

Bootstrap, Survival Analysis and More

Course evaluation!!!!!!

1. Bootstrap
2. Survival Analysis
 - Kaplan-Meier
 - Cox Proportional Hazards Model
3. Mixed Effects Model
4. Non-linear Effects
 - Polynomial
 - Splines

12.1 Bootstrap

Why?

Sometimes we cannot find the standard error thus the confidence interval of an estimator analytically.

We have learned from the statistics class that

$$\text{Var}(aX + bY) = a^2 \text{Var}(X) + b^2 \text{Var}(Y)$$

However, there are quantities for which we cannot calculate the variance analytically.

Idea

1. Resample from our dataset with replacement for many many many times.
2. Perform the same estimation for each sample.
3. Acquire an empirical confidence interval.

Example 1

In [1]:

```
n <- 10000
x <- rnorm(n, mean = 100, sd = 20)
diff(range(x))
```

150.458173135538

In [2]:

```
boot.iter <- 1000
rangeX <- numeric(boot.iter)

set.seed(613)
for (i in 1:boot.iter) {
  boot.index <- sample(1:n, n, replace = T)
  boot.sample <- x[boot.index]
  rangeX[i] <- diff(range(boot.sample))
}
quantile(x = rangeX, probs = c(0.025,0.5,0.975))
hist(rangeX, breaks = 20)
```

2.5%

138.189652382751

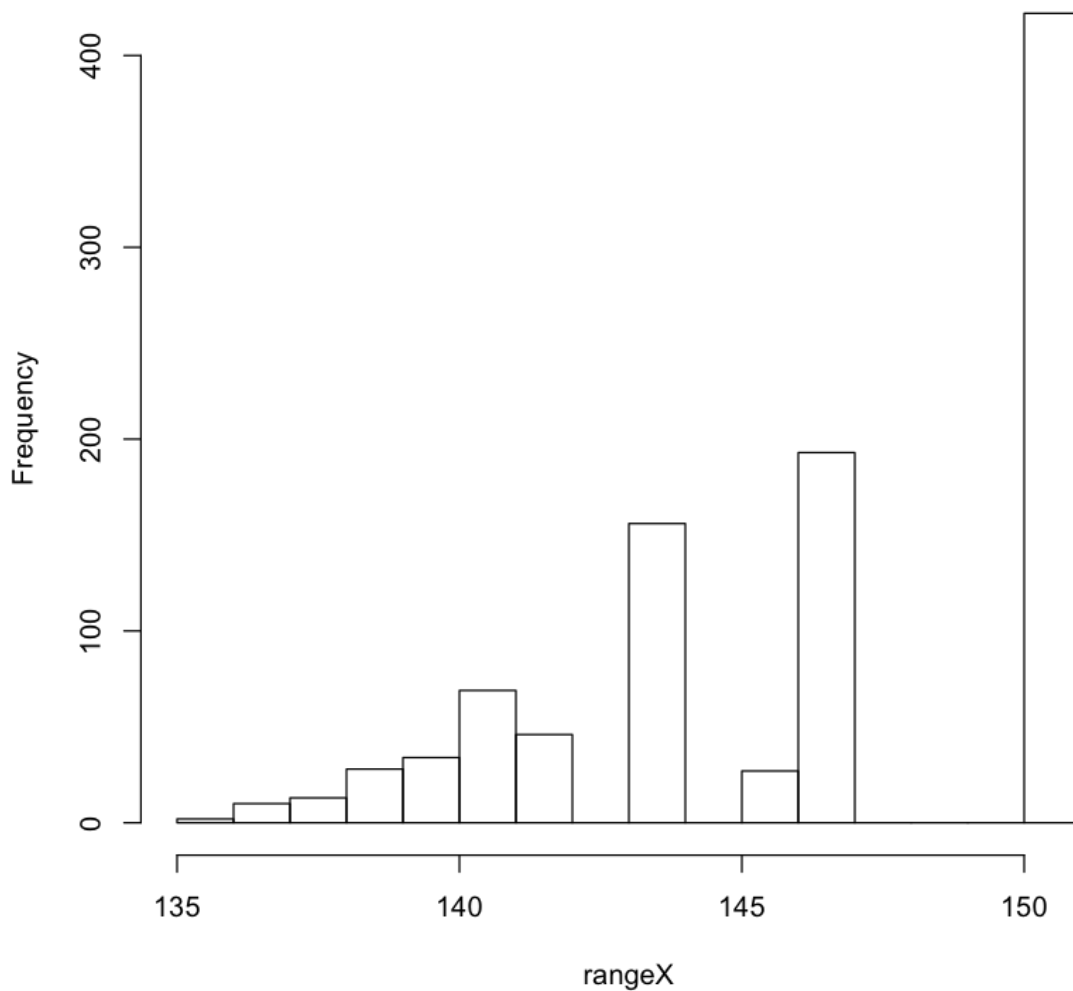
50%

146.713490813787

97.5%

150.458173135538

Histogram of rangeX



Example 2

An example from a bad practice.

Once I came across a paper that calculated the ratio of odds ratios ("ROR") of two binary variables, and claimed that the variable with bigger odds ratio ($\text{ROR} > 1$) had a greater effect.

In [3]:

```
# Illustration of the idea on a different dataset.  
stroke <- read.csv("https://raw.githubusercontent.com/ly129/EPIB  
613_2019/master/stroke.csv")  
head(stroke)
```

A data.frame: 6 × 9

sex	dstr	age	coma	diab	minf	han	dead	obsmonths
<fct>	<fct>	<int>	<fct>	<fct>	<fct>	<fct>	<lgl>	<dbl>
Male	1991-01-02	76	No	No	Yes	No	TRUE	0.16339869
Male	1991-01-03	58	No	No	No	No	FALSE	59.60784314
Male	1991-01-08	74	No	No	Yes	Yes	TRUE	4.73856209
Female	1991-01-11	78	No	Yes	No	Yes	TRUE	0.06535948
Female	1991-01-13	76	No	Yes	No	Yes	FALSE	59.28104575
Male	1991-01-13	48	Yes	No	No	Yes	TRUE	0.10000000

In [4]:

```
fit <- glm(dead~sex+diab+coma+minf, data = stroke, family = binomial())  
exp(coef(fit))
```

(Intercept)

1.24451523693956

sexMale

0.572722712861203

diabYes

1.32594602721775

comaYes

70.2134665384424

minfYes

2.75661076967696

In [5]:

```
# ROR of myocardial infarction vs. diabetes  
ROR_minf_diab <- exp(coef(fit))[5] / exp(coef(fit))[3]  
ROR_minf_diab
```

minfYes: 2.07897660469724

This is in a bad practice statistically...

1. This is simply NOT how statisticians do inference
2. There is no uncertainty (confidence interval).

In [6]:

```
exp(confint(fit))
```

Waiting for profiling to be done...

A matrix: 5 × 2 of type dbl

	2.5 %	97.5 %
(Intercept)	1.0167600	1.525425
sexMale	0.4221004	0.775304
diabYes	0.8414225	2.112287
comaYes	15.4107590	1243.278155
minfYes	1.6799769	4.670801

Let's pretend that the analysis is OK. We still need a confidence interval for this "ROR"...

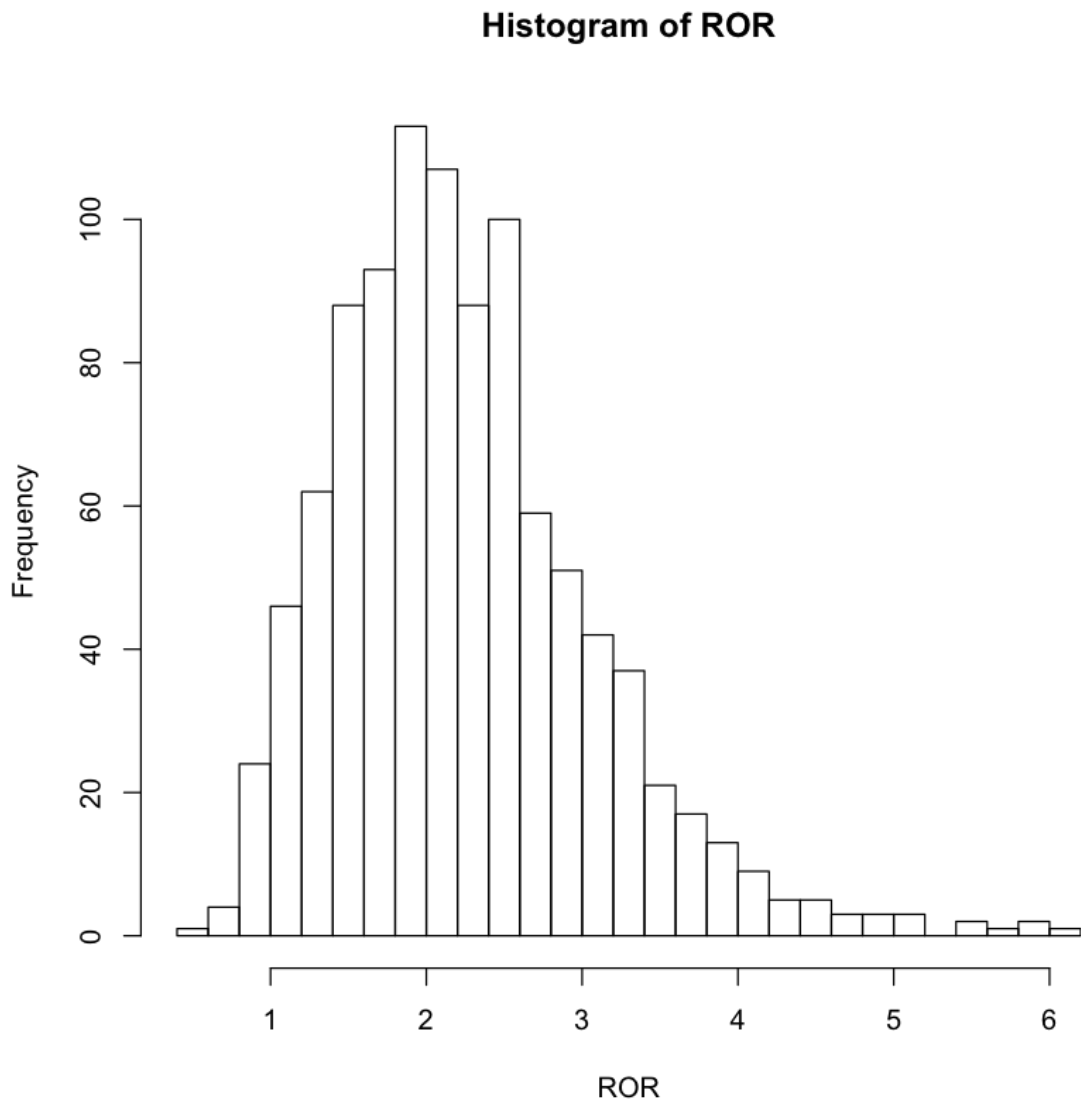
- Statistically intractable.
 - $\text{Var}(X/Y)$ cannot be calculated analytically.
- Solution? Bootstrap!

In [7]:

```
n <- nrow(stroke)
boot.iter <- 1000
ROR <- numeric(boot.iter)

set.seed(613)
for (i in 1:boot.iter) {
  boot.index <- sample(1:n, n, replace = T)
  boot.sample <- stroke[boot.index, ]
  fit <- glm(dead~sex+diab+coma+minf, data = boot.sample, fami
ly = binomial())
  ROR[i] <- exp(coef(fit))[5] / exp(coef(fit))[3]
}
quantile(x = ROR, probs = c(0.025,0.5,0.975))
hist(ROR, breaks = 20)
```

2.5%
0.983909581696174
50%
2.12699557703357
97.5%
4.17774434967227



12.2 Survival Analysis

12.2.1 What is survival analysis

Analysis of time-to-event data

In [8]:

```
library(survival)
# 1=censored, 2=dead
lung <- lung[complete.cases(lung), ]
head(lung)
```

A data.frame: 6 × 10

	inst	time	status	age	sex	ph.ecog	ph.karno	pat.karno	mo
	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	
2	3	455	2	68	1	0	90	90	
4	5	210	2	57	1	1	90	60	
6	12	1022	1	74	1	1	50	80	
7	7	310	2	68	2	2	70	60	
8	11	361	2	71	2	2	60	80	
9	1	218	2	53	1	1	70	80	

In [9]:

```
head(Surv(time = lung$time, event = lung$status))
```

```
[1] 455 210 1022+ 310 361 218
```

12.2.2 Kaplan-Meier Estimator

Non-parametric maximum likelihood estimator

A similar estimator is called the Nelson-Aalen Estimator.

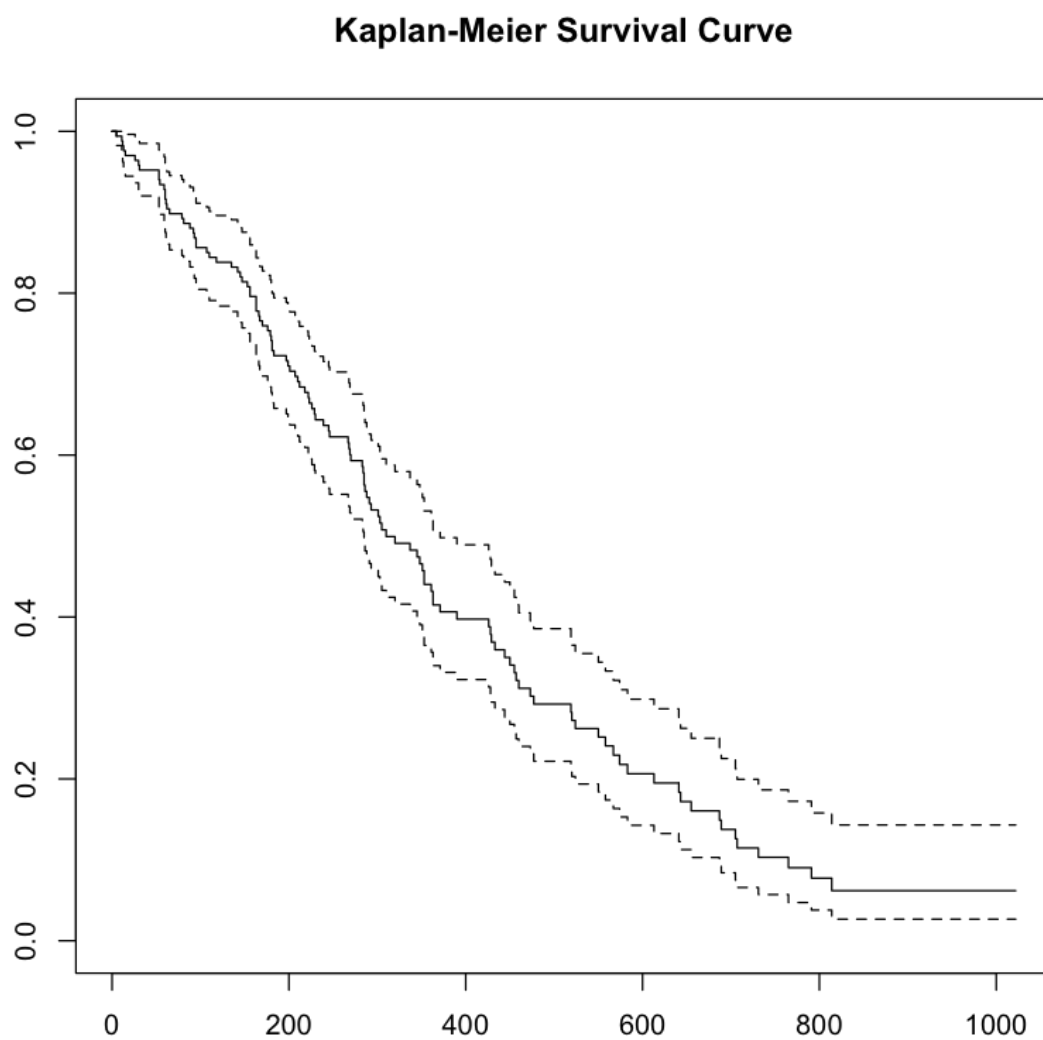
In [10]:

```
km <- survfit(Surv(time, status)~1, conf.int = 0.95, data = lung)
# summary(km)
```



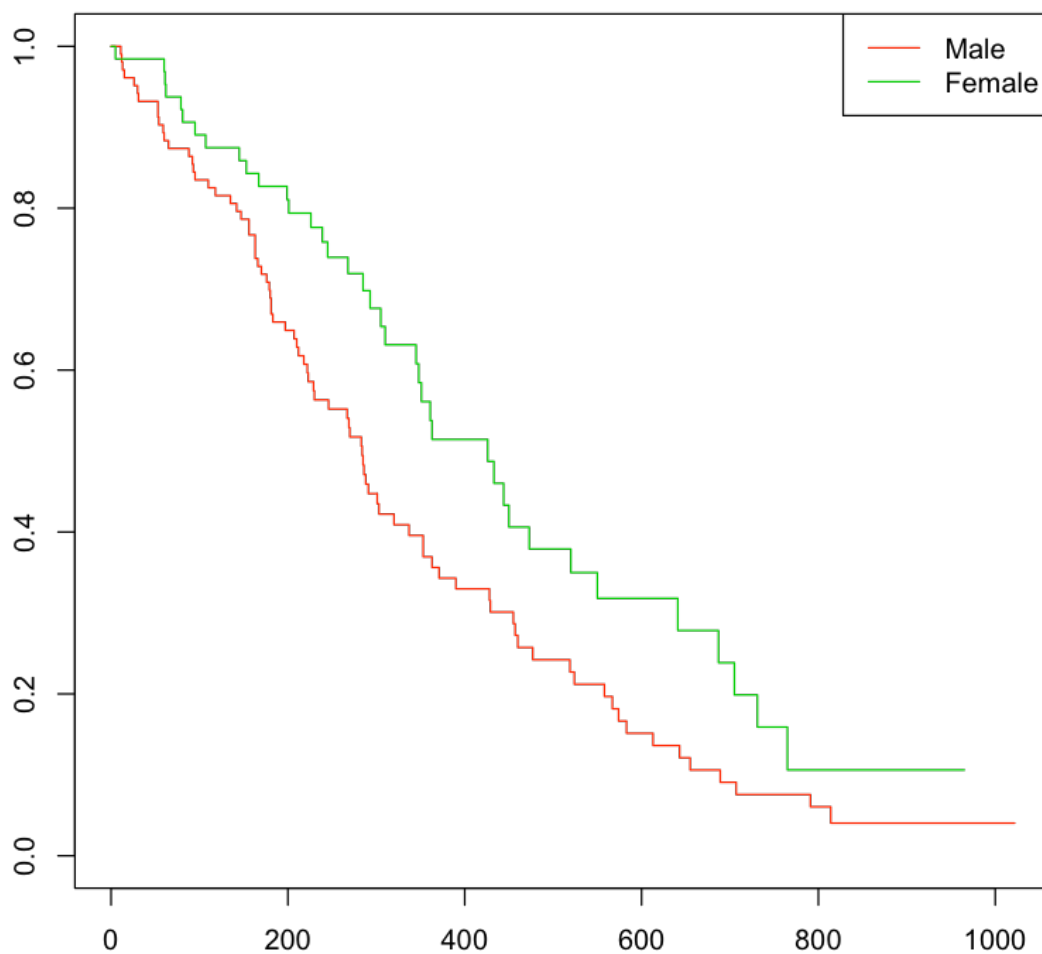
```
In [11]:
```

```
plot(km, conf.int = T, main = "Kaplan-Meier Survival Curve")
```



In [12]:

```
km.sex <- survfit(Surv(time, status)~sex, conf.int = 0.95, data
= lung)
plot(km.sex, col = 2:3)
legend("topright", legend=c("Male", "Female"), col=2:3, lty=c(1,
1))
```

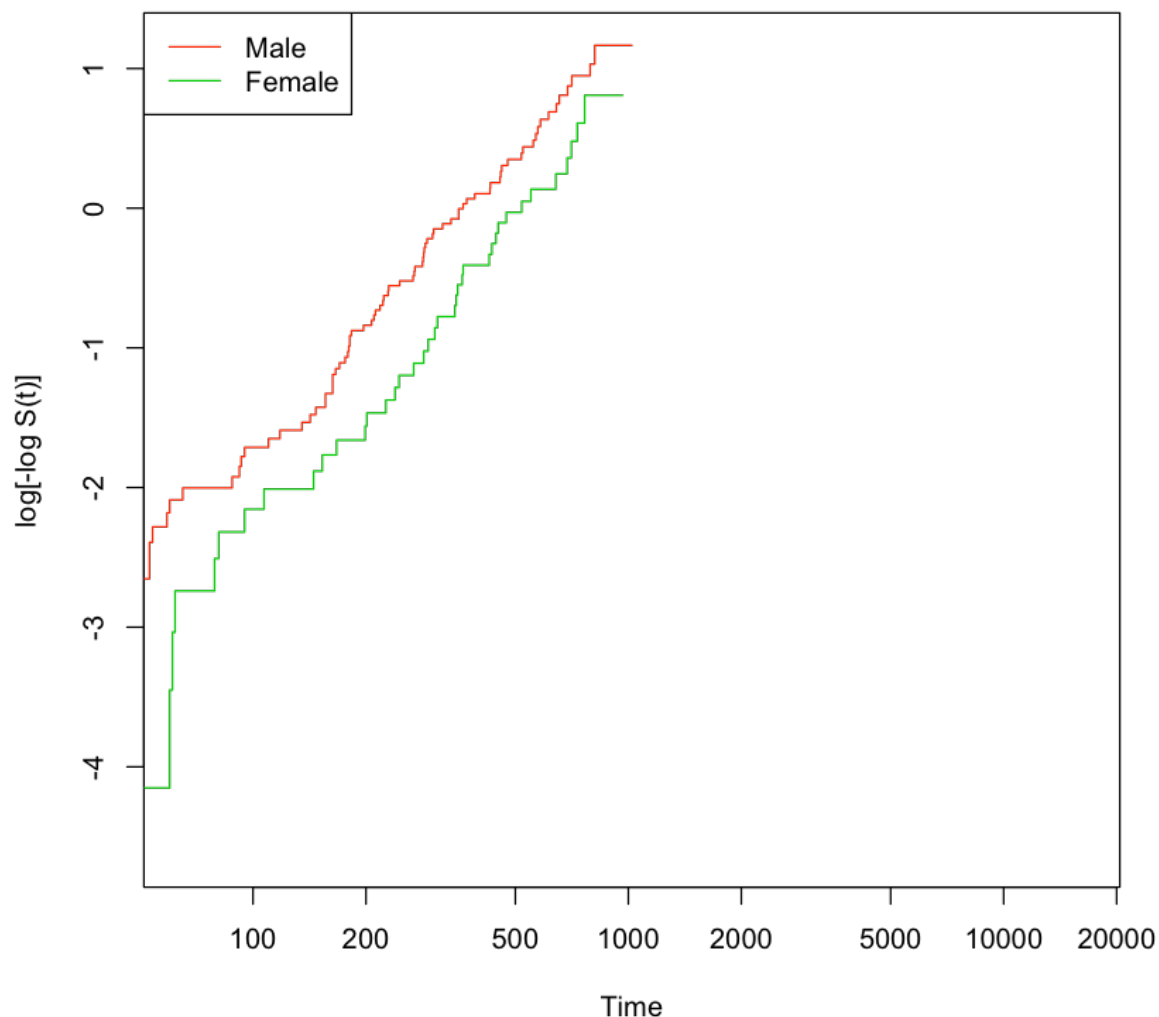


In [13]:

```
# Complementary log-log plot is used to check assumptions visually
# If parallel, proportional hazard assumption holds -> Cox Model (Section 12.2.3)
plot(km.sex, fun = "cloglog", col = 2:3, xlab = "Time", ylab = "log[-log S(t)]",
     main = "Complementary log-log survival plot", log = "x", xlim = 2000)
legend("topleft", legend = c("Male", "Female"), lty = c(1,1), col = 2:3)
```

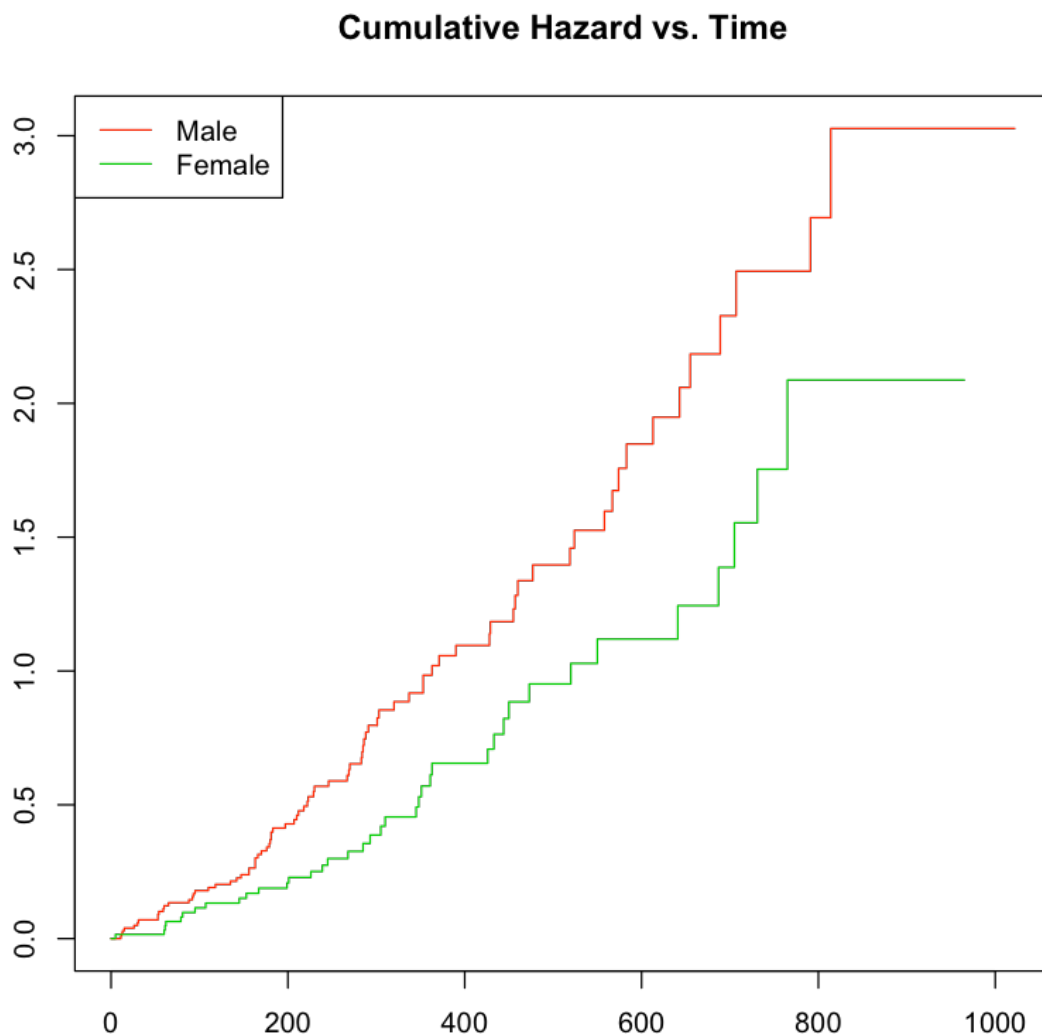
Warning message in xy.coords(x, y, xlabel, ylabel, log):
"1 x value <= 0 omitted from logarithmic plot"

Complementary log-log survival plot



In [14]:

```
# Optional
# Cumulative hazard plot
plot(km.sex, fun = "cumhaz", main="Cumulative Hazard vs. Time",
col = 2:3)
legend("topleft", legend = c("Male", "Female"), lty = c(1,1), co
l = 2:3)
```



Log-rank test

A χ^2 test for inference - does sex affect survival?

In [15]:

```
survdifff(Surv(time, status)~sex, data = lung)
```

Call:

```
survdifff(formula = Surv(time, status) ~ sex, data =  
lung)
```

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
sex=1	103	82	68.7	2.57	6.05
sex=2	64	38	51.3	3.44	6.05

Chisq= 6 on 1 degrees of freedom, p= 0.01

How do we check the effect of multiple categorical variables? Continuous variables?

12.2.3 Cox Proportional Hazards Model

The model

$$h(t) = h_0(t) \cdot \exp(\beta_1 x_1 + \beta_2 x_2 + \dots)$$

Semi-parametric

$h_0(t)$ is an non-parametric baseline hazard

$h(t)$ is the actual hazard given covariates, modeled parametrically by $\beta^\top \mathbf{x}$

Proportional

Under the model setup, the model assumes that $h(t)$ is proportional to $h_0(t)$ for every covariate. Why?

In [16]:

```
fit.cox1 <- coxph(Surv(time,status)~sex, data = lung)
summary(fit.cox1)
```

Call:

```
coxph(formula = Surv(time, status) ~ sex, data = lung)
```

n= 167, number of events= 120

```
      coef exp(coef) se(coef)      z Pr(>|z|)
sex -0.4792    0.6193   0.1966 -2.437   0.0148 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.'
0.1 ' ' 1
```

```
      exp(coef) exp(-coef) lower .95 upper .95
sex    0.6193      1.615    0.4212    0.9104
```

Concordance= 0.567 (se = 0.025)

Likelihood ratio test= 6.25 on 1 df, p=0.01

Wald test = 5.94 on 1 df, p=0.01

Score (logrank) test = 6.05 on 1 df, p=0.01

In [17]:

```
# Multiple Cox regression
fit.cox2 <- coxph(Surv(time,status)~., data = lung)
summary(fit.cox2)
```

```

Call:
coxph(formula = Surv(time, status) ~ ., data = lung)

n= 167, number of events= 120

              coef  exp(coef)    se(coef)      z Pr
(>|z|)
inst      -3.037e-02  9.701e-01  1.312e-02 -2.315 0.
020619 *
age       1.281e-02  1.013e+00  1.194e-02  1.073 0.
283403
sex      -5.666e-01  5.674e-01  2.014e-01 -2.814 0.
004890 **
ph.ecog   9.074e-01  2.478e+00  2.386e-01  3.803 0.
000143 ***
ph.karno  2.658e-02  1.027e+00  1.163e-02  2.286 0.
022231 *
pat.karno -1.091e-02  9.891e-01  8.141e-03 -1.340 0.
180160
meal.cal  2.602e-06  1.000e+00  2.677e-04  0.010 0.
992244
wt.loss   -1.671e-02  9.834e-01  7.911e-03 -2.112 0.
034647 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.'
0.1 ' ' 1

```

	exp(coef)	exp(-coef)	lower .95	upper .95
inst	0.9701	1.0308	0.9455	0.9954
age	1.0129	0.9873	0.9895	1.0369
sex	0.5674	1.7623	0.3824	0.8420
ph.ecog	2.4778	0.4036	1.5523	3.9552
ph.karno	1.0269	0.9738	1.0038	1.0506
pat.karno	0.9891	1.0110	0.9735	1.0051
meal.cal	1.0000	1.0000	0.9995	1.0005
wt.loss	0.9834	1.0169	0.9683	0.9988

```

Concordance= 0.648 (se = 0.03 )
Likelihood ratio test= 33.7 on 8 df, p=5e-05
Wald test              = 31.72 on 8 df, p=1e-04
Score (logrank) test = 32.51 on 8 df, p=8e-05

```

In [18]:

```
fit.cox3 <- coxph(Surv(time,status)~inst+sex+ph.ecog+ph.karno+wt
.loss, data = lung)
```

In [19]:

```
# Model Comparison
print(anova(fit.cox1, fit.cox3))
# So here the full model has significantly better likelihood.
# Therefore, reject the reduced model.
```

Analysis of Deviance Table

Cox model: response is Surv(time, status)

Model 1: ~ sex

Model 2: ~ inst + sex + ph.ecog + ph.karno + wt.loss

s

	loglik	Chisq	Df	P(> Chi)
1	-504.99			
2	-492.90	24.194	4	7.302e-05 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.'
0.1 ' ' 1

Check for proportional hazard assumption

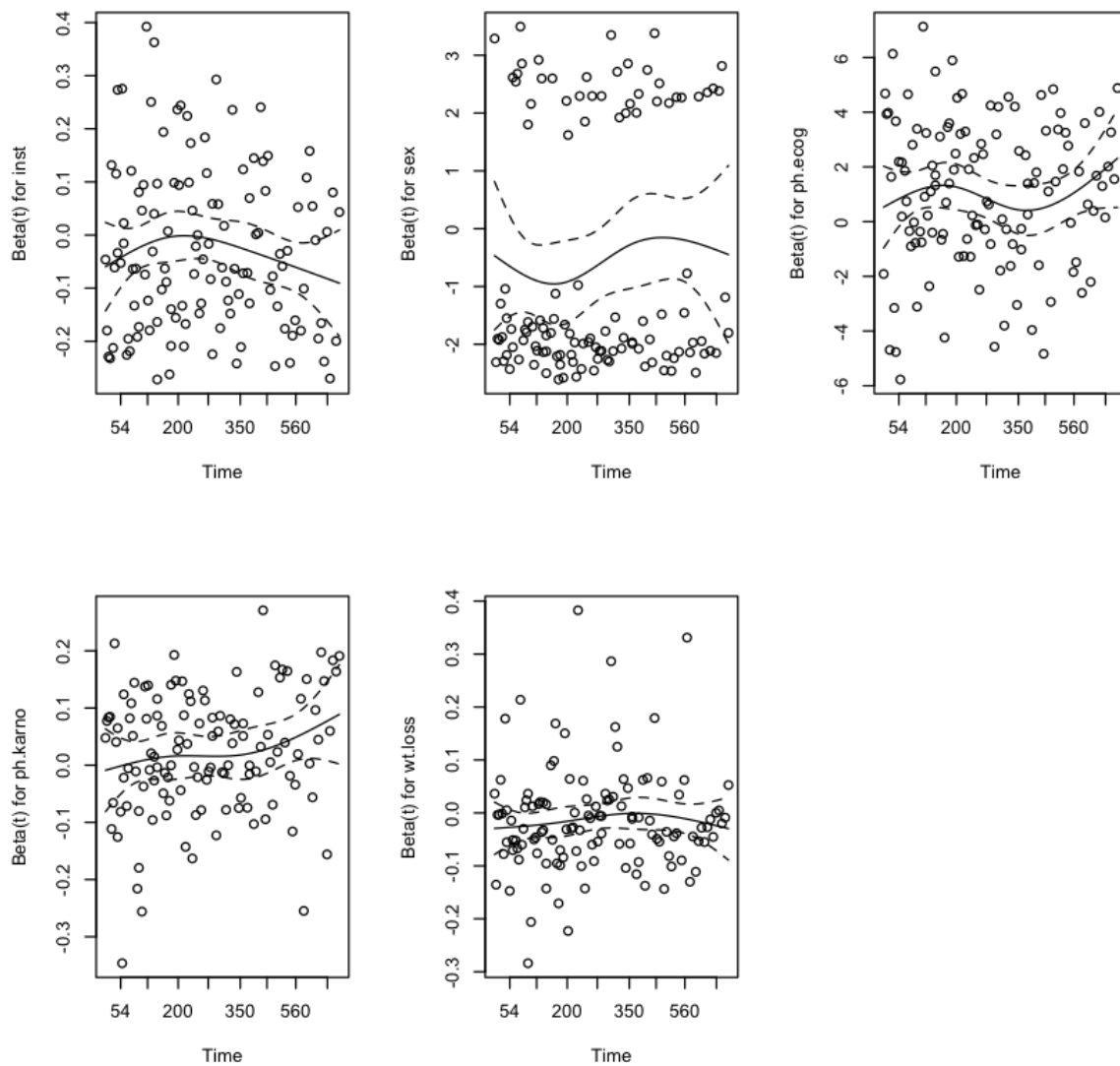
In [20]:

```
cox.zph(fit.cox3)
```

	rho	chisq	p
inst	-0.0831	0.9720	0.3242
sex	0.0993	1.1098	0.2921
ph.ecog	0.0263	0.0926	0.7609
ph.karno	0.1818	3.0106	0.0827
wt.loss	0.0503	0.4122	0.5208
GLOBAL	NA	7.7289	0.1718

In [21]:

```
par(mfrow = c(2,3))  
plot(cox.zph(fit.cox3))
```



12.3 Mixed Effects Model

- Mixture of fixed effects and random effects.
- Used for correlated data, such as longitudinal data

CD4 example - the gold standard teaching data for longitudinal analysis

In [22]:

```
cd4 <- read.table("https://raw.githubusercontent.com/ly129/EPIB6
13_2019/master/cd4.txt", header = TRUE)
cd4$Date <- as.Date(cd4$Date, tryFormats = "%m/%d/%Y")
cd4$Treatment <- cd4$Treatment - 1
head(cd4, 10)
```

A data.frame: 10 × 8

Visit	ID	Date	CD4Pct	ARV	VisAge	Treatment	BaseAge
<int>	<int>	<date>	<dbl>	<int>	<dbl>	<dbl>	<dbl>
1	1	1988-06-29	18.0	0	3.910000	0	3.910000
4	1	1989-01-19	37.0	0	4.468333	0	3.910000
7	1	1989-04-13	13.0	0	4.698333	0	3.910000
13	1	1989-11-30	13.0	0	5.330833	0	3.910000
19	1	1990-06-07	12.0	1	5.848333	0	3.910000
1	2	1988-05-04	1.0	0	3.565000	1	3.565000
4	2	1988-07-21	0.3	0	3.778333	1	3.565000
1	3	1988-05-26	28.0	0	6.124167	0	6.124167
4	3	1988-08-18	28.0	0	6.354167	0	6.124167
7	3	1988-11-10	33.0	0	6.584167	0	6.124167

In [23]:

```
# Total observations  
dim(cd4)
```

1075 8

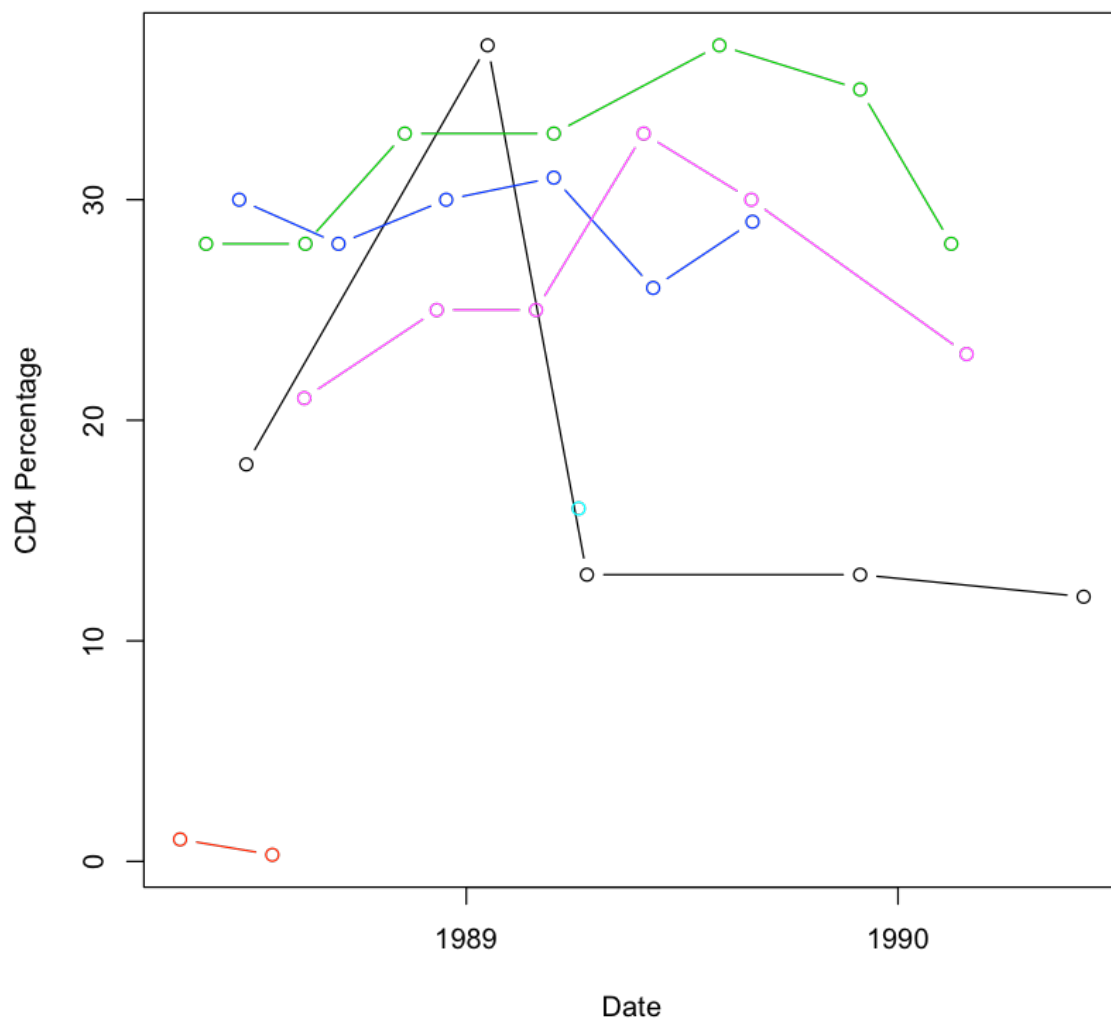
In [24]:

```
# Total patients  
length(unique(cd4$ID))
```

251

In [25]:

```
plot(y = cd4[cd4$ID == 1,]$CD4Pct,  
     x = cd4[cd4$ID == 1,]$Date,  
     type = 'b', xlab = "Date", ylab = "CD4 Percentage", col = 1  
,  
     ylim = range(cd4$CD4Pct[1:27]),  
     xlim = range(cd4$Date[1:27]))  
for (i in 2:6) {  
  lines(y = cd4[cd4$ID == i,]$CD4Pct,  
        x = cd4[cd4$ID == i,]$Date,  
        col = i, type = "b")  
}
```



Everyone should be allowed to have a different intercept and/or slope

Package **lme4**

In [26]:

```
library(lme4)
```

Loading required package: Matrix

In [27]:

```
# Random intercept model  
# We can see that the syntax is exactly the same as in lm()  
fit1 <- lmer(formula = CD4Pct~Date+BaseAge+Treatment+(1|ID), data = cd4)  
summary(fit1)
```

Linear mixed model fit by REML ['lmerMod']

Formula: CD4Pct ~ Date + BaseAge + Treatment + (1 | ID)

Data: cd4

REML criterion at convergence: 7915.1

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-4.4870	-0.4510	-0.0496	0.3666	6.6900

Random effects:

Groups	Name	Variance	Std.Dev.
ID	(Intercept)	131.10	11.450
Residual		53.42	7.309

Number of obs: 1075, groups: ID, 251

Fixed effects:

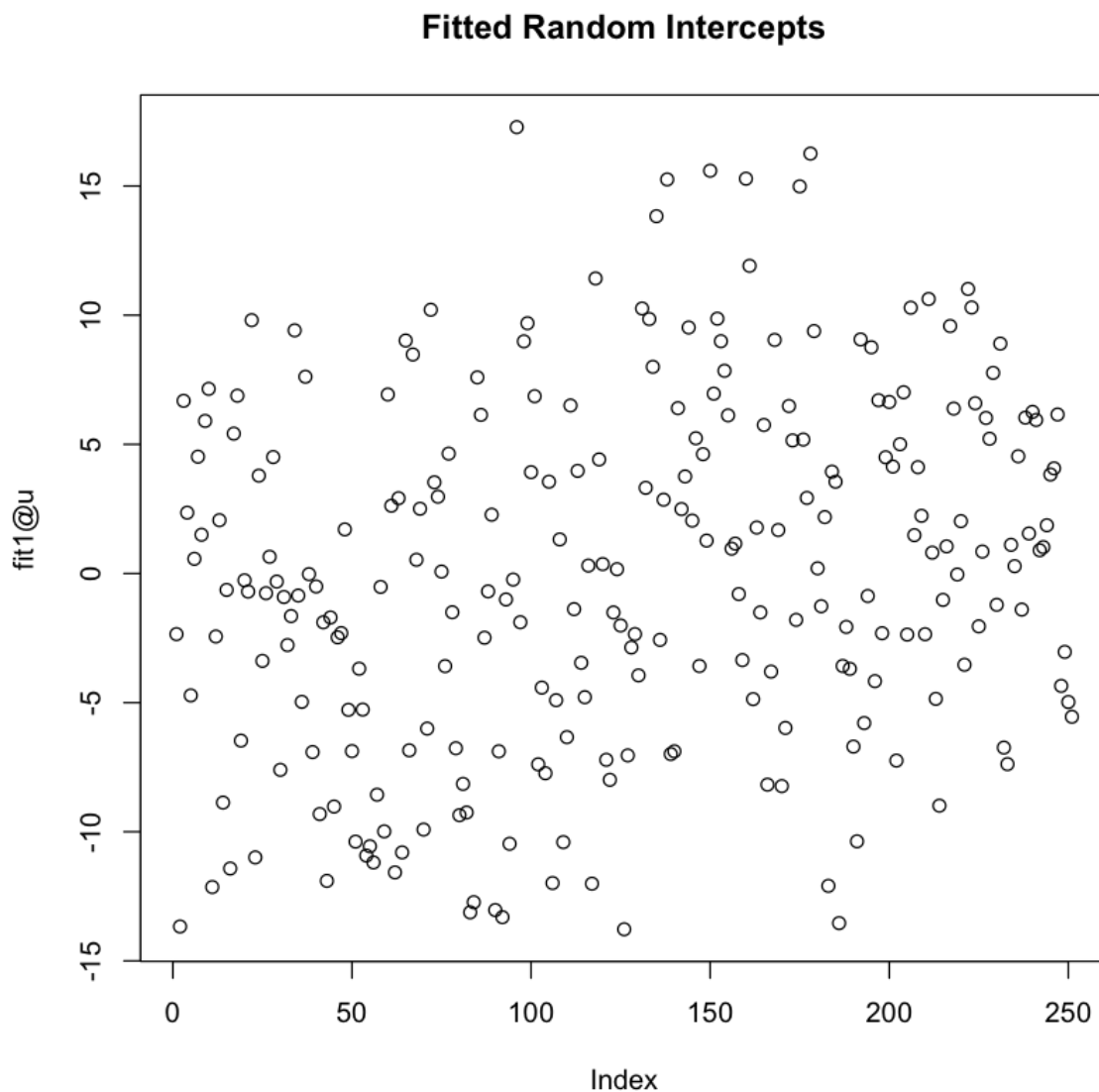
	Estimate	Std. Error	t value
(Intercept)	68.535122	9.556754	7.171
Date	-0.005890	0.001319	-4.466
BaseAge	-1.061973	0.331756	-3.201
Treatment	1.352614	1.537374	0.880

Correlation of Fixed Effects:

	(Intr)	Date	BaseAg
Date	-0.986		
BaseAge	-0.130	0.009	
Treatment	-0.083	0.006	0.009

In [28]:

```
plot(fit1@u, main = "Fitted Random Intercepts")
```



In [29]:

```
# Random intercept + random slope for treatment  
# We can see that the syntax is exactly the same as in glm()  
fit2 <- lmer(formula = CD4Pct~Date+BaseAge+Treatment+(1+Treatment  
t|ID),REML = T, data = cd4)  
summary(fit2)
```

Linear mixed model fit by REML ['lmerMod']
Formula: CD4Pct ~ Date + BaseAge + Treatment + (1 +
Treatment | ID)
Data: cd4

REML criterion at convergence: 7914.7

Scaled residuals:

Min	1Q	Median	3Q	Max
-4.4934	-0.4554	-0.0521	0.3618	6.6931

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
ID	(Intercept)	138.67	11.776	
	Treatment	35.03	5.919	-0.37
Residual		53.44	7.310	

Number of obs: 1075, groups: ID, 251

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	68.287943	9.560849	7.142
Date	-0.005846	0.001319	-4.433
BaseAge	-1.080000	0.332418	-3.249
Treatment	1.362088	1.532521	0.889

Correlation of Fixed Effects:

	(Intr)	Date	BaseAg
Date	-0.986		
BaseAge	-0.131	0.010	
Treatment	-0.087	0.006	0.008

In [30]:

```
# lme4 package also has generalized linear mixed effects model  
# We can see that the syntax is exactly the same as in glm()  
  
glmer(formula = Treatment~BaseAge+ARV+(1|ID), family = binomial(  
) , data = cd4)
```

Generalized linear mixed model fit by maximum likelihood (Laplace

```
Approximation) [glmerMod]  
Family: binomial ( logit )  
Formula: Treatment ~ BaseAge + ARV + (1 | ID)  
Data: cd4  
  
      AIC      BIC    logLik deviance df.resid  
387.3881 407.3084 -189.6941  379.3881     1071  
Random effects:  
Groups Name      Std.Dev.  
ID      (Intercept) 55.83  
Number of obs: 1075, groups: ID, 251  
Fixed Effects:  
(Intercept)      BaseAge      ARV  
-12.07261      -0.04340      0.03993
```

In [31]:

```
# # Another package is nlme  
library(nlme)  
fit.intercept <- lme(fixed = CD4Pct~Date+BaseAge+Treatment, random = ~1|ID, data = cd4)  
fit.intercept.slope <- lme(fixed = CD4Pct~Date+BaseAge+Treatment, random = ~1+Treatment|ID, data = cd4)
```

Attaching package: 'nlme'

The following object is masked from 'package:lme4':

lmList

12.4 Non-linear Effects

Effects of some variables are not linear, e.g. BMI

12.4.1 Polynomial regression

In [32]:

```
set.seed(613)
x <- sort(runif(100, -10, 10))
y <- x^2 + rnorm(100, 0, 5)
plot(function(a){a^2}, xlim = c(-10, 10), lwd = 3, col = "red", y
lim = c(-10, 110))
points(x = x, y = y)

xy <- data.frame(x = x, y = y)
xy$x.square <- x^2

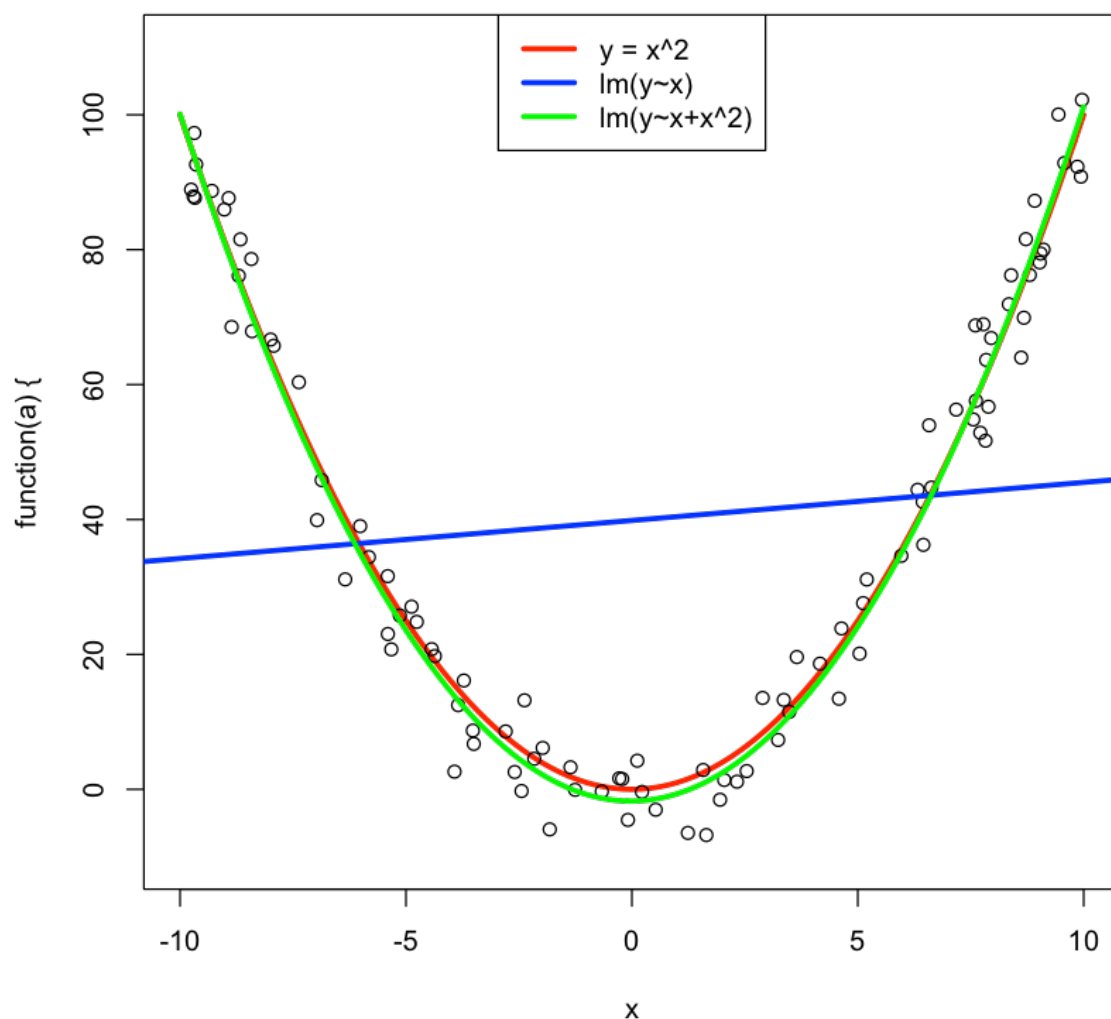
fit1 <- lm(y~x, data = xy); abline(fit1, col = "blue", lwd = 3)
fit2 <- lm(y~x+x.square, data = xy)
xx <- seq(-10, 10, by = 0.1)
fit2
yy <- predict(fit2, newdata = data.frame(x = xx, x.square = xx^2
))
lines(x = xx, y = yy, col = "green", lwd = 3)
legend("top", legend = c("y = x^2", "lm(y~x)", "lm(y~x+x^2)"),
      lty = 1, col = c("red", "blue", "green"), lwd = c(3, 3, 3))
```

Call:

```
lm(formula = y ~ x + x.square, data = xy)
```

Coefficients:

(Intercept)	x	x.square
-1.74201	0.05324	1.02386



12.4.2 Splines

Package **splines**

Most commonly used one is cubic B-splines

Instead of modeling $y \sim x$, we model $y \sim f(x)$, where $f(x)$ is a non-linear function of x .

In [33]:

```
library(splines)
```

In [34]:

```
# 5 knots  
head(bs(x, knots = 5))
```

A matrix: 6 × 4 of type dbl

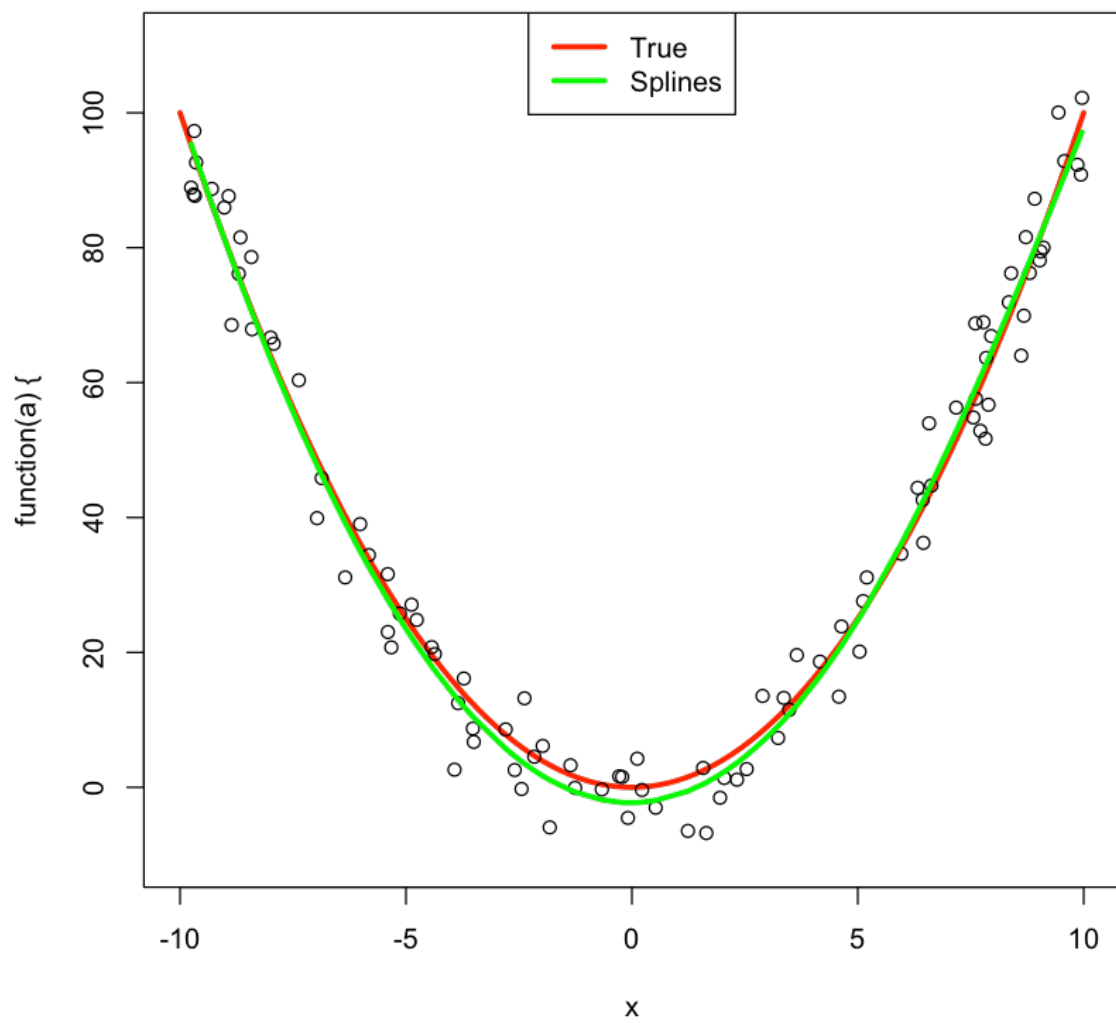
	1	2	3	4
0.00000000	0.000000e+00	0.000000e+00	0	
0.01121977	3.171728e-05	2.987783e-08	0	
0.01391820	4.892770e-05	5.731049e-08	0	
0.01654736	6.932391e-05	9.676367e-08	0	
0.02206406	1.238758e-04	2.316823e-07	0	
0.08836770	2.118711e-03	1.688753e-05	0	

In [35]:

```
fit.splines <- lm(y~bs(x, knots = 5))
```

In [36]:

```
plot(function(a){a^2}, xlim = c(-10,10), lwd = 3, col = "red",  
      ylim = c(-10, 110))  
points(x = x, y = y)  
lines(x, y = predict(fit.splines, newdata = bs(x, knots = 5)), c  
ol = "green", lwd = 3)  
legend("top", legend = c("True", "Splines"), lwd = c(3,3), lty =  
c(1,1), col = c("red", "green"))
```



In []: