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 11,2), 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:

\[
\begin{align*}
z^2 + 2y^2 - 1, \\
x^2 - z, \\
x^2 + yz + 1.
\end{align*}
\]

The solution to this set can be decomposed into two solutions: \(\{z^2 - 2, y^2 - 1\}\) 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, \(x > 0 \land y > 0 \land z > 0\), 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 9). 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) 5,6). Nevertheless, the larger number of variables, the more difficult straightforward decomposition becomes 5). For relatively large problems of zero dimension, one can use the homotopy method to decompose their solutions 9). 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...
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. 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:

\[
\text{Problem (INPUT } i\text{): } \frac{dC_{ij}(t)}{dt} = f_{ij}(C_{i1}(t), C_{i2}(t), \ldots, C_{in}(t), e_i(t), \vec{k}_i), \\
S_i(t) = g_i(C_{i1}(t), \ldots, C_{in}(t), \vec{k}_i),
\]

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, \(d_0 + d_1 t + d_2 t^2\).

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
combining 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

\[
\text{OUTPUT: zero-dimensional prime ideal(s) over } \mathbb{Q}[\bigcup_{i=1}^{n} \vec{k}_i],
\]

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.*

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 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 \(\bigcup_{i=1}^{n} \vec{k}_i\). In this case, we can use a Gröbner basis in terms of
elimination order. Let \(\vec{k}_r\) denote needed variables in \(\bigcup_{i=1}^{n} \vec{k}_i\). The procedure is
(i) calculate a Gröbner basis \(G\) in terms of elimination order \(\bigcup_{i=1}^{n} \vec{k}_i\) \(\vec{k}_r\) \(\Rightarrow\)
\(\vec{k}_r\) 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.
Let $BP = \{BP_i \mid 1 \leq i \leq n\}$ 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 $(s_p, f_1)$ and $(s_p, f_2)$, otherwise, we return $s_p$. This procedure is based on:

$$\sqrt{(I, f \times g)} = \sqrt{(I, f)} \cap \sqrt{(I, g)},$$

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 $d(i, j)$ 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 $d(i, j) (1 \leq j \leq m)$.

(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 $y_1, y_2, \ldots, y_t$ 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, ..., 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$(BP, N, R_F)$

**Input:** $BP$: 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

$s_p \leftarrow BP$

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) \leftarrow \text{Procedure-5}(s_p);

s_p \leftarrow \text{Procedure-6}(s_p, v, p_i);

\text{Call Resultant-factorization}(s_p, N, R_F)

\text{else}

s_p \leftarrow B_P \cup s_p

\text{if} \ s_p \text{ is 0-dimensional then}

\text{return} \ s_p

\text{else}

\text{Perform prime ideal decomposition}^{*1} \text{ of } s_p;

\text{Return 0-dimensional prime ideal(s) among the obtained prime ideals}

\text{end-if}

\text{end-if}

\text{end-while}

\text{end}

The technique introduced in this subsection is based on the following fact. Let ideal \( I \) be \( \{f_1, f_2, \cdots, f_r\}, \) \( (f_i \in k[x_1, x_2, \ldots, x_n]) \), and let \( g_i (1 \leq i < r) \) be the resultant of \( f_i \) 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 \( f_i (1 \leq i \leq r) \) is reducible over \( \mathbb{Q}[x_1, x_2, \ldots, x_n] \), some of \( f_i (1 \leq i < r) \) 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.

\begin{align*}
\text{Problem 1:} & \quad \begin{cases} 
\frac{dC_{11}(t)}{dt} = k_{11}c_1(t) - k_{12}C_{11}(t) - k_{3}C_{11}(t)C_{13}(t) + k_{4}C_{12}(t), \\
\frac{dC_{12}(t)}{dt} = k_{3}C_{11}(t)C_{13}(t) - (k_{4} + k_{15})C_{12}(t), \\
\frac{dC_{13}(t)}{dt} = k_{16} - k_{17}C_{13}(t) + k_{4}C_{12}(t) - k_{3}C_{11}(t)C_{13}(t), \\
S_1(t) = (C_{12}(t) + C_{13}(t))/k_c,
\end{cases}
\end{align*}

\begin{align*}
\text{Problem 2:} & \quad \begin{cases} 
\frac{dC_{21}(t)}{dt} = k_{21}c_2(t) - k_{22}C_{21}(t) - k_{3}C_{21}(t)C_{23}(t) + k_{4}C_{22}(t), \\
\frac{dC_{22}(t)}{dt} = k_{3}C_{21}(t)C_{23}(t) - (k_{4} + k_{25})C_{22}(t), \\
\frac{dC_{23}(t)}{dt} = k_{26} - k_{27}C_{23}(t) + k_{4}C_{22}(t) - k_{3}C_{21}(t)C_{23}(t), \\
S_2(t) = (C_{22}(t) + C_{23}(t))/k_c,
\end{cases}
\end{align*}

where \( c_1(t) \) 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,

\begin{align*}
\text{Problem 2:} & \quad \begin{cases} 
\frac{dC_{21}(t)}{dt} = k_{21}c_2(t) - k_{22}C_{21}(t) - k_{3}C_{21}(t)C_{23}(t) + k_{4}C_{22}(t), \\
\frac{dC_{22}(t)}{dt} = k_{3}C_{21}(t)C_{23}(t) - (k_{4} + k_{25})C_{22}(t), \\
\frac{dC_{23}(t)}{dt} = k_{26} - k_{27}C_{23}(t) + k_{4}C_{22}(t) - k_{3}C_{21}(t)C_{23}(t), \\
S_2(t) = (C_{22}(t) + C_{23}(t))/k_c,
\end{cases}
\end{align*}

where \( c_2(t) \) 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, \( \tilde{k}_1 \) and \( \tilde{k}_2 \) 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 $=[C_{11}, C_{12}, C_{13}, [e_1]]$ 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:

\[
e_i(t) = a_i0 + a_i1 t + a_i2 t^2 + \frac{a_i3 + a_i4 t}{a_7 + a_8 t + t^2} + \frac{a_i5 + a_i6 t}{(a_7 + a_8 t + t^2)^2}
\]  

(6)

with

\[
a_i0 = \frac{2k_3k_{15}d_2k_i + k_2^2k_22k_i17 - \cdots}{k_5k_{11}3(k_{17} - k_{i5})},
\]

\[
a_i1 = \frac{2k_3k_{12}^2k_i2d + \cdots}{k_5k_{11}3(k_{17} - k_{i5})},
\]

\[
a_i2 = \frac{k_5k_{11}3k_i1(k_{17} - k_{i5})}{k_1(k_{17} - k_{i5})},
\]

\[
a_i3 = \frac{k_5^2d_10k_22k_i7 + \cdots}{d_2k_2^2k_3k_{11}},
\]

\[
a_i4 = \frac{-2k_2k_2^2k_2d_2 - \cdots}{d_2k_2^2k_3k_{11}},
\]

\[
a_i5 = \frac{k_2^2k_2d_10k_22k_i7 - \cdots}{k_5d_2^2k_3k_{11}},
\]

\[
a_i6 = \frac{-2k_2k_2d_10k_22k_i7 - \cdots}{k_5d_2^2k_3k_{11}},
\]

\[
a_i7 = \frac{-d_2k_i17 + \cdots}{k_5d_2},
\]

\[
a_i8 = \frac{k_5d_11 + 2d_2}{k_5d_2}.
\]

(7)

From a biological assumption $C_{ij}(0) = 0$ ($i = 1, 2$), we obtained relations, $k_i6 = k_i(d_0k_27 + d_1)$. Therefore, in what follows, we substituted $k_{i6}$ with the formulae on the right-hand side.

Next, we had to derive a set of 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) $\{a_{ij} - a_{2j}|0 \leq j \leq 8\}$ (B) $\{a_{ij} - a_{2j}|0 \leq j \leq 2\}$ $\cup$ $\{a_{ij}|i = 1, 2, 3 \leq j \leq 6\}$ (C) $\{a_{1j} - a_{2j}|j = 0, 1, 2, 4\}$ $\cup$ $\{a_{13} - a_{23} - a_{18}a_{24}, \cdots, 2a_{21}^2 - 8a_{22}^2a_{27}^2 + 8a_{24}a_{26}a_{27} - \cdots - a_{23}^2a_{27}a_{28}^2 + a_{23}a_{24}a_{25}\}$. 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, consider Relation (A) suffices, and consequently, we obtained the following set of 12 polynomials:

\[
\{-k_{15}d_12k_{25}d_{21} - 2k_{15}d_12d_{22} + \cdots + 2k_{15}d_22d_{12} + d_10k_{25}d_{22}k_{15} + d_15k_{15}d_{12}k_{25} + d_10k_{25}d_{22}k_{15} + d_10k_{15}d_{12}k_{25} + 2k_{15}d_12k_{25}d_{22} + \cdots\}
\]

(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 $k_c$ and $k_{11}/k_{21}$ 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, $d_{10} = -201719/100000000$, $d_{11} = 100999/25000000$, $d_{12} = -83061/50000000$, $d_{20} = -3/1000$, $d_{21} = 1/500$, 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. $\{k_{17}, k_{15}, k_{13}, k_{14}\}$, 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) minLSSChar 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:
The first three components \([1\text{–}3]\) violate the positive-value condition for the rate constants, and the fourth and fifth \([4\text{ and }5]\) violate the physiological fact: \(k_{12} \neq k_{22}\) meaning difference in \(\text{dox}\) 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:

\[
\begin{align*}
    k_{1121} &= 0.67239667, \\
    k_{12} &= 1.22709628, \\
    k_{22} &= 2.72268751,
\end{align*}
\]

\[
\begin{align*}
    k_{15} &= 0.37006106, \\
    k_{17} &= 0.068209447, \\
    k_{25} &= 0.19991718,
\end{align*}
\]

\[
\begin{align*}
    k_{17} &= 0.033043341, \\
    k_{27} &= 32.67747679.
\end{align*}
\]

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 \(\text{tetR}\) in Experiment 1 is the same as that in Experiment 2. This finding may provide profound insight into the function of \(\text{tetR}\) 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
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*). 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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**References**

15) Boulier, F., Lemaire, F., Sedoglavic, A. and Ugripli, A.: Towards an automated reduction method for polynomial ODE models of biochemical reaction systems,


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