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The Estimation of Rate Constants in Systems of Linear and Nonlinear Differential Equations Using the Polynomial-approximated Least Squares-error and Iterative Search Technique

Katsutoshi Ohkubo, Hiroyuki Sakamoto, and Kohji Tsuchihashi
Department of Synthetic Chemistry, Faculty of Engineering, Kumamoto University,
Kurokami, Kumamoto 860

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A new technique is proposed for estimating the rate constants in systems of linear or nonlinear differential equations, using a polynomial approximation of the observed concentrations of species participating in the reaction and an iterative search technique. The method is implemented by minimizing the errors of the concentrations (of species), as computed by the theoretical equations derived from the linear differential equations or by the trapezoidal averaging simulation, relative to those calculated by the polynomial approximation. The present technique requires the concentrations (at the initial reaction stage) of s-2 species (the s species takes part in the reaction). Two kinetic example, $A\rightleftarrows B\rightleftarrows C$ and $S+E\rightleftarrows ES\rightarrow E+P$, have been used to illustrate and develop the present technique.

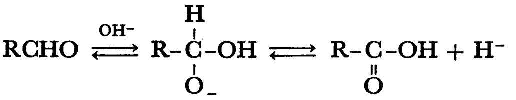
The estimates of the rate constants in systems of linear or nonlinear differential equations have hitherto been performed by means of such numerical methods as the Runge-Kutta integration,[1] the Marquardt method,[2] and Taylor's series expansions.[3] These methods require, however, precision fits to very dense data and much computation time.

The new technique proposed in this paper is based on a polynomial-approximated least squares-error method and an iterative search technique. This technique for estimating the rate constants requires the time-dependence of the concentrations of species participating in the reaction. In order to illustrate and develop the present technique, the following two kinetic examples are used:

Example I

$$A \xrightleftharpoons[k_2]{k_1} B \xrightleftharpoons[k_4]{k_3} C \qquad (1)$$

The example depicted by Eq. (1) represents a reaction like the Cannizzaro reaction, which can be described by linear differential equations:



$$\mathrm{RCHO} \xrightleftharpoons{\mathrm{OH^-}} \mathrm{R{-}\underset{\displaystyle O_-}{\overset{\displaystyle H}{C}}{-}OH} \rightleftarrows \mathrm{R{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}OH + H^-} \qquad (1')$$

(R=alkyl group; $\mathrm{OH^-}$=base catalyst)

Example II

$$S + E \xrightleftharpoons[k_2]{k_1} ES \xrightarrow{k_3} E + P \qquad (2)$$

where S=substrate; E=enzyme; ES=enzyme-substrate complex, and P=product. The classical enzyme model depicted by Eq. (2) is used for a representative reaction described by nonlinear differential equations.

Method of Computation

First Example. The three-variable, four-rate constant isothermal model illustrated by Eq. (1) can be described by the following differential equations on the basis of the law of mass action:

$$\mathrm{d(A)}/\mathrm{d}t = -k_1\mathrm{(A)} + k_2\mathrm{(B)} \qquad \mathrm{(A)_0}\neq 0 \qquad (3a)$$

$$\mathrm{d(B)}/\mathrm{d}t = k_1\mathrm{(A)} - (k_2+k_3)\mathrm{(B)} + k_4\mathrm{(C)} \qquad \mathrm{(B)_0}=0 \qquad (3b)$$

$$\mathrm{d(C)}/\mathrm{d}t = k_3\mathrm{(B)} - k_4\mathrm{(C)} \qquad \mathrm{(C)_0}=0 \qquad (3c)$$

where the parentheses denote the concentrations, typically in M units, and where the subscript zeros stand for the initial concentrations of the species.

The time dependence of (A), (B), or (C) is obtained from Eqs. (3a—c) as:

$$\mathrm{(A)}_{t,\mathrm{calcd}} = k_2k_4\mathrm{(A)_0}/b + C_1\mathrm{e}^{\delta_1 t} + C_2\mathrm{e}^{\delta_2 t} \qquad (4a)$$

$$\mathrm{(B)}_{t,\mathrm{calcd}} = k_1k_4\mathrm{(A)_0}/b - (C_1+C_2)\mathrm{e}^{\delta_1 t} - (C_2+C_4)\mathrm{e}^{\delta_2 t} \qquad (4b)$$

$$\mathrm{(C)}_{t,\mathrm{calcd}} = k_1k_3\mathrm{(A)_0}/b + C_3\mathrm{e}^{\delta_1 t} + C_4\mathrm{e}^{\delta_2 t} \qquad (4c)$$

where $\delta_1=-a+\sqrt{a^2-b}$; $\delta_2=-a-\sqrt{a^2-b}$; $a=(k_1+k_2+k_3+k_4)/2$; $b=k_1k_3+k_2k_4+k_1k_4$; $C_1=((k_2k_4-b)\delta_2-bk_1)\mathrm{(A)_0}/b(\delta_1-\delta_2)$; $C_2=((b-k_2k_4)\delta_1+bk_1)\mathrm{(A)_0}/b(\delta_1-\delta_2)$; $C_3=\delta_2k_1k_3\mathrm{(A)_0}/b(\delta_1-\delta_2)$, and $C_4=\delta_1k_1k_3\mathrm{(A)_0}/b(\delta_2-\delta_1)$.

Second Example. The classical enzyme model represented by Eq. (2) can be described by means of the following nonlinear differential equations:

$$\mathrm{d(S)}/\mathrm{d}t = -k_1\mathrm{(S)(E)} + k_2\mathrm{(ES)} \qquad \mathrm{(S)_0}\neq 0 \qquad (5a)$$

$$\mathrm{d(E)}/\mathrm{d}t = -k_1\mathrm{(S)(E)} + (k_2+k_3)\mathrm{(ES)} \qquad \mathrm{(E)_0}\neq 0 \qquad (5b)$$

$$\mathrm{d(ES)}/\mathrm{d}t = k_1\mathrm{(S)(E)} - (k_2+k_3)\mathrm{(ES)} \qquad \mathrm{(ES)_0}=0 \qquad (5c)$$

$$\mathrm{d(P)}/\mathrm{d}t = k_3\mathrm{(ES)} \qquad \mathrm{(P)_0}=0 \qquad (5d)$$

The trapezoidal averaging technique will no be adopted for solving Eqs. (5a—d). Three increments, $D(i)$ ($i=1$—3), are first defined as:

$$D(1) = k_1\mathrm{(S)(E)}\Delta t; \quad D(2) = k_2\mathrm{(ES)}\Delta t;$$
$$D(3) = k_3\mathrm{(ES)}\Delta t \qquad (6)$$

The increments at the reaction time t, $D(i)_t$, are, then, defined by the use of those at $t-\Delta t$ and $t+\Delta t$, $D(i)_{t-\Delta t}$ and $D(i)_{t-\Delta t}$ respectively:

$$D(i)_t = (D(i)_{t-\Delta t}+D(i)_{t+\Delta t})/2 \quad (D(i)_{-\Delta t}=D(i)_0=0) \qquad (7)$$

where Δt indicates a very small time-interval. The average $D(i)$ values, $D(i)_{\mathrm{av}}$, are represented by:

$$\begin{aligned} D(i)_{\mathrm{av}} &= (D(i)_t+D(i)_{t+\Delta t})/2 \\ &= (D(i)_t+(2D(i)_t-D(i)_{t-\Delta t}))/2 \\ &= 1.5D(i)_t - 0.5D(i)_{t-\Delta t} \qquad (8) \end{aligned}$$

From Eqs. (5a—d), (6), and (8), the average increments of components (C_s) (s=number given for the component), $D(C_s)_{\mathrm{av}}$, are written by:

$$\begin{aligned} D(\mathrm{S})_{\mathrm{av}} &= -D(1)_{\mathrm{av}} + D(2)_{\mathrm{av}}; \\ D(\mathrm{E})_{\mathrm{av}} &= -D(1)_{\mathrm{av}} + D(2)_{\mathrm{av}} + D(3)_{\mathrm{av}}; \\ D(\mathrm{ES})_{\mathrm{av}} &= D(1)_{\mathrm{av}} - D(2)_{\mathrm{av}} - D(3)_{\mathrm{av}}; \\ D(\mathrm{P})_{\mathrm{av}} &= D(3)_{\mathrm{av}} \end{aligned} \tag{9}$$

The concentration of C_s at t, $(C_s)_{t,\mathrm{calcd}}$, is evaluated by means of:

$$(C_s)_{t,\mathrm{calcd}} = (C_s)_0 + \sum^{v} D(C_s)_{\mathrm{av}} \Delta t \quad (v\Delta t = t) \tag{10}$$

In the evaluation of the concentrations of the components participating in Reaction (1) or (2), the rate constants, k_i ($i=1$—4 in Reaction (1) and $i=1$—3 in Reaction (2)), are supplied by:

$$k_i = \min k_i + \sum^{m} 10^{(\gamma-\beta)} \min k_i, \quad \gamma = \mathrm{gauss}\left[\frac{m-1}{9\alpha}\right]$$
$$(m=1, 2, 3, \cdots, \ \beta=0, 1, 2, \cdots, \alpha=10^{\beta}) \tag{11}$$

where min k_i=lower limit of k_i ($1.0\times10^{\delta}$; δ=integral constant); γ=integral number; β=integral constant; α=parameter determining the significant figures for k_i (*viz.*, $k_i=(\beta+1)$ significant figures at $\alpha=10^{\beta}$). If the rate constant, k_i, is to be supplied in the range of 1.0×10^{-5}—1.0×10^{2} under the conditions of $k_i=2$ significant figures ($\beta=1$ and $\alpha=10$), $m=5400$ is required, because $m=9\alpha$ can change the k_i value from $1.0\times10^{\delta}$ to $1.0\times10^{\delta+1}$. As a matter of course, the range of the value for each rate constant (k_i) can be controlled separately in compliance with the desired conditions.

On the other hand, the observed concentration of the s-th component at t, $(C_s)_{t,\mathrm{given}}$, is expressed by the following algebraic polynomial:

$$(C_s)_{t,\mathrm{given}} = a_n t^n + a_{n-1} t^{n-1} + \cdots + a_1 t + a_0 \tag{12}$$

where a_n ($n=0, 1, 2, \cdots$) denotes a coefficient. This polynomial approximation can be performed by the least squares-error analysis of the observed concentrations of C_n at $t=0, 1, 2, 3,$ —, n (n corresponds to the n subscript of a_n in the highest order term of Eq. (12)).

The best set of rate constants is, then, selected from the set satisfying the following F function by means of the iterative search technique (see below):

$$\varepsilon_{p,s} = |(C_s)_{t,\mathrm{calcd}} - (C_s)_{t,\mathrm{given}}|/(C_s)_{t,\mathrm{given}} \tag{13a}$$

$$F = \mathrm{minimize} \sum_{s=1}^{s-1} \sum_{p=1}^{p} \varepsilon_{p,s} \tag{13b}$$

where p is the number of the check points used for the calculation of the F function. In order to cancel the orders of the $(C_s)_{t,\mathrm{calcd}}$ and $(C_s)_{t,\mathrm{given}}$ values, the relative error defined by Eq. (13a) is more useful than the squares error under $(C_s)_{t,\mathrm{given}} \neq 0$. In the reaction system involving s components ($s=1$—3 in Reaction (1) or $s=1$—4 in Reaction (2)), the concentrations of the two components can be evaluated from the material balance.

The iterative search technique is carried out by the following procedure: one of the rate constants, k_j ($j=1, 2, 3, \cdots,$ or j), is repetitively changed in turn with fixed $k_{i(i\neq j)}$ values (k_i=originally estimated or those assumed for the first run), until the set of k_i ($i=1, 2, 3,$ —, and i) values which satisfy the condition described by Eq. (13b) is made identical. This technique requires about 20 s (by FACOM 230-60 computer) for the first example as the computation time for one iteration run under the conditions of $p=1$, $i=4$, $m=5400$, and $\alpha=100$ ($\beta=2$).

In order to obtain reliable k_i values using the above iteration technique, the following factors should be taken into consideration:

(a) During each run of the iteration, the selected k_i group satisfying the F function should not include the lower or upper limit value of k_i. In order to avoid this problem, the k_i values should be supplied over a fairly wide range, or an automatic widening procedure for the range of k_i values should be included in the computation.

(b) If the preliminary estimate of k_i differs by 10^2 or more from the true values, the present technique requires two or three more iterations to obtain reliable values as compared with the case in which the orders of the k_i values are very close to the true ones. It is desirable, therefore, to estimate the order of k_i originally under the condition of the $k_i=1$ significant figure.

It should also be stressed here that check points ($p \geqq i$ are desirable) should be given at the initial early stage of the reaction, because the polynomials of Eq. (12) become more precise at $t \to 0$:

$$\lim_{t\to0} \varepsilon_{p,s} = \lim_{\substack{n\to\infty \\ t\to0}} |(C_s)_{t,\mathrm{calcd}} - (C_s)_{t,\mathrm{given}}|/(C_s)_{t,\mathrm{given}} \approx 0 \tag{14}$$

However, the check point should not always be selected at an initial short time of the reaction, since the polynomials defined by Eq. (12), in which n is sufficiently large, can reproduce the time-conversion curve of $(C_s)_{t,\mathrm{given}}$ obtained from the experiments within the limits of experimental error. The accuracy of the rate constants estimated by the present technique is directly dependent on that of the polynomials and is almost independent of the check point number, so long as the check points ($p \geqq i$) are reasonably selected at suitable reaction times.

Computation Results and Discussion

First Example. Table 1 shows the given kinetic data obtained from Eqs. (4a—c) with the following specifications: $k_1=0.3$, $k_2=0.1$, $k_3=0.6$, $k_4=0.2$, $(\mathrm{A})_0=10.0$, and $(\mathrm{B})_0=(\mathrm{C})_0=0$. We will thus use the simulated concentrations as the given kinetic data, because we can easily compare the estimated rate constants ($k_{i,\mathrm{estimated}}$) with the originally known ones ($k_{i,\mathrm{given}}$) in order to check the accuracy of computations. Using the concentrations of C at $t=0, 1, 2, 3, \cdots, n$, the coefficients of a_n ($n=0, 1, 2, \cdots, n$) in Eq. (12) were evaluated by the least squares-error analysis. The time dependence of the $(C_s)_{t,\mathrm{given}}$ ($s=3$) values under $n=2, 3, 4, 5, 6,$ and 10 is shown in Fig. 1. As Fig. 1 indicates, the higher the order (n) of the polynomial, the more precise the approximation becomes. Moreover, the check points should be taken from those near $t=1.0$, because the $(C_s)_{t,\mathrm{given}}$ ($s=3$) values are evaluated more accurately at $t \approx 1.0$ (for instance, see Table 3). Therefore, we will use the $(C_s)_{t,\mathrm{given}}$ ($s=3$ and $0 \lesssim t \lesssim 1.0$) values evaluated by the following polynomial ($n=10$) approximation:

Table 1. Given kinetic data for first example

$t^{a)}$	(A) $s=1$	(B) $s=2$	(C) $s=3$
0	10.00000	0.00000	0.00000
1	7.50707	1.87874	0.61419
2	5.75746	2.50819	1.73435
3	4.49108	2.66806	2.84087
4	3.55796	2.66279	3.77925
5	2.86353	2.60857	4.52790
6	2.34394	2.54764	5.10843
7	1.95401	2.49372	5.55227
8	1.66095	2.44990	5.88914
9	1.44050	2.42563	6.14387
10	1.27460	2.38930	6.33609
11	1.14972	2.36928	6.48100
12	1.05571	2.35412	6.59018
13	0.98493	2.34267	6.67240
14	0.93163	2.33404	6.73433
15	0.89151	2.32753	6.78096
16	0.86130	2.32263	6.81607
17	0.83855	2.31894	6.84251
18	0.82143	2.31616	6.86241
19	0.80853	2.31407	6.87740
20	0.79882	2.31249	6.88869
21	0.79151	2.31131	6.89718
22	0.78601	2.31042	6.90358
23	0.78186	2.30974	6.90840
24	0.77874	2.30924	6.91202
25	0.77639	2.30885	6.91475
26	0.77462	2.30857	6.91681
27	0.77329	2.30835	6.91836
28	0.77229	2.30819	6.91952
29	0.77153	2.30807	6.92040
30	0.77096	2.30797	6.92106

a) Arbitrary time unit.

$$\begin{aligned}(C_s)_{t,\text{given}}(s=3) &= 4.1951\times10^{-9}t^{10}-2.7882\times10^{-7}t^{9}\\&+8.2055\times10^{-6}t^{8}-1.4329\times10^{-4}t^{7}+1.6659\times10^{-3}t^{6}\\&-1.3737\times10^{-2}t^{5}+8.2424\times10^{-2}t^{4}-3.5191\times10^{-1}t^{3}\\&+8.9409\times10^{1}t^{2}+1.7822\times10^{-3}t+3.6863\times10^{-8}\end{aligned}\tag{15}$$

The $(C_s)_{t,\text{given}}$ values required in Eq. (13a) are supplied from those (at $t=0.7$, 0.8, 0.9, and 1.0) calculated by Eq. (15), and the check points, (p,t), are taken to be: $(p, t)=(1, 0.7)$, $(2, 0.8)$, $(3, 0.9)$, and $(4, 1.0)$. Table 2 lists the $k_{i,\text{estimated}}$ values obtained from Eq. (15) and the following polynomial form of Eq. (4c):

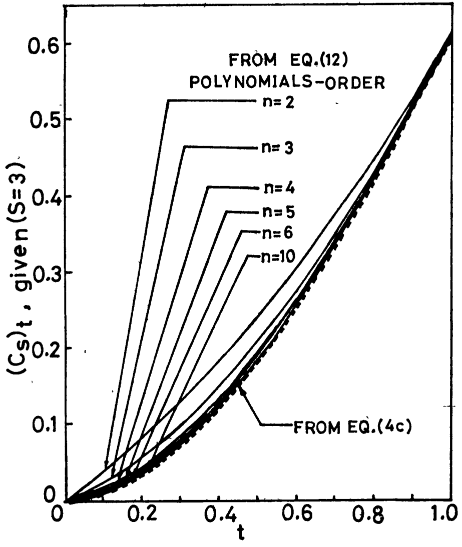


Fig. 1. Plots of $(C_s)_{t,\text{ given}}$ $(s=3)$ *vs.* t.

$$\begin{aligned}(C_s)_{t,\text{calcd}}(s=3) &= k_1k_3(\mathrm{A})_0/b\\&+C_3(1+\delta_1t+\delta_1^2t^2/2+\cdots+\delta_1^nt^n/n!+\cdots)\\&+C_4(1+\delta_2t+\delta_2^2t^2/2+\cdots+\delta_2^nt^n/n!+\cdots)\\&\qquad(n=2,\ 3,\ 4,\ 5,\text{ and }6)\end{aligned}\tag{16}$$

where the notations, b, C_3, C_4, δ_1, and δ_2, are the same as in Eq. (4c). We will here define the following series of errors, ε_k and $\varepsilon_{\max}$, in order to check the accuracy of estimated rate constants; they are also shown in Table 2:

$$\varepsilon_k=\sum_i\varepsilon_i=\sum_i|k_{i,\text{estimated}}-k_{i,\text{given}}|/k_{i,\text{given}}\qquad(i=1,\ 2,\ 3,\ 4)\tag{17}$$

$$\varepsilon_{\max}=\sum_p\varepsilon_{p,3}+\sum_i\varepsilon_i\qquad(p=1,\ 2,\ 3,\ 4;\ i=1,\ 2,\ 3,\ 4)\tag{18}$$

As can be seen from Table 2, the polynomials containing the high-order terms give reliable rate constants.

Let us compare the $k_{i,\text{estimated}}$ values given by Eq. (4c) with those given by Eq. (16) ($n=6$) under the conditions of $(\mathrm{A})_0=10.05$, and $(\mathrm{B})_0=(\mathrm{C})_0=0$ (the check points of (p,t) are the same as those mentioned above). The computation results are: $k_1=0.28$ (0.28); $k_2=0.046$ (0.050); $k_3=0.60$ (0.60); $k_4=0.20$ (0.20), and $\sum_p\varepsilon_{p,3}(\%)=0.844$ (0.922), where the values in parentheses are those evaluated by means of the polynomial ($n=6$) of Eq. (16). Thus, both method give almost

Table 2. Estimates of rate constants for first example
($(\mathrm{A})_0=10.0$; $(\mathrm{B})_0=(\mathrm{C})_0=0$)

		k_i				$\varepsilon_{p,3}$ (%)				$\sum_p\varepsilon_{p,3}$ (%)	ε_k (%)	$\varepsilon_{\max}$ (%)
		k_1	k_2	k_3	k_4	$\varepsilon_{1,3}$	$\varepsilon_{2,3}$	$\varepsilon_{3,3}$	$\varepsilon_{4,3}$			
Exponential function, Eq. (4C)		0.30	0.10	0.60	0.20	—	—	—	—	—	—	—
Polynomial approximation, Eq. (16)	$n=2$	0.22	3.4×10^4	0.59	0.09	7.17	3.63	0.001	3.73	14.5	>200	>214.5
	$n=3$	0.33	0.055	0.56	0.09	2.12	1.18	0.005	1.46	4.77	116.7	121.5
	$n=4$	0.30	0.15	0.60	0.20	0.52	0.30	0.038	0.528	1.39	50.0	51.39
	$n=5$	0.30	0.089	0.60	0.20	0.096	0.065	0.001	0.107	0.269	11.0	11.27
	$n=6$	0.30	0.097	0.60	0.20	0.013	0.011	0.009	0.006	0.039	3.0	3.039

In all cases, $k_i=2$ significant figures and iteration$=3$

TABLE 3. 10^3 $(C_4)_{t,\mathrm{given}}$ VALUES EVALUATED BY TRAPEZOIDAL SIMULATION AND POLYNOMIALS

10t	Simulation$^{a)}$	Polynomial						
		n=1	n=2	n=3	n=4	n=5	n=6	n=10
1	0.0000	2.2170	1.7985	1.5269	1.3401	1.2023	1.0946	0.54248
2	1.0000	4.4340	3.6900	3.2326	2.9288	2.7105	2.5434	1.7204
3	2.9550	6.6510	5.6745	5.1074	4.7444	4.4903	4.2999	3.4102
4	5.1860	8.8680	7.7520	7.1421	6.7660	6.5099	6.3221	5.4732
5	7.6840	11.085	9.9225	9.3269	8.9737	8.7400	8.5722	7.8464
6	10.370	13.302	12.180	11.652	11.348	11.153	11.016	10.449
7	13.190	15.519	14.543	14.109	13.872	13.725	13.624	13.223
8	16.120	17.736	16.992	16.687	16.528	16.432	16.367	16.123
9	19.120	19.953	19.535	19.377	19.299	19.253	19.223	19.114
10	22.170	22.170	22.170	22.170	22.170	22.170	22.170	22.170

a) $\Delta t=0.10$

the same estimates for the rate constants.

Second Example. The given kinetic data, such as the $(C_s)_{t,\mathrm{given}}$, for the classical enzyme model were also simulated with the specifications of $(\mathrm{S})_0=1.00$, $(\mathrm{E})_0=0.10$, $k_1=k_2=k_3=1.0$, and $\Delta t=0.10$ (shown in part in Table 3). In this section, we will try to estimate the best set of rate constants using only the concentrations of the product (P). The coefficients (a_n) of Eq. (12) were estimated similarly by means of least squares-error analysis of the (P) values at $t=0$, 1, 2, 3, —, and n. Table 3 lists the $(C_s)_{t,\mathrm{given}}$ $(s=4)$ values $(0\leq t\leq 1.0)$ as evaluated by the polynomial functions ($n=1$, 2, 3, 4, 5, 6, and 10). As can be seen from Table 3, the lower the order (n) of the polynomial term, the more markedly the $(C_4)_{t,\mathrm{given}}$ values differ from those of the simulation. It is also noticeable that the $(C_4)_{t,\mathrm{given}}$ values become inaccurate as $t\rightarrow 0$, because the rate of the formation of P, $(\mathrm{d(P)}/\mathrm{d}t)_t$ does not increase monotonously during the initial short stage (*i.e.*, $(\mathrm{d(P)}/\mathrm{d}t)_{t\,0}\simeq 0$). Therefore, we will use the $(C_4)_{t,\mathrm{given}}$ values at $t=0.8$, 0.9, and 1.0 for computing the $\varepsilon_{p,s}$ $(s=4)$ values: that is, the check points, (p,t), are taken to be $(p, t)=(1, 0.8)$, $(2, 0.9)$, $(3, 1.0)$. Then, we will estimate the best sets of the k_i group using the $(C_4)_{t,\mathrm{given}}$ values as evaluated by means of the polynomials ($n=1$—10) and the $(C_4)_{t,\mathrm{calcd}}$ values given by the trapezoidal simulation. Thus, the method of the k_i estimation in the Second Example is different from that in the First Example.

The iterative search technique gives the $k_{i,\mathrm{estimated}}$ values for Second Example shown in Table 4. It may be seen from Table 4 that the higher the order of the polynomials used for the $(C_4)_{t,\mathrm{given}}$ evaluation, the lower the errors of $\sum_p \varepsilon_{p,4}$ and ε_k. It may be deduced, therefore, that the accuracy of the $(C_4)_{t,\mathrm{given}}$ values presented in Table 3 directly influences the estimation of the best k_i values.

The present technique used for Second Example can now be shown to be useful for estimating the rate constants in more detail.

In order to check the variation in the k_i estimation with the change in the initial specifications, such as, the concentrations of species and the Δt value,[4] the estimates of the rate constants were performed again with the specifications of $(\mathrm{S})_0=1.01$, $(\mathrm{E})_0=0.1$, and $\Delta t=0.10$, using the $(C_4)_{t,\mathrm{given}}$ values ($t=0.8$, 0.9, and 1.0) obtained from the polynomial ($n=10$) in Table 3. The computed results are: $k_1=1.0$, $k_2=1.0$, $k_3=$

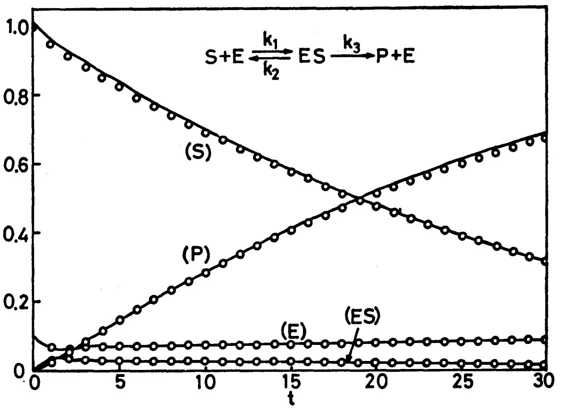


Fig. 2. Computer simulation of second example.
(circle point: given data; solid curve: predicted ones)

TABLE 4. ESTIMATED RATE CONSTANTS ($(\mathrm{S})_0=1.0$ AND $(\mathrm{E})_0=0.1$)

n	k_i			$\varepsilon_{p,4}$ (%)			$\sum_p \varepsilon_{p,4}$(%)	ε_k(%)	$\varepsilon_{\max}$ (%)
	k_1	k_2	k_3	$\varepsilon_{1,4}$	$\varepsilon_{2,4}$	$\varepsilon_{3,4}$			
1	1.1	1.2	1.0	5.27	0.503	3.50	9.27	30.0	39.27
2	1.0	0.89	1.0	3.30	0.08	2.25	5.63	11.0	16.63
3	1.0	0.93	1.0	2.23	0.03	1.42	3.68	7.0	10.68
4	1.0	0.95	1.0	1.63	0.008	1.01	2.65	5.0	7.65
5	1.0	0.96	1.0	1.24	0.034	0.807	2.08	4.0	6.08
6	1.0	0.97	1.0	1.01	0.006	0.604	1.62	3.0	4.62
10	1.0	1.0	1.0	0.047	0.008	0.000	0.055	0.0	0.055

In all cases, $k_i=2$ significant figures, iteration=2, and computation time=2 min.

1.0, and $\sum_{p}\varepsilon_{p,4}=0.20\%$. The above $k_{i,\text{estimated}}$ values give the time-conversion curves of (S), (E), (ES), and (P) shown in Fig. 2. As may be seen from Fig. 2, we can easily predict the time dependence of the intermediate concentration by simulating the reaction using the estimated rate constants.

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