Non-Linear Mixed Effects Models
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1 Introduction

1.1 What, when and why

Non-linear mixed effects models, also known as *non-linear hierarchical models*, are an extension to the more traditional linear mixed-effects models. They are used in scenarios where all of the following features are present [1]:

1. Repeated observations of a continuous variable on each of several *experimental units* (in our case these are individuals, thus individual is considered equivalent to empircial unit in the following section) over time or another condition (e.g. measurements at given heights on a tree) (the *condition variable*);

2. We expect the relationship between the response variable and the condition variable to vary across individuals; and

3. Availability of a scientifically relevant model characterising the behaviour of the individual response in terms of meaningful parameters that vary across individuals and dictate variation in patterns of condition-response (for us this will be the Farquhar-van Cammerer-Berry model).

The final point from the list in 1.1 is where the non-linear aspect is introduced. This is often a mechanistic function describing a physical or chemical system (for example in toxicokineitcs physiologically-based pharmacokinetics models are used or HIV dynamics in "precision medicine"); that is the model is described by by meaningful, interpretable parameters rather than being an empirical best fit.

The analysis tends to have the goal of understanding one or more of the following:

1. The "typical" behaviour of the phenomena (i.e. mean or median values) represented by the model parameters;

2. The variation of these parameters, and hence the phenomena, between individuals; and

3. If some of the variation is inherently associated with individual characteristics.

Individual level prediction can also be of interest (e.g. in medical treatment with highly individual reaction), but is less relevant to this project. From the individual level we are interested in investigating the level of variation between individuals and questioning if this is sufficiently small to allow the "all-purpose" models generally used in photosynthesis describing the parameters and systems of interest.

1.2 The Model

1.2.1 Basic model

Consider an experiment involving repeated measurements of some response variable, Y, across a condition variable T for n individuals. Each individual's characteristics are recorded in A (assumed to be scleronemous) and possible additional initial conditions in U. Let $y_{i,j}$ denote the jth measurement of the response under condition $t_{i,j}$, $j = 1, \ldots, n_i$, for individual i, $i = 1, \ldots, n$. Thus:

$$\begin{aligned} Y &= \bigcup_{i=1}^{n} y_i \\ y_i &= \{y_{i,1}, \ldots, y_{i,n_i}\} \\ T &= \bigcup_{i=1}^{n} t_i \\ t_i &= \{t_{i,1}, \ldots, t_{i,n_i}\} \\ A &= \{a_i, \ldots, a_n\} \\ U &= \{u_1, \ldots, u_n\} \end{aligned} \tag{1}$$

Often T is time and $U = \emptyset$, but it might be the case that T is an increase in some environmental condition and U might be some meta-data available for each of the individuals (for example genotype data in the case of "precision medicine"). For brevity's sake use $x_{i,j} = (t_{i,j}, u_i)$. The assumption that (y_i, u_i, a_i) are independent across i is often included to reflect the belief that individuals are unrelated (this will hold for us, but might require more thought in other situations). For some function f regulating the within-individual behaviour defined by a vector of parameters β_i unique to individual i, we have:

$$y_{i,j} = f\left(x_{i,j}, \beta_i\right) + \epsilon_{i,j}, \quad j = 1, \ldots, n_i \tag{2}$$

We assume that $\mathbb{E}\left(e_{i,j} | u_i, \beta_i\right) = 0$ for all i, j. (2) is called the *individual level model*. To model the population parameters we consider d, a p-dimensional function depending on an r-vector of fixed parameters, or *fixed effects*, β, and a k-vector of *random effects*, b_i, associated with individual i:

$$\beta_i = d\left(a_i, \beta, b_i\right), \quad i = 1, \ldots, n \tag{3}$$

Here, the *population model* in (3) describes how $beta_i$ varies among individuals due to both individual attributes a_i and biological variation in b_i. We assume that the b_i are independent of the a_i, i.e.:

$$\begin{aligned} \mathbb{E}(b_i|a_i) &= \mathbb{E}(b_i) = 0 \\ \mathbb{V}ar(b_i|a_i) &= \mathbb{V}ar(b_i) = D \end{aligned} \tag{4}$$

Here, D is an unstructured covariance matrix and is common to all i. It characterises the degree of unexplained variation in the elements of β_i and associations among them; the ubiquitous assumption is $b_i \sim \mathcal{N}(0, D)$. However, if this set of assumptions regarding the conditional distribution of b_i on a_i is found to be insufficient, then $b_i \sim \mathcal{N}(0, D(a_i))$ is frequently used.

In (3), β_i is considered to have an associated random effect, reflecting the belief that each component varies non-negligibly in the population even after systematic relationships with subject characteristics are accounted for. It may happen that "unexplained" variance in a component of β_i may be very small in magnitude relative to that in the remaining elements. In this situation it is common to drop the negligible quantity entirely. This lacks biological sense as each parameter is part of the "scientifically relevant model" and thus is unlikely to have no associated unexplained variation. Hence, one must recognise that this omission of an element of β_i is adopted to achieve numerical stability in fitting rather than to reflect belief in perfect biological consistency across individuals and analyses in the literature to determine whether elements of β_i are fixed or random effects should be interpreted so.

References

[1] Marie Davidian and David M. Giltinan. Nonlinear models for repeated measurement data: An overview and update. *Journal of Agricultural, Biological, and Environmental Statistics*, 8(4):387–419, December 2003. ISSN 1085-7117, 1537-2693. doi: 10.1198/1085711032697.