

# An inverse problem in reaction kinetics

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**Abstract** In this paper we investigate the problem of extracting information about chemical reactions involving multiple species from the time history of the concentration of each species. The mathematical model of the kinetic system leads to a system of ordinary differential equations. Our focus is to examine whether the species' concentrations as functions of time are sufficient to determine what chemical reactions, and at what reaction rates, have occurred. We show that within the limitation of our model, there may be many candidate reaction systems that could explain the data. Using the notion of sparsity, we provide a quantitative assessment of the question of distinguishability. We further demonstrate that sparsity enforcing approaches, such as minimizing the  $\ell_1$  or the  $\ell_0$  norms are not reliable. Our conclusion is that additional knowledge about the kinetic system will be necessary to reliably solve this inverse problem.

**Keywords** Reaction kinetics · Inverse problems

## 1 Introduction

The problem of identifying reactions and rate constants associated with these reactions arises in chemistry and bio-chemistry. Our work is limited to studying unary reactions of the following type. Suppose  $X_j$ ,  $j = 1, \dots, n$  are the chemical species and their concentrations as a function of time are denoted by  $x_j(t)$ . Reactions considered are of the types

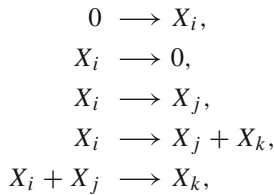
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where 0 is a source or sink. Thus, the resulting system ordinary differential of equations describing the concentrations can at most be bilinear, with the reaction rates acting as coefficients in the equations. The question we set out to answer is whether measurement of concentrations as a function of time, say over a finite time window  $[0, T]$ , is sufficient to determine the reaction rates in the system.

When one considers the possible reactions of the type given for a system involving  $n$  species, one realizes that the number of reactions can be very large. Indeed, counting all possible reactions, the number of reactions, grows as the cube of the number of species. To be precise, if we have  $n$  species, we need to consider  $m = 2n + n(n - 1) + n(n - 1)(n - 2)$  reactions. On the otherhand, we may assume that the concentrations  $x_j(t)$  can be sampled as finely as we wish. So, the inverse problem can be made *overdetermined*, although stability and uniqueness may be an issue.

What we will show in the subsequent is that the problem is actually nonunique. It is possible for a system involving multiple species with different reaction rates to lead to *exactly* the same set of differential equations. This fact has been known for some time [8, 10] and the phenomenon is known in the chemistry literature as *distinguishability*. The analyses done in these articles were somewhat specialized to certain chemical reactions. Our approach, which is quite general although limited to unary reactions, looks for chemical reactions which produce identical systems of differential equations. Our work on distinguishability is closely related to that of Craciun and Pantea [3]. The main difference is that our reactions are all unary, thus allowing for a thorough and simple analysis using ideas from basic linear algebra.

Our analysis shows that the non-uniqueness becomes less severe as the number of chemical reactions become sparse, thus explaining, in part, the success of methods that seek sparse reactions in a system.

We discuss two related work. In Kügler, Gaubitzer and Müller [5], the authors study the Chlorite-Iodide reaction. In their work, the starting point is a chemical reaction network in which likely reactions are already mapped out. The problem is to find the reaction rates from the time history data of the reactants' concentrations while insisting that the network is sparse. Therefore, they are seeking reaction-rate vectors which have the least number of non-zeros and still match the cocentration time series well.

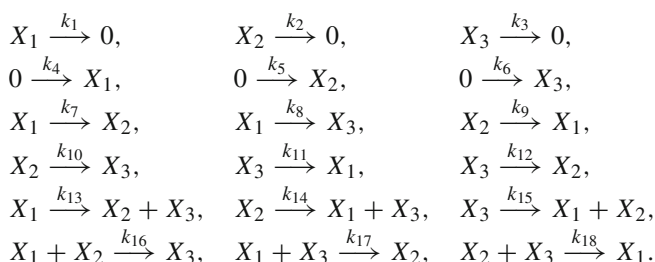
The work of Szederkény [9] considers the more complicated situation where there are stoichiometric reactions. He starts with a reaction network and seeks to find the densest and the sparsest equivalent reaction networks that produce the same differential equations. The approach is based on mixed integer linear programming.

The outline of the paper is as follows. In the next section, we introduce the basic concepts and notation. We show how the reactions can be encoded in a system of differential equations. A formulation of the inverse problem of chemical kinetics is given. Section 3 provides an analysis of the distinguishability issue and attempts to

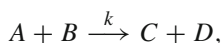
quantify the non-uniqueness in the inverse problem. We provide a way of quantifying the non-uniqueness as a function of sparsity. The final section describes a numerical approach which seeks sparse chemical systems that match the data, and provide numerical evidence indicating its usefulness. The paper ends with a discussion section.

## 2 Inverse problem of chemical kinetics

We begin with some preliminaries. Consider a system in which 3 species react. There will be 18 reactions, which we enumerate as follows:



The first 3 reactions are due to sinks, and the next 3, due to sources. In all there is a reaction rate  $k_j$  associated with each reaction. The basic rule is that if



then their concentrations satisfy

$$-\dot{a} = -\dot{b} = +\dot{c} = +\dot{d} = kab.$$

That is, we assume that the dynamics of the concentrations obey the law of mass action [4]. Using the same rule, we find that  $x_j(t)$  for  $j = 1, 2, 3$ , satisfy a system of ordinary differential equations given by

$$\begin{aligned}
 \dot{x}_1 &= -k_1x_1 + k_4x_1 - k_7x_1 - k_8x_1 + k_9x_2 + k_{11}x_3 - k_{13}x_1 + k_{14}x_2 + k_{15}x_3 \\
 &\quad - k_{16}x_1x_2 - k_{17}x_1x_3 + k_{18}x_2x_3, \\
 \dot{x}_2 &= -k_2x_2 + k_5x_2 + k_7x_1 - k_9x_2 - k_{10}x_2 + k_{12}x_3 + k_{13}x_1 - k_{14}x_2 + k_{15}x_3 \\
 &\quad - k_{16}x_1x_2 + k_{17}x_1x_3 - k_{18}x_2x_3, \\
 \dot{x}_3 &= -k_3x_3 + k_6x_3 + k_8x_1 + k_{10}x_2 - k_{11}x_3 - k_{12}x_3 - k_{13}x_1 + k_{14}x_2 + k_{15}x_3 \\
 &\quad + k_{16}x_1x_2 - k_{17}x_1x_3 - k_{18}x_2x_3.
 \end{aligned} \tag{1}$$

We can write the system in a more compact vector-matrix form as follows. Let  $\mathbf{x} = [x_1, x_2, x_3]^T$  and  $\mathbf{k} = [k_1, \dots, k_{18}]^T$ . The matrix  $M$  is 3-by-18 with entries

$$M(\mathbf{x}) = \begin{bmatrix} -x_1 & 0 & 0 & x_1 & 0 & 0 & -x_1 - x_1 & x_2 & 0 & x_3 & 0 \\ 0 & -x_2 & 0 & 0 & x_2 & 0 & x_1 & 0 & -x_2 - x_2 & 0 & x_3 & \cdots \\ 0 & 0 & -x_3 & 0 & 0 & x_3 & 0 & x_1 & 0 & x_2 & -x_3 - x_3 \\ & & & -x_1 & x_2 & x_3 & -x_1 x_2 - x_1 x_3 & x_2 x_3 \\ \cdots & & & x_1 & -x_2 & x_3 & -x_1 x_2 & x_1 x_3 & -x_2 x_3 \\ & & & x_1 & x_2 & -x_3 & x_1 x_2 & -x_1 x_3 & -x_2 x_3 \end{bmatrix}.$$

The reactions can now be written as

$$\dot{\mathbf{x}} = M(\mathbf{x})\mathbf{k}. \quad (2)$$

This form for the system of equations is general and applies to a system involving  $n$  species. With  $m = 2n + n(n - 1) + n(n - 1)(n - 2)$ , the matrix  $M$  will be of size  $n$ -by- $m$ . If  $\mathbf{k}$  is given, then prescription of initial concentrations,  $\mathbf{x}(0) = \mathbf{x}_0$ , allows us to solve (2) for  $\mathbf{x}(t)$  for  $t > 0$ .

In the inverse problem, we are given measurements of  $\mathbf{x}(t)$  for  $t \in [0, T]$ , i.e.,

$$\mathbf{x}(t) = \mathbf{g}(t), \quad \text{for } 0 \leq t \leq T.$$

The task is to determine the reaction rates  $\mathbf{k}$ . In some cases, instead of continuous time reading, we may be given samples of the concentrations, in which case, the data equation is

$$\mathbf{x}(t_\ell) = \mathbf{g}(t_\ell), \quad \text{for } \ell = 0, 1, \dots, L. \quad (3)$$

For the purpose of this work, we may assume that the inverse problem is formally over-determined. That is, if there are  $n$  species, meaning there are possibly  $m = 2n + n(n - 1) + n(n - 1)(n - 2)$  reactions, we will assume that  $L + 1 > m$ .

One approach to solving the inverse problem numerically is to use the given data and the differential equation (2) to set up an over-determined linear system for  $\mathbf{k}$ . If the time sampling is regular at the rate of  $\Delta t$ . We may approximate the time derivative by a central difference approximation

$$\dot{\mathbf{x}}(t_\ell) \approx \frac{\mathbf{x}(t_{\ell+1}) - \mathbf{x}(t_{\ell-1})}{2\Delta t}.$$

Using the data equation (3) we have, for each time sample  $t_\ell$

$$\frac{\mathbf{g}(t_{\ell+1}) - \mathbf{g}(t_{\ell-1})}{2\Delta t} = M(\mathbf{g}(t_\ell))\mathbf{k}, \quad \text{for } \ell = 1, \dots, L - 1.$$

In the above, the only unknown appearing in the system of  $n$  equations is the  $m$ -vector  $\mathbf{k}$ . Thus, the above represents a linear system with  $n(L - 1)$  equations and  $m$  unknowns.

While the above linear system is over-determined when  $n(L - 1) > m$ , it is not, in general, well conditioned. Indeed, we will show below that there is a null-space associated with the matrix.

### 3 Analysis of distinguishability

In this section we seek to determine if there are two chemical systems, with the same number of species, whose concentration vectors as a function of time are identical if they start with the same initial values. Since the forward problem, described by (2) and some initial concentration vector  $\mathbf{x}_0$  is unique, the only way for two reaction systems to be indistinguishable is for the governing equations to be identical. That is, we wish to know if there are rate vectors  $\mathbf{k}_1$  and  $\mathbf{k}_2$  such that they lead to the same equations of the form (2). In other words, we seek non-trivial pairs  $(\mathbf{k}_1, \mathbf{k}_2)$ , each with positive elements, of

$$M(\mathbf{x})\mathbf{k}^{(1)} = M(\mathbf{x})\mathbf{k}^{(2)}.$$

Since we can rewrite the above as

$$M(\mathbf{x})(\mathbf{k}^{(1)} - \mathbf{k}^{(2)}) = 0,$$

the question amounts to finding the null-space of  $M(\mathbf{x})$ .

To this end, let us examine the structure of (2) more closely. We see that under a permutation of the rate vector  $\mathbf{k}$ , we can write, for the 3-species reaction,

$$M(\mathbf{x}) = [x_1 M_1 \mid x_2 M_2 \mid x_3 M_3 \mid x_1 x_2 M_{1,2} \mid x_1 x_3 M_{1,3} \mid x_2 x_3 M_{2,3}],$$

where

$$M_1 = \begin{bmatrix} -1 & 1 & -1 & -1 & -1 \\ 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix}, \quad M_2 = \begin{bmatrix} 0 & 0 & 1 & 0 & 1 \\ -1 & 1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix},$$

$$M_3 = \begin{bmatrix} 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ -1 & 1 & -1 & -1 & -1 \end{bmatrix}, \quad M_{1,2} = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}, \quad M_{1,3} = \begin{bmatrix} -1 \\ 1 \\ -1 \end{bmatrix}, \quad M_{2,3} = \begin{bmatrix} 1 \\ -1 \\ -1 \end{bmatrix}.$$

In general, if there are  $n$  reactions, we will have submatrices of the form

$$x_i M_i \quad \text{and} \quad x_i x_j M_{i,j},$$

where the entries in matrices  $M_i$  and  $M_{i,j}$  are either equal to zero or one. Under this short-hand notation, we can write  $M(\mathbf{x})$  in general as

$$M(\mathbf{x}) = [x_1 M_1 \mid x_2 M_2 \mid \cdots \mid x_1 x_2 M_{1,2} \mid x_1 x_3 M_{1,3} \mid \cdots \mid x_{n-1} x_n M_{n-1,n}]. \quad (4)$$

Given this structure for  $M(\mathbf{x})$ , we see that what needs to be investigated are the null-spaces associated with each of the  $M_i$  and  $M_{i,j}$ . This is because we can organize the rate vector  $\mathbf{k}$  as

$$\mathbf{k}^T = [\mathbf{k}_1^T \mathbf{k}_2^T \cdots \mathbf{k}_n^T \mathbf{k}_{1,2}^T \cdots \mathbf{k}_{n-1,n}^T].$$

Then (2) can be rewritten in the form

$$\dot{\mathbf{x}} = x_1 M_1 \mathbf{k}_1 + x_2 M_2 \mathbf{k}_2 + \cdots x_i x_j M_{i,j} \mathbf{k}_{i,j} + \cdots + x_{n-1} x_n M_{n-1,n} \mathbf{k}_{n-1,n}. \quad (5)$$

Thus the null-space of  $M(\mathbf{x})$  can be understood by analyzing each of the matrix  $M_s$  where  $s = i$  or  $s = (i, j)$ . The null-vectors of  $M(\mathbf{x})$  are concatenations of the null-vectors of  $M_s$ . The basic problem is, for a given  $\mathbf{k}_s^{(1)}$ , determine if there is a non-trivial  $\mathbf{k}_s^{(2)}$  such that

$$M_s(\mathbf{k}_s^{(1)} - \mathbf{k}_s^{(2)}) = 0, \quad \text{with } \mathbf{k}_s^{(2)} \geq 0.$$

Suppose  $M_s$  has a null-space and let  $V$  be an orthonormal bases for it. Then

$$(\mathbf{k}_s^{(1)} - \mathbf{k}_s^{(2)}) = V\mathbf{z},$$

for some vector  $\mathbf{z}$  whose dimension is that of the null space of  $M_s$ . Let us write

$$\mathbf{k}_s^{(2)} = \mathbf{k}_s^{(1)} - V\mathbf{z}.$$

Because  $\mathbf{k}_s^{(2)}$  is a rate vector, it must be non-negative. Therefore, the problem is to seek  $\mathbf{z}$  such that

$$V\mathbf{z} \leq \mathbf{k}_s^{(1)}, \quad (6)$$

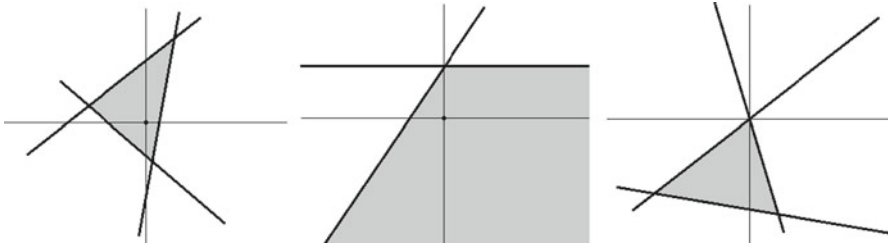
for a given  $\mathbf{k}_s^{(1)}$ . In the following, we will analyze the inequalities further.

### 3.1 The geometry of linear inequalities

The system of linear inequalities in (6) deserves special attention. Since  $\mathbf{k}_s^{(1)}$  is a rate vector, each entry must be nonnegative. Therefore,  $\mathbf{z} = 0$  is a solution to (6). If that were the only solution, then the part of the chemical system associate with matrix  $M_s$  is unique in spite of the presence of a null space. If (6) is satisfied by a set of points which form a non-empty neighborhood of 0, then the part of the chemical system associated with  $M_s$  is nonunique. In particular, given  $\mathbf{k}_s^{(1)}$ , we can pick any  $\mathbf{z} \neq 0$  from this set and calculate  $\mathbf{k}_s^{(2)} = \mathbf{k}_s^{(1)} - V\mathbf{z}$ . Then the set of differential equations corresponding to  $\mathbf{k}_s^{(1)}$  and  $\mathbf{k}_s^{(2)}$  are *identical*.

Let us further examine (6). The set

$$\{V\mathbf{z} \leq \mathbf{k}_s^{(1)}\},$$



**Fig. 1** Possible geometries of the set defined by the inequality (6)

when it is nontrivial, is convex. The set is a polytope region which may be open. Three possibilities for such a region are illustrated in Fig. 1.

To further explore the implications of (6), we could consider for each  $M_s$ , a set of  $\mathbf{k}_s^{(1)}$  with nonnegative entries, and determine if  $\mathbf{z}$  satisfying (6) forms a nonempty neighborhood of 0. While this is an obvious approach, it is unnecessarily explicit since the set of inequalities we need to check are linear. Instead, we consider a vector  $\mathbf{I}_s$  whose entries are either 0 or 1. It will stand as a surrogate for all  $\mathbf{k}_s^{(1)}$  whose zero entries coincide with those of  $\mathbf{I}_s$ , and whose non-zero entries are any positive value. The reason we can use this substitution is because if the set

$$\{V\mathbf{z} \leq \mathbf{I}_s\}, \tag{7}$$

is non-empty in the neighborhood of  $\mathbf{z} = 0$ , then the set

$$\{V\mathbf{z} \leq \mathbf{k}_s^{(1)}\}, \tag{8}$$

is also non-empty as long as the zero entries of  $\mathbf{I}_s$  and  $\mathbf{k}_s^{(1)}$  coincide. To see this, suppose that the set in (7) is a nonempty neighborhood of 0 and  $\mathbf{z}_0$  is a point in this set. Then given a vector  $\mathbf{k}_s^{(1)}$ , if every nonzero entry is greater than 1, then it is clear that  $\mathbf{z}_0$  also lies inside (8). Suppose now that some entries of  $\mathbf{k}_s^{(1)}$  are less than 1. The point

$$\mathbf{z}_t = t\mathbf{z}_0,$$

lies along a ray from 0 to  $\mathbf{z}_0$ . We can reduce  $t$  so that

$$tV\mathbf{z}_0 \leq \mathbf{k}_s^{(1)}.$$

This will be satisfied for some  $t > 0$ . Since the set defined by (7) is convex,  $\mathbf{z}_t$  lies inside it for any  $0 < t \leq 1$ . The last inequality implies that it is also in the set defined by (8). Therefore, if the set defined by (7) has a non-empty neighborhood near 0, then the set defined by (8) also has a non-empty neighborhood near 0. It therefore suffices to consider vectors of the type  $\mathbf{I}_s$  when studying whether (6) is an empty set.

### 3.2 Enumeration of nonunique reaction systems

Next we make an attempt to “quantify” the nonuniqueness aspect of the problem. We will start with a reaction system with a fixed number of species. This fixes the number of reaction rates in the system. Since, as we have shown, the nonuniqueness does not depend on the actual values of the reaction rates, but rather on the number and position of the nonzero entries of the rate vector, we can simply consider reaction rate vectors of a fixed length with 0 and 1 as entries. To cover all possible reactions, we will enumerate this 0-1 rate vectors. If the rate vector is length  $m$ , we start with a vector with one nonzero entry and exhaust all the possible arrangements of such a vector. Then we increase the number of nonzeros by one, and repeat the process of creating all possible vectors of length  $m$ , and so on. We will use  $\mathbf{I}$  to denote one of these  $2^m$  vectors.

To check whether the set in (7) is empty, we solve the optimization problem

$$\max \|\mathbf{z}\|^2 \quad \text{subj } V\mathbf{z} \leq \mathbf{I}. \quad (9)$$

If the maximizer has norm  $\|\mathbf{z}\| > \text{tol}$ , we call the set associated with (7) non-empty.

Note that reactions of the type  $X_i + X_j \rightarrow X_\ell$  has no null space. To see this, let us look at the differential equation describing the concentrations of the species, namely the term

$$x_i x_j M_{i,j} \mathbf{k}_{i,j},$$

in (5). The matrix  $M_{i,j}$  is  $n$ -by- $(n-2)$  and corresponds to the reactions

$$\begin{aligned} \dot{x}_\ell &= k_{i,j}(\ell) x_i x_j, \quad \text{for } \ell \neq i, \ell \neq j \\ \dot{x}_i &= - \sum_{\substack{\ell=1 \\ \ell \neq i \text{ or } j}}^n k_{i,j}(\ell) x_i x_j, \quad \dot{x}_j = - \sum_{\substack{\ell=1 \\ \ell \neq i \text{ or } j}}^n k_{i,j}(\ell) x_i x_j. \end{aligned}$$

One can see that the  $\ell$ th column of the matrix  $M_{i,j}$  is

$$v_\ell = e_\ell - e_i - e_j,$$

where  $\ell$  runs from 1 to  $n$  skipping  $\ell = i$  and  $\ell = j$ . Here  $e_i$  is an  $n$ -dimensional unit vector with a unit entry at position  $i$ . Since  $\ell \neq i$  or  $j$ , the columns are linearly independent. Therefore  $M_{i,j}$  has no null space.

As an illustration, consider reactions of the form  $X_i \rightarrow 0$ ,  $X_i \rightarrow X_j$ , and  $X_i \rightarrow X_j + X_k$  with four species. Because all reactions are considered and the species are indistinguishable,  $M_i = M_j$  for all  $i$  and  $j$  because the two matrices are identical up to row swaps. Then



$$M_1 = \begin{bmatrix} -1 & -1 & -1 & -1 & -1 & -1 & -1 \\ 0 & 1 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 1 & 1 \end{bmatrix}$$

and we can calculate its null basis vectors

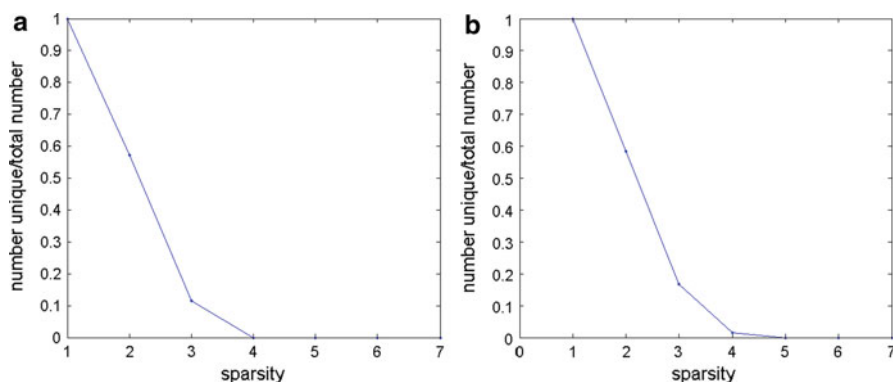
$$V = \begin{bmatrix} 0.3795 & 0.3507 & 0.3286 \\ -0.4682 & -0.4572 & 0.2679 \\ -0.4907 & 0.2392 & -0.4495 \\ 0.2000 & -0.4835 & -0.4756 \\ 0.5794 & -0.1328 & -0.1470 \\ -0.1112 & 0.5899 & -0.1208 \\ -0.0888 & -0.1064 & 0.5965 \end{bmatrix}$$

Next, we generate a set of test vectors to be composed of only 0's and 1's by considering all possible placements of 0's and 1's in a vector of length 7. The total number of vectors generated in this way is  $2^7 = 128$ . For every vector, we solve (9) to see if (7) is empty. The tolerance we used was  $10^{-6}$ .

To quantify the nonuniqueness, we introduce the concept of sparsity. A chemical system is called 'sparse' if its reaction rate vector has very few nonzero entries. Let  $m$  be the number of possible reaction in an  $n$  species system. A measure of sparsity is the number of nonzeros in the rate vector  $\mathbf{k}$ . We will group our rate vectors  $\mathbf{I}$ 's by their number of nonzeros, their sparsity number. For a given sparsity number, we will count the number of instances in which the vectors  $\mathbf{I}$ 's give the unique solution  $\mathbf{z} = 0$ . Therefore, a uniqueness measure for a given sparsity number is the ratio between the number of  $\mathbf{I}$ 's for which (7) is only satisfied by  $\mathbf{z} = 0$  and total number of the vectors of that sparsity class.

We performed the computation described for a system with 4 species and 5 species. The calculations revealed that as we increase the sparsity, allowing for more chemical reactions to take place, the inverse problem is adversely effected. Figure 2 shows the results of our calculations. It can be seen that for the 4- and 5-species systems, we lose uniqueness if there are more than one reaction. The measure of uniqueness drops quickly. To appreciate what lack of uniqueness means, consider a 4-species system. The calculation states that any reaction rate vector with 4 nonzero entries can be replaced with another one with the same number of nonzeros. Similarly, any system with 5 species with 5 reactions can be replaced with another with the same number of reactions. In fact, our analysis shows how to construct these equivalent chemical systems.

The idea of enforcing sparsity in chemical reactions while at the same time fitting the measured concentration data has gained popularity [5,9]. In light of the lack of uniqueness in the system under consideration, one must take caution in using such an approach. We will next show, in numerical examples, that sparsity enforcing approaches to our system of reactions may present some difficulties.



**Fig. 2** Plots of percent uniqueness as a function sparsity. On the *left* is for a system with 4 species, and on the *right*, 5. Note that as the sparsity increases, the issue of distinguishability becomes more severe

#### 4 Sparsity enforcing approaches

A chemical reaction system with  $n$  species leads to large number of possible reactions  $m$  (where  $m$  is cubic in  $n$ ). Moreover, we have shown that there may be many reaction systems whose dynamics are indistinguishable. Of the many systems that are equivalent, we may wish to determine one that has the least number of reactions.

The number of reactions is the number on non-zero entries in  $\mathbf{k}$ . Therefore, the system with the least number of reactions is one that is sparsest. We have shown above that the level of uniqueness is inversely proportional to sparsity. Thus sparsity may have some practical value.

##### 4.1 $\ell_1$ norm

The use of the  $\ell_1$  norm to enforce sparsity has a long history in signal processing [2, 7], and has been used in inverse problems for chemical systems [5, 9]. The idea is to find a chemical reaction system, characterized by  $\mathbf{k}$  that has the smallest  $\ell_1$  norm

$$\|\mathbf{k}\|_1 = \sum_i |k_i| = \sum_i k_i,$$

since  $k_i \geq 0$ .

To fit the data  $\mathbf{g}(t_\ell)$ , we impose the constraint

$$|\mathbf{A}\mathbf{k} - \mathbf{y}| \leq \epsilon,$$

where

$$\mathbf{y} = \frac{1}{2\Delta t} \begin{bmatrix} \mathbf{g}(t_2) - \mathbf{g}(t_0) \\ \mathbf{g}(t_3) - \mathbf{g}(t_1) \\ \vdots \\ \mathbf{g}(t_L) - \mathbf{g}(t_{L-2}) \end{bmatrix}, \quad A = \begin{bmatrix} M(\mathbf{g}(t_1)) \\ M(\mathbf{g}(t_2)) \\ \vdots \\ M(\mathbf{g}(t_{L-1})) \end{bmatrix}.$$

Thus, the problem for solving the inverse problem using  $\ell_1$  to enforce sparsity is a linear program

$$\begin{aligned} \min c^T \mathbf{k} \\ \text{subj } |\mathbf{A}\mathbf{k} - \mathbf{y}| \leq \epsilon, \quad \mathbf{k} \geq 0 \end{aligned}$$

with  $c^T = [1, 1, \dots, 1]$ .

#### 4.1.1 Numerical experiments with $\ell_1$ objective

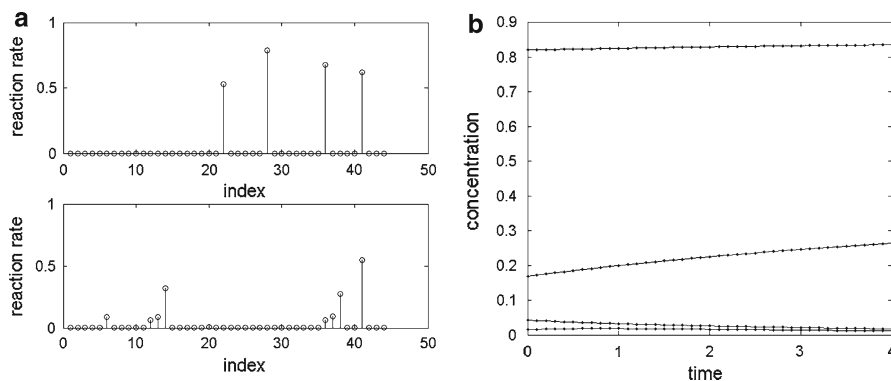
We tested the method described above in numerical experiments. To generate data, we start by choosing a sparsity number for the chemical reactions; i.e., the number of non-zeros in the rate vector  $\mathbf{k}$ . The places where the non-zeros occur are randomly chosen. Then we generate random positive numbers between 0 and 1 for the non-zero entries. To generate data for inversion, we solve the system of ordinary differential equations (2) with random initial data. The concentrations of the species in the system were sampled at regular intervals. The data generated were used to solve the inverse problem with the  $\ell_1$  objective. The tolerance for data fit,  $\epsilon$  is set at  $10^{-3}$ .

We performed many experiments with 4 species and sparsity number equal to 4. We found that even though distinguishability is an issue (see previous section), we were able to find the ‘ground truth’ reaction rate  $\mathbf{k}$  more often than not. When the method fails, it finds a reaction rate vector with more non-zeros than the true rate vector. As an illustration of the failure of the method, we show in Fig. 3a, top, the true rate vector. The concentrations of the 4 species as a function of time are shown in Fig. 3b. The algorithm recovered the rate vector shown in Fig. 3a, bottom. It can be seen that this rate vector has a few more non-zeros than the true one. When the recovered rate vector was used to calculate the concentrations of the species using the same initial data, we found that the concentrations match the data very well—the relative  $\ell_2$  error in the fit was under 0.6%.

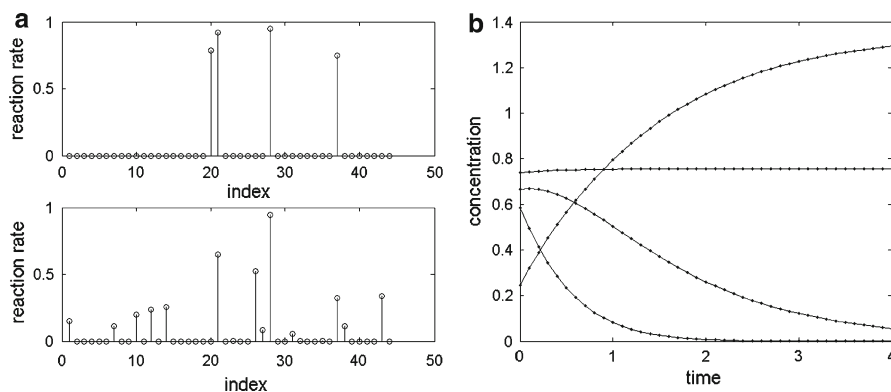
We observed that when the concentrations show a lot of variation in time, e.g., rapid rise or decrease, the algorithm works well. We draw a connection of this observation to the concept of “sufficient excitation” in the study of parameter estimation. For a description to this and related concepts, the reader is referred to [6]. This observation may be useful when confronted with measured data.

#### 4.2 $\ell_0$ norm

As we have seen, the  $\ell_1$  norm enforcement appeared insufficient to give the kind of sparsity results that we were after. We now turn to an approach using a different norm. We choose the functional



**Fig. 3** An example where  $\ell_1$  sparsity enforcement fails. In Fig. 3a (left) we show the true rate vector in the top figure. The figure on the right, Fig. 3b, shows the concentrations of the 4 species as a function of time. These are the data for the inverse problem. Figure 3a, bottom, shows the recovered rate vector  $\mathbf{k}$ . When the recovered rate vector is used to solve for the concentrations, we found that they match the data very well



**Fig. 4** An example where  $\ell_0$  sparsity enforcement fails. In Fig. 4a (left) we show the true rate vector in the top figure. The figure on the right, Fig. 4b, shows the concentrations of the 4 species as a function of time. These are the data for the inverse problem. Fig. 4a, bottom, shows the recovered rate vector  $\mathbf{k}$ . When the recovered rate vector is used to solve for the concentrations, we found that they match the data very well

$$f(\mathbf{k}) = \sum_i (k_i)^q$$

for a parameter  $q > 0$ . As  $q \rightarrow 0$ ,  $f(\mathbf{k})$  approaches the  $\ell_0$  norm. This idea has been considered in the chemical system context [5], and in signal processing [1]. A very small  $q$  gives a very good approximation to the  $\ell_0$  norm. The inverse problem is reformulated as

$$\begin{aligned} &\min f(\mathbf{k}) \\ &\text{subj } |\mathbf{A}\mathbf{k} - \mathbf{y}| \leq \epsilon, \quad \mathbf{k} \geq 0. \end{aligned}$$

This problem can be solved as a constrained nonlinear optimization.

#### 4.2.1 Numerical experiments with the $\ell_0$ objective

The  $\ell_0$  norm approach was tested in the same way as the  $\ell_1$  approach. We used the MATLAB package `fmincon` to solve the constrained nonlinear functional. A randomized reaction rate vector with fixed number of positive non-zeros was generated and used to create data. This data were then used to find  $\mathbf{k}$  through the optimization problem. We solve the optimization problem above with  $q = 10^{-4}$  and  $\epsilon = 10^{-3}$ .

We found that this formulation of the problem recovered the reaction rate vector with better reliability than the  $\ell_1$  method. We show an example calculation where the  $\ell_0$  approach does not work.

We note some observations. The first problem we discovered was that the minimization behaved very poorly if one of the time series was always zero or almost always zero. However, as shown above, the biggest problem was recovering a rate vector that was not the original one. This was because the method became stuck in a minimum that reproduced exactly the same set of differential equations.

## 5 Discussion

Our conclusion is that there is no straight-forward, mathematical way to ‘fight’ the problems posed by indistinguishability. The answer to these problems must come from knowledge of the underlying chemistry. It is very likely that chemists will come at the chemical kinetics inverse problems with knowledge of which reactions are likely, and which are not. This added *a priori* information can be incorporated in the inverse problem, either as additional equalities or bounds on the reaction rate vector  $\mathbf{k}$ .

Our work has shown that we can analyze the issue of distinguishability for our system by using basic linear algebra. We were able to ‘quantify’ the nonuniqueness by parametrizing the problem using the concept of sparsity. The general rule is that the sparser a chemical system, the more likely it is to create a unique ODE. However, it must be pointed out that even very sparse systems are not unique.

We have further shown that sparsity enforcing approaches such as using the  $\ell_1$  and  $\ell_0$  functional of the reaction rate vector  $\mathbf{k}$  are insufficient. While we did observe that these approaches can work in some situations, they fail in others. The numerical experiments we carried out provide further evidence of the need for an approach that incorporates domain chemistry knowledge that could be incorporated as additional side information. The work of Kügler exemplifies such an approach.

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