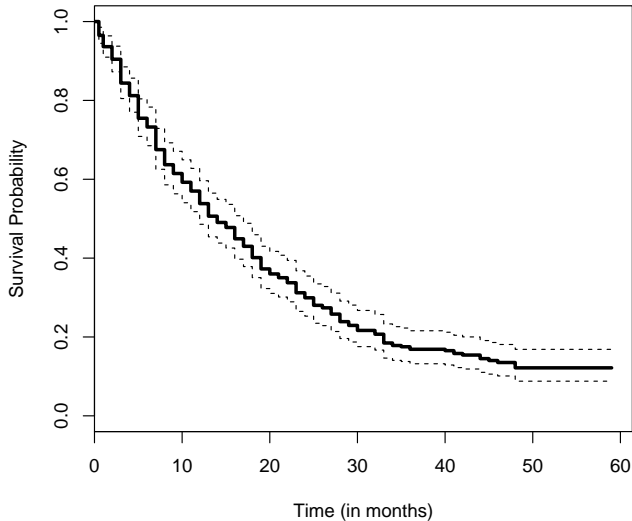
  

fract	polar	format	invest
Min. :349.0	Min. : 0.00	Min. :1.000	Min. :0.0000
1st Qu.:677.0	1st Qu.: 3.00	1st Qu.:1.000	1st Qu.:0.0000
Median :719.0	Median :14.50	Median :1.000	Median :0.0000
Mean :718.8	Mean :15.29	Mean :1.904	Mean :0.4522
3rd Qu.:788.0	3rd Qu.:25.00	3rd Qu.:2.000	3rd Qu.:1.0000
Max. :868.0	Max. :43.00	Max. :8.000	Max. :1.0000

numst2	eltime2	caret2
Min. :0.0000	Min. :0.0000	Min. :0.00000
1st Qu.:0.0000	1st Qu.:0.0000	1st Qu.:0.00000
Median :1.0000	Median :0.0000	Median :0.00000
Mean :0.6306	Mean :0.4873	Mean :0.05414
3rd Qu.:1.0000	3rd Qu.:1.0000	3rd Qu.:0.00000
Max. :1.0000	Max. :1.0000	Max. :1.00000

# Cabinet Durations: Kaplan-Meier



# Exponential Model (AFT form)

```
> KABL.S<-Surv(KABL$durat,KABL$ciep12)
> xvars<-c("fract","polar","format","invest","numst2","eltime2","caretk2")
> MODEL<-as.formula(paste(paste("KABL.S ~ ", paste(xvars,collapse="+"))))
> KABL.exp.AFT<-survreg(MODEL,data=KABL,dist="exponential")
> summary(KABL.exp.AFT)
```

Call:

```
survreg(formula = MODEL, data = KABL, dist = "exponential")
```

	Value	Std. Error	z	p
(Intercept)	3.72460	0.630834	5.90	3.54e-09
fract	-0.00116	0.000905	-1.29	1.98e-01
polar	-0.01610	0.006097	-2.64	8.28e-03
format	-0.09097	0.045544	-2.00	4.58e-02
invest	-0.36937	0.139398	-2.65	8.06e-03
numst2	0.51464	0.129233	3.98	6.83e-05
eltime2	0.72316	0.134999	5.36	8.47e-08
caretk2	-1.30035	0.259566	-5.01	5.45e-07

Scale fixed at 1

Exponential distribution

Loglik(model)= -1025.6    Loglik(intercept only)= -1100.7

Chisq= 150.21 on 7 degrees of freedom, p= 0

Number of Newton-Raphson Iterations: 4

n= 314

# Exponential Model (hazard form)

```
> KABL.exp.PH<-(-KABL.exp.AFT$coefficients)
```

```
> KABL.exp.PH
```

(Intercept)	fract	polar	format	invest
-3.724598700	0.001163784	0.016098468	0.090965318	0.369367997
numst2	eltime2	caretk2		
-0.514643548	-0.723161401	1.300349770		

# Exponential: Hazard Ratios

```
> KABL.exp.HRs<-exp(-KABL.exp.AFT$coefficients)
```

```
> KABL.exp.HRs
```

(Intercept)	fract	polar	format	invest	numst2
0.02412278	1.00116446	1.01622875	1.09523102	1.44681993	0.59771361
eltime2	caretk2				
0.48521587	3.67058030				



# Hazard Ratios: Interpretation

- On average, an investiture requirement *increases* the *hazard* of cabinet failure by  $100 \times (1.447 - 1) = 44.7$  percent.
- On average, an investiture requirement *decreases* the predicted *survival* time by
$$100 \times [1 - \exp(-0.369)] = 100 \times (1 - 0.691)$$
$$= 30.1 \text{ percent.}$$

# Comparing Predicted Survival

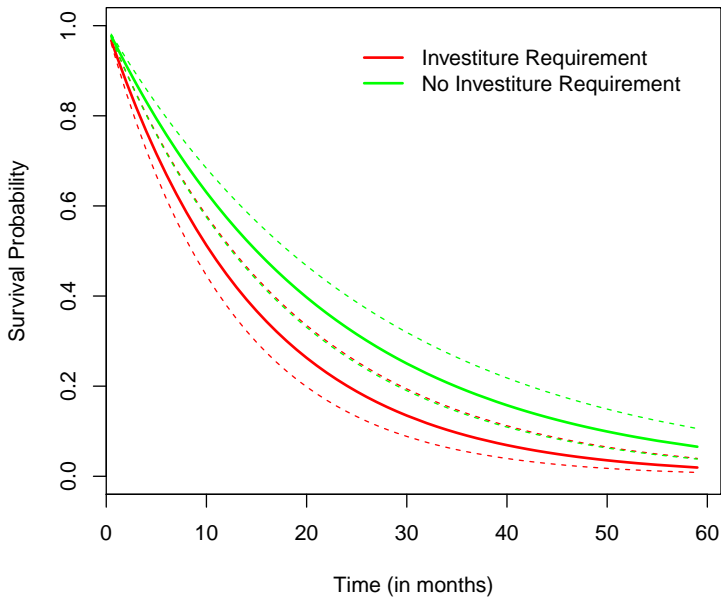
Can use predict, or...

```
KABL.exp<-flexsurvreg(MODEL,data=KABL,dist="exp")

FakeInvest<-t(c(mean(KABL$fract),mean(KABL$polar),mean(KABL$format),1,
               mean(KABL$numst2),mean(KABL$eltime2),mean(KABL$caretk2)))
FakeNoInvest<-t(c(mean(KABL$fract),mean(KABL$polar),mean(KABL$format),0,
                  mean(KABL$numst2),mean(KABL$eltime2),mean(KABL$caretk2)))

plot(KABL.exp,FakeInvest,mark.time=FALSE,col.obs="black",
     lty.obs=c(0,0,0),xlab="Time (in months)",ylab="Survival Probability")
lines(KABL.exp,FakeNoInvest,mark.time=FALSE,col.obs="black",
      lty.obs=c(0,0,0),col=c(rep("green",times=3)))
```

# Comparing Predicted Survival



# The Weibull Model, I

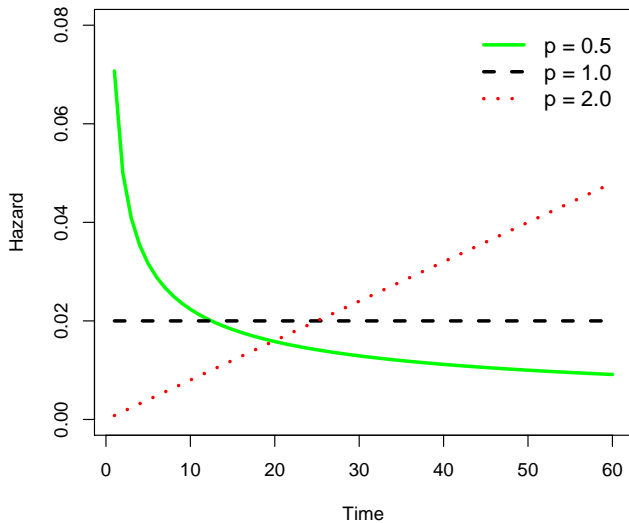
$$h(t) = \lambda p(\lambda t)^{p-1}$$

$$\begin{aligned} S(t) &= \exp \left[ - \int_0^t \lambda p(\lambda t)^{p-1} dt \right] \\ &= \exp(-\lambda t)^p \end{aligned}$$

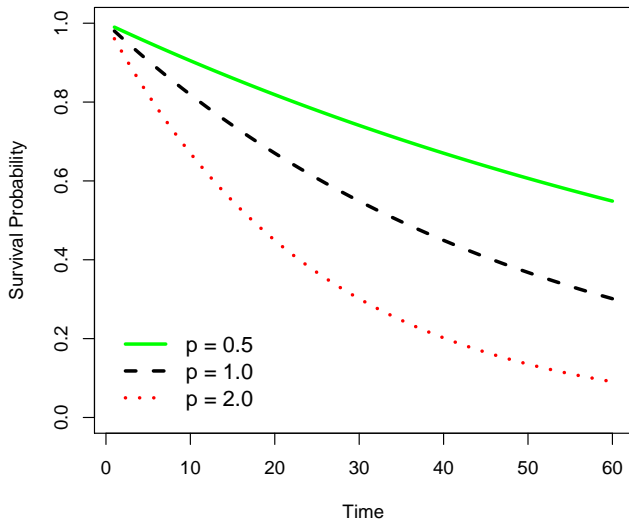
$$f(t) = \lambda p(\lambda t)^{p-1} \times \exp(-\lambda t)^p$$

- $p = 1 \rightarrow$  exponential model
- $p > 1 \rightarrow$  rising hazards
- $0 < p < 1 \rightarrow$  declining hazards

# Weibull Hazards Illustrated



# Weibull Survival



$$\lambda_i = \exp(\mathbf{X}_i\beta)$$



$$T_i = \exp(\mathbf{X}_i\gamma) \times \sigma u_i$$

Means:

$$\rho = 1/\sigma$$

$$\beta = -\gamma/\sigma$$

# Weibull Example (AFT)

```
> KABL.weib.AFT<-survreg(MODEL,data=KABL,dist="weibull")  
> summary(KABL.weib.AFT)
```

Call:

```
survreg(formula = MODEL, data = KABL, dist = "weibull")
```

	Value	Std. Error	z	p
(Intercept)	3.69641	0.491590	7.52	5.51e-14
fract	-0.00106	0.000705	-1.50	1.33e-01
polar	-0.01508	0.004677	-3.22	1.26e-03
format	-0.08675	0.035133	-2.47	1.35e-02
invest	-0.33019	0.106991	-3.09	2.03e-03
numst2	0.46352	0.100367	4.62	3.87e-06
eltime2	0.66381	0.104265	6.37	1.93e-10
caretk2	-1.31758	0.201065	-6.55	5.64e-11
Log(scale)	-0.26079	0.049971	-5.22	1.80e-07

Scale= 0.77

Weibull distribution

Loglik(model)= -1013.5    Loglik(intercept only)= -1100.6

Chisq= 174.23 on 7 degrees of freedom, p= 0

Number of Newton-Raphson Iterations: 5

n= 314

# Weibull Example (hazard)

```
> KABL.weib.PH<-(-KABL.weib.AFT$coefficients)/(KABL.weib.AFT$scale)
```

```
> KABL.weib.PH
```

(Intercept)	fract	polar	format	invest
-4.797770943	0.001374065	0.019573990	0.112598478	0.428574214
numst2	eltime2	caret2		
-0.601628072	-0.861597589	1.710156135		

# Weibull Hazard Ratios

```
> KABL.weib.HRs<-exp(KABL.weib.PH)
```

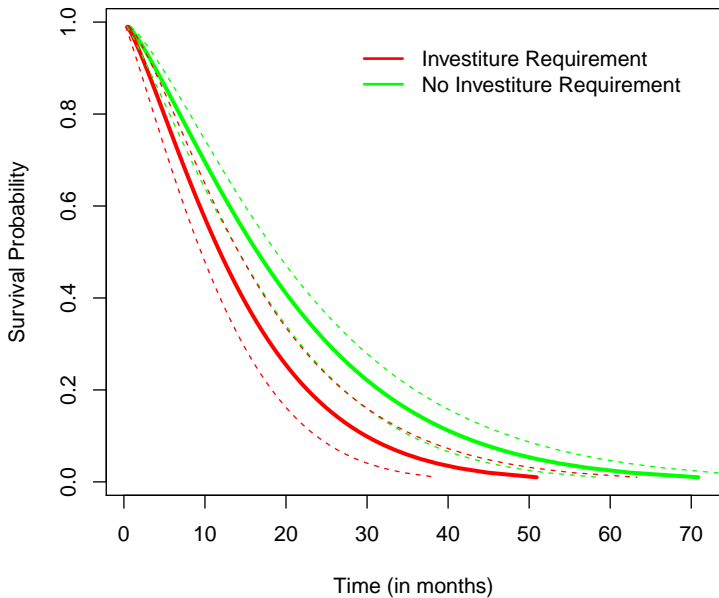
```
> KABL.weib.HRs
```

(Intercept)	fract	polar	format	invest	numst2
0.008248112	1.001375009	1.019766817	1.119182466	1.535067285	0.547918858
eltime2	caretk2				
0.422486583	5.529824807				

Interpretation:

- On average, an investiture requirement *increases* the *hazard* of cabinte failure by  $100 \times (1.535 - 1) = 53.5$  percent.

# Comparing Predicted Survival Curves



# The Gompertz Model (hazard)

$$h(t) = \exp(\lambda) \exp(\gamma t)$$

$$S(t) = \exp \left[ -\frac{e^\lambda}{\gamma} (e^{\gamma t} - 1) \right]$$

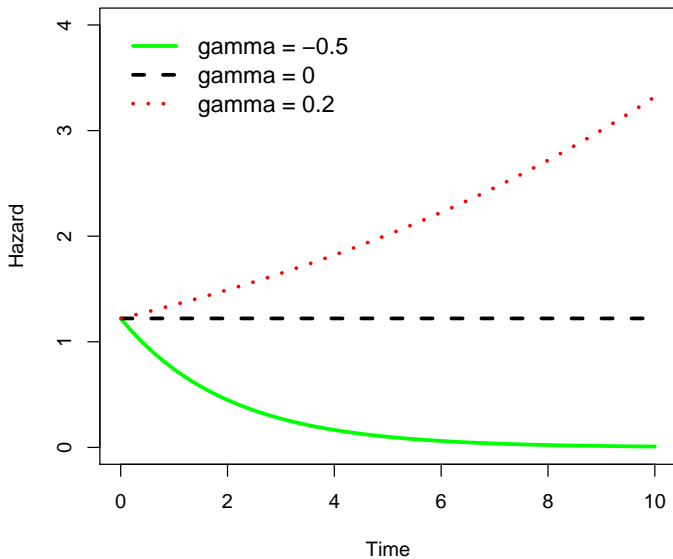
with

$$\lambda_i = \exp(\mathbf{X}_i \beta)$$

$\gamma$  is for “Gompertz”

- $\gamma = 0 \rightarrow$  constant hazard
- $\gamma > 0 \rightarrow$  rising hazard
- $\gamma < 0 \rightarrow$  declining hazard

# Gompertz Hazards





# Gompertz Estimates

```
> library(flexsurv)
> KABL.Gomp<-flexsurvreg(MODEL,data=KABL,dist="gompertz")
> KABL.Gomp
```

```
Call:
flexsurvreg(formula = MODEL, data = KABL, dist = "gompertz")
```

Estimates:

	data	mean	est	L95%	U95%	exp(est)	L95%	U95%
shape		NA	0.02320	0.01150	0.03490	NA	NA	NA
rate		NA	0.01520	0.00407	0.05680	NA	NA	NA
fract	719.00000		0.00140	-0.00039	0.00319	1.00000	1.00000	1.00000
polar	15.30000		0.01890	0.00666	0.03120	1.02000	1.01000	1.03000
format	1.90000		0.10700	0.01590	0.19800	1.11000	1.02000	1.22000
invest	0.45200		0.41200	0.13700	0.68600	1.51000	1.15000	1.99000
numst2	0.63100		-0.60800	-0.86800	-0.34900	0.54400	0.42000	0.70500
eltime2	0.48700		-0.87300	-1.15000	-0.59400	0.41800	0.31600	0.55200
caretk2	0.05410		1.46000	0.94500	1.98000	4.32000	2.57000	7.24000

N = 314, Events: 271, Censored: 43

Total time at risk: 5789.5

Log-likelihood = -1018.317, df = 9

AIC = 2054.634

# The Log-Logistic Model

$$\ln(T_i) = \mathbf{X}_i\beta + \sigma\epsilon_i$$

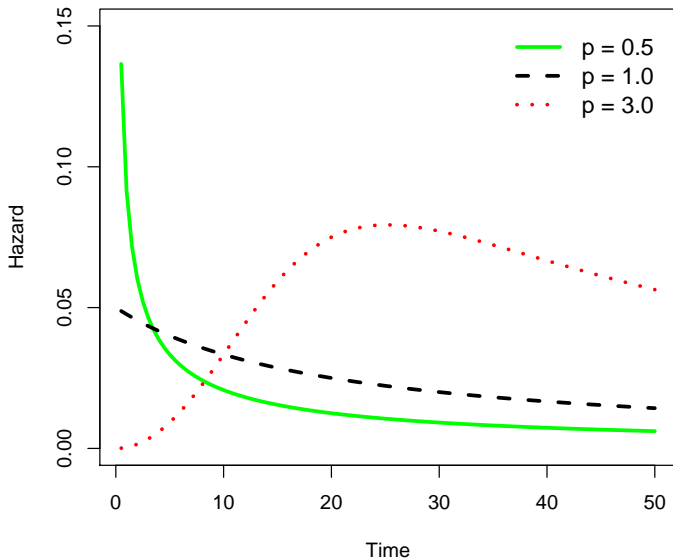
$$S(t) = \frac{1}{1 + (\lambda t)^p}$$

$$h(t) = \frac{\lambda p(\lambda t)^{p-1}}{1 + (\lambda t)^p}$$

$$\begin{aligned} f(t) &= \frac{\lambda p(\lambda t)^{p-1}}{1 + (\lambda t)^p} \times \frac{1}{1 + (\lambda t)^p} \\ &= \frac{\lambda p(\lambda t)^{p-1}}{[1 + (\lambda t)^p]^2} \end{aligned}$$

$$\lambda_i = \exp(\mathbf{X}_i\beta)$$

# Log-Logistics Illustrated



## Example: Log-Logistic

```
> KABL.loglog<-survreg(MODEL,data=KABL,dist="loglogistic")
> summary(KABL.loglog)
```

Call:

```
survreg(formula = MODEL, data = KABL, dist = "loglogistic")
```

	Value	Std. Error	z	p
(Intercept)	3.333841	0.54735	6.09	1.12e-09
fract	-0.000913	0.00079	-1.15	2.48e-01
polar	-0.019092	0.00588	-3.24	1.18e-03
format	-0.096975	0.04315	-2.25	2.46e-02
invest	-0.357403	0.12876	-2.78	5.51e-03
numst2	0.479507	0.12104	3.96	7.45e-05
eltime2	0.627837	0.12405	5.06	4.16e-07
caretk2	-1.252349	0.23151	-5.41	6.32e-08
Log(scale)	-0.568276	0.05116	-11.11	1.14e-28

Scale= 0.567

Log logistic distribution

Loglik(model)= -1024    Loglik(intercept only)= -1099

Chisq= 150.05 on 7 degrees of freedom, p= 0

Number of Newton-Raphson Iterations: 4

n= 314

## Other Parametric Survival Models

- Log-Normal
- Rayleigh (Weibull w/ $p = 2$ )
- Logistic
- $t$
- Generalized Gamma

## R:

- `survreg` (in `survival`)
- `rms` package
- `flexsurv` package
- `eha` package
- `SurvRegCensCov` package (Weibull models)

## Notes on parametric models with time-varying covariate data:

- Stata handles time-varying data with `aplomb`.
- R does not.
  - `survreg` (in the `survival` package) will not estimate models with time-varying data (it will not take a survival object of the form `Surv(start,stop,censor)`).
  - `psm` (in the `rms` package) will also not accept time-varying data.
  - `aftreg` and `phreg` (part of the `eha` package) will accept time-varying data. `phreg` accepts survival objects of the form `Surv(start,stop,censor)`. `aftreg` does as well, and notes in its documentation that “(I)f there are [sic] more than one spell per individual, it is essential to keep spells together by the `id` argument. This allows for time-varying covariates.” In practice, this functions somewhat inconsistently.
- Recommendations: If you want to use R to fit parametric survival models with time-varying covariate data, stick with proportional hazards formulations, and use `phreg`. Also, Weibull models tend to be easier to fit than exponentials in this framework.