11.1 Compartamental modelling

Let us first consider the problem of the identification of $a_i$ and $\lambda_i$ from:

$$x(t) = \sum_{i=1}^{n} a_i \exp(\lambda_i t)$$  \hspace{1cm} (11.1)

where $x(t)$ is measured at $t = t_k$, $k = 1, \ldots, m$. Suppose, also, that the experimental error $\Delta x(t_k)$ on each measure $x(t_k)$ is known. More precisely, it is sufficient to have a bound for this error. It would be interesting to calculate the error on $a_i$ and $\lambda_i$ as a function of the error $\Delta x(t_k)$ of the experimental data. To obtain this relation, let us differentiate (11.1) with respect to $a_i$ and $\lambda_i$. The following equation is obtained:

$$\Delta x(t) = \sum_{i=1}^{n} \exp(\lambda_i t)(\Delta a_i) + \sum_{i=1}^{n} a_i t \exp(\lambda_i t)(\Delta \lambda_i)$$  \hspace{1cm} (11.2)

Substituting (11.2) for $t = t_k$ leads to the linear algebraic system:

$$\Delta x(t_k) = \sum_{i=1}^{n} \exp(\lambda_i t_k)(\Delta a_i) + \sum_{i=1}^{n} a_i t_k \exp(\lambda_i t_k)(\Delta \lambda_i)$$  \hspace{1cm} (11.3)

where $k = 1, \ldots, m$, which includes $2n$ unknowns (the $\Delta a_i$ and the $\Delta \lambda_i$) and $m$ equations.

In order to obtain one solution, at most, we assume that $m > 2n$. Then the linear system (11.3) can be solved using a numerical method for the solution of linear algebraic systems [20] (Gauss method, \ldots) when $m = 2n$ and introducing a functional to minimise it if $m > 2n$. This functional $J$, may be:
$$J = \sum_{k=1}^{m} [\Delta x(t_k) - \sum_i \exp(\lambda_i t_k)(\Delta a_i)]$$
$$- \sum_i a_i t_k \exp(\lambda_i t_k)(\Delta \lambda_i)]^2$$  \hspace{1cm} (11.4)

Its optimum is found by writing:

$$\frac{\partial J}{\partial \Delta a_i} = 0 = \frac{\partial J}{\partial \Delta \lambda_i}$$  \hspace{1cm} (11.5)

This system has 2n equations and 2n unknowns.

In spite of its simplicity this process is sometimes difficult because of numerical singularity of the matrix corresponding to the system (11.3).

When studying simple models (2 or 3 compartments) we know that exchange parameters are explicitly given as a function of $a_i$ and $\lambda_i$. An adaptation of the previous technique may be used for estimating the errors in the $k_{ij}$ parameters.

Another practical method used by A. Guillez (and probably many other people!) when treating pharmacological problems is to perturb the experimental data (within the admissible range associated with the experimental errors). The solution ($a_i$, $\lambda_i$ for example) is calculated for each set of perturbed data and it is easy to use statistical methods to determine the error on each parameter. In fact, the mean and variance are readily obtained from the numerical results. In practice, many pharmacokinetic problems (from the Sandoz laboratories) were solved, and the numerical error evaluated using this empirical approach. The actual results were satisfactory [13].

A more sophisticated technique (called permutation perturbation method) was given by J. Vignes in [71]. In some ways it is a generalization of the previous method, taking the errors of calculation into account. Firstly, J. Vignes makes the distinction between two kinds of error [71]:

a) methods giving an exact result are called direct (numerical) methods. This is the case in the technique of linear algebra.

b) methods which which give approximate results are called approximate (numerical) methods. Results then have a method error.