Determination of Stoichiometric Matrix for Ethanol Production from Xylose by Reduction of Elementary Modes with Ant Colony Systems

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Abstract: Ethanol production is still based on an old technology with performance that requires innovative culture strategies to optimize productivity, ethanol concentration and conversion yield. Furthermore ethanol production of second generation requires using lignocellulosic materials (constituted by 35 to 45\% of xylose). This paper addresses the problem of a determination of a stoichiometric matrix for ethanol production. A new method was proposed in order to simplify the set of elementary modes, an approach of optimization based on natural systems: Ant Colony Systems. The advantage of the presented method comes from the fact that it does not need to calculate distance between a node and a line and that only the knowledge of the coordinates of the elementary modes is necessary. This method was applied to xylose metabolism and a reducing stoichiometric matrix was obtained.

Keywords: Elementary Modes, Yield Analysis, Ant Colony Systems, Ethanol production.

1. INTRODUCTION

This new century presents crucial environmental challenges such as water supply, global warming and new energy sources for substitution of fossil fuels. These two last are closely dependent. Actually, the carbon dioxide CO\textsubscript{2} emissions with greenhouse effects are mainly connected with the use of fossil fuels for transport. Currently, ethanol is the main biofuel used in Europe. Its use reduces CO\textsubscript{2} emissions from 50 to 80\% compared to fossil fuels (Perréon-Delamette 2004). Ethanol production is now based on old technology with performance that requires innovative culture strategies to optimize productivity, ethanol concentration and conversion yield. Furthermore ethanol production requires to use no feed crops but other materials, as lignocellulosic.

Lignocellulosic materials constitute an abundant and cheap feed stock, since its saccharification produce glucose and xylose. Glucose and xylose are produced at a concentration ratio of 55–65\% to 35–45\% during the saccharidification of some organic wastes like wood, paper, agricultural by-products or crops (Ahring and Westermann 1987; Lavarack \textit{et al.} 2002). Optimization of fermentation process with these two compounds, especially xylose, will make possible to have better process yields, with less wastes.

Dynamic optimization of biological process needs to use robust models, with known parameters (\textit{i.e.} Yields, growth constants, \textit{etc.}). The first step is to establish a mass balance model of the process. Furthermore, mass balance models need information on the biological kinetics via yield matrix or stoichiometric matrix. Two approaches have been used in order to estimate this matrix. The first approach is based on a principal analysis compounds (PCA) of experimental data which allows obtaining a pseudo-stoichiometric matrix (Bernard and Bastin 2004; Bernard and Bastin 2005; Aceves-Lara \textit{et al.} 2008). The second approach does not use experimental data, but is based on metabolic model and use a reducing set of Elementary Modes in order to generate the stoichiometric matrix (Provost and Bastin 2004; Provost \textit{et al.} 2006; Provost \textit{et al.} 2007).

Elementary Modes (EMs) are a set of nondecomposable pathways consisting of a minimal set of reactions that function in steady state (Schuster \textit{et al.} 2002). Elementary Mode Analysis has been used for interpreting metabolic function networks, predicting the gene expression patterns and improving strain performance. Unfortunately, its implementation is difficult due to the combinatorial explosion of the number of EMs (Schuster \textit{et al.} 2002), that makes difficult its use in modeling.

Some approaches have been recently proposed in order to obtain a reducing set of nodes. Warner and Urbanczik (Wagner and Urbanczik 2005) calculated a minimal generating set, named generating modes (GM), using a null-space algorithm. This method has as disadvantages that the generating set is not the minimal and that it is necessary to study a convex space (Song and Ramkrishna 2009), Song and Ramkrishna (2009) used a Yield Analysis (YA) in order to reducing the modes. They simplified the polyhedral cone in a bounded convex hull. The convex hull was reduced by choosing an appropriate triangle and after by augmenting the vertex of the convex figure until to have a volume equal to...
99% of the total convex hull. Unfortunately, their method for calculate the first triangle need to calculate all distances and the height of the triangle.

The aim of the present work is to propose a new method to find the stoichiometric matrix. The xylose fermentation is chosen as biological application. For the first time a new method that reduced the EMs with an Ant Colony Systems (ACS) algorithm is presented. The first advantage of this method is that the only information required is the coordinates of EMs and does not need to calculate distance between two points and several lines. Finally, the stoichiometric matrix $K$ is calculated from the reducing set and its structure is determined.

2. METHOD

2.1 Mass Balance Model

Substrates and products are connected by several reactions that can be represented with a metabolic network. Figure 1 shows an example of a metabolic network with the external metabolites represented in bold characters.

In batch stirred tank reactor the mass balance model can be written according to system equation (1):

$$
\begin{align*}
\frac{dB}{dt} &= \mu \cdot B \\
\frac{dS}{dt} &= -N_S \cdot r \cdot B \\
\frac{dP}{dt} &= -N_P \cdot r \cdot B \\
\frac{dC}{dt} &= N_C \cdot r - \mu \cdot B
\end{align*}
$$

(1)

where $B$, $S$ and $P$ represent, respectively, the biomass, substrates, and products; $C$ is the intracellular metabolites vector. The kinetics $\mu$ and $r$ (dim = $n_C \times 1$) represent the constant specific growth rate and the intracellular specific reactions rates. The matrices $N_S$, $N_P$, $N_C$ are the stoichiometric matrix of the metabolic network for the substrate, the products and the internal metabolite (i.e. Metabolic pathway of xylose fermentation Fig 1) with dimensions $n_S \times n_r$, $n_P \times n_r$ and $n_C \times n_r$.

If a quasi steady-state for the intracellular metabolites is assumed (Stephanopoulos et al. 1998; Stephanopoulos 1999)

$$
\frac{dC}{dt} = N_C \cdot r - \mu \cdot C = 0,
$$

Furthermore $\mu \cdot C << N_C \cdot r$, then $N_C \cdot r = 0$.

The intracellular specific reactions rates $r$ can be expresses as a non-negative linear combination of the elementary vectors $e$:

$$
r = \lambda_1 e_1 + \lambda_2 e_2 + \ldots + \lambda_k e_k \quad \text{with} \quad \lambda_k \geq 0
$$

Finally, by defining a stoichiometric matrix $K$ like

$$
K = \left( \begin{array}{c}
N_S \\
N_P \\
N_C
\end{array} \right) E,
$$

where $E$ is the reducing matrix of elementary nodes (Provost and Bastin 2004; Provost et al. 2006; Provost et al. 2007). The classical dynamical model (for the substrate and products) can be represented as a function of metabolic flux as follows:

$$
\frac{d}{dt} \left( \begin{array}{c}
S \\
P
\end{array} \right) = K \cdot r \cdot B.
$$

(2)

In this work $E$ matrix will be calculate by using ant colony systems.

2.2 Ant Colony Algorithms

The optimization based on natural systems, like ants algorithms, dates from the beginning of the 90’s. Ant Colony Optimization (ACO) is a paradigm for designing metaheuristic algorithms for combinatorial optimization problems. The first Ant Algorithm was presented in 1991 (Coloni et al. 1991; Dorigo et al. 1991) and, since then, many variants of the basic principle were reported in the literature. ACO algorithms are based on the behaviour of ant’s colony (Dorigo et al. 1996) in order to find an optimal solution. This method is based on the deposit and evaporation of pheromones.

This algorithm can be explained in a simplified way: ants start moving randomly. Then, when they find their food, they come back towards their colony, marking their way with pheromones. The role of pheromone is to guide other ants towards the food. If other ants find the same way, they stop their random displacements and follow the same one
reinforcing pheromone concentration on their return. This process is a positive feedback, because a way with more pheromone becomes more and more attractive. At the same time, the pheromone evaporates and the least reinforced ways end up disappearing, which leads all the ants to follow the shortest way.

At the beginning, ant colony algorithms, as Ant Systems (AS) and Ant Colony Systems (ACS), were mainly used to produce quasi-optimal solutions for the travelling salesman problem (TSP). After, these algorithms have been modified in order to solve dynamic problems. One of these algorithms is known as CACA (Continuous Ant Colony Algorithm) that takes up some ideas from genetic algorithms (Jayaraman et al. 2000; Rajesh et al. 2001). Another interesting algorithm is IACA (Interactive Ant Colony Algorithm) (Zhang et al. 2005). IACA is based on the idea to discretize the time and the control variables, but without discretizing the state variables. IACA evaluated the complete trajectories traversed by the ants and after that updated the pheromone concentration of each node.

In this paper it was used an algorithm based on an ACS algorithm, since it was proved that ACS is one of the two best ACO algorithms (Stützle and Dorigo 2002). ACS can be described as follows (Dorigo and Gambardella, 1997). The amount of pheromone trail $\tau_{ij}(t)$ associated to the trajectory between $i$ and $j$. arc$(i,j)$ is intended to represent the learned desirability of choosing a node $j$ when the ant is on node $i$ (which also corresponds to the desirability that the $arc(i,j)$ belongs to the convex trajectory built by an ant).

The pheromone trail information is changed during problem solution to reflect the experience acquired by ants during problem solving. Ants deposit an amount of pheromone proportional to the quality of the solutions produced: when higher convex trajectory is generated by an ant a greater amount of pheromone it deposits on the arcs. The main role of pheromone evaporation is to avoid stagnation, that is, the situation in which all ants end up doing the same convex trajectory.

Place $m_a$ ants randomly in nodes.

The ant-decision table $A_i = [a_{ij}(t)]_{N_i}$ of node $i$ is obtained by the composition of the local pheromone trail values with the local heuristic values as follows:

$$a_{ij}(t) = \frac{[\tau_{ij}(t)]^\alpha [\eta_{ij}]^\beta}{\sum_{l\in N_i} [\tau_{il}(t)]^\alpha [\eta_{il}]^\beta}, \forall j \in N_i,$$

(3)

where $\tau_{ij}(t)$ is the amount of pheromone trail on $arc(i,j)$ at time $t$, $\eta_{ij} = d_{ij}$ ($d_{ij}$ is the Euclidian distance between nodes $i-j$) is the heuristic value of moving from node $i$ to node $j$, $N_i$ is the set of neighbours of node $i$, and $\alpha$ and $\beta$ are two parameters that control the relative weight of pheromone trail and heuristic value.

Let $q$ be a random variable uniformly distributed over $[0, 1]$, and $q_0 \in [0, 1]$ be a tuneable parameter. This state transition rule favours transitions toward nodes connected by short edges and with a large amount of pheromone. The pseudorandom-proportional rule $p_{ij}^k(t)$, used by ant $k$ located in node $i$ to choose the next node $j$ ($j \in N_i^k$), is the following: if $q < q_0$ then:

$$p_{ij}^k(t) = \begin{cases} 1 & \text{if } j = \arg \max a_{ij}(t) \\ 0 & \text{otherwise} \end{cases}.$$

(4)

otherwise, when $q > q_0$

$$p_{ij}^k(t) = \frac{a_{ij}(t)}{\sum_{l \in N_i^k} a_{il}(t)},$$

(5)

where $N_i^k \subseteq N_i$ is the set of nodes in the neighbourhood of node $i$ that ant $k$ has not visited yet.

When all ants completed their turns the pheromone updates $\tau_{ij}(t)$ are performed by applying the rule:

$$\tau_{ij}(t) \leftarrow (1 - \rho) \cdot \tau_{ij}(t) + \rho \cdot \Delta \tau, \ 0 \leq \rho \leq 1.$$

(6)

$\rho$ is the pheromone decay coefficient and $\Delta \tau$ is the distance covered by ants.

Parameters $\alpha = 1$, $\beta = 5$ and $m_a = 100$ were chosen according to Dorigo et al. (1996). Otherwise, the parameters $\rho = 0.9$, $\tau_{ij}(0) = 0.0001$ were obtained empirically after several simulations.

### 2.3 Reduction of EMs with ACS using the Yield Analysis

Song and Ramkrishna (2009) showed that Yield Analysis can simplify the polyhedral cone formed with the EMs into a convex hull. This simplification represents a projection in a space of lower order by normalizing the EMs to one compound. For the purpose of illustration of the method proposed here, let us consider a set of EMs with 100 elements randomly distributed between $[0, 1]$ (Figure 2a).

Fig. 2a. Elements randomly distributed.
(1) It is necessary to find the convex hull that encloses all the points (Figure 2b). Matlab function “ConvHull” (Mathworks) was used here in order to obtain the convex hull.

![Convex Hull](image)

**Fig. 2b. Convex hull that enclose all points.**

(2) Here ACS is used to maximize the distance between three nodes. It means that the method look for the triangle with the longest contour (Figure 2c).

![Triangle](image)

**Fig. 2c. Triangle found by ACS algorithm.**

(3) Another node is adding by choosing the node that produces the higher area. Adding of new nodes is continued until there is an area equal to 99% of the total hull convex area (Figure 2d).

![Reducing Convex Hull](image)

**Fig. 2d. Reducing convex hull.**

3. STOICHIOMETRIC MATRIX FOR XYLOSE FERMENTATION

3.1 Metabolic network data

Only a metabolic network is used in order to obtain the reduced potential stoichiometric matrix and no experimental data are required in this first step. Figure 1 shows the metabolic network for xylose fermentation, with a total of 37 reactions (Table 1).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Stoichiometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>v1</td>
<td>XYL + NADH → XOL + NAD</td>
</tr>
<tr>
<td>v2</td>
<td>XYL + NADPH → XOL + NADP</td>
</tr>
<tr>
<td>v3</td>
<td>XOL → XOLs</td>
</tr>
<tr>
<td>v4</td>
<td>XOL + NAD → XUL + NADH</td>
</tr>
<tr>
<td>v5</td>
<td>XUL + ATP → XSP + ADP</td>
</tr>
<tr>
<td>v6</td>
<td>Ru5P → XSP</td>
</tr>
<tr>
<td>v7</td>
<td>Ru5P → RSP</td>
</tr>
<tr>
<td>v8</td>
<td>RSP + XSP → STP + GAP</td>
</tr>
<tr>
<td>v9</td>
<td>XSP + EP → FSP + GAP</td>
</tr>
<tr>
<td>v10</td>
<td>GAP + 2 NADP → Ru5P + CO2 + 2 NADPH</td>
</tr>
<tr>
<td>v11</td>
<td>GAP + FDP</td>
</tr>
<tr>
<td>v12</td>
<td>FSP + ATP = DHAP + GAP + ADP</td>
</tr>
<tr>
<td>v13</td>
<td>DHAP = GAP</td>
</tr>
<tr>
<td>v14</td>
<td>DHAP + NADH → GOL + NAD</td>
</tr>
<tr>
<td>v15</td>
<td>GOL → GOLs</td>
</tr>
<tr>
<td>v16</td>
<td>GAP + NAD + ADP = PG3 + NADH + ATP</td>
</tr>
<tr>
<td>v17</td>
<td>PG3 + PEP</td>
</tr>
<tr>
<td>v18</td>
<td>PEP + ADP = PYR + ATP</td>
</tr>
<tr>
<td>v19</td>
<td>PYR → ACD + CO2</td>
</tr>
<tr>
<td>v20</td>
<td>ACD + NADH → ETH + NAD</td>
</tr>
<tr>
<td>v21</td>
<td>ACD + NADHm = ETH + NAdm</td>
</tr>
<tr>
<td>v22</td>
<td>ACD + NADP = ACT + NADPH</td>
</tr>
<tr>
<td>v23</td>
<td>PYR + NAdm + CoAm = AcCoAm + CO2 + NADHm</td>
</tr>
<tr>
<td>v24</td>
<td>OAAm + NADH → ETH + NAD</td>
</tr>
<tr>
<td>v25</td>
<td>OAAm + AcCoAm = ICT + CoAm</td>
</tr>
<tr>
<td>v26</td>
<td>ICT + NADm → AKG + CO2 + NADHm</td>
</tr>
<tr>
<td>v27</td>
<td>ICT + NADPm = AKG + CO2 + NADPm</td>
</tr>
<tr>
<td>v28</td>
<td>AKG + NADm + ADP = ICT + ATP + CO2 + NADHm</td>
</tr>
<tr>
<td>v29</td>
<td>SUC + 0.5 NADm = MAL + 0.5 NADHm</td>
</tr>
<tr>
<td>v30</td>
<td>MAL + NAdm = OAAm + NADHm</td>
</tr>
<tr>
<td>v31</td>
<td>STP = GAP → FDP + E4P</td>
</tr>
<tr>
<td>v32</td>
<td>PYR + ATP + CO2 = OAA + ADP</td>
</tr>
<tr>
<td>v33</td>
<td>ACT = AcAm</td>
</tr>
<tr>
<td>v34</td>
<td>ACT + CoA + 2 ATP = AcCoA + 2 ADP</td>
</tr>
<tr>
<td>v35</td>
<td>1.04 AKG + 0.57 E4P + 0.31 OAA + 2.36 AcCoA + 0.31 CoA + 2.68 NAD + 0.53 NADPH + 1.51 NADHm + 30.48 ADP</td>
</tr>
<tr>
<td>v36</td>
<td>ATP → ADP + MAINT</td>
</tr>
<tr>
<td>v37</td>
<td>NADH → NAD</td>
</tr>
</tbody>
</table>

The first step is to determine the Elementary Modes, these were calculated with METATOOL 2005 (Kamp and Schuster 2006). A total of 113 EMs are obtained. From these elements were calculated with METATOOL 2005 (Kamp and Schuster 2006). A total of 113 EMs are obtained. From these elements and equation (1) and (2), the equation (7) is obtained:

$$\frac{d}{dt} \frac{S}{P} = \frac{-N_x}{N_p} E_o \cdot r_o \cdot B.$$  \hspace{1cm} (7)

External metabolites can be decomposed in $S = [XYL]^T$ and $P = [CO2, ETH, ACT, B, GOL, XOOL]^T$. $E_o$ is the matrix of elementary modes $(37 \times 113)$ and $r_o$ is the vector of reactions rates $(113 \times 1)$.

Procedure of section 2.3 was applied to $E_o$. In a first time the convex hull from $E_o$ was found. After the ACS algorithm was used in order to find the triangle with the largest perimeter. Finally new nodes were added until the area was equal to 99%.

Figure 3 shows the optimal cost obtained for several iterations when the area of the first triangle was obtained. It is clear that ACS founds optimal point in little iterations. Figure 4 shows the convex hull for the xylose fermentation in the yield space $(Y_B, Y_{ETH})$. The 113 elementary modes ($E_o$) are represented as circles ($\circ$), the extreme pathways are symbolised by ($\circ$) and the minimal generator $E_r$ with ($\bullet$).
Fig. 3. Evolution of cost function with cycles.

Fig. 4. Convex hull for xylose fermentation ($Y_{ETH}$ ethanol yield, $Y_B$ biomass yield).

A total of five elementary modes were obtained, the matrix $E_o$ was reduced to $E_r$ (37×5). Then the reduced model can be written as follows:

$$\frac{d[S]}{dt} = K_r \cdot r_r \cdot B.$$  \hspace{1cm} (8)

By eliminating the internal metabolites between the reactions, the following set of fundamental macro-reactions that connect the extracellular substrates and the end-products is obtained:

$$e_1: \quad 2.2XYL \longrightarrow \frac{r_1}{3} \longrightarrow CO_2 + 2XOL$$

$$e_2: \quad 9.54XYL \longrightarrow \frac{r_2}{3} \longrightarrow 7.02CO_2 + 4.29ETH + B + 5.28XOL$$

$$e_3: \quad 609.67XYL \longrightarrow \frac{r_3}{3} \longrightarrow 415.65CO_2 + 221.78ETH \quad + \quad (9)$$

$$9.09B + 357.57XOL$$

$$e_4: \quad 1.11XYL \longrightarrow \frac{r_4}{3} \longrightarrow 2.22CO_2 + 1.67ETH$$

$$e_5: \quad 0.6XYL \longrightarrow \frac{r_5}{3} \longrightarrow CO_2 + ETH$$

The original vector $r_o$ (113×1) is reduced to $r_r$ (5×1); then $K_r = \left( \frac{N_S}{N_P} \right) E_r$ has the following form:

$$K_r = \begin{bmatrix}
-2.2 & -9.54 & -609.67 & -1.1 & -0.6 \\
1.0 & 7.02 & 415.65 & 2.22 & 1 \\
0 & 4.29 & 221.78 & 1.67 & 1 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0.13 & 9.09 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
2.0 & 5.28 & 357.57 & 0 & 0
\end{bmatrix}$$  \hspace{1cm} (10)

The $K_r$ matrix includes the potential reactions that describe the xylose fermentation.

3.2 Experimental data

Experimental data (Table 2) were used in order to determine the number of potential reactions by applying a PCA. This method was proposed by Bernard and Bastin (Bernard and Bastin 2004; Bernard and Bastin 2005) and it was successfully used in biohydrogen production (Aceves-Lara et al. 2008).

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>B (g/L)</th>
<th>CO_2 (g/L)</th>
<th>GOL (g/L)</th>
<th>ACT (g/L)</th>
<th>ETH (g/L)</th>
<th>XYL (g/L)</th>
<th>XOL (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>18.11</td>
<td>2.03</td>
<td>3.18</td>
<td>0</td>
<td>30.36</td>
<td>73.09</td>
<td>4.94</td>
</tr>
<tr>
<td>2.28</td>
<td>15.58</td>
<td>2.16</td>
<td>3.35</td>
<td>0</td>
<td>52.19</td>
<td>55.39</td>
<td>3.45</td>
</tr>
<tr>
<td>3.72</td>
<td>17.24</td>
<td>2.29</td>
<td>3.52</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>4.78</td>
<td>17.22</td>
<td>2.37</td>
<td>3.53</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>5.85</td>
<td>17.20</td>
<td>2.44</td>
<td>3.62</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>7.47</td>
<td>16.39</td>
<td>2.53</td>
<td>3.62</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>9.37</td>
<td>13.43</td>
<td>2.61</td>
<td>4.15</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>11.43</td>
<td>16.89</td>
<td>2.49</td>
<td>4.14</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>13.90</td>
<td>16.59</td>
<td>2.78</td>
<td>4.20</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
<tr>
<td>15.97</td>
<td>15.97</td>
<td>2.82</td>
<td>4.25</td>
<td>0</td>
<td>75.67</td>
<td>79.36</td>
<td>5.69</td>
</tr>
</tbody>
</table>

Figure 5 shows the percentage of cumulated variance as function of number of potential reactions. From an experimentally point of view, in the considered case, only four reaction are necessary to explain the 99.8% and five for explain the 99.9% of cumulated variance. This result is comparable to the result obtained for the matrix $K_r$.

Fig. 5. Percentage of total variance by total reactions.
4. CONCLUSIONS

Dynamic optimization of bioprocess needs robust balance models in order to improve it. These models require a stoichiometric matrix. Several approaches are proposed in literature, some need experimental data and another only the knowledge of the metabolic network. Approaches that used metabolic network information are based in the Elementary Modes. Usually, a metabolic network has many Elementary Modes then in a first time it is necessary to reduce it. Elementary Modes reduction is a hard task that may imply several calculus. In this work a new approach was proposed in order to reduce the Elementary Modes. This method is based in an Ant Colony Systems algorithm and can describe the 99% of reactions from a metabolic network. It was used to obtain the stoichiometric matrix from xylose fermentation. Finally, experimental data was used to obtain the number of reactions that can describe the system. It was found that five reactions are necessary in order to explain the 99.9% of cumulated variance. This is comparable to result obtained with the method proposed in this work.

This previous work was dedicated to obtain a stoichiometric matrix $K_f$. Future work will be addressed to phenomenological aspect, more precisely to the determination of the reactions rate vector $r_i = f_i (XYL, CO_2, ETH, ACT, B, GOL, XOL)$. 

5. ACKNOWLEDGEMENTS

The authors gratefully acknowledge the INRA, FUTUROL project for the support that made this study possible and to Peter Winterton for his English corrections.

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