Application of Genetic Algorithm to Chemical Kinetics: Systematic Determination of Reaction Mechanism and Rate Coefficients for a Complex Reaction Network

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We develop a systematic computational approach, which includes the genetic algorithm (GA) search method, to the minimal bromate reaction system, to automate the determination of its reaction mechanism and rate coefficients. We take the 10 species of the system as given, and then determine all possible bimolecular elementary reaction steps and all possible combinations of these steps that fulfill the given overall reaction. The optimization criteria used in the GA are chosen to be the following: The reaction mechanism must have an unstable focus, or must have oscillations; has specified ranges of periods of oscillations; and has specified ranges of inflow conditions. With rate coefficients given by Field, Körös, and Noyes[1], we find reaction mechanisms with four and five elementary reaction steps that show oscillations but do not fit well the experimental $[Br^-]_0$ - $[BrO_3^-]_0$ oscillation domain. We then determine, by GA, a set of rate coefficients in one particular five-step reaction mechanism that gives very good agreement with all comparable experiments. The Noyes, Field, Thompson model mechanism[2] for this reaction has seven elementary reaction steps. The first five, with our GA determined rate coefficients, are sufficient for the good agreement with experiment; the last two are not necessary. We believe that the example developed here in detail shows the utility and promise of GA methods in chemical kinetics.

I. Introduction

Genetic algorithms (GAs) are optimization methods of parallel computations designed to achieve a stated goal. Their first application to chemical kinetics[3] was on a simple model of reactions from a reservoir of F (food) to a reservoir of T (ATP), and the reverse, via two intermediates A and B. Both the A → B and B → A reactions were catalyzed by enzymes and both F and T acted as effectors on these enzymes. Michaelis−Menten noncompetitive allosteric binding mechanisms were assumed for the four effector reactions. The eight parameters in these reactions were then chosen by GA with the optimization of the flow from F to T, and its reverse, according to specific cellular needs, as the concentrations of the reservoirs of F and T were varied externally. The method yielded parameters for systems that successfully (adequately) switched the flows as required and thus survived; it also could change the reaction mechanism itself by eliminating an enzyme entirely, say for the B to A conversion. The results were interesting: No system was a global winner; successful (surviving) systems developed by selection reciprocal regulation and negative feedback solely due to the optimization requirement; a variety of regulatory systems survived, thus allowing for biodiversity.

In this article, we investigate several types of applications of GA methods to solving problems in chemical kinetics, which include searches for reaction mechanisms and rate coefficients. For purpose of illustration, we choose the Ce-catalyzed minimal bromate system, which has been investigated in some detail. This nonlinear open system can be in a stable stationary state, node, or focus, or in a unstable focus, which suggests, but does not necessitate, a stable limit cycle. For the system, we assume that the reacting species (either 9 or 10) are given. We then find solutions for the following searches:

1. A search for elementary steps which individually satisfy the stoichiometric conditions of charge and mass conservation; and the sum of elementary steps, each multiplied by an appropriate stoichiometric number, must satisfy the overall reaction of the system.

2. Searches with different optimization criteria: search for unstable focus, oscillations, specified period, specified inflow concentrations, and so forth.

3. Searches for different oscillatory reaction mechanisms (sets of elementary steps) and inflow conditions (flows rates and concentrations that lead to oscillations) for given rate coefficients and a postulated reaction mechanism.

4. A search for sets of rate coefficients in given reaction mechanisms to fit available experiments on oscillations (period and shape).

II. Search for Elementary Steps in Steady States

We choose as an illustration the minimal bromate reaction system,[4,5] and assume as given the chemical species

$$BrO_3^-,\ HBrO_2,\ HOBr,\ BrO_2^{\bullet},\ Br^-,\ H^+,\ Ce^{4+},\ Br_2,\ Ce^{3+},\ H_2O \quad (1)$$

This reaction has been modeled by several mechanisms; one is the NFT mechanism,[2] which is an important part of the FKN (Field−Körös−Noyes) mechanism[1] of the oscillatory Belousov−Zabotinskii reaction,[6,7] Its complex behavior has been studied experimentally in a continuous-flow stirred tank reactor (CSTR).[8] The rate equations for such open system are

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described in a vector form by

$$\frac{d\mathbf{C}}{dt} = \boldsymbol{\upsilon} \cdot f(\mathbf{C}) + k_0(\mathbf{C} - \mathbf{C}_0) \quad (2)$$

where $f(\mathbf{C})$ is the mass action rates of individual reactions; $\mathbf{C}$ is a concentration vector for the species; υ_{SR} is a stoichiometric matrix of the species, and R is the number of elementary reaction steps; $\mathbf{C}_0$ is a feed (BrO_3^-, Br^-, H^+, Ce^{3+}) concentration vector; and $k_0(\mathbf{C} - \mathbf{C}_0)$ describes the flow terms with flow rate k_0. In **steady states**, there are element balance conditions for the reactions[9]

$$\mathbf{A} \cdot \delta\mathbf{n} = \mathbf{0} \quad (3)$$

where the system formula matrix (or atomic matrix) $\mathbf{A}$ is given by

$$\mathbf{A} = \begin{pmatrix} 1 & 1 & 1 & 1 & 1 & 0 & 0 & 2 & 0 & 0 \\ 3 & 2 & 1 & 2 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \end{pmatrix} \quad (4)$$

and the element balance vector $\delta\mathbf{n}$ is

$$\delta\mathbf{n} = (\delta_{BrO_3^-}, \delta_{HBrO_2}, \delta_{HOBr}, \delta_{BrO_2^\bullet}, \delta_{Br^-}, \delta_{H^+}, \delta_{Ce^{4+}}, \delta_{Br_2}, \delta_{Ce^{3+}}, \delta_{H_2O}) \quad (5)$$

The set of null space vectors of the matrix $\mathbf{A}$ represents the independent reactions, which satisfies the stoichiometric condition of mass conservation. If we select all possible bimolecular reactions among all the species, but permit H_2O and H^+ to be additional reactants, and impose conservation of atoms and charge, then we find that linear combinations of the independent reactions yield 7 elementary steps

1. $Br^- + BrO_3^- + 2H^+ \leftrightharpoons HBrO_2 + HOBr$
2. $Br^- + HBrO_2 + H^+ \leftrightharpoons 2HOBr$
3. $Br^- + H^+ + HOBr \leftrightharpoons Br_2 + H_2O$ (6)
4. $BrO_3^- + H^+ + HBrO_2 \leftrightharpoons 2BrO_2^\bullet + H_2O$
5. $Ce^{3+} + BrO_2^\bullet + H^+ \leftrightharpoons Ce^{4+} + HBrO_2$
6. $Ce^{4+} + BrO_2^\bullet + H_2O \leftrightharpoons BrO_3^- + Ce^{3+} + 2H^+$
7. $2HBrO_2 \leftrightharpoons BrO_3^- + H^+ + HOBr$

which constitute precisely the NFT mechanism. This result is accidental; for example, it is not the result in the Citri−Epstein mechanism for the chlorite-iodide reaction.[10]

A. Overall Reaction. In the literature,[2] the NFT mechanism is represented by the following overall reaction

$$BrO_3^- + 4Ce^{3+} + 5H^+ \rightarrow 4Ce^{4+} + HOBr + 2H_2O \quad (7)$$

In this section, we check the consistency between the overall reaction 7 and elementary steps 6; we need to find out how many of each of the elementary steps 6 are necessary for the generation of the overall reaction. We designate the stoichiometric vector attached to the overall reaction 7 as

$$\mathbf{n}_{overall} = (-1, 0, 1, 0, 0, -5, 4, 0, -4, 2) \quad (8)$$

where the negative sign is for a reactant and the positive for a product (see the order of species in 5). From the overall reaction 7, we see that there are 4 intermediates, Br^-, $HBrO_2$, $BrO_2^\bullet$, Br_2. To obtain the overall reaction, we add up the elementary steps, each of the elementary reactions being multiplied by a stoichiometric number.[11] In the result, we require that the stoichiometric coefficients of the intermediates are equal to zero.[11] In other words, the total number of i^{th} intermediates created by all S steps, f_i, must vanish, that is

$$f_i = \sum_{s=1}^{S} b_{is} n_s = 0 \quad (9)$$

or in matrix form

$$\mathbf{B}\mathbf{n}_s = \mathbf{0} \quad (10)$$

where n_s is the stoichiometric number for the s^{th} reaction step, and b_{is} is the stoichiometric coefficient of i^{th} intermediates in the s^{th} step. Therefore, the null space of the matrix $\mathbf{B}$ represents the overall reactions. To satisfy the overall reaction 7, there must be included at least one of the following vector sets of elementary reaction steps in the NFT mechanism 6

$$\mathbf{v} = \{(4, 5, 7), (4, 6, 7), (5, 6, 7), (1, 2, 4, 5), (1, 2, 4, 6), (1, 2, 5, 6)\} \quad (11)$$

Consider the set $\mathbf{v}_1 = (4, 5, 7)$ as an example, where the matrix $\mathbf{B}$ is given by the stoichiometric coefficients of the intermediates Br^-, $HBrO_2$, $BrO_2^\bullet$, Br_2 in the steps (4,5,7)

$$\mathbf{B}(\mathbf{v}_1) = \begin{pmatrix} 1 & -1 & 2 \\ -2 & 1 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \quad (12)$$

Then, the null space of $\mathbf{B}(\mathbf{v}_1)$ yields a stoichiometric number vector $\mathbf{n}_{\mathbf{v}_1} = (-2, -4, 1)$ and the overall reaction (8) is $\mathbf{n}_{\mathbf{v}_1} \cdot \mathbf{v}_1$. As a result, there are **3** three-step, **13** four-step, **16** five-step, and **7** six-step combinations that satisfy this requirement. We apply GAs to search for oscillatory reaction mechanisms among those sets of reactions.

B. Steady States and Independent and Dependent Species. Because the number of species is greater than the number of steady-state equations for the above sets of reactions, we have to find relations between independent and dependent species to solve the steady-state equations. There exists a matrix β[12] such that

$$\boldsymbol{\beta}\upsilon = \mathbf{0} \quad (13)$$

where the rank of $\boldsymbol{\beta}$ is the number of dependent species (concentrations). Because the matrix $\mathbf{v}$ is the stoichiometric matrix, eq 13 indicates conservation of atoms, or combinations of atoms, in a steady state. Multiplying both sides of the rate equations (2) by $\boldsymbol{\beta}$, we have $\boldsymbol{\beta}(\mathbf{C}_0 - \mathbf{C}) = \mathbf{0}$, and then defining

$$\boldsymbol{\beta} = (\boldsymbol{\beta}_{dep}, \boldsymbol{\beta}_{ind}), \mathbf{C} = \begin{pmatrix} \mathbf{C}_{dep} \\ \mathbf{C}_{ind} \end{pmatrix}, \mathbf{C}_0 = \begin{pmatrix} \mathbf{C}_{0dep} \\ \mathbf{C}_{0ind} \end{pmatrix}$$

the relationship between independent and dependent concentra-

tions can be obtained by

$$\mathbf{C}_{\mathrm{dep}} = \alpha\mathbf{C}_{\mathrm{ind}} - \alpha\mathbf{C}_{0\mathrm{ind}} + \mathbf{C}_{0\mathrm{dep}} \tag{14}$$

where rank($\boldsymbol{\beta}$) = rank($\boldsymbol{\beta}_{\mathrm{dep}}$), and $\alpha = -\boldsymbol{\beta}_{\mathrm{dep}}{}^{-1}\boldsymbol{\beta}_{\mathrm{ind}}$. Then solving $\mathbf{C}_{\mathrm{ind}} = \mathbf{0}$, we obtain dependent steady-state concentrations $\mathbf{C}_{\mathrm{s,dep}}$ from 14. For the full set of reaction steps (NFT), we have (excluding H_2O, for which the concentration is considered to be constant)

$$\mathbf{v} = \begin{pmatrix} 1 & 0 & 0 & 1 & 0 & -1 & -1 \\ -1 & 1 & 0 & 1 & -1 & 0 & 2 \\ -1 & -2 & 1 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -2 & 1 & 1 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 2 & 1 & 1 & 1 & 1 & -2 & -1 \\ 0 & 0 & 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 \end{pmatrix} \tag{15}$$

and $\boldsymbol{\beta}$ is obtained by

$$\boldsymbol{\beta} = \begin{pmatrix} 1 & 1 & 1 & 1 & 1 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 \\ 2 & -\frac{41}{10} & -\frac{3}{2} & -\frac{27}{5} & \frac{49}{5} & -\frac{87}{10} & -5 & -\frac{2}{5} & 5 \\ -\frac{53}{14} & -\frac{81}{28} & \frac{1}{28} & -\frac{61}{14} & 5 & -\frac{57}{28} & -\frac{7}{4} & 3 & \frac{7}{4} \end{pmatrix} \tag{16}$$

where $\boldsymbol{\beta}_{\mathrm{ind}}$ (4 by 5) is the part of $\boldsymbol{\beta}$ matrixes taking from the first column to the fifth, and $\boldsymbol{\beta}_{\mathrm{dep}}$ (4 by 4) is the rest of the matrix component. From eq 14, the dependent steady-state concentrations $[H^+]_s$, $[Ce^{4+}]_s$, $[Br_2]_s$, $[Ce^{3+}]_s$ are obtained from the independent steady-state concentrations $[BrO_3^-]_s$, $[HBrO_2]_s$, $[HOBr]_s$, $[BrO_2^{\bullet}]_s$, and $[Br^-]_s$. We see that the first two row vectors in $\boldsymbol{\beta}$ express the conservation of bromine and cerium atoms, respectively, whereas the two bottom lines were chosen to be orthogonal to both the two rows and to the columns of $\mathbf{v}$.

Linear stability analysis of steady state is obtained by expanding the rate eqs 2 around a given steady state, $\mathbf{C}_s$, ($\mathrm{d}\mathbf{C}_s/\mathrm{d}t = \mathbf{0}$); for a small perturbation $\delta\mathbf{C}$, the rate equations up to the linear term is

$$\frac{\mathrm{d}\delta\mathbf{C}}{\mathrm{d}t} = \mathbf{J}(\mathbf{C}_s)\delta\mathbf{C} \tag{17}$$

where the Jacobian matrix is $J_{ij}(\mathbf{C}_s) = \mathrm{d}/\mathrm{d}\delta C_j(v \cdot f(\mathbf{C}) + k_0(\mathbf{C} - \mathbf{C}_0))_i|_{\mathbf{C}_s}$. Eigenvalues of the Jacobian are negative and real for a node; for a stable focus, there is a pair of conjugate eigenvalues with negative real part; for an unstable focus, there is a pair of conjugate eigenvalues with positive real part.

III. Use of Genetic Algorithms to Search for Oscillatory Mechanisms: A Robust Parallel Search in Complex Spaces

In this section, a genetic algorithm method[13] is used to search for oscillatory mechanisms in 3-step, 4-step, and 5-step combinations as discussed in the previous section. Full descriptions of genetic algorithms can be found in the literature.[13,14] We briefly summarize the structure of genetic algorithms. GAs operate on sets of strings of numbers, which are changed from generation to generation. This transformation of the pool of numerical strings is governed by simple laws, which are analogues of the processes of selection, crossover and mutation in the gene pool which occur during the evolution of a biological population (survival of main part of a gene during a transfer from one generation to the next through the occurrence of crossover and mutation toward larger fitness values). A simple GA involves nothing more complex than copying strings and swapping partial strings, but still manifests a powerful robust optimization procedures. Our GA has the three operations: *reproduction*, *crossover*, and *mutation*.

A. Reproduction. The GA works with a binary coding of parameter sets, which represent rate coefficients, inflow concentrations, species, and so forth. We encode a parameter into a binary string. If a parameter space is a rate coefficient, which can be represented as power of ten, 10^{-P} ($-10 \le P \le 10$), then a simple binary coding is

$$P = 10 - 20 \cdot \frac{R}{(2^{18} - 1)} \tag{18}$$

where $0 \le R \le 2^{18} - 1$. We set the string length to 18 bits and R is encoded into a binary string. For example, if $R = 12970_{10}$ the binary string of R is 000011001010101010_2, and the rate coefficient is 9.07×10^{-7}. The string length determines the length of the discretized search (parameter) space. An individual has a set of parameters represented by a binary string (chromosome). Reproduction is a process in which individual strings are copied according to their objective (typically scalar) fitness function, f, determined by optimization criteria; strings with a higher fitness value have a higher probability of transferring into the next generation (offspring). Thus, designing of the fitness function from the optimization criteria is an essential part of GAs. In our study, we search for an unstable focus, located inside a stable limit cycle, which is common for chemical oscillators. We use the Jacobian of the kinetic equations to detect unstable foci, which have a pair of complex conjugate eigenvalues with positive real part. Our trial fitness function[14] is given by

$$f = A + B\tanh((e^x + 1)(x + 1)) - \mathrm{Ce}^{-y^2/D} \tag{19}$$

where $A = 70$, $B = 10$, $C = 50$, $D = 10^{-5}$, and x is the real part and y is the imaginary part of the Jacobian matrix given in eq 17. The fitness function assigns each individual a fitness value according to the steady states of the system: node (lowest fitness), stable focus, and unstable focus (highest fitness). The reproduction operator can be implemented in algorithmic form in a number of ways. We employ a biased roulette wheel where each string in the population (a group of individuals) has a roulette wheel slot sized in proportion to its fitness. One way to do this is to calculate a set of partial sums of the fitness for each individual, $\{S_1,...,S_m = \sum_{i=1}^{m} f_i,..,S_n\}$, where the positive f_i ($1 \le i \le n$) is each individual fitness. We create a random number S_R between S_1 and the total sum of all individuals's fitness values, S_n. Then we select an individual from the population, such that the selected individual with fitness f_m is the one in which the last element in the set of the partial sums is not greater than the random number S_R, that is, where $S_m \le S_R \le S_{m+1}$ is satisfied. In this way, more strings of higher fitness have a higher number of offspring in the succeeding generation (probabilistic transition rule). In addition, we automatically transfer strings, for which fitness values correspond to unstable foci, to the next generation (*elitism*).

B. Crossover and Mutation Operators. To avoid the convergence to a single point in the parameter space of succeeding generations, genetic operators such as crossover and

TABLE 1: Domains of Oscillations in $[Br^-]_0$−$[BrO_3^-]_0$ Subspace and Periods of Oscillation from Experiments,[4] TFFK,[5] and Group I and II Reaction Mechanisms Provided by the GA[a]

inflow	$[BrO_3^-]_0$	$[Br^-]_0$	period
experiment	$(1.00-1.60)\times10^{-1}$	$(3.20-6.00)\times10^{-4}$	155−490
TFFK(6-steps)	$(0.70-1.10)\times10^{-1}$	$(2.50-3.40)\times10^{-4}$	240−620
	GA		
group I			
(1,2,4,5)	$(1.42-1.96)\times10^{-1}$	$(1.36-2.15)\times10^{-4}$	81−581
(1,2,4,5,6)	$(1.42-1.96)\times10^{-1}$	$(1.36-2.15)\times10^{-4}$	81−473
(1,2,4,5,7)	$(1.42-1.96)\times10^{-1}$	$(1.36-2.15)\times10^{-4}$	81−540
group II			
(1,2,3,4,5)	$(1.50-2.00)\times10^{-1}$	$(4.07-6.15)\times10^{-4}$	100−581
NFT steps	$(1.50-2.00)\times10^{-1}$	$(4.07-6.15)\times10^{-4}$	100−600

[a] See text. Constant constraints of calculation: $[Ce^{3+}]_0 = 3\times10^{-4}$ M $[H^+]_0 = 0.75$ M and $k_0 = 5\times10^{-3}$ sec^{-1}. The oscillatory domains for two different groups of mechanisms obtained by the genetic algorithm are calculated with the FKN rate coefficients in Table II; The experimental domain is an estimated value from Figure 3 given in Bar-Eli and Geiseler (ref 4); the domain of the TFFK mechanism from Figure 3 given in Bar-Eli and Field (ref 5), where the periods are calculated.

mutation are employed. The action of crossover takes two strings and recombines them; it produces new strings (children) by cutting the given strings at the same points (crossover point), swapping alternate fragments between the two, and joining the fragment together. For the involved individuals, the selection process creates random numbers between 0 and 1 for a pair of strings, and if the random number is less than a given crossover probability, P_c, then crossover will occur between a pair of strings; we use one point crossover ($P_c = 0.5$) and a cross point is chosen randomly. The action of mutation is to flip one or more bits in the bit string. For mutation, let P_m be the mutation probability per bit for each string; if the choice of the random number for a given bit is less than P_m, then the bit is changed. We set $P_m = 0.08$. The above genetic procedures are terminated when all individuals in the population become unstable foci.

IV. Search for Different Oscillatory Reaction Mechanisms and Inflow Concentrations that Lead to Oscillations for Given Rate Coefficients

Bar-Eli and Geiseler[4] carried out experiments to determine the oscillation domain in the $[Br^-]_0$-$[BrO_3^-]_0$ subspace under fixed inflow concentrations $[Ce^{3+}]_0 = 3\times10^{-4}$ M, $[H^+]_0 = 0.75\ M$ and a given flow rate $k_0 = 5\times10^{-3}$ sec^{-1}. They show that oscillations occur in the range of inflow concentrations: 1.00×10^{-1} M $< [BrO_3^-]_0 < 1.60\times10^{-1}$ M and 3.2×10^{-4} M $< [Br^-]_0 < 6.00\times10^{-4}$ M, and in the range of period: 155−490 (see Table 1). The experimental domain is estimated from Figure 3 given in Bar-Eli and Geiseler.[4] To compare with the experimental oscillation domain in the $[Br^-]_0$-$[BrO_3^-]_0$ subspace, Bar-Eli and Geiseler used the NFT mechanism with the FKN rate coefficients to calculate the various oscillatory domains corresponding to the different flow rates, proton concentrations and Ce^{3+} inflow concentrations.

In section IIA, we have shown that there are 3 different three-step, 13 four-step, and 16 five-step possible mechanisms that are compatible with the overall reaction 6. We use the GA approach for searching which of these possible reaction mechanisms have oscillation domains compatible with the numerical results obtained by Bar-Eli and Geiseler,[4] and Bar-Eli and Field.[5] We use FKN rate coefficients (see Table 2) and focus the search space for $[Br^-]_0$ on $R_1\times10^{-4}$ and for $[BrO_3^-]_0$ on $R_2\times10^{-1}$ ($0 \le R_1, R_2 \le 10$) under fixed inflow concentrations $[Ce^{3+}]_0 =$ $3\times10^{-4}\ M$, $[H^+]_0 = 0.75\ M$ and a given flow rate $k_0 = 5\times10^{-3}$ sec^{-1}. The GA (written in Mathematica 4.0) was carried out for 10 populations, each of which has 8 individuals (string size: 18 bits) and up to 120 generations. CPU time (Pentium II

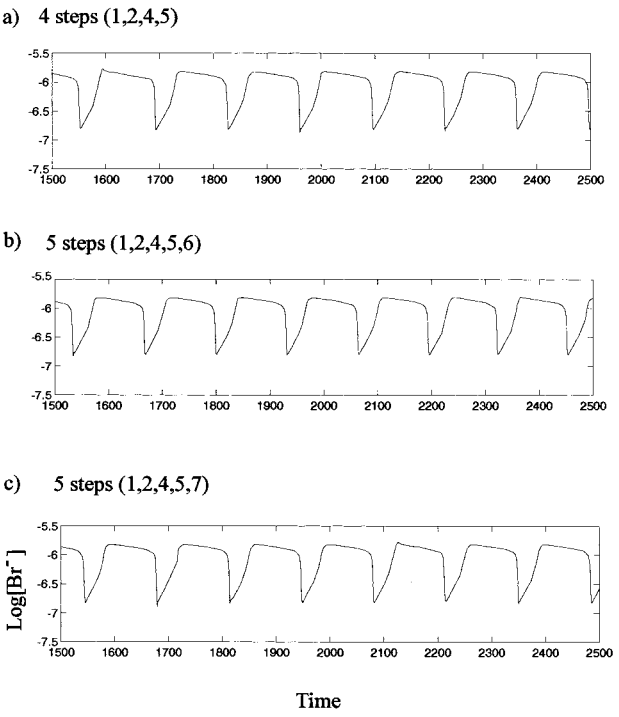

Figure 1. Calculated oscillations for the group I mechanisms: (a) the 4-step mechanism (1,2,4,5); (b) 5-steps (1,2,4,5,6); (c) the 5-step mechanism (1,2,4,5,7) at $[Br^-]_0 = 1.80\times10^{-4}$ M, $[BrO_3^-]_0 = 1.95\times10^{-1}$ M, $[Ce^{3+}]_0 = 3\times10^{-4}$ M, $[H^+]_0 = 0.75$ M, and $k_0 = 5\times10^{-3}$ sec^{-1}. The figure shows that the form of the oscillations are shifted only in phase among these 3 reaction mechanisms; the 4 step (1,2,4,5) is an irreducible mechanism, and the elementary steps 6 or 7 are not essential for an oscillatory mechanism.

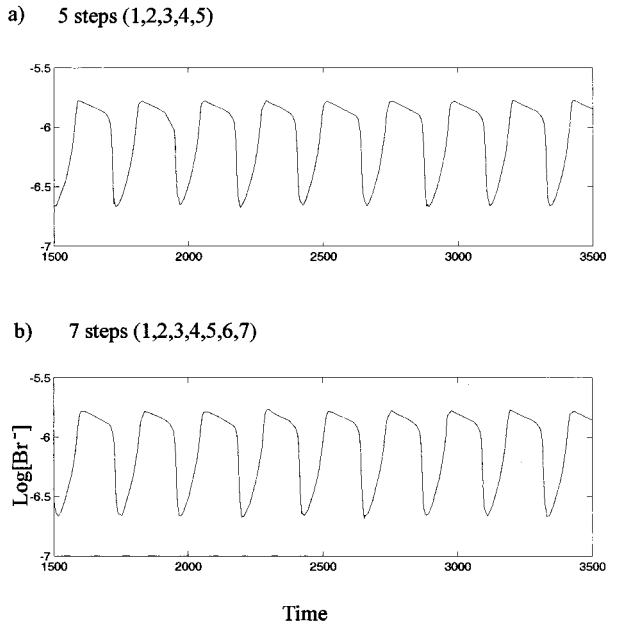

Figure 2. Calculated oscillations for the group II mechanisms: (a) the 5-step mechanism (1,2,3,4,5); (b) the 7-step mechanism (1,2,3,4,5,6,7) at $[Br^-]_0 = 5.13\times10^{-4}$ M and $[BrO_3^-]_0 = 1.76\times10^{-1}$ M, $[Ce^{3+}]_0 = 3\times10^{-4}$ M, $[H^+]_0 = 0.75$ M, and $k_0 = 5\times10^{-3}$ sec^{-1}. In the figure, the forms of the oscillations in these two sets are identical; the 5 step (1,2,3,4,5) is an irreducible set, and steps 6 and 7 are not essential steps in the 7 NFT steps with the FKN rate coefficients.

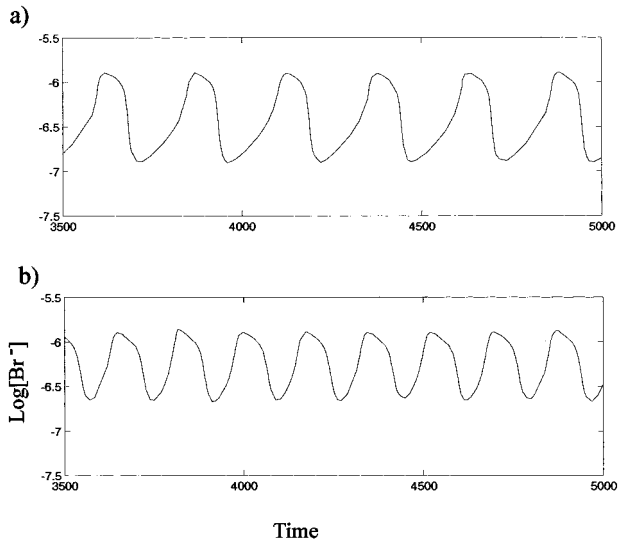

Figure 3. The shapes of temporal wave and periods for the 5-step mechanism (1,2,3,4,5) at the two experimental points in the $[Br^-]_0$−$[BrO_3^-]_0$ domain with the rate coefficients used in Table 5. The two experimental points: (a) $[Br^-]_0 = 4.20 \times 10^{-4}$ M and $[BrO_3^-]_0 = 1.25 \times 10^{-1}$ M and (b) $[Br^-]_0 = 4.80 \times 10^{-4}$ M, $[BrO_3^-]_0 = 1.40 \times 10^{-1}$ M. It shows the periods from (a) and (b), which are 253 and 183, are in excellent agreement with the experimental values, 260 and 183, respectively. Calculation constants: $k_0 = 5 \times 10^{-3}$ sec^{-1}, $[Ce^{3+}]_0 = 3 \times 10^{-4}$ M, $[H^+]_0 = 0.75$ *M*. The shapes are very similar to the experimental wave form but a direct comparison of shapes between the calculation and the experiment with these parameters is not feasible.

TABLE 2: Various Sets of Rate Coefficients for the NFT Mechanism

rate coeff	FKN	TFFK	TFF	"Lo"	"Hi"
k_1	2.1	2	2	2	2
k_{-1}	1.0×10^4	3.2	3.2	10	1.0×10^4
k_2	2.0×10^9	3.0×10^6	3.0×10^6	2.0×10^6	2.0×10^9
k_{-2}	5.0×10^{-5}	2.0×10^{-5}	2.0×10^{-5}	5.0×10^{-5}	5.0×10^{-5}
k_3	8.0×10^9	3.0×10^9	8.0×10^9	8.0×10^9	8.0×10^9
k_{-3}	110	2	110	110	110
k_4	1.0×10^4	42	42	10	7.0×10^3
k_{-4}	2.0×10^7	4.2×10^7	4.2×10^7	2.0×10^7	2.0×10^7
k_5	6.5×10^5	8.0×10^4	8.0×10^4	6.0×10^5	6.0×10^5
k_{-5}	2.4×10^7	8.9×10^3	8.9×10^3	2.0×10^6	5.0×10^7
k_6	9.6	0	0	10	10
k_{-6}	1.3×10^{-4}	0	0	1.5×10^{-6}	4.2×10^{-5}
k_7	4.0×10^7	3.0×10^3	3.0×10^3	2.0×10^3	2.0×10^9
k_{-7}	2.1×10^{-10}	1.0×10^{-8}	1.0×10^{-8}	1.0×10^{-8}	1.0×10^{-8}

[a] The FKN rate coefficients by Field, Körös, and Noyes; TFF by Tyson, Field, and Försterling; TFFK by Tyson, Field, Försterling, and Kshirsagar (see details (ref 5)): "Lo" and "Hi" (thermodynamically consistent) rate coefficients suggested by Tyson (ref 17).

400 MHz) necessary to complete the search is about 4−6 h (10−20 s from one generation to the next).

We find no chemical oscillations in any of the three 3 -step reaction sets (no unstable foci and no hysteresis were found).

The GA reveals that there are two different groups of oscillatory mechanisms in the 4 -step and 5 -step sets (see Table 1). The first group of reaction sets of elementary steps (group I) consists of the reactions (1,2,4,5), (1,2,4,5,6), and (1,2,4,5,7). These sets have 9 species (no Br_2) with 4 independent species (concentrations). We see from Figure 1 (calculated at $[BrO_3^-] = 1.80 \times 10^{-1}$ M and $[Br^-]_0 = 1.95 \times 10^{-4}$ M) that the form of the oscillations are shifted only in phase among these 3 reaction mechanisms; thus, the 4 step (1,2,4,5) is an irreducible mechanism and the elementary steps 6 or 7 are not essential for an oscillatory mechanism. In the (1,2,4,5) mechanism, we find (see Table 1) that oscillations occurs in the range of the inflow domain $[BrO_3^-]_0$−$[Br^-]_0$: 1.42×10^{-1} M ≤ $[BrO_3^-]_0$ ≤ 1.96×10^{-1} M and 1.36×10^{-4} M ≤ $[Br^-]_0$ ≤ 2.15×10^{-4} M, and in the range of period: 81−581. Periods in Table 1 are shown around the middle of the lower and upper limits of $[BrO_3^-]_0$ (fixed $[Br^-]_0$); a sharp increase in period occurs near the boundary of $[BrO_3^-]_0$ in the upper limit of the oscillation domain.

The second group (group II) consist of reactions (1,2,3,4,5) and (1,2,3,4,5,6,7). The two sets involve 10 species of which 5 are independent species. At $[BrO_3^-]_0 = 1.76 \times 10^{-1}$ M and $[Br^-]_0 = 5.13 \times 10^{-4}$ M (see Figure 2) the forms of the oscillations in these two sets are identical; therefore, the 5 step (1,2,3,4,5) is an irreducible set and steps 6 and 7 are (again) not essential steps in the 7 NFT steps with the FKN rate coefficients. In the (1,2,3,4,5) mechanism, oscillations occur in the range of the inflow domain $[BrO_3^-]_0$−$[Br^-]_0$: 4.07×10^{-4} $M \le [Br^-]_0 \le 6.15 \times 10^{-4}$ *M* and 1.50×10^{-1} $M \le [BrO_3^-]_0 \le 2.00 \times 10^{-1}$ *M*, and in the range of period: 100−600.

In the mechanisms of both group *I* and *II*, there are five essential species,[15] $HBrO_2$, HOBr, $BrO_2^{\bullet}$, Br^-, Ce^{3+}, which are necessary to have oscillations in the NFT mechanism. Although the above oscillatory domains are near the experimental one, and the periods and shapes of the oscillations are compatible with the experimental results, both group I and II reaction mechanisms with the FKN rate coefficients do not fit experimental results well (see Table 1); the $[Br^-]_0$ range for the 4-step mechanism (1,2,4,5) is off from the experiment, whereas the $[BrO_3^-]_0$ range on the 5-step mechanism (1,2,3,4,5) is off. In the next section, we focus on the 4 and 5 step mechanisms in group I and II. We do a GA search for rate coefficients that yield unstable foci at four experimental points in the $[Br^-]_0$−$[BrO_3^-]_0$ space and then find excellent agreements with the experiments.

V. Search for Sets of Rate Coefficients in Given Reaction Mechanisms to Fit Available Experiments on Oscillations (Period and Shape)

There have appeared a number of numerical studies,[4,5,16] for the minimal bromate system that compare the results of computer simulations for different mechanisms with the experimental data for the oscillatory regime.[4] However, none of the suggested mechanisms with given rate coefficients reproduce the experimental $[Br^-]_0$−$[BrO_3^-]_0$ domain well (see, for example, the range of the $[Br^-]_0$ and $[BrO_3^-]_0$ inflow for the TFFK and the NFT mechanisms in Table 1). Furthermore, large discrepancies (see Table 2) of the rate coefficients assigned to the different mechanisms[5] are found. In this section, we search for rate coefficients for the 4- or 5-step mechanisms that fit the experimental domain. To do so, we search for rate coefficients that yield unstable foci in the reaction mechanisms for all four experimental conditions in the $[Br^-]_0$−$[BrO_3^-]_0$ inflow domain. Those experimental points are $[Br^-]_0 = 3.90 \times 10^{-4}$ *M* and $[BrO_3^-]_0 = 1.12 \times 10^{-1}$ *M*, $[Br^-]_0 = 4.20 \times 10^{-4}$ *M* and $[BrO_3^-]_0 = 1.25 \times 10^{-1}$ *M*, $[Br^-]_0 = 4.80 \times 10^{-4}$ *M* and $[BrO_3^-]_0 = 1.40 \times 10^{-1}$ *M*, and $[Br^-]_0 = 5.30 \times 10^{-4}$ *M* and $[BrO_3^-]_0 = 1.55 \times 10^{-1}$ *M*, where experimental periods are available for the last 3 points (see Table 4). We use the FKN equilibrium constants K_{eq}, thus ensuring thermodynamically consistent rate coefficients, for obtaining backward rate coefficients from the forward ones; thus, there are four forward rate coefficients (parameters) for the 4-step mechanism and 5 rate coefficients for the 5-step mechanism to be found with the GA. Because it is difficult to search for rate coefficients fulfilling

TABLE 3: Range of the Five Forward Rate Coefficients Generated by the GA for the 5 -step Mechanism (1,2,3,4,5)[a]

rate coeff	range
k_1	1.28−9.37
k_2	$(0.09-5.74)\times 10^{10}$
k_3	$(0.01-1.74)\times 10^{9}$
k_4	$(1.18-18.6)\times 10^{4}$
k_5	$(4.23-10.2)\times 10^{5}$

[a] The GA optimizes four unstable focus conditions at the four experimental points: $[Br^-]_0 = 3.90\times10^{-4}$ M and $[BrO_3^-]_0 = 1.12\times10^{-1}$ M, $[Br^-]_0 = 4.20\times10^{-4}$ M and $[BrO_3^-]_0 = 1.25\times10^{-1}$ M, $[Br^-]_0 = 4.80\times10^{-4}$ M, and $[BrO_3^-]_0 = 1.40\times10^{-1}$ M, $[Br^-]_0 = 5.30\times10^{-4}$ M, and $[BrO_3^-]_0 = 1.55\times10^{-4}$ M. The FKN equilibrium constants are used to obtain the five backward rate coefficients. Constant constraints of calculation: $[Ce^{3+}]_0 = 3\times10^{-4}$ M, $[H^+]_0 = 0.75$ M, and $k_0 = 5\times10^{-3}$ s^{-1}.

TABLE 4: Comparison of Oscillatory Domain in $[BrO_3^-]_0$−$[Br^-]_0$ Subspace and Periods Between the 5-step Mechanism (1,2,3,4,5) and the Experiments[a]

$[Br^-]_0\times10^{-4}$	$[BrO_3^-]_0\times10^{-1}$	period	range of $[BrO_3^-]_0\times10^{-1}$ (fixed $[Br^-]_0$)
	experiment		
3.65	1.10	493	1.08−1.20
4.20	1.25	260	1.16−1.45
4.80	1.40	185	1.27−1.58
5.30	1.55	156	1.39−1.64
	5-step mechanism		
3.87	1.10	565	1.08−1.16
4.20	1.25	253	1.14−1.35
4.80	1.40	183	1.24−1.54
5.30	1.55	151	1.36−1.58

[a] The range of $[BrO_3^-]_0$, for which oscillations exists, is calculated at each fixed $[Br^-]_0$. The five forward rate coefficients are chosen from the range in Table 3: $k_1 = 2.91$, $k_2 = 1.01\times10^{10}$, $k_3 = 2.77\times10^{7}$, $k_4 = 6.94\times10^{4}$, $k_5 = 4.60\times10^{5}$. The FKN equilibrium constants are used to obtain the five backward rate coefficients. Constant constraints of calculation: $[Ce^{3+}]_0 = 3\times10^{-4}$ M, $[H^+]_0 = 0.75$ M and $k_0 = 5\times10^{-3}$ s^{-1}. The oscillatory range of the 5-step mechanism with the rate coefficients obtained with the GA shows very good agreement with the experimental domain.

the given specification in the GA, we take two steps to find the rate coefficients in the experimental domain: First, we search for rate coefficients in the range from 10^{-4} to 10^4 times of the FKN rate coefficients, for which oscillations occur at the third experimental point: $[Br^-]_0 = 4.8\times10^{-4}$ *M* and $[BrO_3^-]_0 = 1.4\times10^{-1}$ *M*, (note that k_0, $[Ce^{3+}]_0$, and $[H^+]_0$ are fixed; see the previous section), and then use these results to search for the rate coefficients in the range from 10^{-2} to 10^2 times of those coefficients to satisfy simultaneously unstable foci at the 4 experimental points.

The GA reveals that in the first step of the GA search trial, no oscillations in the 4 -step mechanism (1,2,4,5) occur at the experimental point, $[Br^-]_0 = 4.8\times10^{-4}$ *M* and $[BrO_3^-]_0 = 1.4\times10^{-1}$ M; in other words, the 4 step (1,2,4,5) mechanism exhibits oscillations, but not in the right range of the $[Br^-]_0$−$[BrO_3^-]_0$ space, that is, the 4 -step mechanism fails to reproduce the experimental domain. On the other hand, for the 5-step mechanism (1,2,3,4,5), Table 3 shows the range of the five forward rate coefficients, which yield the simultaneously the 4 unstable foci. In Table 4, we show five forward rate coefficients, $k_1 = 2.91$, $k_2 = 1.01\times10^{10}$, $k_3 = 2.77\times10^{7}$, $k_4 = 6.94\times10^{4}$, $k_5 = 4.60\times10^{5}$, which are chosen from the range of the values provided by the GA and that give very good agreement with all comparable experiments: the 4 periods in the 5-step mechanism at the 4 experimental inflow concentrations, and

TABLE 5: Oscillation Domains in $[Br^-]_0$-$[BrO_3^-]_0$ Space for the 4-step Mechanism (1,2,4,5) and the 5-step Mechanism (1,2,3,4,5) with the Rate Coefficients in Table *V*[a]

GA	$[BrO_3^-]_0\times10^{-1}$	$[Br^-]_0\times10^{-4}$
	4-step mechanism	
(1,2,4,5)	1.13−1.63	1.54−1.95
	5-step mechanism	
(1,2,3,4,5)	1.06−1.56	3.72−5.46

[a] Constant constraints of calculation: $[Ce_3^+]_0 = 3\times10^{-4}$ *M*, $[H^+]_0 = 0.75$ M and $k_0 = 5\times10^{-3}$ sec^{-1}. The 4-step (1,2,4,5) mechanism exhibits oscillations, but not in the right range of the $[Br^-]_0$−$[BrO_3^-]_0$ space, whereas the oscillation domain generated by the 5-step mechanism (1,2,3,4,5) is in very good agreement with the experiment (see Table I).

oscillatory ranges of $[BrO_3^-]_0$, at four fixed $[Br^-]_0$. Temporal wave forms at the two experimental points: $[Br^-]_0 = 4.20\times10^{-4}$ *M*, $[BrO_3^-]_0 = 1.25\times10^{-1}$ *M* and $[Br^-]_0 = 4.80\times10^{-4}$ *M*, $[BrO_3^-]_0 = 1.40\times10^{-1}$ *M* are shown in Figure 3, which shows that the period of waves generated by the 5-step mechanism is in excellent agreement with the experiments. The shape of waves is very similar to the experimental waves[4] but a direct comparison of the calculated waves with the experimental ones is not feasible. A referee suggested that we lower the values of k_2 and k_4, each by a factor of 10^3. For those choices of k_2 and k_4, we find no oscillations in the 5-step mechanism with reaction steps (1,2,3,4,5), nor in the 7 step NFT mechanism, within the ranges of inflow condition of the experiments available.

Although the 4-step mechanism displays oscillation, it fails to reproduce the experimental oscillation domain. The 5-step mechanism, which is made up of the 4-steps in the 4-step mechanism plus the additional reaction step 3, which is $Br^- + H^+ + HOBr \rightleftharpoons Br_2 + H_2O$, manages to reproduce the experimental domain. It follows that the reaction step 3 is essential for reproduction of the experiments.

With use of the above five forward rate coefficients yielding unstable foci for all four experimental conditions and the FKN equilibrium constants, we search again which ones of the 3, 4, and 5 steps reaction mechanisms discussed in section IIB have oscillation domains in $[Br^-]_0$ on $R_1\times10^{-4}$ M and $[BrO_3^-]_0$ on $R_2\times10^{-1}$ M ($0 \le R_1, R_2 \le 10$). We set $[Ce^{3+}] = 3\times10^{-4}$ M, $[H^+]_0 = 0.75$ M and flow rate 5×10^{-3} sec.$^{-1}$ The GA shows that no reaction mechanism other than group I and II as described in section IIIA have oscillations in the above assigned range. Thus, the oscillatory mechanisms in section IIIA remain the same; the smallest number of reaction steps is four in group I and five in group II, that is, steps (1,2,4,5) and (1,2,3,4,5), respectively. In conclusion, the oscillation domains in $[Br^-]_0$−$[BrO_3^-]_0$ space for the 4-step mechanism (1,2,4,5), which does not reproduce the experiments and the 5-step mechanism (1,2,3,4,5), which does reproduce the experiments are given in Table 5.

VI. Conclusions

The main part of this paper is the application of a genetic algorithm to chemical kinetics to determine the reaction mechanism and rate coefficients for a complex reaction network, for which we choose the minimal bromate system. Starting with 10 given chemical species for the minimal bromate reaction system,[4,5] we develop a computer code, which includes the genetic algorithm search method, to automate the determination of the reaction mechanisms and (thermodynamically consistent) rate coefficients to fit the given experimental $[Br^-]_0$−$[BrO_3^-]_0$ oscillation domain. The first part of the code incorporates

element balance conditions for reactions in steady states to determine possible elementary reaction steps. Then the Horiuti theory[11] is used to determine the possible mechanisms compatible with the overall reactions of the minimal bromate reaction system. Next, we use a genetic algorithm to search which ones of these possible mechanisms have oscillatory domains in the $[Br^-]_0-[BrO_3^-]_0$ region as suggested by experiments. The GA with the FKN rate coefficients revealed two groups of oscillatory mechanisms; group I consists of reactions (1,2,4,5), (1,2,4,5,6), and (1,2,4,5,7) in the NFT steps, and group II consists of reactions (1,2,3,4,5) and (1,2,3,4,5,6,7). Group I has 9 species (no Br_2) with 4 independent species, whereas group II has 10 species with 5 independent species. On the basis of the forms and domains of oscillation in the $[Br^-]_0-[BrO_3^-]_0$ space, and the periods, we find that the 4 step (1,2,4,5) mechanism in group I and the 5 step (1,2,3,4,5) mechanism in group II are irreducible sets. Therefore, for both group I and II mechanisms, the steps 6 or 7 in NFT steps are not essential for the oscillations. Both mechanisms with the FKN rate coefficients, however, fail to fit well the experimental oscillatory domain in the $[Br^-]_0$-$[BrO_3^-]_0$ space. Thus, the last part of the code is to use the GA to determine the range of rate coefficients to fit the experimental $[Br^-]_0-[BrO_3^-]_0$ oscillation domain for the 4 step (1,2,4,5) and 5 step (1,2,3,4,5) mechanisms. With the FKN equilibrium constants, the 4 step (1,2,4,5) mechanism exhibits oscillation, but not in the right range of the $[Br^-]_0-[BrO_3^-]_0$ space. On the other hand, the 5 step (1,2,3,4,5) mechanism yields very good agreement with comparable experiments with determination of the range of the five forward rate coefficients. The 5 steps (1,2,3,4,5) is made up of the 4-step mechanism plus step 3 in NFT set (6), which indicates that step 3 is essential for reproduction of the experimental results.

Because of the generality of the procedures discussed here, we believe that the genetic algorithm optimization is useful and promising for determining reaction mechanisms and rate coefficients for complex reaction networks.

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References and Notes

(1) Field, R. J.; Noyes, R. M.; Körös, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 8649.
(2) Noyes, R. M.; Field, R. J.; Thompson, R. C. *J. Am. Chem. Soc.* **1971,** *93*, 7315.
(3) Gilman, A.; Ross, J.,*Biophys. J*, **1995,** *69*, 1321.
(4) Bar-Eli, K.; Geiseler, W. *J. Phys. Chem.* **1983,** *87*, 3769.
(5) Bar-Eli, K.; Field, R. J. *J. Phys. Chem.* **1990,** *94*, 3660.
(6) Field, R. J.; Noyes, R. M.; Körös, E. *J. Am. Chem. Soc.* **1972,** *94*, 8649.
(7) Field, R. J.; In *Oscillations and Travelling Waves in Chemical Systems*; Field, R. J., Burger, M., Eds.; Wiley-Interscience: New York, 1985; pp 55−92.
(8) (a) Geiseler, W.; Bar-Eli K. *J. Phys. Chem.* **1981,** *85*, 908. (b) Dekepper, P.; Boissonade, J. In *Oscillations and Travelling Waves in Chemical Systems*; Field, R. J., Burger, M., Eds.; Wiley-Interscience: New York, 1985; pp 223−256.
(9) Smith, W. R.; Missen, R. W. *Chemical Reaction Equilibrium Analysis*; Wiley-Interscience: 1982.
(10) Citri, O.; Epstein, I. R. *J. Phys. Chem.* **1987**, *91*, 6034.
(11) Horiuti, J. *Ann. NY. Acad. Sci.* **1973**, *213*, 5.
(12) K. Bar-Eli, In *Nonlinear Dynamics in Chemical Systems*; Vidal, C., Pacault, A., Eds.; Springer-Verlag: New York, 1981; pp 228−239.
(13) Mitchell, M. *An Introduction to Genetic Algorithms*; MIT Press: 1996.
(14) Gilman, A. Ph.D. Thesis, Stanford University, 1999.
(15) Eiswirth, M.; Freund, A.; Ross, J. *Adv. Chem. Phys.* **1991,** *80*, 127.
(16) Bar-Eli, K.; Ronkin, J. *J. Phys. Chem* . **1984,** *88*, 2844.
(17) Tyson, J. J.; In *Oscillations and Travelling Waves in Chemical Systems*; Field, R. J., Burger, M., Eds.; Wiley-Interscience: New York, 1985; pp 93−144.