Combining Different Mathematical Optimization Methods:
A New "Hard-modelling" Approach for Chemical Kinetics

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Abstract.

A novel *"hard-modeling"* computational approach is proposed to analyse the kinetic data monitored spectrometrically acquired to multiwavelength (MW). It is based in a robust mathematical optimization algorithm AGDC(MW) that allows the simultaneous determination of the values of the rate constants (k_r) of the r-*th* reaction and of the molar absorption coefficients ($\varepsilon_{j,\lambda}$) of all the chemical species (j-*th*) involved in the reaction kinetic system at the wavelength λ. The approach is the result of combining 3 different methodologies of mathematical optimization and an evident improvement in the values of the optimized parameters has been obtained in comparison with the application of a single method. The procedure consists in the sequential application of the optimization methods where the optimized parameters determined by each one of the methods are taken like the set of the initial estimates of the next method to be applied to the objective function

A comparative study was performed between the results obtained from the application of each method with those obtained from the combining approach of 3 optimization methods. The results of this approach reveal the correct mathematical optimization of complex kinetic system involving a large number of parameters of very different orders of magnitude.

1. Introduction

Kinetic reactions monitored spectrometrically have been classically treated using *"hard-modeling"* computational approaches where the parameters are optimized from the

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objective function which is the solution of the ordinary differential equations (ODE) of the kinetic system. The parameters include the rate constants (k_r) of the r-*th* reaction and of the molar absorption coefficients ($\varepsilon_{j,\lambda}$) of all the chemical species (j-*th*) involved in the reaction kinetic system at the wavelength λ. The simultaneous determination of the rate constants and the molar absorption coefficients is a difficult task for classic mathematical optimization methods due to the large number of parameters to optimize and the very different order of magnitude of both types of parameters.

We propose a robust methodology of unconstrained mathematical optimization that permits the simultaneous computational determination of a high number of parameters of different orders of magnitude, based on the superposition and combining of different optimization methods. It is especially designed for the simultaneous optimization of the rate constants and molar absorption coefficients of all the species involved in the kinetic process by monitoring the absorbance measured at MW. The optimization methods that we apply in this paper use the updated version of the mathematical optimization algorithm AGDC [1], which we modified suitably for application to the treatment of absorbance data monitored at multiwavelength named AGDC(MW) [2,3]. It is a robust algorithm of gradient of second order that can be used with success for such purposes, both in a Regression analysis and in any other different one as long as the aim is to search for the minimum of a function in the *hyperspace* defined by the parameters to be optimized. We designed and applied it for the first time and with excellent results in the MACROTER and MICROTER [4,5] programs for the determination of Thermodynamic Ionization Constants (macroscopic and microscopic) of polyfunctional substances. Our team [6,7] determined the corresponding apparent ionization constants of several substances of pharmacological interest, computing spectrophotometric and potentiometric data acquired simultaneously in a continuous flow system. We have applied this successfully in the field of Chemical Kinetis computing of kinetic experimental results on absorbance monitored at a single wavelength [8] and at multiwavelength [9]. A series of papers, under the generic title of "*Computation in Kinetics*"[10-13] kinetic data from potentiometric and spectrophotometric techniques [KILET-MINUIT] were computed, obtaining kinetic and Activation thermodynamic parameters in simple systems with good results. AGDC(MW) has been applied for the determination of concentrations of multicomponent mixtures [14] and initial concentrations and rate constants in kinetic analysis of homogeneous mixtures [15]. This robust algorithm has been applied for the resolution of both, static and dynamic multicomponent mixtures obtaining excellent results. [16,17]

The literature contains some works about the computational kinetic treatment using different methodologies. Application of methods based on Artificial Neural Networks (ANN) techniques in their different types [18-21]; the use of curve resolution techniques (CR), a self-

modeling extension (SMCR) and with the addition of the Dynamic Monte Carlo search (DMC-SMCR) [22]. Other versions of CR are also applied for purely kinetic aims (modelling and determination of kinetic parameters), as is the case with MCR-ALS, in which there is also a Alternative Least Squares (ALS) [23,24]. Other applications in Chemical Kinetics are the OPKINE-2 algorithm [25], whose treatment determines sensitivity coefficients, and the so-called Kalman filter algorithm [26-28], which evaluates spectrophotometric data, allowing the prediction of concentrations and reaction rate constants.

2. Optimization Methods

The classic procedure used in optimization techniques consists in performing the joint and simultaneous optimization of all the parameters in a single process. This procedure derives from the mathematical condition imposed by the sum of quadratic deviations (SQD) function, according to which its partial derivatives with respect to each of the parameters must be zero, giving rise to a single homogeneous set of equations from whose solution one obtains the complete set of parameters to be optimized. For the minimization of the SQD function, we used in this paper the mathematical optimization algorithm AGDC(MW), which permits the treatment of absorbance data monitored at MW. We apply this using several procedures, obtaining different optimization methods whose behavior and results we wished to assess and which will be detailed below.

The study carried out with data acquired at MW provided much broader experimental information than the corresponding study carried out with data acquired at a single wavelength (SW). However, MW data treatment for the joint and simultaneous optimization of k and ε is very complex owing to the high number of parameters and the difference in the order of magnitude among them. With a view to clarifying this issue, we considered a kinetic model of first-order consecutive reaction: $B_1 \rightarrow B_2 \rightarrow B_3$. If the treatment is carried out at SW it is necessary to optimize 5 parameters (2 values of k_r and 3 of ε) while when performed at MW (for example, at 10 wavelengths) the number of parameters to be optimized rises to 32 (2 values of k_r and 30 of ε). When the number of parameters is very high and, additionally, their orders of magnitude are very different (in our case $k=10^{-3}$ and $\varepsilon=10^4$) the treatment involves matrices and vectors of large dimensions (32 x 32 for the previous case), formed by elements of very different orders of magnitude and hence with many risks of error in performing the numerous mathematical calculations to be carried out later. When such complex calculations are not performed rigorously, erroneous results are obtained that lead the overall optimization process to fail.

To circumvent these difficulties, we addressed the problem by adopting a criterion often used in scientific methodology (especially in the field of Physics and Physical

Chemistry), according to which the overall treatment of a complex system can be decomposed into the superposition of simplified individualized treatments applied to simpler systems whose overall behavior is identical to that of the original system. The individualized treatments will correspond to each of the groups having similar characteristics (k and ε). This was ideal in our case, since the experimental measurements of the absorbance values at each wavelength are independent; *i.e.*, there is no mutual interaction between the measurements of absorbance values at each wavelength.

In the previous example ($B_1 \rightarrow B_2 \rightarrow B_3$), the classic model of treatment considers the global problem, which involves performing a single optimization process of 32 parameters. On applying the above treatment criterion, the procedure is broken down into 2 stages; as many as there are classes of parameters. In one of them we optimized 2 parameters (k) in a single process and in the other we performed 10 individual processes of optimization on 3 parameters (the ε values of each of the 3 species for each wavelength). The order and sequence of performing these processes determined the type of method. Let us consider the following:

Method 1 (M1). All the parameters (k and ε) are optimized jointly and simultaneously in a single process (classic methodology). The motion vector defining the parameters in each iteration is the one defined in the AGDC(MW) algorithm, determining a single Hessian matrix and a single gradient vector.

Method II. The optimization process is split into two individual processes, one for the values of k and the other for the values of ε. This dual process introduces a series of particularities in the identity of the gradient vectors and of the Hessian matrices that must be taken into account.

Method II.A.(M2A). Here one carries out a first optimization process of the rate constants, maintaining the values of the molar absorption coefficients invariable. The process ends when the convergence criterion is reached. When divergence has been detected, a second optimization process is carried out without modifying the values of the rate constants obtained in the preceding optimization process.

Method II.B. (M2B). Two consecutive individual process are performed, one for each groups of parameters, initially performing a single iteration with a view to approximating the value of k to its final optimum value. Following this, the second process is developed aimed at improving the values of ε, starting in the same way with a single iteration. This dual sequential process of individual iterations is repeated as many times as is necessary until the

criteria of convergence imposed for both groups of parameters are reached. At this moment, the dual consecutive process ends, thus obtaining the final optimized values of k and ε.

3. Theoretical Aspects

Let us consider a chemical system formed by n_r chemical reactions where n_s chemical species can be involved. According to IUPAC's norms [29], the r-*th* chemical reaction can be expressed by the generic equation,

$$0 = \sum_{j=1}^{n_s} v_{j,r} B_j \qquad (1)$$

where, B_j a chemical species involved in the system of reactions, r $(1,\ldots, n_r)$, the number of chemical reaction, j $(1,\ldots, n_s)$ number of chemical species, the stoichiometric coefficient of the species B_j in the r-*th* reaction, $v_{j,r} < 0$ when B_j plays only the role of reactant in the r-*th* reaction and $v_{j,r} > 0$ when B_j plays only the role of product in the r-*th* reaction. When the reaction is an elementary or concerted one, the absolute values of the kinetic order $(z_{l,r})$ and stoichiometric coefficient of B_j coincide, that is $|v_{l,r}| = |z_{l,r}|$. The rate differential equation of the chemical species B_j in the r-*th* is given by

$$\frac{d[B_j]}{dt} = k_r v_{j,r} \prod_{l=1}^{n_s} [B_l]^{|z_{l,r}|} \qquad (2)$$

where B_l are the species playing only the role of reactants in the r-th reaction $(v_{l,r} < 0)$ and k_r the kinetic rate constant of the r-*th* reaction. Each chemical species can take part in several reactions and the rate differential equations will be the sum extended over those reactions where the reactant B_l appears, obtaining a system of ordinary differential equations (ODE) according to the generic equation,

$$\frac{d[B_j]}{dt} = \sum_{r=1}^{n_r} k_r v_{j,r} \prod_{l=1}^{n_s} [B_l]^{|z_{l,r}|} \qquad (3)$$

The general solution of the system of rate ordinary differential equations give the explicit function of the concentrations of the all species with the time $([B_j]_{t_i})$.

The chemical system constituted by 2 first order consecutive reactions has been studied in the present work and can be represented as

$$v_{1,1} B_1 \xrightarrow{k_{12}} v_{2,1} B_2$$

$$v_{2,2} B_2 \xrightarrow{k_{23}} v_{2,3} B_3$$

Considering $v_{1,1} = v_{2,2} = -1$ and $v_{2,1} = v_{2,3} = 1$, we have

$$B_1 \xrightarrow{k_{12}} B_2 \xrightarrow{k_{23}} B_3$$
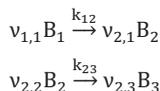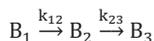
According this, the system of ordinary differential equations can be expressed using matrix notation as

$$\frac{d}{dt}\begin{vmatrix}[B_1]\\[B_2]\\[B_3]\end{vmatrix} = \begin{vmatrix}-k_{12} & 0 & 0\\ k_{12} & -k_{23} & 0\\ 0 & k_{23} & 0\end{vmatrix}\begin{vmatrix}[B_1]\\[B_2]\\[B_3]\end{vmatrix} \qquad (4)$$

When $[B_1]_0 \neq 0$ and $[B_2]_0 = [B_3]_0 = 0$, the integration of the ODE gives the following expressions of the concentrations for B_1, B_2 and B_3

$$[B_1] = [B_1]_0 e^{-k_{12}t}$$

$$[B_2] = \frac{[B_1]_0 k_{12}}{k_{23}-k_{12}}\left(e^{-k_{12}t} - e^{-k_{23}t}\right) \qquad (5)$$

$$[B_3] = [B_1]_0 - [B_1] - [B_2] = [B_1]_0\left(1 - \frac{k_{23}}{k_{23}-k_{12}}e^{-k_{12}t} + \frac{k_{12}}{k_{23}-k_{12}}e^{-k_{23}t}\right)$$

Serious problems arise as regards indistinguishability and /or non-unique identifiability, which lead to ambiguities in the solution of ODE system, where the function has 2 identical mathematical solutions that sometimes lead any curve-fitting method to fail.

Since the experimental data correspond to the monitoring of the total absorbance of the sample *(A$_{i,\lambda}$)*, it must be the magnitude that participates directly in the process of mathematical minimization, expressed as the sum of contribution of all species showing absorption at that wavelength. The mathematical optimization consists of the minimization of the numerical function of the **S**um of **Q**uadratic **D**eviations (*SQD*), extended for a n_t number of data, n_w number of wavelengths, and n_s number of species, is given by the expression:

$$SQD = \sum_{i=1}^{n_t}\sum_{\lambda=1}^{n_w}\left[\sum_{j=1}^{n_s} c_{i,j}\ \varepsilon_{j,\lambda} - (A_{i,\lambda})_{exp}\right]^2 = minimum \qquad (6)$$

To determine the *SQD* function it is necessary to know the concentration of all the species $c_{i,j}$ within the time interval considered from the set of exact solutions (5) for the kinetic system of 2 first order consecutive reactions. Nevertheless, in order to generalize the validity of application of the method to any kinetic system, we have performed the mathematical resolution of the set of differential equations by a numerical method. The solution of this type of differential equation is sometimes difficult, owing both to the characteristics of the systems and to the values taken by the rate constants, occasionally leading to *"stiff"* problems. The proposed treatment uses the Gear algorithm to solve the sets of differential equations and affords excellent results even in the case of complex systems with notable *"stiff"* characteristics. Next, the actual optimization process is begun; this is carried out by application of the AGDC(MW) algorithm. It consists of the minimization of *SQD* through the development of an iterative process in which the vector of movement is determined and at all times is subject to strict control. A rigorous analysis is made of its

elements, being suitably corrected in the event of detecting any errors, thereby ensuring that the minimum will be reached.

4. Computational Aspects

KINAGDC(MW) [1] is the common generic program used by us in all the above methodologies (M1, M2A and M2B) and is based on computational application of the AGDC(MW) algorithm. Each optimization method has a particular version of that algorithm arising from its adaptation to the peculiarities of the method, which we have denoted by adding to the generic name of the KINADGC(MW) program the letters that identify the version (M1, M2A and M2B) corresponding to each method. When the program computes using the combining of all methods, the name of the approach is KINADGC(MW)-COMB

The differences between the different versions of the algorithm corresponding to each of the different methods are *a)* the sequential order of execution of the different steps and *b)* calculation of the different gradient vectors and Hessian matrices, whose constitutive elements are different for each method and whose identities are detailed in the Appendix

4.1. KINADGC(MW)-M1 version.

This is the version of the program corresponding to Method 1, in which one performs a single optimization process of all the parameters that one wishes to determine (k and ε). It is the initial version that we previously used in the computational treatment applied to different fields Thermodynamics, Chemical Kinetics, Chemical Analysis, Modelling validation, etc.) The KINADGC(MW)-M1 program is represented step-by-step in Scheme 1.

Scheme I

1. Input data (matrix of $\nu_{j,r}$, number of reactions, species, experimental data, matrix of $\varepsilon_{j,\lambda}$ convergence criterion (CC), etc…

2. Establish the rate differential equations system and its solution (Gear algorithm) [31,32] obtaining $[B_{j,i}]_{CALC}$

3. Calculate the absorbance $(A_{i,\lambda})_{CALC}$

4. Determinate of the $SQD^{(m)}$ function [eq.(6)]

5. AGDC(MW) ALGORITHM

 5.1. Compute the $g^{(m)}$ and $H^{(m)}$ (Gradient vector and Hessian Matrix) [33]

 5.2. Compute $[H^{(m)}]^{-1}$ by Gauss elimination method and improvement by sucessive aproximations method.

 5.3. Calculate the components of the vector of movement $(p^{(m)} = - (H^{(m)})^{-1} g^{(m)})$

5.4. Control and correction of the vector of movement $\boldsymbol{p}^{(m)}$

   5.4.1. Direction of $\boldsymbol{p}^{(m)}$

      5.4.1.1   If $\boldsymbol{H}^{(m)}$ is singular, set $\boldsymbol{p}^{(m)} = -\boldsymbol{g}^{(m)}$, and go to 5.4.2

      5.4.1.2   If $\boldsymbol{p}^{(m)}\,\boldsymbol{g}^{(m)} < \delta$ (δ = scalar close to zero), set $\boldsymbol{p}^{(m)} = -\boldsymbol{g}^{(m)}$ and go to 5.5.2.

      5.4.1.3   If $\boldsymbol{p}^{(m)})\,\boldsymbol{g}^{(m)} > 0$ set $\boldsymbol{p}^{(m)} = -\boldsymbol{p}^{(m)}$

   5.4.2. Length of $\boldsymbol{p}^{(m)}$

      5.4.2.1.   Compute the scalar $(\alpha^{(m)})$ by the method of Hartley

      5.4.2.2. $\boldsymbol{X}^{(m+1)} = \boldsymbol{X}^{(m)} + \alpha^{(m)}\,\boldsymbol{p}^{(m)}$

      5.4.2.3.   If the Goldstein-Armijo criterion is satisfied go to 5.5.

      5.4.2.4. $\alpha^{(m)} = \alpha^{(m)} / 2$ and go to 5.4.2.2

5.5. Calculate $SQD^{(m+1)}$ from $X^{(m+1)}$ values

5.6.   If convergence is not attained ($\left| SQD^{(m+1)} - SQD^{(m)} \right| > CC$), set $m = (m + 1)$ and go to 2

6. Statistic Residual Analysis.

7. END.

Comments about the Scheme I. In step 5, the optimization process is performed by applying AGDC(MW), which begins (step 5.1) with the determination of the elements forming the gradient vectors and the Hessian matrices (g_{M1} and H_{M1}), formed by elements in which partial derivatives do not appear with respect to the kinetic constants and the molar absorption coefficients and whose identities are shown in the APPENDIX. Accordingly, one performs a single optimization process that finishes at step 5.6 when the convergence (CC) is satisfied.

4.2 KINADGC(MW)-M2A Version.

     This version corresponds to method 2A and consists in performing 2 individualized optimization processes for each group of parameters. First, only the rate constants are optimized until convergence is reached (1st process), and then the molar absorption coefficients of all species are optimized at each wavelength, maintaining the values of the previously optimized *rate constants* invariable.

KINADGC(MW)-M2A is shown step-by-step in Scheme II

Scheme II

1. Input data (matrix of $v_{j,r}$, number of reactions, species, experimental data, matrix of $\varepsilon_{j,\lambda}$ convergence criterion (CC), etc.

2. Rate differential equations system and solution (Gear algorithm) [31,32] obtaining $[B_{j,i}]_{CALC}$

3. Calculate the absorbance $(A_{i,\lambda})_{CALC}$

4. Determinate of the $SQD^{(m)}$ function [eq.(6)]

5. AGDC(MW) ALGORITHM *(Optimization of the rate constants)*

5.1. Compute the $g^{(m)}$ and $H^{(m)}$ (Gradient vector and Hessian Matrix) [33] *(See APPENDIX)*

5.2. Compute $[H^{(m)}]^{-1}$ by Gauss elimination method and improvement by sucessive aproximations method.

5.3. Calculate the components of the vector of movement $(p^{(m)} = - (H^{(m)}{}^{-1} g^{(m)})$

5.4. Control and correction of the vector of movement $p^{(m)}$

   5.4.1. Direction of $p^{(m)}$

      5.4.1.1 If $H^{(m)}$ is singular, set $p^{(m)} = -g^{(m)}$, and go to 5.4.2
      5.4.1.2 If $p^{(m)} g^{(m)} < \delta$ (δ = scalar close to zero), set $p^{(m)} = -g^{(m)}$ and go to 5.5.2.
      5.4.1.3 If $p^{(m)}) g^{(m)} > 0$ set $p^{(m)} = -p^{(m)}$

   5.4.2. Length of $p^{(m)}$

      5.4.2.1. Compute the scalar $(\alpha^{(m)})$ by the method of Hartley
      5.4.2.2. $X^{(m+1)} = X^{(m)} + \alpha^{(m)} p^{(m)}$
      5.4.2.3. If the Goldstein-Armijo is satisfied go to 5.5.
      5.4.2.4. $\alpha^{(m)} = \alpha^{(m)} / 2$ and go to 5.4.2.2

5.5. Calculate $SQD^{(m+1)}$ from $X^{(m+1)}$ values

5.6. If convergence is not attained ($| SQD^{(m+1)} - SQD^{(m)} | > CC$), set $m = (m + 1)$ and go to 2

6. AGDC(MW) ALGORITHM *(Optimization of the molar absorption coefficients)*

6.1. Compute the $g^{(m)}$ and $H^{(m)}$ (Gradient vector and Hessian Matrix) [33] *(See APPENDIX)*

6.2. Compute $[H^{(m)}]^{-1}$ by Gauss elimination method and improvement by sucessive aproximations method.

6.3. Calculate the components of the vector of movement $(p^{(m)} = - (H^{(m)})^{-1} g^{(m)})$

6.4. Control and correction of the vector of movement $p^{(m)}$
   6.4.1. Direction of $p^{(m)}$
      6.4.1.1 If $H^{(m)}$ is singular, set $p^{(m)} = -g^{(m)}$, and go to 6.4.2
      6.4.1.2 If $p^{(m)} g^{(m)} < \delta$ (δ = scalar close to zero), set $p^{(m)} = -g^{(m)}$ and go to 6.5.2.
      6.4.1.3 If $p^{(m)}) g^{(m)} > 0$ set $p^{(m)} = -p^{(m)}$

   6.4.2. Length of $p^{(m)}$

      6.4.2.1. Compute the scalar $(\alpha^{(m)})$ by the method of Hartley
      6.4.2.2. $X^{(m+1)} = X^{(m)} + \alpha^{(m)} p^{(m)}$
      6.4.2.3. If the Goldstein-Armijo is satisfied go to 6.5.

      6.4.2.4. $\alpha^{(m)} = \alpha^{(m)} / 2$ and go to 6.4.2.2

6.5. Calculate $SQD^{(m+1)}$ from $X^{(m+1)}$ values

7. Statistic Residual Analysis.

8. END.

Comments about Scheme II. The first four steps are identical to those of Method M1 in Scheme I. The differences between Method 2A (Scheme II) ad M1 are as follows: **a)** In the elements forming the gradient vectors and Hessian matrices appearing in step 5 of Scheme II, the partial derivatives of the SQD function are in all cases defined only with respect to the rate constants, and in step 6 these derivatives are only defined with respect to the molar absorption coefficients (see APPENDIX), and **b)** Step 5 is developed iteratively (from 5.1 to 5.6) until convergence is reached whereas step 6 (from 6.1 to 6.5) does not correspond to an iterative process; instead it is executed only once in order to polish the results obtained in step 5.5.

4.3. *KINADGC(MW)-M2B version*

This version corresponds to Method 2B, in which the two optimization processes are developed independently for each group of parameters, using an alternate individual treatment that starts with the rate constants, followed by the set of molar absorption coefficients, and so on successively until convergence and optimum SQD values are reached. The KINADGC(MW)-M2B program is represented step-by-step in Scheme III

Scheme III

1. Input data (matrix of $\nu_{j,r}$, number of reactions, species, experimental data, matrix of $\varepsilon_{j,\lambda}$ convergence criterion (CC), etc.

2. Establish the rate differential equations system and its solution (Gear algorithm) [31,32] obtaining $[B_{j,i}]_{CALC}$

3. Calculate the absorbance $(A_{i,\lambda})_{CALC}$

4. Determinate of the $SQD^{(m)}$ function [eq.(6)]

5. AGDC(MW) ALGORITHM *(Optimization of the rate constants)*

   5.1. Compute the $\boldsymbol{g}^{(m)}$ and $\boldsymbol{H}^{(m)}$ (Gradient vector and Hessian Matrix) [33] *(See Appendix)*

   5.2. Compute $[\boldsymbol{H}^{(m)}]^{-1}$ by Gauss elimination method and improvement by sucessive aproximations method.

   5.3. Calculate the components of the vector of movement $(\boldsymbol{p}^{(m)} = -(\boldsymbol{H}^{(m)})^{-1}\boldsymbol{g}^{(m)})$

   5.4. Control and correction of the vector of movement $\boldsymbol{p}^{(m)}$

      5.4.1. Direction of $\boldsymbol{p}^{(m)}$

5.4.1.1 If $H^{(m)}$ is singular, set $p^{(m)} = - g^{(m)}$, and go to 5.4.2

5.4.1.2 If $p^{(m)} g^{(m)} < \delta$ (δ = scalar close to zero), set $p^{(m)} = - g^{(m)}$ and go to 5.5.2.

5.4.1.3 If $p^{(m)}) g^{(m)} > 0$ set $p^{(m)} = - p^{(m)}$

5.4.2. Length of $p^{(m)}$

5.4.2.1. Compute the scalar ($\alpha^{(m)}$) by the method of Hartley

5.4.2.2. $X^{(m+1)} = X^{(m)} + \alpha^{(m)} p^{(m)}$

5.4.2.3. If the Goldstein-Armijo criterion is satisfied go to 5.5.

5.4.2.4. $\alpha^{(m)} = \alpha^{(m)} / 2$ and go to 5.4.2.2

6. AGDC(MW) ALGORITHM (*Optimization of the molar absorption coefficients*)

6.1. Compute the $g^{(m)}$ and $H^{(m)}$ (Gradient vector and Hessian Matrix) [33] *(See Appendix)*

6.2. Compute $[H^{(m)}]^{-1}$ by Gauss elimination method and improvement by sucessive aproximations method.

6.3. Calculate the components of the vector of movement $(p^{(m)} = -(H^{(m)})^{-1} g^{(m)})$

6.4. Control and correction of the vector of movement $p^{(m)}$

6.4.1. Direction of $p^{(m)}$

6.4.1.1 If $H^{(m)}$ is singular, set $p^{(m)} = - g^{(m)}$, and go to 6.4.2

6.4.1.2 If $p^{(m)} g^{(m)} < \delta$ (δ = scalar close to zero), set $p^{(m)} = - g^{(m)}$ and go to 6.5.2.

6.4.1.3 If $p^{(m)}) g^{(m)} > 0$ set $p^{(m)} = - p^{(m)}$

6.4.2. Length of $p^{(m)}$

6.4.2.1. Compute the scalar ($\alpha^{(m)}$) by the method of Hartley

6.4.2.2. $X^{(m+1)} = X^{(m)} + \alpha^{(m)} p^{(m)}$

6.4.2.3. If the Goldstein-Armijo criterion is satisfied go to 6.5.

6.4.2.4. $\alpha^{(m)} = \alpha^{(m)} / 2$ and go to 6.4.2.2

6.5 Calculate $SQD^{(m+1)}$ from $X^{(m+1)}$ values

6.6 If convergence is not attained ($| SQD^{(m+1)} - SQD^{(m)} | > CC$), set $m=(m + 1)$ and go to 2

7. Statistic Residual Analysis.

8. END

Comments about Scheme III. The first four steps are identical to those appearing in both Schemes I and II, corresponding to methods M1 and M2A. The differences between Method M2B (SCHEME III) and the others are as follows: *a)* The elements composing the gradient vectors and Hessian matrices in step 5 correspond to the partial derivatives of SQD with

respect to the rate constants whereas in step 6 the partial derivatives of these vectors and matrices are defined with respect to the molar absorption coefficients (Appendix) and *b)* Neither of the steps corresponds to an iterative process since –as may be seen from Scheme III- there is no final stage in which two consecutive SQD values are compared. The sequence of execution of these steps is alternate and consecutive until convergence is reached in step 6.6.

The computational work has been performed using Matlab [34] for the design and performing of the specific computational executable programs (##.m type) using "M" language for the main program, functions and subroutines according to the algorithms of the different mathematical optimization methods considered in the present work. We have a previous version written in FORTRAN which uses for their compilation the SVS C^3 (Silicon Valley Systems) compiler with a source program constituted by more than 1000 lines and the executable application has a size of 330 KB and can be executed in DOS.

5. Results and Discussion

The mechanism chosen to perform the present study comprises 2 consecutive first-order reactions in which the kinetic data measured at three wavelengths are computed. The model is very versatile and its range of applications fairly broad since it appears quite often both in the field of Chemical Kinetics and in other fields (Compartmental model, Chemical Engineering, etc).

$$B_1 \xrightarrow{\;k_{12}\;} B_2 \xrightarrow{\;k_{23}\;} B_3$$
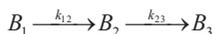
The study consisted in applying the different optimization methods proposed here to a set of synthetic data in which noise within the range of experimental noise was imposed. We performed several experiments in which we applied the different optimization methods to experimental data on total Absorbance/time, starting out from different initial estimates for the parameters to be optimized. We systematically varied the magnitudes affecting the process with a view to assaying as broad a range as possible and determining, by means of the corresponding comparative studies, the individual effect of each of the variables involved in the optimization process used by each method. We also assayed the behavior of the application of the different methods under the most and least favorable conditions in which the optimization process was implemented, then comparing the results obtained in each case. The values of the kinetic parameters that served to generate the data were $k_{12} = 1.0$ h^{-1} and $k_{23} = 0.5$ h^{-1} and those of the molar absorption coefficients are shown in **Table I**.

Table 1

	$\varepsilon(B_1)/mol^{-1}Lcm^{-1}$	$\varepsilon(B_2)/mol^{-1}Lcm^{-1}$	$\varepsilon(B_3)/mol^{-1}Lcm^{-1}$
λ_1	1200	1100	1600
λ_2	1400	1200	700
λ_3	1700	900	500

The experiments performed and the results obtained are shown in **Table 2**, which has been split into three parts corresponding to each of the methods applied, each of the columns corresponding to each experiment performed. The different rows show the values of the initial estimates of the parameters to be optimized, the final values and that corresponding to the sum of quadratic deviations (SQD) function (SQD_{FINAL}).

Method 1(M1) (Exp.1.) The values used for the *initial estimates* of the rate constants (k_{12} and k_{23}) were almost double those that served to generate the data (100% deviation). However, the values of the initial estimates of the molar absorption coefficients of the three species at three wavelengths were very close to the true values (deviation around $\pm0.5\%$). Despite this, the values of the molar absorption coefficients were not modified along the optimization process and the optimized values of the rate constants proved to be appreciably different from those used to generate the data. The Hessian matrix was singular in all iterations and the vector of movement follows always Steepest Descent direction. Moreover, the value of SQD_{FINAL} was unacceptable since its order of magnitude was 10^{-1}, indicating a much higher mean error for each of the data computed than the experimental error. From this it may be concluded that application of Method M1 affords result that are very divorced from reality and hence unacceptable owing to the complete failure of the process of optimizing the 11 parameters when performed jointly and simultaneously.

Table 2

Parameter Values	Method 1 (M1)			Method 2.A (M2A)			Method 2.B (M2B)	
	Exp. 1	Exp. 2	Exp. 3	Exp. 4	Exp. 5	Exp. 6	Exp. 7	Exp. 8
Init.estimates k_{12}	2.0	1.1	1.1	0.10	0.10	0.10		0.9
Init.estimates k_{23}	1.0	0.4	0.4	0.05	0.05	0.05	0.6	0.6
Init. estimates $\varepsilon(B_1)\lambda_1$	1205 1395	1250 –	1500 –	1205 1395	1500 1200	1225 1375	1205 1395	1250 –

$\varepsilon (B_1) \lambda_2$ $\varepsilon (B_1) \lambda_3$	1695	–	–	1695	1600	1715	1695	–
Init. estimates $\varepsilon (B_2) \lambda_1$	1095	1050	1400	1095	1400	1110	1095	1050
$\varepsilon (B_2) \lambda_2$	1195	–	–	1195	1400	1180	1195	–
$\varepsilon (B_2) \lambda_3$	905	–	–	905	1000	915	905	–
Init. estimates $\varepsilon (B_3) \lambda_1$	1605	1700	1900	1605	1900	1375	1695	1700
$\varepsilon (B_3) \lambda_2$	705	–	–	705	500	710	705	–
$\varepsilon (B_3) \lambda_3$	505	–	–	505	700	510	505	–
Optimized k_{12}	1.706	1.097	0.966	1.006	1.626	1.028	1.114	0.948
Optimized k_{23}	0.320	0.376	0.024	0.499	0.248	0.508	0.479	0.378
Optimized $\varepsilon (B_1) \lambda_1$	1205	1250	1500	1200	1195	1202	1205	1185
$\varepsilon (B_1) \lambda_2$	1395	–		1397	1428	1387	1398	–
$\varepsilon (B_1) \lambda_3$	1695	–		1700	1772	1707	1707	–
Optimized $\varepsilon (B_2) \lambda_1$	1095	1050	1400	1099	1138	1095	1095	1142
$\varepsilon (B_2) \lambda_2$	1195	–		1198	1227	1195	1230	–
$\varepsilon (B_2) \lambda_3$	905	–		904	1062	918	979	–
Optimized $\varepsilon (B_3) \lambda_1$	1605	1700	1900	1599	1735	1595	1598	1654
$\varepsilon (B_3) \lambda_2$	705	–		702	521	707	697	–
$\varepsilon (B_3) \lambda_3$	505	–		499	265	505	487	–
SQD_{FINAL}	0.91E-1	0.35E-2	0.276	0.26E-4	0.46E-2	0.76E-3	0.48E-4	0.16E-3

Method 1(M1) (Exp. 2). Faced with the negative results obtained in Exp. 1, we tested a lower number of parameters, considering a single wavelength and starting the process with values of the *initial estimates* closer to the true values (Exp. 2). The results showed that the molar absorption coefficients remained unaltered along the optimization process and that the values of the rate constants underwent only slightly significant changes

Method 1 (M1) (Exp. 3). This experiment was undertaken to assess the influence of the deviations in the values of the initial estimate in the case of the molar absorption coefficients. We started out from the values of the *initial estimates* of the molar absorption coefficients that were most different from the real ones, maintaining the same values of the initial estimates as those used in Exp. 2. The results obtained were similar to those of the previous case because the molar absorption coefficient values did not vary significantly and the corresponding optimized values of the rate constants were appreciably different from the real values.

Method 2A (M2A) (Exp. 4). In this case, we started out with values of the *initial estimates* of the rate constants that were very distant from the correct values, while a deviation of ±5 units was imposed on the values of the molar absorption coefficients. The optimized values of the rate constant proved to be very close to the correct values (6/1000 and 7/50000) and were acceptable since they had an error of 0.6%. In turn, the values of the molar absorption coefficients (of all the chemical species at all wavelengths) were modified along the process, following an asymptotic trend towards the true values . The value of the SQD_{FINAL} function was 2.5 x 10^{-5}, which implies a mean error for each of the data of 1.5 x 10^{-4}, similar to the experimental error imposed (*noise*) and hence acceptable.

Method 2A (M2A) (Exp.5). In this experiment, we maintained the values of the initial estimates of the rate constants used in Exp 4, attributing very different (with respect to the real ones) values to the molar absorption coefficients. This represents the opposite case to Exp 4. Values very different from the real values were obtained for the optimized constants and in the case of the molar absorption coefficients we obtained incorrect values that afforded a very high value for the SQD_{FINAL} function, which was unacceptable.

Method 2A(M2A) (Exp. 6). Here we started out with rate constant values that departed strongly from the real ones by imposing a deviation of ±2% on the molar absorption coefficients. The results of the optimization gave values of the rate constants with errors of the order of 3/100 and 9/50, although the results obtained were better than those obtained in Exp 5 for the optimized values of the molar absorption coefficients. The final value of the SQD_{FINAL} function was 7.5 x 10^{-4}, implying a mean error of 2.2 x 10^{-3} units of absorbance.

Method 2B (M2B) (Exp. 7). The initial estimates of both the rate constants and of the molar absorption coefficients were close to the values that were used to generate the absorbance data. However, the optimized values of the rate constants proved to be unacceptable and the values of the molar absorption coefficients did not vary ostensibly along the development of the process. Additionally, the value of SQD_{FINAL} remained unaltered along the process, pointing to the failure of the optimization process when M2B is applied individually

Method 2B (M2B) (Exp. 8). In view of the failures obtained in the previous experiments, we imposed very favorable starting conditions on the initial estimates in order to facilitate the optimization when applying Method 2B (values very close to the real ones for the initial estimates of the rate constants at a single wavelength). Despite such favorable conditions, the optimized values of the rate constants were different from the real ones, affording a SQD_{FINAL} value that was too high.

6. Conclusions

Upon the analysis of the results of the experiments shown in Table 2, where the optimization methods are applied individually (M1, M2A and M2B) we observed that the values of the optimized parameters and the analysis of Residuals (step 7 of Schemes I, II and III) prove to be slightly poor. Nevertheless, these results were substantially improved (Table 3) when the combining of the three optimization methodologies [KINAGDC(MW)-COMB] is applied sequentially, that is, when the optimized parameters determined by each one of the methods are taken like the set of the initial estimates of the next method to be applied to the objective function. The values of the optimized parameters shown in Table 3 (k and ε), obtained after application of the combining method, present errors less than 1% in all cases and the obtained value of the SQD_{FINAL} (0.52 E-5) is of one order of magnitude lower than the best value (0.48 E-4) determined in the cases of individual applications of each single method (M1, M2A and M2B).

Table 3

Parameter Values	Initial Estimates	Optimized Combining Approach: [KINADGC(MW) –COMB]
k_{12}	2.0	1.01
k_{23}	1.0	0.497
$\varepsilon\ (B_1)\ \lambda_1$	1225	1205
$\varepsilon\ (B_1)\ \lambda_2$	1375	1393
$\varepsilon\ (B_1)\ \lambda_3$	1715	1715
$\varepsilon\ (B_2)\ \lambda_1$	1110	1100
$\varepsilon\ (B_2)\ \lambda_2$	1180	1194
$\varepsilon\ (B_2)\ \lambda_3$	915	909
$\varepsilon\ (B_3)\ \lambda_1$	1375	1595
$\varepsilon\ (B_3)\ \lambda_2$	710	701
$\varepsilon\ (B_3)\ \lambda_3$	510	497
SQD_{FINAL}	0.91E-1	0.52 E-5

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Appendix

$$\mathbf{g} = \begin{pmatrix} \sum_i^{Nt} \sum_j^{Nw} \frac{\partial f_{i,j}}{\partial k_1} RES_{i,j} \\ \vdots \\ \sum_i^{Nt} \sum_j^{Nw} \frac{\partial f_{i,j}}{\partial k_n} RES_{i,j} \\ \sum_i^{Nt} c_{i,1} RES_{i,1} \\ \vdots \\ \vdots \\ \sum_i^{Nt} c_{i,Ns} RES_{i,Nl} \end{pmatrix}$$

Gradient vector of Method 1

$$H = \begin{pmatrix} \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_1} \right)^2 & \cdots & \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_1} \right) \left(\frac{\partial f_{i,j}}{\partial k_n} \right) & \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_1} \right) c_{i,1} & \cdots & \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_1} \right) c_{i,Ns} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_n} \right) \left(\frac{\partial f_{i,j}}{\partial k_1} \right) & \cdots & \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_n} \right)^2 & \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_n} \right) c_{i,1} & \cdots & \sum_i^{Nt} \sum_j^{Nw} \left(\frac{\partial f_{i,j}}{\partial k_n} \right) c_{i,Ns} \\ \sum_i^{Nt} \sum_j^{Nw} c_{i,1} \left(\frac{\partial f_{i,j}}{\partial k_1} \right) & \cdots & \sum_i^{Nt} \sum_j^{Nw} c_{i,1} \left(\frac{\partial f_{i,j}}{\partial k_n} \right) & \sum_i^{Nt} c_{i,1}^2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \sum_i^{Nt} \sum_j^{Nw} c_{Ns,1} \left(\frac{\partial f_{i,j}}{\partial k_1} \right) & \cdots & \sum_i^{Nt} \sum_j^{Nw} c_{Ns,1} \left(\frac{\partial f_{i,j}}{\partial k_n} \right) & 0 & \cdots & \sum_i^{Nt} c_{Ns,1}^2 \end{pmatrix}$$

Hessian matrix of Method 1

$$\mathbf{g}_k = \begin{pmatrix} \sum_i^{Nt} \sum_j^{Nw} \frac{\partial f_{i,j}}{\partial k_1} RES_{i,j} \\ \sum_i^{Nt} \sum_j^{Nw} \frac{\partial f_{i,j}}{\partial k_2} RES_{i,j} \\ \vdots \\ \vdots \\ \sum_i^{Nt} \sum_j^{Nw} \frac{\partial f_{i,j}}{\partial k_n} RES_{i,j} \end{pmatrix}$$

Gradient vector of rate constants (Methods 2A and 2B)

$$\mathbf{H}_k = \begin{pmatrix} \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_1}\right)^2 & \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_1}\right)\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_2}\right) & \cdots & \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_1}\right)\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_n}\right) \\[4mm] \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_2}\right)\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_1}\right) & \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_2}\right)^2 & \cdots & \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_2}\right)\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_n}\right) \\[2mm] \vdots & \vdots & \vdots & \vdots \\[2mm] \vdots & \vdots & \vdots & \vdots \\[2mm] \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_n}\right)\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_1}\right) & \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_n}\right)\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_2}\right) & \cdots & \sum_i^{Nt}\sum_j^{Nw}\left(\dfrac{\partial\, f_{i,j}}{\partial\, k_n}\right)^2 \end{pmatrix}$$

Hessian matrix of rate constants (Methods 2A and 2B)

$$\mathbf{g}_\varepsilon = \begin{pmatrix} \sum_i^{Nt} c_{i,1}\; RES_{i,1} \\[3mm] \sum_i^{Nt} c_{i,2}\; RES_{i,2} \\[2mm] \vdots \\[2mm] \vdots \\[2mm] \sum_i^{Nt} c_{i,Ns}\; RES_{i,Ns} \end{pmatrix}$$

Gradient vector of absorption molar coefficients (Methods 2A and 2 B)

$$\mathbf{H}_\varepsilon = \begin{pmatrix} \sum_i^{Nt} c_{i,1}^2 & \sum_i^{Nt} c_{i,1}\, c_{i,2} & \cdots & \sum_i^{Nt} c_{i,2}\, c_{i,Ns} \\[3mm] \sum_i^{Nt} c_{i,2}\, c_{i,1} & \sum_i^{Nt} c_{i,2}^2 & \cdots & \sum_i^{Nt} c_{i,2}\, c_{i;Ns} \\[2mm] \vdots & \vdots & \vdots & \vdots \\[2mm] \vdots & \vdots & \vdots & \vdots \\[2mm] \sum_i^{Nt} c_{i,Ns}\, c_{i,1} & \sum_i^{Nt} c_{i,Ns}\, c_{i,2} & \cdots & \sum_i^{Nt} c_{i,Ns}^2 \end{pmatrix}$$

Hessian matrix of absorption molar coefficients (Methods 2A and 2B)