

The capability of Several Population-based Approach Software to Analyze Sparse Drug Plasma Concentration Data after Intravenous Bolus Injection

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ABSTRACT

Monolix, NONMEM, and WinBUGS-PKBUGS are among the available software packages for population-based modeling. The sparse-data of drug plasma concentration *versus* time (*Cp-time*) is prevalent in clinically based studies involving patients. It is not ethical in this case, to collect many and large volumes of blood samples. This study was aimed to simulate the capability of Monolix, NONMEM, and WinBUGS-PKBUGS to analyze very sparse *Cp-time* data after an intravenous bolus drug administration and to estimate the minimum number of *Cp-time* data required for an adequate analysis. Data of *Cp-time* were obtained based on simulation using the pharmacokinetic one-compartment open model following an intravenous bolus administration of 50 mg of a hypothetical drug. In this respect, six random values of *k* (rate constant of elimination) and *Vd* (volume of distribution) with mean and standard deviation values of $0.3 \pm 0.1/\text{h}$ and 30 ± 10 L, respectively, were used to create simulated *Cp-time* data of 6 subjects. Simulated *Cp-time* data in each subject were randomly ranked to choose data based on the intended number of samples in each subject. Several sparse *Cp-time* data scenarios, starting from a minimal state, i.e., with a total of 6 *Cp-time* data (1 datum per subject) to a rich-data with 48 *Cp* data-points (8 data per subject), were examined. The goodness-of-fit evaluations, as well as the similarity of individual values of *k* and *Vd* to the respective real values ($p > 0.05$), indicate that nonlinear-mixed-effect-model using Monolix, NONMEM, and WinBUGS-PKBUGS can appropriately describe sparse *Cp-time* data even with only 2 data per subject. This fact is an important finding to support the demand of analytical tool for a limited number of *Cp-time* data such as obtained in the therapeutic drug monitoring event.

Keywords: Monolix, NONMEM, WinBUGS-PKBUGS, sparse-data, therapeutic drug monitoring

INTRODUCTION

In 1972, Sheiner and colleague introduced the so-called nonlinear mixed effect model, starting the era of the population-based modeling approach. This approach assumes, a particular parameter or variable, for example, the rate constant of elimination, *K*, is considered determined by a population or fixed effect value and inter-individual variability, resulting in a different *K* parameter value in each subject. This approach directly focuses on the population data, allowing analyses of the sparse-data commonly

faced in clinical studies involving patients (Sheiner *et al.*, 1972). This approach also allows the correlation of a particular parameter such as clearance (*CL*), distribution volume (*Vd*) or elimination rate constant (*K*) to specific covariates such as sex, age, body weight, or serum creatinine in a quantitative manner (Jonsson and Karlsson, 1998; Wählby *et al.*, 2001). NONMEM is the first (Sheiner *et al.*, 1972) and the gold standard (Frame, 2006; Keizer *et al.*, 2013) software in population-based approach, allowing quantitative analyses of the clinical data such as in a therapeutic drug

monitoring (TDM) (Shaker *et al.*, 2013). NONMEM provides fast, robust, accurate, and precise computation (Plan *et al.*, 2012). The first-order conditional estimation (FOCE) with interaction is a commonly used estimation method in NONMEM (Wang, 2007).

Several free or free-for-academic alternative tools for population modeling are available. Monolix is an example of the free-for-academic software, developed since 2003. The computation is based on SAEM (Stochastic Approximation Effect Model) algorithm using MATLAB library engine (Chan *et al.*, 2011) developed based on a thorough statistical theory, providing a fast and efficient calculation (Lavielle and Mentré, 2007). Monolix, which is currently maintained by Lixoft company, provides an excellent graphical user interface, facilitating a more practical application (Lavielle, 2014).

Another free tool in population pharmacokinetic-pharmacodynamic analyses is PKBUGS running under WinBUGS environment (Lunn *et al.*, 2002). WinBUGS is a general Bayesian modeling framework that can be used to analyze several different purposes and applications, using Markov chain Monte Carlo (MCMC) techniques. *Bayesian inference Using Gibbs Sampling (BUGS) project* has been initiated by MRC Biostatistics Unit, at University of Cambridge, in collaboration with Imperial College School of Medicine at St Mary's, London (Lunn *et al.*, 2002; Ntzoufras, 2011).

Recently, we have reported the capability of a population-based approach to analyze limited data in the per-oral administration scenario (Nugroho *et al.*, 2017). However, it is not yet clear to what extent of sparse-condition can be adequately described, mainly using several different administration routes. This research was aimed to analyze very sparse Cp-time data after an intravenous bolus drug administration and to estimate the minimum number of Cp-time data required for an adequate analysis.

MATERIAL AND METHODS

Preparation of Data simulation

We simulated the data of Cp *versus* time after intravenous-bolus administration of 50mg of a hypothetical compound using Microsoft® Excel® 365 (running on Windows 10 machine) (Liengme, 2015) based on the one-compartment open model with intravenous bolus injection for Cp (Welling, 1986) as presented in Equation 1.

$$Cp = \frac{Dose}{Vd} \cdot e^{-Kt} \dots\dots\dots(1)$$

This step resulted in the creation of the rich-data of Cp, i.e., 48 data point of 6 subjects at eight time points post dosing (at 0.25; 0.5; 1; 2; 3; 4; 6 and 8h). Each individual-parameter of K and Vd was randomly selected based on the mean and standard of deviation of $0.3 \pm 0.1/h$ and $30 \pm 10L$ (Figure 1 A). Furthermore, the sparse-data were originated based on a random selection of the rich-data by choosing 2 and 1 data/datum per subject. This step resulted in 12 data points and 6 data points from 6 subjects (Figure 1 B and C).

Data analysis

Monolix (stand alone, version 2018R2, running on Windows 10 machine), WinBUGS (version 1.3 and 1.4) – PKBUGS (version 1.0), and NONMEM (version 7.4, using Gfortran compiler, directed using PLTTools lite version 6) (Frame, 2006) were used to model the rich-data and the sparse-data. The structural model to describe the simulated Cp data by intravenous bolus administration was based on the one-compartmental open model, as presented in Equation 1. Moreover, the inter-individual variability is determined by an exponential error model (equation 2).

$$P_i = \theta \cdot \exp(\eta_i) \dots\dots\dots(2)$$

Term θ is the population value, or the fixed effect parameter of P. P_i is the individual estimate value, and η_i is the inter-individual variation, assumed to be independently and normally distributed with mean zero and variance ω^2 . The interindividual variability was applied for K and Vd. The residual error is described by the additive error model (equation 3).

$$Fp_{ij} = Fo_{ij} + \varepsilon_1 \dots\dots\dots(3)$$

Term Fp_{ij} is the prediction of the j^{th} evaluated functions (Cp). Fo_{ij} is the measured value of the evaluated function (Cp), and ε represents the residual deviation of the predicted from the observed value and is assumed to be independent and distributed with mean zero and variance σ^2 . The analysis of the population parameters θ , ω^2 , and σ^2 was performed using the SAEM algorithm (Monolix), MCMC (WinBUGS-PKBUGS), and the first-order conditional estimation (FOCE) with interaction method (NONMEM).

In Monolix, analyses were performed using the structural one compartment intravenous bolus model with K and Vd parameters provided in Monolix library. No covariate was applied while the covariance implemented the default diagonal pattern.

Table I. The comparison of the individual parameter of K and Vd of the rich-data, the sparse-data with 12 data-points (2 data per subject) and the sparse-data with 6 data-points (one datum per subject) estimated by Monolix, NONMEM, and WinBUGS-PKBUGS (data are presented as mean \pm standard of deviation).

Data	K (per hour)			Vd (L)		
	Monolix	NONMEM	WinBUGS-PKBUGS	Monolix	NONMEM	WinBUGS-PKBUGS
rich-data	0.3 \pm 0.1	0.3 \pm 0.1	0.3 \pm 0.1	30.0 \pm 11.0	30.0 \pm 11.0	30.0 \pm 11.0
*sparse-12	0.3 \pm 0.1	0.3 \pm 0.1	0.3 \pm 0.0	29.2 \pm 9.4	29.1 \pm 9.4	28.9 \pm 8.9
**sparse-6	0.5 \pm 0.1 [#]	0.4 \pm 0.0 [#]	0.4 \pm 0.1 [#]	14.9 \pm 0.3 [#]	18.4 \pm 7.0 [#]	16.7 \pm 1.4 [#]

* Sparse-data with 12 data-points (2 data per subject); ** Sparse-data with 6 data-points (1 datum per subject); [#] Mean parameter values were significantly different from the respective reference ones ($p < 0.05$)

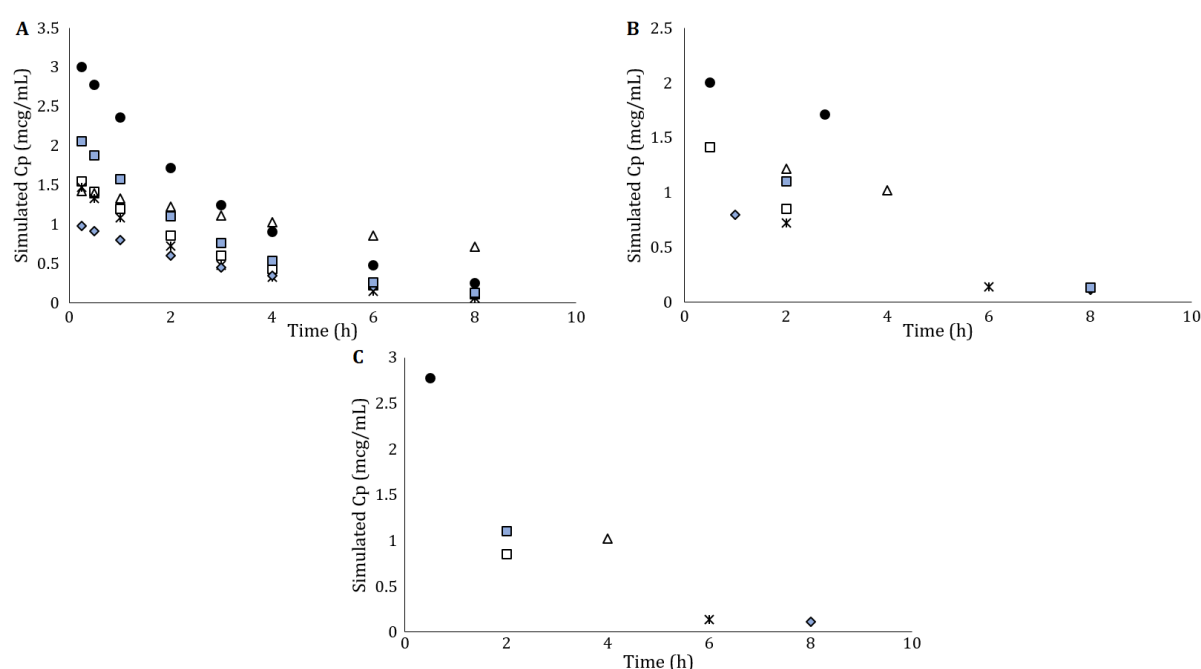


Figure 1. Data of the rich-data (panel A) and the sparse-data with 12 data-points (2 data per subject) (panel B) and the sparse-data with 6 data-points (1 datum per subject) (panel C) of plasma concentration (Cp) versus time profile of a 50mg theoretical compound delivered by an intravenous bolus injection, simulated in 6 subjects (1: filled-circle, 2: open-triangle, 3: star, 4: open-square, 5: filled-diamond, 6: filled-square).

Data were assumed to follow a log-normal distribution. The calculation was performed using 0.3/h and 30L as initial estimates of K and Vd, respectively. The initial estimates of the random error (η) were 0.1, and 0.1 for K and Vd, respectively. Additive error model was calculated, with the initial values of sigma of 0.001.

Modeling in NONMEM was performed using the provided one-compartment oral model (ADVAN 1 trans 1) with K and Vd parameters provided in NONMEM PK library. No covariate was applied while the covariance implemented the default diagonal pattern. The calculation was

performed using 0.3/h and 30L as initial estimates of K and Vd, respectively. The initial estimates of the random error (η) were 0.1 and 0.1 for both K and Vd. Additional residual error model was used, with the initial values of 0.1.

Analyses in WinBUGS were performed using the structural one compartment intravenous bolus model with clearance (Cl) and Vd parameters provided in PKBUGS add-in. No covariate was applied. The calculation was performed using 15 L/h and 30L as initial estimates of Cl and Vd, respectively. The initial estimates of the random error (η) were 10% for both Cl and Vd.

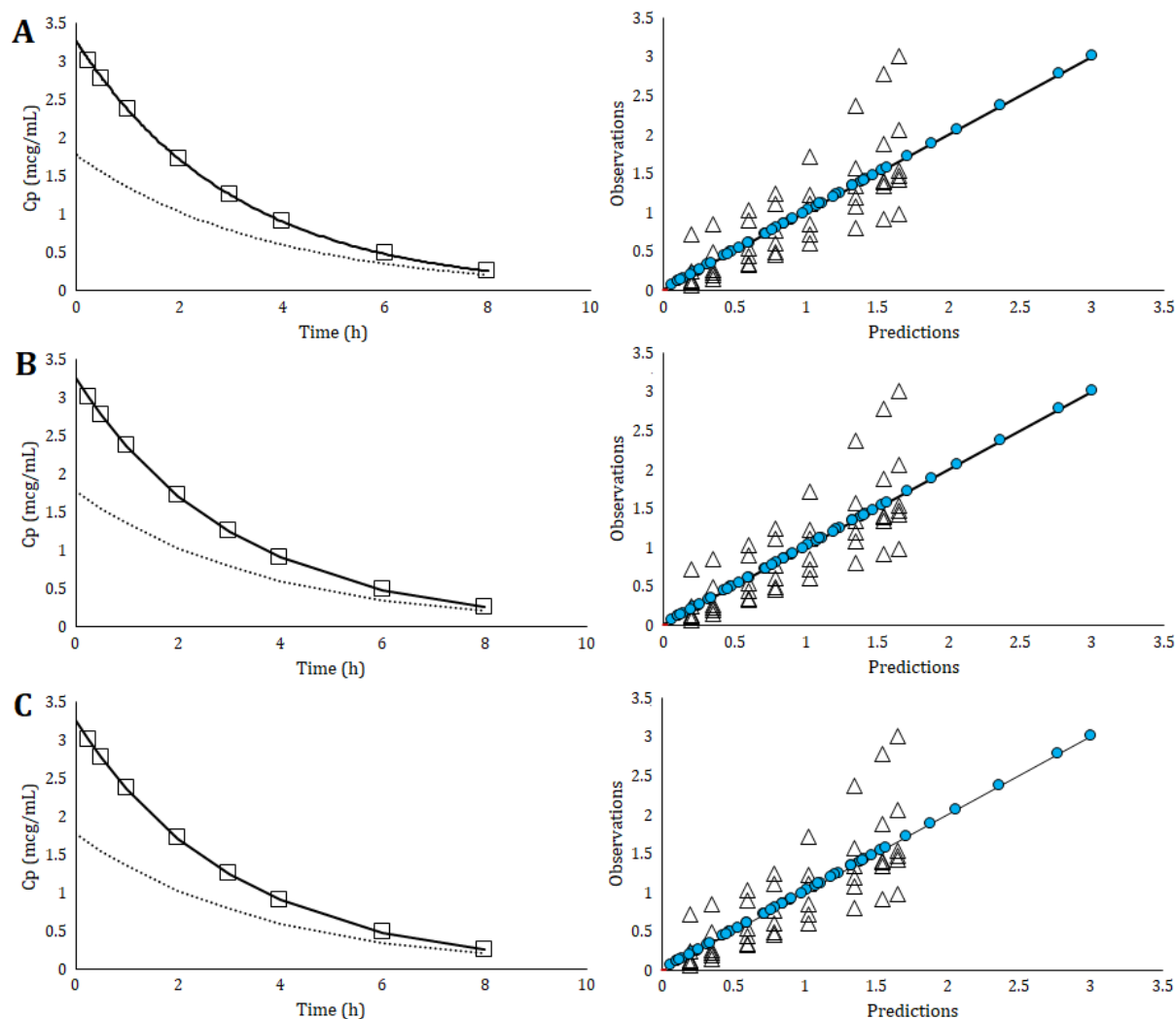


Figure 2. The goodness-of-fit evaluation of the rich-data of Cp in Monolix (A), NONMEM (B) and WINBUGS-PKBUGS (C) i.e., 1) the typical examples of individual fitting (subject number 1) of the “observed” Cp data (DV) with the individual (solid-curve) and population model (dotted-curve) predictions (left panels), and 2) the correlation of DV versus population model prediction (open-triangle) and the individual model prediction of Cp (closed-circle) (right panels).

Parameter K was estimated based on the estimation of Cl and Vd values. While PKBUGS is running in WinBUGS 1.3, to obtain more flexible MCMC, the final model was exported to WinBUGS 1.4 platform using “Print model” menu.

The adequacy of modeling in all cases was analyzed based on the goodness-of-fit evaluations. These evaluations consisted of 1) the individual fitting with the individual and population model prediction curves; 2) the correlation of DV, namely the dependent variable (the “observed” Cp) versus population model prediction of Cp and the

individual model prediction of Cp. Such evaluations are considered crucial to judge the adequacy of specific modeling analyses (Mohammed *et al.*, 2012; Owen and Fiedler-Kelly, 2014; Zheng *et al.*, 2014).

The post-hoc individual parameter values of K and Vd obtained from the analyses of the sparse-data using Monolix, WinBUGS-PKBUGS, and NONMEM were compared to the respective individual values of the parameters. Due to a normal distribution of all data tested based on Shapiro-Wilkes method using OpenStat 2014

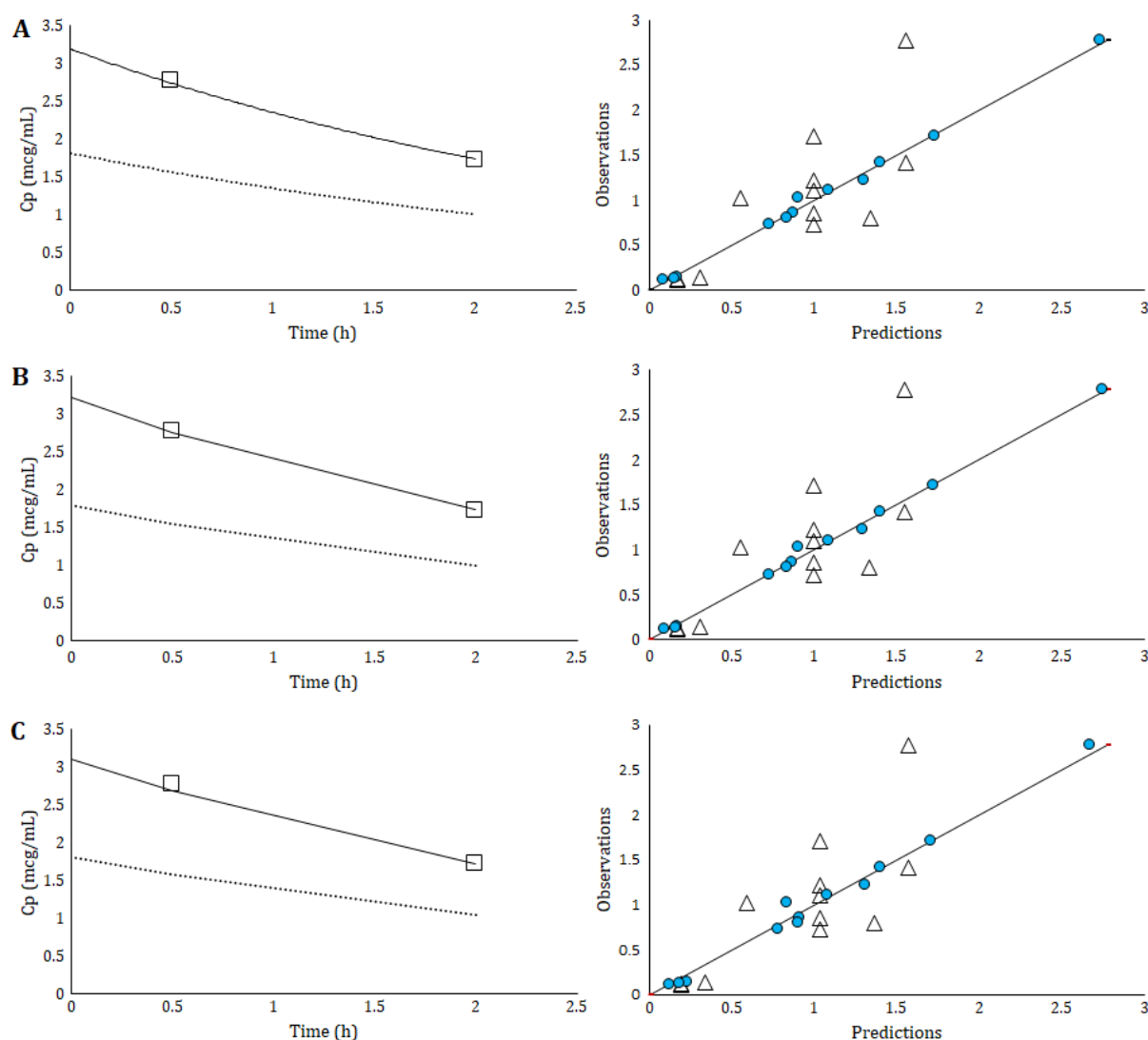


Figure 3. The goodness-of-fit evaluation of the sparse-data with 2 data per subject of Cp in Monolix (A), NONMEM (B) and WINBUGS-PKBUGS (C) i.e. 1) the typical examples of individual fitting (subject number 1) of the “observed” Cp data (DV) with the individual (solid -curve) and population model (dotted-curve) predictions (left panels), and 2) The correlation of DV versus population model prediction (open-triangle) and the individual model prediction of Cp (closed-circle) (right panels).

(Miller, 2012), the comparison of the mean values of K and Vd of the sparse-data to the rich-data values were performed based on the paired t-test method using Microsoft® Excel® 365.

RESULTS AND DISCUSSION

Although each population-based modeling software package has a different of complex calculation algorithms, the goodness-of-fit evaluations demonstrate that all the packages, i.e., Monolix, NONMEM, and WinBUGS-PKBUGS properly

analyze the rich-data as well as the sparse-data with 12 or even 6 data-points. In all cases, a proper population fitting of the Cp data is indicated by the absence of a specific pattern or shape such as sigmoid, or shoe shapes. Moreover, the individual prediction indicates an ideal situation, where most of the DV and individual-prediction of Cp coincide on the line of identity. The analyses in Monolix, NONMEM and WinBUGS-PKBUGS, are presented in Figure 2 (the rich-data of Cp), Figure 3 (the sparse - 12 data points), and Figure 4 (the sparse - 6 data points).

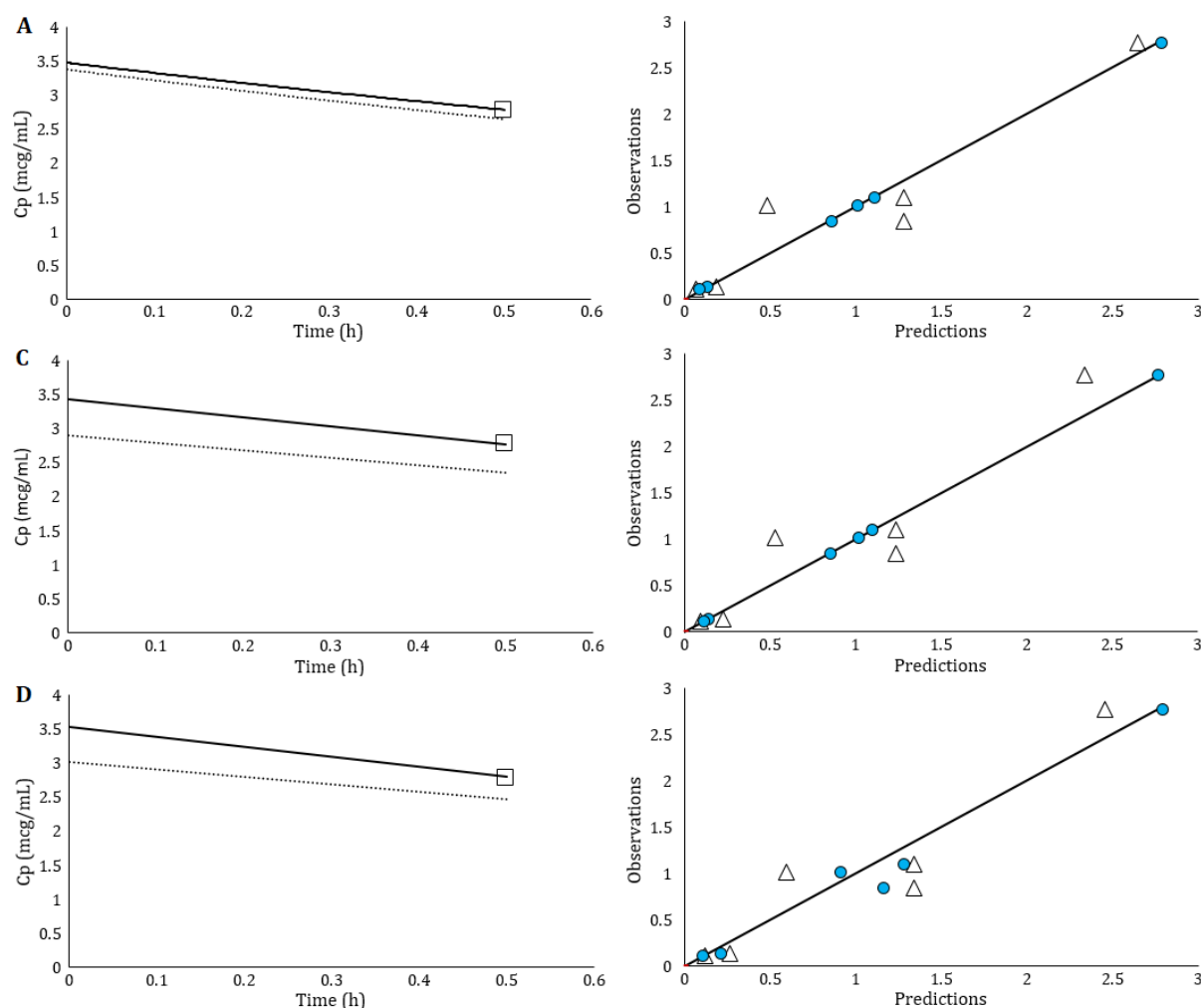


Figure 4. The goodness-of-fit evaluation of the sparse-data with 1 datum per subject of Cp in Monolix (A), NONMEM (B) and WINBUGS-PKBUGS (C) i.e. 1) the typical examples of individual fitting (subject number 1) of the “observed” Cp data (DV) with the individual (solid-curve) and population model (dotted-curve) predictions (left panels), and 2) the correlation of DV versus population model prediction (open-triangle) and the individual model prediction of Cp (closed-circle) (right panels).

Furthermore, we analyzed the individual pharmacokinetic parameter values of K and Vd of the sparse-data to the respective reference K and Vd values used to simulate the Cp data, based on a paired t-test (Table I). In all comparisons, the K and Vd values estimated by using Monolix, NONMEM and WinBUGS-PKBUGS of the sparse-data with 12 data-points are similar to the respective reference values ($p > 0.05$). Moreover, although the fitting analyses are adequate with all software packages, the estimated K and Vd values of the sparse-data with 6 data-points are significantly different from the reference values ($p < 0.05$). The average percentage ratios of K values of the sparse 6 data-

points to the reference values are in the range of 188% (Monolix), 184% (NONMEM) and 161% (WinBUGS-PKBUGS). Similarly, such percentage ratios of Vd values are in the range of 56% (Monolix), 69% (NONMEM), and 62% (WinBUGS-PKBUGS).

Those facts demonstrate that sparse-data obtained with a limited number of subjects (6) and a limited number of samples (2) per subject, can be appropriately fitted in all cases. In agreement with our previous report with the sparse per-oral Cp data (Nugroho *et al.*, 2017), the conditions again highlight the power of population modeling to analyze the sparse-data. This finding is important,

concerning the possibility of an accurate analysis with minimal data obtained in clinical studies involving patients such as in the case of a therapeutic drug monitoring of certain drugs. In such instances, sparse-data are collected from patients (Parke and Charles, 1998; Shaker *et al.*, 2013). The conventional approach with a two-stage approach cannot analyze such conditions as this classical method requires a rich-data situation (Nugroho *et al.*, 2017).

We could consider that, with the case of an intravenous bolus injection of a compound following a one-compartmental open model, the minimum data-points of population modeling analyses is 12. However, we should realize that it could be related to the less complexity of the model, with only 2 model parameters (K and V_d), and without the involvement of any covariate for the analyses. In modeling cases involving more parameters, with or without any covariates, the calculation is more complicated (Mould and Upton, 2013), and the minimum number of samples might be different. It is important to find such guidance in estimating the minimum samples required for those cases, including per-oral administration of a compound following a multi-compartment open model. This information will be helpful in the preparation of an *in vivo* studies in patients. The appropriate scenarios can be proposed to ascertain a valid analysis of the limited data

Furthermore, the fact that Monolix, NONMEM, and WinBUGS-PKBUGS demonstrated similar power in population modeling is also essential, especially for the future of the extensive application of population-modeling in Indonesia and other developing countries. It is related to the limited budget allocation support in most institutions to buy an annual and relatively expensive license cost of the commercial software package. Monolix is free for any educational use, while WinBUGS-PKBUGS is an entirely free-software package for everyone willing to perform a population-based approach based on Bayesian Statistics implementing an MCMC method (Lunn *et al.*, 2002).

CONCLUSION

Population-based approach appropriately describes the sparse-data in an intravenous bolus injection scenarios. Such capability is essential to achieve the ideal therapeutic outcome based on therapeutic drug monitoring. Monolix (free-for-academic) and WinBUGS-PKBUGS (completely free) software packages have comparable

performances to NONMEM, the gold standard of population based software. The possibility to use a completely free software package can facilitate a more extensive application of population modeling to facilitate an optimum therapeutic outcome in Indonesia.

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