SYNOPSIS

In the kinetics of the two-step, consecutive, first-order, irreversible reaction,

\[
\begin{align*}
&k_1 & & k_2 \\
&A &\rightarrow & B &\rightarrow & C
\end{align*}
\]

the equations for the time-dependence of the intermediate, B, the product, C, and the co-product, D (which is the species formed in both the steps) are given by non-linear, transcendental equations which contain the sum of two exponential terms. The equation for the product is symmetric with respect to the interchange of the two rate coefficients between the two steps, leading to dual pairs of solutions for the rate coefficients from product formation data. The evaluation of both the rate coefficients from the product, co-product or intermediate concentration versus time data requires optimization in two dimensions. Though a number of non-linear regression and optimization techniques have been employed, there has been no systematic and comprehensive analysis of the effect of the random errors, that are invariably present in all experimental data, on the accuracy of the consecutive rate coefficients resolved from such data.

The evaluation of the three rate coefficients of the three-step reaction

\[
\begin{align*}
&k_1 & & k_2 & & k_3 \\
&A &\rightarrow & B &\rightarrow & C &\rightarrow & E
\end{align*}
\]

from the concentration of the product E versus time data requires optimization in three dimensions; there are six sets of solutions due to the symmetry present in the equation.
MODIFICATION OF PROGRAM 5 WITH INCREASED NUMBER OF STARTS

WHERE THERE IS SOME DOUBT THAT THE PROGRAM FOR FOUR-DIMENSIONAL SEARCH USING THE LATIN HYPERCUBE OF JUST TEN STARTING POINTS, IT CAN BE MODIFIED BY USING THE FOLLOWING NETWORK OF 385 STARTING POINTS; THE CO-ORDINATES OF ONLY THREE OF THE FOUR PARAMETERS, J0, K0 AND L0, ARE STATED AS DATA IN LINES 1501-1597, M0 BEING GIVEN BY (1-L0) AS SPECIFIED BY THE EXTRA LINE 65.

40 DIM J0(500): DIM K0(500): DIM L0(500): DIM M0(500): DIM X(100): DIM Y(100): DIM Z(100): DIM V(100): DIM R(100)
60 READ J0(E), K0(E), L0(E)
65 M0(E) = 1 - L0(E)

1500 REM USING A LARGER SET OF INITIAL ESTIMATES OF J, K AND L
1501 DATA .05, .05, .05, .05, .20, .05, .05, .35, .05, .05, .50
1502 DATA .05, .05, .65, .05, .05, .80, .05, .05, .95, .05, .15, .05
1503 DATA .05, .15, .20, .05, .15, .35, .05, .15, .50, .05, .15, .65
1504 DATA .05, .15, .80, .05, .15, .95, .05, .25, .05, .25, .20
1505 DATA .05, .25, .35, .05, .25, .50, .05, .25, .65, .05, .25, .80
1506 DATA .05, .25, .95, .05, .35, .05, .35, .20, .05, .35, .35
1507 DATA .05, .35, .50, .05, .35, .65, .05, .35, .80, .05, .35, .95
1508 DATA .05, .45, .05, .45, .20, .05, .45, .35, .05, .45, .50
1509 DATA .05, .45, .65, .05, .45, .80, .05, .45, .95, .05, .55, .05
1510 DATA .05, .55, .20, .05, .55, .35, .05, .55, .50, .05, .55, .65
1511 DATA .05, .55, .80, .05, .55, .95, .05, .65, .05, .65, .20
1512 DATA .05, .65, .35, .05, .65, .50, .05, .65, .65, .05, .65, .80
1513 DATA .05, .65, .95, .05, .75, .05, .75, .20, .05, .75, .35
1514 DATA .05, .75, .50, .05, .75, .65, .05, .75, .80, .05, .75, .95
1515 DATA .05, .85, .05, .85, .20, .05, .85, .35, .05, .85, .50
1516 DATA .05, .85, .65, .05, .85, .80, .05, .85, .95, .05, .95, .05
1517 DATA .05, .95, .20, .05, .95, .35, .05, .95, .50, .05, .95, .65
1518 DATA .05, .95, .80, .05, .95, .95, .15, .05, .15, .15, .20
1519 DATA .15, .15, .35, .15, .15, .50, .15, .15, .65, .15, .15, .80
1520 DATA .15, .15, .95, .15, .25, .05, .15, .25, .20, .15, .25, .35
1521 DATA .15, .25, .50, .15, .25, .65, .15, .25, .80, .15, .25, .95
1522 DATA .15, .35, .05, .15, .35, .20, .15, .35, .35, .15, .35, .50
1523 DATA .15, .35, .65, .15, .35, .80, .15, .35, .95, .15, .45, .05
The time-dependence of a system property \((Z)\), such as the photometric absorbance, in the two-step reaction is governed by an equation containing the two rate coefficients in two exponential terms, and two pre-exponential coefficients, which are constants consisting of the rate coefficients and the molar system properties of \(A, B\) and \(C\). The evaluation of the two rate coefficients and the two pre-exponential parameters from system property versus time data requires optimization in four dimensions

\[
|Z - Z_\infty| = P \exp(-k_1t) + Q \exp(-k_2t)
\]

But, Acton has severely admonished attempts to optimize all the four parameters of such equations, which are highly ill-conditioned there are many, different sets of solutions of the four parameters that will fit even the most accurate data equally well; in the presence of random errors in the data, he warns, such exercises will be futile. This throws into doubt the validity of the rate coefficients that have been resolved from spectrokinetic data by different workers.

The present investigation is concerned with the questions raised above: how far accurate are the rate coefficients of two- (and three-) step, consecutive, first-order reactions resolved from concentration data and whether Acton's admonition against optimization of the four parameters is fully valid in the case of the system property data in two-step reactions. To find the answers, data of concentration/absorbance versus time were generated, using the appropriate equation, for various hypothetical combinations of the rate coefficients (and the two additional parameters in the case of the absorbance data) for 24 readings extending up to about 80% of the course of the reaction. Random, normal deviates, of mean zero and standard deviation 1, randomly taken from a handbook of statistical tables were incorporated, one in each reading, after appropriate adjustment so that they represented correctly the chosen error level. Six sequences each containing 24 random, normal deviates were used to produce six replications of each experiment under a given set of conditions. The level of datum errors
ranged from 0 to 1% or 0 to 10% in the simulations for the different cases. When rounded of to four decimal places, these simulated data resembled real, experimental data and each set of data was subjected to optimization of the parameters for different ranges of the extent of reaction.

The universally adopted Gaussian or the Least Squares norm, which minimizes the sum of the squares of the deviations (S) of the readings from that predicted for each by the system equation, is employed as the criterion for the optimization.

The downhill simplex minimization, due to Nelder and Mead (1965), was chosen as the principal tool of optimization. It does not use derivatives of the objective function to be minimized and always reaches a minimum in the error hypersurface, even if it is a local one, and not the global one, which is associated with the best estimates of the parameters. The routine is, however, very slow in converging to the minimum. By using a number of starting points, as many minima as possible can be located and the one among them with the lowest value of S is taken as giving the best estimates of the parameters. A number of restarts may be required and, as hundreds, or even thousands, of iterations may be needed, a high-speed, personal computer is used. Separate programs written in QBASIC are employed for each case. The program can also check up whether the value of S associated with the optimized parameters is a minimum by comparison with the points lying close by in all the dimensions. In the case of optimization in two-dimensions, the parameters optimized by the Nelder-Mead routine are verified by the Deming method, which employs a fast-converging, gradient routine, but requires initial inputs of the parameters that are close to their final estimates to attain convergence. The optimized estimates of the parameter in every simulation are tabulated, as are the maximum errors in the estimates of the rate coefficients found in the six replications at various levels of datum error. The latter set the upper limit for the presence of datum errors that would permit a reasonably accurate evaluation of the rate coefficients in actual experiments.
The simulations in two dimensions face no problems. Two pairs of solutions for the two rate coefficients can be obtained corresponding to two minima located on the error surface. The rate coefficients are recovered with accuracy when only round-off errors are present in the data. In the case of the product formation data, the two minima have identical values of $S$ and the error map is symmetric about the diagonal axis, as dictated by the symmetry of the equation for product formation. As the datum error level increases, the minima get shallower, and in many cases move towards each other, coalescing to single minimum located on the diagonal axis of the error map; at this point the estimates of the two rate coefficients are identical. Coalescence may occur at different error levels depending on the actual errors that enter each reading and their exact sequence. In the case of the co-product formation data, the error surface has no symmetry. Two minima can be located, one the global with a lower value of $S$, which at low datum error levels gives estimates of the rate coefficients that are closest to their true, i.e., assumed, values. As the datum error level increases, the global minimum is raised, and at some point the two minima may crossover, the weaker minimum now having a lower value of $S$ and associated with the wrong pair of estimates of the rate coefficients. Because of coalescence and crossover in the product and co-product cases, respectively, the datum error level of 0.5% represents the upper limit in most cases for satisfactory evaluation of the rate coefficients. Their estimates are good up to the 0.2% datum error level, even for the difficult cases where the two rate coefficients are close to each other in magnitude. In general, errors in the estimates decrease with increasing number of readings and it is advisable to collect data covering at least 70% of the reaction. While one rate coefficient is underestimated, the other is overestimated. In the case of the data pertaining to the formation of the intermediate, the second minimum is usually far away from the global. Even at the datum error level of 2%, the rate coefficients can be estimated quite accurately, since the absolute errors entering the data are smaller, as the relative concentration of the
intermediate reaches a maximum in the course of the reaction which is less than unity.

In the case of the three-dimensional optimization employed for product formation in the three step reaction, the situation is similar to that in the two dimensional case. The rate coefficients are recovered with errors of less than 30% up to the 0.2% datum error level. There are six minima with identical values of $S$ located symmetrically on the error hypersurface, corresponding to the six sets of solutions for the three rate coefficients. As the datum error level increases, two, or all the three, minima may coalesce.

System property data were simulated on the basis of a normalized equation in order to keep the number of simulations within manageable limits. A Latin hypercube containing ten starting points is used to locate as many minima as possible, but where there is doubt that the global minimum might have been missed, a larger set of 385, or more, starting points can be employed. Contrary to Acton's statement, all the four parameters can be estimated accurately for reactions in which one step is at least twice as fast as the other, when the data are accurate to four decimals, except in an odd case. However, the estimates deteriorate rapidly as random errors are introduced in the data. There are many minima – twenty four of them can be expected in theory – corresponding to many sets of solutions as stated by Acton and if their $S$ values are of the same magnitude, they all will fit the data more or less equally well. Some of the minima are coalesced ones and some others crossed-over ones, even at very low datum error levels. It is difficult to discriminate between them, as they differ very little in their $S$ values, and to choose the right one which is associated with estimates of the parameters that are close to their true values, which are unknown, of course, in the real situation. The least squares norm may have to be ignored and a sub-global minimum may chosen under certain circumstances. It is suggested that every kinetic run is followed to at least the 80% stage of the reaction and triplicated to make the task of discriminating between the different solutions.
easier. Usually both the rate coefficients are either overestimated or both are underestimated. The two pre-exponential parameters are in many cases estimated poorly, which need not alarm the kineticist. Despite these complexities, the simulation results show that, contrary to Acton’s misgivings, it will be possible to evaluate the two rate coefficients fairly accurately, and the other two parameters somewhat satisfactorily, by optimization of absorbance and other system property data, if the datum error level is 0.2% or less when the faster step is at least thrice as fast as the slower, for a somewhat narrow corridor of the values of the pre-exponential coefficients. Therefore, the ground is very slippery but not totally untraversable as cautioned by Acton: system property data can be used for a reasonably successful optimization of the parameters, provided that the limits indicated in this work are adhered to and proper discretion is employed in assessing the various minima.

The use of the Nelder-Mead routine is illustrated by application to four instances of actual experimental data: Gale and Eadie’s (1974) data on the hydrolysis of urea giving carbon dioxide as the product, Kaufler’s (1906) data on the hydrolysis of 1,7-dicyanonaphthalene, yielding ammonia as the co-product, Sindhu Jayaraj’s (1998) photometric absorbance data obtained in these laboratories in the two-step substitution reaction that follows the near-instantaneous formation of a charge-transfer complex between chloranil and excess p-touidine in tetrahydrofuran; and Lowry and Traill’s (1931) polarimetric data on the mutarotation of aluminium benzoylcamphor in carbon tetrachloride, which is actually a reaction in which both the steps are reversible and the rate coefficients are apparent rather than absolute ones.

The literature has been surveyed up to mid-2003, but there has been a paucity of publications since 1990. The resolution of the kinetics of consecutive reactions remains a much neglected subject, as is the Nelder-Mead routine which has a charming elegance despite its slowness to converge.