

Introduction

Cohort population approximates multivariate normal distribution with a discrete number of point distributions (cohorts) so that their first and second moments are identical. This discretization interprets part of between subject variability (BSV) as unexplained (residual) variability that permits applying the likelihood estimation of parameters from a single observation per subject data. For a cohort population, BSV is reduced to the variability between a finite number of cohorts and the residual variability accounts for the reminder of unexplained variability. The Gauss quadrature rules naturally define the distribution of model parameters for a cohort population as the sum of weighted delta functions centered at the quadrature nodes [1]. We previously applied the Gauss-Hermite cohort population to approximate the multivariate normal distribution with the diagonal covariance matrix [2].

Objectives

- To represent a cohort population as a mixture of populations with zero variances
- To compare estimates of population parameters for cohort and FOCE methods
- To demonstrate that cohort population permits estimates of the full covariance matrix for one compartment model with simulated sparse data

Methods

One compartment model was used to simulate drug plasma concentrations in 60 subjects at times 0.5, 1, 2, 4, 8, and 16 h. The $\log(\text{CL})$ and $\log(\text{V})$ values were normally distributed with mean $(\log(0.3), \log(3))$ (L/h, L) and variance $\Omega=(\omega_{\text{CL}}^2, \omega_{\text{CLV}}, \omega_{\text{VCL}}, \omega_{\text{V}}^2)=(0.04, 0.01, 0.01, 0.09)$. The constant residual error was assumed with $\sigma^2 = 0.09$. Simulations were performed using R version 4.3.2. The sparse data consisted of one observation per subject such that each observation time was shared by 10 subjects. The Gauss-Hermite cohort distributions for CL and V consisted of 1 and 3 cohorts. The 1-cohort population model was implemented as naïve pooled data. For the 3-cohohort model $\Omega=L^T L$, where L was the lower triangular matrix. The 3-cohort model was coded using mixture of 9 populations representing the product of 3x3 cohorts of means determined by the Gauss-Hermite quadrature nodes and zero variances. The mixing parameters were calculated from the quadrature weights. The cohort models were implemented in NONMEM 7.5 (ICON plc). For assessment of multi-log-normal distribution estimates of CL and V, one compartment model used for simulations was coded in NONMEM. The 1-cohort model parameters were estimated by the first-order (FO) method and 3×3 -cohort by the first-order conditional estimation (FOCE) method. Metrics used for comparison of all estimation methods included parameter estimates, their relative standard errors (RSEs), and objective function values (OFVs).

- Cholesky decomposition of the covariance matrix for $(\log \text{CL}, \log \text{V})$

$$\Omega = \begin{pmatrix} \omega_{\text{CL}}^2 & \omega_{\text{CLV}} \\ \omega_{\text{CLV}} & \omega_{\text{V}}^2 \end{pmatrix} = \begin{pmatrix} L_{11} & 0 \\ L_{21} & L_{22} \end{pmatrix}^T \begin{pmatrix} L_{11} & 0 \\ L_{21} & L_{22} \end{pmatrix}$$

- Gauss-Hermite probability density function for 3×3 cohort population. w_i denote the weights for the Gauss-Hermite quadrature rule and ξ_i are the nodes

$$pdf\left(\begin{matrix} x \\ y \end{matrix}\right) = \sum_{i=1}^3 \sum_{j=1}^3 \frac{w_i}{\sqrt{\pi}} \frac{w_j}{\sqrt{\pi}} \delta\left(\begin{pmatrix} x \\ y \end{pmatrix} - \begin{pmatrix} \log \theta_{\text{CL}} \\ \log \theta_{\text{V}} \end{pmatrix} - \sqrt{2} \begin{pmatrix} L_{11} & 0 \\ L_{21} & L_{22} \end{pmatrix} \begin{pmatrix} \xi_i \\ \xi_j \end{pmatrix}\right)$$

$$\begin{aligned} w_1 &= 0.2954089751509, \xi_1 = -1.224744871391589 \\ w_2 &= 1.181635900604, \xi_2 = 0 \\ w_3 &= 0.2954089751509, \xi_3 = 1.224744871391589 \end{aligned}$$

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Results

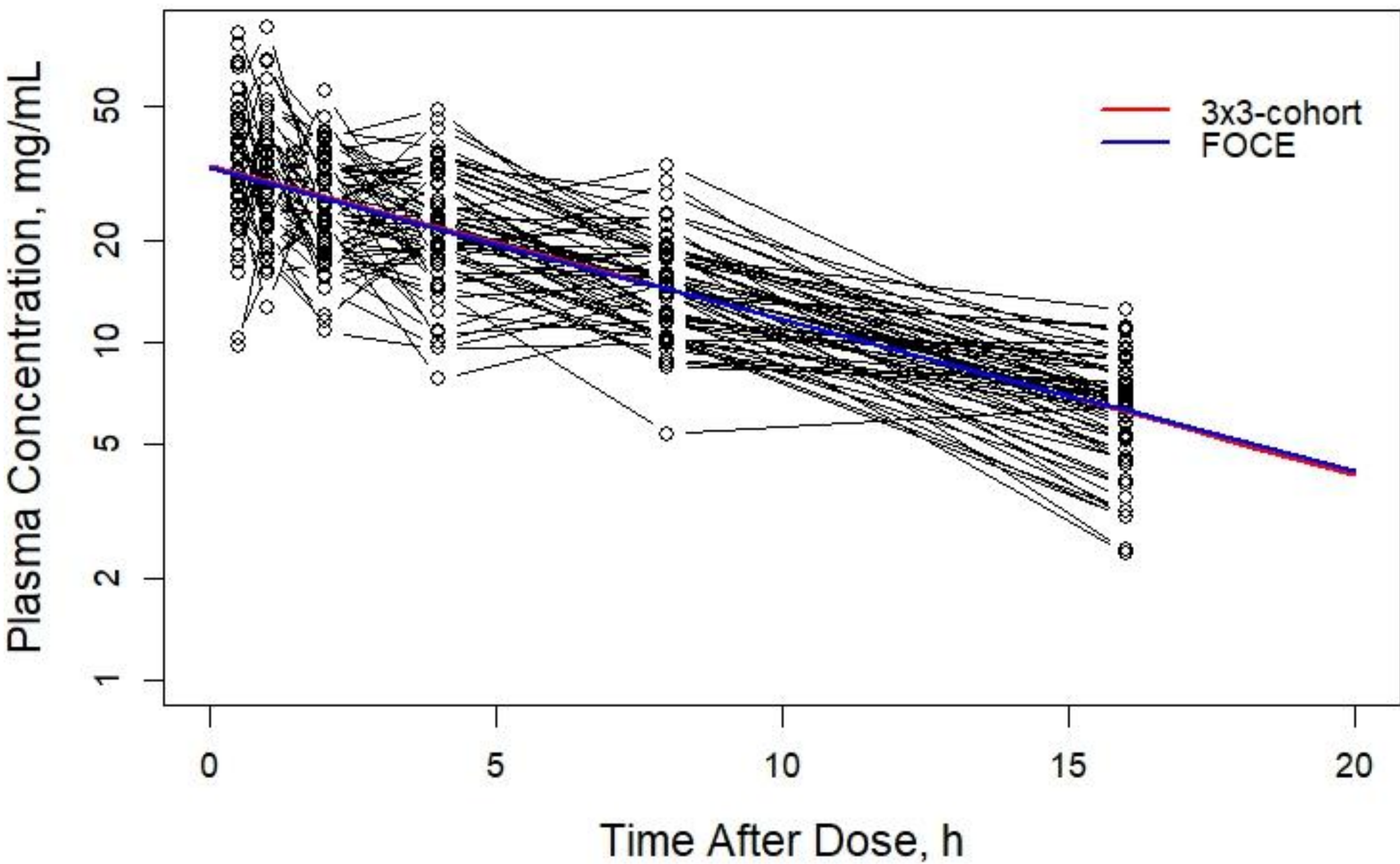


Fig. 2. Simulated time courses of drug plasma drug concentrations for 60 subjects using one compartmental model. Each subject had 6 observations at times 0.5, 1, 2, 4, 8, and 16 h. The lines represent typical model predictions obtained by two estimation methods. Parameter values used for simulations are shown in Table 1.

Parameter	True Value	1 Cohort	3×3 Cohort	FOCE
θ_{CL} , L/h	0.3	0.322 (2.6)	0.311 (2.9)	0.316 (2.5)
θ_{V} , L	3	3.07 (2.9)	3.02 (4.4)	3.07 (3.4)
ω_{CL}^2	0.04	NA	0.0158*	0.0128 (31.6)
ω_{CLV}	0.01	NA	0.0163*	0.018 (186)
ω_{V}^2	0.09	NA	0.065*	0.0731 (20.4)
L_{11}	0.197	NA	0.108 (26.1)	0.0915*
L_{21}	0.0333	NA	0.064 (90.2)	0.0666*
L_{22}	0.3	NA	0.255 (13.3)	0.270*
σ^2	0.09	0.152 (7.5)	0.107 (7.3)	0.0947 (7.5)
OFV	NA	-317.3	-358.0	-356.9

* Secondary parameter

Table 1. Estimates (%RSE) population parameters obtained by the fitting one compartment model to the dense data shown in Fig. 2.

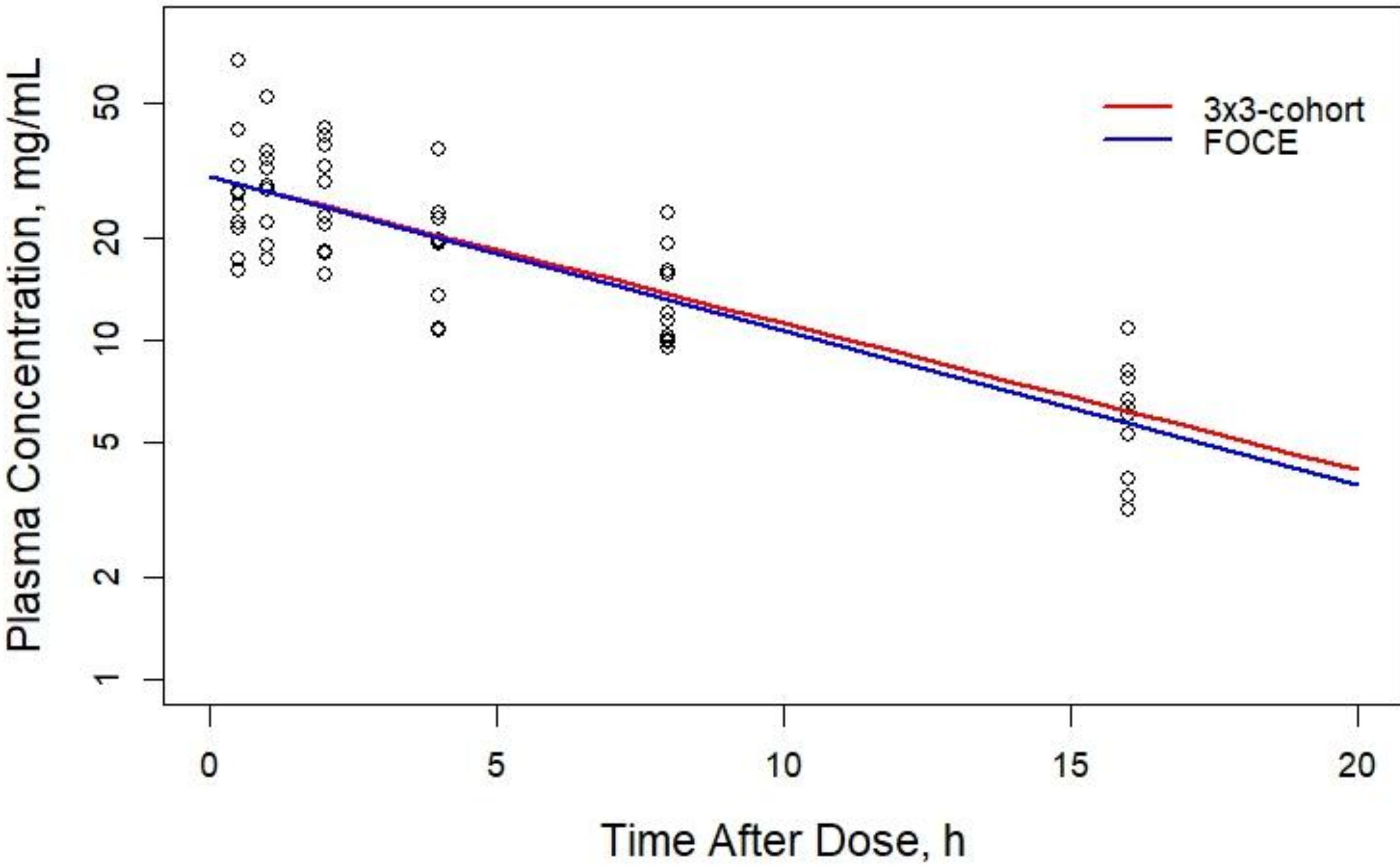


Fig. 2. Drug plasma concentrations randomly selected for 60 subjects from the dense dataset from Fig. 1. Each subject had only 1 observation. There were 10 observation at each time point. The lines represent typical model predictions obtained by two estimation methods. Parameter values used for simulations are shown in Table 2.

Parameter	True Value	1 Cohort	3×3 Cohort	FOCE
θ_{CL} , L/h	0.3	0.345 (5.9)	0.329 (2.7)	0.345**
θ_{V} , L	3	3.3 (6.5)	3.31 (3.3)	3.31**
ω_{CL}^2	0.04	NA	0.0928*	0.025**
ω_{CLV}	0.01	NA	0.0538*	0.0203**
ω_{V}^2	0.09	NA	0.0882*	0.0608**
L_{11}	0.197	NA	0.245 (15.6)	0.135*
L_{21}	0.0333	NA	0.181 (77.3)	0.0823*
L_{22}	0.3	NA	0.297 (10.7)	0.247*
σ^2	0.09	0.126 (14.8)	0.0304 (2.3)	0.081**
OFV	NA	-64.2	-65.1	-64.6

* Secondary parameter

** Standard errors of parameter estimates were not obtained

Table 2. Estimates (%RSE) population parameters obtained by the fitting one compartment model to the sparse data shown in Fig. 3.

Conclusions

The 1-cohort estimation method yielded accurate estimates of typical values of CL and V for both dense and sparse data. The 3×3 -cohort and FOCE estimates of all model parameters were similar for the dense data with similar %RSEs. The FOCE estimates for the sparse data were more accurate but the %RSE were not available. The 3×3 -cohort estimates for dense data were less accurate but their %RSEs were relatively small. The cohort population estimates of typical values and covariance matrix can be obtained with reasonable precision for sparse data when the standard estimation methods fail.

References

- [1] Davis PJ, Rabinowitz P, Methods of Numerical Integration. Academic Press Inc., San Diego, 1984.
- [2] PAGE 32 (2024) Abstr 10864 [www.page-meeting.org/?abstract=10864]