

Gauss-Hermite cohort population estimates of between subject variability for sparse data

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Introduction

Given a population model, sparse data occur when the number observations per each subject is less than the number of structural parameters. In such instances, the variances of between subject variability (BSV) and residual error cannot be estimated with acceptable precision. The cohort population assumes that the distribution of model parameters among subjects is discrete. An example of one cohort population is naïve pool data where the structural model parameters have the same values for all subjects. If a cohort population is assumed for a population model, 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. We applied the Gauss-Hermite cohort population to approximate the multivariate normal distribution [1].

Objectives

- To compare the estimates of population parameters for the Gauss-Hermite cohort and multi variate normal distributions for one compartment model with dense simulated data
- To demonstrate that the Gauss-Hermite cohort distribution permits estimates both mean and BSV parameters for one compartment model with simulated sparse data

Methods

One compartment model was used to simulate drug plasma concentrations in 20 subjects at times 1, 2, 4, 8 and 16 h. The CL and V values were log-normally distributed with the mean (0.3, 3) (L/h, L) and variance diag(0.04, 0.09). The proportional residual error was assumed with the CV = 0.1. Simulations were performed using R (version 4.3.2). The sparse dataset consisted of one observation per subject such that each observation time was shared by 4 subjects. The Gauss-Hermite cohort distributions for CL and V consisted of 1, 3, and 5 cohorts. The likelihood of observations and Fisher Information Matrix (FIM) were coded as R functions OBJ and FIM using reference equations [1], [2]. The minimization of the objective function was performed by the Nelder-Mead algorithm implemented in R [3]. The standard errors of parameter estimates were calculated as the square roots of the diagonal elements of the FIM. For assessment of multinormal distribution estimates of CL and V, the one compartment model used for simulations was coded in NONMEM 7.5 (ICON plc). Two methods of estimation were applied: first-order conditional estimation (FOCE), and importance sampling (IMP). Metrics used for comparison of all estimation methods included parameter estimates, their relative standard errors (RSEs), and objective function values (OFVs).

Results

Gauss-Hermite probability density function for N cohort population. w_i^N denote the weights for the Gauss-Hermite quadrature rule and ξ_i^N are the nodes [4].

$$pdf(x) = \sum_{i=1}^N \frac{w_i^N}{\sqrt{\pi}} \delta(x - \theta - \sqrt{2}\omega\xi_i^N)$$

$$N = 1: \quad w_1^1 = 1, \quad \xi_1^1 = 0$$

$$N = 3: \quad w_1^3 = 0.2954089751509, \xi_1^3 = -1.224744871391589 \\ w_2^3 = 1.181635900604, \quad \xi_2^3 = 0 \\ w_3^3 = 0.2954089751509, \xi_3^3 = 1.224744871391589$$

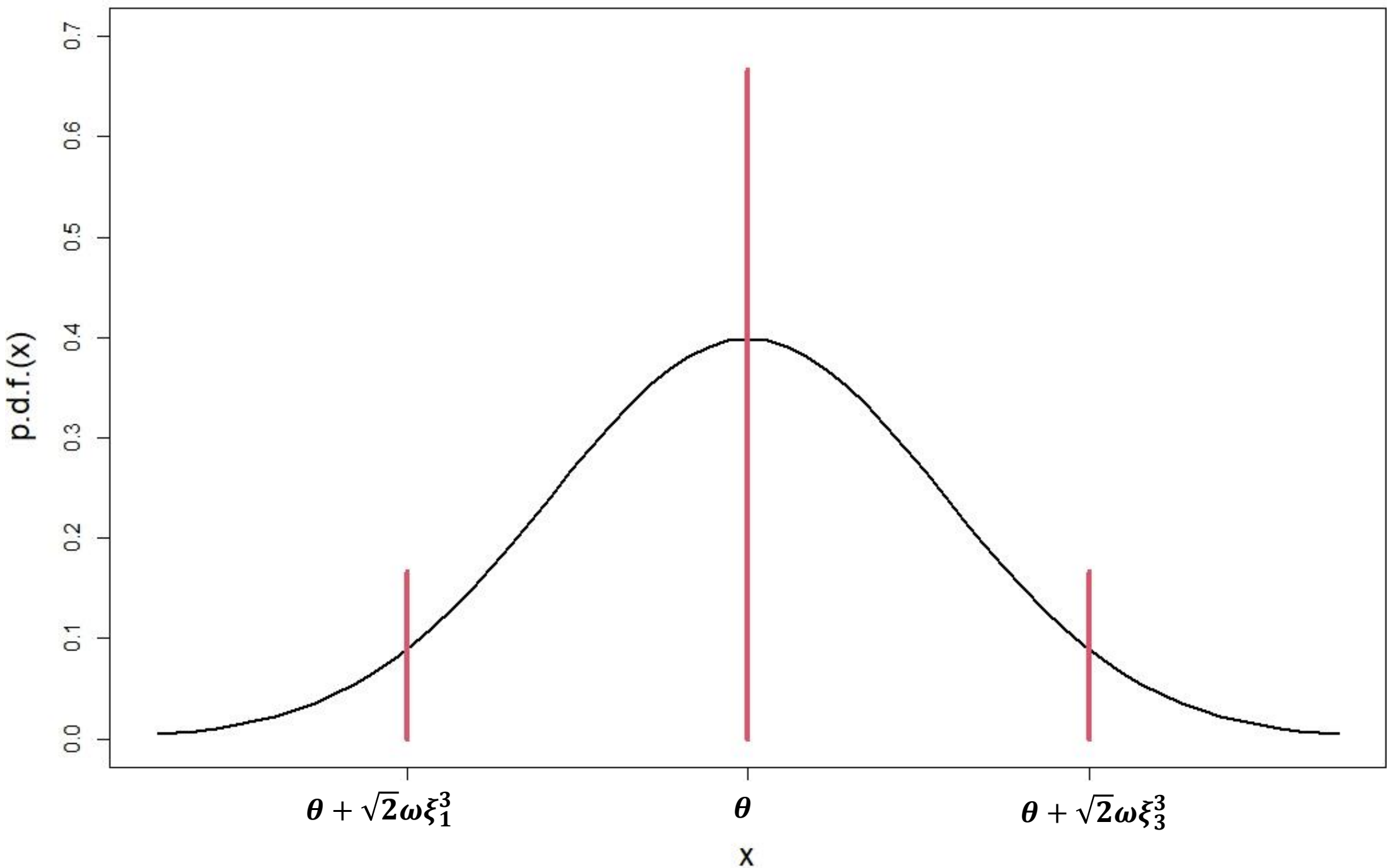


Fig. 1. Approximation the p.d.f. for normal distribution with the mean $\theta = 0$ and standard deviation $\omega = 1$ (black line) with the 3 cohort Gauss-Hermite p.d.f (red lines).

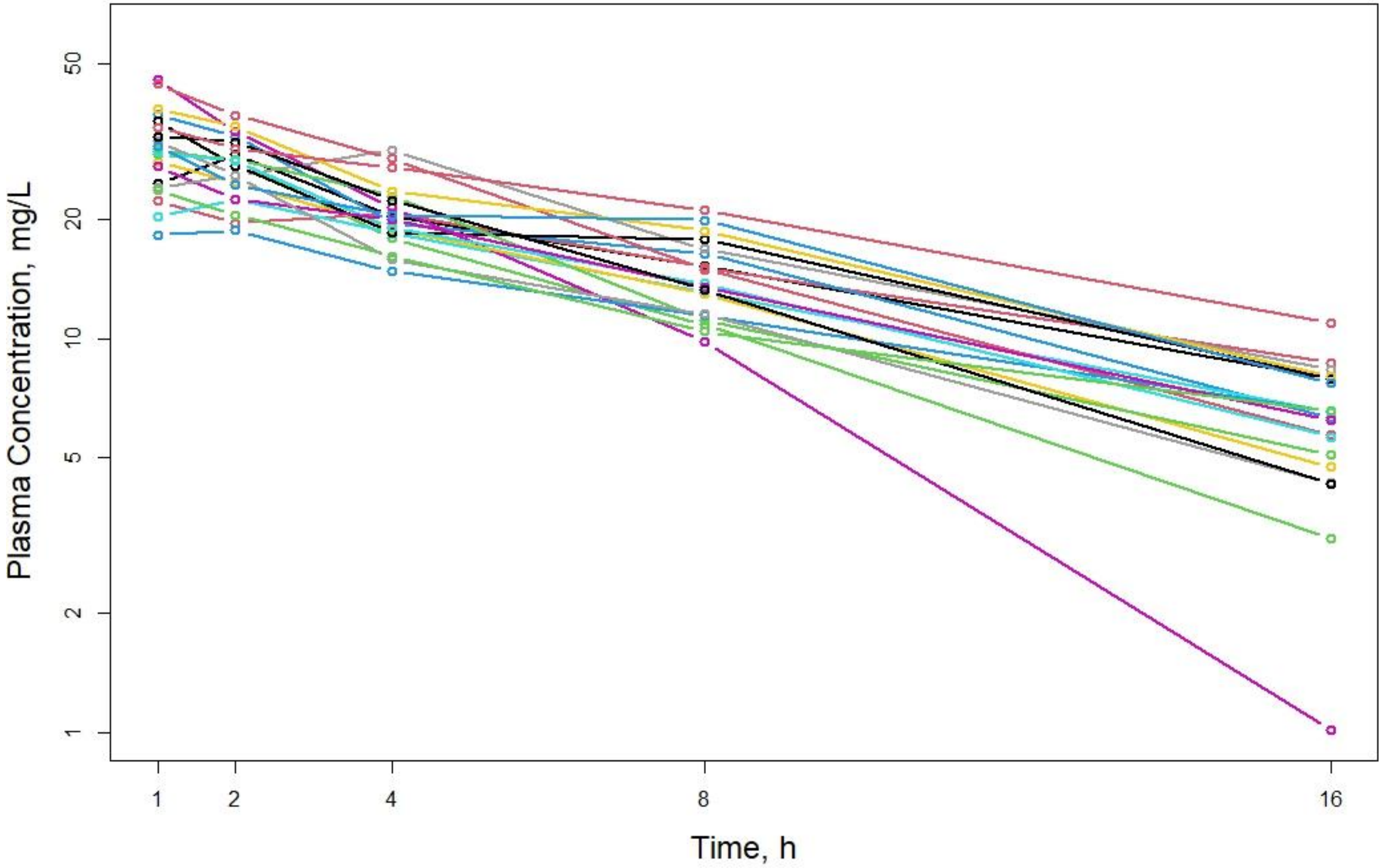


Fig. 2. Simulated time courses of drug plasma drug concentrations for 20 subjects using one compartmental model. Each subject had 5 observations at times 1, 2, 4, 8, and 16 n. Parameter values used for simulations are shown in Table 1.

Parameter	True Value	1 Cohort	3 Cohort	5 Cohort	FOCE	IMP
meanCL, L/h	0.3	0.31 (1.9)	0.282 (2.1)	0.276 (2.7)	0.315 (4.3)	0.313 (4.4)
meanV, L	3	0.309 (2.8)	2.906 (2.0)	2.88 (15.7)	3.01 (5.2)	3.02 (5.5)
CV ²	0.01	0.058 (11.6)	0.019 (27.3)	0.0137 (16.3)	0.0095 (21.1)	0.0097 (17.5)
varlogCL, (L/h) ²	0.04	NA	0.0313 (16.5)	0.0296 (20.1)	0.0352 (28.4)	0.0365 (27.4)
varlogV, L ²	0.09	NA	0.0635 (14.5)	0.0876 (14.2)	0.0515 (35.7)	0.0564 (37.1)
OFV	NA	570.34	516.54	503.97	492.65	491.66

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

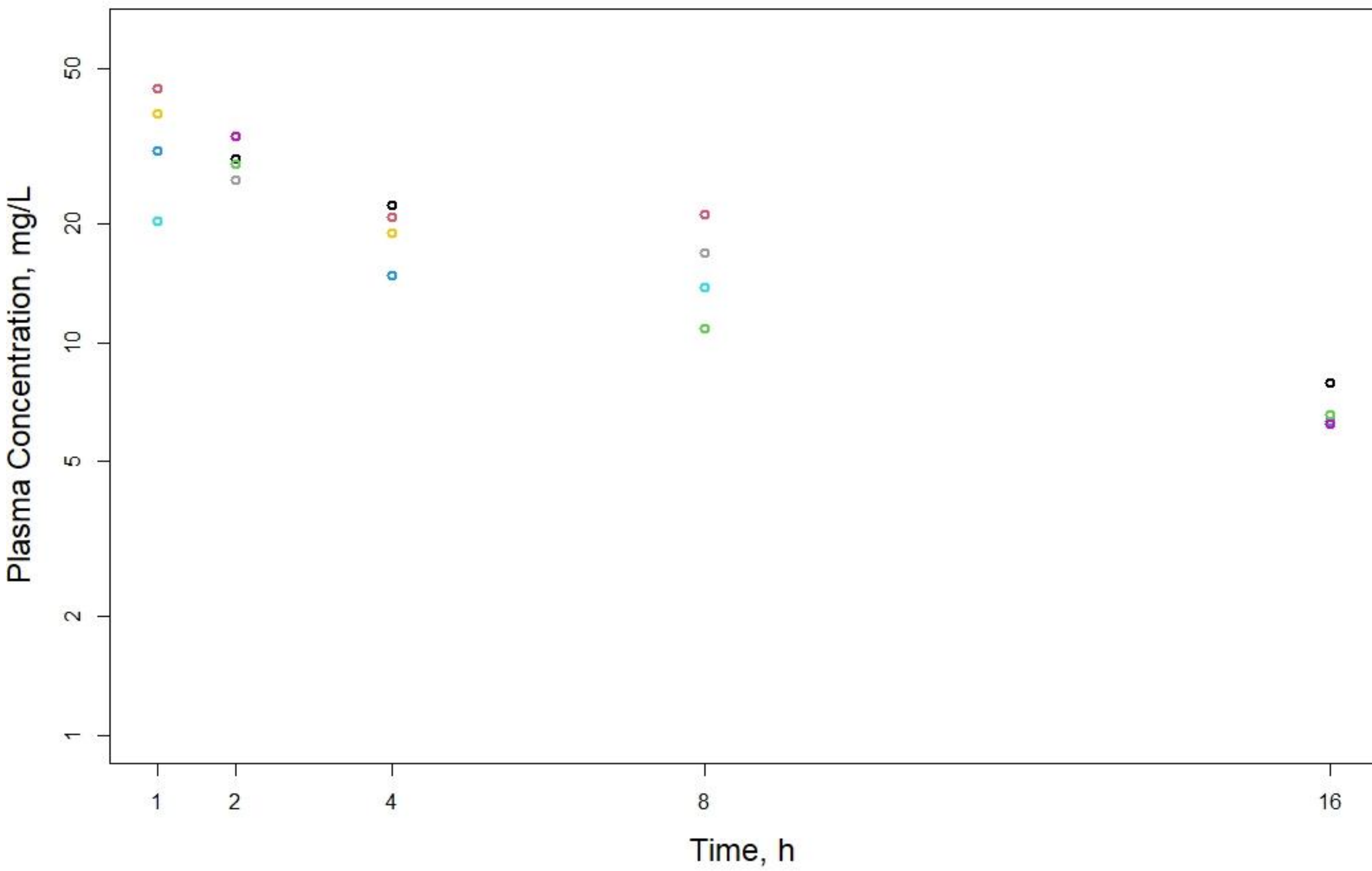


Fig. 3. Drug plasma concentrations randomly selected for 20 subjects from the dense dataset from Fig. 1. Each subject had only 1 observation. There were 4 observation at each time point.

Parameter	True Value	1 Cohort	3 Cohort	5 Cohort	FOCE	IMP
meanCL, L/h	0.3	0.3 (6.7)	0.312 (2.8)	0.268 (4.8)	0.301 (NA)	0.298 (3.7)
meanV, L	3	0.285 (6.8)	3.04 (2.6)	3.16 (3.8)	2.85 (NA)	2.89 (5.7)
CV ²	0.01	0.042 (38.1)	0.0026 (74.8)	0.0043 (74.4)	0.043 (NA)	0.039 (30.1)
varlogCL, (L/h) ²	0.04	NA	0.0313 (16.5)	0.0313 (27.5)	0.004 (NA)	0.0013 (261)
varlogV, L ²	0.09	NA	0.0635 (14.5)	0.0543 (18.6)	0.009 (NA)	0.0085 (102)
OFV	NA	109.82	107.54	110.7	109.82	110.03

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

Conclusions

The 5 cohort estimation method applied to the dense data yielded values of estimates and OFVs that were very close to ones obtained by the FOCE and IMP methods. Both FOCE and IMP methods did not estimate accurately BSV for the sparse data. The 3 cohort estimates of BSV differed from the true values by less than 40%. The Gauss-Hermite cohort population estimates can be obtained with reasonable precision for sparse data when the standard estimation methods fail.

References

[1] Pinheiro JC and Bates DM (1995) Approximations to the log-likelihood function in the nonlinear mixed-effects model. J Comp Graph Stat 4:12-35
[2] Philpou AN and Roussas GG (1975) Asymptotic normality of the maximum likelihood estimate in the independent but not identically distributed case. Annals Inst Stat Math 27:45-55
[3] Press WH, Teukolsky SA, Vetterling WT, Flannery BP (1992) Numerical Recipes in Fortran 77. The Art of Scientific Computing. Volume 1. Cambridge University Press, Cambridge.
[4] Davis PJ, Polonsky I, Numerical Integration, Differentiation, and Integration. In Abramowitz M, Stegun IA (Eds.), Handbook of Mathematical Functions. Dover Publications, Ne York, 1970.