

**2025**

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## **Table of contents**

2025 PDC .

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**1**

2 1.

## 2.1

## 3 2.

### 3.1

( : , , ) ( : ) . ,

(Bradford Hill) , (Biological Gradient)' .

1 .

\_\_\_\_\_

\_\_\_\_\_

Strength of association

Consistency

Specificity

Temporality

- Dose-response

Plausibility

Coherence

Experiment

Analogy

\_\_\_\_\_

, . , .

### 3.2

- (Linear Relationship): , 2 2 .
- (Non-linear Relationships): - .

- (Threshold Effects): ( ) , .
  - (Saturation Effects): .
  - U J (U-shaped or J-shaped Relationships): U , . J , .
- U ( : , , ) , , , U , J .

2

/

(Linear)

( ) ,

( ) ,

(Threshold)

(Saturation)

U , , A

(U-shaped)

J ,

(J-shaped)

## 4 3.

### 4.1 : ,

(Exposure) (Dose) (dose)  
, (Absorption), (Distribution), (Metabolism), (Elimination) (ADME)

.  
- , . ' ' ' ' ,  
, ( , ) , , ,  
, (biomarker) .

### 4.2 :

(Gaussian distribution) . “ (skewed to the  
right)” .10 0 , .  
) , , (mixed models) .

### 4.3 :

, (Censoring) (Survival Analysis)  
(Right Censoring) ( : )  
, (non-informative) , Kaplan-Meier

- : ,
- : ,



, , ,  
 , (Competing Risks)  
 , , ,  
 , , , Kaplan-Meier  
 (Cumulative Incidence Function, CIF) (cause-specific hazard function),  
 (subdistribution hazard function)  
 :  
 , (Information Bias) , (Detection Bias)  
 .18  
 , (Healthy Worker Effect) (Selection Bias) .3  
 , .18  
 .18  
 , (Ascertainment Bias) (Sampling Bias)  
 .14 , ( , )  
 , ( )  
 - ( : , (SMR) ) .18 ,  
 :  
 “ 3 ( ) .21 (Confounding) 3 (Effect Modification) .20  
 , “ ”  
 , , , ( : , ) (Precision Epidemiology)  
 ,  
 (product terms) , (stratification) .4 ,  
 ( : ) , (Odds Ratio, OR) OR  
 (Relative Risk, RR) (Biological Plausibility) -

# 5

## 5.1 Exposure (Dose) and Health

```
if(!require(tidyverse)) install.packages("tidyverse")
if(!require(ggplot2)) install.packages("ggplot2")
if(!require(knitr)) install.packages("knitr")
if(!require(kableExtra)) install.packages("kableExtra")
```

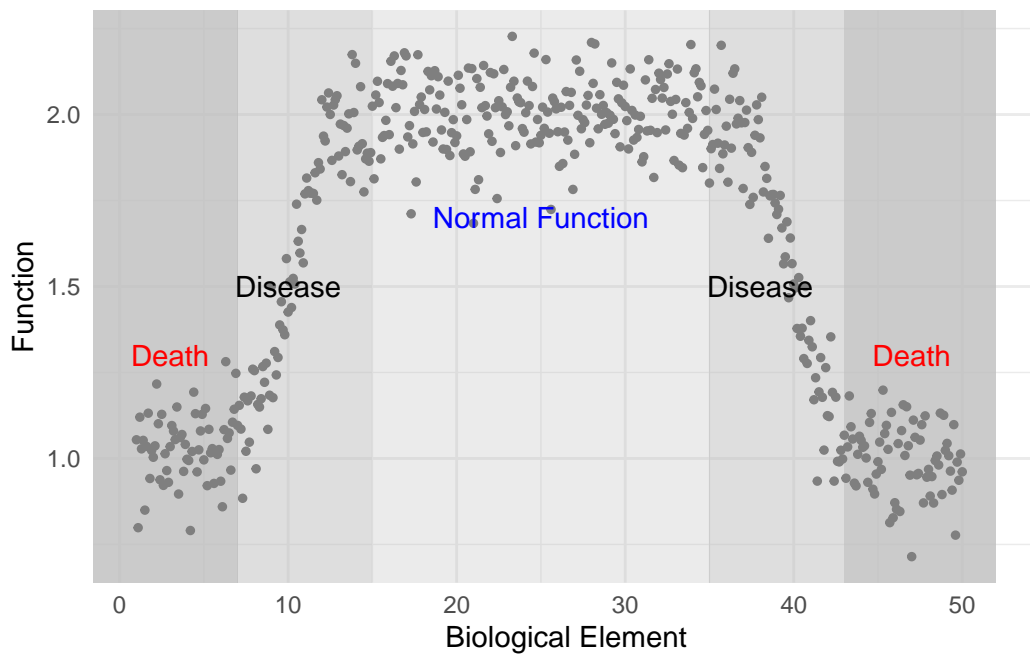
```
trace.e <- seq(1,50, by=0.1)
#normal range = 15~35
trace.e.h=function (x) {
  ifelse(x<20, 1/(1+exp(-x+10)),
        ifelse(x<30, rnorm(1, 1/(1+exp(-19)), 0.01),
              1/(1+exp(-19))-1/(1+exp(40-x))
        )
  )
}
hstatus<-trace.e.h(trace.e)+rnorm(length(trace.e), 1, 0.1)
basic = tibble(trace.e, hstatus)
```

```
basic %>%
  ggplot(aes(x= trace.e, y = hstatus)) +
  scale_x_continuous(name="Biological Element") +
  scale_y_continuous(name="Function") +
  theme_minimal()+
```

```

geom_rect(data=basic[1,],aes(xmin=-Inf, xmax=7 , ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=7,    xmax=15, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=15,   xmax=35, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=35,   xmax=43, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=43,   xmax=52, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_point(size=1, color = 'grey50') +
annotate(geom="text", x=c(3,47), y=c(1.3, 1.3), label="Death",    color="red") +
annotate(geom="text", x=c(10,38), y=c(1.5, 1.5), label="Disease", color="black") +
annotate(geom="text", x=25,      y=1.7,      label="Normal Function",color="blue")

```



Y

## 5.2 1:

```

basic = basic %>%
  mutate(disease = -1*hstatus+5,
         exp.b    = -1*trace.e +50)

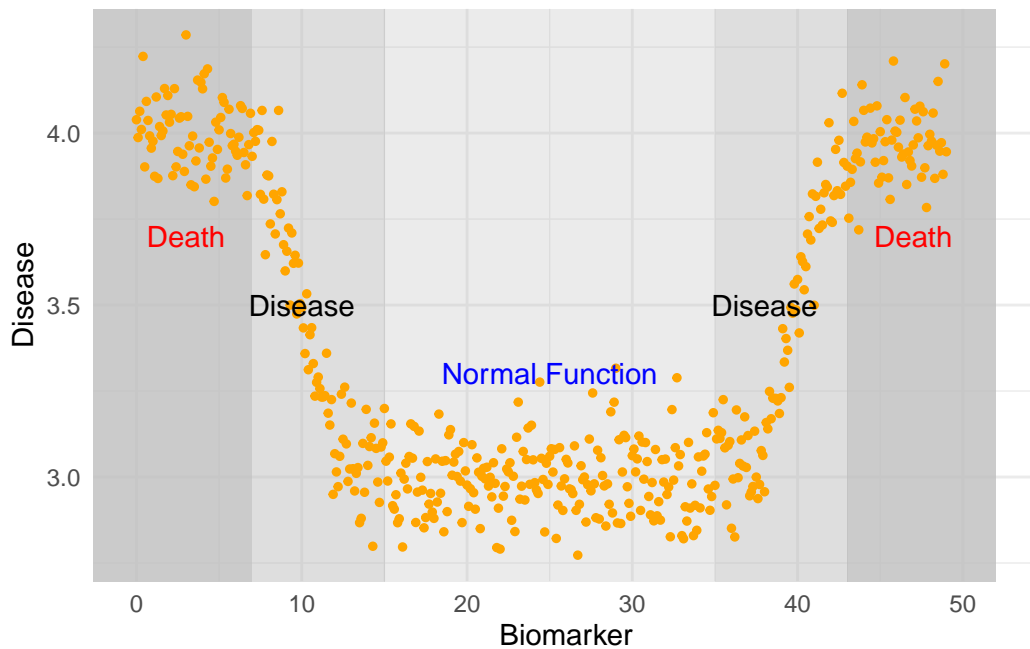
fig1 = basic %>%
  ggplot(aes(x= exp.b, y = disease))+

```

```

theme_minimal()+
scale_x_continuous(name="Biomarker") +
scale_y_continuous(name="Disease") +
geom_rect(data=basic[1,],aes(xmin=-Inf, xmax=7 , ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=7,      xmax=15, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=15,     xmax=35, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=35,     xmax=43, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_rect(data=basic[1,],aes(xmin=43,     xmax=52, ymin=-Inf, ymax=Inf), fill= 'grey', alpha=0.5) +
geom_point(size=1, color = 'orange') +
annotate(geom="text", x=c(3,47), y=c(3.7, 3.7), label="Death", color="red") +
annotate(geom="text", x=c(10,38), y=c(3.5, 3.5), label="Disease", color="black") +
annotate(geom="text", x=25, y=3.3, label="Normal Function",color="blue")
fig1

```

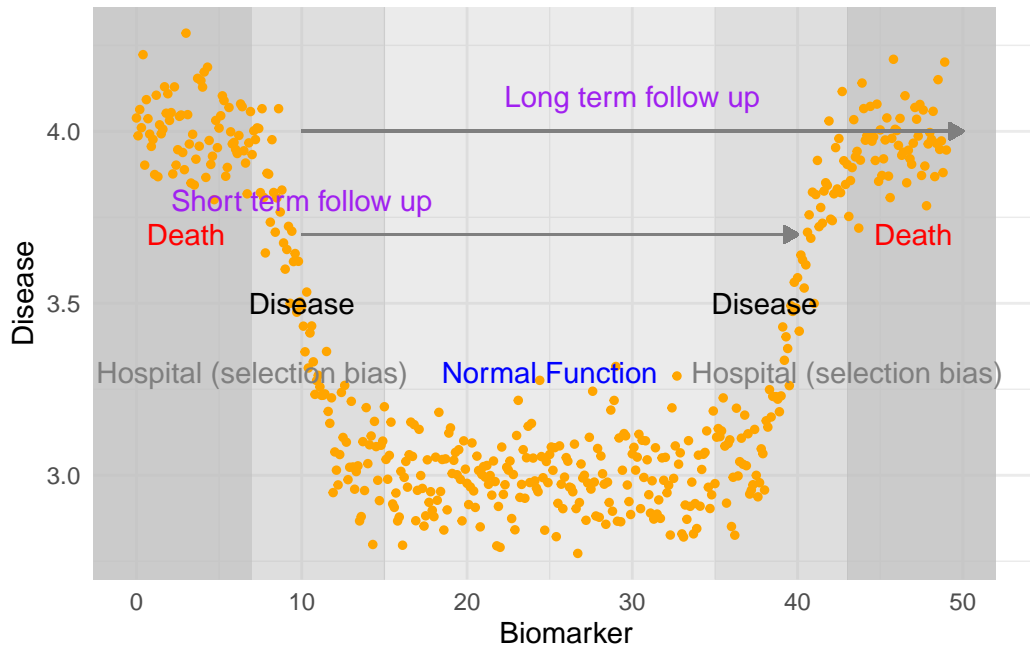


### 5.3 (community base cohort study)

J-shap

U-shap

```
fig1 +
  annotate(geom="text", x=c(7, 43), y=c(3.3, 3.3), label="Hospital (selection bias)", color="grey50", size=0.5) +
  annotate(geom="text", x=c(10), y=c(3.8), label="Short term follow up", color="purple", size=0.5) +
  geom_segment(aes(x=10, xend=40, y=3.7, yend=3.7), size = 0.5, color='grey50',
    arrow = arrow(length = unit(0.2, "cm"), type = "closed")) +
  annotate(geom="text", x=c(30), y=c(4.1), label="Long term follow up", color="purple", size=0.5) +
  geom_segment(aes(x=10, xend=50, y=4, yend=4), size = 0.5, color='grey50',
    arrow = arrow(length = unit(0.2, "cm"), type = "closed"))
```



,  
 , short-term follow up  
 , long term follow up  
 , short-term follow up U-shap , long  
 term follow up J-shap

## 5.4 : sigmoid curve vs linear regression

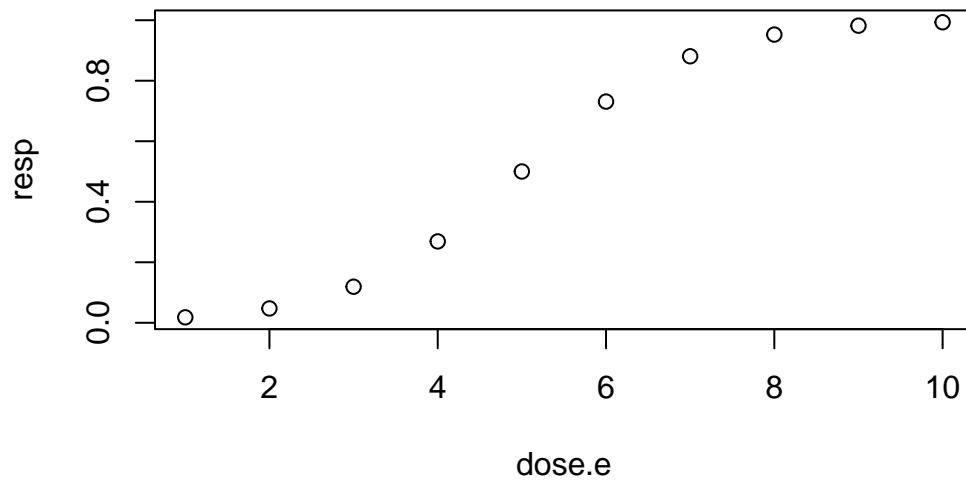
) sigmoid curve  
 ? LD50 . LD50 50% . LD50  
 50%

dose.e	resp
1	0.0179862
2	0.0474259
3	0.1192029
4	0.2689414
5	0.5000000
6	0.7310586
7	0.8807971
8	0.9525741
9	0.9820138
10	0.9933071

```
sigmoid.f = function(x){
  1/(1+exp(5-x))
}

df = tibble(
  dose.e = c(1:10),
  resp   = sigmoid.f(dose.e)
)
df %>% kbl() %>%
  kable_paper("hover", full_width = F)
```

```
plot(df)
```



LD50        ,        LD70        .

```
set.seed(50)
x<-seq(0, 10, 0.01)
y<-sigmoid.f(x)+rnorm(length(x), mean=0, sd=0.1)
pb<-c(rnorm(500, 0, 0.001), rnorm(300, 0, 0.01), rnorm(100, 0.1, 0.05),rnorm(101, -0.1, 0.05))
resp = y + pb
ld70.sm = x[which( sigmoid.f(x) >0.69 & sigmoid.f(x) < 0.71)] %>% min(.)
ld70.sm
```

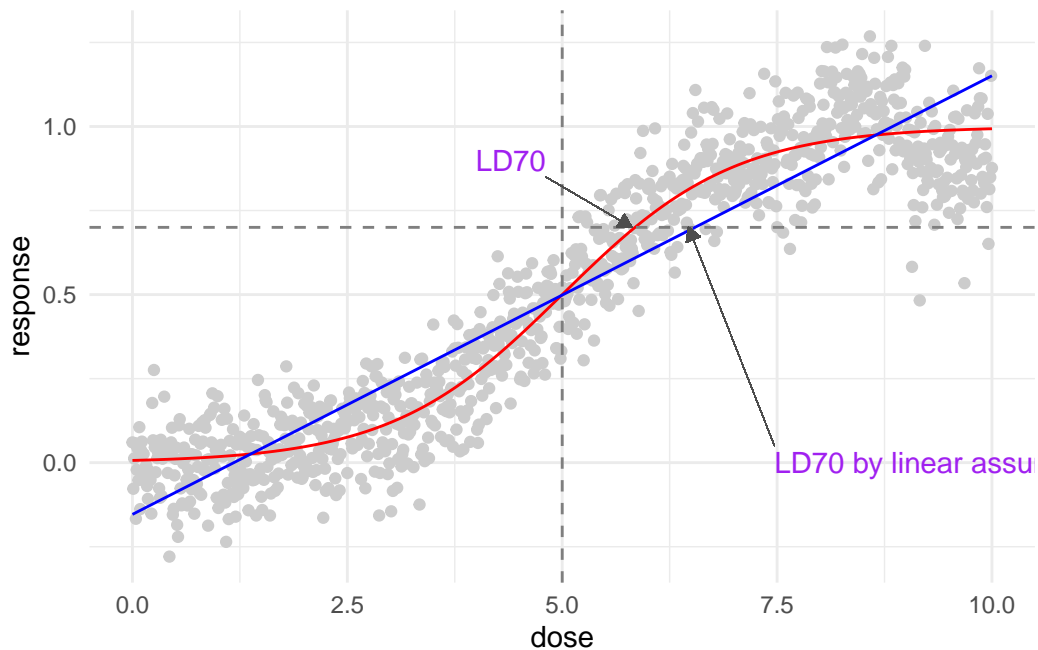
[1] 5.81

```
mod1<-glm(resp ~ poly(x, 1))
pred1<-predict(mod1)
ld70.lm = x[which(pred1 >0.69 & pred1 <0.71)] %>% min(.)
ld70.lm
```

[1] 6.47

```
df = tibble(dose = x, response= resp)
df %>%
  ggplot(aes(x=dose, y=response)) +
```

```
geom_point(color = 'grey80') + theme_minimal()+
geom_line(aes(y= sigmoid.f(dose)), color = 'red') +
geom_line(aes(y= predict(lm(response ~ poly(dose, 1)))), color = 'blue') +
geom_vline(xintercept = 5, linetype=2, color='grey50') +
geom_hline(yintercept = 0.7, linetype=2, color='grey50') +
annotate(geom="text", x=ld70.sm -1, y=0.9, label="LD70",
         color="purple", hjust=1) +
geom_segment(aes(x=ld70.sm -1, xend=ld70.sm, y=0.85, yend=0.7), size = 0.1, color='grey30',
            arrow = arrow(length = unit(0.2, "cm"), type = "closed")) +
annotate(geom="text", x=ld70.lm +1, y=0.0, label="LD70 by linear assumption",
         color="purple", hjust=0) +
geom_segment(aes(x=ld70.lm +1, xend=ld70.lm, y=0.05, yend=0.7), size = 0.1, color='grey30',
            arrow = arrow(length = unit(0.2, "cm"), type = "closed"))
```



LD70

?

## 5.5

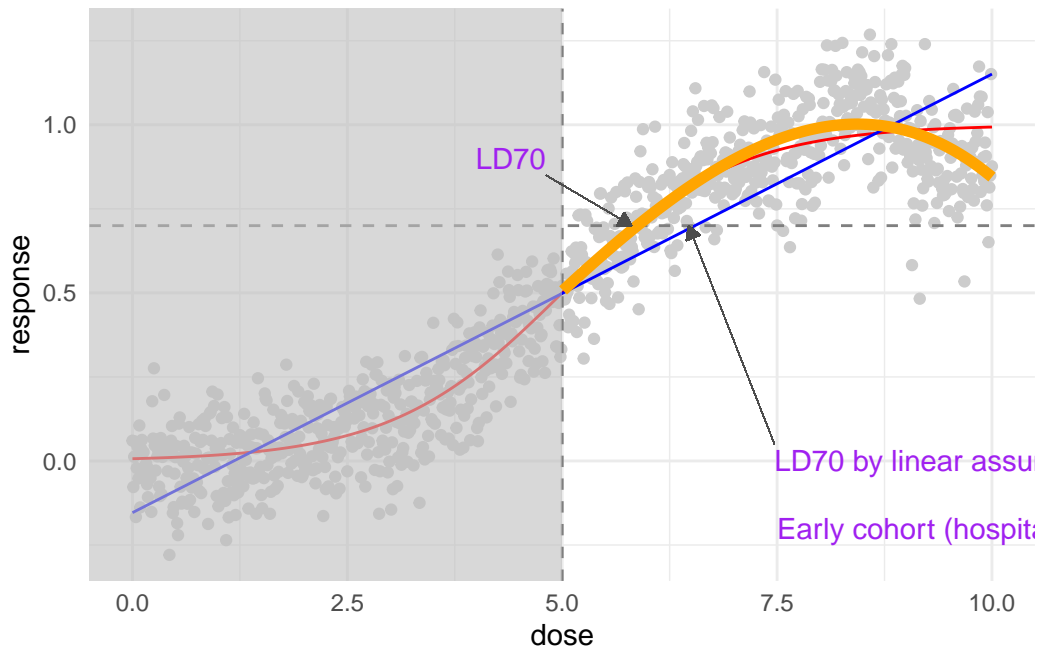


```

early_cohort = df %>% filter(dose > 5)

df %>%
  ggplot(aes(x=dose, y=response)) +
  geom_point(color = 'grey80') + theme_minimal()+
  geom_line(aes(y= sigmoid.f(dose)), color = 'red') +
  geom_line(aes(y= predict(lm(response ~ dose))), color = 'blue') +
  geom_vline(xintercept = 5, linetype=2, color='grey50') +
  geom_hline(yintercept = 0.7, linetype=2, color='grey50') +
  ## add 1
  annotate(geom="text", x=c(7.5), y=c(-0.2),
    label="Early cohort (hospital base)", color="purple", hjust=0) +
  geom_rect(data=df[1,],aes(xmin=-Inf, xmax=5, ymin=-Inf, ymax=Inf),
    fill= 'grey', alpha=0.6) +
  geom_line(data= early_cohort,
    aes(y= predict(lm(response ~ poly(dose,3)))), color = 'orange', size = 2) +
  annotate(geom="text", x=ld70.sm -1, y=0.9, label="LD70",
    color="purple", hjust=1) +
  geom_segment(aes(x=ld70.sm -1, xend=ld70.sm, y=0.85, yend=0.7), size = 0.1, color='grey30'
    arrow = arrow(length = unit(0.2, "cm"), type = "closed")) +
  annotate(geom="text", x=ld70.lm +1, y=0.0, label="LD70 by linear assumption",
    color="purple", hjust=0) +
  geom_segment(aes(x=ld70.lm +1, xend=ld70.lm, y=0.05, yend=0.7), size = 0.1, color='grey30'
    arrow = arrow(length = unit(0.2, "cm"), type = "closed"))

```

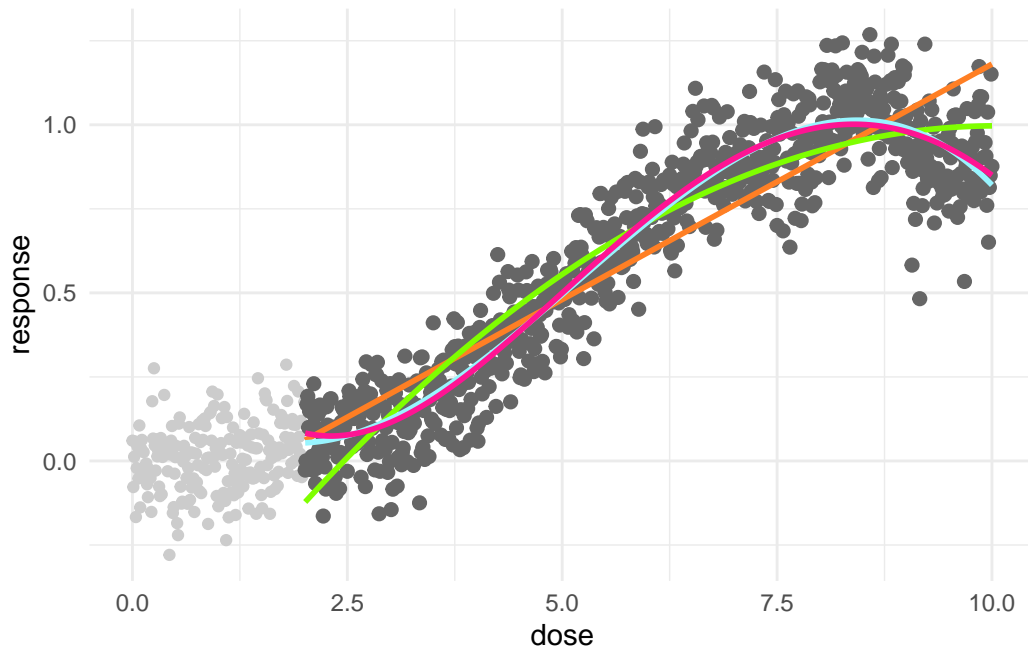


## 5.6

. Dose 2 .

```
# subcohort 2nd phase (1st phase is hospital base cohort)
s2c <- df %>% filter(dose > 2)
s2m1<-lm(data=s2c, response ~ poly(dose, 1))
s2m2<-lm(data=s2c, response ~ poly(dose, 2))
s2m3<-lm(data=s2c, response ~ poly(dose, 3))
s2m4<-lm(data=s2c, response ~ poly(dose, 4))

df %>%
  ggplot(aes(x=dose, y=response)) +
  geom_point(color = 'grey80') + theme_minimal()+
  geom_point(data=s2c, color = 'grey40', size = 2) +
  geom_line(data=s2c, aes(y=predict(s2m1)), color = 'chocolate1', size = 1) +
  geom_line(data=s2c, aes(y=predict(s2m2)), color = 'chartreuse1', size = 1) +
  geom_line(data=s2c, aes(y=predict(s2m3)), color = 'cadetblue1', size = 1) +
  geom_line(data=s2c, aes(y=predict(s2m4)), color = 'deeppink1', size = 1)
```



(low) . , ?.

```
anova(s2m1, s2m2, s2m3, s2m4)
```

#### Analysis of Variance Table

Model 1: response ~ poly(dose, 1)

Model 2: response ~ poly(dose, 2)

Model 3: response ~ poly(dose, 3)

Model 4: response ~ poly(dose, 4)

	Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
1	798	18.9099				
2	797	13.4734	1	5.4365	440.8574	< 2e-16 ***
3	796	9.8806	1	3.5928	291.3455	< 2e-16 ***
4	795	9.8036	1	0.0770	6.2423	0.01267 *

---

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

? ( . )

?

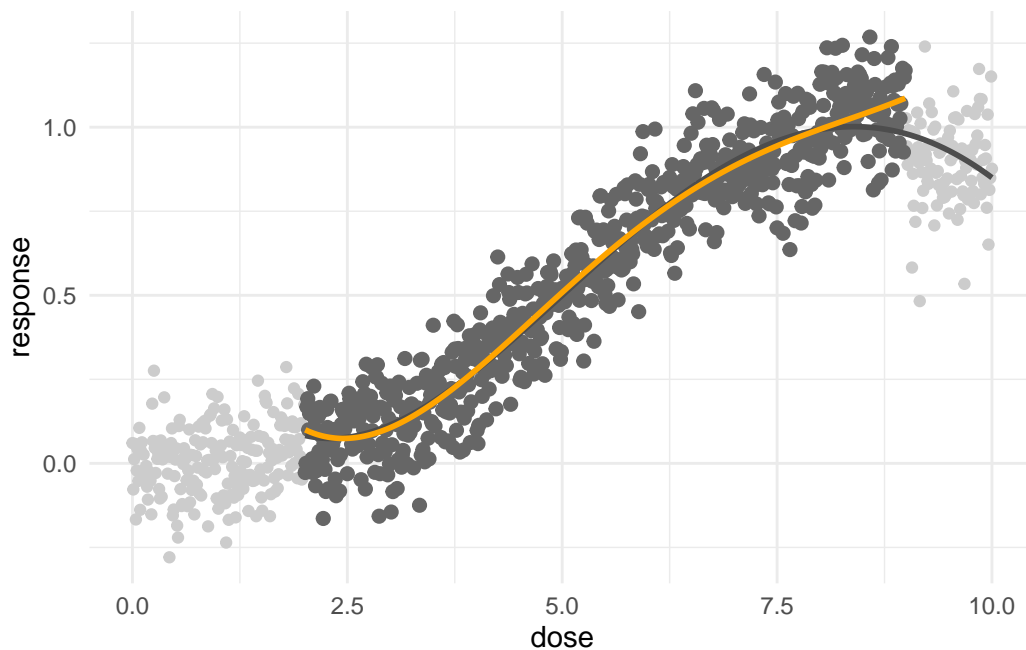
9

```

s3c <- df %>% filter(dose >2) %>% filter(dose <9)
s3m1<-lm(data=s3c, response ~ poly(dose, 1))
s3m2<-lm(data=s3c, response ~ poly(dose, 2))
s3m3<-lm(data=s3c, response ~ poly(dose, 3))
s3m4<-lm(data=s3c, response ~ poly(dose, 4))

df %>%
  ggplot(aes(x=dose, y=response)) +
  geom_point(color = 'grey80') + theme_minimal()+
  geom_point(data=s3c, color = 'grey40', size =2 ) +
  #geom_line(data=s2c, aes(y=predict(s2m1)), color = 'grey30', size = 1) +
  geom_line(data=s2c, aes(y=predict(s2m4)), color = 'grey30', size = 1) +
  #geom_line(data=s3c, aes(y=predict(s3m1)), color = 'orange', size = 1)
  geom_line(data=s3c, aes(y=predict(s3m4)), color = 'orange', size = 1)

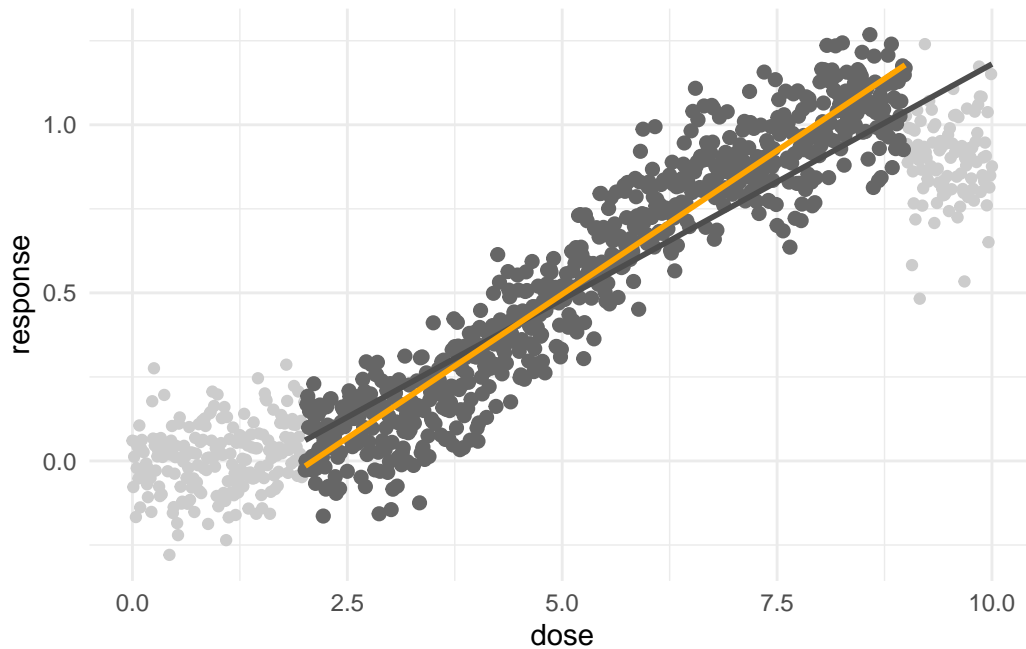
```



```

df %>%
  ggplot(aes(x=dose, y=response)) +
  geom_point(color = 'grey80') + theme_minimal()+
  geom_point(data=s3c, color = 'grey40', size =2 ) +
  geom_line(data=s2c, aes(y=predict(s2m1)), color = 'grey30', size = 1) +
  #geom_line(data=s2c, aes(y=predict(s2m4)), color = 'grey30', size = 1) +
  geom_line(data=s3c, aes(y=predict(s3m1)), color = 'orange', size = 1)

```



```
#geom_line(data=s3c, aes(y=predict(s3m4)), color = 'orange', size = 1)
```

3

```
library(gam)
#####
s4c = df %>% filter(dose < 9)
s4m1<-lm(data=s4c, response ~ poly(dose, 1))
s4m3<-lm(data=s4c, response ~ poly(dose, 3))
s4ms<-lm(data=s4c, response ~ sigmoid.f(dose-5))
s4mg<-gam(data=s4c, response ~ s(dose, 20))
anova(s4m1, s4m3, s4ms, s4mg)
```

#### Analysis of Variance Table

```
Model 1: response ~ poly(dose, 1)
Model 2: response ~ poly(dose, 3)
Model 3: response ~ sigmoid.f(dose - 5)
Model 4: response ~ s(dose, 20)
```

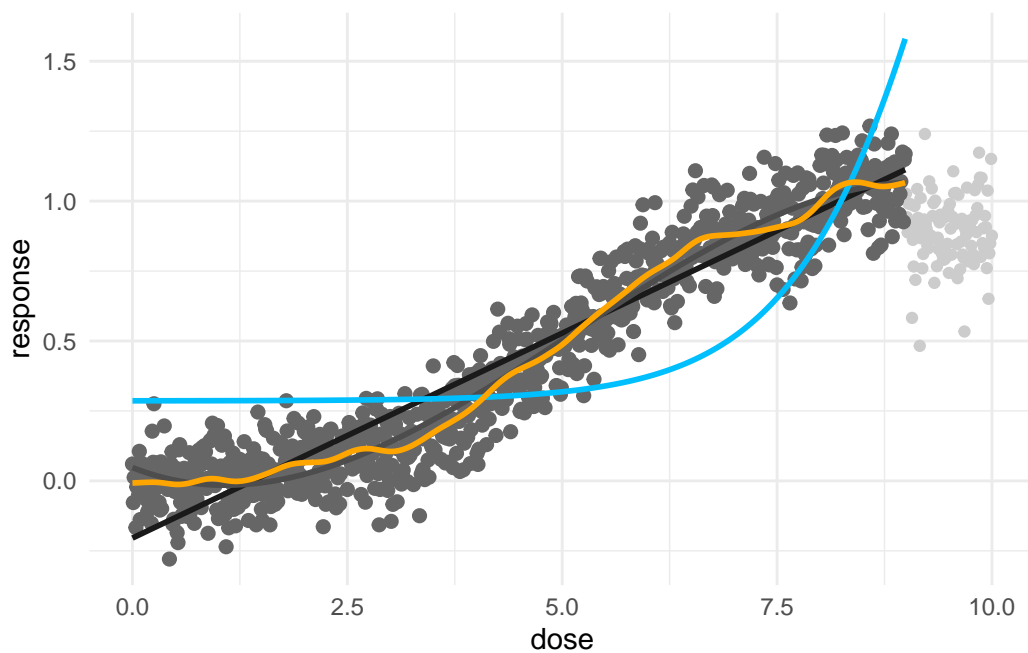
	Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
1	898	14.876				

2	896	10.064	2.000	4.812	233.61	< 2.2e-16	***
3	898	67.272	-2.000	-57.208	2777.26	< 2.2e-16	***
4	879	9.053	18.999	58.219	297.52	< 2.2e-16	***

---

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

```
df %>%
  ggplot(aes(x=dose, y=response)) +
  geom_point(color = 'grey80') + theme_minimal()+
  geom_point(data=s4c, color = 'grey40', size = 2) +
  geom_line(data=s4c, aes(y=predict(s4m1)), color = 'grey10', size = 1) +
  geom_line(data=s4c, aes(y=predict(s4m3)), color = 'grey30', size = 1) +
  geom_line(data=s4c, aes(y=predict(s4ms)), color = 'deepskyblue', size = 1) +
  geom_line(data=s4c, aes(y=predict(s4mg)), color = 'orange', size = 1)
```



### 5.6.1 Take home message

1. :

- (SMR) , - .

2. :

- - , .
3. :
- - , .
  - LD50( ) .
  - , .
4. : , - .

5.7 Threshold (change point )

threshold threshold point , piecewise regression , . piecewise regression

threshold points (piecewise regression)	codes
total	Resp = + 1 · Dose + 2 · ( Dose - ) + + 0
If Dose <	Resp= + 1 · Dose + 0
If Dose >	Resp= - 2 · +( 1 + 2 ) · Dose + 0
model selection	minimal AIC value

5.7.1

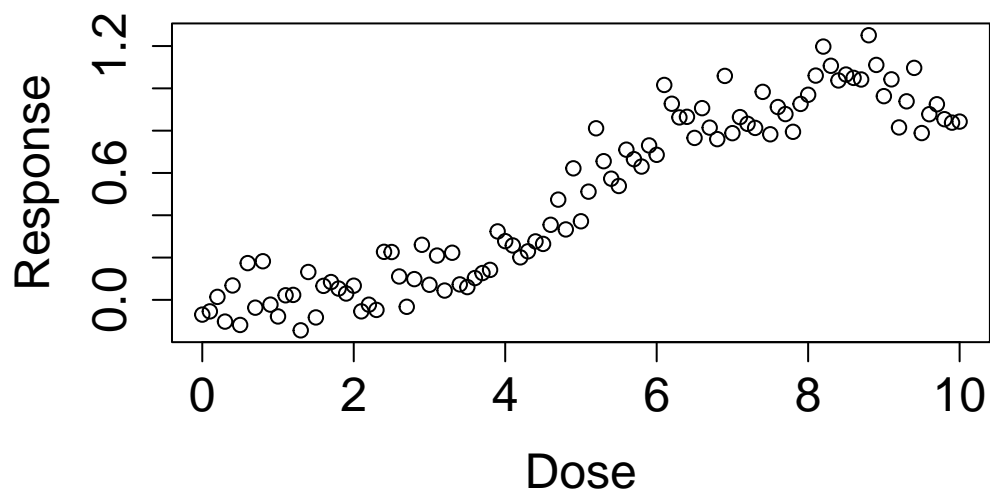
. (Dose) (Resp) . threshold .

```
set.seed(0)
dose <- seq(0,10, 0.1)
length(dose)
```

[1] 101

```
pb<-c(rnorm(50, 0, 0.001), rnorm(30, 0, 0.01), rnorm(10, 0.1, 0.05),rnorm(11, -0.1, 0.05))
resp <-1/(1+exp(-(dose-5)))+rnorm(length(dose), 0, 0.1)+pb

plot(dose, resp, xlab='Dose', ylab='Response', cex.lab=1.5, cex.axis=1.5, cex.main=1.5, cex..
```



```
cohort<-data.frame(dose, resp, pb)
```

### 5.7.2 threshold

1	5	.	matrix (outdata)	.	outdata	threshold point	intercept,
beta for before threshold, and its p value,				beta for post threshold and its			
pvalue	AIC	.	.	therhold	1	5	.

```
cpdose <- ifelse(dose -1 >0, dose -1, 0)
cpm <- glm(resp ~ dose + cpdose)
summary(cpm)$aic
```

```
[1] -92.20184
```

```
cpdose <- ifelse(dose -5 >0, dose -5, 0)
cpm <- glm(resp ~ dose + cpdose)
summary(cpm)$aic
```

```
[1] -86.9744
```



? threshold 1 . 2 , 2.5 .

```
thr_fun <- function(thres){  
  cpdose <- ifelse(dose - thres > 0, dose - thres, 0)  
  cpm <- glm(resp ~ dose + cpdose)  
  aic <- summary(cpm)$aic  
  data.frame(  
    'threshold' = thres,  
    'aic'       = aic)  
}
```

```
# ?  
dose[which(dose == 1):which(dose == 5)]
```

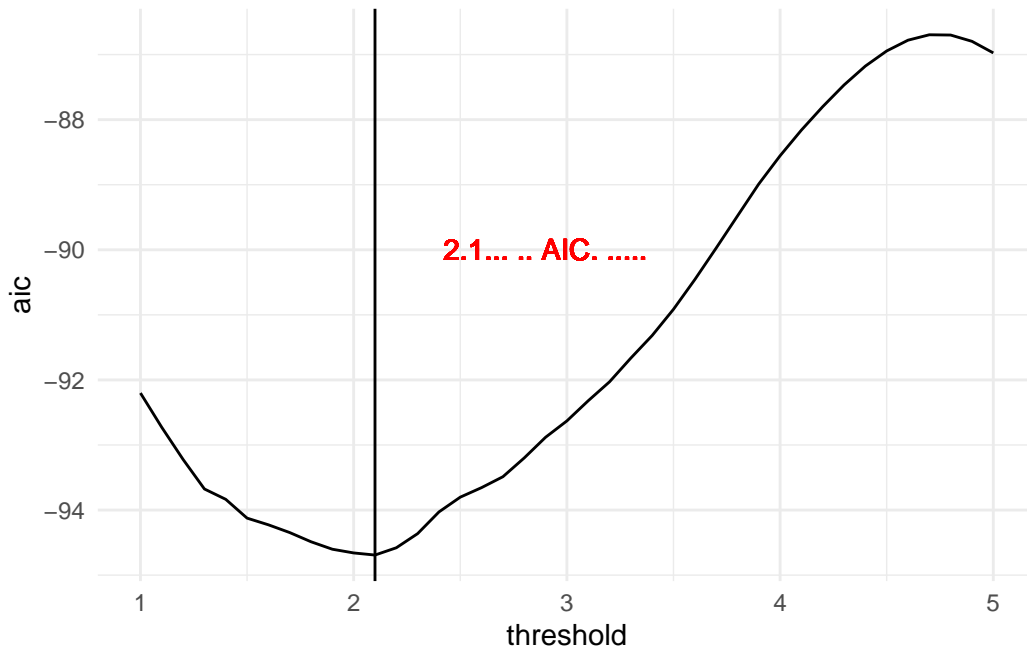
```
[1] 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7 2.8  
[20] 2.9 3.0 3.1 3.2 3.3 3.4 3.5 3.6 3.7 3.8 3.9 4.0 4.1 4.2 4.3 4.4 4.5 4.6 4.7  
[39] 4.8 4.9 5.0
```

```
simul_list <- list()  
simul_list <- lapply(dose[which(dose == 1):which(dose == 5)],  
                    thr_fun
```

```
simul_dat <- do.call(rbind, simul_list)
```

```
library(ggplot2)  
opt.thres <- simul_dat$threshold[which.min(simul_dat$aic)]  
  
simul_dat %>%  
  ggplot(aes(x = threshold, y = aic)) +  
  geom_line() +  
  geom_vline(xintercept = opt.thres) +
```

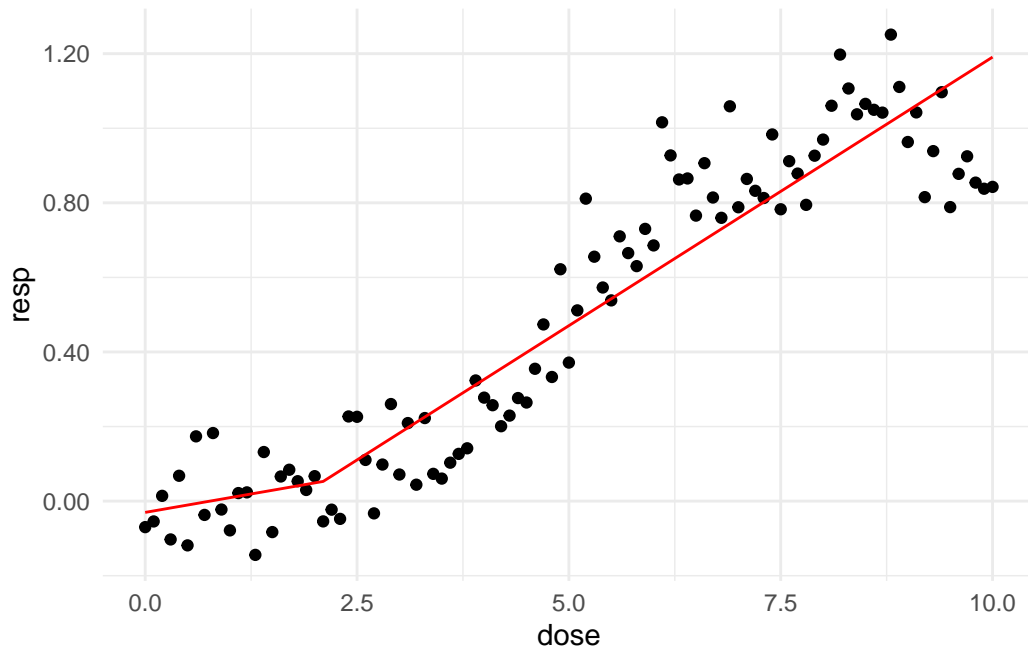
```
geom_text(x = opt.thres + 0.8, y = -90, color = 'red',
          label = paste0(round(opt.thres, 3), ' AIC .') ) +
theme_minimal()
```



2.1 threshold

```
thres = 2.1
f_cpdose <- ifelse(dose - thres > 0, dose - thres, 0)
f_cpm <- glm(resp ~ dose + f_cpdose)
```

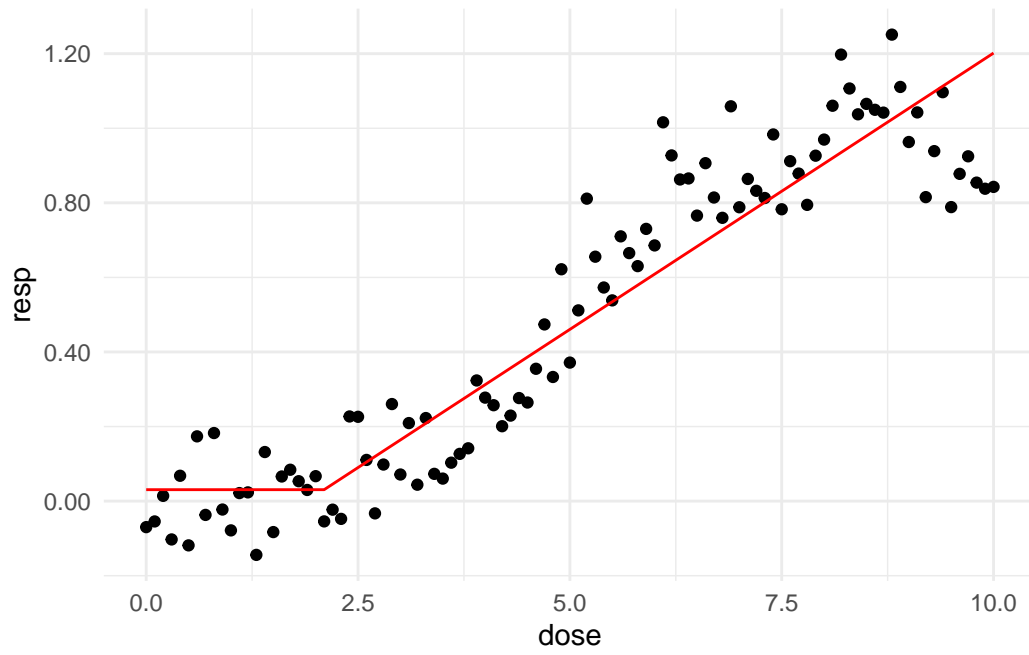
```
prepwlm <- predict(f_cpm)
scaleFUN <- function(x) sprintf("%.2f", x)
cohort %>%
  ggplot(aes(x= dose, y = resp)) +
  geom_point() +
  theme_minimal() +
  scale_y_continuous(labels = scaleFUN) +
  geom_line(aes(y = prepwlm), color = 'red')
```



threshold                      ? dose    predose                      .

```
thres = 2.1
f_cpdose <- ifelse(dose - thres >= 0, dose - thres, 0)
f_predose <- ifelse(dose - thres <= 0, 0, dose - thres )
f_cpm    <- glm(resp ~ f_predose + f_cpdose)
```

```
prepwlm <- predict(f_cpm)
scaleFUN <- function(x) sprintf("%.2f", x)
cohort %>%
  ggplot(aes(x= dose, y = resp)) +
  geom_point() +
  theme_minimal() +
  scale_y_continuous(labels = scaleFUN) +
  geom_line(aes(y = prepwlm), color = 'red')
```



## 6 - : Gompertz

```
(Gompertz) - . ggplot2 , nls.multstart  
, investr .
```

### 6.1 Gompertz

, - . S , .

A: (asymptote) .

(Mu): (maximum slope) .

(Lambda): (lag-phase) . , .

.

```
#  
if(!require("tidyverse")) install.packages("tidyverse");library(tidyverse)  
if(!require("nls.multstart")) install.packages("nls.multstart");library(nls.multstart)  
if(!require("investr")) install.packages("investr");library(investr)
```

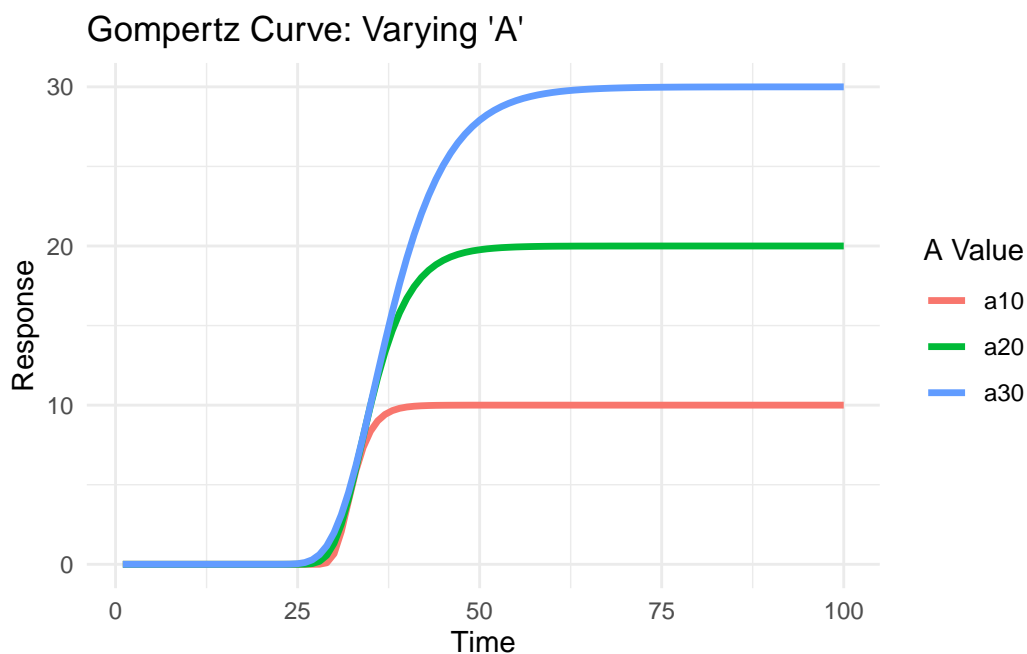
```
# Gompertz  
gompertz <- function(time, a, mu, lambda) {  
  a * exp(-exp(mu * exp(1) / a * (lambda - time) + 1))  
}
```

```
# Gompertz  
# A  
tibble(time = 1:100) %>%  
  mutate(  
    a10 = gompertz(time, a = 10, mu = 2, lambda = 30),  
    a20 = gompertz(time, a = 20, mu = 2, lambda = 30),  
    a30 = gompertz(time, a = 30, mu = 2, lambda = 30)  
  ) %>%  
  pivot_longer(  
    cols = starts_with("a"),
```

```

names_to = "parameter_a",
values_to = "response"
) %>%
ggplot(aes(x = time, y = response, color = parameter_a)) +
geom_line(size = 1.2) +
labs(
  title = "Gompertz Curve: Varying 'A'",
  x = "Time",
  y = "Response",
  color = "A Value"
) +
theme_minimal()

```



```

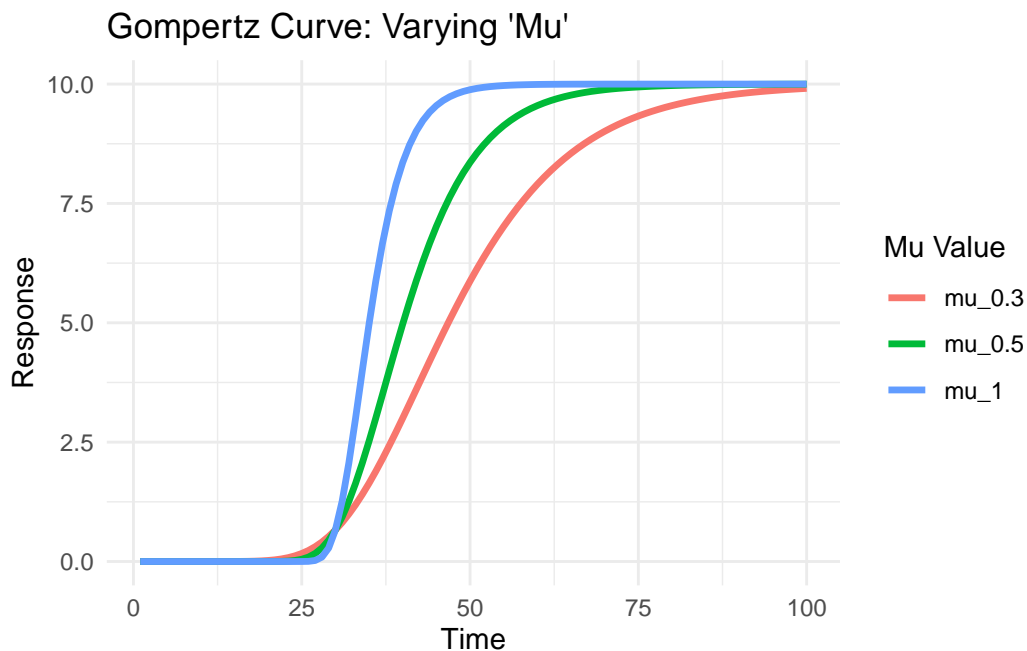
# Gompertz
# Mu
tibble(time = 1:100) %>%
  mutate(
    mu_1 = gompertz(time, a = 10, mu = 1, lambda = 30),
    mu_0.5 = gompertz(time, a = 10, mu = 0.5, lambda = 30),
    mu_0.3 = gompertz(time, a = 10, mu = 0.3, lambda = 30)
  ) %>%
  pivot_longer(

```

```

    cols = starts_with("m"),
    names_to = "parameter_a",
    values_to = "response"
  ) %>%
  ggplot(aes(x = time, y = response, color = parameter_a)) +
  geom_line(size = 1.2) +
  labs(
    title = "Gompertz Curve: Varying 'Mu'",
    x = "Time",
    y = "Response",
    color = "Mu Value"
  ) +
  theme_minimal()

```



```

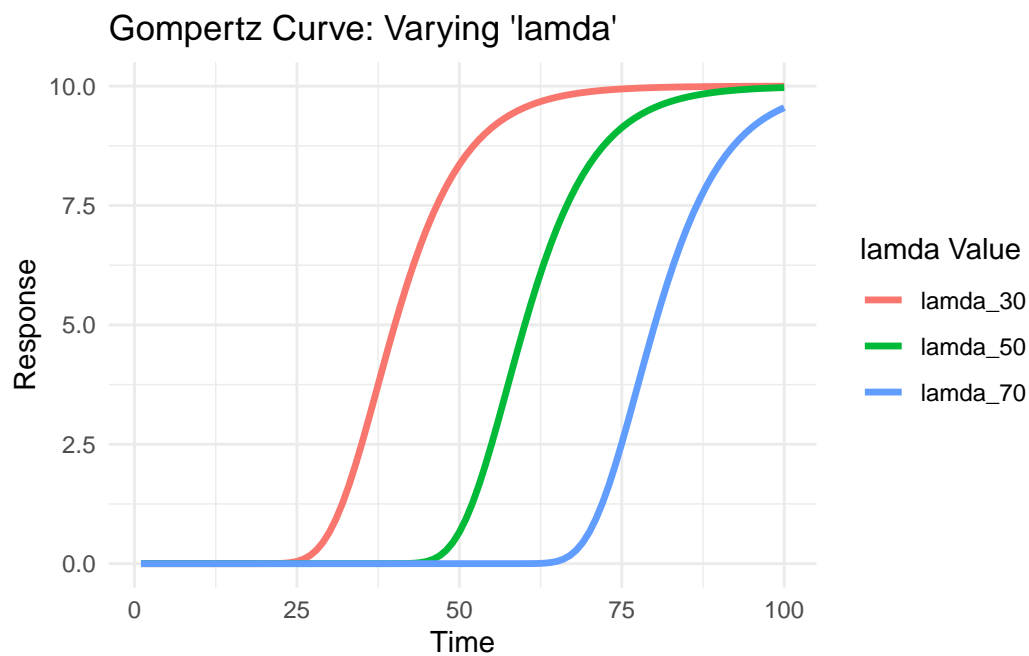
# Gompertz
# lamda
tibble(time = 1:100) %>%
  mutate(
    lamda_30 = gompertz(time, a = 10, mu = 0.5, lambda = 30),
    lamda_50 = gompertz(time, a = 10, mu = 0.5, lambda = 50),
    lamda_70 = gompertz(time, a = 10, mu = 0.5, lambda = 70)
  ) %>%

```

```

pivot_longer(
  cols = starts_with("l"),
  names_to = "parameter_a",
  values_to = "response"
) %>%
ggplot(aes(x = time, y = response, color = parameter_a)) +
geom_line(size = 1.2) +
labs(
  title = "Gompertz Curve: Varying 'lamda'",
  x = "Time",
  y = "Response",
  color = "lamda Value"
) +
theme_minimal()

```



### 6.1.0.1

- tibble ggplot2 . , .

```

#
set.seed(0)

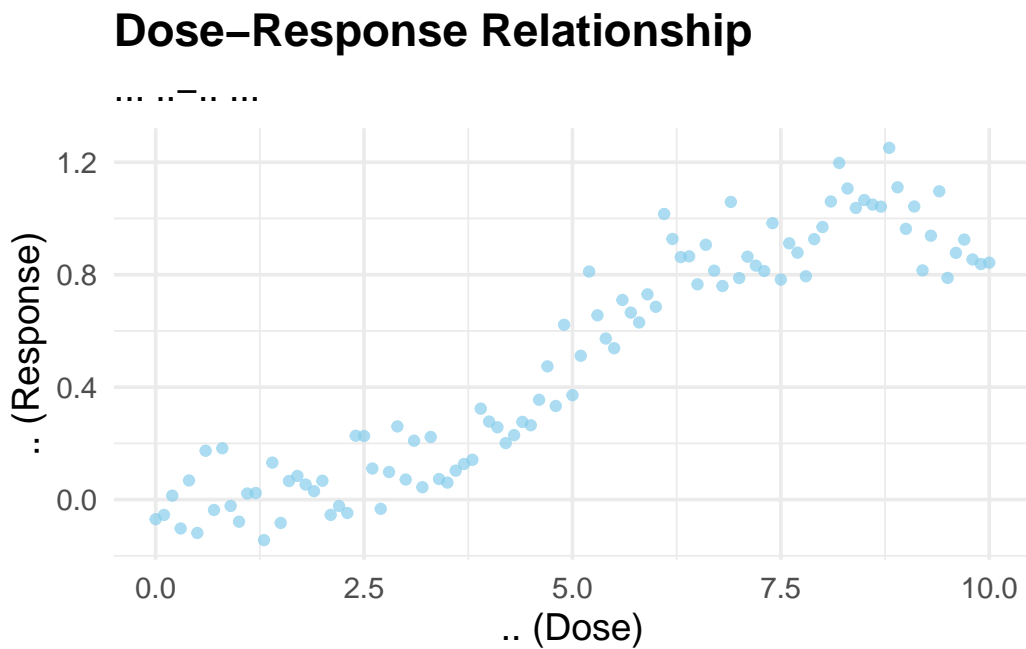
```



```
dose <- seq(0, 10, 0.1)
pb <- c(rnorm(50, 0, 0.001), rnorm(30, 0, 0.01), rnorm(10, 0.1, 0.05), rnorm(11, -0.1, 0.05))
resp <- 1 / (1 + exp(-(dose - 5))) + rnorm(length(dose), 0, 0.1) + pb

# tibble
cohort <- tibble(dose, resp, pb)

ggplot(cohort, aes(x = dose, y = resp)) +
  geom_point(color = "skyblue", alpha = 0.7) +
  labs(
    title = "Dose-Response Relationship",
    subtitle = " - ",
    x = " (Dose)",
    y = " (Response)"
  ) +
  theme_minimal(base_size = 14) +
  theme(plot.title = element_text(face = "bold"))
```



### 6.1.0.2 Gompertz

```
nls(
  ~ 1 / (1 + exp(-(a * x^b))), data = investr, start = c(a = 0.1, b = 1),
  lower = c(a = 0.01, b = 0.01), upper = c(a = 10, b = 10),
  control = nls.multstart(),
  confint = TRUE, conf.level = 0.95
)
```

```
# nls_multstart
nls_fit <- nls_multstart(
  resp ~ gompertz(dose, a, mu, lambda),
  data = cohort,
  start_lower = c(a = 0, mu = 0, lambda = 0),
  start_upper = c(a = 2, mu = 1, lambda = 10),
  iter = 250
)
```

```
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
```

```
#
print(summary(nls_fit))
```

Formula: resp ~ gompertz(dose, a, mu, lambda)

Parameters:

	Estimate	Std. Error	t value	Pr(> t )
a	1.00934	0.03107	32.48	<2e-16 ***
mu	0.29314	0.02754	10.64	<2e-16 ***
lambda	3.20596	0.15811	20.28	<2e-16 ***

---

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

Residual standard error: 0.1106 on 98 degrees of freedom

Number of iterations to convergence: 23

Achieved convergence tolerance: 1.49e-08

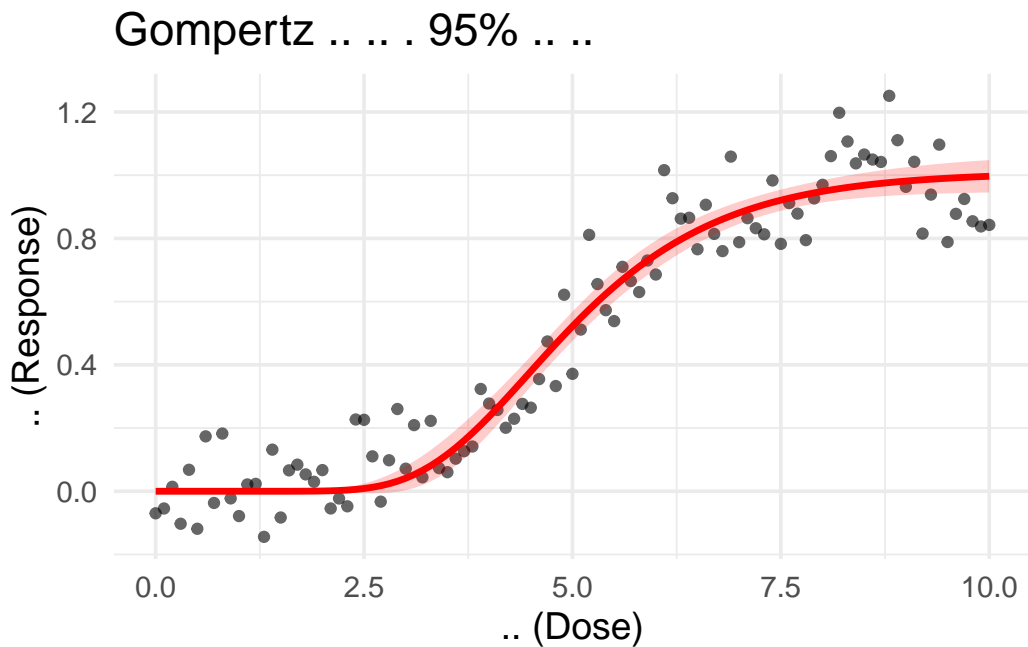
```
#
#
cohort_ci <- investr::predFit(
  nls_fit,
```

```

newdata = cohort,
interval = "confidence",
level = 0.95
) %>%
as_tibble() %>%
mutate(dose = cohort$dose)

ggplot(cohort, aes(x = dose, y = resp)) +
  geom_point(alpha = 0.6) +
  geom_line(data = cohort_ci, aes(y = fit), color = "red", size = 1.2) +
  geom_ribbon(data = cohort_ci, aes(ymin = lwr, ymax = upr, y = fit), fill = "red", alpha = 0.5) +
  labs(title = "Gompertz 95% CI", x = "Dose", y = "Response") +
  theme_minimal(base_size = 14)

```



### 6.1.0.3 3: (Extrapolation)

. AIC(Akaike Information Criterion) , AIC  
 . AIC  
 , (Extrapolation) . (dose -5 ~ 0 10 ~ 15)  
 Gompertz .

```
#
poly2_fit <- glm(resp ~ poly(dose,2),data = cohort)
poly3_fit <- glm(resp ~ poly(dose,3),data = cohort)

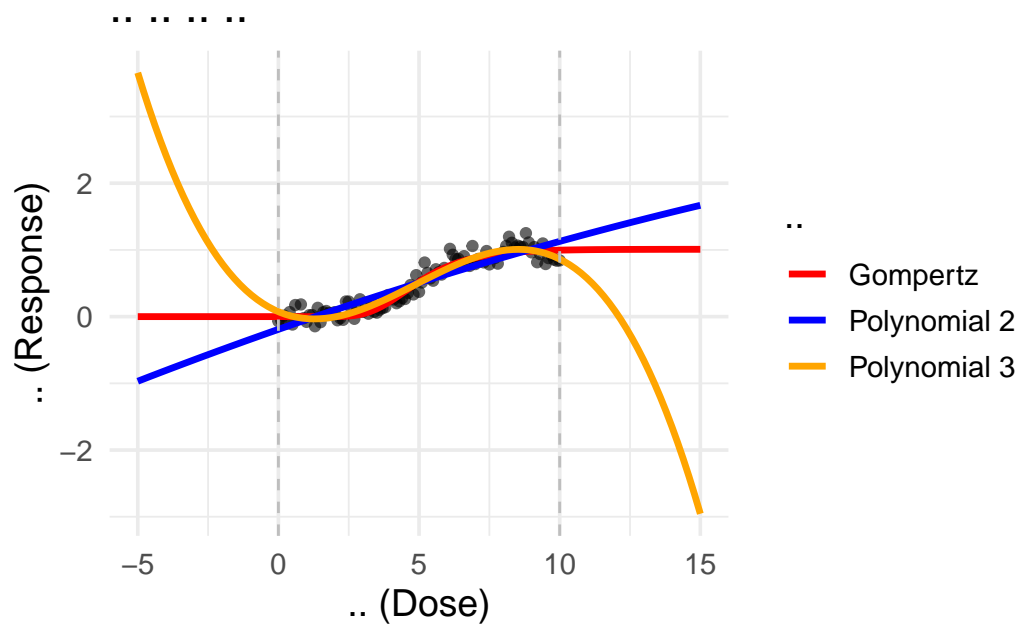
# AIC
AIC(nls_fit, poly2_fit, poly3_fit)
```

```
      df      AIC
nls_fit    4 -153.22741
poly2_fit  4  -87.32223
poly3_fit  5 -154.38409
```

```
# (extrapolation)
extrapolated_data <- tibble(dose = seq(-5, 15, length.out = 100))

extrapolated_data <- extrapolated_data %>%
  mutate(
    gompertz_pred = predict(nls_fit, newdata = .),
    poly2_pred = predict(poly2_fit, newdata = .),
    poly3_pred = predict(poly3_fit, newdata = .)
  )

ggplot(cohort, aes(x = dose, y = resp)) +
  geom_point(alpha = 0.6) +
  geom_line(data = extrapolated_data, aes(y = gompertz_pred, color = "Gompertz"), size = 1.2) +
  geom_line(data = extrapolated_data, aes(y = poly2_pred, color = "Polynomial 2"), size = 1.2) +
  geom_line(data = extrapolated_data, aes(y = poly3_pred, color = "Polynomial 3"), size = 1.2) +
  geom_vline(xintercept = range(cohort$dose), linetype = "dashed", color = "gray") +
  scale_color_manual(values = c("Gompertz" = "red", "Polynomial 2" = "blue", "Polynomial 3" = "green")) +
  labs(title = " ", x = " (Dose)", y = " (Response)", color = " ") +
  theme_minimal(base_size = 14)
```



# 7 MixedModel

```
if(!require("tidyverse")) install.packages("tidyverse");library(tidyverse)
if(!require("nls.multstart")) install.packages("nls.multstart");library(nls.multstart)
if(!require("investr")) install.packages("investr");library(investr)
if(!require("nlme")) install.packages("nlme");library(nlme)
if(!require("boot")) install.packages("boot");library(boot)
```

(Gompertz) , , -

## 7.1

- S (Gompertz, Logistic) . (Hill) .

### 7.1.1

- :  $y(\text{dose}) = \frac{a}{1 + \exp(-b(\text{dose} - c))}$ 
  - S ,
  - a:
  - b: ( )
  - c: LD50( 50% )
- :  $y(\text{dose}) = \frac{a \cdot \text{dose}^b}{c^b + \text{dose}^b}$ 
  - , , -
  - b: (Hill Coefficient), ( )
  - c: LD50( 50% )

### 7.1.2 :

(Gompertz, Logistic, Hill) , AIC(Akaike Information Criterion)  
. AIC , AIC .

```
# Gompertz
gompertz <- function(dose, a, mu, lambda) {
  a * exp(-exp(mu * exp(1) / a * (lambda - dose) + 1))
}

#
logistic <- function(dose, a, b, c) {
  a / (1 + exp(-b * (dose - c)))
}

#
hill <- function(dose, a, b, c) {
  (a * dose^b) / (c^b + dose^b)
}

# LD50
ld50_logistic <- function(model) {
  coefs <- coef(model)
  ld50 <- coefs["c"]
  return(ld50)
}

#
set.seed(0)
dose <- seq(0, 10, 0.1)
pb <- c(rnorm(50, 0, 0.001), rnorm(30, 0, 0.01), rnorm(10, 0.1, 0.05), rnorm(11, -0.1, 0.05))
resp <- 1 / (1 + exp(-(dose - 5))) + rnorm(length(dose), 0, 0.1) + pb
cohort <- tibble(dose, resp)

#
nls_gompertz <- nls_multstart(
  resp ~ gompertz(dose, a, mu, lambda),
  data = cohort,
  start_lower = c(a = 0, mu = 0, lambda = 0),
  start_upper = c(a = 2, mu = 1, lambda = 10),
  iter = 250 # iter
)
```

```
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
```

```
nls_logistic <- nls_multstart(
  resp ~ logistic(dose, a, b, c),
  data = cohort,
  start_lower = c(a = 0, b = 0, c = 0),
  start_upper = c(a = 2, b = 1, c = 10),
  iter = 250 # iter
)
```

```
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
Error in nlsModel(formula, mf, start, wts) :
  singular gradient matrix at initial parameter estimates
```

```
nls_hill <- nls_multstart(
  resp ~ hill(dose, a, b, c),
  data = cohort,
  start_lower = c(a = 0, b = 0, c = 0),
```



```

start_upper = c(a = 2, b = 10, c = 10),
iter = 250 # iter
)

```

```

# AIC
aic_values <- AIC(nls_gompertz, nls_logistic, nls_hill)
print(aic_values)

```

```

          df      AIC
nls_gompertz 4 -153.2274
nls_logistic 4 -160.6434
nls_hill      4 -156.0963

```

AIC

.

```

          AIC
nls_gompertz -153.2274
nls_logistic -160.6434
nls_hill     -156.0963

```

```

Logistic  AIC -160.6434 .
,
.

```

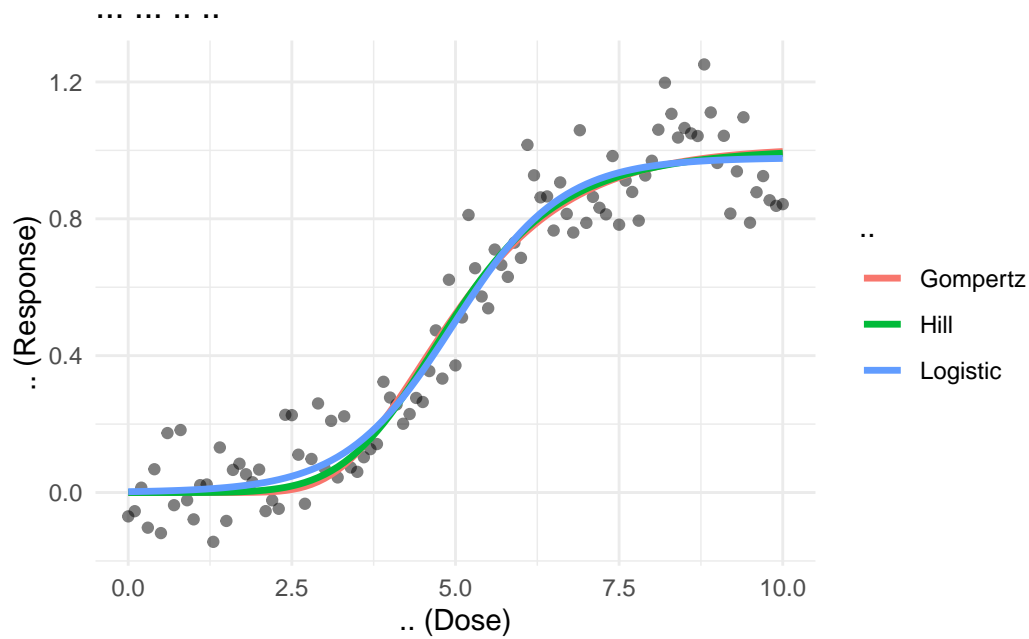
```

#
cohort_predicted <- cohort %>%
  mutate(
    Gompertz = predict(nls_gompertz),
    Logistic = predict(nls_logistic),
    Hill = predict(nls_hill)
  ) %>%
  pivot_longer(
    cols = c(Gompertz, Logistic, Hill),
    names_to = "Model",
    values_to = "Predicted_Response"
  )

ggplot(cohort, aes(x = dose, y = resp)) +
  geom_point(alpha = 0.5) +

```

```
geom_line(data = cohort_predicted, aes(y = Predicted_Response, color = Model), size = 1.2)
labs(
  title = " ",
  x = " (Dose)",
  y = " (Response)",
  color = " "
) +
theme_minimal()
```



## 7.2 : (Covariates)

### 7.2.1 :

- :
- :

```

# nlme
library(nlme)
library(tidyverse)

# Gompertz
gompertz <- function(dose, a, mu, lambda) {
  a / (1 + exp(-mu * (dose - lambda)))
}

#
set.seed(123)
dose <- seq(0, 10, 0.1)
n_dose <- length(dose)

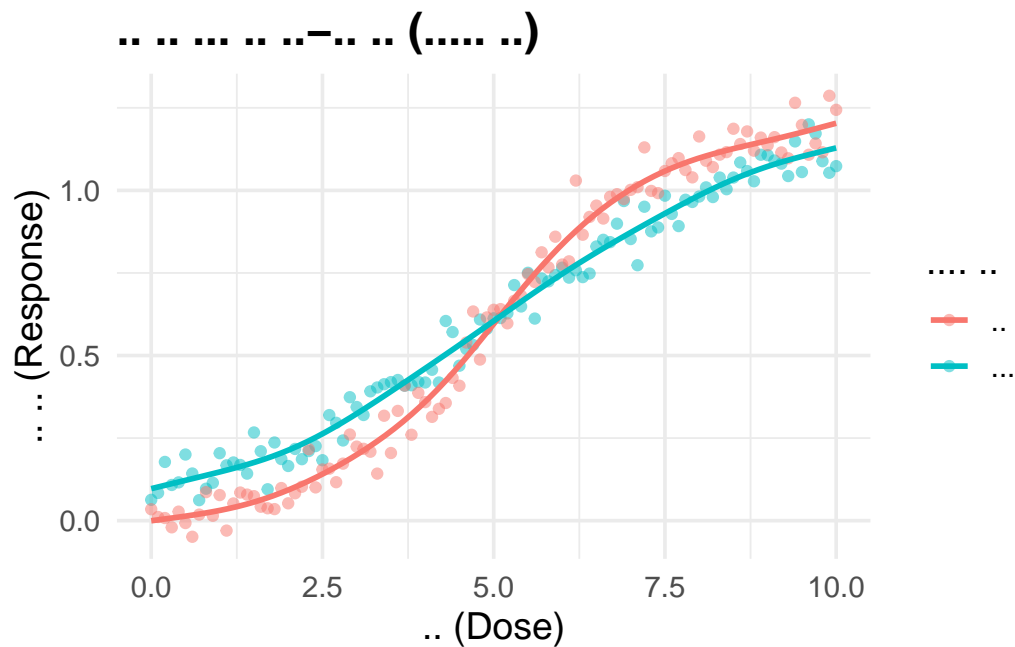
#           ( Gompertz )
resp_nonshift <- gompertz(dose, a = 1.2, mu = 0.5, lambda = 5) + rnorm(n_dose, 0, 0.05)

#           ( Gompertz )
resp_shift <- gompertz(dose, a = 1.2, mu = 0.8, lambda = 5) + rnorm(n_dose, 0, 0.05)

#
cohort_full <- tibble(
  dose = rep(dose, 2),
  shift = factor(c(rep(" ", n_dose), rep(" ", n_dose))),
  resp = c(resp_nonshift, resp_shift)
)

#
ggplot(cohort_full, aes(x = dose, y = resp, color = shift)) +
  geom_point(alpha = 0.5) +
  geom_smooth(method = "gam", formula = y ~ s(x), se = FALSE) +
  labs(
    title = "           -      (      )",
    x = "      (Dose)",
    y = "      (Response)",
    color = "      "
  ) +
  theme_minimal(base_size = 14) +
  theme(plot.title = element_text(face = "bold"))

```



```
#
#      Gompertz
# fixed = a + mu + lam ~ shift shift      a, mu, lam
nlme_fit <- nlme(
  model = resp ~ a / (1 + exp(-(mu * (dose - lam))))),
  data = cohort_full,
  fixed = a + mu + lam ~ shift,
  random = a + mu + lam ~ 1 | shift,
  start = c(a = c(1.2, 1.2), mu = c(0.5, 0.8), lam = c(5, 5)),
  control = list(pnlsTol = 0.01)
)
#
#summary(nlme_fit)

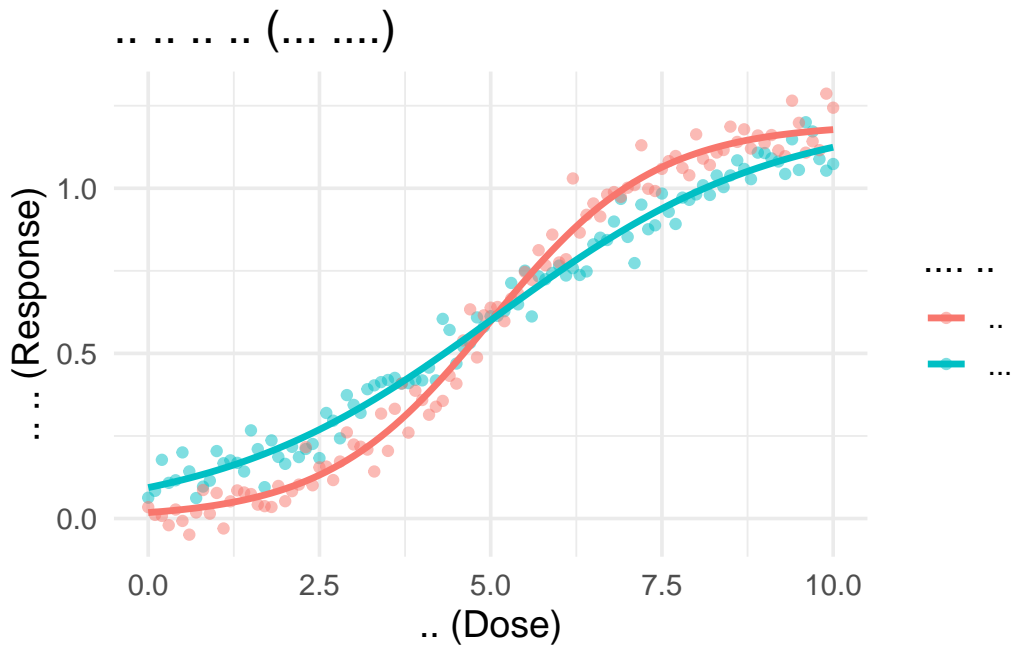
#
cohort_full$nlme_pred <- predict(nlme_fit)

#
ggplot(cohort_full, aes(x = dose, y = resp, color = shift)) +
  geom_point(alpha = 0.5) +
  geom_line(aes(y = nlme_pred, group = shift), size = 1.2) +
  labs(
    title = "      (      )",
```

```

x = " (Dose)",
y = " (Response)",
color = " "
) +
theme_minimal(base_size = 14)

```



```
summary(nlme_fit)
```

Nonlinear mixed-effects model fit by maximum likelihood

Model:  $\text{resp} \sim a/(1 + \exp(-(\mu * (\text{dose} - \text{lam}))))$

Data: cohort\_full

	AIC	BIC	logLik
	-634.3112	-591.3037	330.1556

Random effects:

Formula:  $\text{list}(a \sim 1, \mu \sim 1, \text{lam} \sim 1)$

Level: shift

Structure: General positive-definite, Log-Cholesky parametrization

	StdDev	Corr	
a.(Intercept)	9.047340e-07	a.(In) m.(In)	
mu.(Intercept)	1.149202e-06	0	
lam.(Intercept)	1.844210e-06	0	0

Residual 4.719949e-02

Fixed effects: a + mu + lam ~ shift

	Value	Std.Error	DF	t-value	p-value
a.(Intercept)	1.195727	0.01404366	195	85.14359	0.0000
a.shift	0.029480	0.03142533	195	0.93811	0.3493
mu.(Intercept)	0.835771	0.02898145	195	28.83812	0.0000
mu.shift	-0.345475	0.03510659	195	-9.84075	0.0000
lam.(Intercept)	5.000389	0.05323858	195	93.92415	0.0000
lam.shift	0.082515	0.14068227	195	0.58653	0.5582

Correlation:

	a.(In)	ashft	m.(In)	mshft	lm.(I)
a.shift	-0.447				
mu.(Intercept)	-0.685	0.306			
mu.shift	0.565	-0.680	-0.826		
lam.(Intercept)	0.770	-0.344	-0.527	0.435	
lam.shift	-0.291	0.910	0.200	-0.581	-0.378

Standardized Within-Group Residuals:

	Min	Q1	Med	Q3	Max
	-2.53316379	-0.67449163	-0.07048116	0.62151401	3.28479392

Number of Observations: 202

Number of Groups: 2

```
# p-value      (tidy )
# fixed effects      .
#fixed_effects <- summary(nlme_fit)$tTable
# p-value      . (t-value      (DF)      )
#p_values <- 2 * (1 - pt(abs(fixed_effects[, "t-value"]), fixed_effects[, "DF"]))
# p-value      summary      .
#fixed_effects_with_p <- cbind(fixed_effects, `p-value` = p_values)
#print(fixed_effects_with_p)
```

	(Value)	p-value	
a.(Intercept)	1.195727	0.0000	** (a)** .
a.shift	0.029480	0.3493	a .
			p-value 0.05 .
mu.(Intercept)	0.835771	0.0000	** (mu)** .

mu.shift	-0.345475	0.0000		<b>mu</b>
			. p-value	0.0001 ,
lam.(Intercept)	5.000389	0.0000	**	(lam)** .
lam.shift	0.082515	0.5582		<b>lam</b>
			.	.
***	(mu)	***	.	
-	.			