GSERM - Oslo 2019
Parametric Survival Models

January 10, 2019 (morning session)

A General Parametric Model

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

get to continuous density with limit to 0

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

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

Likelihood

if Ci is 0, then the left term contributes, otherwise Ci=1 then the right term contributes

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

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

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

The Exponential Model

$$h(t) = \lambda$$

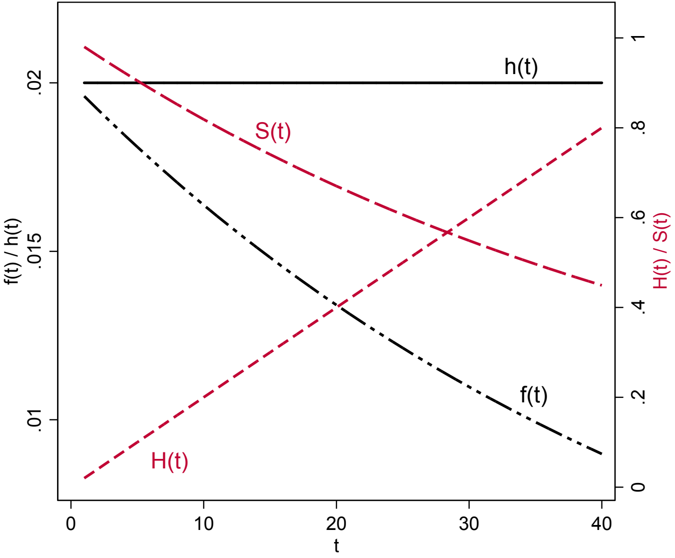
simple naive model makes hazard a constant

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

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

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

The Exponential Model, Illustrated



Covariates

non-negative due to exp

h still flat.

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

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

related to drawing a zero count in Poisson

Exponential (log-)Likelihood

product of survivor and hazard

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

suvivor

"hazard rate form"

Exponential: “AFT”

(accelerated failure time model, alternative way to get exponential form)

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

these covariates do not change the hazard rate, but scale the duration to event (which is mathematically equivalent to changing the hazard)

=> it is the same model.

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

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

Interpretation: Hazard Ratios

identical observations
except for one predictor
X_k

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

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

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

we can get a hazard ratio
(relative risk) for a marginal
change in exactly one
parameter using the
exponential of the predictor

More Generally

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

instead of X_k + 1,we
introduce delta unit change

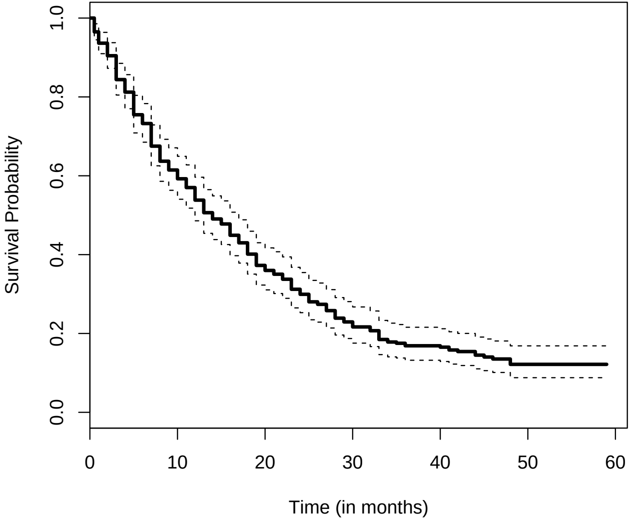
$$\text{HR}_{\frac{i}{j}} = \frac{\exp(\mathbf{X}_i\hat{\beta})}{\exp(\mathbf{X}_j\hat{\beta})}$$

multivariate ratio (more than
one predictor changes)

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          caretk2       
 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
```

it is an AFT model, negative coefficient means decrease of duration to event.

means it is an exponential model

4 is nice and low number

Exponential Model (hazard form)

just take the negatives to get 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

hazard can be
increased by arbitrayr
positive number

- 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
$$\begin{aligned} 100 \times [1 - \exp(-0.369)] &= 100 \times (1 - 0.691) \\ &= 30.1 \text{ percent.} \end{aligned}$$

survival time can only
be decreased by at
max. 100%

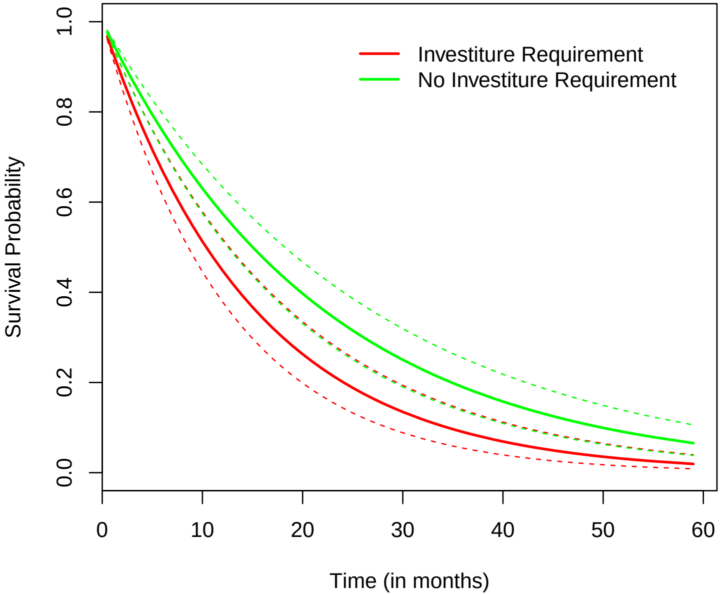
Comparing Predicted Survival

survival function predicted not empirical -- thus continuous, not discrete

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



nice way to present results

The Weibull Model, I

most basic model is constant h, next step, monotic increase/decrease model.

p=1 reverts to the basic exponential model

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

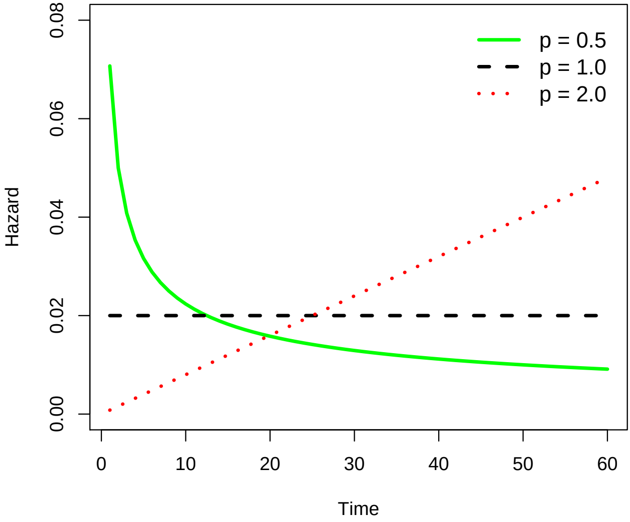
0<p<1 decrease
p>1 increase
p=1 constant

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

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

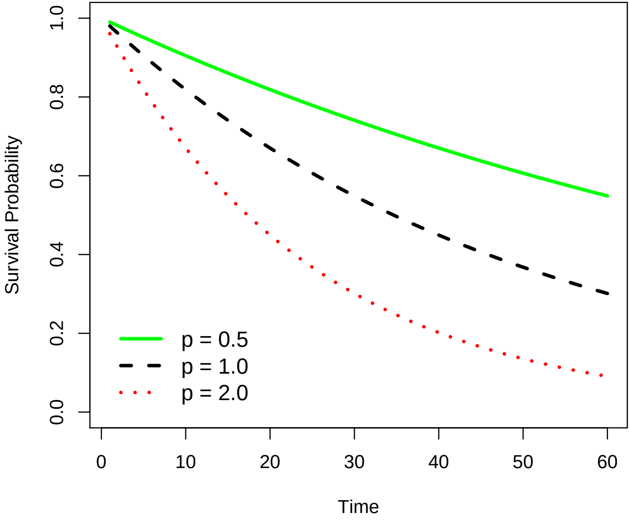
- $p = 1 \rightarrow$ exponential model
- $p > 1 \rightarrow$ rising hazards
- $0 < p < 1 \rightarrow$ declining hazards

Weibull Hazards Illustrated



green =
asymptotic to zero
as it cant be
negative

Weibull Survival



Covariates

covariate proportionally shift the hazard function

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

Weibull: AFT

error is not exponential, it is scaled

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

Means:

$$p = 1/\sigma$$

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

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
```

compared to previous slide, scale := sigma, if scale<1, then p>1 and the other way round.

scale can be substantively interesting as well, e.g p=1 constant, or not constant hazard rate??

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      caretk2
-0.601628072 -0.861597589  1.710156135
```

Weibull Hazard Ratios

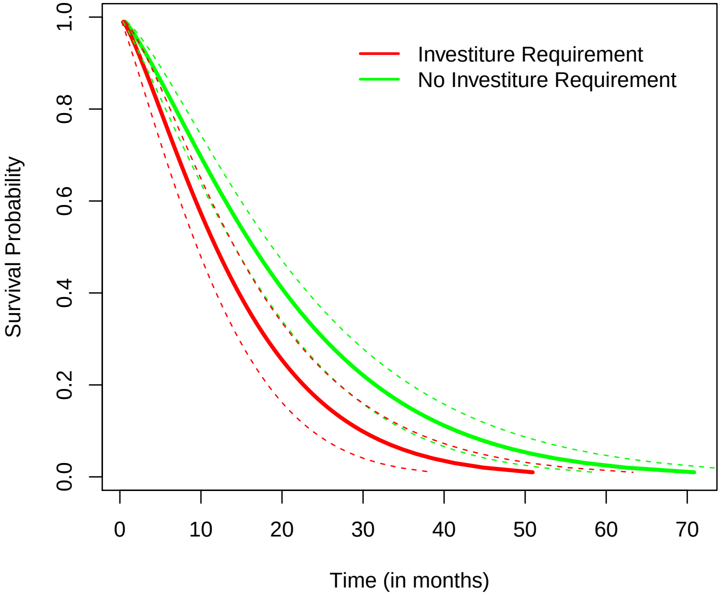
```
> KABL.weib.HRs<-exp(KABL.weib.PH)

> 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.

  typical example for a paper.

Comparing Predicted Survival Curves



The Gompertz Model (hazard)

gamma = 0, constant
gamma < 0, increase
gamma > 0, decrease

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

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

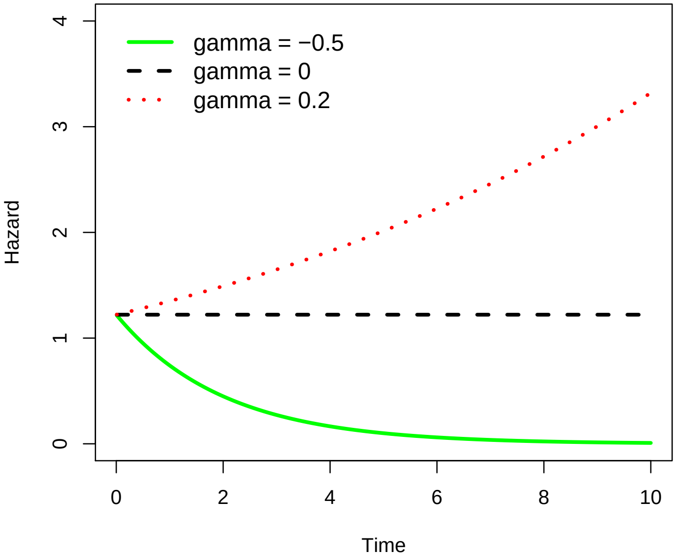
with

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

γ 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

non-monotonic.

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

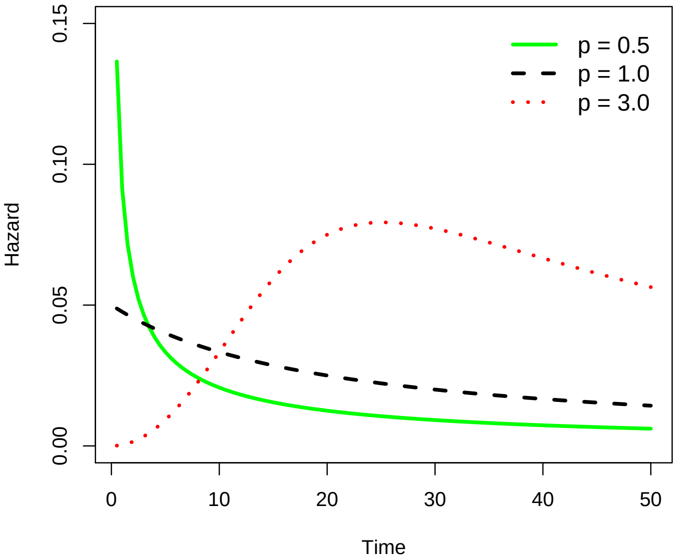
$$S(t) = \frac{1}{1+(\lambda t)^p}$$

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

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

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

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
```

you cannot turn it into a hazard model, because it is not proportional.

purely AFT model

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

3 parameter model

lambda, baseline hazard
p, shape)
3rd parameter, based on gamma distribution

(if 3rd parameter=1, you get a weibull model,
which again can reduce to exponential model)

Software

R:

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

Software

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. works only 50% of times
- 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.