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Original Paper

Algebraic Approaches to Underdetermined Experiments in Biology

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We sometimes meet an experiment in which its rate constants cannot be determined in this experiment only; in this case, it is called an underdetermined experiment. One of methods to overcome underdetermination is to combine results of multiple experiments. Multiple experiments give rise to a large number of parameters and variables to analyze, and usually even have a complicated solution with multiple solutions, which situation is unknown to us beforehand. These two difficulties: underdetermination and multiple solutions, lead to confusion as to whether rate constants can intrinsically be determined through experiment or not. In order to analyze such experiments, we use 'prime ideal decomposition' to decompose a solution into simpler solutions. It is, however, hard to decompose a set of polynomials with a large number of parameters and variables. Exemplifying a bio-imaging problem, we propose one tip and one technique using 'resultant' from a biological viewpoint.

1. Introduction

In biological problems, we sometimes meet an underdetermined experiment. Underdetermination arises from insufficient data from a single experiment to determine concrete values of rate constants. We proposed a method to overcome such underdetermination by combining two experiments in the previous papers [1),2)], to allow the rate constants for Parkinson's disease diagnosis to be determined. In this paper, we also propose an approach for determining rate constants by combining multiple experiments.

Combination of multiple experiments, however, yields two difficulties. One is the existence of a large number of parameters and variables. The other is that a solution to a system of equations is decomposed into multiple distinct solutions that are of various dimensions. For instance, imagine that a set of polynomials describing some experiment is: $\{z^2-2, y^2+2y-1, xy+xz-yz+x-z-2\}$. The solution to this set can be decomposed into two solutions: $\{z^2-2, y+z+1\}$ of one dimension, and $\{z^2-2, y-z+1, x-z\}$ of zero dimension. We cannot determine the variables, x, y and z, with the former, but we can determine them with the latter. Further, under a biologically acceptable condition, $x>0 \wedge y>0 \wedge z>0$, this decomposition means the variables are identifiable ($x=z=\sqrt{2}, y=\sqrt{2}-1$) because the only latter solution is biologically reasonable. It is necessary to perform decomposition to analyze a system because we cannot know beforehand whether experiments have a biologically acceptable solution. Indeed, the isochronicity of an oscillator system and the multibody system were analyzed through ideal decomposition [3),4)]. Such decomposition of algebraic equations is called *prime ideal decomposition*. We hence have to perform prime ideal decomposition of a set of polynomials with a large number of parameters and variables. Here we show one tip and one technique for efficient calculation using 'resultant.'

State of the arts

One can use various methods to decompose a zero-dimensional ideal (solution) [5)–8)]. Nevertheless, the larger number of variables, the more difficult straightforward decomposition becomes [9)]. For relatively large problems of zero dimension, one can use the homotopy method to decompose their solutions [10)]. The homotopy method is known to be a robust method for finding all isolated zero-dimensional solutions [11)]. Since the homotopy method starts with a randomly generated seed, it sometimes fails to trace its true solutions, indicating that some higher-dimensional solutions make this method halt. This method is more efficient, but is less robust than our method because, for multiple experiments, we usually have to deal with an ideal (solution) of higher dimension like the bio-imaging experiment addressed in this paper.

For an ideal of higher dimension, one can use a method shown in Ref. 12). This method is sometimes more efficient than ours when the degree of a given set of polynomials is low, but often halts without answer or is less efficient when the degree is high as the example addressed here. As another method for higher dimension, one can use the regular chains theory to decompose an ideal [13)], but

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it cannot often decompose an ideal generated by a lot of variables. Last, as a numerical method, one can use a marching method for tracing curves [14]. This method is efficient, but can fail to trace all solutions because it starts to trace from its singularity points. We hence propose algebraic approaches here because some other methods are sometimes efficient, but can fail to obtain all solutions and to decompose them.

2. Problem

A problem with respect to an underdetermined experiment i is described as a system of differential equations as follows:

$$\begin{aligned} \text{Problem (INPUT } i\text{): } \mathrm{d}C_{ij}(t)/\mathrm{d}t &= f_{ij}(C_{i1}(t), C_{i2}(t), \ldots, C_{in_i}(t), e_i(t), \vec{k_i}), \\ S_i(t) &= g_i(C_{i1}(t), \ldots, C_{in_i}(t), \vec{k_i}), \end{aligned} \tag{1}$$

where $C_{ij}(t)$ $(1 \leq j \leq n_i)$ denotes a concentration of chemical j in t, and $e_i(t)$ is a concentration of an external data that we can never eliminate with Experiment i only. $\vec{k_i}$ are rate constants to determine, and $S_i(t)$ denotes a polynomial to fit experimental data as a polynomial, for instance, $d_{i0} + d_{i1}t + d_{i2}t^2$.

The aim is to determine concrete values of $\vec{k_i}$. For this purpose, first, we have to perform two eliminations by using algebraic approaches. One is elimination of $C_{ij}(t)$ that we cannot observe individually. We can observe only combination of chemical concentrations, described by g_i. The other is elimination of $e_i(t)$ by combing other problems (experiments). Next, through these two eliminations, a set of Problems $1, 2, \ldots$ is converted to a set of polynomials over $\mathbb{Q}[d_{ij}, \vec{k_i}]$ $(i = 1, 2, \ldots, j = 0, 1, 2)$ denoted by s_p. The solution of s_p usually divides into multiple solutions. We hence have to perform prime ideal decomposition of s_p. Last, when we find zero-dimensional prime ideal(s) biologically acceptable and non-zero ones not acceptable, the zero one is a targeted solution thereby we can determine $\vec{k_i}$ $(i = 1, 2, \ldots)$. That is, the output of INPUT $1, 2, \ldots$ is

$$\text{OUTPUT: zero-dimensional prime ideal(s) over } \mathbb{Q}[\bigcup_{i=1} \vec{k_i}], \tag{2}$$

which will provide us with concrete values of $\vec{k_i}$ $(i = 1, 2, \ldots)$.

3. Methods

In Section 2, we mention two eliminations and prime ideal decomposition. First, to perform one elimination of chemical concentrations, $C_{ij}(t)$ $(1 \leq j \leq n_i)$ in Eq. (1), we use the differential elimination method [15)–17)] ⋆1.

Next, to perform the other elimination of $e_i(t)$ in Eq. (1), we combine multiple experiments (problems) that lead to a linear relation of $\{e_i(t) | i = 1, 2, \ldots\}$. For instance, in case of two experiments with a relation, $e_1(t) - e_2(t) = 0$, we obtain a set of polynomials over $\mathbb{Q}[d_{ij}, \vec{k_i}]$ (denoted by s_p) that make $e_1(t) = e_2(t)$ an identity in t.

Last, to decompose s_p, we perform prime ideal decomposition. For this purpose, one can use the subroutine `minAssChar` supplied by the `Singular 3-1-0` software [18)] or *ICS* command of `Epsilon 0.618 (C) 2003 by Dongming Wang`. But, it takes much time to decompose a set of polynomials with a lot of variables, and we hence explain one tip and propose one technique in the next sub-sections.

3.1 A Tip for Decomposition

From a viewpoint of biology, we sometimes do not need to determine all of the variables in $\bigcup_{i=1} \vec{k_i}$. In this case, we can use a Gröbner basis in terms of elimination order. Let $\vec{k_r}$ denote needed variables in $\bigcup_{i=1} \vec{k_i}$. The procedure is (i) calculate a Gröbner basis G in terms of elimination order $(\bigcup_{i=1} \vec{k_i}) \setminus \vec{k_r} \gg \vec{k_r}$. (ii) perform prime ideal decomposition of $G \cap \mathbb{Q}[\vec{k_r}]$ denoted by G_E. It usually takes less time to decompose G_E than G or the original set because of less number of variables. It may be worth noting that all of these partial solutions cannot possibly be extended to a full solution according to Extension Theorem, but it seems like rare case in practical models.

3.2 A Technique for Decomposition

From another viewpoint of biology, we can use 'not-equal' condition that means $k_{ij} \neq k_{il}$ $(j \neq l)$ as well as $k_{ij} \neq 0$. Here we have implemented an efficient 'resultant-factorization technique' where this condition is used during calculation. This technique is implemented as follows:

⋆1 When a system of differential equations is composed only of linear terms, we can use the ordinary elimination method using Gröbner base via Laplace transformation [2)].

Let $B_P = \{B_{Pi} \mid 1 \leq i \leq n\}$ be an original set of polynomials.

(1) Procedure-1(s_p, s_f): for an input of a set of polynomials, s_p, and a set of factors, s_f, we remove factors from each polynomial in s_p, and return its result. In biological problems, we assume the above-mentioned 'not-equal' condition, indicating that s_f contains $k_{ij} - k_{il} (j \neq l)$ as well as a positive-value condition, k_{ij}.

(2) Procedure-2(s_p): for an input of a set of polynomials, s_p, we remove redundant elements like p, p and $p, -p \in s_p$, and return its result.

(3) Procedure-3 (constant_check)(s_p): for an input of a set of polynomials, s_p, we check whether s_p contains a monomial. If so, we trim this input and halt because this set violates the 'not-equal' condition.

(4) Procedure-4(s_p): for an input of a set of polynomials, s_p, if some element in s_p can be factorized into multiple factors over $\mathbb{Q}$, say, $f_1 \times f_2$ we return a list of set of polynomials, say, corresponding $\langle s_p, f_1 \rangle$ and $\langle s_p, f_2 \rangle$, otherwise, we return s_p. This procedure is based on:

$$\sqrt{\langle I, f \times g \rangle} = \sqrt{\langle I, f \rangle} \cap \sqrt{\langle I, g \rangle}, \tag{3}$$

where I is an ideal, f and g are polynomials.

(5) Procedure-5 (variable_choice)(s_p): for an input of a set of polynomials, s_p, returns a variable to remove in the next (resultant) procedure. The procedure to choose a variable is below:

If in s_p there is a variable that is contained by only one polynomial, we return this variable and the polynomial containing it. In this case, it is unnecessary to actually calculate resultants in the next (resultant) procedure because the resultant of polynomials p and q in x is q^r, where q does not have a variable x, and r is the degree of x in p.

Otherwise, we choose a variable as mentioned below:

(a) We calculate $\mathrm{d}(i, j)$ as the degree of variable $x_i \, (1 \leq i \leq n)$ in a given polynomial $p_j \, (1 \leq j \leq m)$. Then we denote by d_i the maximum value among $\mathrm{d}(i, j) \, (1 \leq j \leq m)$.

(b) If only one d_k provides the minimum among $d_i (1 \leq i \leq n)$, return x_k. Otherwise, that is, if multiple d_i's provide the same minimum, let $y_1, y_2, \ldots, y_l$ be variables that provide this minimum. We calculate $n_i \, (1 \leq i \leq l)$ as the number of polynomials that contain variable $y_i \, (1 \leq i \leq l)$.

(c) If only one n_k provides the minimum among $n_i \, (1 \leq i \leq l)$, return y_k. Otherwise, that is, if multiple n_i's provide the same minimum, let $z_1, z_2, \ldots, z_j$ be variables that provide this minimum. We calculate $t_i \, (1 \leq i \leq j)$ as the number of terms in the polynomials that contain $z_i \, (1 \leq i \leq j)$. Return z_k that provides the minimum and appear at first in calculation.

As an accompanying output of the above (a)-(c), we return a polynomial that contains the returned variable, and has the minimum number of terms.

(6) Procedure-6 (resultant)(s_p, v, p_i) returns a set of resultants calculated based on the variable and polynomial (v, p_i) chosen in Procedure-5 (variable_choice). That is, we return a set of resultants of polynomials $p_i \in s_p$ and $p_j \in s_p \, (i \neq j)$ in variable v.

We perform the following Resultant-factorization algorithm, using the procedures $1, 2, \ldots, 6$ above. In this algorithm, we set N empirically, and set R_F $\{k_{ij} - k_{il} \mid j \neq l\} \cup \{k_{ij}\}$. Note that Procedure-4 can bring about branches of procedures so that the main routine is recursively called.

Algorithm Resultant-factorization
Specification: Resultant-factorization(B_P, N, R_F)
Input: B_P: a set of polynomials, N: the number of element where the computation exit while-loop, R_F: the factors to remove in Procedure-1
Output: zero-dimensional prime ideal(s),
begin
$s_p \leftarrow B_P$
while TRUE **do**
 $s_p \leftarrow$ Procedure-1(s_p, R_F);
 $s_p \leftarrow$ Procedure-2(s_p);
 $s_p \leftarrow$ Procedure-3(s_p)
  if Procedure-3 halt **then** halt;
 $list \leftarrow$ Procedure-4(s_p)
  for each element s_p **in** $list$ **do**
   if the number of element of s_p is greater than N **then**

```
    (v, p_i) ← Procedure-5(s_p);
    s_p ← Procedure-6(s_p, v, p_i);
    Call Resultant-factorization(s_p, N, R_F)
  else
    s_p ← B_P ∪ s_p
    if s_p is 0-dimensional then
      return s_p
    else
      Perform prime ideal decomposition *1 of s_p;
      Return 0-dimensional prime ideal(s) among the obtained prime ideals
    end-if
  end-if
 end-for
end-while
end
```

The technique introduced in this subsection is based on the following fact. Let ideal I be $\langle f_1, f_2, \cdots, f_r\rangle$, $(f_i \in k[x_1, x_2, \ldots, x_n])$, and let g_i $(1 \le i < r)$ be the resultant of f_1 and f_{i+1} with respect to, say, x_1. Then $\langle g_1, g_2, \ldots, g_{r-1}\rangle \subseteq I \cap k[x_2, x_3, \ldots, x_n]$ holds, leading to $I = \langle f_1, f_2, \ldots, f_r, g_1, g_2, \ldots, g_{r-1}\rangle$. Even when neither of f_i $(1 \le i \le r)$ is reducible over $\mathbb{Q}[x_1, x_2, \ldots, x_n]$, some of g_i $(1 \le i < r)$ are sometimes reducible, resulting in usage of Eq. (3) in Procedure-4.

4. Bio-imaging Example

We exemplify experiments for bio-imaging of living mice. Two experiments are illustrated in **Fig. 1**. Experiments 1 and 2 correspond to Problems 1 and 2 in Eqs. (4) and (5) respectively.

$$\text{Problem 1: } \begin{cases} \mathrm{d}C_{11}(t)/\mathrm{d}t = k_{11}e_1(t) - k_{12}C_{11}(t) - k_3C_{11}(t)C_{13}(t) + k_4C_{12}(t), \\ \mathrm{d}C_{12}(t)/\mathrm{d}t = k_3C_{11}(t)C_{13}(t) - (k_4+k_{15})C_{12}(t), \\ \mathrm{d}C_{13}(t)/\mathrm{d} = k_{16} - k_{17}C_{13}(t) + k_4C_{12}(t) - k_3C_{11}(t)C_{13}(t), \\ S_1(t) = (C_{12}(t)+C_{13}(t))/k_c, \end{cases} \tag{4}$$

*1 Because of summation ($s_p \leftarrow B_P \cup s_p$ in the above), this prime ideal decomposition is easier to calculate that that of B_P only.

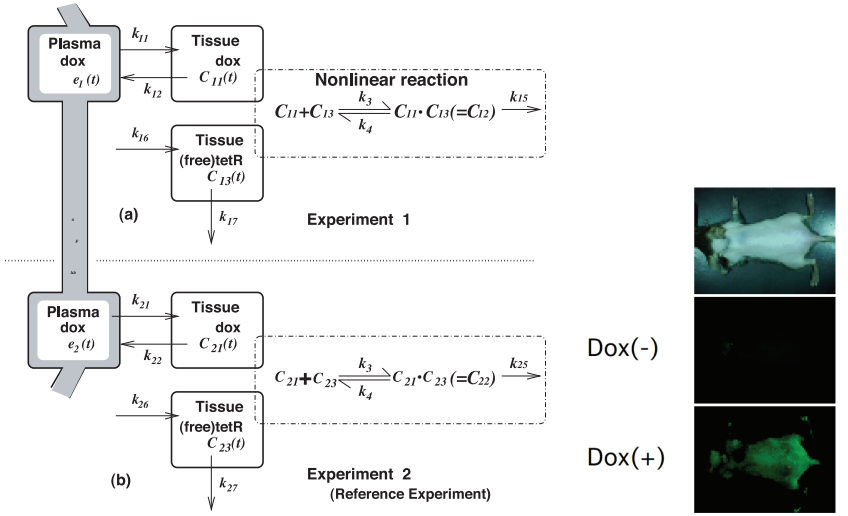

Fig. 1 The experiments for bio-imaging. (a) Experiment 1. (b) Experiment 2. In biology, such an experiment is sometimes called 'reference experiment' because this is much the same as Experiment 1 except for the observed part.

where $e_1(t)$ denotes an external data, and we can observe only the amount of $(C_{12}(t) + C_{13}(t))/k_c$ to fit as $d_{10} + d_{11}t + d_{12}t^2$, which form suffices in this bio-imaging experiment.

Likewise,

$$\text{Problem 2: } \begin{cases} \mathrm{d}C_{21}(t)/\mathrm{d}t = k_{21}e_2(t) - k_{22}C_{21}(t) - k_3C_{21}(t)C_{23}(t) + k_4C_{22}(t), \\ \mathrm{d}C_{22}(t)/\mathrm{d}t = k_3C_{21}(t)C_{23}(t) - (k_4 + k_{25})C_{22}(t), \\ \mathrm{d}C_{23}(t)/\mathrm{d} = k_{26} - k_{27}C_{23}(t) + k_4C_{22}(t) - k_3C_{21}(t)C_{23}(t), \\ S_2(t) = (C_{22}(t) + C_{23}(t))/k_c, \end{cases} \tag{5}$$

where $e_2(t)$ denotes an external data, and we can observe only $(C_{22}(t)+C_{23}(t))/k_c$ to fit as $d_{20} + d_{21}t + d_{22}t^2$. Note that variables k_c, k_3 and k_4 are common in Problems 1 and 2.

5. Result

We determined the rate constants, $\vec{k_1}$ and $\vec{k_2}$ in Problems 1 and 2

through our method. First, we derived a formula containing only $e_1(t), \vec{k_1}$, $(e_2(t), \vec{k_2})$ and t by applying the differential elimination package, `diffalg` with ranking=$[[C_{11}, C_{12}, C_{13}], [e_1]]$ ($[[C_{21}, C_{22}, C_{23}], [e_2]]$) to Problem 1 (2) in Eq. (4) (in Eq. (5)) over MAPLE 11.02. Together with partial fraction decomposition, $e_i(t)$ $(i = 1, 2)$ are obtained as follows:

$$e_i(t) = a_{i0} + a_{i1}t + a_{i2}t^2 + \frac{a_{i3} + a_{i4}t}{a_{i7} + a_{i8}t + t^2} + \frac{a_{i5} + a_{i6}t}{(a_{i7} + a_{i8}t + t^2)^2} \tag{6}$$

with

$$a_{i0} = \frac{2k_3k_{i5}d_{i2}k_c + k_{i5}^2k_{i2}k_{17} - \cdots}{k_{i5}k_{i1}k_3(k_{i7} - k_{i5})},$$

$$a_{i1} = \frac{2k_3k_{i5}^2k_cd_{i2} + k_3d_{i1}k_ck_{i5}^2k_{i7} + 2k_3k_{i5}k_cd_{i2}k_{i7}}{k_{i5}k_{i1}k_3(k_{i7} - k_{i5})},\ a_{i2} = \frac{k_{i5}k_cd_{i2}k_{i7}}{k_{i1}(k_{i7} - k_{i5})},$$

$$a_{i3} = \frac{k_{i5}^2d_{i0}k_{i2}k_{i7} + 2k_{i5}^2d_{i2} - k_{i5}k_{i2}k_{i7}d_{i1} - \cdots}{d_{i2}k_{i5}^2k_3k_{i1}}$$

$$a_{i4} = \frac{-2k_{i2}k_{i5}^2d_{i2} - 2k_{i5}k_{i2}k_4d_{i2} + 2k_{i2}k_4k_{i7}d_{i2}}{d_{i2}k_{i5}^2k_3k_{i1}},$$

$$a_{i5} = \frac{k_{i5}^2d_{i1}k_{i7}^2d_{i0} - 4k_{i5}^3d_{i2}d_{i0} - k_{i5}^3d_{i1}d_{i0}k_{i7} + \cdots}{k_{i5}^3d_{i2}^2k_3k_{i1}},$$

$$a_{i6} = \frac{-2k_{i5}^2d_{i2}k_4d_{i0}k_{i7} - 2k_{i5}^2k_4d_{i2}d_{i1} - \cdots}{k_{i5}^3d_{i2}^2k_3k_{i1}},$$

$$a_{i7} = \frac{-d_{i0}k_{i7} + k_{i5}d_{i0}}{k_{i5}d_{i2}},\ a_{i8} = \frac{k_{i5}d_{i1} + 2d_{i2}}{k_{i5}d_{i2}}. \tag{7}$$

From a biological assumption $C_{i2}(0) = 0$ $(i = 1, 2)$, we obtained relations, $k_{i6} = k_c(d_{i0}k_{i7} + d_{i1})$. Therefore, in what follows, we substituted k_{i6} with the formulae on the right-hand side.

Next, we had to derive a set polynomials that makes $e_1(t) = e_2(t)$ an identity in t. From Eq. (6), we obtained polynomials w.r.t. a_{ij} $(i = 1, 2, 0 \leq j \leq 8)$. These polynomials themselves were complicated, but prime ideal decomposition of them yielded the following three relations: (A) $\{a_{1j} - a_{2j} | 0 \leq j \leq 8\}$ (B) $\{a_{1j} - a_{2j} | 0 \leq j \leq 2\} \cup \{a_{ij} | i = 1, 2, 3 \leq j \leq 6\}$ (C) $\{a_{1j} - a_{2j} | j = 0, 1, 2, 4\} \cup \{a_{13} - a_{23} - a_{18}a_{24} + a_{24}a_{28}, \ldots, 2a_{25}^2 - 8a_{23}^2a_{27}^2 + 8a_{24}a_{26}a_{27}^2 - \cdots - a_{24}^2a_{27}a_{28}^4 + a_{23}a_{24}a_{28}^5\}$. Relation (B) violates the 'not-equal' condition: $k_{ij} \neq 0$. Relation (C) is not biologically acceptable because the last term of (C) contains $\{a_{2j} | 0 \leq j \leq 8\}$ only, meaning that this term is an artificial constraint composed only of the rate constants of Experiment 2. Thus consideration of Relation (A) suffices, and consequently, we obtained the following set of 12 polynomials:

$$\{-k_{15}d_{12}k_{25}d_{21} - 2k_{15}d_{12}d_{22} + k_{25}d_{22}k_{15}d_{11} + 2k_{25}d_{22}d_{12}, d_{10}k_{25}d_{22}k_{15} - d_{10}k_{25}d_{22}k_{17} - d_{20}k_{15}d_{12}k_{25} + d_{20}k_{15}d_{12}k_{27}, (-d_{10}k_{25}d_{22}k_{17} + d_{20}k_{15}d_{12}k_{25} + d_{10}k_{25}d_{22}k_{15} - d_{20}k_{15}d_{12}k_{27})(d_{10}k_{25}d_{22}k_{15} - d_{10}k_{25}d_{22}k_{17} - d_{20}k_{15}d_{12}k_{25} + d_{20}k_{15}d_{12}k_{27}), -2k_{15}^2d_{12}^2k_{25}^2d_{22}d_{20} + 2k_{15}^2d_{12}^2k_{27}d_{22}k_{25}d_{20} - k_{15}^2d_{12}^2k_{25}^2d_{21}^2 - 4k_{15}^2d_{12}^2d_{22}k_{25}d_{21} - 4k_{15}^2d_{12}^2d_{22}^2 + \cdots\}. \tag{8}$$

Notice that k_c, k_3 and k_{11}, k_{21} always appear in the form $k_c \times k_3$ and k_{11}/k_{21}, respectively, throughout the formulae; each of $k_c \times k_3$ and k_{11}/k_{21} is accordingly dealt with as single variables k_{c3} and k_{1121} hereafter.

As mentioned in Section 3, to extract a zero-dimensional solution from set (8), we have to decompose it. Before decomposition, we substituted rationalized experimental data, $d_{10} = -201719/100000000$, $d_{11} = 100991/25000000$, $d_{12} = -83061/500000000$, $d_{20} = -3/1000, d_{21} = 1/500$, and $d_{22} = -1/2500$ into the set (8). There are two cases for decomposition.

(i) When the rate constants we need to determine are limited, it is sufficient to decompose an elimination ideal of the set (8) w.r.t. the limited variables. For instance, it took around 30 seconds to decompose an elimination ideal w.r.t. $\{k_{17}, k_{15}, k_{c3}, k_4\}$, using *ICS* command of `Epsilon 0.618 (C) 2003 by Dongming Wang` over MAPLE 11.02 with Intel® Xeon® W5590 `CPU 3.33 GHz` processor.

(ii) Considering when we have to determine all of the rate constants, we tried three packages: (a) *ICS* command of `Epsilon 0.618` over MAPLE 11.02, (b) *minAssChar* command of `Singular 3-1-0`, and (c) our implemented program of 'resultant-factorization technique' addressed in Section 3.2 over `Risa/Asir Ver. 20090215`. With the same machine as (i), it took around (a) 2040 (b) 3960 (c) 2.3 seconds to decompose Set (8). Through three methods, we have found Set (8) to be decomposed into the following six components:

[**1** $\{k_{15}, k_{17}, k_{25}\}$
[**2** $\{k_{15}, k_{25}, k_{27}\}$
[**3** $\{k_{15}, k_{25}, 200000k_{1121} - 83061\}$
[**4** $\{k_{12} - k_{22}, k_{15} - k_{17}, k_{25} - k_{27}, 145865k_{17}k_{27} + 15102k_{17} - \cdots\}$
[**5** $\{k_{12} - k_{22}, k_{17} - k_{27}, 300000k_{1121} - 201719, \ldots\}$
[**6** $\{ k_{17} - k_{27}, 68083149004k_{15} + 627193611k_{25} + 2329559010k_{27} - 4846277106,$
$-271342259053609005k_{25} + 4112660587955645061 0k_{27}^2$
$-165667449307180431811k_{27} + 5483547450607526748,$
$(5884748387k_{27} - 232955901)k_{25} + \cdots, \ldots\}$.

The first three components [1–[3 violate the positive-value condition for the rate constants, and the fourth and fifth [4 and [5 violate the physiological fact: $k_{12} \neq k_{22}$ meaning difference in **dox** between Experiments 1 and 2. Only the last component [6 is biologically acceptable and zero-dimensional, providing us with concrete values of the rate constants. The solution to the last component is composed of 3 elements. For one of these 3 elements, there is a unique element satisfying the positive-value condition. This element is:

$$\begin{cases} k_{1121} = 0.67239667, \\ k_{12} = \ \ 1.22709628, \\ k_{22} = \ \ 2.72268751, \end{cases} \begin{cases} k_4 = \ \ 0.37006106, \\ k_{15} = 0.068209447, \\ k_{25} = 0.19991718, \end{cases} \begin{cases} k_{17} = k_{27} = 0.033043341, \\ k_{c3} = \qquad 32.67747679. \end{cases} \quad (9)$$

We have confirmed that the three packages provided the same result. **Figure 2** represents an actual application of the resultant-factorization technique to set (8). The complete list of this section is given at http://sites.google.com/site/codes86/.

6. Discussion

In this paper, we have extracted a biologically acceptable and zero-dimensional solution with which we can identify the rate constants by combining two experiments. In view of the last component [6 in Section 5, this component contains an equality $k_{17} = k_{27}$. This equality corresponds to a physiological feature that the degradation rate of free **tetR** in Experiment 1 is the same as that in Experiment 2. This finding may provide profound insight into the function of tetR in tissues in the near future.

Here we propose the combining-multiple-experiments method to overcome underdetermination of a single experiment. We had to deal with the set of polynomials (8), which corresponds to the combined experiments and consists of 12 polynomials having 9 variables corresponding to the rate constants. This system might be accordingly thought of as being overdetermined because the number of polynomials is more than that of variables. However, the dimension of the ideal generated by these 12 polynomials is calculated as 6, indicating that this system is actually underdetermined. Nevertheless, we can determine the rate constants using these polynomials because, through prime ideal decomposition, we found that their non-zero dimensional component are not biologically acceptable, but their zero component is biologically acceptable. Such a confusing system is difficult to analyze.

To overcome underdetermination of a single experiment, one might think that it would be good to combine multiple experiments until their solution itself is zero dimensional. Under 'not-equal' conditions of rate constants, however, this

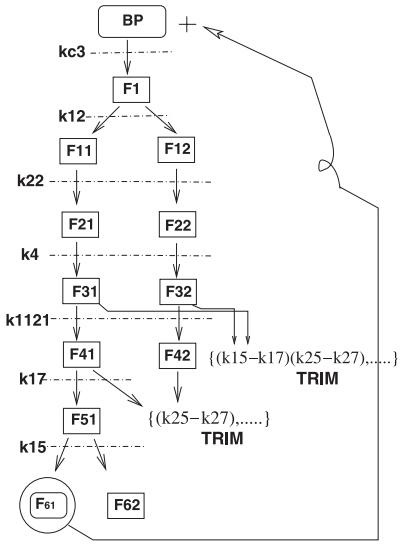

Fig. 2 Application of the resultant-factorization technique to the real-life example. $k_?$ denotes a variable eliminated at each resultant Procedures 5, 6 in Algorithm Resultant-factorization. The factor $(k_{15} - k_{17})$ or $(k_{25} - k_{27})$ can be ignored from biological knowledge (Procedure-3).

scheme sometimes provides us with no biologically acceptable solution. Indeed, if we combine another experiment with the two experiments introduced here, we usually obtain no biologically acceptable solution. This is why we use prime ideal decomposition and look into its output.

Applicability

In analyzing chemical reactions, it is known to be necessary to confirm whether rate constants can be determined from the observed data (called *identifiability problem*) [19)–21)]. Recently, in Ref. 22), they considered chemical reaction networks where two sets of rate constants produce exactly the same dynamics, that is, the constants are unidentifiable. To identify the constants in such a case, we need to design other networks (corresponding to 'experiments' in this paper) of a distinct nature so that the combined networks produce a zero-dimensional prime ideal, confirming by the technique introduced in Section 3.2.

7. Concluding Remarks

In this paper, we propose algebraic approaches to analyse and solve underdetermined systems. To overcome underdetermination, we have to combine multiple experiments, which bring about complicated formulas with a large number of parameters and variables. Through use of the resultant-factorization technique under a biological condition, 'not-equal' condition, we were able to decompose the system and to determine the desired rate constants efficiently.

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