Solution - Sheet 03

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```r
library(nlme)
load("SimulatedTreatmentEffect-3pLL.RData")
```

```r
##Part a)
##In 3pLL model the first parameter theta_1=0 for the entire dataset.
model.3pLL.001 <-
  gnls(
    resp ~ (0 + (th4-0) / (1 + (exp((conc - th2) * th3)))),
    data = conc.resp.df,
    params = list(th2 + th3 + th4 ~ 1),
    start = c(1, 2, 100),
    control = gnlsControl(nlsTol = 0.1)
  )
model.3pLL.001
```

```
## Generalized nonlinear least squares fit
##   Model: resp ~ (0 + (th4 - 0)/(1 + (exp((conc - th2) * th3))))
##   Data: conc.resp.df
##   Log-likelihood: -228.6547
##
## Coefficients:
##       th2       th3       th4
##  0.959338  2.305889 99.081280
##
## Degrees of freedom: 68 total; 65 residual
## Residual standard error: 7.143413
```

The lower asymptote, θ_1, is 0 and the upper asymptote, θ_4 is 99.081280, which is nearly close to 100. At θ_2=0.959338, we got the half-maximal response which is (0.959338+99.081280)/2 = 50.02. The parameter θ_3=2.305889 > 0, which signifies a decreasing profile for increasing concentrations.

```r
##Part b)
##In 3pLL model the first parameter theta_11,theta_12,theta_13=0 for the entire dataset.
dum1 <- ifelse(conc.resp.df$treat == "T1", 1, 0)
dum2 <- ifelse(conc.resp.df$treat == "T2", 1, 0)
dum3 <- ifelse(conc.resp.df$treat == "T3", 1, 0)

model.3pLL.002 <- gnls(
  resp ~ th4 * dum3 +
```

```r
    (0 + (th4-0) / (1 + (exp((conc - th2) * th3)))),
  data = conc.resp.df,
  params = list(th2 + th3 + th4 ~ 1),
  start = c(1, 2, 100),
  control = gnlsControl(nlsTol = 0.1)
)
model.3pLL.002
```

```
## Generalized nonlinear least squares fit
##   Model: resp ~ th4 * dum3 + (0 + (th4 - 0)/(1 + (exp((conc - th2) * th3))))
##   Data: conc.resp.df
##   Log-likelihood: -300.7103
##
## Coefficients:
##       th2       th3       th4
##  1.271901  3.373962 80.102577
##
## Degrees of freedom: 68 total; 65 residual
## Residual standard error: 20.61115
```

The lower asymptote, θ_1, is 0 and the upper asymptote, θ_4 is 80.102577, which is actually not really close to 100. At θ_2=1.271901, we got the half-maximal response which is (1.271901+80.102577)/2 = 40.69. The parameter θ_3=3.373962 > 0, which signifies a decreasing profile for each increasing concentrations.

```r
##Part c)
model.3pLL.003 <- gnls(
  resp ~ (0 + (th4-0) / (1 + (exp((conc - th21) * th31)))) * (dum1)
    + (0 + (th4-0) / (1 + (exp((conc - th22) * th32 )))) * (dum2),
  data = conc.resp.df,
  params = list(th21 + th22 + th31 + th32 + th4 ~ 1),
  start = c(1, 1, 2, 2, 100),
  control = gnlsControl(nlsTol = 0.1, apVar = TRUE)
)
model.3pLL.003
```

```
## Generalized nonlinear least squares fit
##   Model: resp ~ (0 + (th4 - 0)/(1 + (exp((conc - th21) * th31)))) * (dum1) +      (0 + (th4 - 0)/(1 +
##   Data: conc.resp.df
##   Log-likelihood: -313.5675
##
## Coefficients:
##       th21       th22       th31       th32        th4
##  0.7304149  1.1886932  2.3739178  2.4848554 99.2201308
##
## Degrees of freedom: 68 total; 63 residual
## Residual standard error: 25.29317
```

The model use parameter θ_4 is shared across all three treatments and, θ_2 and θ_3 are estimated separately for the first and the second treatment. Lower asymptote θ_1 is zero. $\theta_2$1 0.730, $\theta_2$2 1.189 and the upper asymptote is 99.22, which is nearly close to 100. The parameter θ_{31}=2.3477416 > 0 and θ_{32}=2.4848554 > 0, a higher value for the slope parameter, demonstrates a steeper decrease of the curve.

```r
#Part d)
anova(model.3pLL.001, model.3pLL.002)
```

```
##                Model df      AIC      BIC    logLik
## model.3pLL.001     1  4 465.3094 474.1874 -228.6547
## model.3pLL.002     2  4 609.4207 618.2987 -300.7103
```

Both AIC and BIC value increases after adding the treatment 3 in the second model, which further increases p-value but not enough to cross the significance level of 5%, hence we can clearly reject the null hypothesis that both models are equivalent. This indicates that the second model has a significantly better fit and thus, we can difference between all the three treatment groups can be easily seen.

Exercise 4

$$f(x) = y = \theta_1 + \frac{\theta_4 - \theta_1}{1+\exp\left((x-\theta_2)\theta_3\right)}$$

a) Calculate slope of 4pLL model at concentration "θ_2".

$$\frac{d}{df} f(x) = \frac{(\theta_4-\theta_1)\left(\exp((x-\theta_2)\theta_3)\right).(-\theta_3)}{\left[1+\exp((x-\theta_2)\theta_3)\right]^2}$$

$$\left.\frac{d}{df} f(x)\right]_{x=\theta_2} = \frac{(\theta_4-\theta_1)\left(\exp((\theta_2-\theta_2).\theta_3)\right).(-\theta_3)}{\left[1+\exp((\theta_2-\theta_2)\theta_3)\right]^2}$$

$$= \boxed{-\frac{\theta_3}{4}(\theta_4-\theta_1)}$$

b) Show that $\theta_3 > 0$, it holds $\lim\limits_{x\to\infty} \theta_1 + \frac{\theta_4-\theta_1}{1+\exp((x-\theta_2)\theta_3)} = \theta_1$

and that for $\theta_3 < 0$, it holds, $\lim\limits_{x\to\infty} \theta_1 + \frac{\theta_4-\theta_1}{1+\exp((x-\theta_2)\theta_3)} = \theta_4$

From lecture,

for $\theta_3 > 0$, $\lim\limits_{x\to\infty} (x-\theta_2)\theta_3 = \infty$

holds s.t. $\lim\limits_{x\to\infty} \theta_1 + \underbrace{\frac{\theta_4-\theta_1}{\underbrace{1+\exp(\underbrace{(x-\theta_2)\theta_3}_{x\to\infty\ \to\infty})}_{x\to\infty\ \to\infty}}}_{x\to\infty\ \to 0} = \theta_1$

Hence

Similarly, for $\theta_3 < 0$, $\lim\limits_{x\to\infty} (x-\theta_2)\theta_3 = -\infty$, s.t.

$$\lim_{x\to\infty} \theta_1 + \frac{\theta_4-\theta_1}{\underbrace{1+\underbrace{\exp((x-\theta_2)\theta_3)}_{x\to\infty\ \to 0}}_{=1}} = \theta_4$$

Hence, $\theta_1 + \theta_4 - \theta_1 = \theta_4$.

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c) Show the equivalence of (sigmoidal) Emax model as defined in lecture, Define the parameters of the model in terms of parameter $\theta_1, \theta_2, \theta_3, \theta_4$.

we know, 4plL model,

$$f_{4pll}(x) = \theta_1 + \frac{\theta_4 - \theta_1}{1 + \exp((x - \theta_2)\theta_3)}$$

Also,

$$f_{sigmoidal}(x) = E_0 + \frac{x^n \cdot E_{max}}{x^n + ED50^n} \quad \text{——— (I)}$$

where, n – Hill parameter (usually $n > 0$)

For ~~estimating~~ defining parameters of model, let's assume w.l.o.g. $\underline{\underline{\theta_4 > \theta_1}}$.

Now, we assume case 1 :- $\theta_3 < 0$
case 2 :- $\theta_3 > 0$.

Case 1 :- $\theta_3 < 0$.

$$f_{4pll}(x) = \theta_1 + \frac{\theta_4 - \theta_1}{1 + \left(\frac{x}{\theta_2}\right)^{\theta_3}} \quad \text{——— (II)}$$

Now, we know, for $\theta_3 < 0$,

$E_0 = \theta_1$

$E_{max} = \theta_4 - \theta_1$

$n = -\theta_3 > 0$ [since $\theta_3 < 0$]

and, $ED50 = \theta_2$

Now, we plug into equation (I), we get,

$$f_{sigm}(x) = \theta_1 + (\theta_4 - \theta_1) \cdot \frac{x^{-\theta_3}}{x^{-\theta_3} + \theta_2^{-\theta_3}}$$

$$= \theta_1 + (\theta_4 - \theta_1) \cdot \frac{1}{1 + \left(\frac{x}{\theta_2}\right)^{\theta_3}}$$

[divide by x^{θ_3} both numerator and denominator].

$= \text{(II)} = f_{4pll}(x)$.

Analogously,

Case II: $\theta_3 > 0$.

$$E_0 = \theta_1$$
$$E_{max} = \theta_1 - \theta_4$$
$$n = \theta_3 > 0 \qquad [\text{since } \theta_3 > 0]$$
$$ED_{50} = \theta_2$$

plug these values in eq^n (1), again we get,

$$f_{sigm}(x) = \theta_4 + \frac{(\theta_1 - \theta_4)\, x^{\theta_3}}{x^{\theta_3} + \theta_2^{\theta_3}}.$$

Now, divide both Nr. & dr. by $\frac{1}{\theta_2^{\theta_3}}$,

$$= \theta_4 + (\theta_1 - \theta_4) \cdot \left[\frac{\left(\frac{x^{\theta_2}}{\theta_2^{\theta_3}}\right)}{1 + \frac{x^{\theta_3}}{\theta_2^{\theta_3}}} \right].$$

$$= \theta_4 + (\theta_1 - \theta_4)\left(1 - \frac{1}{\frac{x^{\theta_3}}{\theta_2^{\theta_3}} + 1}\right)$$

$$= \cancel{\theta_4} + \theta_1 \cancel{- \theta_4} + (\theta_4 - \theta_1)\frac{1}{\left(\frac{x^{\theta_3}}{\theta_2^{\theta_3}} + 1\right)}$$

$$= \theta_1 + \frac{(\theta_4 - \theta_1)}{1 + \left(\frac{x}{\theta_2}\right)^{\theta_3}} = f_{4pll}(x) = (ii).$$