Estimation, Inference and Monitoring for Functional Data Using Non-Linear Mixed Effects Models

May 20, 2022

1 Introduction, Aims and Methods

The dissertation will deal with the modeling and estimation of daily curves that describe the operational characteristics of a process. Typical settings where curves are of interest are encountered in manufacturing and in biological laboratories. The main operational characteristic is summarized through the relationship between two variables , which we model in parametric form. This relationship and hence the curve usually varies with time (day to day variability). We will deal with investigating variability over time and discuss ways of monitoring the underling process. Since, we use parametric models, the variability of the process is equivalent to the variability of the daily parameters and monitoring of the process can be achieved by monitoring the daily parameter vectors. Our motivating application is in the field of RIA - IRMA curves. Typically, these curves are used in diagnostic laboratories to obtain estimates of patient-specific biomarker levels through inverse regression. Each subsection that follows presents the main technical areas we will deal with.

1.1 Nonlinear Regression

Nonlinear regression is a form of regression analysis in which data are modeled by a function which is a nonlinear combination of the model parameters and depends on one or more independent variables. The data are fitted by a method of successive approximations. In our case, we will assume an non-linear model to describe the relationship between two variables. More specifically in RIA-IRMA studies, we will initially assume a 4 parameter logistic (4PL) model. Later, we will extend our results to a 5 parameter logistic (5PL) model.

1.2 Functional Data Analysis

Functional data analysis (FDA) is a branch of statistics that analyzes data providing information about curves, surfaces or anything else varying over a continuum. In its most general form, under an FDA framework, each sample element of functional data is considered to be a random function. In our special case, the physical continuum over which these functions are defined is time. Intrinsically, functional data are infinite dimensional. We overcome this difficulty by assuming parametric forms of these curves. The random behavior of the curves is then equivalent to the random behavior of the parameter vector that describes a curve. We will first assume, that the daily parameter vector is a random draw from a multivariate distribution. We will also assume that this generating distribution can also be modeled parametrically. This leads to an nonlinear mixed model approach. Later, we will investigate multivariate time series structures for the parameter vector.

1.3 Statistical Quality Control

The use of statistical methods in the monitoring and maintaining of the quality of products and services. We will focus on statistical process control, using multivariate control charts to monitor the parameters of interest. This is crucial in the RIA-IRMA setting since out of control curves lead to disease miss-diagnosis. In practice, this may mean that the experiment to obtain the curve must be repeated or the laboratory has to sick alternative kit providers.

1.4 Dose response curves

A dose response curve is a plot of a measure of biological function versus the concentration of a drug or hormone. The term “dose” is often used loosely. In its strictest sense, the term only applies to experiments performed with animals or people, where you administer various doses of drug. The term “dose-response curve” is also used more loosely to describe in vitro experiments where you apply known concentrations of drugs such as in our RIA - IRMA applications.

2 Our motivating application : Analysis of the AHEPA Data

The AHEPA nuclear medicine lab conducts various diagnostic tests by measuring appropriate biomarker levels. We focus here on biomarkers (hormones) related to the proper function of the thyroid. Patient hormone levels on a given day are not measured directly in the lab but are estimated through the relationship between the hormone level (dose) and the response, antibody-bound counts per minute (cpm), obtained after an experiment is conducted in the morning of that day. The experiment is conducted by a lab technician who uses known dose levels that are included in a kit of standards shipped by the manufacturer. Using these standard doses (2 replicates per dose level) the relationship between dose and response (cpm), that is the dose response curve, is established for that day. This dose response curve is then checked using control samples that are contained in the same kit. Typically 2 levels of control dose are used to check the curve and may involve replicates for each level. Given that the curve is deemed adequate, the curve is then used to estimate patient hormone levels for that day. For a given patient's blood sample with an unknown hormone level the same experiment is conducted using the same kit and a response (cpm) is obtained. The unknown hormone level is then estimated by inverse regression on that day's curve. In the data used in this thesis, the hormone FT4 involved 6 dose levels for the standards. We note here that the AHEPA hospital lab constructs the dose response curves using a monotone cubic spline algorithm fitted to the average cpm values per dose level. In this thesis we estimate the dose response curves using multi-parameter (parametric) logistic models.

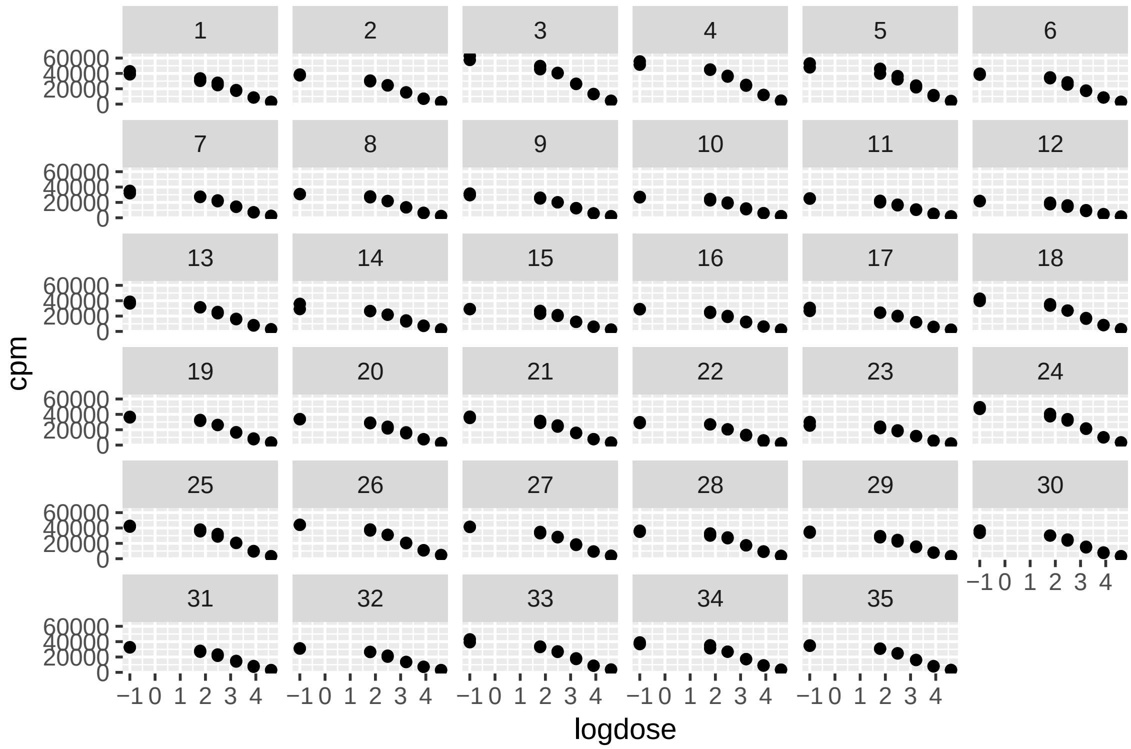

Figure 1

3 Estimation of Individual Curves

Our data contained RIA measurements for all calendar days of 2018 for FT4. For this hormone and for each date, we first fitted a 4 parameter logistic model. Since the response is count variable, we worked with the Poisson distribution for the response. Figure 1 and 2 show our data.

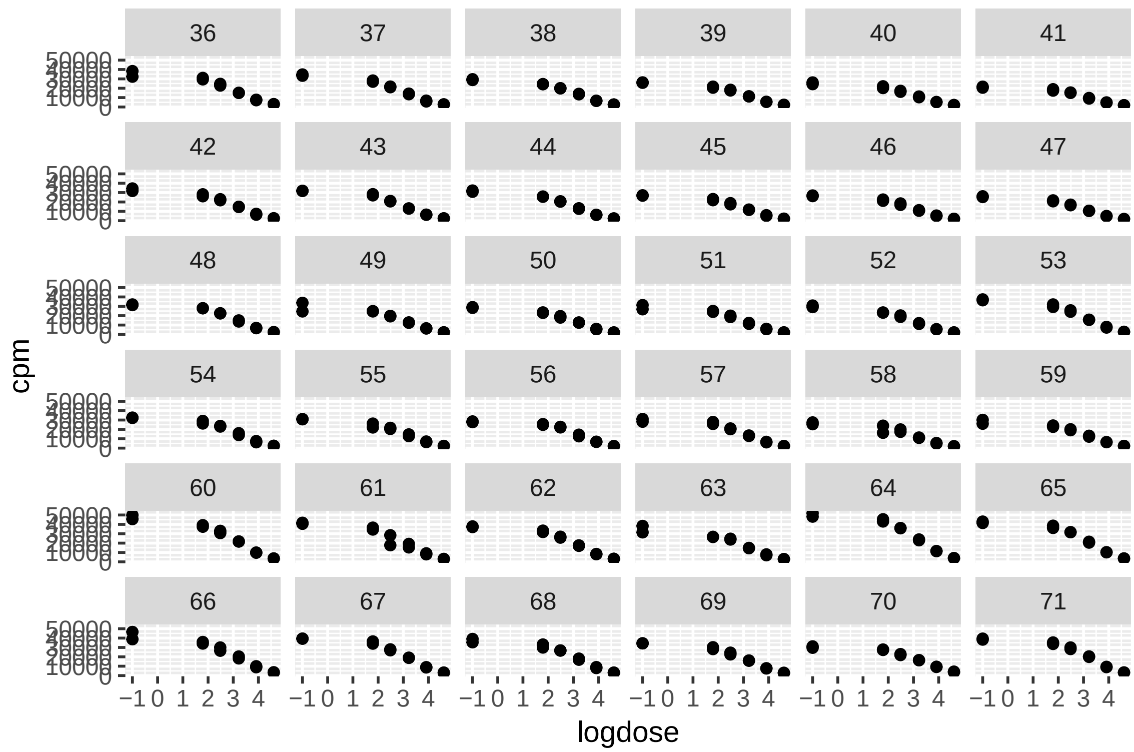
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
cpm
logdose

Figure 2

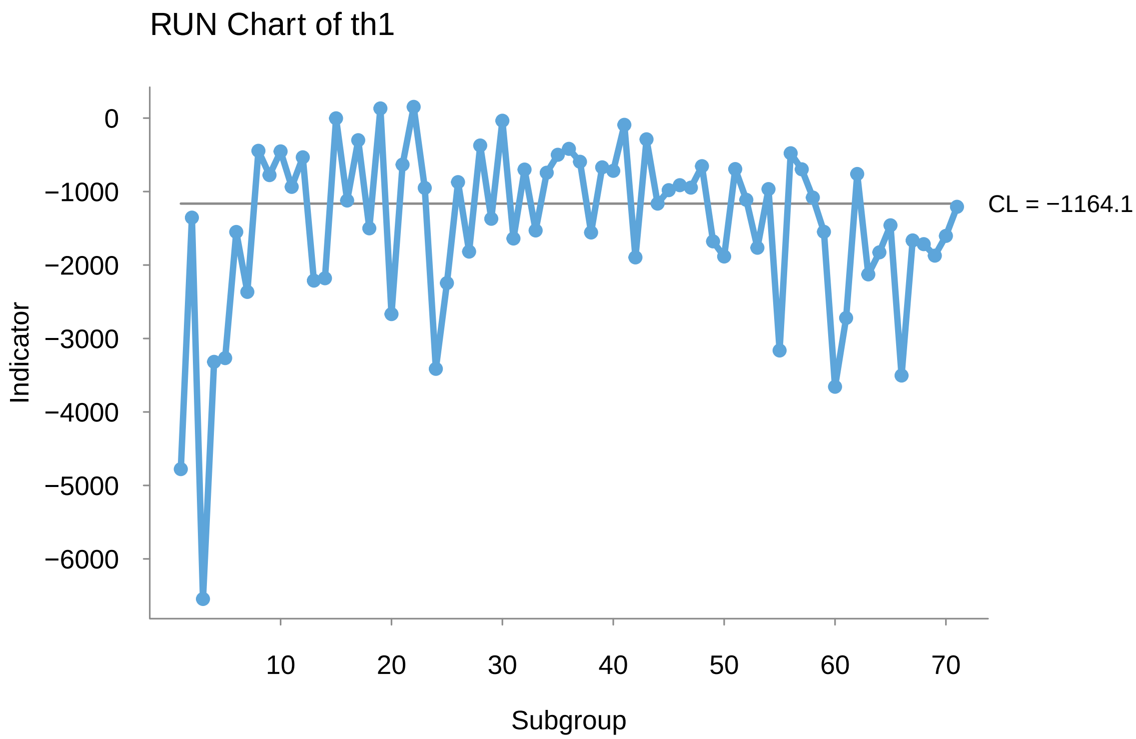
RUN Chart of th1
0
−1000
−2000
−3000
−4000
−5000
−6000
Indicator
10
20
30
40
50
60
70
Subgroup
CL = −1164.1

Figure 3

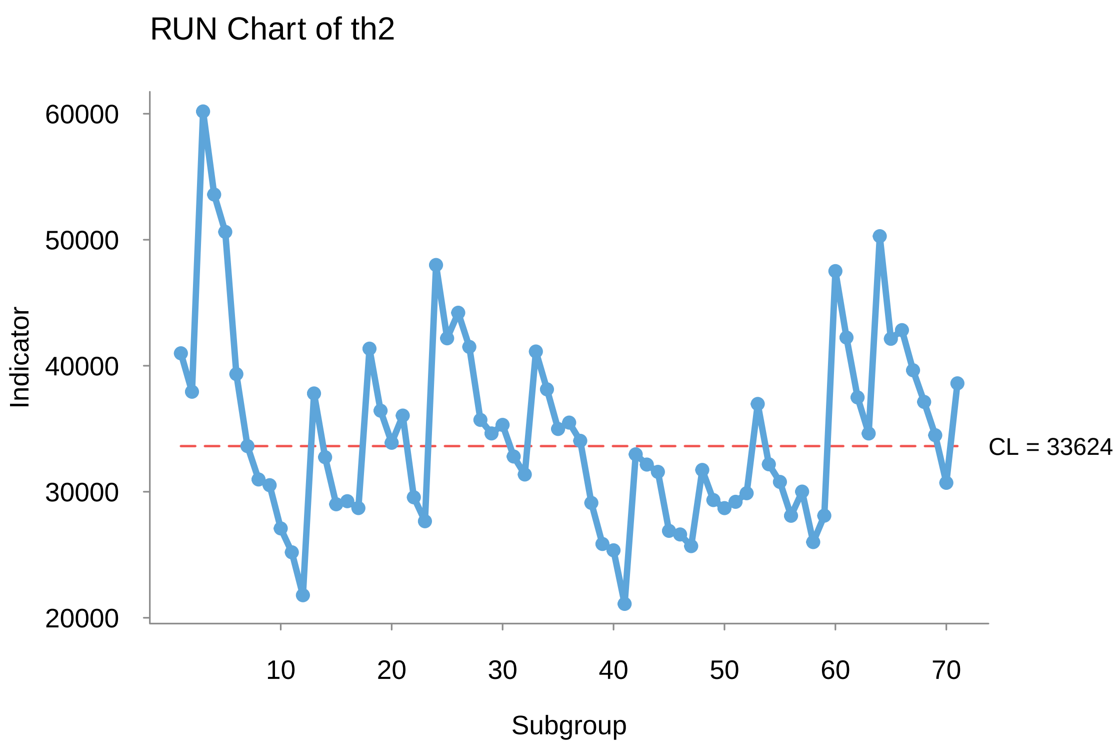
RUN Chart of th2
60000
50000
40000
30000
20000
Indicator
CL = 33624
10
20
30
40
50
60
70
Subgroup

Figure 4

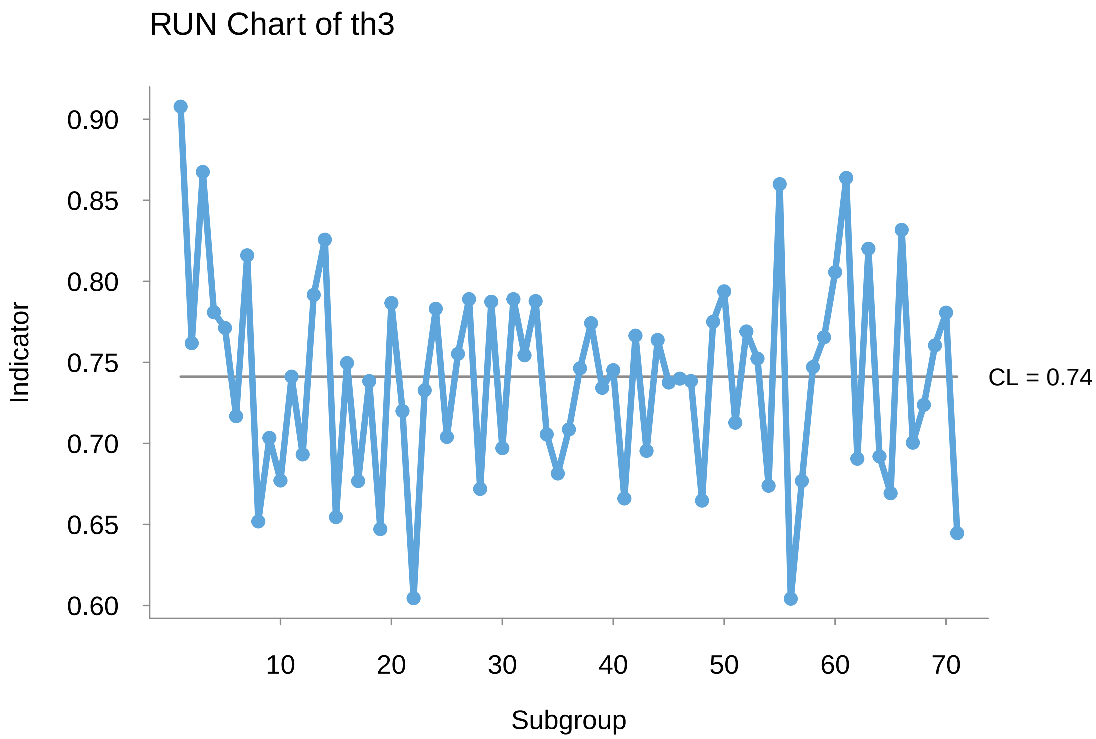
RUN Chart of th3
Indicator
0.90
0.85
0.80
0.75
0.70
0.65
0.60
CL = 0.74
10
20
30
40
50
60
70
Subgroup

Figure 5

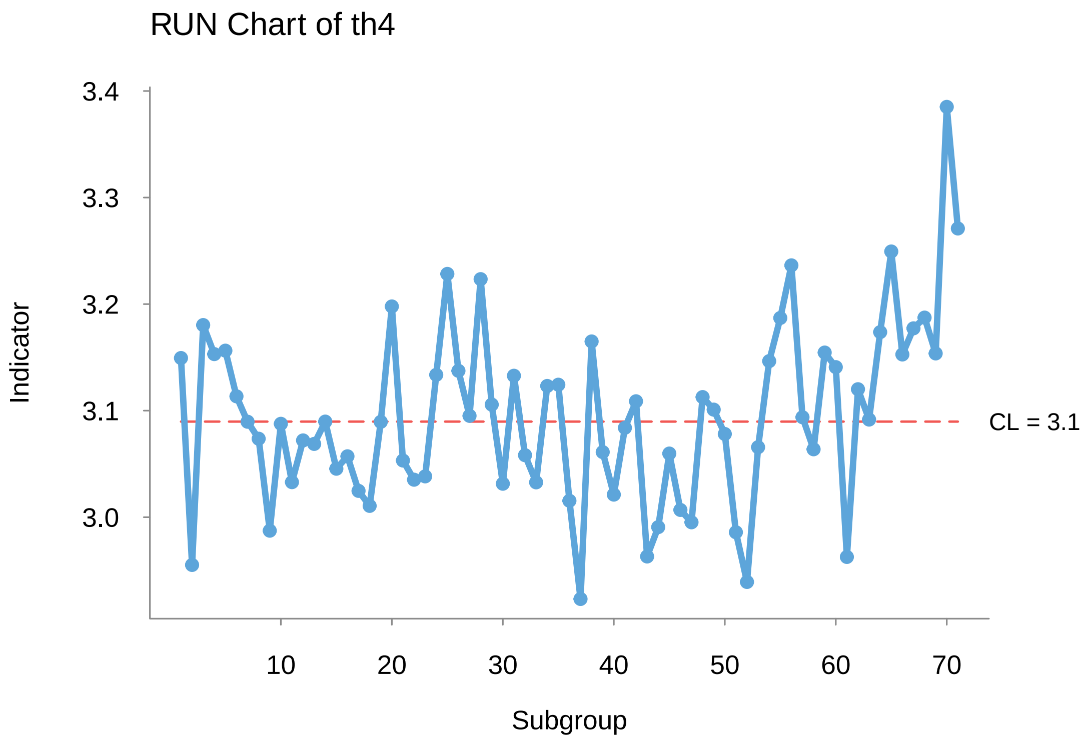
RUN Chart of th4
Indicator
3.4
3.3
3.2
3.1
3.0
CL = 3.1
10
20
30
40
50
60
70
Subgroup

Figure 6

3.1 Logistic curve with four parameters

The four parameter logistic curve is given by:

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

In the four parameter logistic curve, we have that θ_2 is the lower horizontal asymptote, θ_1 is the upper horizontal asymptote, θ_4 is the value of x at the point of inflection of the curve and θ_3 is a numeric scale parameter on the x $axis$.

4 Estimation in the fixed effects Poisson model

4.1 Fixed effects model with common parameter values for all days

We assume 2 replicates per dose level. Let $\boldsymbol{\theta}$ denote the 4×1 vector of parameters.

$$\begin{aligned} Y_{ijr} &\sim^{ind} Poisson(\mu_{ij}),\ i = 1, \dots, I,\ j = 1, \dots, J,\ r = 1, 2, \\ \mu_{ij}(\boldsymbol{\theta}) &= \theta_2 + \frac{\theta_1 - \theta_2}{1 + e^{\frac{\theta_4 - x_{ij}}{\theta_3}}}, \end{aligned} \tag{4.1}$$

where i indicates day, j indicates dose level and r indicates replicate.

We write the parameter vector as:

$$\boldsymbol{\theta} = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \\ \theta_4 \end{bmatrix}$$

We write the loglikelihood as:

$$l(\boldsymbol{\theta}) = \sum_{i=1}^{k} l_i(\boldsymbol{\theta})$$

where

$$l_i(\theta) = -2k \sum_{j=1}^{m} \mu_j + \sum_{j=1}^{m} y_{.j.} \ln \mu_j - \sum_{j=1}^{m} \sum_{r=1}^{2} lny_{ijr}!$$

with

$$\mu_j(\boldsymbol{\theta}) = \theta_2 + \frac{\theta_1 - \theta_2}{1 + e^{\frac{\theta_4 - x_j}{\theta_3}}}$$

The 4 estimating equations are obtained by setting the derivatives to zero,

$$\frac{\partial l(\theta)}{\partial \boldsymbol{\theta}} = 2k\sum_{j=1}^{m}\frac{\partial \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}(\frac{\bar{y}_{.j.}-\mu_j(\boldsymbol{\theta})}{\mu_j(\boldsymbol{\theta})})$$

$$\frac{\partial l(\theta)}{\partial \boldsymbol{\theta}} = 2k\sum_{j=1}^{m}\frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}[\bar{y}_{.j.}-\mu_j(\boldsymbol{\theta})] = \mathbf{0}_4.$$

Thus, the loglikelihood is

$$\begin{aligned}
lnL &= -2k\sum_{j=1}^{m}\mu_j + \sum_{j=1}^{m}\sum_{i=1}^{k}\sum_{r=1}^{2} y_{ijr}\ln\mu_j - \sum_{i=1}^{k}\sum_{j=1}^{m}\sum_{r=1}^{2}\ln(y_{ijr}!) \\
&= -2k\sum_{j=1}^{m}\mu_j + \sum_{j=1}^{m}\ln\mu_j\sum_{i=1}^{k}\sum_{r=1}^{2} y_{ijr} - \sum_{i=1}^{k}\sum_{j=1}^{m}\sum_{r=1}^{2} lny_{ijr}! \\
&= -2k\sum_{j=1}^{m}\mu_j + 2k\sum_{j=1}^{m}(\bar{y}_{.j.})\ln\mu_j - \sum_{i=1}^{k}\sum_{j=1}^{m}\sum_{r=1}^{2} lny_{ijr}!
\end{aligned}$$

$$\frac{\partial lnL}{\partial \theta_l} = -2k\sum_{j=1}^{m}\frac{\partial \mu_j(\boldsymbol{\theta})}{\partial \theta_l} + \sum_{j=1}^{m}(y_{.j.})\frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial \theta_l},\ l = 1,\ldots,4$$

An estimate of the parameters is obtained by solving the nonlinear system of equations $-2k\sum_{j=1}^{m}\frac{\partial \mu_j(\boldsymbol{\theta})}{\partial \theta_l} + \sum_{j=1}^{m}(y_{.j.})\frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial \theta_l} = 0,\ l = 1,\ldots,4$

In vector form, the estimating equations are given by:

$$\frac{\partial lnL}{\partial \boldsymbol{\theta}} = 2k\sum_{j=1}^{m}\frac{\partial \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}(\frac{\bar{y}_{.j.}-\mu_j(\boldsymbol{\theta})}{\mu_j(\boldsymbol{\theta})})$$

$$\frac{\partial lnL}{\partial \boldsymbol{\theta}} = 2k\sum_{j=1}^{m}\frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}[\bar{y}_{.j.}-\mu_j(\boldsymbol{\theta})] = \mathbf{0}_4.$$

The matrix of second derivatives is:

$$\frac{\partial^2 lnL}{\partial \boldsymbol{\theta}\partial \boldsymbol{\theta}'} = 2k\sum_{j=1}^{m}(\frac{\partial^2 \ln \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}\partial \boldsymbol{\theta}'}[\bar{y}_{.j.}-\mu_j(\boldsymbol{\theta})] - \frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}\frac{\partial \mu_j(\theta)}{\partial \boldsymbol{\theta}'})$$

$$\frac{\partial^2 lnL}{\partial \boldsymbol{\theta}\partial \boldsymbol{\theta}'} = 2k\sum_{j=1}^{m}\frac{\partial^2 \ln \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}\partial \boldsymbol{\theta}'}[\bar{y}_{.j.}-\mu_j(\boldsymbol{\theta})] - 2k\sum_{j=1}^{m}\frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}\frac{\partial \mu_j(\theta)}{\partial \boldsymbol{\theta}'}$$

Is easilly seen that the Fisher Information matrix is:

$$I(\boldsymbol{\theta}) = -E[\frac{\partial^2 lnL}{\partial\boldsymbol{\theta}\partial\boldsymbol{\theta}'}]$$
$$I(\boldsymbol{\theta}) = 2k\sum_{j=1}^{m}\frac{\partial \ln \mu_j(\boldsymbol{\theta})}{\partial\boldsymbol{\theta}}\frac{\partial\mu_j(\theta)}{\partial\boldsymbol{\theta}'},$$

and

$$\hat{\boldsymbol{\theta}} \sim AN(\boldsymbol{\theta}, I^{-1}(\boldsymbol{\theta}))$$

4.2 Fixed effects model with day-specific parameters

$$\begin{aligned} Y_{ijr} &\sim^{ind} Poisson(\mu_{ij}),\ i=1,\ldots,k,\ j=1,\ldots,m,\ r=1,2, \\ \mu_{ij} &= \theta_{i2} + \frac{\theta_{i1}-\theta_{i2}}{1+e^{\frac{\theta_{i4}-x_{ij}}{\theta_{i3}}}}, \end{aligned} \tag{4.2}$$

We write the parameter vector as:

$$\boldsymbol{\theta} = \begin{bmatrix} \theta_{11} \\ \theta_{12} \\ \theta_{13} \\ \theta_{14} \\ - \\ \theta_{21} \\ \theta_{22} \\ \theta_{23} \\ \theta_{24} \\ - \\ \vdots \\ - \\ \theta_{k1} \\ \theta_{k2} \\ \theta_{k3} \\ \theta_{k4} \end{bmatrix} = \begin{bmatrix} \boldsymbol{\theta_1^*} \\ \boldsymbol{\theta_2^*} \\ \vdots \\ \boldsymbol{\theta_k^*} \end{bmatrix}$$

We write the loglikelihood as:

$$\begin{aligned} l(\boldsymbol{\theta}) &= \sum_{i=1}^{k} l_i(\boldsymbol{\theta}) \\ &= \sum_{i=1}^{k} l_i(\boldsymbol{\theta_i}) \end{aligned}$$

where

$$l_i(\theta) = -2\sum_{j=1}^{m}\mu_{ij} + \sum_{j=1}^{m}\ln(\mu_{ij})y_{ij.} - \sum_{j=1}^{m}\sum_{r=1}^{2} ln y_{ijr}!$$

with

$$\mu_{ij}(\boldsymbol{\theta}) = \theta_{i2} + \frac{\theta_{i1} - \theta_{i2}}{1 + e^{\frac{\theta_{i4} - x_j}{\theta_{i3}}}}$$

The $4 * 1$ estimating equations are obtained by setting the derivatives to zero,

$$\frac{\partial l(\theta)}{\partial \boldsymbol{\theta}} = -2\sum_{j=1}^{m} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_{il}} + \sum_{j=1}^{m} (y_{ij.}) \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_{il}},$$

$$\begin{aligned} \ln L &= -2\sum_{i=1}^{k}\sum_{j=1}^{m} \mu_{ij} + \sum_{i=1}^{k}\sum_{j=1}^{m} \ln(\mu_{ij}) \sum_{r=1}^{2} y_{ijr} - \sum_{i=1}^{k}\sum_{j=1}^{m}\sum_{r=1}^{2} lny_{ijr}! \\ &= -2\sum_{i=1}^{k}\sum_{j=1}^{m} \mu_{ij} + \sum_{i=1}^{k}\sum_{j=1}^{m} \ln(\mu_{ij}) y_{ij.} - \sum_{i=1}^{k}\sum_{j=1}^{m}\sum_{r=1}^{2} lny_{ijr}! \end{aligned}$$

$$\frac{\partial lnL}{\partial \theta_{il}} = -2\sum_{j=1}^{m} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_{il}} + \sum_{j=1}^{m} (y_{ij.}) \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_{il}}, \ l = 1, \ldots, 4$$

An estimate of the parameters is obtained by solving the nonlinear system of equations $-2\sum_{j=1}^{m} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_{il}} + \sum_{j=1}^{m} (y_{ij.}) \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_{il}} = 0, \ l = 1, \ldots, 4 \ i = 1, \ldots, k$

Figures 3,4,5 and 6 shows simple univariate control charts for the estimated parameters (AHEPA data).

4.3 Fixed effects model with day-specific parameters and parameter θ_3 fixed

$$\begin{aligned}
Y_{ijr} &\sim^{ind} Poisson(\mu_{ij}),\ i=1,\ldots,k,\ j=1,\ldots,m,\ r=1,2, \\
\mu_{ij} &= \theta_{i2}+\frac{\theta_{i1}-\theta_{i2}}{1+e^{\frac{\theta_{i4}-x_{ij}}{\theta_3}}},
\end{aligned} \tag{4.3}$$

We write the parameter vector as:

$$\boldsymbol{\theta}=\begin{bmatrix}\theta_{11}\\ \theta_{12}\\ \theta_{14}\\ -\\ \theta_{21}\\ \theta_{22}\\ \theta_{24}\\ -\\ \vdots\\ -\\ \theta_{k1}\\ \theta_{k2}\\ \theta_{k4}\\ -\\ \theta_3\end{bmatrix}=\begin{bmatrix}\boldsymbol{\theta_1^*}\\ \boldsymbol{\theta_2^*}\\ \vdots\\ \boldsymbol{\theta_k^*}\\ \theta_3\end{bmatrix}$$

We write the loglikelihood as:

$$\begin{aligned}
l(\boldsymbol{\theta}) &= \sum_{i=1}^{k} l_i(\boldsymbol{\theta}) \\
&= \sum_{i=1}^{k} l_i(\boldsymbol{\theta_i^*},\theta_3)
\end{aligned}$$

where

$$l_i(\boldsymbol{\theta_i},\theta_3) = 2\sum_{j=1}^{m}[\bar{y}_{ij}\ln\mu_{ij}(\boldsymbol{\theta_i},\theta_3)-\mu_{ij}(\boldsymbol{\theta_i},\theta_3)]-\sum_{j=1}^{m}\sum_{r=1}^{2}y_{ijr}!$$

with

$$\mu_{ij}(\boldsymbol{\theta_i}, \theta_3) = \theta_{i2} + \frac{\theta_{i1} - \theta_{i2}}{1 + e^{\frac{\theta_{i4} - x_{ij}}{\theta_3}}}$$

The $3k+1$ estimating equations are obtained by setting the derivatives to zero,

$$\begin{aligned}
\frac{\partial l(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}_i^*} &= \frac{\partial l_i(\boldsymbol{\theta_i^*}, \theta_3)}{\partial \boldsymbol{\theta}_i^*} \\
&= 2\sum_{j=1}^{m} \frac{\partial \mu_{ij}(\theta)}{\partial \boldsymbol{\theta_i^*}} (\frac{\bar{y}_{ij.} - \mu_{ij}(\boldsymbol{\theta})}{\mu_{ij}(\boldsymbol{\theta})});\ i = 1, \ldots, k \\
\frac{\partial l(\boldsymbol{\theta})}{\partial \theta_3} &= \sum_{i=1}^{k} \frac{\partial l_i(\theta_1^*, \theta_3)}{\partial \theta_3} \\
&= 2\sum_{i=1}^{k}\sum_{j=1}^{m} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3} (\frac{\bar{y}_{ij.} - \mu_{ij}(\boldsymbol{\theta})}{\mu_{ij}(\boldsymbol{\theta})})
\end{aligned}$$

.

Since θ_3 appears in each day specific curve, the $3k+1$ have to be solved simultaneously which for large k becomes computationally infeasible. We instead the maximize loglikelihood by using the profile likelihood

$$\begin{aligned}
l_p(\theta_3) &= \max_{\theta_1^*, \theta_2^*, \ldots, \theta_k^*} l(\theta_1^*, \theta_2^*, ..., \theta_k^*, \theta_3) \\
&= \max_{\theta_1^*, \theta_2^*, \ldots, \theta_k^*} \sum_{i=1}^{k} l_i(\boldsymbol{\theta_i^*}, \theta_3) \\
&= \sum_{i=1}^{k} \max_{\theta_i^*} l_i(\boldsymbol{\theta_i^*}, \theta_3),
\end{aligned}$$

which implies k seperate maximizations.
The mles are given by:

$$\hat{\theta}_3 = \arg\max_{\theta_3} l_p(\theta_3)$$

$$\hat{\theta_i^*} = \arg\max_{\theta_i^*} l(\theta_i^*, \hat{\theta}_3)$$

It can be shown, that $l_p(\hat{\theta}_3) = \max_{\theta_{13} = \cdots = \theta_{I3}} l(\boldsymbol{\theta})$

5 Likelihood Ratio Test

Using the Ahepa data, we test two hypotheses:

1) The parameters we may constant for day to day, that is:

$H_{01}: \; \theta_{11} = \cdots = \theta_{I1}, \; \theta_{12} = \cdots = \theta_{I2}, \; \theta_{13} = \cdots = \theta_{I3}, \; \theta_{14} = \cdots = \theta_{I4}$

2) The slope at the inflection point is constant for all curves, that is:

$H_{02}: \; \theta_{13} = \cdots = \theta_{I3},$

We first apply the likelihood ratio test to test H_{01}. We compute the likelihood ratio test statistic, $2[lnL(\hat{\theta}) - lnL(\hat{\theta}_{H_{01}})]$, where $\hat{\theta}$ is the mle for the full model and $\hat{\theta}_{H_{01}}$ is the mle for the restricted model. Under H_{01}, the test statistic asymptotically follows $\chi^2_{4(I-1)}$. In our case, χ^2_{280}. The observed value of the test statistic is $2(145843157 - 145465468) = 755378$. The corresponding asymptotic p-value is $P(\chi^2_{280} > 755378) = 0$ which leads to reject the null hypothesis.

Then, we apply the likelihood ratio test to test H_{02}. We compute the likelihood ratio test statistic, $2[lnL(\hat{\theta}) - lnL(\hat{\theta}_{H_{02}})]$, where $\hat{\theta}$ is the mle for the full model and $\hat{\theta}_{H_{02}}$ is the mle for the restricted model. Under H_{02}, the test statistic asymptotically follows $\chi^2_{(I-1)}$. In our case, χ^2_{70}. The observed value of the test statistic is $2(145843157 - 145841906) = 2502$. The corresponding asymptotic p-value is $P(\chi^2_{280} >) = 0$ which leads to reject the null hypothesis.

We can choose between the three models using the $AIC = -2\ln(\hat{L}) + 2 \times$(number of estimated parameters in the model) .

In our models, we have:

$AIC(full) = -2 \times (145843157) + 2 \times (4 \times 71) =$

$AIC(H_{02}) = -2 \times (145841906) + 2 \times (3 \times 71 + 1) =$

$AIC(H_{01}) = -2 \times (145465468) + 2 \times (4) =$

6 Non-Linear Mixed Models

In this section, we assume that the day-specific parameter vectors, $\boldsymbol{\theta}_i = (\theta_{i1}, \theta_{i2}, \theta_{i3}, \theta_{i4})^T$, are iid draws from a multivariate normal distribution. This results in an nonlinear mixed effects model. By denoting day by i, dose level by j and replicate by r, we have:

$$
\begin{aligned}
Y_{ijr}|\boldsymbol{\theta}_i &\sim^{ind} Poisson(\mu_{ij}(\boldsymbol{\theta}_i)),\ i = 1, \ldots, k,\ j = 1, \ldots, m,\ r = 1, 2, \\
\mu_{ij}(\boldsymbol{\theta}_i) &= \theta_{i2} + \frac{\theta_{i1} - \theta_{i2}}{1 + e^{\frac{\theta_{i4} - x_{ij}}{\theta_{i3}}}}, \\
\boldsymbol{\theta}_i &\sim_{iid} N(\boldsymbol{\mu}_\theta, \boldsymbol{\Sigma}_\theta),
\end{aligned}
\tag{6.1}
$$

$$
\boldsymbol{\mu}_\theta = \begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \\ \mu_4 \end{bmatrix}, \boldsymbol{\Sigma}_\theta = \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} \\ \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 \end{bmatrix}
$$

Let $\boldsymbol{\theta} = [\theta_1^T, \theta_2^T, \ldots, \theta_k^T]^T$. Also, let $\boldsymbol{y}_i = [y_{i11}, y_{i12}, y_{i21}, y_{i22}, \ldots, y_{im1}, y_{im2}]^T$ and $\boldsymbol{y} = (\boldsymbol{y}_1^T, \ldots, \boldsymbol{y}_k^T)^T$ We denote the likelihood by $L(\boldsymbol{\mu}_\theta, \boldsymbol{\phi}_\theta|\boldsymbol{y})$ and the log-likelihood by $l(\boldsymbol{\mu}_\theta, \boldsymbol{\phi}_\theta|\boldsymbol{y})$, where $\boldsymbol{\phi}_\theta = (\sigma_1^2, \sigma_{12}, \sigma_{13}, \sigma_{14}, \sigma_2^2, \sigma_{23}, \sigma_{24}, \sigma_3^2, \sigma_{34}, \sigma_4^2)$. We have

$$\begin{aligned}
L(\boldsymbol{\mu}_\theta, \boldsymbol{\phi}_\theta|\boldsymbol{y}) &= f_{\boldsymbol{Y}}(\boldsymbol{y}|\boldsymbol{\mu}_\theta, \boldsymbol{\phi}_\theta) \\
&= \int f(\boldsymbol{y}, \boldsymbol{\theta}) d\boldsymbol{\theta} \\
&= \int f(\boldsymbol{y}|\boldsymbol{\theta}) f(\boldsymbol{\theta}) d\boldsymbol{\theta} \\
&= \int f(\boldsymbol{y}|\boldsymbol{\theta}) \prod_{i=1}^{k} f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i \\
&= \int \prod_{i=1}^{k} f(\boldsymbol{y}_i|\boldsymbol{\theta}_i) \prod_{i=1}^{k} f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i \\
&= \prod_{i=1}^{k} \int f(\boldsymbol{y}_i|\boldsymbol{\theta}_i) f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i \\
l(\boldsymbol{\mu}_\theta, \boldsymbol{\phi}_\theta|\boldsymbol{y}) &= \sum_{i=1}^{k} \log \int f(\boldsymbol{y}_i|\boldsymbol{\theta}_i) f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i
\end{aligned} \tag{6.2}$$

We have

$$f(\boldsymbol{y}_i|\boldsymbol{\theta}_i) = \frac{1}{\prod_{j=1}^{m} \prod_{r=1}^{2} (y_{ijr!})} \exp(2 \sum_{j=1}^{m} (\bar{y}_{ij.} \log \mu_{ij}(\boldsymbol{\theta}_i) - \mu_{ij}(\boldsymbol{\theta}_i))). \tag{6.3}$$

Thus,

$$\begin{aligned}
l(\boldsymbol{\mu}_\theta, \boldsymbol{\phi}_\theta|\boldsymbol{y}) &= \sum_{i=1}^{k} \log \int \frac{1}{\prod_{j=1}^{m} \prod_{r=1}^{2} (y_{ijr!})} \exp(2 \sum_{j=1}^{m} (\bar{y}_{ij.} \log \mu_{ij}(\boldsymbol{\theta}_i) - \mu_{ij}(\boldsymbol{\theta}_i))) f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i \\
&= \sum_{i=1}^{k} \log[\frac{1}{\prod_{j=1}^{m} \prod_{r=1}^{2} (y_{ijr!})} \int \exp(2 \sum_{j=1}^{m} (\bar{y}_{ij.} \log \mu_{ij}(\boldsymbol{\theta}_i) - \mu_{ij}(\boldsymbol{\theta}_i))) f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i] \\
&\propto \sum_{i=1}^{k} \log[\int e^{(2 \sum_{j=1}^{m} (\bar{y}_{ij.} \log \mu_{ij}(\boldsymbol{\theta}_i) - \mu_{ij}(\boldsymbol{\theta}_i)))} f(\boldsymbol{\theta}_i) d\boldsymbol{\theta}_i] \\
&\propto \sum_{i=1}^{k} \log \int e^{(2 \sum_{j=1}^{m} (\bar{y}_{ij.} \log \mu_{ij}(\boldsymbol{\theta}_i) - \mu_{ij}(\boldsymbol{\theta}_i)))} \frac{e^{-\frac{1}{2}(\boldsymbol{\theta}_i - \boldsymbol{\mu}_\theta)^T \boldsymbol{\Sigma}_\theta^{-1} (\boldsymbol{\theta}_i - \boldsymbol{\mu}_\theta)}}{(2\pi)^{4/2} |\boldsymbol{\Sigma}_\theta|^{1/2}} d\boldsymbol{\theta}_i
\end{aligned} \tag{6.4}$$

7 Further Research

We will conduct simulation studies to investigate the statistical properties of our procedures concerning the fixed effects models. Furthermore, we will pursue algorithms for estimation in the non-linear mixed model with discrete response (eg Poisson,Negatine Bionomial). Later, we will investigate multivariate time series structures for the parameter vector. Also, we will extend the methods of the statistical quality control for functional data.

8 Bibliography

1) Centofanti, F., Lepore, A., Menafoglio, A., Palumbo, B., Vantini, S. (2020). Functional Regression Control Chart
2) Miguel Flores , Salvador Naya , Rubén Fernández-Casal , Sonia Zaragoza,Paula Raña 3 and Javier Tarrío-Saavedra (2020) . Constructing a Control Chart Using Functional Data
3) Gerda Claeskens, Emilie Devijver, Irene Gijbels (2021). Nonlinear mixed effects modeling and warping for functional data using B-splines∗
4)Yakuan Chen (2017). Methods for functional regression and nonlinear mixed-effects models with applications to PET data
5)Huet, S. , Bouvier, A. , Poursat, M.A. and Jolivet, E. (2004). Statistical Tools for Nonlinear Regression, Springer
6) Maisey, M.N., Britton, K.E. and Gilday, D.L. (1991). Clinical Nuclear Medicine, Springer
7) Motulsky, H. and Christopoulos, A. (2004). Fitting Models to Biological Data Using Linear and Nonlinear Regression, Oxford
8) Ritz, C. and Streibig, J.C. (2008). Nonlinear Regression with R, Springer
9) Xu-Feng, N. (2004). Statistical Procedures for Testing Homogeneity of Water Quality Parameter

9 Appendix

9.0.1 Derivatives of four parameter logistic model

$$
\begin{aligned}
\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1} &= \frac{1}{1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}}} \quad , \quad \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1} = \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\left(\frac{1}{1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}}}\right) \\
\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2} &= 1 - \frac{1}{1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}}} \quad , \quad \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2} = \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\left(1 - \frac{1}{1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}}}\right) \\
\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3} &= \frac{(\theta_2 - \theta_1)(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{x_{ij} - \theta_4}{\theta_3^2})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2} \quad , \quad \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3} = \frac{1}{\mu_{ij}(\boldsymbol{\theta})} \frac{(\theta_2 - \theta_1)(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{x_{ij} - \theta_4}{\theta_3^2})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2} \\
\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4} &= \frac{(\theta_2 - \theta_1)(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{1}{\theta_3})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2} \quad , \quad \frac{\partial \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4} = \frac{1}{\mu_{ij}(\boldsymbol{\theta})} \frac{(\theta_2 - \theta_1)(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{1}{\theta_3})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2}
\end{aligned} \tag{9.1}
$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1^2} = 0,$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1^2} = -\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1}}{(\mu_{ij}(\boldsymbol{\theta})^2)} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_2} = 0,$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_2} = -\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2}}{(\mu_{ij}(\boldsymbol{\theta})^2)} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_3} = \frac{(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{-x_{ij}+\theta_4}{\theta_3^2})}{(1 + e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2}$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_3} = -\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3}}{(\mu_{ij}(\boldsymbol{\theta})^2)} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})} \frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_3}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_4} = \frac{-(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{1}{\theta_3})}{(1 + e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2}$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_4} = -\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4}}{(\mu_{ij}(\boldsymbol{\theta})^2)} \frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})} \frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1 \theta_4}$$

9.1 Logistic curve with five parameters

The five parameter logistic curve is given by:

$$f(x) = \theta_2 + \frac{\theta_1 - \theta_2}{(1 + e^{\frac{\theta_4 - x}{\theta_3}})^{\theta_5}}$$

9.1.1 Derivatives of five parameter logistic model

$$\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_1} = \frac{1}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{\theta_5}} \tag{9.2}$$

$$\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2} = 1 - \frac{1}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{\theta_5}} \tag{9.3}$$

$$\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3} = \frac{(\theta_2 - \theta_1)\theta_5(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{\theta_5 - 1}(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{x_{ij}-\theta_4}{\theta_3^2})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{2\theta_5}} \tag{9.4}$$

$$\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4} = \frac{(\theta_2 - \theta_1)\theta_5(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{\theta_5 - 1}(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{1}{\theta_3})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{2\theta_5}} \tag{9.5}$$

$$\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_5} = \frac{(\theta_2 - \theta_1)(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{\theta_5} ln(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^{2\theta_5}} \tag{9.6}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2^2} = 0$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2^2} = (-\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2}}{(\mu_{ij}(\boldsymbol{\theta})^2)})\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2 \theta_3} = \frac{(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{x_{ij}-\theta_4}{\theta_3^2})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2}$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2 \theta_3} = (-\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3}}{(\mu_{ij}(\boldsymbol{\theta})^2)})\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2 \theta_3}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2 \theta_4} = \frac{(e^{\frac{\theta_4 - x_{ij}}{\theta_3}})(\frac{1}{\theta_3})}{(1+e^{\frac{\theta_4 - x_{ij}}{\theta_3}})^2}$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2 \theta_4} = (-\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4}}{(\mu_{ij}(\boldsymbol{\theta})^2)})\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_2 \theta_4}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3^2} = \frac{(\theta_2-\theta_1)(e^{\frac{\theta_4-x_{ij}}{\theta_3}})(\frac{x_{ij}-\theta_4}{\theta_3^2})[\frac{x_{ij}-\theta_4}{\theta_3^2} - e^{\frac{\theta_4-x_{ij}}{\theta_3}}\frac{x_{ij}-\theta_4}{\theta_3^2} - \frac{2}{\theta_3} - e^{\frac{\theta_4-x_{ij}}{\theta_3}}\frac{2}{\theta_3}]}{(1+e^{\frac{\theta_4-x_{ij}}{\theta_3}})^3}$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3^2} = (-\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3}}{(\mu_{ij}(\boldsymbol{\theta})^2)})\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3^2}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3 \theta_4} = \frac{(\theta_2-\theta_1)(e^{\frac{\theta_4-x_{ij}}{\theta_3}})(\frac{1}{\theta_3^2})[\frac{x_{ij}-\theta_4}{\theta_3} - e^{\frac{\theta_4-x_{ij}}{\theta_3}}\frac{x_{ij}-\theta_4}{\theta_3} - 1 - e^{\frac{\theta_4-x_{ij}}{\theta_3}}]}{(1+e^{\frac{\theta_4-x_{ij}}{\theta_3}})^3}$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3 \theta_4} = (-\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4}}{(\mu_{ij}(\boldsymbol{\theta})^2)})\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_3 \theta_4}$$

$$\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4^2} = \frac{(\theta_2-\theta_1)e^{\frac{\theta_4-x_{ij}}{\theta_3}}\frac{1}{\theta_3}(1-e^{\frac{\theta_4-x_{ij}}{\theta_3}})}{(1+e^{\frac{\theta_4-x_{ij}}{\theta_3}})^3}]$$

$$\frac{\partial^2 \ln \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4^2} = -\frac{\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4}}{(\mu_{ij}(\boldsymbol{\theta})^2)})\frac{\partial \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4} + \frac{1}{\mu_{ij}(\boldsymbol{\theta})}\frac{\partial^2 \mu_{ij}(\boldsymbol{\theta})}{\partial \theta_4^2}$$