

# A generalized Fisher equation and its utility in chemical kinetics

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**Abstract:** A generalized Fisher equation (GFE) relates the time derivative of the average of the intrinsic rate of growth to its variance. The GFE is an exact mathematical result that has been widely used in population dynamics and genetics, where it originated. Here we demonstrate that the GFE can also be useful in other fields, specifically in chemistry, with models of two chemical reaction systems for which the mechanisms and rate coefficients correspond reasonably well to experiments. A bad fit of the GFE can be a sign of high levels of measurement noise; for low or moderate levels of noise, fulfillment of the GFE is not degraded. Hence, the GFE presents a noise threshold that may be used to test the validity of experimental measurements without requiring any additional information. In a different approach information about the system (model) is included in the calculations. In that case, the discrepancy with the GFE can be used as an optimization criterion for the determination of rate coefficients in a given reaction mechanism.

## I. Introduction

In 1930 Fisher (1) proposed an equation for population dynamics that relates the time derivative of the average of the intrinsic rate of growth of the different alleles (or species) to its variance. It has become known as the fundamental law of population genetics. In 2005 we suggested (2) that a generalization of this equation may be valid in a variety of other fields including chemical kinetics.

Fisher information, a related subject, has been used in a study of the electron density distribution in position and momentum space for determining the transition state trajectory in simple chemical reactions (3). For other generalizations of the Fisher equation, see refs. 2-10 in (2), and for an extensive treatment of Fisher information as a basis of theoretical physics see (4).

The generalized form of Fisher equation (GFE) holds for temporal functions which are different from zero (for chemical reaction systems this means strictly positive) with continuous second-order derivatives. These Fisher equations are exact results, which are independent of the detailed kinetics of the process: they are valid whether the evolution equations are linear or nonlinear, local or nonlocal in space and or time (2). Here we show that the GFE can be useful in chemical kinetics. This is tested with two chemical

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reaction systems, for which both the reaction mechanism and the rate coefficients are reasonably well known and correspond to experiments. The use of the GFE is new for chemical kinetics, a subject used in many fields other than chemistry, such as biology, biotechnology, chemical engineering, materials science, etc.

In the section “Generalized form of the Fisher equation” we define the notation to write the GFE as in (5). Then, in “Use of the GFE for testing experimental measurements” we discuss the effect of noise.

If the agreement with the GFE is calculated using experimentally measured concentrations—or concentrations generated with a nominal model—and rates of growth analytically calculated with a set of rate coefficients, the fit to the GFE depends on the values of these rates coefficients. For a given reaction system, optimal rate coefficients yield minimum deviation from the GFE. Hence the GFE can be used as a general criterion in optimization procedures, such as genetic algorithms, simulated annealing, or scatter search, for the determination of rate coefficients. This is explored in “Application of the GFE to the determination of the optimal set of rate coefficients of a reaction mechanism”, with an analysis of the sensitivity to changes in rate coefficients.

For systems for which we know only the reactant species: reactants, intermediates and products, we first need to guess, or determine, reaction pathways, and the reaction mechanisms, that is the sequence of elementary reaction steps that lead from reactants to products. Various methods, such as correlation metric construction, temporal dependence of responses to external perturbations, and methods for oscillatory reaction systems, have been presented in earlier work (6). Once this is accomplished then the Fisher equation can be applied as indicated in the prior paragraphs.

## II. Generalized form of the Fisher Equation (GFE)

We consider only temporal not spatial processes (2). In order to write down the GFE we need to define several terms. The temporal evolution of the concentration of species  $u$  at time  $t$  is  $x_u(t)$ , and the fraction of each species is:

$$f_u(t) = \frac{x_u(t)}{\sum_{u=1}^N x_u(t)} \quad [1]$$

where  $N$  is the total number of species, and  $\sum_{u=1}^N f_u(t) = 1$ . The intrinsic rate of growth is defined by:

$$r_u(t) = \frac{1}{x_u(t)} \frac{dx_u(t)}{dt} \quad [2]$$

which gives for the rate of growth averaged over all the species:

$$\overline{r(t)} = \sum_{u=1}^N r_u(t) \gamma_u(t) \quad [3]$$

and for the variance of the intrinsic rate of growth:

$$\overline{\Delta r^2(t)} = \sum_{u=1}^N [(r)_u(t) - \overline{r(t)}]^2 \gamma_u(t) \quad [4]$$

The average of the derivatives of the rates of growth is:

$$\overline{\frac{dr_u(t)}{dt}} = \sum_{u=1}^N \frac{dr_u(t)}{dt} \gamma_u(t) \quad [5]$$

With these definitions we can write the GFE:

$$\frac{d\overline{r(t)}}{dt} = \overline{\Delta r^2(t)} + \overline{\frac{dr_u(t)}{dt}} \quad [6]$$

The derivation of the GFE for population genetics is due to Nagylaki (5) and is reproduced in (2). If the intrinsic rates of growth are constant (which in chemical kinetics happens only for first and zero order reactions) then the last term in the GFE is zero and

we return to the original Fisher equation,  $\frac{d\overline{r}}{dt} = \overline{\Delta r^2} > 0$ . This results in the condition that the average fitness of the population always grows. This equation has a clear physical meaning: the larger the variance (diversity), the larger the increase in the average fitness.

For chemical reactions the sum over  $u$  in the equations above is a sum over the chemical species varying in time in the reacting system. All the terms of the Fisher equation are zero for systems in a stationary state, for which the concentrations of all intermediates are constant.

It should be noticed that almost no assumptions are required for the equation to hold: the  $x_u(t)$  only need to be different from zero (for chemical concentrations this means strictly positive), with continuous second-order derivatives.

### III. Use of the GFE for testing experimental measurements

Given a reaction mechanism, a model, for a particular reaction, and rate coefficients as determined from experiments, we can calculate all the terms in GFE (Eq. 6). Theoretically, there is a perfect equivalence between the two sides of the equation; in practice, however, when performing the calculations a difference may appear due to numerical errors. We will illustrate this with two examples: the Citri-Epstein model of the chlorite-iodide reaction (7) and the so-called Oregonator model of the Belousov-

Zhabotinskii reaction (8). The detailed reactions and parameters of these models are given in Tables I and II.

In order to evaluate the level of difference that is reasonable to expect between the two sides of the GFE, we compare them by means of two measures: a relative distance between them, and a correlation coefficient. We define the relative distance,  $d$ , as:

$$d = \frac{\int_{t_1}^{t_2} |s_1(t)^2 - s_2(t)^2| dt}{\int_{t_1}^{t_2} (s_1(t)^2 + s_2(t)^2) dt} \quad [7]$$

where  $s_1(t)$  and  $s_2(t)$  are the left and the right-hand sides of the GFE equation. This indicator measures the relative difference between both sides, and it can have values between 0 (when both sides are identical) and 1 (when they are very different). Another possible measure is Pearson's correlation coefficient (9), which gives the quality of the fit of one side of the equation to the other, and is defined as:

$$\rho = \frac{\sum_{l=1}^n (s_1(l) - \bar{s}_1)(s_2(l) - \bar{s}_2)}{\sqrt{\sum_{l=1}^n (s_1(l) - \bar{s}_1)^2} \sqrt{\sum_{l=1}^n (s_2(l) - \bar{s}_2)^2}} \quad [8]$$

where  $n$  is the total number of samples. In this case,  $\rho$  is 1 if both sides are equal; hence, in order to use two easily comparable measures we will make use of  $d$  and  $(1-\rho)$ .

By numerically integrating the dynamic equations of the models, we obtain a time series of the concentrations  $x_n(t)$ . Alternatively, these time series can be obtained directly from experimental data. From these concentrations, the terms in equations 1-5 can be calculated by using numerical differentiation when needed, and the GFE (Eq. 6) can be evaluated. In order to test the accuracy of the computations the left and right-hand sides of the GFE are plotted in Figs. 1 and 2, which show a good match for both the Oregonator and the Chlorite-Iodide system. The results of expressions 7-8 are as follows: for the Chlorite-Iodide,  $d = 1.1357 \cdot 10^{-5}$  and  $(1-\rho) = 7.9605 \cdot 10^{-12}$ ; and for the Oregonator,  $d = 6.80 \cdot 10^{-2}$  and  $(1-\rho) = 1.9028 \cdot 10^{-5}$ . In both cases the two measures—the relative distance and the Pearson correlation coefficient, subtracted from one—give very good agreement with the prediction of the Fisher equation. The small deviations from zero are due to numerical errors, which are larger for the Oregonator due to the strongly stiff character of its dynamical equations (this may be due in part to the fact that the range of values of the rate coefficients in the Oregonator extend over a much larger range than they do in the Chlorite-Iodide system). The deviations from zero may be reduced if the derivatives are analytically calculated, in which case these values are, for the Chlorite-Iodide:  $d = 1.5373 \cdot 10^{-6}$ ,  $(1-\rho) = 3.6413 \cdot 10^{-11}$ ; and, for the Oregonator:  $d = 1.19 \cdot 10^{-2}$ ,  $(1-\rho) = 4.9326 \cdot 10^{-6}$ . We have included the values obtained with numerical differentiations for two reasons: first, they can be calculated even if no model of the system is available; and second, to give an idea of the level of difference that is reasonable to expect in that case.

The terms of the GFE can be calculated from the data obtained by numerical integration of the kinetic equations. This yields a discrete set of time series and the derivatives must be approximated by means of a numerical method. Different sets of rate coefficients, as well as control parameters, may change the time series obtained from

numerical integration, but the GFE always holds. When differences on the computation of left and right hand sides of the GFE are found, they are due to numerical errors in the calculation of the derivatives.

Suppose now that in the modeling of a reaction mechanism, one or several of the actually involved species have been left out. Or consider a different possibility: that, although all of the species have been included in the mechanism, not all of them have been considered (i.e. measured) in a certain experiment. In both cases the GFE holds, despite the fact that there are some species missing from the calculations. This also applies to the case in which there are fixed measurement errors; this is, when some of the concentrations  $x_u(t)$  are affected by a multiplicative or additive bias.

Measurement noise, however, may spoil the fit of the GFE. Let  $x_u(t)$  be the real concentration and assume that its measure,  $\tilde{x}_u(t)$ , is affected by heteroscedastic noise (13) following a normal distribution. The measurement value is:

$$\tilde{x}_u(t) = x_u(t) + \Delta x_u(t) \quad [9]$$

where the error  $\Delta x_u(t)$  is a normally distributed random variable, with zero mean and a standard deviation consisting of a fixed and a proportional term:

$$\sigma = r_1 x_u(t) + r_2 \quad [10]$$

In order to show the magnitude of the effect of noise, we can introduce it in the simulations and calculate the agreement with the GFE for different values of  $(r_1, r_2)$ . In Fig. 3 we plot the correlation between  $r_1$  and the relative distance  $d$ , for the Chlorite-Iodide and Oregonator. For simplicity,  $r_2$  has been fixed to  $10^{-13}$  for the former case and  $10^{-15}$  for the latter. It can be noticed that for low or moderate noise levels the agreement with the GFE is still good, which means that the Fisher-related calculations have some degree of robustness. This agreement is gradually spoiled as  $r_1$  increases; the threshold may be considered to be approximately of the order of 10% of the nominal concentrations. Hence, the disagreement with the GFE can be taken a sign of the existence of measurement noise. This Fisher's noise-threshold represents the limit of validity of the measured data and it is of universal application.

#### IV. Application of the GFE to the determination of the optimal set of rate coefficients of a reaction mechanism

**A. Use of dynamical models for calculation of the GFE.** Let us suppose first that we are given a time series of concentrations,  $x(t)$ , which can be obtained from experiments. As in the previous section, the terms of the GFE can be obtained by numerically differentiating these concentrations in order to calculate Eqs. 2-5. Since no additional information is required, these calculations can always be carried out.

Now let us suppose that, additionally, we have a model of the reaction mechanism. This means we have a set of dynamical equations expressing the time derivatives of the concentrations as a function of the concentrations and the rate coefficients,

$\frac{dx(t)}{dt} = f(k^*, x)$ , where the  $k^*$  are the nominal values of the rate coefficients. If these nominal values are known, it is possible to calculate the time derivatives of the concentrations analytically. However, if instead of the nominal values,  $k^*$ , we use an estimation of them,  $k^e$ , the estimated derivatives,  $\frac{dx^e(t)}{dt}$ , will differ from the real ones:

$$\frac{dx^e(t)}{dt} = f(k^e, x) \neq \frac{dx(t)}{dt} = f(k^*, x) \quad [11]$$

The mismatch between both sets of derivatives increases with the mismatch between nominal and estimated rate coefficients: if both sets are equal, the mismatch will be zero; if they are very different, the mismatch will be large.

With the estimated derivatives,  $\frac{dx^e(t)}{dt}$ , and the given experimental concentrations,  $x(t)$ , we can calculate the estimated rates of growth (Eq. 2), as well as their average (Eq. 3) and variance (Eq. 4). Then the left-hand side (LHS) of the GFE (Eq. 6) can be obtained by direct numerical differentiation of the average rate of growth. As for the right-hand side (RHS) of the GFE, it consists of the sum of two terms. The first one is the variance, which has already been calculated. And the second term is the average of the derivative of the rates of growth, which may be obtained as in Eq. 5 by numerical differentiation.

If all of its terms are correctly calculated the GFE holds (LHS = RHS). However, if there is a mismatch in the derivatives, the GFE presents a mismatch between its left-hand and right-hand sides (LHS  $\neq$  RHS). Therefore, if all the terms in the GFE are calculated with the experimental concentrations,  $x(t)$ , and the analytical derivatives,  $\frac{dx^e(t)}{dt}$ , this presents a mismatch unless the estimation of the rate coefficients matches the nominal values. From the point of view of optimization, this is an inverse problem, similar to most parameter estimation problems arising in dynamic systems modeling (10). The expected discrepancy can be used to construct an optimization criterion for the inverse problem, as it will be shown in “Fisher-based optimization procedure for determining the rate coefficients”. First we comment the degree of discrepancy that is reasonable to expect when the rate coefficients are changed as explained.

**B. System identifiability and parameter sensitivities.** Let us calculate the time derivatives of the concentrations analytically, as explained in the previous paragraph. We change the value of one of the rate coefficients to 90% of its nominal value, and keep the remaining rate coefficients at their nominal values. Then we calculate the degree of disagreement of both sides of the GFE by means of the two measures defined in Eqs. 7-8. By repeating this process for all of the rate coefficients, we obtain a table showing how much the agreement is affected by a 10% change in each of the rate coefficients.

These results are presented in Table III for the Chlorite-Iodide and Oregonator. Two conclusions can be extracted from this table. The first is that the Chlorite-Iodide model is more sensitive to changes in its parameters (i.e. rate coefficients) than the Oregonator. The second is that both models are quite sensitive to changes in some rate coefficients (for example,  $k_1$ - $k_6$  for the Chlorite-Iodide), and much less sensitive to changes in the rest. This coincides with the fact that, in the literature, different values for  $k_7$ - $k_{10}$  have been reported, sometimes—for example for  $k_8$ —different by several orders of magnitude.

The reason is that even large changes in these rate coefficients have very little influence in the system's "output" (be it the species concentrations or the terms in the GFE).

As a conclusion, in the two considered models there are identifiability issues that can prevent some of the rate coefficients from being determined accurately by any method.

**C. Fisher-based optimization procedure for determining the rate coefficients.** We have observed substantial variation of the fit of the GFE with variations of the rate coefficients in the reaction models, as described in the previous subsection. This fact allows the suggestion that the mismatch of the GFE may be used as a criterion in an optimization procedure to find the optimal values of the rate coefficients.

Thus, the objective function to minimize in the optimization procedure is the relative distance between both sides of the GFE,  $d$  (Eq. 7). For this purpose, the terms in the GFE are calculated as explained in the section "Use of dynamical models for calculation of the GFE".

The task of finding the set of rate coefficients that minimizes  $d$  constitutes a highly nonlinear, multimodal problem that must be solved with a global optimization method such as genetic algorithms, simulated annealing, or others. In the last decade, several genetic algorithms have been proposed for finding the optimal set of rate coefficients for reduced models of reaction mechanisms (11). In those formulations, the optimization problem entails the evaluation of an objective function which compares predicted and measured species concentrations. This means that the model equations must be integrated for each set of rate coefficients under evaluation, and then an objective function is constructed which measures the difference between the experimental results and those obtained from the model. In our approach, however, we do not compare experimental and predicted concentrations, but use the GFE instead as our general optimization criterion.

We have chosen an evolutionary algorithm, the scatter search-based metaheuristic presented in (12,13), which compares favorably to other techniques. For both models, the search is conducted simultaneously for the 10 rate coefficients, for which only a rough knowledge of their values is assumed: the upper and lower bounds of these parameters span 2 orders of magnitude.

We applied the proposed method to the Chlorite-Iodide model, using a computer with an Intel Xeon Quad-core processor (2.50 GHz, 3GB/core) in a Matlab environment. The values of the rate coefficients obtained after 1 hour are given in Table IV. The difference between  $k_1-k_6$ , on the one hand, and  $k_7-k_{10}$ , on the other, is clear. As is shown in Table III, the system is highly sensitive to changes in  $k_1-k_6$ ; hence, these coefficients can be identified with precision. Conversely, changes in  $k_7-k_{10}$  have almost no influence in the system, so they are difficult to estimate. The parameters can be determined with much more precision if we make the reasonable assumption that the value of at least one coefficient (say  $k_1$ ) is known. In that case, we can modify the initial estimation of the

coefficients,  $k_i^0$ , and obtain a scaled version as  $k_i^s = k_i^0 \frac{k_1}{k_1^0}$ . Then we calculate the percentage error of each scaled parameter ( $PE_i$ ) with respect to the respective nominal value,  $k_i^s$ , as:

$$Pe_i = 100 \frac{k_i^e \frac{k_i}{k_i^e} - k_i}{k_i} = 100 \frac{\frac{k_i^e}{k_i^e} - \frac{k_i}{k_i}}{\frac{k_i}{k_i}} \quad [12]$$

If we do so, the relative error in the estimation of  $k_2-k_6$  (last column in Table IV) is between 0.1% and 4.2%. As for  $k_7-k_{10}$ , the errors are larger and may be of an order of magnitude. These are reasonable values, since these differences do not alter significantly the system behavior. Furthermore, in the literature it is possible to find estimations of some of these parameters that differ by several orders of magnitude.

Analogous results for the Oregonator are shown on Table V. They were obtained in 22 minutes; a more refined estimation may be achieved with longer running times.

If several rate coefficients are known, the time needed for obtaining a good estimate of the remaining ones is reduced. For example, if only  $k_1, k_2, k_3$  in the Oregonator have to be found, an estimation with the respective errors of 3%, 1%, and 7% is obtained in approximately 1 minute. Or, if only  $k_1$  has to be found, an estimation with an error smaller than 1% is obtained in a few seconds. It should also be noticed that quite large bounds have been allowed for the rate coefficient values. If it is possible to tighten these bounds due to a better prior knowledge of the reasonable range of values, the computation time is reduced accordingly.

All the optimization results obtained with the scatter search-based metaheuristic were cross-checked by solving the same problems with another competitive global optimization method, the GLOBALm algorithm (14). This method arrived to the same results but with a further significant reduction in computation time, up to one order of magnitude. Thus, all the computations described in this study can be carried out in a few minutes in standard low cost personal computers.

## V. Discussion

We believe the present work to be a useful contribution to the analysis and structure of chemical kinetics. All the terms in the GFE can be computed from the time series of concentrations of a given reaction system, that can be calculated from deterministic equations or measured from experiments.

The GFE holds for subsystems of reaction systems with fewer than all reacting species. Disagreement with that applicability is a good indication of problems with the measurements or the computations. Especially significant is the sensitivity of the GFE to noisy data. The GFE presents a *noise threshold*, which represents the limit of the validity of the experimental data with universal application.

The deviation of the GFE calculated with a kinetic model and experimental measurements provides a general criterion for optimization procedures for the determination of some or all of the rate coefficients, by means of such procedures as genetic algorithms, simulated annealing, and scatter search.

Further uses of GFE in chemical kinetics will no doubt be developed in time. An interesting direction might be that of the use of this approach for developing and verifying the mechanisms of reaction systems.



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ANNEX: TABLES (to be submitted as separate files)

**Table I.** Model reactions and nominal rate coefficients of the Citri-Epstein mechanism for the Chlorite-Iodide (7). The dynamical variables appearing in the differential equations are the following concentrations:  $x_1 = [\text{Cl(III)}]$ , which is a common variable for  $[\text{HClO}_2]$  and  $[\text{ClO}_2^-]$ ,  $x_2 = [\text{HOCl}]$ ,  $x_3 = [\text{HIO}_2]$ ,  $x_4 = [\text{HOI}]$ ,  $x_5 = [\text{I}^-]$ , and  $x_6 = [\text{I}_2]$ . The CSTR condition is modeled by adding to the differential equations the term:  $k_0((x_i)_0 - x_i)$ , where  $k_0 = 10^{-2} [\text{s}^{-1}]$  and the  $(x_i)_0$  are:  $(x_1)_0 = 3.187 \cdot 10^{-3} [\text{M}]$ ,  $(x_3)_0 = 8.563 \cdot 10^{-3} [\text{M}]$ ,  $(x_2)_0 = (x_4)_0 = (x_5)_0 = (x_6)_0 = 0$ . The dynamical equations can be thus deduced directly from this information.

Number	Reaction	Nominal rate coefficients
1	$\text{H}^+ + \text{Cl(III)} + \text{I}^- \rightarrow \text{HOCl} + \text{HOI}$	$k_1 = 3.5586 [\text{M}^{-1}\text{s}^{-1}]$
2	$\text{H}^+ + \text{HOI} + \text{I}^- \rightarrow \text{I}_2 + \text{H}_2\text{O}$	$k_2 = 4.0836 \cdot 10^9 [\text{M}^{-1}\text{s}^{-1}]$
3	$\text{I}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{HOI} + \text{I}^-$	$k_3 = 0.1434 [\text{s}^{-1}]$
4	$\text{HClO}_2 + \text{HOI} \rightarrow \text{HOCl} + \text{HIO}_2$	$k_4 = 1.9620 [\text{M}^{-1}\text{s}^{-1}]$
5	$\text{HOCl} + \text{I}^- \rightarrow \text{HOI} + \text{Cl}^-$	$k_5 = 1.4 \cdot 10^8 [\text{M}^{-1}\text{s}^{-1}]$
6	$\text{H}^+ + \text{HIO}_2 + \text{I}^- \rightarrow 2\text{HOI}$	$k_6 = 8.9125 \cdot 10^3 [\text{M}]$
7	$2\text{HOI} \rightarrow \text{H}^+ + \text{HIO}_2 + \text{I}^-$	$k_7 = 25 [\text{M}^{-1}\text{s}^{-1}]$
8	$2\text{HIO}_2 \rightarrow \text{HOI} + \text{IO}_3^- + \text{H}^+$	$k_8 = 3 \cdot 10^2 [\text{M}^{-1}\text{s}^{-1}]$
9	$\text{HIO}_2 + \text{HOI} \rightarrow \text{I}^- + \text{IO}_3^- + 2\text{H}^+$	$k_9 = 2.3 \cdot 10^8 [\text{M}^{-1}\text{s}^{-1}]$
10	$\text{HOCl} + \text{HIO}_2 \rightarrow \text{Cl}^- + \text{IO}_3^- + 2\text{H}^+$	$k_{10} = 10^2 [\text{M}^{-1}\text{s}^{-1}]$

**Table II.** Model reactions and nominal rate coefficients of the Oregonator as described in (8). The dynamical variables appearing in the differential equations are  $x_1 = [\text{HBrO}_2]$ ,  $x_2 = [\text{Br}^-]$ , and  $x_3 = [2\text{Ce(IV)}]$ . Other concentrations are fixed as  $[\text{HOBr}] = 0.01 [\text{M}]$ ,  $[\text{BrO}_3^-] = 0.06 [\text{M}]$ . The dynamical equations as given in (Field) can be obtained from this information.

Number	Reaction	Nominal rate coefficients
1	$\text{BrO}_3^- + \text{Br}^- \leftrightarrow \text{HBrO}_2 + \text{HOBr}$	$k_1 = 1.34 [\text{M}^{-2}\text{s}^{-1}]$ $k_{-1} = 10^4 [\text{M}^{-1}\text{s}^{-1}]$
2	$\text{HBrO}_2 + \text{Br}^- \leftrightarrow 2\text{HOBr}$	$k_2 = 1.6 \cdot 10^9 [\text{M}^{-2}\text{s}^{-1}]$ $k_{-2} = 5 \cdot 10^{-5} [\text{M}^{-1}\text{s}^{-1}]$
3	$\text{BrO}_3^- + \text{HBrO}_2 \leftrightarrow 2 \text{HBrO}_2 + 2\text{Ce(IV)}$	$k_3 = 8 \cdot 10^3 [\text{M}^{-2}\text{s}^{-1}]$ $k_{-3} = 4.8 \cdot 10^{11} [\text{M}^{-2}\text{s}^{-1}]$
4	$2 \text{HBrO}_2 \leftrightarrow \text{BrO}_3^- + \text{HOBr}$	$k_4 = 4 \cdot 10^7 [\text{M}^{-1}\text{s}^{-1}]$ $k_{-4} = 1.6 \cdot 10^{-10} [\text{M}^{-2}\text{s}^{-1}]$
5	$2\text{Ce(IV)} \leftrightarrow \text{Br}^-$	$k_5 = 1 [\text{M}^{-1}\text{s}^{-1}]$ $k_{-5} = 1 \cdot 10^{-3} [\text{M}^{-1}\text{s}^{-1}]$

**Table III.** Sensitivity of the Chlorite-Iodide and Oregonator models to a 10% change in each of the rate coefficients,

one at a time. In the GFE calculations, the derivatives of the concentrations,  $\frac{dx_u(t)}{dt}$ , are analytically calculated from the model equations. In those equations, the values of the concentrations  $x_u(t)$  are obtained from the nominal model; and the rate coefficients  $k_i$  are those being tested. For the nominal values,  $d = 1.5373 \cdot 10^{-6}$ ;  $(1-\rho) = 3.6413 \cdot 10^{-11}$  (Chlorite-Iodide);  $d=0.0119$ ;  $(1-\rho) = 4.9326 \cdot 10^{-6}$  (Oregonator).

Chlorite-Iodide			Oregonator		
$k_i = 0.9k_i^*$	$d$	$1-\rho$	$k_i = 0.9k_i^*$	$d$	$1-\rho$
$k_1$	0.9988	0.8931	$k_1$	0.0121	$1.2273 \cdot 10^{-4}$
$k_2$	1.0000	0.9221	$k_{-1}$	0.0113	$5.4558 \cdot 10^{-5}$
$k_3$	1.0000	0.9308	$k_2$	0.0128	$1.3873 \cdot 10^{-4}$
$k_4$	0.0463	0.0032	$k_{-2}$	0.0058	$2.8135 \cdot 10^{-6}$
$k_5$	0.9991	0.8824	$k_3$	0.0246	$3.9629 \cdot 10^{-5}$
$k_6$	0.1598	0.0104	$k_{-3}$	0.0119	$4.8906 \cdot 10^{-6}$
$k_7$	$1.5373 \cdot 10^{-6}$	$3.6413 \cdot 10^{-11}$	$k_4$	0.0121	$4.9997 \cdot 10^{-6}$
$k_8$	$1.5373 \cdot 10^{-6}$	$3.6413 \cdot 10^{-11}$	$k_{-4}$	0.0119	$4.9327 \cdot 10^{-6}$
$k_9$	$1.5373 \cdot 10^{-6}$	$3.6413 \cdot 10^{-11}$	$k_5$	0.0118	$5.0100 \cdot 10^{-6}$
$k_{10}$	$1.5373 \cdot 10^{-6}$	$3.6413 \cdot 10^{-11}$	$k_{-5}$	0.0119	$4.9326 \cdot 10^{-6}$

**Table IV.** Values of the rate coefficients resulting from the optimization for the Chlorite-Iodide. The last column shows the error made if it is assumed that  $k_i$  is known and the remaining coefficients can be scaled as in Eq. 12. The symbols are defined in the text.

	$k_i^*$	$\frac{k_i^*}{k_1^*}$	$k_i^*$	$\frac{k_i^*}{k_1^*}$	% Error
$k_1$	3.5586	1	1.2432	1	-
$k_2$	$4.0836 \cdot 10^9$	$1.1475 \cdot 10^9$	$1.4281 \cdot 10^9$	$1.1487 \cdot 10^9$	0.10 %
$k_3$	0.1434	$4.0300 \cdot 10^{-2}$	$5.0172 \cdot 10^{-2}$	$4.0357 \cdot 10^{-2}$	0.14 %
$k_4$	$1.9620 \cdot 10^7$	$5.5134 \cdot 10^6$	$7.1415 \cdot 10^6$	$5.7444 \cdot 10^6$	4.19 %
$k_5$	$1.4 \cdot 10^8$	$3.9341 \cdot 10^7$	$4.9002 \cdot 10^7$	$3.9416 \cdot 10^7$	0.19 %
$k_6$	$8.9125 \cdot 10^3$	$2.5045 \cdot 10^3$	$3.0603 \cdot 10^3$	$2.4616 \cdot 10^3$	1.71 %
$k_7$	25	7.0251	1	0.8044	88.55 %
$k_8$	$3 \cdot 10^3$	$8.4302 \cdot 10^2$	$10^4$	$8.0438 \cdot 10^3$	854.16 %
$k_9$	$2.3 \cdot 10^2$	64.6314	10	8.0438	87.55 %
$k_{10}$	$10^3$	$2.8101 \cdot 10^2$	$1.3979 \cdot 10^4$	$1.1244 \cdot 10^4$	3901.28 %

**Table V.** Values of the rate coefficients resulting from the optimization for the Oregonator. The last column shows the error made if it is assumed that  $k_1$  is known and the remaining coefficients can be scaled as in Eq. 12. The symbols are defined in the text.

	$k_1^*$	$\frac{k_2^*}{k_1^*}$	$k_3^*$	$\frac{k_4^*}{k_1^*}$	% Error
$k_1$	1.34	1	4.2307	1	-
$k_{-1}$	$10^4$	$7.4627 \cdot 10^3$	$3.3202 \cdot 10^4$	$7.8478 \cdot 10^3$	5.16 %
$k_2$	$1.6 \cdot 10^9$	$1.1940 \cdot 10^9$	$5.0211 \cdot 10^9$	$1.1868 \cdot 10^9$	0.60 %
$k_{-2}$	$5 \cdot 10^{-5}$	$3.7313 \cdot 10^{-5}$	$2.9228 \cdot 10^{-4}$	$6.9085 \cdot 10^{-5}$	85.15 %
$k_3$	$8 \cdot 10^3$	$5.9702 \cdot 10^3$	$2.1348 \cdot 10^4$	$5.0460 \cdot 10^3$	15.48%
$k_{-3}$	$4.8 \cdot 10^{11}$	$3.5821 \cdot 10^{11}$	$2.4526 \cdot 10^{12}$	$5.7971 \cdot 10^{11}$	61.84 %
$k_4$	$4 \cdot 10^7$	$2.9851 \cdot 10^7$	$4.4446 \cdot 10^7$	$1.0506 \cdot 10^7$	64.81 %
$k_{-4}$	$1.6 \cdot 10^{-10}$	$1.1940 \cdot 10^{-10}$	$3.2000 \cdot 10^{-11}$	$7.5638 \cdot 10^{-12}$	93.67 %
$k_5$	1	0.7463	2.2882	0.5409	27.52 %
$k_{-5}$	$10^{-5}$	$7.4627 \cdot 10^{-6}$	$9.8717 \cdot 10^{-5}$	$2.3333 \cdot 10^{-5}$	212.66 %

ANNEX: FIGURES (to be submitted as separate files)

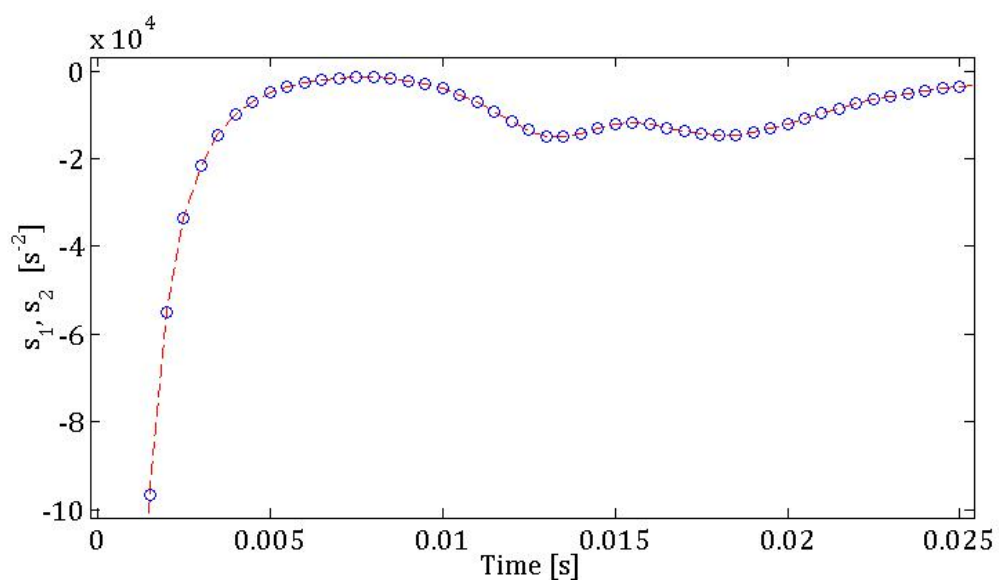


Fig. 1. Left-hand side ( $s_1$ , blue circles) and right-hand side ( $s_2$ , dashed red line) of the GFE for the Oregonator (detail)

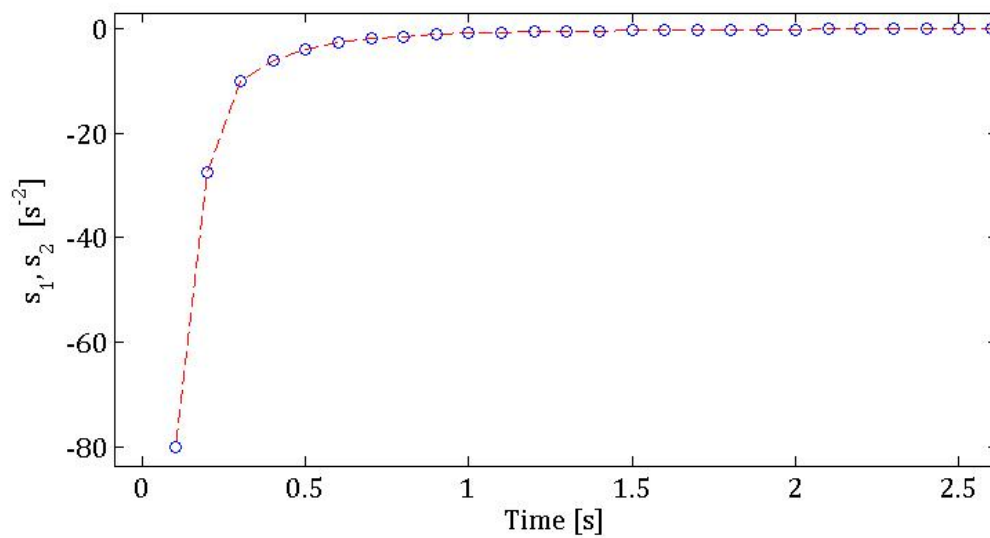
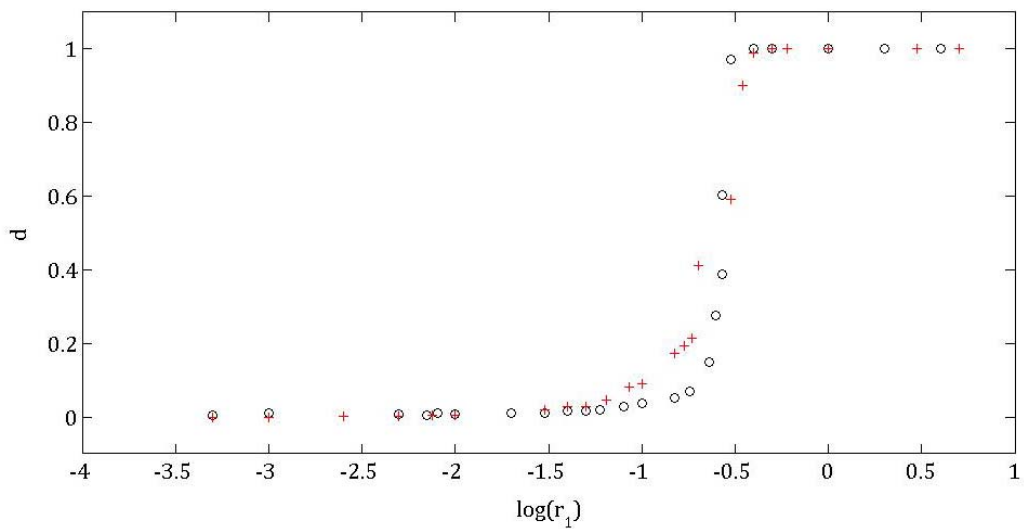


Fig 2. Left-hand side ( $s_1$ , blue circles) and right-hand side ( $s_2$ , dashed red line) of the GFE for the Chlorite-Iodide (detail)



**Fig. 3.** Correlation between noise level ( $r_1$ ) and relative distance ( $d$ ) for the Chlorite-Iodide (red crosses) and Oregonator (black circles)