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ANALYSIS OF BIOCHEMICAL MECHANISMS USING *MATHEMATICA* WITH APPLICATIONS

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Abstract. Biochemical mechanisms with mass action kinetics are usually modeled as systems of ordinary differential equations (ODE) or bipartite graphs. We present a software module for the numerical analysis of ODE models of *biochemical mechanisms of chemical species and elementary reactions (BMCSER)* within the programming environment of CAS *Mathematica*. The module *BMCSER* also visualizes the bipartite graph of biochemical mechanisms. Numerical examples, including a double phosphorylation model, are presented demonstrating the scientific applications and the visualization properties of the module.

1. Introduction. A biochemical species participates on the left or the right side of a reaction as a reactant or a product, respectively. A biochemical mechanism is a set of elementary reactions, describing the exact events that are required for the conversion of reactants into products. The nonnegative integer species coefficients that account for the number of molecules in an elementary

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reaction are referred to as *stoichiometric coefficients*. Mass action types of kinetics with positive rate constants will be used to define the rate of each elementary reaction.

Typically biochemical mechanisms are modeled either as systems of differential equations or as graphs. An ordinary differential equations (ODE) system that models a biochemical mechanism describes the time evolution of the concentrations of the chemical species. Bipartite graphs with two types of nodes, for species and reactions, are also used to model biochemical mechanisms. The bipartite graph model provides a description of all of the connections among the different chemical species and elementary reactions. The connection between the different models has been studied extensively in recent years, see for example [6, 28, 20].

Symbolic solutions of ODE models of biochemical mechanisms usually cannot be obtained since the systems are nonlinear and of high order. Therefore, solving ODE model systems of biochemical mechanisms numerically is one of the few possible approaches.

The aim of this work is to present the software module *BMCSER* for the numerical analysis of solutions of ODE models of biochemical mechanisms. *BMCSER* is implemented in *Mathematica* and has some of the following capabilities:

i) generate a biochemical mechanism for given (by the user) arbitrary positive rate constants and stoichiometric coefficients;

ii) generate the ODE system for the concentrations of the biochemical species;

iii) compute and visualize the solutions of the ODE system for given rate constants and initial conditions;

iv) generate the bipartite graph of a biochemical mechanism.

In Sec. 2 we define a biochemical mechanism with mass action kinetics and describe the bipartite graph and the ODE system model. In Sec. 3 the *Mathematica* software module *BMCSER* is described. This module is used to study the ODE model of the double phosphorylation network in Sec. 4.

2. Preliminaries. We introduce biochemical mechanisms with n species A_i, $i = 1, \ldots, n$, and m elementary reactions of the form:

$$\sum_{i=1}^{n} \alpha_{ij} A_i \xrightarrow{k_j} \sum_{i=1}^{n} \beta_{ij} A_i,\ j = 1, \ldots, m, \tag{1}$$

where α_{ij} and β_{ij} are small non-negative integer constants; $k_j > 0,\ j = 1, \ldots, m$ are the *rate constants* [5, 21, 22, 19].

The constants $\alpha_{ij} \geq 0$ and $\beta_{ij} \geq 0$ are usually equal to zero, one or two and are referred to as *stoichiometric coefficients* that account for the number of molecules of species A_i participating in the jth elementary reaction in (1). If the forward reaction and its reverse exist in (1) we call this type of reaction reversible.

An example of a chemical mechanism of the form (1) is

$$\begin{aligned} A_2 + A_3 &\xrightarrow{k_1} 2A_1, \\ A_3 &\xrightarrow{k_2} A_1, \\ A_1 &\xrightarrow{k_3} A_3, \\ A_2 &\xrightarrow{k_4} A_1, \\ A_1 &\xrightarrow{k_5} A_2. \end{aligned} \tag{2}$$

The vector of concentrations x_i of species A_i will be denoted by $x = (x_1, \ldots, x_n)$; similarly $k = (k_1, \ldots, k_m)$ will denote the vector of rate constants.

If for $y \in \mathbb{R}^n$, $y_i \geq 0$ $(y_i > 0)$ for all i we will write $y \geq 0$ $(y > 0)$. It is clear that $k > 0$ as rate constants and $x \geq 0$ as concentrations.

If we assume *mass action kinetics* rates for (1), then the corresponding *rate functions* are the polynomials

$$v_j(k, x) = k_j \prod_{i=1}^{n} x_i^{\alpha_{ij}},\ j = 1, \ldots, m. \tag{3}$$

Thus the vector of rate functions is $v(k, x) = (v_1(k, x), \ldots, v_m(k, x))$.

Let x' denote the derivative of $x(t)$ with respect to time t. The ordinary differential equations (ODE) model of a biochemical mechanism (1) can be represented as

$$x_i'(t) = \sum_{j=1}^{m} M_{ij} v_j(k, x),\ i = 1, \ldots, n \tag{4}$$

where

$$M_{ij} = \beta_{ij} - \alpha_{ij}$$

are the entries of the stoichiometric matrix M with dimension $(n \times m)$ and $v_j(k, x)$ are the rate functions (3).

The differential equation system (4) can be written in a compact form as

$$x'(t) = Mv(k,x) = f(k,x). \tag{5}$$

If we add an initial condition $x(0) \geq 0$ to the ODE system (4), then we obtain an initial value problem. The solution $x(t)$ of the initial value problem describes the time evolution of the species concentrations for a given initial condition. The forward invariance of the non-negative orthant guarantees that $x(t) \geq 0$ if $x(0) \geq 0$ as long as the solution $x(t)$ exists [29].

For the biochemical mechanism (2) we have the stoichiometric matrix

$$M = \begin{pmatrix} 2 & 1 & -1 & 1 & -1 \\ -1 & 0 & 0 & -1 & 1 \\ -1 & -1 & 1 & 0 & 0 \end{pmatrix}$$

and the rate functions

$$v(k,x) = (k_1x_2x_3, k_2x_3, k_3x_1, k_4x_2, k_5x_1)^T.$$

The model equations for (2) are then given by:

$$\begin{aligned} x_1' &= 2k_1x_2x_3 + k_2x_3 - k_3x_1 + k_4x_2 - k_5x_1, \\ x_2' &= -k_1x_2x_3 - k_4x_2 + k_5x_1, \\ x_3' &= -k_1x_2x_3 - k_2x_3 + k_3x_1. \end{aligned} \tag{6}$$

Any biochemical mechanism (1) can be represented as a directed bipartite graph [10]. A bipartite graph has two non-intersecting sets of nodes and directed edges (or arcs) that always start at a node from one set and end at a node from the other set. Below we define the bipartite graph of biochemical mechanisms.

We define the bipartite digraph G of a biochemical reaction network (1) as follows (see [20, 5, 22]): Let the set of the chemical species be $V_1 = \{A_1, A_2, \ldots, A_n\}$ and the set of elementary reactions be $V_2 = \{B_1, B_2, \ldots, B_m\}$. There is a directed edge from A_k to B_j if and only if species A_k is a reactant in reaction j, equivalently, if the stoichiometric coefficient $\alpha_{kj} > 0$ in (1). There is a directed edge from B_j to A_i if and only if A_i is a product in reaction j. The latter means that the stoichiometric coefficient $\beta_{ij} > 0$ in (1). If a stoichiometric coefficient $\alpha_{kj} = 0$, then we do not draw a directed edge between A_k and B_j. Similarly if $\beta_{ij} = 0$, then no directed edge is drawn between A_i and B_j. The set of directed edges denoted by $E(G)$ consists of edges (A_k, B_j) starting at A_k

and ending at B_j, and (B_j, A_i) starting at B_j and ending at B_j. The bipartite digraph (directed graph) can be defined as $G = \{V, E(G)\}$, where $V = V_1 \bigcup V_2$ is the set of nodes and $E(G)$ is the set of directed edges. The bipartite graph of the running example (2) is depicted in Fig. 2.

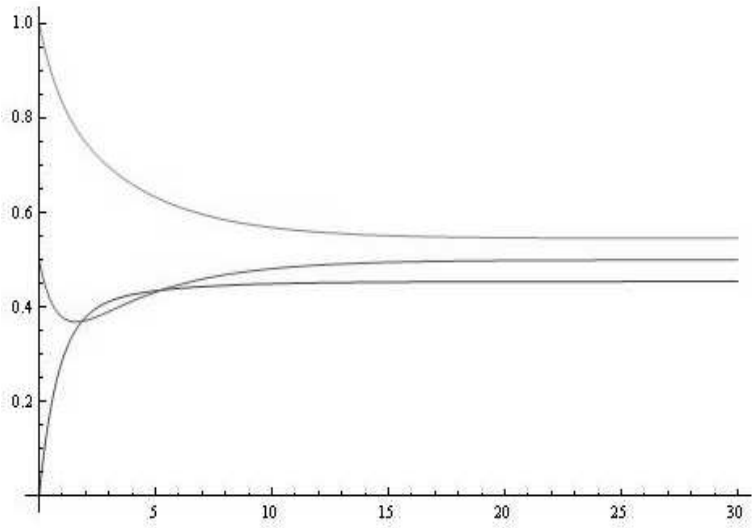

Fig. 1. Solutions for the control example (6) with reaction rate coefficients: $k_1 = 0.1$; $k_2 = 0.2$; $k_3 = 0.3$; $k_4 = 0.4$; $k_5 = 0.5$ and initial conditions: $x_1(0) = 0$; $x_2(0) = 0.5$; $x_3(0) = 1$; $t_0 = 0$, $t_1 = 30$.

3. Models studied using *BMCSER*. The *Mathematica* software module *BMCSER* has been developed (intellectual property) for studying the dynamic properties of biochemical mechanisms (1) with n species A_i, $i = 1, \ldots, n$ and m elementary reactions, along with their bipartite graph representations.

The software module (see Fig. 8, Appendix) offers the following options to the user:

i) generation of a biochemical mechanism with given by the user arbitrary positive rate constants k_j, $j = 1, 2, \ldots, m$;

ii) generation of the rate functions (3);

iii) generation and explicit presentation of the differential equations system for the chemical species concentrations;

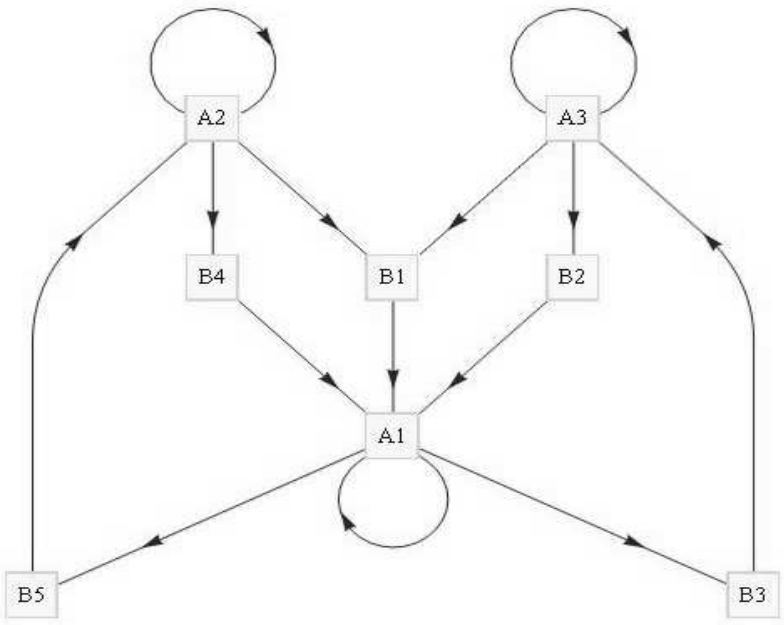

Fig. 2. Bipartite graph of the reaction mechanism (2) obtained with the programming environment *Mathematica*

iv) visualization of the solutions of the differential equations system (4) (or in a compact form (5)) as functions of the time t;

v) generation and visualization of the bipartite digraph of the chemical mechanism.

Next we present some examples and discuss the module's capabilities. For the running example, (6), we let the rate constants be

$$k_1 = 0.1; k_2 = 0.2; k_3 = 0.4; k_4 = 0.4; k_5 = 0.5$$

and the initial conditions:

$$x_1(0) = 0; x_2(0) = 0.5; x_3(0) = 1$$

The sample solution is plotted in Fig. 1.

The corresponding bipartite digraph of the reaction mechanism (2) is shown in Fig. 2.

4. Application. A mathematical model of double phosphorylation. Models of phosphorylation reaction networks have been extensively studied in recent years. Networks of proteins MAP-kinases (MAPK) are parts of many signaling networks. There are mainly three types of mechanisms associated with MAPK networks: sequential distributive, processive and mixed [3, 13, 4, 18, 26]. Here we study the sequential distributive double phosphorylation model using *BMCSER*.

The biochemical mechanism involves nine species: A, A_p, A_pp, AE_1, A_pE_1, A_pE_2, $A_{pp}E_2$, E_1, E_2 where A is used either for MAPK or MAPK, E_1 for mono-phosphorylated MAPKKK or double-phosphorylated MAPKK and E_2 for MAPKK'ase and MAPK'ase. The twelve elementary reactions describe the double phosphorylation network:

$$
\begin{aligned}
&A + E_1 \underset{k_2}{\overset{k_1}{\rightleftarrows}} AE_1 \xrightarrow{k_3} A_p + E_1 \underset{k_5}{\overset{k_4}{\rightleftarrows}} A_pE_1 \xrightarrow{k_6} A_{pp} + E_1 \\
&A_{pp} + E_2 \underset{k_8}{\overset{k_7}{\rightleftarrows}} A_{pp}E_2 \xrightarrow{k_9} A_p + E_2 \underset{k_{11}}{\overset{k_{10}}{\rightleftarrows}} A_pE_2 \xrightarrow{k_{12}} A + E_2.
\end{aligned} \tag{7}
$$

We assume that the concentrations of the species are denoted as follows: x_1 for A_1, x_2 for E_1, x_3 for AE_1, x_4 for A_p, x_5 for A_pE_1, x_6 for A_{pp}, x_7 for E_2, x_8 for $A_{pp}E_2$ and x_9 for A_pE_2. If all reaction rates above are taken with mass action kinetics, we obtain the following system of differential equations:

$$
\begin{aligned}
x_1'(t) &= -k_1x_1x_2 + k_2x_3 + k_{12}x_9 \\
x_2'(t) &= -k_1x_1x_2 - k_4x_2x_4 + k_2x_3 + k_3x_3 + (k_5 + k_6)x_5 \\
x_3'(t) &= -(k_2 + k_3)x_3 + k_1x_1x_2 \\
x_4'(t) &= -k_4x_2x_4 - k_{10}x_4x_7 + k_3x_3 + k_5x_5 + k_9x_8 + k_{11}x_9 \\
x_5'(t) &= -(k_5 + k_6)x_5 + k_4x_2x_4 \\
x_6'(t) &= -k_7x_6x_7 + k_6x_5 + k_8x_8 \\
x_7'(t) &= -k_{10}x_4x_7 - k_7x_6x_7 + k_8x_8 + k_9x_8 + (k_{11} + k_{12})x_9 \\
x_8'(t) &= -(k_8 + k_9)x_8 + k_7x_6x_7 \\
x_9'(t) &= -(k_{11} + k_{12})x_9 + k_{10}x_4x_7,
\end{aligned} \tag{8}
$$

where the stoichiometric matrix for the network (7) is:

$$M = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ -1 & 1 & 1 & -1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 1 & -1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 1 \end{pmatrix}$$

and the vector of rate functions is

$$v(k,x) = (k_1x_1x_2, k_2x_3, k_3x_3, k_4x_2x_4, k_5x_5, k_6x_5, \\ k_7x_6x_7, k_8x_8, k_9x_8, k_{10}x_4x_7, k_{11}x_9, k_{12}x_9)^T.$$

For the double phosphorylation example, (7), sample solutions are plotted in Fig. 3.

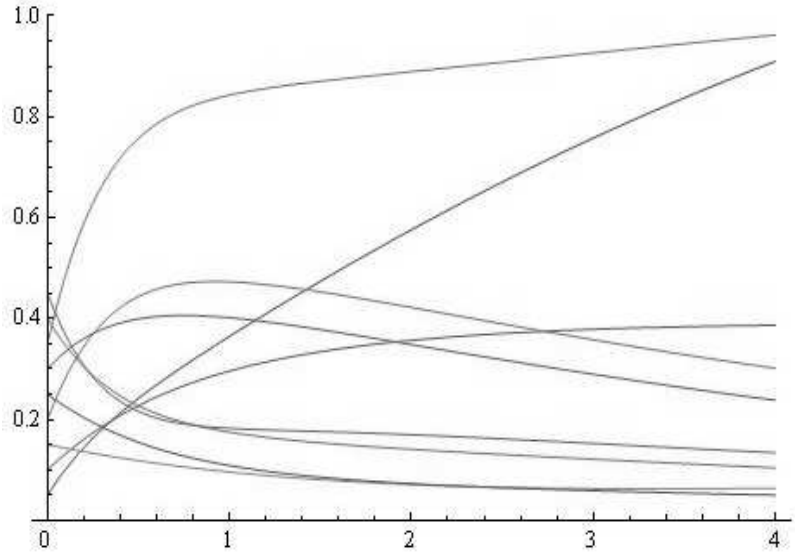

Fig. 3. Numerical solutions of the ODE model (8) of the double phosphorylation network (7) using programming module *BMCSER*

We note that the *Mathematica* module *BMCSER* can be used for studying other reaction networks such as the one from [9] (here we use k_i for phosphorylation and l_i for dephosphorylation reactions):

$$
\begin{aligned}
&E_1 + A_{i-1\,P} \underset{k_{3i-1}}{\overset{k_{3i-2}}{\rightleftarrows}} A_{i-1\,P}E_1 \xrightarrow{k_{3i}} E_1 + A_{i\,P}, \quad i = 1, \ldots, n \\
&E_2 + A_{i\,P} \underset{l_{3i-1}}{\overset{l_{3i-2}}{\rightleftarrows}} A_{i\,P}E_2 \xrightarrow{l_{3i}} E_2 + A_{i-1\,P}, \quad i = 1, \ldots, n.
\end{aligned} \tag{9}
$$

For other similar results, see [4, 11].

5. Discussion. In this section we discuss some of the numerical features of *BMCSER*. The module is implemented in *Mathematica* because it can perform both numerical and symbolic computations, and has graphing capabilities.

Taking into account the fact that some solutions of nonlinear systems of ODE's of large dimension are very unstable (see Fig. 4), the module *BMCSER* provides sensitivity analysis. Specifically, the module implements existing high-speed numerical methods based on the Runge-Kutta method [8].

At each step the program exercises control over the computational errors, which is accomplished using the well-known operators AccuracyGoal, PrecisionGoal and WorkingPrecision. Plotting a solution of higher dimensional systems of differential equations is a difficult problem, since the solution's amplitude is

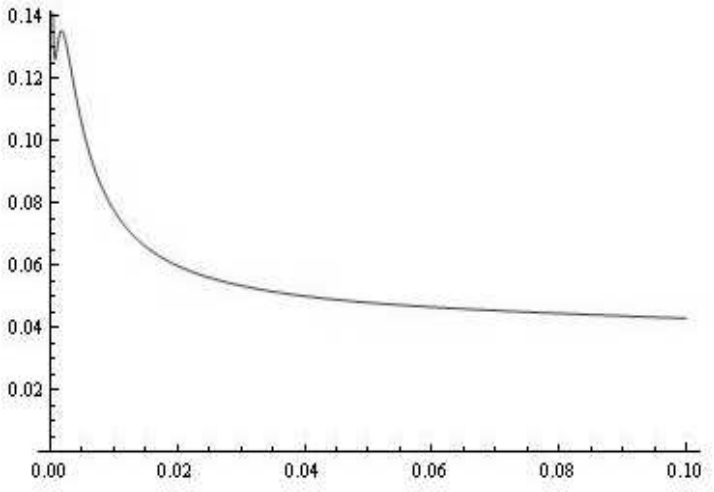

Fig. 4. Typical numerically unstable solution

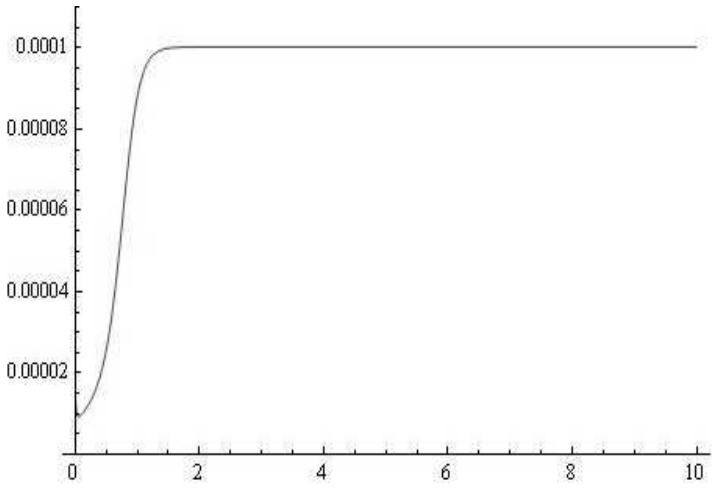

Fig. 5. Typical numerical solution with low amplitude

usually very small (see Fig. 5). In order to avoid this particular problem, another *Mathematica* function that automatically regulates the monitor and plotting characteristics is used. We have also used *Mathematica* modified operators for computer animation such as Manipulate[Dynamic&Show[Plot[...]]].

A similar software module implemented in *Mathematica* analyzing differential equations models of chemical reactions is discussed in [23, 27]. In comparison, *BMCSER* is a part of a larger module (intellectual property) which can be used to analyze, apart from biochemical mechanism models, also fibril elongation models [25, 1] and general ligand-gated receptor models [16, 17].

Software products used to analyze chemical reaction models implemented in software environments other than *Mathematica* are reported in [7, 12, 14, 15, 24, 31, 2, 30]. Many of these other packages are aimed at performing different types of analysis of biochemical reaction networks models. *COPASI* is used mainly for sensitivity analysis and estimating parameter values [14]. *GraTeLPy* is used to test large mass-action kinetics models for multistability, oscillations or Turing instability based on the structure of the bipartite graph [30].

6. Conclusion. The developed module *BMCSER* is an extension of *Mathematica*. It can be used for the analysis of mass-action kinetics ODE models. Obtaining the numerical solutions of a model ODE system requires only entering the initial conditions and the rate constants.

We note the module's bipartite graph drawing capabilities, in particular,

graphing as many as possible non-intersecting directed edges. The visual representation of the bipartite graph can be used for finding cycles [28, 20]. Positive and negative cycles are present in the bipartite graph of a biochemical mechanism, if its ODE model shows multistability or oscillations for some set of parameter values [6, 28, 20]. Finding parameter values such that the ODE model is multistable is an important problem and will be the subject of a future work.

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Appendix

```
Print["A (bio)chemical mechanism with n species A_i, i=1,...,n, and m elementary reactions
is represented as: "];

Print["∑_{i=1}^{n} α_[[i,j]] A_i  --k_j-->  ∑_{i=1}^{n} β_[[i,j]] A_i : j=1,...,m, where k_j>0 are the rate constants.
The constants α_[[i,j]]⩾0 and β_[[i,j]]⩾0 are integers called stoichiomeric coefficients."];

Print["An example of a chemical mechanism is given below:"];

Print["A_2+A_3 --k1--> 2A_1 "];
Print["A_3 --k2--> A_1 "];
Print["A_1 --k3--> A_3 "];
Print["A_2 --k4--> A_1 "];
Print["A_1 --k5--> A_2 "];

Print["If mass action kinetics is used for the above mechanism, then the corresponding rate
functions are:"];

Print[" v[[j]]= k[[j]]*∏_{i=1}^{i1} x_[[i]]^{α_[[i,j]]}; j=1,...,m."];

i1 = Input["Input i: "];
Print["i = ", i1];
j1 = Input["Input j: "];
Print["j = ", j1];

Print["Input the stoichometric coefficients α_[[i,j]]"];
α = Input[Array[α_## &, {i1, j1}]]
Print["α= ", MatrixForm[α]];

Print["Input the stoichometric coefficients β_[[i,j]]"];
β = Input[Array[β_## &, {i1, j1}]]
Print["β= ", MatrixForm[β]];

Print["The stoichometric matrix M=β-α "];
Print["M=β-α= ", MatrixForm[M = β - α]];
```

Fig. 6

```
Print["Input the rate constants  k[[j]]"];
k = Range[j1];
For[j = 1, j ≤ j1, j++,
  k[[j]] = Input["kj" j];
 ];
Print["k= ", k];
v = Range[j1];
For[j = 1, j ≤ j1, j++,
  v[[j]] = k[[j]] * ∏_{i=1}^{j1} x[[i]]^{a[[i,j]]};
 ];
Print["v= ", v];

Print["The DE model of a mass-action mechanism is: "];

Print["X[[1]]'[t] ==2*k[[1]]*X[[2]][t]*X[[3]][t]+k[[2]]*X[[3]][t]-k[[3]]*X[[1]][t]+k[[4]]*X[[2]][t]-k[[5]]*X[[1]][t]"];

Print["X[[2]]'[t] ==-k[[1]]*X[[2]][t]*X[[3]][t]-k[[4]]*X[[2]][t]+k[[5]]*X[[1]][t]"];

Print["X[[3]]'[t] ==-k[[1]]*X[[2]][t]*X[[3]][t]-k[[2]]*X[[3]][t]+k[[3]]*X[[1]][t]"];

X10 = Input["Input initial condition - X1[0]"]; (* 0 *)
Print["Initial condition X10 = ", X10];
X20 = Input["Input initial condition - X2[0]"]; (* 0.5 *)
Print["Initial condition X20 = ", X20];
X30 = Input["Input initial condition - X3[0]"]; (* 1 *)
Print["Initial condition X30 = ", X30];

t0 = Input["Input t0, for which we shall investigate model"];
Print["t0 = ", t0];
t1 = Input["Input t1, for which we shall investigate model"];
Print["t1 = ", t1];

Print["Graphics of the solutions of the system of differential equations as functions of the time t"];

NDSolve[{X1'[t] == 2 * k[[1]] * X2[t] * X3[t] + k[[2]] * X3[t] - k[[3]] * X1[t] + k[[4]] * X2[t] - k[[5]] * X1[t],
   X2'[t] == -k[[1]] * X2[t] * X3[t] - k[[4]] * X2[t] + k[[5]] * X1[t],
   X3'[t] == -k[[1]] * X2[t] * X3[t] - k[[2]] * X3[t] + k[[3]] * X1[t],
   X1[0] == X10, X2[0] == X20, X3[0] == X30}, {X1, X2, X3}, {t, t0, t1}];

Plot[Evaluate[{X1[t], X2[t], X3[t]} /. First[%]], {t, t0, t1}, PlotRange → All]
```

Fig. 7. The model of the (BMCSER) via the programming environment Mathematica

```
i = 3
j = 5
Input the stoichometric coefficients α[[i,j]]
{{0, 0, 1, 0, 1}, {1, 0, 0, 1, 0}, {1, 1, 0, 0, 0}}
```

$$\alpha = \begin{pmatrix} 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 \end{pmatrix}$$

```
Input the stoichometric coefficients β[[i,j]]
{{2, 1, 0, 1, 0}, {0, 0, 0, 0, 1}, {0, 0, 1, 0, 0}}
```

$$\beta = \begin{pmatrix} 2 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 \end{pmatrix}$$

```
The stoichometric matrix M=β-α
```

$$M=\beta-\alpha = \begin{pmatrix} 2 & 1 & -1 & 1 & -1 \\ -1 & 0 & 0 & -1 & 1 \\ -1 & -1 & 1 & 0 & 0 \end{pmatrix}$$

```
Input the rate constants  k[[j]]
k= {0.1, 0.2, 0.3, 0.4, 0.5}
v= {{0.1 x[[2]] x[[3]]}, {0.2 x[[3]]}, {0.3 x[[1]]}, {0.4 x[[2]]}, {0.5 x[[1]]}}
The DE model of a mass-action mechanism is:
X[[1]]'[t] ==2*k[[1]]*X[[2]][t]*X[[3]][t]+k[[2]]*X[[3]][t]-k[[3]]*X[[1]][t]+k[[4]]*X[[2]][t]-k[[5]]*X[[1]][t]
X[[2]]'[t] ==-k[[1]]*X[[2]][t]*X[[3]][t]-k[[4]]*X[[2]][t]+k[[5]]*X[[1]][t]
X[[3]]'[t] ==-k[[1]]*X[[2]][t]*X[[3]][t]-k[[2]]*X[[3]][t]+k[[3]]*X[[1]][t]
Initial condition X10 = 0
Initial condition X20 = 0.5
Initial condition X30 = 1
t0 = 0
t1 = 30
```

Fig. 8. The test provided on our control example