Monolix Instructions

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Instructions to run the Non-linear mixed-effects models in the Monolix[1] version 2023R1 GUI to reproduce results described in Murphy, Q.M. et al, Mathematical Biosciences (2024).

1 Required Files

Below we list and describe files needed to run the Non-linear mixed-effects models in the Monolix version 2023R1 GUI. The files used for input are in a tab delimited format (`.txt`).

1. **Structural Model Files:** files containing model to which data is fit
   (a) '`Monolix_Exponential_fit_function.txt`': used for fitting to Exponential Model (Eq. 3)
   (b) '`Monolix_PowerLaw_fit_function.txt`': used for fitting to Exponential Model (Eq. 4)
2. **Data files:** files containing data for fitting. Description of file contents are given in Section 3.
   (a) Serum IgG Data:
      - '`IgG_data_Exponential_Model.txt`'
      - '`IgG_data_PowerLaw_Model.txt`'
   (b) Serum IgA Data:
      - '`IgA_data_Exponential_Model.txt`'
      - '`IgA_data_PowerLaw_Model.txt`'

2 Running Monolix [1] (version 2023R1)

2.1 Loading data files

1. Navigate to the '`Data file`' tab
2. Select '`BROWSE...`'
3. Upload one of the data files in Section 1

4. Formatting Data: assign each column from the data file to a column type using the drop down menu in the Monolix header line. There is an additional step for the serum IgA data file.

   (a) Serum IgG and IgA data sets:
   - Above the '`ID`' column, select '`ID`' for the Monoloix header
   - Above the '`Time`' column, select '`TIME`' for the Monoloix header
   - Above the '`log10_A_data`' column, select '`OBSERVATION`' for the Monoloix header
   - Above the '`Disease`' column, select '`CATEGORICAL COVARIATE`' for the Monoloix header

   (b) Serum IgA data sets:
   - Above the '`Censoring`' column, select '`CENSORING`' for the Monoloix header

2.2 Loading Model for fitting (Exponential or Power-law)

1. Navigate to the '`Structural Model`' tab
2. Select '`BROWSE...`'
3. Upload one of the structural model files listed in Section 1. Select the '`Monolix_Exponential_fit_function.txt`' file if you intend to fit using the exponential model (Eq. 3) or the '`Monolix_PowerLaw_fit_function.txt`' file if you intend to fit using the power-law model (Eq. 4).

2.3 Select observation model, parameter distributions, and categorical covariates

1. Navigate to the '`Statistical model & Task`' tab.
2. Ensure that all '`Tasks`' are enabled (or checked).
3. Enable the '`Use linearization method`' using the toggle.
4. Observation Model:

   (a) Under the '`Observation model`' section:
   - Select '`CONSTANT`' as the '`ERROR MODEL`.'
   - Select '`NORMAL`' as the '`DISTRIBUTION`.'

5. Parameter Distributions:

   (a) Under the '`Individual model`' section:
   - Select '`LOGNORMAL`' as the '`DISTRIBUTION`' for the parameter α.
   - Select '`LOGNORMAL`' as the '`DISTRIBUTION`' for the parameter k.
   - Enable check marks for the '`RANDOM EFFECTS`' for parameters α and k.

6. Categorical Covariates:

   (a) Under the '`Individual model`' section:
   - Add a categorical covariate by selecting the '`DISCRETE`' button next to '`Add covariate:`'

- Select the '`Function`' as '`Disease`'
- '`Name`' the covariate '`tDisease`'
- Select the '`ALLOCATE`' button to allocate '`N`', '`L`', and '`S`' to represent the prior immunological status for *naïve*, *low symptomatic*, and *symptomatic* patients, respectively
- Select '`G_N`' as the '`Ref.`' category
- Accept the changes by selecting the '`ACCEPT`' button
- Enable new categorical covariate with *naive* group as reference:
  - If fitting to IgG data: check the boxes for '`tDisease`' as the categorical covariate for parameters α **and** k.
  - If fitting to IgA data: check the box for '`tDisease`' as the categorical covariate for the parameter α.

2.4 Initial guess for parameters

1. Navigate to the '`Initial estimates`' tab
2. Enter initial guesses for α, k, their respective standard deviations, and error parameter a.

2.5 Run algorithm

1. Navigate to the '`Statistical model & Task`' tab
2. Select the '`RUN`' button to run the algorithm.
3. Adjust initial guesses in the '`Initial estimates`' tab as needed and '`RUN`' algorithm again. The final '`RUN`' should be done without the '`Use linearization method`' enabled.

3 Description of data files

Description of each column of the Monolox data files.

1. Serum IgG Data:

   (a) '`IgG_data_Exponential_Model.txt`'
   - '`ID`': identifier of the patient
   - '`Time`': time of observation record, t, where $t = \{31, 35, 49, 111, 321\}$ when available.
   - '`log10_A_data`': $\log_{10}-$ transformed IgG endpoint titers at time of observation
   - '`Disease`': immunological status prior to vaccination; *naïve* (N), *low symptomatic* (L), or *symptomatic* (S)

   (b) '`IgG_data_PowerLaw_Model.txt`'
   - '`ID`': identifier of the patient
   - '`Time`': transformed time of observation record $\log_{10}(t) - \log_{10}(28)$, where $t = \{31, 35, 49, 111, 321\}$ when available.
   - '`log10_A_data`': $\log_{10}-$ transformed IgG endpoint titers at time of observation
   - '`Disease`': immunological status prior to vaccination; *naïve* (N), *low symptomatic* (L), or *symptomatic* (S)

2. Serum IgA Data:

   (a) '`IgA_data_Exponential_Model.txt`'

   - '`ID`': identifier of the patient
   - '`Time`': time of observation record, t, where $t = \{35, 111, 321\}$ when available.
   - '`log10_A_data`':
     - If the reported IgA data at the time of observation was at or above the limit of detection $\text{LOD}^a = 100$, the $\log_{10}-$ transformed IgA endpoint titers at time of observation is written
     - If the reported IgA data at the time of observation was below the limit of detection $\text{LOD}^a = 100$, the $\log_{10}-$ transformed limit of detection, $\log_{10}\text{LOD}^a = 2$, at time of observation is written
   - '`Disease`': immunological status prior to vaccination; *naïve* (N), *low symptomatic* (L), or *symptomatic* (S)
   - '`Censoring`':
     - If the reported IgA data at the time of observation was a true observation (at or above the limit of detection, then a 0 is written at the time of observation
     - If the reported IgA data at the time of observation was below the limit of detection $\text{LOD}^a = 100$, then a 1 is written at the time of observation

   (b) '`IgA_data_PowerLaw_Model.txt`'

   - '`ID`': identifier of the patient
   - '`Time`': transformed time of observation record $\log_{10}(t) - \log_{10}(28)$, where $t = \{35, 111, 321\}$ when available.
   - '`log10_A_data`':
     - If the reported IgA data at the time of observation was at or above the limit of detection $\text{LOD}^a = 100$, the $\log_{10}-$ transformed IgA endpoint titers at time of observation is written
     - If the reported IgA data at the time of observation was below the limit of detection $\text{LOD}^a = 100$, the $\log_{10}-$ transformed limit of detection, $\log_{10}\text{LOD}^a = 2$, at time of observation is written
   - '`Disease`': immunological status prior to vaccination; *naïve* (N), *low symptomatic* (L), or *symptomatic* (S)
   - '`Censoring`':
     - If the reported IgA data at the time of observation was a true observation (at or above the limit of detection, then a 0 is written at the time of observation
     - If the reported IgA data at the time of observation was below the limit of detection $\text{LOD}^a = 100$, then a 1 is written at the time of observation

References

[1] France Lixoft SAS, Antony. Monolix. *Version 2020R1*, 2023.