On the Calculation of Terminal Phase Half-life and Missing Not At Random

Shu Zhang, Sc.D.[1], Wei Lu, Ph.D.[2], Xia Luo, M.S.[3]
[1]Eisai Inc., 155 Tice Boulevard, NJ 07677
[2]Peking University, 38Xueyuan Road, Beijing 100191, China
[3]Vertex Pharmaceuticals Inc., 675 Kendall Street, Cambridge, MA 02142

Abstract

Terminal phase half-life ($t_{1/2}$) is an important pharmacokinetic parameter characterizing a compound. Underestimating $t_{1/2}$ can result in a shorter-than-necessary dosing interval, which in turn can cause undesired accumulation of the compound in the body.

The population $t_{1/2}$ is estimated by first estimating $t_{1/2}$ for each subject, and then take the average of all the $t_{1/2}$s to obtain the mean $t_{1/2}$. However, in current practice, the estimated $t_{1/2}$ for some subjects may be deemed unreliable based on certain "reliability criteria"; as a result, these $t_{1/2}$s are discarded, rendering the $t_{1/2}$ for those subjects a missing value. In this work, we examine the missingness mechanism and the overall impact of the missing values on the estimated parameters, and apply that concept to the case of estimating mean $t_{1/2}$; we demonstrate that in some cases, excluding these "unreliable" $t_{1/2}$s can result in the biasness of the mean $t_{1/2}$. We propose some alternative methods to estimate the mean $t_{1/2}$, in particular, use sensitivity analysis, Pattern Mixture Model (PMM) and censoring method. We implement our methods through simulation, and show the improvement of our methods over the "traditional" method.

Key Words: Half-life, MNAR, sensitivity, PMM, censor

1. Introduction

In a pharmacokinetics (PK) study, one of the main purposes is to understand how a chemical compound behaves once entering a human body. In other words, pharmacokinetics is a study of "what the body does to the drug". Once entering a human body, a drug typically undergoes absorption, distribution, metabolism and excretion phases, and metabolism and excretion together are also referred to as "elimination". Figure 1 depicts a "typical" time-concentration profile for an oral dosing in linear scales.

There are a number of important PK parameters that are used to characterize a compound's behavior. These parameters include, but are not limited to,

C_{max} (= maximum concentration)

t_{max} (= time to reach C_{max})

$AUC_{0\text{-}t}$ (= area under the time-concentration curve from time *0* to *t*,

where *t* is the time the last concentration is observed)

$AUC_{0\text{-}inf}$ (= area under the time-concentration curve from time 0 to infinity)
$AUC_{0\text{-}inf}$ = $AUC_{0\text{-}t}$ +$AUC_{t\text{-}inf}$ (see Figure 2). $AUC_{t\text{-}inf}$ is termed the "extrapolated AUC", and is obtained through extrapolating the regression slope described in later section.)

$t_{1/2}$ (=terminal phase half-life, i.e., the time required for a quantity to fall to half its value as measured at the beginning of the time period).

Half-life is an important pharmacokinetic parameter that characterizes the elimination of the compound. Estimated $t_{1/2}$ is important in determining the dosing interval. If $t_{1/2}$ is estimated incorrectly, the subsequent dosing interval can be predicted incorrectly, and thus causing undesired concentration level in a subject's body, such as below-therapeutic level, or unintended accumulation which may in turn cause undesired toxicity or side effect.

In general, $t_{1/2}$ is estimated using Non-Compartmental Analysis (NCA) through a two-step procedure: first, a $t_{1/2}$ is estimated for each subject; in the second step, the mean $t_{1/2}$ is estimated and will be used as the estimate of the population $t_{1/2}$.

In the first step, the half-life is obtained through the following regression model (see Figure 3 for illustration):

$$Ln\ (C_j) = \beta_0 - \beta_1\ (time_j) + \varepsilon_j$$
$$\varepsilon_j \sim N\ (\mu, \sigma^2)$$

where C = Concentration, $j = t^*....t$, t^* is the first time point in the elimination phase after Tmax that is deemed appropriate to estimate the $t_{1/2}$, and t is the last time point when concentration is observed / measureable. The estimated slope parameter $\hat{\beta}_1$ is used as the elimination rate constant, k_e, and $t_{1/2}$ is calculated through the following formula:

$$t_{1/2} = \ln (2) / k_e$$

However, in some cases, the estimated k_e for an individual is deemed unreliable; the list below summarizes the most commonly used criteria to determine whether an estimated k_e falls into an "unreliable" category:

1. There should be at least three post- C_{max} concentrations in the terminal phase that will be used to estimate k_e, and these concentrations should not include the concentration at T_{max} (i.e., at least 3 points in terminal phase).
2. The duration of time over which k_e is estimated should generally be at least twice the subsequently estimated terminal phase half-life ($t_{1/2}$) (i.e., $t - t^* \geq 2 \bullet t_{1/2}$) .
3. The adjusted regression coefficient (R^2_{adj}) should be generally greater than 0.90 (i.e., $R^2_{adj} \geq 0.90$).
4. The extrapolated area in AUC ($AUC_{t\text{-}inf}$) in subsequently estimated $AUC_{0\text{-}inf}$ should not be greater than 20% of $AUC_{0\text{-}inf}$ (i.e., $AUC_{t\text{-}inf} < 20\% \bullet AUC_{0\text{-}inf}$).

If any of the above criteria is not met for an individual, the ke for that individual will be discarded, rendering the $t_{1/2}$ for that individual a missing value. Further, when calculating the mean $t_{1/2}$ for the population, these k_es are excluded from the calculation due to the missingness.

This raises a question: what is the impact of these missing values on the biasness of the mean $t_{1/2}$, if we only use observed $t_{1/2}$ for the estimation?

In this work, we examine the missingness mechanism and the overall impact of the missing values on the estimated parameters, and apply that concept to the case of estimating mean $t_{1/2}$; we demonstrate that excluding these "unreliable" $t_{1/2}$s can result in the biasness of the mean $t_{1/2}$. We propose some alternative methods to estimate the mean $t_{1/2}$, in particular, use sensitivity analysis, Pattern Mixture Model (PMM) and censoring method. We implement our methods through simulation, show the result of the simulation, and compare them vs. the results obtained from the "traditional" method. We conclude this work with some discussions on the advantages and limitations of our methods.

2. Methods

2.1 Missingness Mechanism

In general, missingness can be classified into three categories:

1) Missing completely at random (MCAR), which assumes that missingness does not depend on either observed or unobserved data.
2) Missing at random (MAR), which means that missingness is independent of the unobserved outcomes after accounting for the appropriate observed data in the model.
3) Missing not at random (MNAR). MNAR means that missingness depends on the unobserved values, and cannot be predicted solely based on subject's observed data.

The mechanism of the missingness has an important impact on the biasness of the parameters that are estimated using only the observed data. In the first case (MCAR), the estimated parameters remain unbiased; in the second case (MAR), if appropriate statistical models are used, the estimated parameters can still remain unbiased; however, in the case of MNAR, if only observed data are used, the estimated parameters in general will be biased.

Applying these principles to the case of calculating $t_{1/2}$, we can examine the potential causes of the missingness for each scenario, and determine, based on the reasons of missingness, its impact on the estimated parameter – the mean $t_{1/2}$. It needs to be noted that the potential causes discussed below are neither exhaustive nor mutually exclusive; i.e. each scenario may be caused by multiple reasons, and we can only postulate the most likely cause.

1) Less than 3 points in the terminal phase

Figure 4 depicts such a scenario. As can be seen, this is most likely due to a long absorption phase; so by the time of the last sample collection, it has not or has just reached the elimination phase.

2) $t - t^* \geq 2 \bullet t_{1/2}$.
   Similar to the previous scenario, this scenario is also likely caused by a long absorption phase (see Figure 4).

3) $R^2_{adj} < 0.90$.
   This scenario most likely reflects a high variability (see Figure 5).

4) $AUC_{t\text{-}inf} > 20\% \bullet AUC_{0\text{-}inf}$.
   As can be seen in Figure 6, this is most likely due to a long half-life.

To summarize, the scenarios that can result in a $t_{1/2}$ being discarded are either due to a subject having a long absorption, or high variability, or a long half-life. Further, linking these reasons of missingness to the missingness mechanism, we can see that in the case of a long absorption, we do not have enough information on the elimination phase, and there is no reason to assume that this subject has a long $t_{1/2}$, so we consider this case MCAR. The high variability has nothing to do with unobserved $t_{1/2}$, so it is also a MCAR. However, in the case of $AUC_{t\text{-}inf} > 20\% \bullet AUC_{0\text{-}inf}$, the missingness is due to the subject having a long half-life, i.e., the missingness of a subject's $t_{1/2}$ depends on the unobserved $t_{1/2}$ itself, then this is clearly a case of MNAR, and we will focus our attention to this case. In particular, we will focus on the scenario of $AUC_{t\text{-}inf} > 20\% \bullet AUC_{0\text{-}inf}$.

In this case, i.e., some $t_{1/2}$s are discarded due to the subject's $AUC_{t\text{-}inf} > 20\% \bullet AUC_{0\text{-}inf}$, in other words, these $t_{1/2}$s are missing because these subjects have a long $t_{1/2}$, it is easy to see that the mean $t_{1/2}$ using only observed data is an underestimate of the true population mean $t_{1/2}$, a systematic bias. We propose to use sensitivity analysis, Pattern Mixture Model (PPM) and censoring method to handle these MNARs in the next section.

2.2 Sensitivity Analysis

Notice that all $t_{1/2}$s in the case of $AUC_{t\text{-}inf} > 20\% \bullet AUC_{0\text{-}inf}$ have been calculated for each individual at the first place. They were discarded only after the fact that using these estimated $t_{1/2}$ to calculate $AUC_{0\text{-}inf}$ and $AUC_{t\text{-}inf}$, the $AUC_{t\text{-}inf}$ is greater than $20\% \bullet AUC_{0\text{-}inf}$. So instead of excluding these $t_{1/2}$s in the calculation of mean $t_{1/2}$ as in the traditional method, we can conduct a sensitivity analysis by simply including these $t_{1/2}$s to calculate mean $t_{1/2}$, and compare the result vs. the traditional method. If the results are similar, then there is no enough evidence to conclude an MNAR, or a biasness in the mean $t_{1/2}$; however, if the results differ significantly, then it is a clear indication that an MNAR and a biasness is highly possible.

2.3 Pattern Mixture Model (PMM)

Pattern Mixture Model (PMM) is one of the main classes of models widely used to handle MNAR data. To use this model in our problems, we first define the following notations.

Let **Y** be a vector representing the outcome variable, in our case, $t_{1/2}$. With some missing values in **Y**, **Y** can be decomposed into two sub-vectors: $\mathbf{Y}_{obs}$ and $\mathbf{Y}_{mis}$, where $\mathbf{Y}_{obs}$ are the observed **Y**s, and $\mathbf{Y}_{mis}$ are the missing **Y**s. We further define a vector of indication variable, **R**, to indicate the missingness status for each Y:

$$\mathbf{Y}_{all} = (\mathbf{Y}_{obs}, \mathbf{Y}_{mis}).$$

$R_i = 1$, if Y_i is observed, $i=1.....n$
$= 0$, otherwise

If **Y** can be expressed as a function of some covariates, **X**, then the joint distribution of **Y** and **R** in the PMM model can be expressed as follows:

$$P(\mathbf{Y}_{obs}, \mathbf{Y}_{mis}, \mathbf{R} \mid \mathbf{X}) = p(\mathbf{Y}_{obs}, \mathbf{Y}_{mis} \mid \mathbf{R}, \mathbf{X})\, p(\mathbf{R} \mid \mathbf{X})$$

Since there is no covariate in our problem, the PMM model can be simplified as

$$p(\mathbf{Y}_{obs}, \mathbf{Y}_{mis}, \mathbf{R})$$
$$= p(\mathbf{Y}_{obs}, \mathbf{Y}_{mis} \mid \mathbf{R})\, p(\mathbf{R})$$
$$= p(\mathbf{Y}_{obs} \mid \mathbf{R})\;\; p(\mathbf{Y}_{mis} \mid \mathbf{Y}_{obs}, \mathbf{R})\;\; p(\mathbf{R})$$

This model implies that conditioning on **R**, the missingness status, there can be different distributions of **Y**s. In other words, $\mathbf{Y}_{obs}$ may have a different distribution from $\mathbf{Y}_{mis}$. Our interest is to estimate the mean of $\mathbf{Y}_{all}$. This can be achieved by integrating over $p(\mathbf{Y}_{all})$, the marginal distribution of **Y**, and the marginal distribution of **Y** can be obtained through integrating over the joint distribution of $\mathbf{Y}_{all}$ and **R** over **R**, i.e., take some weighted average over all missingness status, if both $p(\mathbf{Y}_{all})$ and $p(\mathbf{R})$ are observed.

However, in our case, $p(\mathbf{R})$ and $p(\mathbf{Y}_{obs} \mid \mathbf{R})$ are observed, but not $p(\mathbf{Y}_{mis} \mid \mathbf{Y}_{obs}, \mathbf{R})$, so we need to impose some identifying restrictions on $p(\mathbf{Y}_{mis} \mid \mathbf{Y}_{obs}, \mathbf{R})$. In other words, we need to impute some values to the missing $t_{1/2}$s, and then take some weighted average to obtain the mean $t_{1/2}$.

The missing $t_{1/2}$ problem has some similarities with the problem of "below quantification limit (BQL) in concentration data, in that a quantity is unobserved either because the quantity is too small (below the limit of quantification), or the quantity is too large (too long of a $t_{1/2}$). So we can borrow some ideas from the methods to handle BQL data to our problem.

In the BQL problem, a BQL value is usually imputed as 0, or the QL (quantification limit), or one-half of QL. In 2001, Professor S. Beal published a paper[1] that summarized 7 commonly used methods to deal with the BQL problem, and one of the methods is the PMM model; however, the difference between our problem vs. BQL problem is that, in our problem, it is not clear what the "quantification limit" is, i.e., we know we have $t_{1/2}$s that are longer than we can measure; however, there is no pre-existing "quantification limit" or a threshold as in the concentration data, so we cannot simply apply the methods

summarized in Beals' paper. We need to first define our own "quantification limit" or threshold and then use that in our imputation.

One natural and evident candidate for the imputation is to use the boundary value itself on an individual level. As mentioned before, in the case of $AUC_{t\text{-}inf} > 20\%\ AUC_{0\text{-}inf}$, some individual's $t_{1/2}$ are excluded because their $AUC_{t\text{-}inf} > 20\%\ AUC_{0\text{-}inf}$. However, if we can find a $t_{1/2,\ bdy}$, such that with that $t_{1/2,\ bdy}$, that subject's $AUC_{t\text{-}inf,\ bdy} = 20\%\ AUC_{0\text{-}inf,\ bdy}$, then that subject's $t_{1/2,\ bdy}$ will not be discarded, and we will not have a missing $t_{1/2}$ for that subject (see Figure 7). We know $t_{1/2,\ bdy} <$ true $t_{1/2}$; but to impute $t_{1/2,\ bdy}$ as $t_{1/2}$ is definitely better than to completely discard $t_{1/2}$ and treat it as missing.

To find $t_{1/2,\ bdy}$, we first fix the $AUC_{t\text{-}inf,\ bdy}$ at $20\%AUC_{0\text{-}inf,\ bdy}$, i.e., assuming

$$AUC_{0\text{-}t} / AUC_{t\text{-}inf,\ bdy} = 4.0$$

In the above equation, $AUC_{0\text{-}t}$ is observed, but $AUC_{t\text{-}inf,\ bdy}$ is unknown, though it can be solved through the above equation. The $AUC_{t\text{-}inf,\ bdy}$ obtained through the above equation implies that it equals $20\%\ AUC_{0\text{-}inf,\ bdy}$. We can then use the formula below to calculate $k_{e,\ bdy}$, and further use $k_{e,\ bdy}$ to calculate $t_{1/2,\ bdy}$.

$$AUC_{t\text{-}inf} = C_{last} / k_e$$

Alternatively, instead of using boundary values from each individual, we can use some quantities based on observed $t_{1/2}$s from the observed population. We know the missing $t_{1/2}$s are long $t_{1/2}$s, so we can consider the following statistics based on all observed $t_{1/2}$s, and use them to impute the missing $t_{1/2}$s:

1) the upper limit of the 95% CI for mean $t_{1/2}$
2) the 90 percentile of the $t_{1/2}$
3) maximum $t_{1/2}$

2.4 Censoring Method

As discussed previously, we do not know the exact value of these missing $t_{1/2}$s; but we do know that they are longer than certain values. So these missing $t_{1/2}$s can be considered as censored variables, we just need to find the censoring values, i.e., the "threshold" at which they are censored. We can then use likelihood function that handles censoring data to solve for the mean $t_{1/2}$.

For the censoring values, we can simply use all the threshold or statistics proposed in the PMM section, i.e.,

1) boundary value $t_{1/2,\ bdy}$ for each subject,
2) the upper limit of the 95% CI for mean $t_{1/2}$ based on all observed $t_{1/2}$s ,
3) the 90 percentile based on all observed $t_{1/2}$s
4) maximum $t_{1/2}$ based on all observed $t_{1/2}$s.

Note that instead of imputing these quantities on the missing $t_{1/2}$s as in PMM, we only use them as the censoring values for the missing $t_{1/2}$ here; and for the purpose of making inference of the mean $t_{1/2}$, there is no need to impute the $t_{1/2}$ for each subject, we can simply obtain the estimated mean $t_{1/2}$ by solving the likelihood function. Also note that there is another main difference between PMM and censoring method. As mentioned before, in PMM, the $\mathbf{Y}_{obs}$ may have a different distribution than $\mathbf{Y}_{mis}$; while in censoring method, they are assumed to come from the same distribution, and the reason for the missingness is due to the fact that these values are beyond certain threshold and cannot be measured, and are thus censored.

The general form of the likelihood function that contains some censored data can be expressed as the following:

$$L(\mathbf{Y};\theta)=\prod_{i:Ri=1} f(yi;\theta) \prod_{i:Ri=0} S(yi;\theta)$$

where

$$S(y_i;\theta) = 1 - F(y_i;\theta).$$

Since we assume a normal distribution for the **Y**, i.e.,

$$Y_i \sim N(\mu, \sigma^2)$$

It follows that

$$S(y_i;\theta) = 1 - \Phi((c-\mu)/\sigma)$$

where c = censoring value

We can estimate μ directly from the likelihood function, and SAS Proc Lifereg can be used to obtain the estimates.

3. Simulations and Results

We implement the proposed methods in our simulation, and compare the results vs. the traditional method.

For the simulation, we generated 2 types of random concentration-time profiles: 1) the "typical" profile with true mean $t_{1/2}$ = 7 hours, and 2) long half-life profile with true mean $t_{1/2}$ = 35 hours. We then created 100datasets, and each dataset contains 100 subjects. These 100 subjects are a mixture of the two types of concentration-time profiles, based on certain proportion. For example, we may have 70 subjects with "typical" profile, 30 with long $t_{1/2}$. We examined three different proportions of the long $t_{1/2}$s: 30%, 20%, and 10%. For each dataset, we calculated true mean $t_{1/2}$. We also estimated the $t_{1/2}$ for each subject using WinNonlin. Since the subjects with long $t_{1/2}$ had their estimated $AUC_{t\text{-}inf}$ > 20% $AUC_{0\text{-}inf}$, their estimated $t_{1/2}$s are potentially missing (in traditional method).

Then for each dataset, we calculated sample means using 10 methods: Method 1) the traditional method, which excludes all $t_{1/2}$s if the $AUC_{t\text{-}inf}$ based on the estimate $t_{1/2}$ > 20% $AUC_{0\text{-}inf}$, Method 2) the sensitivity method, which includes all the estimated $t_{1/2}$ even though their $AUC_{t\text{-}inf}$ > 20% $AUC_{0\text{-}inf}$, Method 3-6) the PMM method using the four

different quantities (the boundary value $t_{1/2, bdy}$ for each subject, or the upper limit of the 95% CI for mean $t_{1/2}$, the 90 percentile or maximum $t_{1/2}$ based on all observed $t_{1/2}$s) as the imputation values, and Method 7-10), the censoring method using the four different quantities as in the PMM method but as the censoring values.

We then take the average of the 100 datasets to obtain overall results for each of the 10 methods, as well as the overall true mean. For each method, the estimated overall mean ($\bar{t}_{1/2}$) is compared with the overall true mean ($\mu_{t1/2}$) , and percent bias (=absolute value ($\bar{t}_{1/2}$ - $\mu_{t1/2}$) / $\mu_{t1/2}$) is also calculated. For the 9 methods except traditional method, we also calculated bias reduction (= %improvement) from traditional method (= absolute value of (% bias from each of the 9 methods – % bias from the traditional method) / % bias from traditional method). The results are presented in Table 1.

It can be seen from the table that for the traditional method, the %bias increases with increased missing data. Even when there are only 10% missing, the traditional method underestimates the mean $t_{1/2}$ by 27%, quite a substantial bias. When the missingness reaches 20%, the bias reaches 43%. The %bias seems to close or higher than 2 times the %missing.

Table 1. Simulation Results

% Missing	10			20			30		
	Hour	% Bias	% Improvement	Hour	% Bias	% Improvement	Hour	% Bias	% Improvement
True t1/2	9.86			12.60			15.34		
Traditional	7.17	27		7.17	43		7.14	53	
Sensitivity	8.71	12	21	10.26	19	43	11.77	23	65
Pmm_uclm	7.20	27	0	7.23	43	1	7.23	53	1
Pmm_p90	7.37	25	3	7.56	40	5	7.73	50	8
Pmm_max	7.62	23	6	8.08	36	13	8.44	45	18
Pmm_20pct	8.11	18	13	9.05	28	26	9.95	35	39
Cens_uclm	7.31	26	2	7.47	41	4	7.61	50	7
Cens_p90	7.45	24	4	7.78	38	8	8.13	47	14
Cens_max	7.71	22	7	8.35	34	16	9.00	41	26
Cens_20pct	8.23	17	15	9.51	24	33	11.01	28	54

The biasness improved over the traditional methods for all the 9 alternative methods, but with different levels of bias reduction. Overall, they still underestimate the true mean, and the % improvement increases along with increased missingness.

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The sensitivity analysis has improved the %bias over traditional method substantially for all the three missingness proportions, and not surprisingly, the more missingness, the more improvement. When the missingness reaches 30%, the sensitivity analysis reduced bias by 65%. Even when there is only 10% missingness, there is a 21% improvement over the traditional method.

Among the four PMM models that used different imputation values, from the least, minimal improvement to the largest improvement, are

the upper limit of the 95% CI for mean $t_{1/2}$ based on all observed $t_{1/2}$s ,
the 90 percentile $t_{1/2}$ based on all observed $t_{1/2}$s
maximum $t_{1/2}$ based based on all observed $t_{1/2}$s
boundary value $t_{1/2, bdy}$ for each subject

In the PMM model with boundary value $t_{1/2, bdy}$ for each subject as the imputation value, the %improvement over the traditional method is almost proportional, although higher, than the % missingness.

The censoring method is uniformly better, though not significantly, than the PMM, and the %bias reduction over the PMM also increases along with the increase of %missingness. Overall, the censoring method exhibits similar pattern as the PMM models in the order of bias reduction, and from the least improvement to the largest improvement, it is

the upper limit of the 95% CI for mean t1/2 based on all observed $t_{1/2}$s
the 90 percentile t1/2 based on all observed $t_{1/2}$s
maximum t1/2 based on all observed $t_{1/2}$s
boundary value $t_{1/2, bdy}$ for each subject.

4. Discussions

In this work, we demonstrated that using traditional method to estimating mean $t_{1/2}$, i.e., to exclude "unreliable" $t_{1/2}$s, can sometimes result in MNAR and thus introduce bias in the estimated population $t_{1/2}$. We showed that this bias increases along with the proportion of missingness (= the $t_{1/2}$s excluded from the calculation of the mean $t_{1/2}$).

In general, in an MNAR, there is no reliable way to test the MNAR assumption, as well as any imputation method. The common solution to this problem is to conduct various sensitivity analyses, to test different assumptions and imputation methods, and compare the results. However, our problem is a special case, in that the missingness is due to some "reliability criteria" that did not take into account of potential biasness in the parameter estimation. In other words, the "missing values" do exist, particularly in the case of $AUC_{t\text{-}inf} > 20\%\ AUC_{0\text{-}inf}$, making it easier to test the MNAR assumption as well as the proposed imputations.

In this work, we used "sensitivity analysis" to specifically mean including all the "missing values" in the calculation of the mean. We showed that such analysis is important in identifying potential bias, as well as reducing the bias. We also proposed other imputation methods, and we showed that using the PMM model with the boundary value $t_{1/2,\ bdy}$ as the imputation value is very beneficial. It is easy to implement, and it will never overestimate the true $t_{1/2}$, as the methods using values from the observed subjects might be.

The PMM model also has a very sensible biological interpretation. It states that in the general population, there might be some subpopulations, each with its own distinct distribution of the $t_{1/2}$. For example, the true $t_{1/2}$s may differ in these subpopulations due to genetic polymorphism, or due to the impairment of renal or hepatic functions.

There are some limitations in this work that need to be addressed in future work. One limitation is that we only focused on the case that the missingness is due to $AUC_{t\text{-}inf} > 20\%\ AUC_{0\text{-}inf}$. However, as pointed out previously, the reasons for a $t_{1/2}$ being deemed unreliable can be complicated, and may not be either exhaustive or mutually exclusive. Further work is needed to explore more complicated scenario that result in "unreliable" estimate of $t_{1/2}$ and missing data.

As in many other PK parameter estimation problems, the variability of these estimates is not adequately addressed in this work. In addition to biasness, the efficiency of the parameter estimate should also be considered, especially when there are missing data.

Figure 1. Concentration-Time Profile, Linear Scale
($t_{1/2}$ = 6 hours)

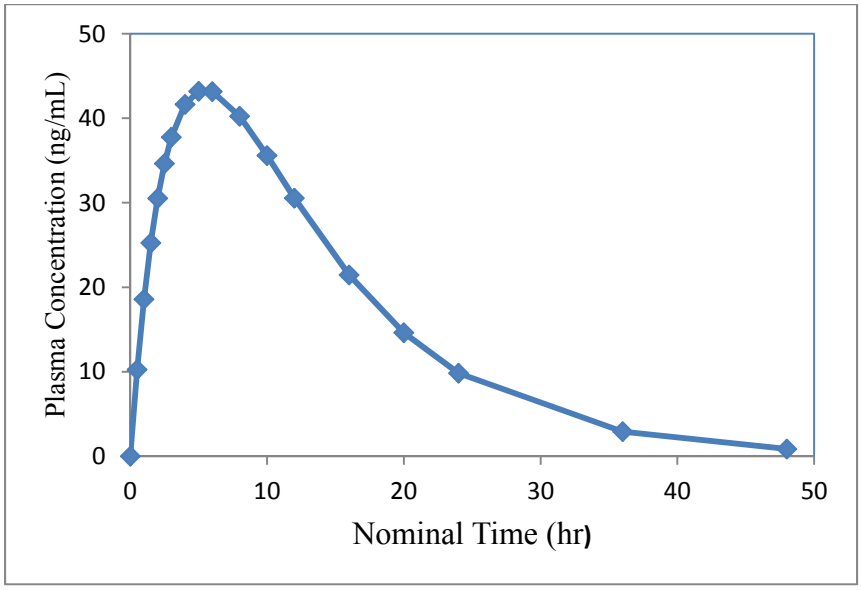


Figure 2. $AUC_{0\text{-}inf}$ = $AUC_{0\text{-}t}$+$AUC_{t\text{-}inf}$
($t_{1/2}$ = 33 hours)

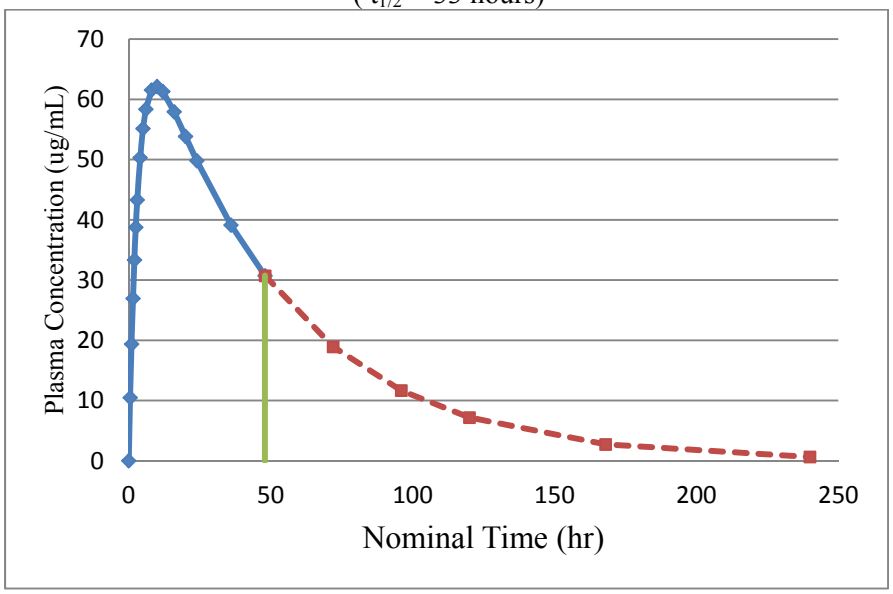


Figure 3. Concentration – Time Profile, Semi-log Scale
($t_{1/2}$ = 6 hours)

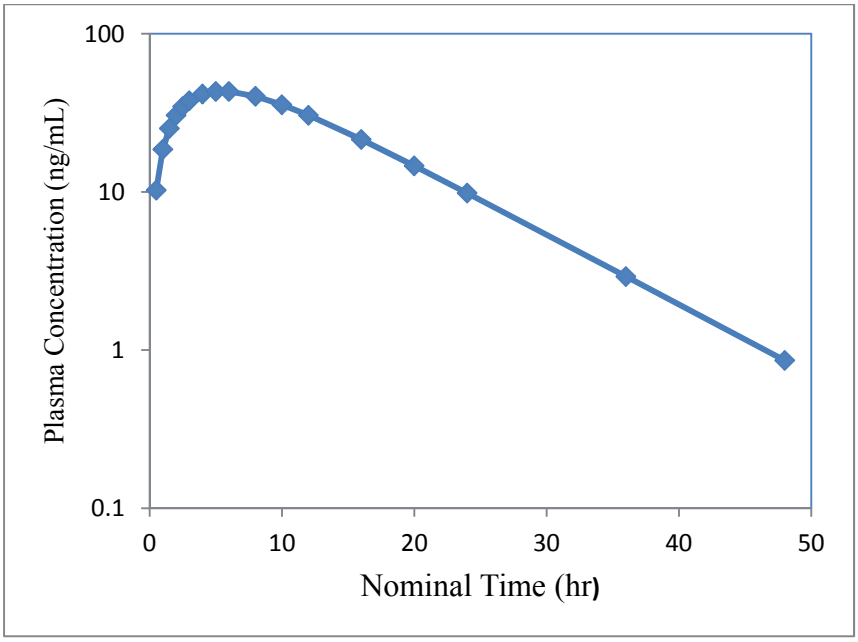


Figure 4. Long Absorption and Distribution – MCAR
($t_{1/2}$ = 6 hours)

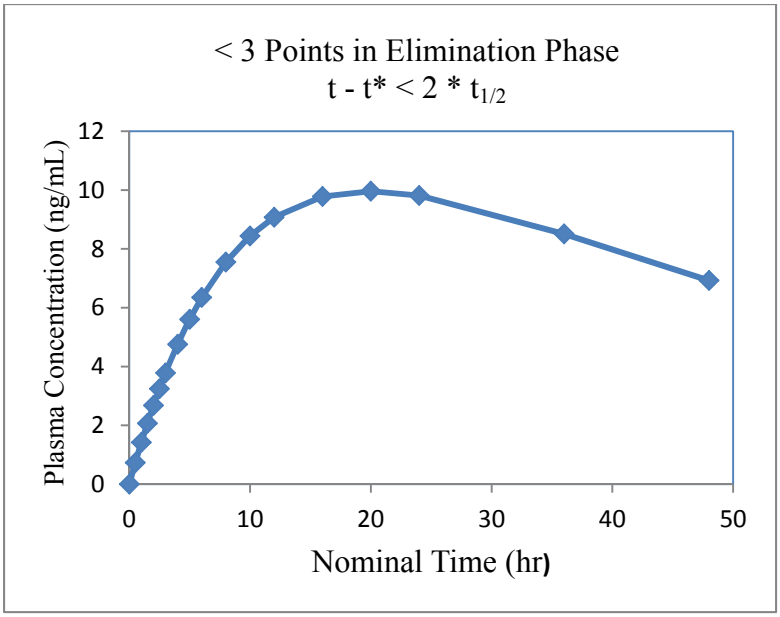


Figure 5. High Variability – MCAR
($t_{1/2}$ = 6 hours)

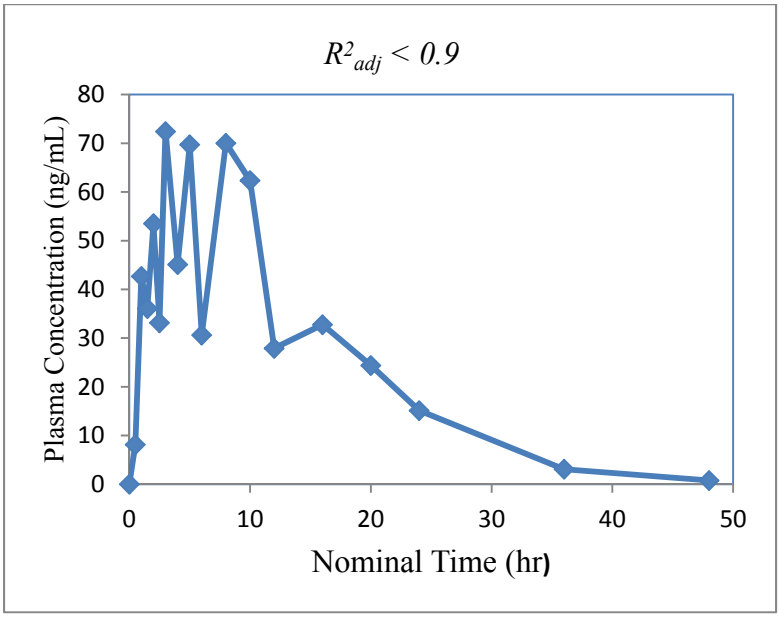


Figure 6. Long Half-life – MNAR
($t_{1/2}$ = 33 hours)

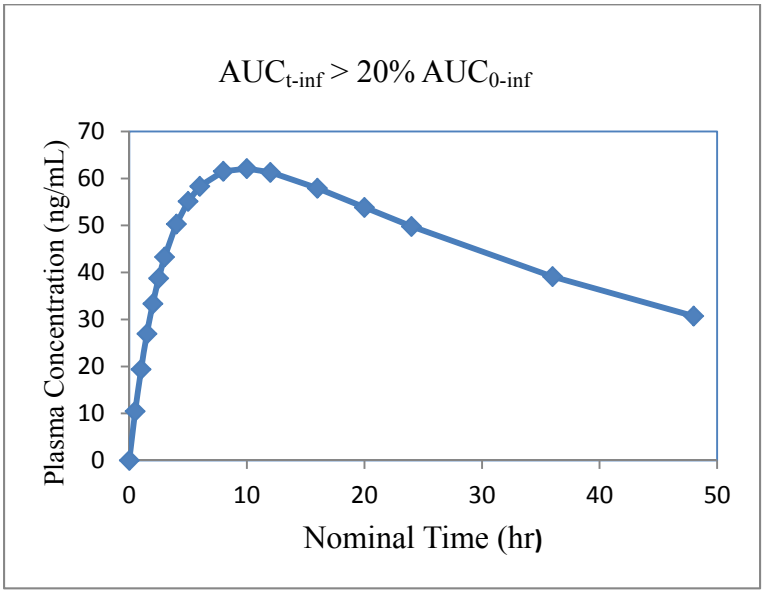
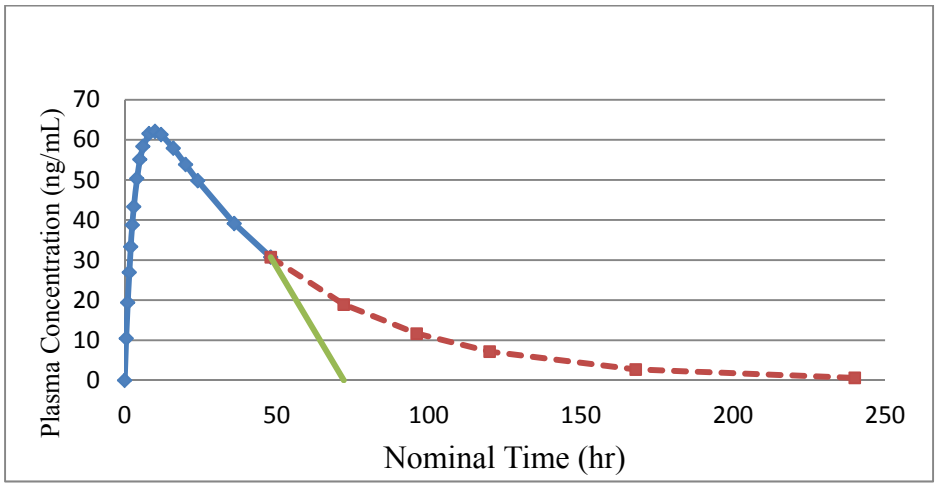


Figure 7. $AUC_{0\text{-}t,\ bdy} = 20\%\ AUC_{0\text{-}inf,\ bdy}$
($t_{1/2}$ = 33 hours)



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