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A New Numerical Calculation Method for Deconvolution in Linear Compartment Analysis of Pharmacokinetics[1)]

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A new numerical calculation method of the deconvolution specialized for the linear compartment analysis of pharmacokinetics was presented. In this method, the deconvolution was carried out from numerical data of precursor obtained directly in unequal interval of time and an empirical exponential equation for successor. From the assumption for the integrated weight function to be simple increasing function, the divergence of calculation was protected completely. In the experiment of model calculation, the accuracy and the precision were proved to be practically sufficient for pharmacokinetic studies.

Keywords——pharmacokinetics; deconvolution; convolution; linear compartment analysis; compartment model; numerical calculation; non-linear curve fitting

The deconvolution which means the reverse calculation of the convolution is often useful for linear compartment analysis in pharmacokinetic studies. Drug absorption rate process from pharmaceutical preparations, metabolic rate process in a whole body, and elimination rate process of drug metabolites, etc. can be analyzed without assumption of proper kinetic models by the application of deconvolution calculation. These examples of applications have been reported by some authors.[3-5)] The deconvolution calculation methods used commonly, such as the rectangular approximation and the improvements based on the preciser approximation for examples of trapezoidal or Simpson's numerical integration, have generally some defects as follows. Firstly, these calculations require the data at equal intervals of time, so that the proper interpolation is often necessary before the calculation because data are usually obtained at unequal intervals of time in pharmacokinetics. Secondary, the divergence of results frequently occurs in these calculations due to the comparably larger error of pharmacokinetic data and the lack of protection for the divergence at each step of calculation. The weakness of divergence, especially, decreases greatly the usefulness of deconvolution and it must be the reason why only few examples of application were reported in spite of theoretical benefit such as needlessness of kinetic model.

This report intends to present a new deconvolution method by which the divergence is successfully protected and the unequal interval data are directly used. This numerical calculation method is made by utilizing the feature of linear compartment analysis. Namely, the numerical data and the empirical equation are combined for the deconvolution and moreover, a simple increasing function is assumed for the integrated weight function.

In a network of rate process which is expressed by the simultaneous differential equation of the first order, for example, as shown in Fig. 1, if $A(t)$ and $B(t)$ are the function of

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time for precursor and successor, respectively, the relationship between these functions is expressed by the next convolution.

$$B(t) = \int_0^t C(\theta) \cdot A(t-\theta) d\theta \tag{1}$$

where $C(t)$ is called the weight function which expresses a proportional of successor as function of time after ingestion by unit pulse, that is the instantaneous introduction of the unit amount in the system.[5)]

From the partial integration, Eq. 2 is obtained,

$$B(t) = \left[G(\theta) \cdot A(t-\theta) \right]_0^t - \int_0^t G(\theta) \cdot A'(t-\theta) d\theta \tag{2}$$

where $A'(t)$ and $G(t)$ are the derived function of $A(t)$ by time and the integrated function of weight function, $C(t)$, respectively, and expressed as follows,

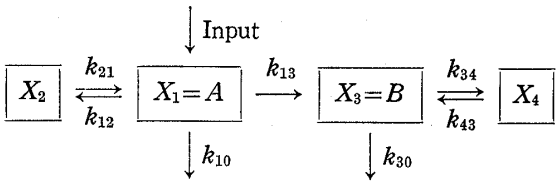
$$A'(t) = \frac{d\{(At)\}}{dt} \tag{3}$$

$$G(t) = \int_0^t C(t) dt \tag{4}$$

$C(t)$ is limited to positive value in pharmacokinetics because no level of substance in body can show negative value. Thus, $G(t)$ must be a monotone increasing function of time. When $G(t)$ is given as in Fig. 2, $G(t)$ between t_{i-1} and t_i can be described by linear approximation as

$$G(t) = \frac{G_i - G_{i-1}}{t_i - t_{i-1}} (t - t_i) + G_i \tag{5}$$

where G_{i-1} and G_i are G values at the times of t_{i-1} and t_i, respectively.



$$\frac{dX_1}{dt} = -K_1X_1 + k_{21}X_2$$

$$\frac{dX_2}{dt} = k_{12}X_1 - k_{21}X_2$$

$$\frac{dX_3}{dt} = k_{13}X_1 - K_3X_3 + k_{43}X_4$$

$$\frac{dX_4}{dt} = k_{34}X_3 - k_{43}X_4$$

$$K_1 = k_{10} + k_{12} + k_{13}$$

$$K_3 = k_{30} + k_{34}$$

Fig. 1. Linear Compartment Model Used for the Calculation Experiment

k's are the first order rate constants, and X's are the amounts in the compartments.

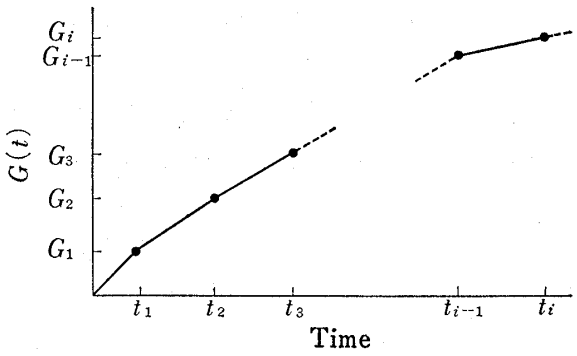


Fig. 2. Time Course of the Integrated Weight Function Assumed for Deconvolution

From the substitution of Eq. 5 to Eq. 2 and the evaluation of G_0 value to be zero, the next equation is obtained,

$$B_j = G_jA_0 - \sum_{i=1}^{j} \int_{t_{i-1}}^{t_i} \left\{ \frac{G_i - G_{i-1}}{t_i - t_{i-1}} (\theta - t_i) + G_i \right\} \cdot A'(t_j - \theta) d\theta \tag{6}$$

where B_j means $B(t)$ value at time, tj, and A_0 means the initial value of $A(t)$.

In the linear compartment model, the empirical equation which expresses levels of substance in body is always shown by the sum of the exponential terms as follows, which

have two kinds of parameters, *i.e.*, the hybrid rate constants and the coefficients, which are usually estimated from non-linear curve fitting by the least square method.

$$A(t) = \sum_{k=1}^{m} A_k e^{-\alpha_k t} \tag{7}$$

From substitution of Eq. 7 to Eq. 6, the next equation is derived

$$B_j = G_j A_0 - \sum_{i=1}^{j} \left\{ \frac{G_i - G_{i-1}}{t_i - t_{i-1}} ASX(i,j) - \frac{G_i t_{i-1} - G_{i-1} t_i}{t_i - t_{i-1}} AX(i,j) \right\} \tag{8}$$

where

$$AX(i,j) = \int_{i-1}^{i} A'(t_j - \theta) d\theta$$

$$= \sum_{k=1}^{m} A_k \{ e^{-\alpha_k (t_j - t_i)} - e^{-\alpha_k (t_j - t_{i-1})} \} \tag{9}$$

$$ASX(i,j) = \int_{i-1}^{i} \theta \cdot A'(t_j - \theta) d\theta$$

$$= t_i \sum_{k=1}^{m} A_k e^{-\alpha_k (t_j - t_i)} - t_{i-1} \sum_{k=1}^{m} A_k e^{-\alpha_k (t_j - t_{i-1})}$$

$$- \sum_{k=1}^{m} \frac{A_k}{\alpha_k} \left\{ e^{-\alpha_k (t_j - t_i)} - e^{-\alpha_k (t_j - t_{i-1})} \right\} \tag{10}$$

From rearrangement of Eq. 8, G_j is orderly calculated by Eq. 11,

$$G_j = \frac{B_j + \sum_{i=1}^{j-1} G_i \{ P(i+1, j) + Q(i, j) \}}{A_0 - Q(j, j)} \tag{11}$$

where

$$P(i,j) = AX(i,j) - \frac{1}{t_i - t_{i-1}} ASX(i,j) + \frac{t_{i-1}}{t_i - t_{i-1}} AX(i,j) \tag{12}$$

$$Q(i,j) = \frac{1}{t_i - t_{i-1}} ASX(i,j) - \frac{t_{i-1}}{t_i - t_{i-1}} AX(i,j) \tag{13}$$

If a calculated G_j is smaller than G_{j-1}, new G value is obtained as follows from assumption that G_j is equal to G_{j-1} in j—1 and j—th equations of the successive equation, Eq. 8.

$$G_j = G_{j-1} = \frac{B_{j-1} + B_j + \sum_{i=1}^{j-2} G_i \{ P(i+1,j) + P(i+1,j-1) + Q(i,j) + Q(i,j-1) \}}{2A_0 - P(j,j) - Q(j-1,j-1) - Q(j-1,j) - Q(j,j)} \tag{14}$$

Moreover, if G_j is smaller than G_{j-k}, this retrospective calculation continues until the increasing G value is obtained as $G_j > G_{j-k-1}$ (see Chart 2). From this calculation, the divergence of G value is completely protected in each step of deconvolution calculation. The C value in Eq. 1 can be obtained by proper numerical differentiation of G, by the method described in the experimental part.

The accuracy of the present method was evaluated from the model calculation which is constructed by two compartment model connected by an irreversible rate process as shown in Fig. 1. The parameter values used are listed in Table I.

The level in compartment 1 as precursor, $A(t)$, and in compartment 3 as successor, $B(t)$ were computed at the same times in 5, 15, 30, 60, 90, 120, 150, and 180 min. The deconvolution calculations were carried out by the rectangular, the trapezoidal, and the present method by means of digital computer in order to compare the accuracy and the precision among these methods. However, the calculations in the former two methods were carried out with the linear interpolation at five minutes intervals. In the rectangular method C value was calculated by next equation,

$$C_j = (\bar{B}_j - \sum_{i=2}^{j} \bar{A}_i C_{j-i+1}) / \bar{A}_1 \tag{15}$$

where $\bar{A}_i$ and $\bar{B}_j$ were the arithmetic averages of A_{i-1} and A_i, and B_{j-1} and B_j,

respectively. In the trapezoidal method G value was calculated by the next equation,

$$G_j = \left(\frac{2\beta_j}{H} - 2\sum_{i=1}^{j-1} A_i G_{j-1}\right)/A_0 \qquad (16)$$

TABLE I. Kinetic Parameters Used for the Calculation Experiment

k_{12}[a]	4.70×10^{-3} min^{-1}	α_1[b]	1.34×10^{-1} min^{-1}	A_1[b]	2.29×10
k_{21}	1.18×10^{-2}	α_2	1.13×10^{-2}	A_2	8.49×10^{-2}
k_{10}	4.06×10^{-2}	α_3	3.74×10^{-2}	B_1	-3.45×10
k_{13}	8.84×10^{-2}	α_4	1.83×10^{-2}	B_2	5.45×10^{-1}
k_{34}	9.19×10^{-4}			B_3	3.25×10
k_{43}	1.92×10^{-2}			B_4	1.39
k_{30}	3.55×10^{-2}			C_1	1.39×10^{-1}
K_1	1.34×10^{-1}			C_2	7.47×10^{-3}
K_3	3.64×10^{-2}				

a) Rate constant shown in Fig. 1.
b) See Chart 1.

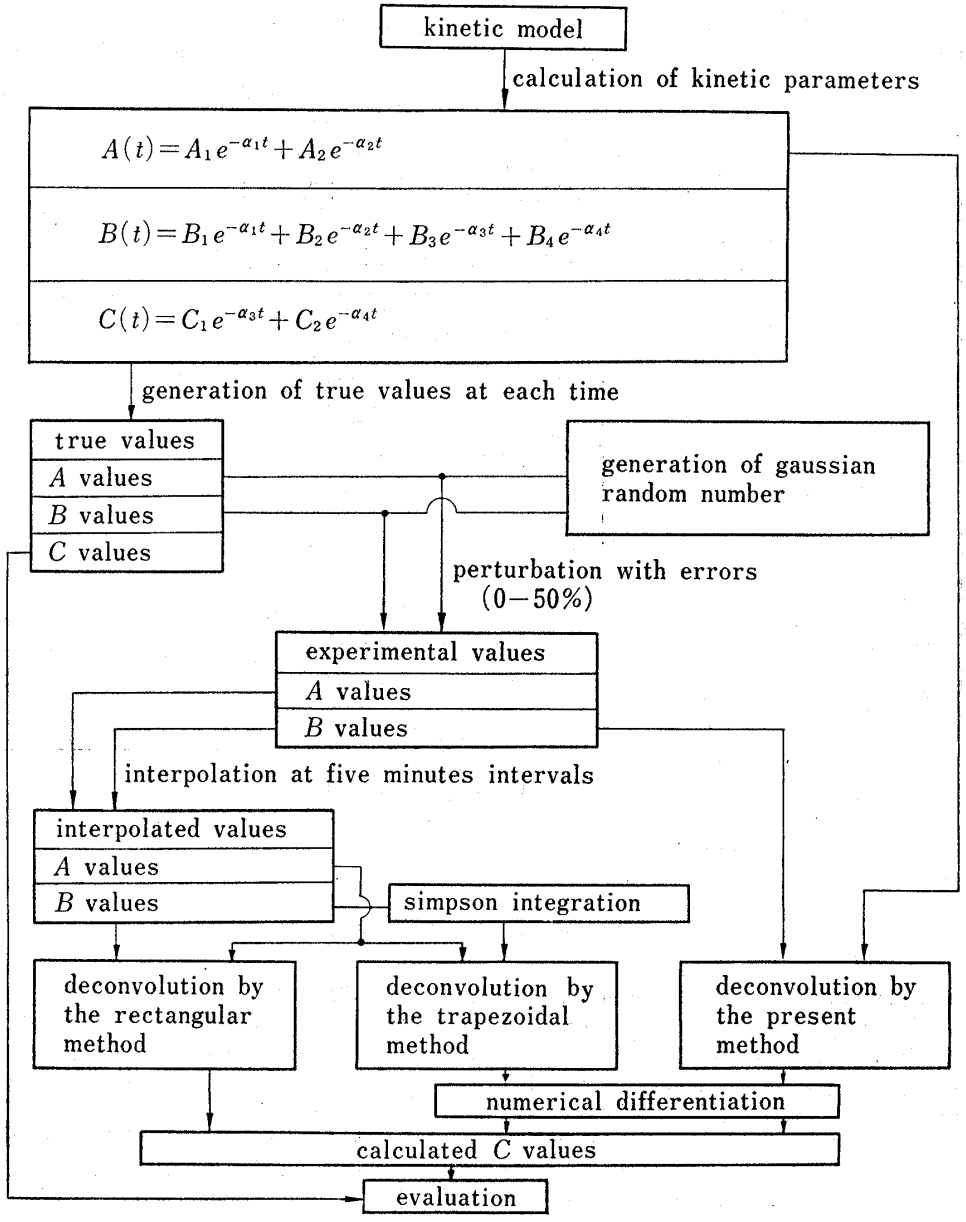


Chart 1. Evaluation System in the Calculation Experiment

where β_j was the integrated value of $B(t)$ from $t=0$ to $t=t_j$ by means of Simpson's numerical integration method, and H was the interval of deconvolution calculation which was five minutes in this case.

Experimental

Computation——The computation was carried out by HITAC 8800/8700 digital computer in the computer center of the University of Tokyo. The programs for the calculation were written in Fortran by the authors. The calculation system used for the evaluation experiment was shown in Chart 1. And the main computation flow of the present method was also shown in Chart 2.

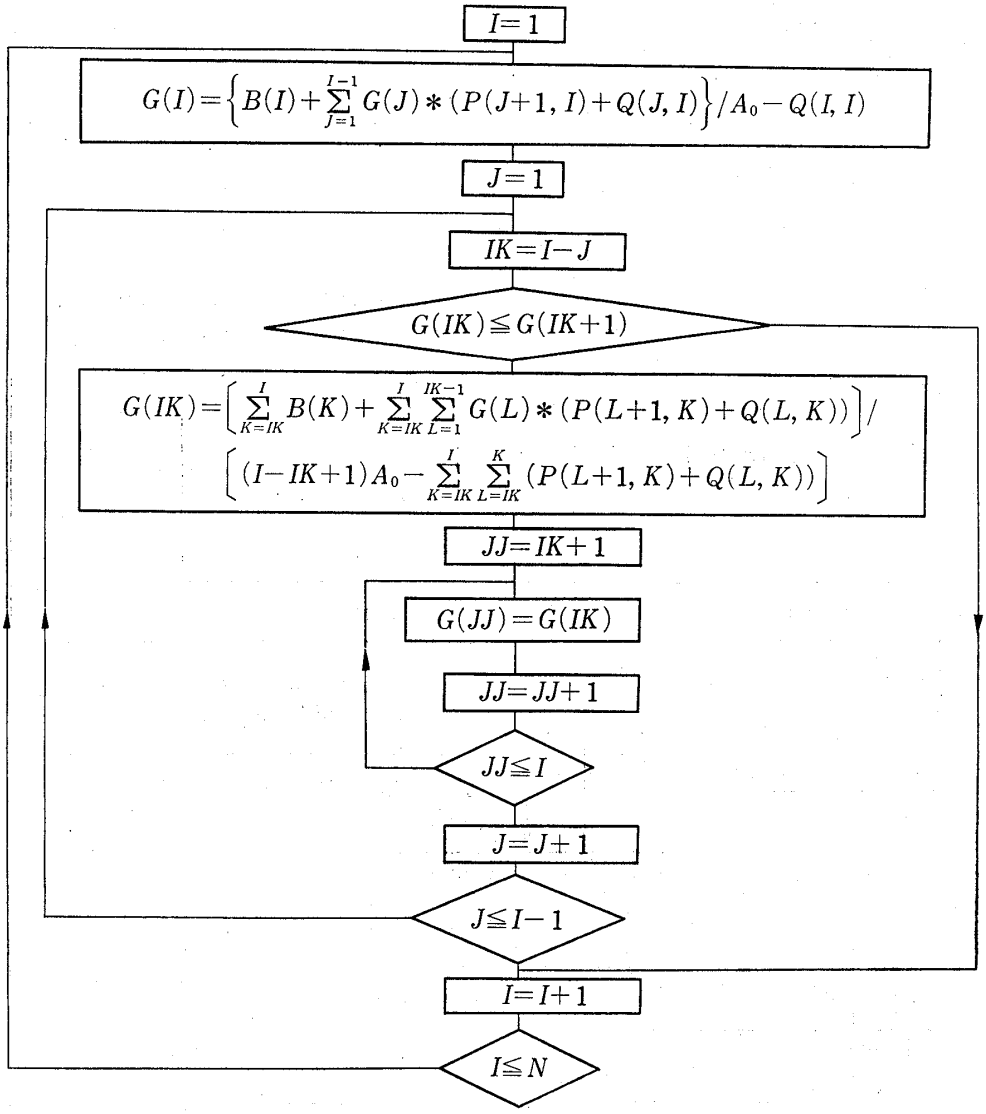


Chart 2. Main Calculation of the Present Method

Numerical Differentiation——The numerical differentiation of G value was calculated from the algebraic quadratic equation which was determined to pass through three points centered the calculating point, that is G_{i-1}, G_i and G_{i+1}, except G_1 and G_n. The value of C_1 was obtained from the quadratic equation to pass through G_1, G_2, and G_3 as mentioned above, and for C_n was assumed the slope between G_{n-1} and G_n since G_n value was close to G_{n-1} while the interval between t_{n-1} and t_n was long in usual pharmacokinetic data.

Divergence——For avoidance of divergence with the deconvolution calculation in the cases of the rectangular and the trapezoidal methods, G_i value was assumed to be equal with G_{i-1} when the calculated G_i value was smaller than G_{i-1}, and this retrospective calculation continued until the increasing G value was obtained in the same way as the present method. If the retrospective calculation reached to G_1, the divergence was concluded.

Results and Discussion

The values obtained by three kinds of deconvolution from the data perturbed with ten per cent of the Gaussian error were shown in Fig. 3. The values obtained by the present mehod agreed better with the true values which were shown by solid line in Fig. 3 than the values by the rectangular and the trapezoidal method.

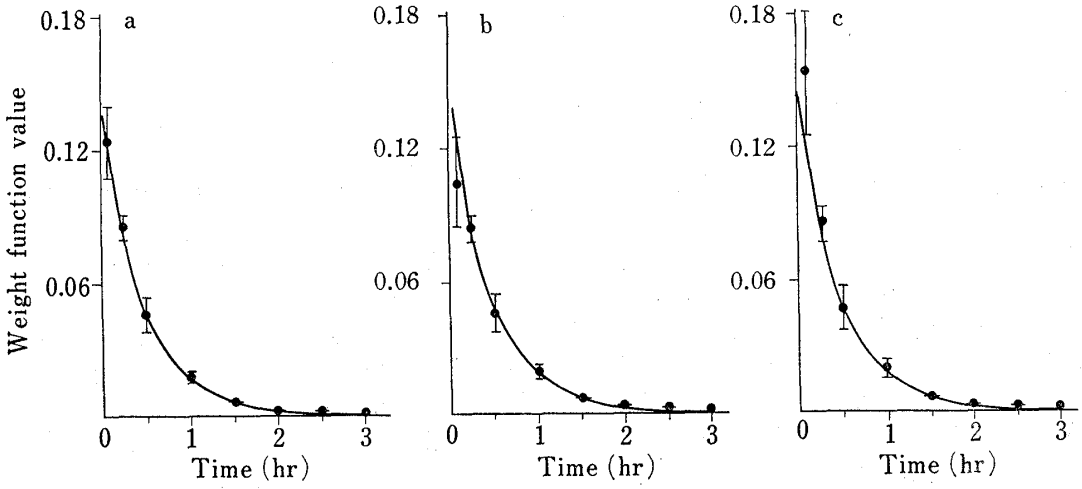


Fig. 3. Weight Function Values Calculation by the Present, the Rectangular and the Trapezoidal Method in the Calculation Experiment

a: the present method, b: the rectangular method, c: the trapezoidal method
Solid circle is the calculated value with standard deviation shown in Table II for the data perturbed by ten per cent of the Gaussian error to the true value. Solid line follows the true value of weight function.

Table II. Deviation Per Cent of the Calculated Weight Function Values from the True Values and their Variations by the Added Gaussian Errors

Method Error (%)	Present			Rectangular			Trapezoidal		
	DC_1	SQ	MD	DC_1	SQ	MD	DC_1	SQ	MD
0	−6.86	3.49	6.60	−23.6	11.2	11.8	15.1	6.29	8.86
1.0	−7.08 ±0.95	3.36 ±0.33	6.47 ±0.32	−23.5 ±0.60	10.3 ±0.11	11.4 ±0.61	15.9 ±0.30	6.19 ±0.59	8.79 ±0.43
2.5	−3.40 ±2.4	4.22 ±0.94	7.24 ±0.79	−21.8 ±1.3	13.0 ±2.2	12.7 ±1.1	15.0 ±0.20	9.56 ±1.6	10.9 ±0.92
5.0	−5.50 ±4.3	3.18 ±0.29	6.30 ±0.29	22.8 ±5.4	12.6 ±3.7	12.5 ±1.8	13.3 ±11	9.12 ±3.9	10.5 ±2.3
10.0	0.62 ±14.5	10.3 ±1.6	11.3 ±0.92	−15.5 ±18	21.2 ±4.8	16.2 ±1.9	24.3 ±23	27.4 ±17	18.0 ±5.4
25.0	−4.43 ±27	27.7 ±5.6	18.4 ±1.9	−20.3 ±36	54.4 ±14	26.0 ±3.2	1.43 ±65	Diverged	
50.0	26.0 ±110	260 ±144	55.4 ±16	−5.43 ±63	303 ±91	61.1 ±9.3	33.3 ±16.3	298 ±85	60.6 ±8.5

DC_1: deviation (%) of the initial weight function value (C_1)
SQ : sum of square of deviation (%) in eight points of time
MD : mean deviation (%) in eight points of time calculated as, $\sqrt{SQ/8}$
± : standard deviation of three calculation experiments

The deviations of results from the true value, that is the accuracy, in various experiments were listed in Table II. The zero per cent of error expressed in Table II meant the deconvolution from the true values, eight figures, of A and B. The deviation of the values of C calculated from the true values was sufficiently different among the calculation methods, even when the true values of A and B were used for calculation and the intervals

for deconvolution were also the same in the methods. The accuracy of the initial value of the weight function, C_1, in the deconvolution had been pointed out to be the problem for its large deviation.[6] In the present method the deviation of C_1 was only minus 6.9 per cent of true value and sufficiently smaller than the rectangular method, minus 23.6 per cent, and also than the trapezoidal method, plus 15.1 per cent.

The sum of squares in the deviated ratios, SQ, to the true value at eight calculated points and the mean deviation, MD, calculated from Eq. 18 and 19 as follows were also listed in the Table II.

$$\mathrm{SQ} = \sum_{i=1}^{n} \left(\frac{C_i - T_i}{T_i}\right)^2 \tag{17}$$

$$\mathrm{MD} = \sqrt{\mathrm{SQ}/n} \tag{18}$$

where C_i was the value of C caluclated at the time, t_i, and T_i was the true value at the same time.

The mean deviation of the present method from the true values of A and B was 6.6 per cent while these values of the rectangular and the trapezoidal method were 11.8 and 8.9 per cent, respectively. Thus, the present method was shown to be more accurate not only in the initial point but also in the succeeding calculations than the other methods. Since the deviation of C_1, 6.9%, was very similar to the mean deviation, 6.6%, the present method could not be concluded to have larger error in the initial point than the succeeding points, while the other two methods had sufficiently larger deviations of C_1 than the mean deviations.

The perturbed data of A and B with the Gaussian random errors as mentioned above were used for the precision test of the deconvolution method. This test was independently repeated three times at each percentage of the error added and at each calculation method. The deviations obtained by this test and the standard deviation of the deviation from three times repeats were also listed in the Table II.

The deviation of C_1 and the mean deviation in the present method were not affected by the perturbation with the Gaussian error of five per cent and less. And they were also sufficiently smaller than the other methods. The Gaussian error of five per cent means sixty-three per cent of data to have less deviation than five per cent of the true value. Since this magnitude of error is not too precise for phamacokinetic data, the present method could be concluded to be useful and practically precise enough for the pharmacokinetic study. This conclusion was further supported by the good reproducibility of the deconvolution calculation repeated three times by perturbations with independent error.

6) K. Umemura, The Proceeding of 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970, Vol. IV, p. 46.