

# Chapter 30

## Stoichio Simulation of FACSP From Graph Transformations to Differential Equations



J. Philomenal Karoline, P. Helen Chandra, S. M. Saroja Theerdus Kalavathy and A. Mary Imelda Jayaseeli

**Abstract** In this paper, a methodology to derive ordinary differential equations (ODEs) using graph transformation technique is developed for Michaelis–Menten kinetics. This approach is based on a variant of the construction of critical pairs. It has been executed using the AGG tool and validated for FACSP.

**Keywords** Rate of reaction · Fuzzy artificial cell system · Parallel conflicts  
Sequential dependencies · Stoichiometric matrix · Place transition net

### 1 Introduction

Multiset processing is a simple technique, easy to be used by biologists, which contrasts with most continuous models and simulation systems. Abstract Rewriting System on Multisets (ARMS), a class of P systems based on multiset processing but with a simple membrane structure, was introduced with the aim of modelling chemical systems. It is a stochastic model where rules are applied probabilistically [1].

In particular, ARMS is based on stoichiometric chemistry, and if the number of elements in the system is large, then the behaviour of the system is similar to the behaviour of models based on differential equations [2].

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In [3], a new device, Fuzzy ARMS in Artificial Cell System with Proteins on Membrane (FACSP), is developed for which the structure is analysed on its parameters. In [4], a methodology has been developed to model Michaelis–Menten kinetic reactions networks in terms of DPO graph transformation.

In [5], the chemical reaction kinetics is rephrased in terms of stochastic graph transformations. The ODEs that describe the evolution of concentrations of chemical species over time are derived. It is based on stochastic graph transformation [6] which combines rules to capture the reactive behaviour of the system with a specification of rate constants governing the speed at which the reaction occur.

However, it is of great interest to study the dynamical properties of FACSP, and we have considered to apply mathematical methods developed for analysing differential equations.

In this paper, the formation of our work is designed as follows: first a background and related works are given. Then molecular representation of FACSP is deliberated, and critical pair analysis of DPO graph transformation rules using AGG tool is done. Stoichiometric matrix and the incidence matrix of the PT net are obtained.

## 2 Preliminaries

In [5], a stoichiometric matrix is obtained which relates each elementary reaction to each molecular species in the system by the aggregate effect the reaction has on that species population. The rate laws are extracted, and a rate law vector of length  $n$  is produced. A multiplication of this vector and the stoichiometric matrix produces a system of ordinary differential equations:

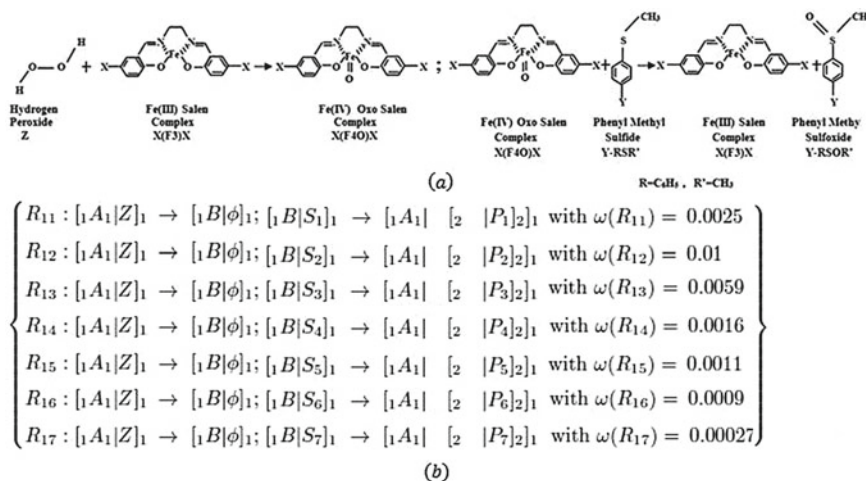
$$d[X]/dt = S \cdot R \quad (1)$$

where  $d[X]/dt$  is the differential with respect to time  $t$ , of a chemical species  $X$  in the system,  $S$  is the stoichiometric matrix, and  $R$  is the rate law vector.

In [7], the translation of Petri nets whose transitions are labelled by rate constants, to differential equations, is discussed.

### 2.1 The Graph Transformation System [5]

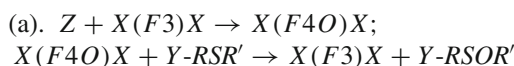
A type graph representing molecules using graph transformations is discussed in [5]. Here atoms are represented as square nodes. The round nodes are atom-specific bonding nodes. A bond between atoms is represented by an edge between two of these bonding nodes. Each bonding node is connected to only one atom node. The formal definitions of typed graph transformation system and Accountable GTS are also given in [5].



**Fig. 1** a Oxidation of sulphides and b evolution rules for FACSP

## 2.2 FACSP (Fuzzy Artificial Cell Systems With Proteins On Membranes) [3]

**Oxidation of Sulphides:** Oxidation of aryl methyl sulphides using iron–salen complexes as catalyst in presence of hydrogen peroxide as oxidant is followed kinetically and is described in [8]. Chemically the reaction takes place through formation of intermediate oxo compound of the catalyst and in second step the oxidation of substrate following regeneration of catalyst. The general reaction rule is presented in (a), and the structure is shown in Fig. 1a.



The structure of (a) is represented in Fig. 1a. In [3], the authors carried out catalytic reactions of aryl methyl sulphides varying the substitution at  $Y$  as H, Cl, Br, CH<sub>3</sub>, OCH<sub>3</sub>, F and NO<sub>2</sub> groups. In case  $X = H$  and  $Y$  varying as seven substitutions, (a) consists of seven reaction rules.

Fuzzy ARMS in Artificial Cell Systems with Proteins on Membranes (FACSP) has been introduced in which the evolution rules (Fuzzy rewriting rules) are the seven reaction rules and the Fuzzy data are oxidant, catalyst and substrate (Fig. 1b).

### 3 Graph Transformations for FACSP

We present the molecular representation of FACSP using graph transformation system and the derivation of ordinary differential equation for the reactions through critical pair analysis using AGG tools.

#### 3.1 Molecular Representation of FACSP Using Graphs

Let us consider the first evolution rule ( $R_{11}$ ) in FACSP from Sect. 2. The structure of the corresponding reaction rule is shown in Fig. 2 in which the formation of intermediate iron (IV)–oxo salen complex of parent molecule is described. The complex acts as a catalyst for the oxidation of phenyl methyl sulphide to phenyl methyl sulfoxide. At the end of the reaction, the catalyst, iron (III)–salen complex is regenerated. The species hydrogen peroxide ( $Z$ ), iron (III)–salen complex ( $A_1$ ), iron (IV)–oxo salen complex ( $B$ ), phenyl methyl sulphide ( $S_1$ ) and phenyl methyl sulfoxide ( $P_1$ ) in Fig. 2 are represented as molecules. Each molecule consists of bonds that connect two atoms. The intuitive representation of molecules consists of atoms as nodes and bonds as edges that directly connect them.

The type graph is produced in AGG (Fig. 3a) for all atoms and groups in FACSP. In this type graph, atoms and groups such as O, Fe, N, S, H, C, Cl, Br, F, CH<sub>3</sub>, OCH<sub>3</sub> and NO<sub>2</sub> are represented as square nodes, each distinct species having its own node type. The round nodes represented are atom-specific bonding nodes. All bonding

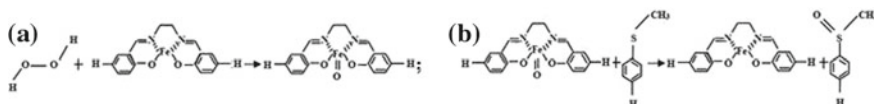


Fig. 2 Reaction rule  $R_{11}$

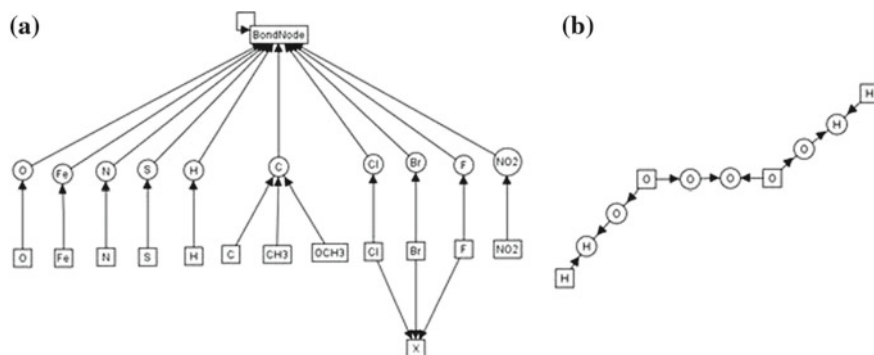


Fig. 3 **a** Type graph for FACSP and **b** type graph for the molecule hydrogen peroxide

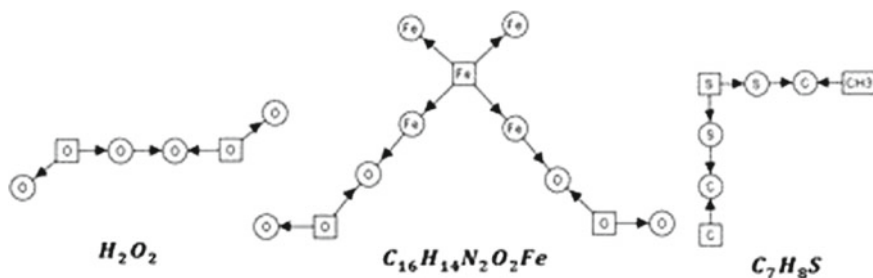


Fig. 4 Graph depicting starting materials for FACSP, produced in AGG

nodes are subtypes of the generic bond node type. Finally, the atoms chlorine (Cl), bromine (Br) and fluorine (F) are grouped as halogens, which is denoted by  $X$ .

A bond connecting H and O is represented by an edge [arrows with filled arrowheads, (Fig. 3b)]. The bond node oxygen is connected to atom node O and that of hydrogen is connected to atom node H. Oxygen has two bonds satisfying the valency two. The atoms and groups C, CH<sub>3</sub> and OCH<sub>3</sub> have the same bonding node type (C) associated with them.

In our problem, atom C is less electronegative than atoms N and S; C and N are less electronegative atoms than O atom. H is the least electronegative atom compared with all other atoms. Thus, a bond between H and any other atom would go from H.

The type graph contains C and H node types, and so the methyl group is represented as a single CH<sub>3</sub> node type. The critical pair analysis constructs an overlap between the graphs on the left-hand side and right-hand side of the evolution rules. The single CH<sub>3</sub> node is expressed in terms of C atom nodes, H atom nodes, C bonding nodes and H bonding nodes. The node CH<sub>3</sub> and the edges between them would constitute a total of 10 nodes.

The type graphs are drawn (Fig. 4) for the starting materials ( $Z$ ), ( $A_1$ ) and ( $S_1$ ) representing, namely, hydrogen peroxide, iron (III)–salen complex and phenyl methyl sulphide respectively taking as molecular identity rules. The LHS and RHS of this molecular identity rules are same and contain only the graph of a particular molecule.

Type graphs are obtained to all possible general rules in FACSP using the above methodology. The type graph of molecules in the reaction rule  $R_{11}(a)$  and  $R_{11}(b)$  is shown in Figs. 5 and 6. Each one is added as a molecular identity rule. Fig. 7 depicts the abstraction of the reaction rule  $R_{11}$  in Fig. 2.

### 3.2 Critical Pair Analysis for FACSP

A critical pair analysis is done between each general reaction rule and each molecular identity rule.

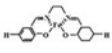
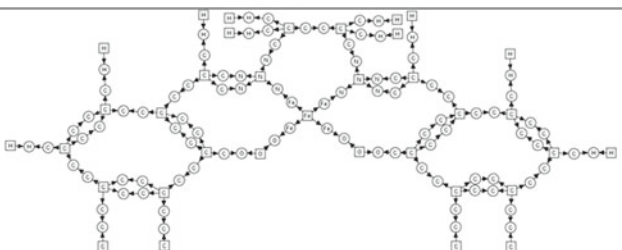

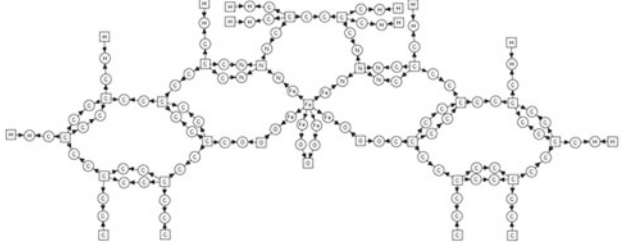
Chemical Formula	Structural Formula	Graph Representation
$C_{16}H_{14}N_2O_2Fe$		
$C_{16}H_{14}N_2O_2Fe$		

Fig. 5 Type graph for the molecule  $A_1$  and  $B$  in FACSP


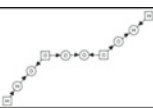

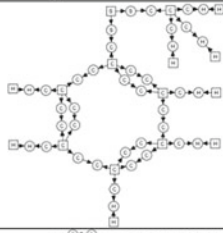

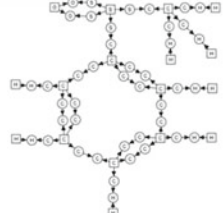
$H_2O_2$		
$C_7H_8S$		
$C_7H_8OS$		

Fig. 6 Type graph for the molecule  $Z$ ,  $S_1$  and  $P_1$  in FACSP

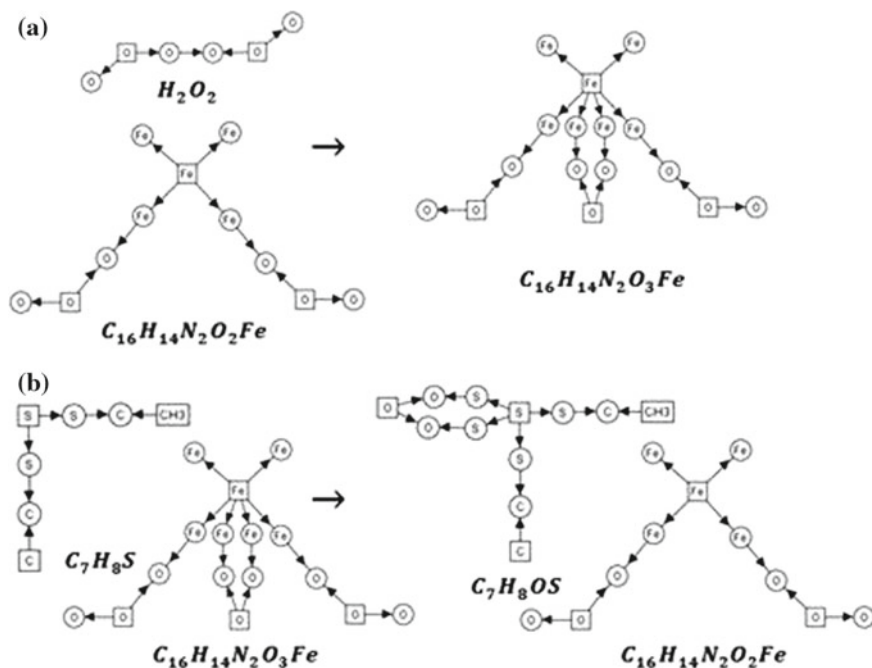
Fig. 7  $R_{11}(a)$ -top,  $R_{11}(b)$ -bottom

Fig. 8 Critical analysis—parallel conflicts (PC) and sequential dependencies (SD)

	$H_2O_2$ ( $Z$ )		$C_{16}H_{14}N_2O_2Fe$ ( $A_1$ )		$C_7H_8S$ ( $S_1$ )	
	PC	SD	PC	SD	PC	SD
$R_{11}(a)$	1	0	2	0	0	0
$R_{11}(b)$	0	0	0	2	1	0

The parallel conflict and sequential dependencies are verified by the application of the general rule to the molecule (LHS) at the match given by the critical overlapping and the application of the general rule to the molecule (RHS) at the match given by the critical overlapping respectively. The results of the first iteration are given in Fig. 8. Each entry signifies how many of the overlappings were critical for each pair. Critical pair analysis checks all possible unions of  $L$  and  $M$  for parallel conflict analysis and  $R$  and  $M$  for sequential dependence analysis.

In a similar manner, the molecular identity rules are obtained, and hence, the critical pair analysis is done for all reaction rules in FACSP. The result of the critical pair analysis is given in Fig. 9.

For the FACSP reaction studied, the results obtained after applying the reaction rule to the overlappings at their critical matches are compared. There are two critical overlappings wherever there is a conflict with  $A_1$  which is shown in Fig. 10. The critical nodes and edges in this overlapping (Fe) are covered by the shaded area.

	Z		A <sub>1</sub>		B		S <sub>1</sub>		S <sub>2</sub>		S <sub>3</sub>		S <sub>4</sub>		S <sub>5</sub>		S <sub>6</sub>		S <sub>7</sub>		P <sub>1</sub>		P <sub>2</sub>		P <sub>3</sub>		P <sub>4</sub>		P <sub>5</sub>		P <sub>6</sub>		P <sub>7</sub>	
	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD	PC	SD		
R <sub>11</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>11</sub> (b)	0	0	0	2	4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	
R <sub>12</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>12</sub> (b)	0	0	0	2	4	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	
R <sub>13</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>13</sub> (b)	0	0	0	2	4	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	
R <sub>14</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>14</sub> (b)	0	0	0	2	4	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	
R <sub>15</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>15</sub> (b)	0	0	0	2	4	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0		
R <sub>16</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>16</sub> (b)	0	0	0	2	4	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	
R <sub>17</sub> (a)	1	0	2	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
R <sub>17</sub> (b)	0	0	0	2	4	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	

Fig. 9 Critical pair analysis—parallel conflicts (PC) and sequential dependencies (SD)

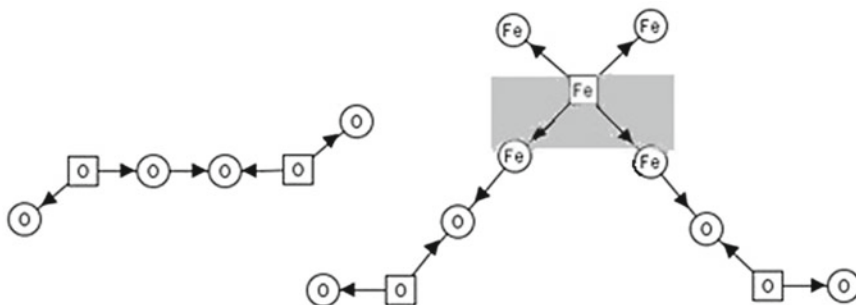


Fig. 10 Critical overlapping between  $R_{11}$  and  $A_1$  (critical graph elements are contained within the shaded area)

The other types of nodes and edges in the critical overlappings are identical and same. Due to the symmetry around the critical Fe atom node, two overlappings arise. They have no significance to the selection of a reaction or to the outcome. So, they are equivalent and hence we have got an isomorphism between the corresponding transformations. Since the molecules involved are very small, these overlappings are reduced to 1 in all cases. We then have reduced this entry in Fig. 9 to 1 which is the obtained stoichiometric matrix (Fig. 12). It is immediate to obtain the ODEs.

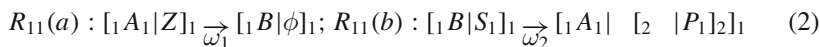
## 4 Stochastic Graph Transformation System for FACSP

In a chemical system, the reaction speed is captured by the rate constant as a measure of the reactivity of the given components. In FACSP, reaction rules that act on the molecules are specified by rewriting rules and rate constant represents the membership value. Assigning the membership values (rate constants) to rules of a graph transformation system, we obtain a stochastic graph transformation system.



### 4.1 Stoichiometric Matrix for FACSP

Consider the evolution rule



which comprise an example reaction mechanism for FACSP. If it is known for each reaction, how many molecules of each chemical species is created or destroyed, we can build up a matrix for the reactions in (2).

Each entry in the stoichiometric matrix corresponds to the aggregate number of molecules consumed or produced in a reaction, negative for consumption and positive for production. The first reaction in (2) with the membership value  $\omega_1$  consumed one molecule of  $Z$ , the entry for  $\omega_1$  and  $Z$  in the matrix would be  $-1$ . Similarly, the entry for  $\omega_1$  and  $A_1$  in the matrix would be  $-1$ . Also the first reaction in (2) with the membership value  $\omega_1$  produced one molecule of  $B$ , the entry for  $\omega_1$  and  $B$  in the matrix would be  $1$ . Proceeding like this, we build up a stoichiometric matrix for the reaction (2) which is tabulated in Fig. 11a.

In a similar way, we are able to build up the stoichiometric matrix (Fig. 12) for all the reactions in the seven evolution rules of FACSP.

The membership law for FACSP is defined such that the membership coefficient for each row is multiplied by the concentration of those species which are destroyed. For example, the membership law for the corresponding oxidation of sulphides in (2):  $\omega_1[Z][A_1]$  for the reaction  $R_{11}(a)$  and  $\omega_2[B][S_1]$  for  $R_{11}(b)$ .

The membership law matrix for the reactions in (2) is shown in Fig. 11b. In a similar manner, we are able to define membership law for all reactions in the seven evolution rules of FACSP.

We multiply the membership law matrix by stoichiometric matrix, and hence, we have obtained the following ODE's.

$$d[A_1]/dt = -\omega_1[Z][A_1] + \omega_2[B][S_1];$$

$$d[Z]/dt = -\omega_1[Z][A_1];$$

$$d[B]/dt = \omega_1[Z][A_1] - \omega_2[B][S_1];$$

	Z	A <sub>1</sub>	B	S <sub>1</sub>	P <sub>1</sub>
ω <sub>1</sub>	-1	-1	1	0	0
ω <sub>2</sub>	0	1	-1	-1	1

ω <sub>1</sub>	ω <sub>2</sub>
ω <sub>1</sub> [Z][A <sub>1</sub> ]	ω <sub>2</sub> [B][S <sub>1</sub> ]

Fig. 11 a Stoichiometric matrix for  $R_{11}$  and b membership law matrix for  $R_{11}$

$$d[S_1]/dt = -\omega_2[B][S_1];$$

$$d[P_1]/dt = \omega_2[B][S_1].$$

### 4.2 Place Transition Net Representing FACSP Reaction Mechanism

In [7], it is described how a discrete Petri net can be converted into a continuous one by allowing places to have a positive real number of tokens representing the concentration of that particular chemical species in the system. The ODEs can be deduced from the incidence matrix for such a Petri net.

M.V. \ M	Z	A <sub>1</sub>	B	S <sub>1</sub>	S <sub>2</sub>	S <sub>3</sub>	S <sub>4</sub>	S <sub>5</sub>	S <sub>6</sub>	S <sub>7</sub>	P <sub>1</sub>	P <sub>2</sub>	P <sub>3</sub>	P <sub>4</sub>	P <sub>5</sub>	P <sub>6</sub>	P <sub>7</sub>
$\omega_1$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_2$	0	1	-1	-1	0	0	0	0	0	0	1	0	0	0	0	0	0
$\omega_3$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_4$	0	1	-1	0	-1	0	0	0	0	0	0	1	0	0	0	0	0
$\omega_5$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_6$	0	1	-1	0	0	-1	0	0	0	0	0	0	1	0	0	0	0
$\omega_7$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_8$	0	1	-1	0	0	0	-1	0	0	0	0	0	0	1	0	0	0
$\omega_9$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_{10}$	0	1	-1	0	0	0	0	-1	0	0	0	0	0	0	1	0	0
$\omega_{11}$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_{12}$	0	1	-1	0	0	0	0	0	-1	0	0	0	0	0	0	1	0
$\omega_{13}$	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
$\omega_{14}$	0	1	-1	0	0	0	0	0	0	-1	0	0	0	0	0	0	1

Fig. 12 Stoichiometric matrix for FACSP, M-molecules, M.V.-membership values

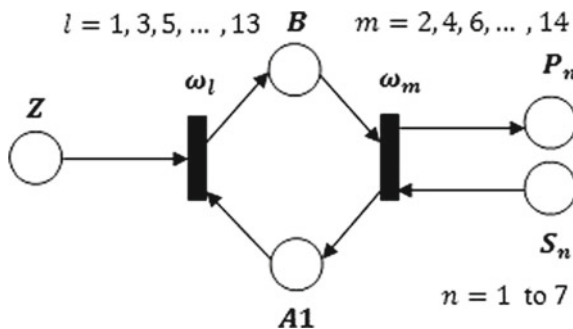


Fig. 13 PT Net for FACSP

In our problem, the incidence matrix for a place transition net with places  $Z, A_1, B, S_n, P_n$  where  $n = 1$  to  $7$  and transitions  $\omega_l, \omega_m$  where  $l = 1, 3, 5, \dots, 13$  and  $m = 2, 4, 6, \dots, 14$  are shown in Fig. 13. It is obviously similar to the stoichiometric matrix (Fig. 12) and hence we are able to obtain the ODEs.

## 5 Conclusion

We have derived ordinary differential equations from the stoichiometric matrix by doing critical pair analysis from the graph transformation system using AGG tools. In the same way, we have obtained the stoichiometric matrix using stochastic graph transformation by assigning membership values to the evolution rules. Again we have obtained the incidence matrix of a petri net representing the FACSP mechanism which is similar to the stoichiometric matrix of the FACSP.

We have observed that once a stoichiometric matrix is established, the ODEs could be derived. Also it is understood that it is enough to encode the graph transformation system into a place transition net to find the stoichiometric matrix. This approach has been demonstrated by means of oxidation of sulphides reactions following Michaelis–Menten kinetics using the AGG tool and validated for FACSP.

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