New Procedure for Optimal Design of Sequential Experiments in Kinetic Models

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The high correlation between preexponential factors and activation energies is a severe drawback in the estimation of kinetic parameters. This difficulty is generally overcome using two different techniques, i.e., reparametrization and parameter separation. It has been demonstrated that in sequential experimental design the former technique can only occasionally lead to better numerical results, with no theoretical advantage over the non-reparametrized model. In this work we show that the separability property can be a convenient tool also for the optimization of experiment planning. A numerical example is considered, and both cases of constant absolute and relative errors are examined.

Introduction

Kinetic rate models can be written as

$$\mathbf{r} = \mathbf{f}(\mathbf{X},\theta) \tag{1}$$

where $\mathbf{r}$ is the vector of measured rates, $\mathbf{X}$ is the vector of the operating variables, and θ are the unknown parameters.

Typically the kinetic rate models can be cast into the form

$$r_i = \sum_j k_{ij} e^{-E_{ij}/RT} f_{ij}(\mathbf{c}|\alpha)$$

where k_{ij} indicate preexponential factors and E_{ij} activation energies. f_{ij} are suitable functions of concentrations $\mathbf{c}$, and the parameters α are related to the orders of the reactions.

Thus the kinetics of a single irreversible reaction is described by

$$r = k e^{-E/RT} c_1^{\alpha} c_2^{\beta} \ldots \tag{2}$$

The high correlation between preexponential factors and activation energies makes it difficult to estimate kinetic parameters accurately.

The influence of this correlation on convergence in the iterative estimation of the parameters θ can be successfully reduced if the reparametrization suggested by Box (1965) is introduced, namely,

$$k'_{ij} = k_{ij} e^{-E_{ij}/RT} \tag{3}$$

$$r = k' \exp\left[-\frac{E}{R}\left(\frac{1}{T} - \frac{1}{T^*}\right)\right] c_1^{\alpha} c_2^{\beta} \ldots \tag{4}$$

where T^* is a reference temperature.

Since k' and E turn out to be much less correlated than the original parameters k and E, the estimation procedure is considerably easier.

Another strategy based on the method of separation of variables (Lawton and Sylvestre, 1971; Golub and Pereyra, 1976) makes it possible to carry out the whole estimation procedure in terms of the parameters E, α, and β (which in the sequel will be referred to as nonlinear parameters, due to the fact that they enter relation 2 nonlinearly), with k being evaluated, in the case of a single irreversible reaction, by the relation of conditional optimality given by the expression

$$k = \mathbf{H}^+(E,\alpha,\beta)\mathbf{r} \tag{5}$$

where $\mathbf{r}$ is the vector $\{r_i\}$ and $\mathbf{H}^+$ is the pseudoinverse of the vector

$$h_i = e^{-E/RT} c_{1i}^{\alpha} c_{2i}^{\beta} \ldots \tag{6}$$

the general definition of the pseudoinverse of an $m \times n$ matrix $\mathbf{A}$ of rank r being given by

$$A^+ = \mathbf{K}\begin{pmatrix} \mathbf{R}^{-1} & 0 \\ 0 & 0 \end{pmatrix}\mathbf{H}^T$$

where $\mathbf{R}$ is a nonsingular $r \times r$ matrix and $\mathbf{K}$ and $\mathbf{H}$ are two orthogonal matrices given by the (not uniquely defined) orthogonal decomposition of $\mathbf{A}$

$$\mathbf{A} = \mathbf{HRK}^T$$

Another approach, based on normal equations and direct substitution, has been recently proposed by Chen and Aris (1992) for a simple case.

A typical Gauss–Newton step of the regression procedure based on least squares is provided by

$$\theta^{(n+1)} = \theta^{(n)} - (D\boldsymbol{H}^{\perp}\rho)^+ \mathbf{H}^{\perp}\rho \tag{7}$$

where θ is the vector $\{E,\alpha,\beta\}$, ρ are the residuals (experimental values minus computed values of the reaction rates), $\mathbf{H}^{\perp}$ is defined as $(1 - \mathbf{H}^+\mathbf{H})$, and $D\boldsymbol{H}^{\perp}$ is the Frechet derivative of the matrix $\mathbf{H}^{\perp}$ (Golub, 1976), defined as

$$D\boldsymbol{H}^{\perp}(\theta^{(n)}) = \frac{\partial H_{ij}^{\perp}(\theta^{(n)})}{\partial\theta}$$

At convergence, the standard deviations of $\{E,\alpha,\beta\}$ can be estimated employing the usual approximation based on the Hessian matrix of the likelihood function, whereas the variance of k can be evaluated using the general relation

$$V_k = \left(\frac{\partial \mathbf{H}^+}{\partial E} \quad \frac{\partial \mathbf{H}^+}{\partial \alpha} \quad \frac{\partial \mathbf{H}^+}{\partial \beta}\right)\begin{pmatrix} V_{EE} & V_{E\alpha} & V_{E\beta} \\ V_{\alpha E} & V_{\alpha\alpha} & V_{\alpha\beta} \\ V_{E\beta} & V_{\alpha\beta} & V_{\beta\beta} \end{pmatrix}\begin{pmatrix} \frac{\partial \mathbf{H}^+}{\partial E} \\ \frac{\partial \mathbf{H}^+}{\partial \alpha} \\ \frac{\partial \mathbf{H}^+}{\partial \beta} \end{pmatrix} \tag{8}$$

The aim of optimal design of sequential experiments is to determine values of the independent variables T, c_1, c_2, ... at which to take the new experiment(s), so that a suitable

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norm of the expected variance–covariance matrix of the parameters after the new experiments is least.

If random errors are normally distributed with constant variance σ^2, the variance–covariance matrix can be approximated by

$$\mathbf{V} = (\mathbf{F}^T\mathbf{F})^{-1}\sigma^2 \tag{9}$$

where $F_{ij} = (\partial f/\partial\theta_j)(X_i,\theta_j)$ (Bard, 1974).

A frequently used norm is the volume of the confidence region, whose linear approximation with respect to θ is given by (Agarwal and Brisk, 1985)

$$(\theta - \hat{\theta})^T(\mathbf{F}^T\mathbf{F})(\theta - \hat{\theta}) = \epsilon$$

where $\hat{\theta}$ is the current vector of parameters and ϵ is a constant depending on the number of degrees of freedom, the selected probability level, and the error variance.

In fact it can be shown that the volume of the confidence region is inversely proportional to the determinant of $\mathbf{V}$ (Box and Lucas, 1959).

It has been demonstrated by Rimensberger and Rippin (1986) that the introduction of a reparametrization does not change the sequence of optimal settings for the independent variables, even if minor numerical improvements are produced, as reported by Agarwal and Brisk (1985).

In fact the confidence region volume is proportional to

$$|\mathbf{G}|\,|(\mathbf{F}^T\mathbf{F})^{-1}|^{1/2}$$

where $\mathbf{G}$ is the transformation matrix

$$\mathbf{G} = \begin{bmatrix} \frac{\partial k'_1}{\partial k_1} & \frac{\partial k'_1}{\partial k_2} & \cdots \\ \frac{\partial k'_2}{\partial k_1} & \frac{\partial k'_2}{\partial k_2} & \cdots \\ \cdots & \cdots & \cdots \end{bmatrix}$$

Since the elements of $\mathbf{G}$ do not depend on the independent variables T, c_1, and c_2, there is no difference in minimizing $|(\mathbf{F}^T\mathbf{F})|^{1/2}$ or $|\mathbf{G}|\,|(\mathbf{F}^T\mathbf{F})|^{-1/2}$ with respect to the independent variables for the determination of optimal settings.

On the other hand transformation (eqs 5 and 6) does depend on the independent variables T_i, c_{1i}, and c_{2i}.

This means that differences are to be expected between the transformation approach and the separation of variables approach in the general optimization strategy. In particular the latter approach will be shown to be more amenable to a numerical solution due to a simplified analytical form.

Design Procedures Using Separable Models

The example reported by Agarwal and Brisk (1985) is used to illustrate the method. It can be generalized to multivariate reversible models along the guidelines discussed in Doví et al. (1987).

The kinetic model is given by

$$r = g = k\phi(E,\alpha,\beta|T,x_1,x_2) = ke^{-E/RT}p_1^{\alpha}p_2^{\beta}$$

with the limitations

$$p_{1,\min} \le p_1 \le p_{1,\max}$$

$$p_{2,\min} \le p_2 \le p_{2,\max}$$

$$T_{\min} \le T \le T_{\max}$$

The assumption of constant pressure (made by Agarwal and Brisk) has been dropped, so that the introduction of a third inert component could be avoided.

The kinetic rates r_i can be considered subject to normally distributed random errors with variance σ^2 given by

$$\sigma^2 = ar^b$$

which is the common way of representing heteroscedasticity of data (Reilly et al., 1977). Suppose the estimates k, E, α, and β have been obtained after the first N experiments and let $\mathbf{V}_\theta$ be the variance–covariance matrix of the estimates of the nonlinear parameters E, α, and β obtained using the minimization method, whose general iteration is given by relation 7.

Let us suppose further that the criterion used for optimal design is given by the minimization of the determinant of the expected variance–covariance matrix $\tilde{\mathbf{V}}$ obtained after the new experiment.

In this case we have (Bard, 1974)

$$\tilde{\mathbf{V}}^{-1} = \left[\frac{\mathbf{B}^T\mathbf{B}}{\sigma^2} + \mathbf{V}_\theta^{-1}\right] = \max \tag{10}$$

where $\mathbf{B}$ is the vector $(Dg/DE, Dg/D\alpha, Dg/D\beta)$ computed at the new setting. Dg/DE, $Dg/D\alpha$, $Dg/D\beta$ indicate total derivatives of g, i.e., they take into account changes in k, according to relation 5, as the parameters E, α, and β vary.

We shall examine first the case $\{b = 2\}$ which corresponds to constant relative errors. Relation 10 can be written as

$$\det\begin{bmatrix} \frac{g_1^2}{ag^2} + V^{-1}_{\theta,11} & \frac{g_1g_2}{ag^2} + V^{-1}_{\theta,12} & \frac{g_1g_3}{ag^2} + V^{-1}_{\theta,13} \\ \frac{g_1g_2}{ag^2} + V^{-1}_{\theta,21} & \frac{g_2^2}{ag^2} + V^{-1}_{\theta,22} & \frac{g_2g_3}{ag^2} + V^{-1}_{\theta,23} \\ \frac{g_1g_3}{ag^2} + V^{-1}_{\theta,31} & \frac{g_2g_3}{ag^2} + V^{-1}_{\theta,32} & \frac{g_3^2}{ag^2} + V^{-1}_{\theta,33} \end{bmatrix} = \max$$

where

$$g_1 = \frac{\partial k}{\partial E}\phi - \frac{k}{RT}\phi = \xi_1\phi$$

$$g_2 = \frac{\partial k}{\partial \alpha}\phi + k\phi \ln p_1 = \xi_2\phi$$

$$g_3 = \frac{\partial k}{\partial \beta}\phi + k\phi \ln p_2 = \xi_3\phi$$

$$g = k\phi$$

Setting

$$ak^2V^{-1}_{\theta,ij} = u_{ij}$$

we obtain

$$\det[\xi_i\xi_j + u_{ij}] = \max \tag{11}$$

Due to the one-to-one correspondence between $\xi_1 \rightarrow T$, $\xi_2 \rightarrow p_1$, and $\xi_3 \rightarrow p_2$, the optimization can be carried out in terms of the ξ after suitable modifications of the constraints.

On the other hand simple algebraic manipulations change problem 11 into

$$\Psi = \xi_1^2(u_{22}u_{33} - u_{23}^2) + \xi_2^2(u_{11}u_{33} - u_{13}^2) + \xi_3^2(u_{22}u_{11} - u_{12}^2) + 2\xi_1\xi_2(u_{13}u_{23} - u_{12}u_{33}) + 2\xi_1\xi_3(u_{12}u_{23} - u_{22}u_{13}) + 2\xi_2\xi_3(u_{12}u_{13} - u_{11}u_{23}) = \max \tag{12}$$

Stationary points of this expression can be determined solving a 3×3 system of linear equations. However, since

Table 1. Flow Chart of the Algorithm for Optimal Settings Computation

1. Set $k = 1$
2. Set $a = 0$
3. Set $\xi_k = \xi_k^{(a)}$
4. Compute
$$\xi_{j\neq k} = \frac{u_{kj}}{u_{kk}}\xi_k$$
5. If $\xi_{j,\min} \le \xi_j \le \xi_{j,\max}$
   Compute the objective function at $\xi_k^{(a)},\xi_j$
   and goto 12
6. If $k = 1$ then set $m = 2$ else if $k = 2$ then set $m = 3$ else set $m = 1$
7. Set $b = 0$
8.
$$\xi_{i\neq k,m} = \frac{\xi_m^{(b)}(u_{ik}u_{mk} - u_{im}u_{kk}) + \xi_k^{(a)}(u_{im}u_{mk} - u_{mm}u_{ik})}{u_{mk}^2 - u_{mm}u_{kk}}$$
9. If $\xi_{j,\min} \le \xi_j \le \xi_{j,\max}$
   Compute the objective function at
   $\xi_k^{(a)},\xi_m^{(b)},\xi_i$
   and goto 11
10. Compute the objective function at
    $\xi_k^{(a)},\xi_m^{(b)},\xi_i^{(0)}$
    Compute the objective function at
    $\xi_k^{(a)},\xi_m^{(b)},\xi_i^{(1)}$
11. If $b = 0$ then set $b = 1$ and goto 8
12. If $a = 0$ then set $a = 1$ and goto 3
13. Set $k = k + 1$. If $k > 3$ then stop
14. Goto 2

there are no linear terms in ξ, the solution cannot be located on interior point of the feasible domain. Thus the solution of this maximization problem can be obtained by combinatorially setting some of the ξ_i to their upper (lower) limits and solving a simplified system of linear equations with respect to the remaining variables.

The overall combinatorial scheme and the corresponding optimal values of ξ_j are illustrated in Table 1, where the notation $\xi_i^{(0)} = \xi_{i,\min}$ $\xi_i^{(1)} = \xi_{i,\max}$ has been used.

On the other hand the strong correlation reduction between nonlinear parameters after the separation procedure can be taken advantage of. In fact if off diagonal elements of $\mathbf{V}_\theta$ can be neglected, $\mathbf{V}_\theta^{-1}$ will also be nearly diagonal. Thus if

$$u_{ij} \sim u_{ij}\delta_{ij}$$

the maximization problem reduces to

$$q_1^2\left(\frac{\partial k}{\partial E} - \frac{k}{RT}\right)^2 + q_2^2\left(\frac{\partial k}{\partial \alpha} + k \ln p_1\right)^2 + q_3^2\left(\frac{\partial k}{\partial \beta} + k \ln p_2\right)^2 = \max$$

where

$$q_1^2 = u_{22}u_{33}$$

$$q_2^2 = u_{11}u_{33}$$

$$q_3^2 = u_{11}u_{22}$$

This problem can be easily solved by separate optimization of

$$\left|\frac{\partial k}{\partial E} - \frac{k}{RT}\right| = \max$$

(i.e., $T = T_{\max}$ or $T = T_{\min}$ according to the current magnitudes of k and $\partial k/\partial E$ and the sign of $\partial k/\partial E$) and

$$\left|\frac{\partial k}{\partial \alpha} + k \ln p_1\right| = \max$$

$$\left|\frac{\partial k}{\partial \beta} + k \ln p_2\right| = \max$$

Table 2. Initial Experimental Conditions

expt no.	T, °C	p_1	p_2
1	45.0	0.35	0.65
2	53.0	0.30	0.70
3	60.0	0.28	0.72
4	68.0	0.38	0.45
5	75.0	0.25	0.55
6	85.0	0.15	0.60

Table 3. Initial Estimates[a]

	10% noise		40% noise	
	A & B[c]	this work	A & B[c]	this work
k (10^{-3})	>20	7.11	>20	6.94
E, kcal/mol	12.450[b]	14.761	>15	14.221

[a] True values: $k = 4.62$, $E = 11.6$. [b] Reported value is inferred from graph. [c] Agarwal and Brisk (1985).

Table 4. Estimates of Reaction Orders

	true value	after 6 expts	after 15 expts
α	0.33	0.35 ± 0.02	0.34 ± 0.005
β	1	0.996 ● 0.04	0.999 ● 0.018

subject to

$$p_{1,\min} \le p_1 \le p_{1,\max}$$

$$p_{2,\min} \le p_2 \le p_{2,\max}$$

In order to estimate the degree of accuracy of the approximation described, let us neglect the quadratic terms in the off-diagonal variables u_{ij} contained in relation 12 (in fact if the correlation coefficients $u_{ij}/(u_{ij}u_{jj})^{1/2}$ are large, the approximation could not be used anyway). We obtain

$$\Psi = \xi_1^2u_{22}u_{33} + \xi_2^2u_1u_{33} + \xi_3^2u_{22}u_{11} - 2\xi_1\xi_2u_{12}u_{33} - 2\xi_1\xi_3u_{13}u_{22} - 2\xi_2\xi_3u_{23}u_{11}$$

and consequently

$$\frac{\Delta\Psi}{\Psi_0} \approx 2\frac{\xi_1^{(0)}\xi_2^{(0)}u_{12}u_{33} + \xi_1^{(0)}\xi_3^{(0)}u_{13}u_{22} + \xi_2^{(0)}\xi_3^{(0)}u_{23}u_{11}}{\xi_1^{(0)2}u_{22}u_{33} + \xi_2^{(0)2}u_{11}u_{33} + \xi_3^{(0)2}u_{22}u_{33}}$$

where the symbols $\xi_1^{(0)}$, $\xi_2^{(0)}$, $\xi_3^{(0)}$, and Ψ_0 refer to the approximate solution and $\Delta\Psi$ is the change of the objective function brought about by nonzero values of u_{12}, u_{13}, and u_{23}. Thus for any predetermined value of the ratio $\Delta\Psi/\Psi_0$, it is possible to decide if the approximation described can be employed.

Let us consider now the case of constant absolute error. We have to maximize

$$\det\left[\frac{\mathbf{B}^T\mathbf{B}}{a} + \mathbf{V}_\theta^{-1}\right] = \frac{1}{a}\det \mathbf{V}_\theta^{-1}[a + \mathbf{B}\mathbf{V}_\theta\mathbf{B}^T]$$

which corresponds to the maximization of

$$\exp\left(\sum \gamma_i\xi_i\right)\sum_{ij}\xi_i\xi_jV_{\theta ij} = \max \qquad (13)$$

where

$$\gamma_1 = \frac{2E}{k} \qquad \gamma_2 = \frac{2\alpha}{k} \qquad \gamma_3 = \frac{2\beta}{k}$$

subject to suitable bounds on the ξ. Stationary points of this problem are given by

$$\gamma_s + \frac{\sum_i V_{\theta is}\xi_i}{\sum_{ij} V_{\theta ij}\xi_i\xi_j} = 0$$

i.e.,

$$\gamma_1 + \frac{\sum_i V_{\theta i1}\xi_i}{\sum_{ij} V_{\theta ij}\xi_i\xi_j} = 0 \qquad (14)$$

$$\gamma_1 \sum_i V_{\theta i2}\xi_i = \gamma_2 \sum_i V_{\theta i1}\xi_i \qquad (15)$$

$$\gamma_1 \sum_i V_{\theta i3}\xi_i = \gamma_3 \sum_i V_{\theta i1}\xi_i \qquad (16)$$

Relations 15 and 16 make it possible to express ξ_1 and ξ_2 as linear functions of ξ_3. Substituting in 14 gives an equation in the single variable ξ_3. Thus by scanning a suitable range of ξ_3, we can locate all the stationary points of $\{\xi_1,\xi_2,\xi_3\}$. This makes it possible to locate stationary points inside the feasible domain.

In this case too, maxima on the domain boundary can be determined by combinatorially setting some of the ξ_i to their upper (lower) limits and repeating the procedure described above for the remaining variables.

Values of the heteroscedasticity parameter b other than 0 or 2 generally lead to objective functions more difficult to optimize due to the nonstraightforward determination of all unconstrained maxima. However, knowing optimum settings for the cases $b = 0$ and $b = 2$ can provide guidance concerning the optimum values for intermediate cases.

Thus a general outline of the method has been completely described.

Benefits Resulting from the Use of Separable Models in the Design Procedure

Any procedure for the design of sequential experiments consists of two steps: (1) Estimation of parameters by means of regression calculations using the experimental data available. (2) Determination of optimum variable settings for the next experiment(s).

If parameters are highly correlated, the first step is generally difficult and can be dealt with only using special techniques, such as reparametrization and separation of variables, the latter technique possessing the additional advantage of reducing the number of independent parameters.

The second step is a difficult task, because it implies a nonconvex, nonlinear maximization. It is generally tackled by setting up a grid over the permitted experimental region, each point of the grid being used as a starting point for a local convex maximization. By reducing the dimensions of the grid meshes (i.e., increasing the number of grid points), we can be confident that the global maximum has been located. However, if the number of variables exceeds 2, this procedure can be computationally prohibitive, even if the selected grid is comparatively coarse. Thus a frequent compromise is to limit the selection of new experimental settings to the points of the grid, at each of which the objective function is evaluated (Rimensberger and Rippin, 1986).

As has been pointed out in the introduction, the use of reparametrization does not alleviate this difficulty, whereas the method of separation of parameters leads, as demonstrated in the previous paragraph, to a simple combinatorial algorithm, capable of locating the global minimum with a modest number of evaluations of the objective function.

Thus the benefit resulting from the use of separable models is two-fold: (a) After each experiment the information available is used effectively for the estimation of parameters. This can prevent additional unnecessary experiments. (b) Globally optimum settings are determined after each regression step, so that each new experiment provides the largest amount of information.

Traditional techniques are less likely to determine the same sequence of parameters and settings, due to the numerical difficulties described above. This can lead to a greater number of experiments than necessary.

Table 5. Correlation Factors between Parameters (40% Noise)

Reparametrized Model

$\ln k'$	$\ln(E/R)$	α	β
1	0.9699	0.9874	0.9574
	1	0.9700	0.9251
		1	0.9035
			1

Separated Model

E	α	β
1	0.0668	0.0437
	1	0.0201
		1

A Numerical Example

To test the validity of the procedure described we have simulated an experimental campaign, using the model and the initial six experimental data points proposed by Agarwal and Brisk (1985), and report the results in Table 2. Although partial pressures instead of molar fractions were used, we were able to use the same numerical values with partial pressure being expressed in atmospheres and the preexponential factor possessing suitable dimensions.

To reproduce the test we added random 10% and 40% relative and absolute errors to the exact data in the initial set, as well as in the rate data obtained by simulating the reaction at the optimum settings determined. The results obtained are reported for the four cases, but a comparison with those provided by Brisk and Agarwal is possible only for the two constant relative error cases.

In both the low (10%) and high (40%) noise level cases the initial estimates of E, α, and β were different from those proposed by Agarwal and Brisk (1985), with a lower objective function than that obtained using their proposed values, which were the starting values used in our minimization procedure (see Table 3). In other words separation of parameters determines the global minimum, whereas the non-reparametrized model as well as the reparametrized model locates a local optimum, which seems to coincide with the results obtained by Rimensberger and Rippin (1986).

The values of α and β are estimated very precisely and accurately even using only the first 6 data points, as compared with a 38.9% deviation after 15 experiments if the reparametrized model is used (see Table 4).

Similarly the initial correlation coefficients between the nonlinear parameters are considerably lower than those between parameters in reparametrized and non-reparametrized models (see Table 5).

Table 6. Numerical Results Using 6 Initial Data Points

exp. no.	T	$p1$	$p2$	noise, %	error	k	E, kcal/mol	exp. no.	T	$p1$	$p2$	noise, %	error	k	E, kcal/mol
7	90.00	0.10	0.40	10	r	7.3793 ± 4.8%	14.1493 ± 6.7%	19	90.00	0.10	0.40	10	r	6.4736 ± 2.4%	12.6402 ± 2.7%
	90.00	0.10	0.40	10	a	6.3857 ± 4.5%	13.1487 ± 5.3%		90.00	0.10	0.40	10	a	6.7835 ± 2.4%	12.7713 ± 2.6%
	90.00	0.10	0.40	40	r	6.8146 ± 17.8%	14.0882 ± 8.1%		90.00	0.10	0.40	40	r	6.8730 ± 8.6%	12.8705 ± 5.1%
	90.00	0.10	0.40	40	a	8.1923 ± 17.8%	14.0013 ± 8.4%		90.00	0.10	0.40	40	a	7.4806 ± 9.5%	13.9817 ± 4.6%
8	90.00	0.10	0.40	10	r	5.7554 ± 4.6%	14.2070 ± 5.0%	20	90.00	0.10	0.40	10	r	6.6672 ± 2.2%	12.1975 ± 2.8%
	90.00	0.10	0.40	10	a	6.0690 ± 4.3%	14.0010 ± 4.6%		90.00	0.10	0.40	10	a	7.0439 ± 2.3%	12.5932 ± 2.8%
	90.00	0.10	0.40	40	r	8.2645 ± 16.2%	14.1571 ± 8.1%		90.00	0.10	0.40	40	r	7.5762 ± 7.0%	12.7698 ± 4.7%
	90.00	0.10	0.40	40	a	8.6476 ± 16.4%	13.7504 ± 9.9%		90.00	0.10	0.40	40	a	7.3631 ± 8.2%	13.4715 ± 4.3%
9	90.00	0.10	0.40	10	r	5.6703 ± 4.0%	13.2016 ± 5.1%	21	90.00	0.10	0.40	10	r	5.8763 ± 2.4%	12.1189 ± 2.5%
	90.00	0.10	0.40	10	a	6.4919 ± 3.4%	14.2210 ± 4.2%		90.00	0.10	0.40	10	a	6.1464 ± 2.6%	12.6519 ± 2.2%
	90.00	0.10	0.40	40	r	8.2350 ± 15.3%	12.8951 ± 8.3%		90.00	0.10	0.40	40	r	7.2753 ± 9.2%	12.7148 ± 4.5%
	90.00	0.10	0.40	40	a	8.5271 ± 15.0%	13.5405 ± 7.7%		90.00	0.10	0.40	40	a	7.6239 ± 9.2%	13.4131 ± 4.6%
10	90.00	0.10	0.40	10	r	7.2244 ± 3.6%	12.9801 ± 4.2%	22	90.00	0.10	0.40	10	r	6.3845 ± 1.9%	12.2481 ± 2.7%
	90.00	0.10	0.40	10	a	7.0176 ± 3.6%	13.0045 ± 5.5%		90.00	0.10	0.40	10	a	6.4271 ± 2.3%	12.7917 ± 2.8%
	90.00	0.10	0.40	40	r	7.6111 ± 16.3%	12.1175 ± 7.8%		90.00	0.10	0.40	40	r	7.3390 ± 8.6%	12.7220 ± 4.4%
	90.00	0.10	0.40	40	a	7.7154 ± 12.7%	11.2634 ± 6.7%		90.00	0.10	0.40	40	a	7.5471 ± 7.3%	13.5179 ± 4.1%
11	90.00	0.10	0.40	10	r	7.4525 ± 3.2%	12.8944 ± 4.9%	23	90.00	0.10	0.40	10	r	6.2354 ± 1.8%	12.7539 ± 2.4%
	90.00	0.10	0.40	10	a	7.0266 ± 3.7%	12.8093 ± 4.4%		90.00	0.10	0.40	10	a	6.3994 ± 1.9%	12.8111 ± 2.4%
	90.00	0.10	0.40	40	r	7.7789 ± 15.3%	12.5193 ± 8.1%		90.00	0.10	0.40	40	r	7.4435 ± 8.9%	12.9742 ± 4.1%
	90.00	0.10	0.40	40	a	8.0838 ± 14.5%	12.0879 ± 6.8%		90.00	0.10	0.40	40	a	8.5527 ± 9.1%	13.3577 ± 4.4%
12	90.00	0.10	0.40	10	r	7.2246 ± 3.4%	12.6077 ± 4.3%	24	90.00	0.10	0.40	10	r	6.3744 ± 2.0%	12.5300 ± 2.5%
	90.00	0.10	0.40	10	a	6.1849 ± 3.2%	12.9571 ± 3.9%		90.00	0.10	0.40	10	a	6.6717 ± 2.1%	12.9010 ± 2.6%
	90.00	0.10	0.40	40	r	7.4473 ± 11.2%	12.2593 ± 7.1%		90.00	0.10	0.40	40	r	7.2331 ± 6.9%	12.9924 ± 4.2%
	90.00	0.10	0.40	40	a	8.1651 ± 11.7%	12.7508 ± 6.9%		90.00	0.10	0.40	40	a	8.4758 ± 6.8%	13.5141 ± 4.4%
13	90.00	0.10	0.40	10	r	6.3364 ± 3.0%	12.6801 ± 3.2%	25	90.00	0.10	0.40	10	r	6.3000 ± 1.6%	12.2951 ± 2.3%
	90.00	0.10	0.40	10	a	6.8146 ± 3.0%	12.8299 ± 3.6%		90.00	0.10	0.40	10	a	6.1959 ± 2.1%	12.7614 ± 2.0%
	90.00	0.10	0.40	40	r	7.8334 ± 11.1%	12.4236 ± 7.3%		90.00	0.10	0.40	40	r	7.4810 ± 7.6%	12.8628 ± 3.5%
	90.00	0.10	0.80	40	a	8.5007 ± 13.1%	13.0416 ± 6.1%		90.00	0.10	0.80	40	a	7.5665 ± 6.9%	13.7333 ± 4.3%
14	90.00	0.10	0.40	10	r	6.1205 ± 3.2%	12.5949 ± 3.2%	26	90.00	0.40	0.40	10	r	6.1648 ± 1.9%	12.5931 ± 2.4%
	90.00	0.10	0.40	10	a	6.5490 ± 3.5%	12.7048 ± 3.6%		90.00	0.40	0.40	10	a	6.8021 ± 1.8%	12.5190 ± 2.4%
	90.00	0.40	0.40	40	r	7.2939 ± 11.4%	12.7201 ± 6.2%	n	90.00	0.40	0.40	40	r	8.1525 ± 7.3%	12.8610 ± 3.7%
	90.00	0.40	0.80	40	a	8.2402 ± 12.4%	13.0333 ± 6.0%		90.00	0.10	0.80	40	a	8.2598 ± 7.7%	13.6185 ± 3.5%
15	90.00	0.10	0.40	10	r	6.4804 ± 3.1%	12.2319 ± 3.7%	27	90.00	0.10	0.40	10	r	5.7563 ± 2.1%	12.1926 ± 2.3%
	90.00	0.10	0.40	10	a	6.1026 ± 2.3%	12.3933 ± 3.6%		90.00	0.10	0.40	10	a	6.8933 ± 2.0%	12.6593 ± 2.5%
	90.00	0.40	0.40	40	r	7.7050 ± 11.1%	12.5215 ± 5.7%		90.00	0.10	0.40	40	a	8.1166 ± 6.2%	12.6733 ± 4.0%
	90.00	0.40	0.40	40	a	7.6865 ± 10.8%	13.2483 ± 6.0%		90.00	0.10	0.80	40	a	7.3416 ± 7.4%	13.3722 ± 3.1%
16	90.00	0.40	0.40	10	r	5.9528 ± 2.2%	12.1901 ± 3.3%	28	90.00	0.10	0.80	10	r	6.2148 ± 1.9%	12.1875 ± 2.3%
	90.00	0.40	0.40	10	a	6.7050 ± 3.2%	12.6590 ± 3.3%		90.00	0.10	0.80	10	a	6.2146 ± 1.8%	12.6587 ± 2.5%
	90.00	0.40	0.40	40	r	8.1591 ± 11.9%	12.9257 ± 5.7%		90.00	0.10	0.40	40	r	7.4385 ± 6.0%	12.9959 ± 3.2%
	90.00	0.40	0.40	40	a	8.5018 ± 10.6%	13.6281 ± 5.5%		90.00	0.10	0.80	40	a	7.9737 ± 6.3%	13.5081 ± 3.2%
17	90.00	0.40	0.40	10	r	5.8084 ± 2.3%	12.1677 ± 2.8%	29	90.00	0.10	0.80	10	r	7.0531 ± 1.7%	12.2964 ± 2.0%
	90.00	0.40	0.40	10	a	7.0296 ± 2.7%	12.6568 ± 3.8%		90.00	0.10	0.80	10	a	6.6296 ± 1.6%	12.7655 ± 2.3%
	90.00	0.40	0.40	40	r	7.4676 ± 10.0%	12.9263 ± 5.5%		90.00	0.10	0.80	40	r	7.5459 ± 7.4%	12.9093 ± 3.3%
	90.00	0.40	0.40	40	a	8.4217 ± 12.1%	13.4823 ± 4.8%		90.00	0.10	0.80	40	a	8.5293 ± 5.7%	13.3011 ± 3.4%
18	90.00	0.40	0.40	10	r	6.1095 ± 2.5%	12.3282 ± 2.8%	30	90.00	0.10	0.80	10	r	7.1231 ± 1.6%	12.5632 ± 2.1%
	90.00	0.40	0.40	10	a	6.9795 ± 2.4%	12.4901 ± 3.1%		90.00	0.10	0.80	10	a	6.7217 ± 1.8%	12.6147 ± 2.0%
	90.00	0.40	0.40	40	r	7.7974 ± 11.7%	12.9902 ± 4.6%		90.00	0.10	0.80	40	r	7.6924 ± 7.0%	12.8876 ± 3.3%
	90.00	0.40	0.40	40	a	8.1113 ± 9.6%	13.5519 ± 5.0%		90.00	0.10	0.80	40	a	7.3804 ± 6.8%	13.3631 ± 3.6%

As for the two parameters k and E, it was not possible to carry out a complete comparison, because the very starting values were different.

After the initial estimate the sequence of optimal alternate experimental settings determination and regression calculations was carried out using the methods described in this paper (i.e., the algorithms defined in Table 1 or by eqs 14–16 for settings determination and the algorithm defined by eq 7 for the estimation of parameters after each new experiment).

The results obtained from this procedure (optimum settings, parameter estimates, and standard deviations of parameters after each additional experiment) are shown in Table 6. They can be summarized as follows: (a) There is hardly any influence of noise level and type of error on optimum settings, and their influence on the estimates obtained after each new experiment is not very strong either, if compared with the results reported by Agarwal and Brisk (1985), which seems to indicate a damping influence of the separation of parameters on the accuracy of the estimates. (b) In no case did the optimal estimates of k and E tend to the true values. (c) The same (upper) value of temperature was called for at each stage, with 12 experiments out of 24 being exactly the same.

This anomalous behavior was attributed to an insufficient number of initial data points (six data points for four parameters). In fact relation 10, computed at the current values of the parameters, is valid only if the latter are sufficiently close to the true values. Otherwise strongly biased estimates may call for the same experiment many times sequentially. On the other hand the same experimental settings may fail to provide enough information for bias correction and eventually this can lead to wrong asymptotic estimates. To test this possibility, we increased the number of initial data points to 12 and repeated the same procedure increasing the number of sequential experiments correspondingly. The results are reported in Table 7.

Table 7. Numerical Results Using 12 Initial Data Points

exp. no.	T	$p1$	$p2$	noise, %	error	k	E, kcal/mol	exp. no.	T	$p1$	$p2$	noise, %	error	k	E, kcal/mol
13	90.00	0.10	0.40	10	r	6.6414 ± 3.8%	12.0097 ± 4.5%	25	90.00	0.40	0.40	10	r	5.3594 ± 1.9%	11.5568 ± 2.5%
	90.00	0.10	0.40	10	a	7.2010 ± 3.6%	11.4204 ± 4.4%		44.70	0.39	0.40	10	a	4.5016 ± 2.2%	11.7075 ± 2.9%
	90.00	0.10	0.40	40	r	6.3393 ± 13.9%	11.2631 ± 7.6%		40.00	0.40	0.40	40	r	2.8932 ± 8.5%	11.6938 ± 3.8%
	90.00	0.10	0.40	40	a	7.2857 ± 16.3%	12.0488 ± 5.9%		90.00	0.40	0.80	40	a	5.3449 ± 7.9%	12.0859 ± 3.8%
14	90.00	0.10	0.40	10	r	5.6694 ± 3.2%	11.1977 ± 4.0%	26	90.00	0.10	0.80	10	r	4.2376 ± 1.7%	11.6536 ± 2.2%
	90.00	0.10	0.40	10	a	5.7731 ± 3.6%	11.0302 ± 4.6%		40.00	0.33	0.40	10	a	5.1395 ± 1.9%	11.4719 ± 2.4%
	90.00	0.10	0.40	40	r	5.3425 ± 14.5%	11.2962 ± 8.4%		40.00	0.10	0.40	40	r	5.5224 ± 8.0%	11.8052 ± 3.5%
	90.00	0.10	0.40	40	a	6.1111 ± 14.5%	12.3135 ± 7.4%		90.00	0.40	0.63	40	a	3.2003 ± 7.0%	12.2091 ± 4.4%
15	90.00	0.10	0.40	10	r	5.2727 ± 3.4%	11.1552 ± 4.1%	27	90.00	0.10	0.80	10	r	4.8092 ± 2.0%	11.4582 ± 1.9%
	90.00	0.10	0.40	10	a	4.1367 ± 3.1%	11.6192 ± 3.5%		40.00	0.40	0.40	10	a	5.3686 ± 2.0%	12.0431 ± 2.5%
	90.00	0.10	0.40	40	r	2.9161 ± 10.9%	11.6445 ± 7.2%		40.00	0.10	0.40	40	r	5.9159 ± 7.9%	11.7441 ± 4.4%
	90.00	0.10	0.40	40	a	3.6844 ± 13.6%	12.0207 ± 6.7%		90.00	0.40	0.40	40	a	4.9733 ± 7.8%	12.2214 ± 3.6%
16	90.00	0.10	0.40	10	r	3.7429 ± 2.7%	11.9322 ± 3.6%	28	90.00	0.10	0.80	10	r	4.8503 ± 2.0%	11.5123 ± 1.9%
	81.70	0.10	0.40	10	a	5.2651 ± 3.3%	11.8252 ± 3.3%		50.40	0.31	0.40	10	a	3.9994 ± 1.7%	12.0790 ± 2.1%
	90.00	0.10	0.40	40	r	5.0146 ± 13.6%	11.7713 ± 5.9%		40.00	0.10	0.40	40	r	3.6423 ± 6.2%	11.8198 ± 4.1%
	58.30	0.10	0.40	40	a	5.5862 ± 12.8%	11.7617 ± 6.7%		90.00	0.40	0.40	40	a	5.1986 ± 7.3%	11.9262 ± 3.7%
17	90.00	0.10	0.40	10	r	3.8124 ± 3.2%	12.0462 ± 3.7%	29	90.00	0.40	0.40	10	r	5.3349 ± 1.5%	11.4377 ± 2.3%
	90.00	0.18	0.40	10	a	5.4974 ± 2.8%	11.7787 ± 3.6%		87.10	0.10	0.80	10	a	5.5751 ± 1.8%	11.7737 ± 2.2%
	90.00	0.10	0.40	40	r	2.9586 ± 11.2%	11.7921 ± 6.0%		90.00	0.40	0.40	40	r	6.4919 ± 7.8%	11.8203 ± 3.2%
	43.30	0.10	0.40	40	a	3.6792 ± 11.7%	11.1752 ± 5.1%		90.00	0.40	0.48	40	a	4.2025 ± 7.6%	11.9760 ± 3.7%
18	90.00	0.10	0.40	10	r	5.0698 ± 2.3%	11.9323 ± 3.7%	30	90.00	0.40	0.80	10	r	4.4326 ± 1.9%	11.5072 ± 1.7%
	90.00	0.22	0.40	10	a	4.8918 ± 3.0%	11.0205 ± 2.8%		90.00	0.10	0.80	10	a	4.6274 ± 1.8%	11.4734 ± 2.1%
	90.00	0.10	0.40	40	r	3.3996 ± 11.8%	11.2988 ± 6.2%		90.00	0.40	0.40	40	r	3.6060 ± 6.7%	11.7604 ± 3.6%
	40.00	0.40	0.40	40	a	3.2536 ± 11.7%	11.1594 ± 5.5%		90.00	0.40	0.61	40	a	4.2140 ± 6.8%	11.5847 ± 2.9%
19	90.00	0.10	0.40	10	r	5.5432 ± 2.3%	11.5032 ± 3.5%	31	90.00	0.40	0.80	10	r	4.4863 ± 1.7%	11.6207 ± 1.9%
	52.70	0.10	0.80	10	a	5.4139 ± 2.6%	11.1904 ± 3.1%		90.00	0.39	0.80	10	a	3.8874 ± 1.7%	11.0437 ± 1.6%
	40.00	0.40	0.40	40	r	3.7274 ± 9.1%	11.7534 ± 5.0%		90.00	0.40	0.40	40	r	6.0253 ± 5.0%	11.7301 ± 2.9%
	40.00	0.40	0.71	40	a	3.7471 ± 9.5%	11.1536 ± 5.1%		90.00	0.40	0.80	40	a	3.9223 ± 6.3%	11.5477 ± 3.8%
20	90.00	0.10	0.80	10	r	5.4572 ± 2.6%	11.3802 ± 2.8%	32	40.00	0.40	0.80	10	r	4.9345 ± 1.5%	11.4024 ± 2.1%
	40.00	0.10	0.80	10	a	3.773 ± 2.7%	11.3283 ± 3.5%		90.00	0.40	0.80	10	a	4.3729 ± 1.7%	11.1355 ± 1.7%
	40.00	0.40	0.40	40	r	3.4385 ± 10.6%	11.4221 ± 5.4%		90.00	0.40	0.40	40	r	5.2331 ± 6.7%	11.7088 ± 2.6%
	40.00	0.40	0.80	40	a	4.7986 ± 9.9%	11.1000 ± 4.2%		90.00	0.40	0.77	40	a	3.1318 ± 6.1%	11.6212 ± 3.7%
21	40.00	0.10	0.40	10	r	4.7280 ± 2.4%	11.5602 ± 2.4%	33	40.00	0.10	0.40	10	r	4.0706 ± 1.6%	11.3981 ± 2.1%
	61.10	0.40	0.40	10	a	3.6517 ± 2.5%	11.8555 ± 3.1%		90.00	0.40	0.80	10	a	3.9950 ± 1.6%	11.7007 ± 2.0%
	40.00	0.40	0.40	40	r	6.2995 ± 11.1%	12.0520 ± 4.8%		90.00	0.40	0.40	40	r	4.2808 ± 4.9%	11.7513 ± 2.8%
	40.00	0.40	0.80	40	a	4.2206 ± 10.5%	11.0418 ± 4.1%		90.00	0.40	0.50	40	a	5.8129 ± 6.5%	11.7909 ± 2.6%
22	40.00	0.10	0.80	10	r	3.6116 ± 2.0%	11.2964 ± 2.5%	34	40.00	0.10	0.80	10	r	4.2748 ± 1.6%	11.4274 ± 1.5%
	90.00	0.40	0.40	10	a	4.4649 ± 2.5%	11.7712 ± 2.7%		81.20	0.21	0.80	10	a	4.2681 ± 1.5%	11.5500 ± 1.8%
	40.00	0.40	0.40	40	r	5.3940 ± 10.9%	11.9953 ± 4.3%		90.00	0.40	0.40	40	r	4.3807 ± 6.7%	11.6319 ± 2.9%
	40.00	0.32	0.80	40	a	3.2357 ± 8.4%	11.3292 ± 4.9%		90.00	0.40	0.40	40	a	4.9032 ± 6.5%	11.7718 ± 3.1%
23	40.00	0.10	0.80	10	r	3.7474 ± 1.8%	11.2242 ± 2.6%	35	90.00	0.10	0.80	10	r	4.9705 ± 1.6%	11.6466 ± 1.4%
	59.00	0.40	0.40	10	a	4.5746 ± 2.2%	12.1217 ± 2.6%		70.60	0.10	0.80	10	a	4.9053 ± 1.1%	11.5449 ± 1.9%
	40.00	0.40	0.40	40	r	5.8582 ± 9.7%	12.1154 ± 4.6%		90.00	0.10	0.40	40	r	4.9629 ± 6.6%	11.6131 ± 2.8%
	71.40	0.40	0.79	40	a	5.1403 ± 8.3%	11.3079 ± 4.6%		90.00	0.40	0.40	40	a	4.0438 ± 5.5%	11.6527 ± 3.0%
24	40.00	0.40	0.80	10	r	4.3556 ± 2.1%	11.3748 ± 2.7%	36	90.00	0.10	0.80	10	r	4.5832 ± 1.5%	11.6816 ± 1.4%
	40.00	0.40	0.40	10	a	4.9662 ± 2.2%	12.1342 ± 2.7%		46.60	0.10	0.80	10	a	4.6496 ± 1.4%	11.5713 ± 1.7%
	40.00	0.40	0.40	40	r	6.1619 ± 8.3%	12.0732 ± 3.8%		90.00	0.10	0.40	40	r	4.9335 ± 5.3%	11.6087 ± 3.3%
	90.00	0.40	0.80	40	a	3.1331 ± 8.3%	11.3227 ± 4.2%		90.00	0.40	0.40	40	a	4.7496 ± 5.6%	11.6982 ± 3.3%

As can easily be seen both k and E are now estimated without bias. Similarly the new optimal settings are distributed in a fairly uniform way in the feasible region.

Conclusions

Separation of preexponential (linear) parameters from the nonlinear ones (activation energies, orders of reaction, etc.) shows two remarkable advantages.

(a) The correlation between the independent (nonlinear) parameters is far less than that between linear and nonlinear parameters in nonseparated models. Since correlation is generally a severe hindrance to precise estimation and interpretation of the individual parameters, its reduction makes it possible to reduce the number of experiments, due to a better use of the information available.

(b) The objective function for the determination of optimum settings turns out to be more easily amenable to global optimization than traditional nonseparated models.

These two properties can increase, to a considerable extent, the overall efficiency of sequential experiment planning.

Nomenclature

a = first parameter in the heteroscedasticity expression of error

b = second parameter in the heteroscedasticity expression of error

$\mathbf{B}$ = vector $(Dg/DE, Dg/D\alpha, Dg/D\beta)$

c_i = concentration of species i (mol/cm^3)

D = Frechet operator of matrix derivative

E = activation energy (kcal/mol)

f = reaction rate as a function of operating variables and parameters

$F_{ij} = (\partial f/\partial\theta_j)(X_i,\theta_j)$

g = reaction rate (mol/cm^3·s)

$g_i = \partial g/\partial\theta_i$

$\mathbf{G}$ = parameter transformation matrix

h_i = see eq 6
$\mathbf{H}$ = pseudoinverse of h_i
k = preexponential factor
p_i = partial pressure (atm)
r = reaction rate (mol/cm^3·s)
T = temperature (K)
$u_{ij} = ak^2V_{\theta,ij}^{-1}$
$\mathbf{V}$ = variance–covariance matrix
x_1 = mole fraction of component 1
x_2 = mole fraction of component 2
$\mathbf{X}$ = vector of independent variables

Greek Symbols

α = order of reaction
β = order of reaction
$\gamma_i = 2\theta_i/k$
$\xi_1 = \partial k/\partial E - k/RT$
$\xi_2 = \partial k/\partial \alpha + k \ln p_1$
$\xi_3 = \partial k/\partial \beta + k \ln p_2$
θ = parameters
σ^2 = variance
ϕ = reaction rate divided by the preexponential factor

Superscripts

* = reference temperature
+ = pseudoinverse
$\perp = 1 - \mathbf{H}^+\mathbf{H}$

Literature Cited

Agarwal, A. K.; Brisk, M. L. Sequential Experimental Design for Precise Parameter Estimation. 1. Use of Reparametrization. *Ind. Eng. Chem. Process Des. Dev.* **1985**, *24*, 203–207.

Bard, Y. *Nonlinear Parameter Estimation*; Academic Press: New York, 1974.

Box, G. E. P.; Hunter, W. G. The Experimental Study of Physical Mechanisms. *Technometrics* **1965**, *7*, 23–31.

Chen, N. H.; Aris, R. Determination of Arrhenius Constants by Linear and Nonlinear Fitting. *AIChE J.* **1992**, *38* (4), 626–628.

Dovi, V. G.; Arato, E.; Maga, L. A more general formulation of separable least squares. *Math. Model.* **1987**, *8*, 20–25.

Golub, E. H.; Pereyra, V. The differentiation of pseudo-inverses and nonlinear least squares whose variables separate. *SIAM J. Numer. Anal.* **1973**, *10* (2), 413–432.

Golub, E. H.; Pereyra, V. *Generalized Inverses and Applications*; Academic Press: New York, 1976.

Lawton, W. H.; Sylvestre, E. A. Elimination of linear parameters in nonlinear regression. *Technometrics* **1971**, *13*, 461–467.

Reilly, P. M.; Bajramovic, R.; Blau, G. E.; Branson, D. R.; Sauerhoff, M. W. Guidelines for the Optimal Design of Experiments to Estimate Parameters in First Order Kinetic Models. *Can. J. Chem. Eng.* **1977**, *55*, 614–622.

Rimensberger, T.; Rippin, D. W. T. Comments on "Sequential Experimental Design for Precise Parameter Estimation. 1. Use of Reparametrization". *Ind. Eng. Chem. Process Des. Dev.* **1986**, *25*, 1042–1044.

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