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ON INFERECES ON PHARMACOKINETIC PARAMETERS

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Abstract

There are pharmacokinetic parameters which characterize drug blood concentrations as $C_{\max}$, $t_{\max}$, AUC and so on. These parameters are inferred by sampling from subjects. Although small sample size is better from clinical viewpoint, statistically it is better that it is larger. In this article, we compare methods of inference on AUC from full and sparse samples.

1. Overview

It is natural that the request to want to infer from small samples appropriately happens from a clinician. To infer an area under the blood concentration time curve AUC, we have the following methods: first, we obtain a 95% confidence interval by a point inference on AUC by using the trapezoidal rule and its variance (e.g., [4, 5]), in another case, we assume one compartment model and obtain an inference on AUC by

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inferring parameters in the model. Note that in the first case, we do not assume any models and obtain a confidence interval independent from administration methods. In the second case, we assume the type of model, but we obtain inferences on parameters by using the least squares method, so we can generalize this method to any other model. However, we have some attention to get a 95% confidence interval.

In this article, we compare 95% confidence intervals by the trapezoidal rule and inferences about parameters for a full data and its sparse data. In our case, for full data, the confidence interval from the trapezoidal rule case is narrower than that of inferences on parameters, for sparse data the result turns out reverse.

We also discuss the case where pharmacokinetic parameters do not follow normal distributions but follow log-normal distributions.

2. Inferences on *AUC*

For subjects j $(j = 1, ..., n)$, let Y_{ij} be blood concentrations at time t_i $(i = 1, ..., a)$, and let

$$\overline{Y_i} = \frac{1}{n}\sum_{j=1}^{n} Y_{ij}$$

be the sample mean at t_i, where $t_0 = 0$.

2.1. Data

In this paper, we use the following full data and sparse data refer from Kasai et al. [1]:

Full data

		blood concentrations (ng/mL)					
No.	time	1	2	4	6	8	12
1		17	116	174	106	58	32
2		44	204	263	177	113	53

3	181	391	361	258	155	45
4	42	267	385	291	195	72
5	131	287	302	205	142	44
6	91	317	388	247	155	55
7	55	276	397	287	177	40
8	-	127	292	165	100	47
9	93	286	266	169	101	30
Mean	82	252	314	212	133	46
SD	54	89	75	63	43	13

Sparse data

		blood concentrations (ng/mL)					
No.	time	1	2	4	6	8	12
1		17	-	-	106	-	-
2		44	-	-	177	-	-
3		181	-	.-	258	-	-
4		-	267	-	-	195	-
5		-	287	-	-	142	-
6		-	317	-	-	155	-
7		-	-	397	-	-	40
8		-	-	292	-	-	47
9		-	-	266	-	-	30
mean		82	252	314	212	133	46
SD		54	89	75	63	43	13

2.2. The trapezoidal rule

It is well-known that the inference on the mean $\overline{AUC}$ from $\bar{Y}_i$ is given by

$$\overline{AUC} = \frac{1}{2}\left[(t_1 - t_0)\bar{Y}_0 + \sum_{i=1}^{a}(t_{i+1} - t_{i-1})\bar{Y}_i + (t_a - t_{a-1})\bar{Y}_a\right]. \qquad (2.1)$$

Next we consider the variance of $\overline{AUC}$. In (2.1) if we set

$$\begin{cases} c_1 = (t_1 - t_0)/2 & i = 0, \\ c_i = (t_{i+1} - t_i)/2 & i = 1, \ldots, a-1, \\ c_a = (t_a - t_{a-1})/2 & i = a, \end{cases}$$

then

$$\overline{AUC} = \sum_{i=0}^{a} c_i \bar{Y}_i.$$

Hence the variance $\mathrm{Var}(\overline{AUC})$ of $\overline{AUC}$ is given by

$$\mathrm{Var}(\overline{AUC}) = \mathrm{Var}\left(\sum_{i=0}^{a} c_i \bar{Y}_i\right) = \sum_{i,k=0}^{a} c_i c_k \mathrm{Cov}(\bar{Y}_i, \bar{Y}_k), \qquad (2.2)$$

where $\mathrm{Cov}(\bar{Y}_i, \bar{Y}_k)$ is the covariance of $\bar{Y}_i$ and $\bar{Y}_k$, and

$$\mathrm{Cov}(\bar{Y}_i, \bar{Y}_k) = \frac{1}{n}\mathrm{Cov}(Y_i, Y_k)$$

for $Y_i = (Y_{i1}, \ldots, Y_{in})$, $Y_k = (Y_{k1}, \ldots, Y_{kn})$. Note that equations (2.1) and (2.2) are independent of models and administration methods.

From (2.1) and (2.2), we have the 95% confidence interval for the mean of AUC as follows. Because $\overline{AUC}$ follows the t-distribution with degree of freedom

$$\nu = \frac{\left[\sum_{i=0}^{a} c_i^2 \mathrm{Var}(\bar{Y}_i)\right]^2}{\sum_{i=0}^{a} \dfrac{c_i^4 \left[\mathrm{Var}(\bar{Y}_i)\right]^2}{n_i - 1}},$$

the 95% confidence interval is given by

$$\overline{AUC} - t_{(\nu,0.025)}\sqrt{\mathrm{Var}(\overline{AUC})}$$

$$\leq \mu_{AUC} < \overline{AUC} + t_{(\nu,0.025)}\sqrt{\mathrm{Var}(\overline{AUC})}.$$

For details see [4] and [5]. Especially in the case of the full data as above, we have $\overline{AUC} = 19998.028$, $\mathrm{Var}(\overline{AUC}) = 29155.09$. We also have $\nu = 34.01887671$ and then $t_{(\nu,0.025)} = 2.0659$. Therefore the 95% confidence interval is given by $1645.278 \leq \mu_{AUC} < 2350.777$. For the sparse data above, we have $1609 \leq \mu_{AUC} < 2559$ (by $\overline{AUC} = 2084$, $\mathrm{Var}(\overline{AUC}) = 27114$, and $\nu = 3.67$). As a matter of course, the interval becomes wider than that of the case of full data.

2.3. One compartment model case

We consider an inference on AUC in the case of one compartment model. In the oral route, the blood concentration is given by

$$y = C_0 \frac{k_a}{k_a - k_e}\left(- e^{-k_a t} + e^{-k_e t} \right),$$

where C_0 is an "initial concentration", k_e is an elimination rate constant, and k_e is an absorption rate constant (and usually assumed $k_a > k_e$). In this case

$$AUC = \frac{C_0}{k_e}.$$

By inferring parameters C_0, k_a, k_e as in (2.3) from data, we obtain a point inference on AUC. To infer parameters, we use the least squares method, for example, we can do it by Solver in Excel. The results are given in Section 2.4.

Next we consider a confidence interval on AUC. To consider the distribution of AUC, we assume that C_0, k_a and k_e follow normal distributions independently. In general, the following hold. For details, see standard texts of probability and statistics.

Theorem 2.1. *Let X and Y be random variables following normal distributions. Assume that $X \sim N(\mu_X, \sigma_X^2)$ and $Y \sim N(\mu_Y, \sigma_Y^2)$, respectively. Then the density function of the random variable $V = X/Y$ is given by*

$$p_v(v) = \frac{b(v)d(v)}{a^3(v)} \frac{1}{\sqrt{2\pi}\sigma_X\sigma_Y}\left[\Phi\left(\frac{b(v)}{a(v)}\right) - \Phi\left(-\frac{b(v)}{a(v)}\right)\right]$$

$$+ \frac{\exp(-c/2)}{a\hat{}2(v)\pi\sigma\_X\sigma\_Y},$$

where

$$a(v) = \sqrt{\frac{v^2}{\sigma_X^2} + \frac{1}{\sigma_Y^2}}, \quad b(v) = \frac{\mu_X v}{\sigma_X^2} + \frac{\mu_Y}{\sigma_Y^2}, \quad c = \frac{\mu_X}{\sigma_X^2} + \frac{\mu_Y}{\sigma_Y^2},$$

$$d(v) = \exp\frac{b^2(v) - ca(v)}{2a\hat{}2(v)}, \quad \Phi(z) = \int_{-\infty}^{z} \frac{1}{2\pi}\exp\left(-\frac{z^2}{2}\right)dz.$$

Especially if X and Y follow the standard normal distribution, then $V = Y/X$ follows the Cauchy distribution.

Theorem 2.2. *Take random samples with sample sizes n_1, n_2 from normal populations $N(\mu_1, \sigma_1^2)$, $N(\mu_2, \sigma_2^2)$, respectively. If $\sigma_1 = \sigma_2$, then $F = \overline{\sigma_1^2} / \overline{\sigma_2^2}$ follows the F-distribution which depends on the degrees of freedom $(n_1 - 1, n_2 - 2)$.*

It follows from Theorem 2.1 that $AUC = C_0/k_e$ follows the Cauchy distribution under the assumption $C_0 \sim N(\mu_a, \sigma_a^2)$ and $k_e \sim N(\mu_b, \sigma_b^2)$, and the sample distribution of C_0/k_e is determined from Theorem 2.2. However, the distribution following AUC is the Cauchy distribution which is a long-tail distribution, and it does not good situation to infer AUC if ever the variance is known.

2.4. Inference on *AUC* in model case

We estimate parameters in (2.3) by using Solver in Excel under the initial data

$C_0 = 200$, $k_a = 10$, and $k_e = 1$, then we obtain $C_0 = 237.611$, $k_a = 78.01914$, $k_e = 0.073401$ and hence $AUC = 3237.142$ ($t_{\max} = 0.089405$, $C_{\max} = 236.0568$). By plotting sample data and estimated values, we have Figure 2.1 as the following. The solutions for (2.3) depend on initial values strongly. For example, if we choose $C_0 = 500$, $k_a = 0.5$, $k_e = 0.1$ as initial values, then we have $C_0 = 658.9822$, $k_a = 0.350636$, $k_e = 0.35064$ and $AUC = 1879.9822$ ($t_{\max} = 2.851887$, $C_{\max} = 242.4197$) and Figure 2.2.

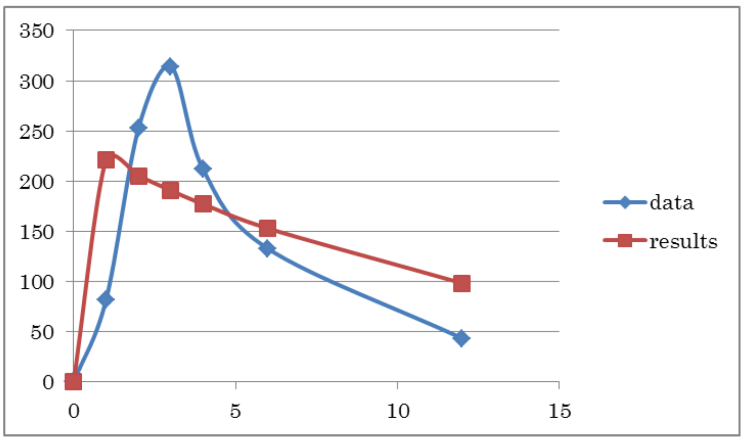

Figure 2.1.

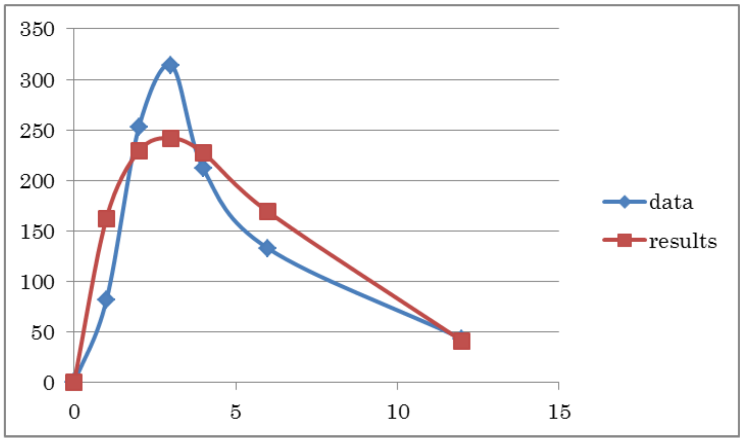

Figure 2.2.

By choosing suitable initial data for the full data in Section 2.1, we obtain the following results:

No.	a	b_1	b_2	AUC
1	345.2307	0.280176	0.280176	1232.192
2	577.6283	0.281009	0.281009	2055.553
3	1002.172	0.350149	0.350152	2862.104
4	828.4158	0.264275	0.264242	3135.07
5	776.3402	0.322709	0.322729	2405.548
6	873.0468	0.30889	0.308888	2826.421
7	848.1441	0.274999	0.275004	3084.115
8	497.5818	0.250054	0.250057	1989.876
9	690.9409	0.348126	0.348138	1984.675
Mean	716.9113	0.300567	0.300567	2385.199

Note that the bottom row does not show the means of above nine values but show the inferences on means in the full data. Under the assumption that AUC follows a normal distribution, we have the 95% confidence interval $1909.104 \leq \mu_{AUC} < 2885.463$.

Now we consider the inference on AUC of Sparse data as in Section 2.1. We cannot infer 2 data for any subject, we put together the data as follows:

Compaction of Sparse data

		blood concentrations (ng/mL)					
No.	time	1	2	4	6	8	12
1, 4, 7		17	267	397	106	195	40
2, 5, 8		44	287	292	177	142	47
3, 6, 9		181	317	266	258	155	30

We have then

Inferences on the above compaction of sparse data

No.	a	b_1	b_2	AUC
1, 4, 7	716.3407	0.291483	0.291483	2457.574
2, 5, 8	688.6612	0.303138	0.303276	2270.737
3, 6, 9	845.4129	0.337671	0.337672	2503.654

and the 95% confidence interval $2104.254 \leq \mu_{AUC} < 2717.057$.

2.5. Comparison

We summarize the results in the last section as follows.

	full data	sparse data
trapezoidal rule case	1645.278 - 2350.777	1609 - 2559
compartment model case	1909.104 - 2885.463	2104.254 - 2717.057

For full data, the width of the 95% confidence interval of the trapezoidal rule case is narrower than that of the compartment model. This is the reason why the degree of freedom is less by considering the correlations. However, for the sparse data the result reverses. In this case, effects of variances are greater than that of the degree of freedom. We seem that our results depend on data as in Section 2.1, and for another data, we may have different results.

3. Concluding Remarks

In this paper, we consider confidence intervals on full and sparse data.

3.1. Curve fitting and *AUC*

In parameter inferences as in Section 2.4, the subject $j = 5$ attains the smallest minimum square error (Figure 3.1). For other subjects, to fit curves in excretion phases do not bad, points at $t_1 = 1$ and around maximum concentration points are bad. The means case is given in Figure 3.2.

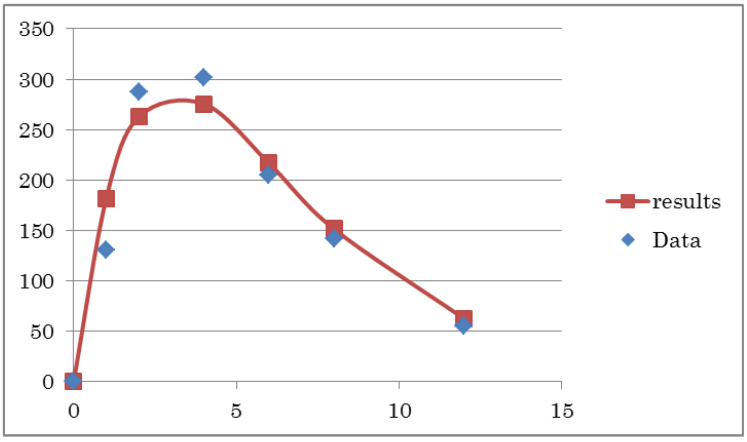

Figure 3.1.

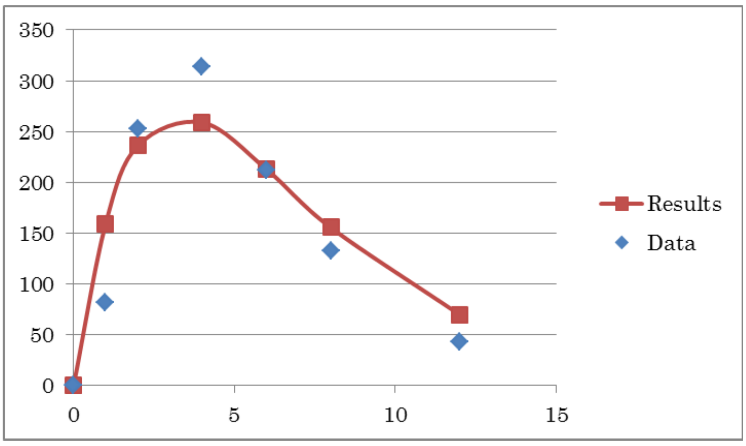

Figure 3.2.

Hence, it seems that the inferences on *AUC* estimate it to be smaller than that of the true value. It also holds for the case of the trapezoidal rule because areas of tails do not include. By the results as in the last section, estimates for the trapezoidal rule are less than that of one parameter case.

3.2. Log-normal distributions

In Section 2, we consider inferences on *AUC*. In the case where we use the trapezoidal rule, we assume that *AUC* follows a normal distribution. Alternatively, in Theorem 2.1, we assume that C_0 and k_e follow normal distributions. However, it is

natural to see that pharmacokinetic parameters follow log-normal distributions (e.g., [3, 4]).

Let $X_1, ..., X_n$ be i.i.d. random variables following a normal distribution $N(\mu_X, \sigma_X^2)$, then the mean $\overline{X}$ of $X_1, ..., X_n$ follows a *t*-distribution with degree of freedom $n-1$ if the variance σ_X^2 is unknown (else follows a normal distribution). It follows that the 95% confidence interval for $\overline{X}$ is given by

$$\overline{X} - t_{(n-1,\,0.025)} \frac{u_X}{\sqrt{n}} \leq \mu_X < \overline{X} + t_{(n-1,\,0.025)} \frac{u_X}{\sqrt{n}}.$$

For a random variable X following a normal distribution $N(\mu_X, \sigma_X^2)$, Y follows a log-normal distribution if $X = \log Y$. The sample mean $\overline{X}$ of $X_1, ..., X_n$ corresponds to the geometric mean

$$G_Y = \sqrt[n]{Y_1 Y_2 \cdots Y_n}$$

of $Y_1, Y_2, \cdots, Y_n$. By means of the above formula, we have the 95% confidence interval for G_y

$$\exp\left(\overline{X} - t_{(n-1,\,0.025)} \frac{u_X}{\sqrt{n}}\right) \leq G_Y < \exp\left(\overline{X} + t_{(n-1,\,0.025)} \frac{u_X}{\sqrt{n}}\right).$$

If we assume that AUC follows a log-normal distribution, then for Full data as in Section 2.1, we have a 95% confidence interval on AUC by $1501.084311 \leq G_{AUC} < 2434.237878$.

For the one compartment model, under notations as in Section 2.4, we have $AUC = C_0 / k_e$, and by taking logarithm of both sides, we obtain

$$\log AUC = \log C_0 - \log k_e.$$

By assuming C_0 and k_e follow log-normal distributions, we have AUC follows a log-normal distribution by the reproductive property of normal distributions. By the above equation, we can get a 95% confidence interval $1835.58039 \leq G_{AUC} <$

2910.205569 for Full data. In this case, AUC for the trapezoidal rule is narrower than that of one compartment model, and as same as for 95% confidence intervals.

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