

### A.2.2 Pharmacokinetics; a NLME comparison

**Model description** The ‘one-compartment open model’ is commonly used in pharmacokinetics. It can be described as follows. A patient receives a dose  $D$  of some substance at time  $t_d$ . The concentration  $c_t$  at a later time point  $t$  is governed by the equation

$$c_t = \frac{D}{V} \exp \left[ -\frac{Cl}{V}(t - t_d) \right]$$

where  $V$  and  $Cl$  are parameters (the so-called ‘Volume of concentration’ and the ‘Clearance’). Doses given at different time points contribute additively to  $c_t$ . Pinheiro & Bates (2000, Ch. 6.4) fitted this model to a dataset using the S-Plus routine `nlme`. The linear predictor used by Pinheiro & Bates (2000, p. 300) is:

$$\begin{aligned} \log(V) &= \beta_1 + \beta_2 Wt + u_V, \\ \log(Cl) &= \beta_3 + \beta_4 Wt + u_{Cl}, \end{aligned}$$

where  $Wt$  is a continuous covariate, and  $u_V \sim N(0, \sigma_V^2)$  and  $u_{Cl} \sim N(0, \sigma_{Cl}^2)$  are random effects. The model specification is completed by the requirement that the observed concentration  $y$  in the patient is related to the true concentration by  $y = c_t + \varepsilon$ , where  $\varepsilon \sim N(0, \sigma^2)$  is a measurement error term.

**Results** Estimates of hyper-parameters are shown in the following table:

	$\beta_1$	$\beta_2$	$\beta_3$	$\beta_4$	$\sigma$	$\sigma_V$	$\sigma_{Cl}$
ADMB-RE	-5.99	0.622	-0.471	0.532	2.72	0.171	0.227
Std. Dev	0.13	0.076	0.067	0.040	0.23	0.024	0.054
<code>nlme</code>	-5.96	0.620	-0.485	0.532	2.73	0.173	0.216

The differences between the estimates obtained with ADMB-RE and `nlme` are caused by the fact that the two methods use different approximations of the likelihood function. ADMB-RE uses the Laplace approximation, while the method used by `nlme` is described in Pinheiro & Bates (2000, Ch. 7).

The time taken to fit the model by ADMB-RE was 17 seconds, while the computation time for `nlme` (under S-Plus 6.1) was 7 seconds.

**Files** <http://otter-rsch.com/admbre/examples/pheno/pheno.html>

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