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Section III. Experiences with systems and programs

Analysis of fractional turnover rates by exponential regression

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A recent article (Leonhardt et al. Comput. Methods Prog. Biomed. 32 (1990) 345–350) described the analysis of biological turnover data using a model involving an exponential decay from an initial value to a plateau. The authors included a BASIC program for this analysis, claiming that no comparable programs have been published. In fact, there are many programs available which can be used for this purpose and several are greatly superior to that proposed.

Exponential decay; Nonlinear regression; Pharmacokinetics; Turnover rate

1. Introduction

A common protocol in a pharmacokinetic or turnover experiment is to inject or feed an animal with a bolus dose of an identifiable (often radioactive) compound and watch its disappearance with time. In a simple one-compartment situation, the decline will approach zero along an exponential curve. However, if there is a second compartment which clears only slowly, the data will approximate an exponential approach to a limiting plateau. This behaviour is modelled by Eqn. 1,

$$A = A_0 + A_1 \exp(-KT) \qquad (1)$$

where K is a rate constant, A_0 is the plateau, A_1 is the amplitude; the limiting value of A at zero time is given by $A_0 + A_1$.

The biological importance of estimating the parameters of Eqn. 1 (K, A_0 and A_1) have been mentioned by Leonhardt et al. [1], who also described a BASIC computer program (EXREG) to determine these three parameters. This program follows a very similar procedure to that described by Hoare [2]; a series of K values are chosen, then A_0 and A_1 are estimated by some sort of linear regression routine. The K value, and corresponding A_0 and A_1 values, which gives the smallest sum of squares is then taken as the best fit.

This procedure is unobjectionable as far as it goes. However, the authors claim that a "comparable program has apparently not been published before". If by "comparable" the authors mean a program which will achieve the same result, they are certainly mistaken. There are both published and commercial programs for fitting Eqn. 1 and other nonlinear functions. Moreover, these programs include additional features such as calculating standard errors of all parameters, allowing weighting of the data in various ways, and giving graphical output. The purpose of this report is to alert others of the existence of such software so that they are not also tempted to "reinvent the wheel".

One of the first general nonlinear regression programs suitable for personal computers was

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published by the present author [3]. While this was limited to equations with two parameters and would not cope with Eqn. 1, an enhanced five parameter version called DNRP53 was distributed privately and later published [4]. A number of similar programs have been published in this and other journals (for example, see Refs. 5–9), while several commercial packages such as GraFit, GraphPAD InPlot and SigmaPlot will easily cope with Eqn. 1. Here, I will compare two of these with EXREG.

2. Results and discussion

Leonhardt et al. [1] give some data (their Table 4) which consist of a series of measurements of radioactivity (cpm) as a function of time. These data were used to compare the performance of EXREG, DNRP53 and GraphPAD InPlot. The results from DNRP53 ($K = 24.75 \pm 2.38\%$ per h; $A_0 = 45.02 \pm 8.16$ cpm; and $A_1 = 507.4 \pm 35.38$ cpm) and GraphPAD are virtually indistinguishable, while EXREG gave results which are slightly different ($K = 25.35\%$ per h; $A_0 = 45.57$ cmp; and $A_1 = 497.7$ cpm). Presumably, this difference stems from the fact that EXREG does not locate the true minimum sum of squares (3068), resulting in a residual standard error which is inflated by 0.46% from 15.36 to 15.46 cpm.

Both DNRP53 and GraphPAD Inplot give standard errors of all fitted parameters, and the two gave almost identical values in the current analysis. On the other hand, Leonhardt et al. [1] do not calculate standard errors of any of the parameters, although they do give a formula for the "coefficient of variation of K", which they calculate to be 3.995% for their data. What this actually means is unclear, since the formula they use has units of cpm^2, while K has units of % per h.

As noted by Leonhardt et al. [1], some thought must be given to the appropriate statistical weight to be given to each observation. It may be, as they claim, that their particular data are best analysed with equal weights, but there will be other situations when this may not be true. Unfortunately, the EXREG program offers no alternative, although it could be so modified. By contrast, many of the other programs cited here already permit a variety of weighting schemes.

In conclusion, there are several programs available in the literature and commercially for nonlinear regression analysis of Eqn. 1 or virtually any other equation. All of these programs are more versatile than EXREG and some include graphics capability.

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