GRAPH-THEORETIC APPROACH FOR IDENTIFYING CATALYTIC OR METABOLIC PATHWAYS

Liang-Tseng Fan*, Shahram Shafie, Botond Bertók, Ferenc Friedler, Dong-Yup Lee, Hodong Seo, Sun Won Park, and Sang-Yup Lee

ABSTRACT

Stoichiometrically exact and potentially feasible catalytic or metabolic pathways can be found by synthesizing the networks of plausible elementary or metabolic reactions constituting such pathways, respectively. The current contribution presents a mathematically exact algorithmic approach for carrying out the necessary synthesis, which is profoundly complex combinatorially. The approach is based on the unique graph-representation in terms of P-graphs (process graphs), a set of axioms, and a group of combinatorial algorithms. The inclusion or exclusion of a step of each elementary or metabolic reaction in the pathway of interest hinges on the general combinatorial properties of feasible reaction networks. At the outset, a brief overview is given of successful applications to date, followed by an outline of the methodology, on which the approach is based. The approach is illustrated by implementing it to three new examples comprising two catalytic reactions, catalytic combustion of hydrogen and reduction of nitrogen oxide, and one metabolic reaction, involved in the production of ethanol by yeast. The efficacy of the approach is discussed in light of the results obtained from these examples. Finally, a brief discourse is given of our current and future efforts.

Key Words: pathway, catalytic reaction, metabolic reaction, algorithmic identification, graph-theoretic.

I. INTRODUCTION

The determination of reaction pathways is one of the most important functions that should be performed in exploring the kinetics of catalyzed chemical reactions or biochemical reactions, the latter being generally catalyzed by enzymes. A reaction pathway, comprising the steps of elementary reactions, routes the precursors (starting reactants) to the targets (final products) of the reaction and vice versa, i.e., a reaction pathway signifies the mechanism of the reaction. The reaction pathway per se, either catalytic or metabolic, generates no information on the rate, reversibility, equilibrium, and extent of the catalytic or metabolic reaction. Nevertheless, knowledge of the pathways would immensely aid the characterization of catalysts and the understanding of catalytic reactions.

The determination of a reaction pathway consists of two phases. The first entails the identification of all feasible candidate pathways, and the second, the selection of the ultimate pathway from those identified. The establishment of a systematic procedure to execute these two phases would facilitate the determination in light of the fact that the two phases involve vastly different tasks and that each phase poses a unique set of complexities.

Every reaction pathway to be identified in the first phase forms a network of the steps of elementary reactions. In composing the network of any pathway, each elementary reaction among plausible elementary reactions contributes a forward, reverse

*Corresponding author. (Tel: 1-785-532-5586; Fax: 1-785-532-7372; Email: fan@ksu.edu)

L. T. Fan and S. Shafie are with the Department of Chemical Engineering, Kansas State University, Manhattan, KS 66506, U.S.A.

B. Bertók and F. Friedler are with the Department of Computer Science, University of Veszprém, Veszprém, Egyetem u. 10., H-8200, Hungary.

D.-Y. Lee, H. Seo, S. Park, and S. Y. Lee are with the Department of Chemical and Biomolecular Engineering, and Bioinformatics Research Center, Korea Advanced Institute of Science and Technology, 373-1 Guseong-dong, Yuseong-gu, Daejeon 305-701, Korea.

or no step to the network. As such, the number of possible combinations of these three possibilities that must be taken into account is vast even when the number of elementary reactions in the network is modest. Specifically, the number of possible combinations is $(3^n - 1)$ if the number of the candidate elementary reactions is n. The computational complexities encountered in the first phase are enormous. This might account for the paucity of publications along this line.

In the second phase, a limited number of candidate pathways or a mechanism is selected on the basis of the huge knowledge and databases accumulated in the field and in-depth heuristics compiled by individual researchers usually working in focused areas. Such pathways or mechanisms are adaptively modified in light of experimental and computational results; nevertheless, a valid pathway or mechanism might be overlooked. Often, it is exceedingly difficult to statistically discriminate among various analogous mechanisms based on the available experimental or computational results. This implies that all the valid candidate mechanisms should be rigorously identified in the first phase.

The two phases of reaction-pathway determination indeed should be undertaken systematically not only in series but also interactively: The work performed in the second phase could detect a previously unknown active species involved in the reaction of concern, thereby indicating the need to include an additional elementary reaction or reactions in the first phase. It is very common that the sources of elementary reactions necessary to initiate the first phase are the vast amount of information and the databases generated by those engaged in the second phase.

The current work presents a novel graph-theoretic approach for algorithmically and rigorously synthesizing a network of elementary chemical reactions, which corresponds to the reaction pathway or mechanism of a given overall reaction established by the first author and two coauthors of this paper (Fan *et al*. 1999, 2002; Fan *et al*., 2001). This approach represents a network by unique bipartite graphs, namely P-graphs (process graphs) (Friedler *et al*., 1992, 1993; Friedler *et al*., 1995; Friedler *et al*., 1996; Friedler *et al*., 1998; Peters *et al*., 2003).

Hereafter, the graph-theoretic approach for identifying a catalytic or metabolic pathway based on P-graphs will be called our P-graph-based approach, or simply our approach. It is capable of rapidly yielding a complete network, the maximal structure with minimal complexity, from a given set of candidate elementary reactions. Eventually, an exhaustive set of sub-networks corresponding to feasible pathways can be recovered from the maximal structure. The feasible pathways are to be explored experimentally, computationally and/or theoretically for the final selection of reaction pathways. Our approach's efficacy is illustrated by applying it to two catalytic reactions and one biochemical reaction, none of which have been published hitherto. What follows is a brief account of related previous work based on our approach.

When applied to the catalytic synthesis of ammonia from nitrogen and hydrogen through a set of 11 known bimolecular elementary reactions, our P-graph-based approach has recovered all six independent mechanisms available in the literature (Happel, 1972; Horiuti, 1973; Happel and Sellers, 1983; Boudart and Djega-Mariadassou, 1984; Happel and Sellers, 1990). Moreover, 11 additional acyclic combined mechanisms have been identified (Fan *et al*., 2001); among them only 1 was previously known (Happel and Sellers, 1990). Increasing the number of elementary reactions to 14 from 11 through the inclusion of three highly plausible elementary reactions (Hei, 1997) has resulted in 367 acyclic mechanisms, among which 35 are independent. The computational times on a relatively modest-size PC (450 MHz, 128 MB RAM) never exceeded 2 seconds in either case (Fan *et al*., 2001; Fan *et al*., 2002). When applied to the relatively simple catalytic dehydrogenation of butane (C_4H_{10}) to butene (C_4H_8) with five elementary reactions proposed by Temkin (1971), our approach has yielded 2 independent and one acyclic combined pathway. In contrast, Temkin (1971) has obtained only one pathway identical to the independent pathway mentioned above. When applied to the identification of metabolic pathways for the conversion of glucose to pyruvate, originally explored by Seressiotis & Bailey (1988) and Happel and Sellers (1990), our approach has reproduced all the pathways reported by them. Furthermore, a number of additional acyclic feasible pathways has been determined with computational time of less than 1 second, again on a modest-size PC (550 MHz and 250 MB RAM) (Seo *et al*., 2001).

II. METHODOLOGY

The methodology is rooted in two corner stones, two sets of axioms and the representation of the pathways networks by P-graphs. A set of three exacting algorithms has emerged from these corner stones.

1. Axioms

At the outset, it is assumed that the concentrations of all chemical species designated as active intermediates, i.e., those that are neither starting reactants (precursors) nor final products (targets), remain invariant and stationary without exhibiting transient or oscillatory behavior (Happel and Sellers, 1983). Moreover, the overall reaction and the plausible elementary reactions are defined a priori. According to

classical chemical thermodynamics, the overall reaction and all elementary reactions in any mechanism are reversible, and each reaction step, either forward or reverse, is stoichiometrically exact (see, e.g., Aris, 1965; Berry *et al*., 1980; Boudart and Djega-Mariadassou, 1984; Ross, 1993). In addition, the principle of microscopic reversibility prohibits the inclusion of any cycle in a pathway (Happel and Sellers, 1983). These first principles and conditions give rise to the two sets of axioms for any given overall reaction in what follows.

(i) Axioms of Feasible Reaction Pathways

(R1) Every final product (target) is totally produced by the reaction steps represented in the pathway.
(R2) Every starting reactant (precursor) is totally consumed by the reaction steps represented in the pathway.
(R3) Every active intermediate produced by any reaction step represented in the pathway is totally consumed by one or more reaction steps in the pathway, and every active intermediate consumed by any reaction step represented in the pathway is totally produced by one or more reaction steps in the pathway.
(R4) All reaction steps represented in the pathway are defined a priori.
(R5) The network representing the pathway is acyclic.
(R6) At least one elementary-reaction step represented in the pathway activates a starting reactant (precursor).

Since every elementary reaction is reversible, it comprises both forward and reverse steps. As a result, at most either the forward or reverse step of any elementary reaction can be in a pathway to circumvent the formation of a cycle or cycles within it. The directions of the forward and reverse steps of a given elementary reaction are opposite to each other. Hence, they can be simply indicated by opposite arrows, $\rightarrow$ and $\leftarrow$, respectively.

To focus on the combinatorial properties of the network comprising the feasible reaction pathways, the condition imposed by Axiom (R5) is relaxed except for the cycles formed by the forward and reverse steps of individual elementary reactions. The condition imposed by Axiom (R6) is totally relaxed: this axiom does not have any direct bearing on the generation of combinatorially feasible networks. Subsequently, Axioms (R1) through (R5) can be recast as the seven axioms of combinatorially feasible reaction networks.

(ii) Axioms of Combinatorially Feasible Reaction Networks

(T1) Every final product (target) is represented in the network.
(T2) Every starting reactant (precursor) is represented in the network.
(T3) Each reaction step represented in the network is defined a priori.
(T4) Every active species represented in the network has at least one path leading to a final product (target) of the overall reaction.
(T5) Every chemical or active species represented in the network must be a reactant for or a product from at least one reaction step represented in the network.
(T6) A reactant of any elementary reaction represented in the reaction network is a starting reactant (precursor), if it is not produced by any reaction step represented in the network.
(T7) The network includes at most either the forward or reverse step of each elementary reaction represented in the network.

2. P-Graphs

An unambiguous network representation is required in the reaction-pathway determination through the synthesis of a network from elementary reactions if the resultant network is to be mathematically exact so that it can be analyzed formally. P-graphs, which are bipartite directed graphs, serve this purpose (see, e.g., Friedler *et al*., 1992, 1993; Friedler *et al.*, 1995; Blazsik and Imreh, 1996; Friedler *et al*., 1996). The following is a brief description of the P-graphs for representing a network of elementary reactions.

Let O be the set of elementary-reaction steps and M be the set of chemical or active species under consideration; then, $O \subseteq \wp(M) \times \wp(M)$, where $O \cap M = \varnothing$. If (α, β) is a reaction step, i.e., $(\alpha, \beta) \in O$, then α is called the input set, and β, the output set of this step. Pair (M, O) is termed a P-graph with the set of vertices $M \cup O$ and the set of arcs $\{(x, y): y = (\alpha, \beta) \in O \text{ and } x \in \alpha\} \cup \{(y, x): y = (\alpha, \beta) \in O \text{ and } x \in \beta\}$. P-graph (M, O) is identified to be a sub-graph of (M', O'), i.e., $(M, O) \subseteq (M', O')$, if $M \subseteq M'$ and $O \subseteq O'$. The union of P-graphs (M_1, O_1) and (M_2, O_2) results in P-graph $(M_1 \cup M_2, O_1 \cup O_2)$.

In P-graphs, elementary-reaction steps are represented by horizontal bars; chemical and active species, by circles. If a chemical or active species is an input to an elementary-reaction step, an arc to the vertex representing the elementary-reaction step links the vertex representing this species. Similarly, if a chemical or active species is an output from an elementary-reaction step, the vertex representing this step is linked by an arc to the vertex representing the chemical or active species as illustrated in Fig. 1, with a network composed of the forward steps of two elementary reactions of the dehydrogenation of butane (C_4H_{10}) to butene (C_4H_8) (Temkin, 1971).

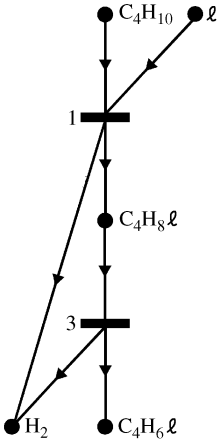

Fig. 1 P-graph representation of the network comprising elementary-reaction steps 1→ and 3→ in the pathway of the dehydrogenation of butane to butene (Fan *et al*., 2002)

P-graph (*M*, *O*) representing a reaction network leading from the starting reactants (precursors) to the final products (targets) of the overall reaction of interest is combinatorially feasible, if it satisfies Axioms (T1) through (T7). Moreover, a network represented by P-graph (*M*, *O*) representing a reaction pathway is *feasible* if it satisfies Axioms (R1) through (R6).

3. Algorithms

The aforementioned axioms and P-graph representation give rise to 3 inordinately efficient algorithms necessary for carrying out the synthesis of a feasible network, i.e., pathway, of elementary reactions. These algorithms are outlined in the following.

(i) Algorithm RPIMSG for Maximal Structure Generation

To minimize the computational difficulty encountered in synthesizing feasible networks of elementary reactions, the mathematical formulations for them should be of minimum complexity. In the framework of our approach, this is accomplished by generating the maximal structure of the reaction networks of interest. The maximal structure contains all combinatorially feasible structures, i.e., reaction networks or pathways, each leading from the starting reactants (precursors) to the final products (targets), without violating the aforementioned Axioms (T1) through (T7).

Note that not every combinatorially feasible structure constitutes a feasible pathway. Such a structure must satisfy the elementary balances, as expressed by Axioms (R1) through (R3); must not contain a cycle satisfying the principle of microscopic reversibility, as expressed by Axiom (R5); and must contain at least one elementary-reaction step activating a starting reactant (precursor), as expressed by Axiom (R6).

A mathematically rigorous algorithm for the maximal structure generation, algorithm RPIMSG, systematically places all the candidate reaction steps and examines their combinatorial feasibility in light of Axioms (T1) through (T7); algorithm RPIMSG represents a slight but judicious adaptation of algorithm MSG originally conceived for the synthesis of a network for the transformation of material species, i.e., a process network (Friedler *et al*., 1992).

For convenience, the initial network structure is constructed at the outset by linking all common nodes representing the chemical or active species in the form of solid circles; the nodes for elementary reactions are in the form of horizontal bars. The direction of any arc linking a pair of these two different nodes, one succeeding the other, is not indicated in the initial structure: Every elementary reaction is bi-directional, and at this juncture, no decision can be made as to which step of this elementary reaction, forward or reverse, should be included in the network; the exception is any arc linking a starting reactant (precursor) to one of the reaction steps activating it.

Algorithm RPIMSG consists of two major parts, reduction and composition. In the former, the chemical species, i.e., starting reactants (precursors), final products (targets), or active species, i.e., intermediates, and the reaction steps that must not belong to the maximal structure are excluded from the initial structure to the maximum extent possible on the basis of Axioms (T1) through (T7). To initiate the latter, every step of each elementary reaction, which has survived the elimination and is deemed plausible for inclusion, is properly identified on the basis of Axiom (T3), and each final product (target) is correctly specified on the basis of Axiom (T1). Hereafter, the maximal structure is constructed step-wise by collecting the reaction steps so as to satisfy Axioms (T4) and (T5).

(ii) Algorithm RPISSG for Solution-Structure Generation

The algorithm for the solution-structure generation, algorithm RPISSG, yields the set of all combinatorially feasible reaction networks (pathways) from the maximal structure of reaction networks. This algorithm is generated through the adaptation of algorithm SSG (Friedler *et al*., 1992) developed for process-network synthesis. Such adaptation has been executed by prudently rewriting the algorithm in the parlance of the graph-theoretic description of the reaction-pathway-identification based on the aforementioned P-graphs and in light of the axioms of the combinatorially feasible reaction networks, i.e., Axioms (T1) through (T7).

(iii) Algorithm PBT for Feasible Pathway Generation

To drastically reduce the computational time necessary to ascertain if each combinatorially feasible reaction network or pathway is indeed a feasible pathway in light of Axioms (R1) through (R5), a branch-and-bound-like algorithm termed a Pathway-Back-Tracking algorithm (algorithm PBT) has been developed (Fan *et al.*, 1999, 2002). Algorithm PBT is capable of generating directly all acyclic feasible pathways; nevertheless, it is more convenient to identify only the independent feasible pathways first when the number of such pathways is large (Happel and Sellers, 1982).

III. CATALYTIC REACTIONS

Two extensively explored catalytic reactions are revisited with our P-graph-based approach. These reactions are catalytic combustion of hydrogen and nitrogen-oxide reduction. For each reaction the approach has identified a number of additional feasible pathways over the available pathways.

1. Catalytic Combustion of Hydrogen

The reaction between H_2 and O_2 on supported platinum catalysts, i.e., the combustion of H_2 on such catalysts, has long been known to occur (Faraday, 1844); various researchers experimentally investigated this reaction (see, e.g., Hanson and Boudart, 1978; Anton and Cadogan, 1991). The earliest mechanism proposed for the reaction involves 5 elementary reactions (Temkin, 1979; Boudart and Djega-Mariadassou, 1984). Recently, two mechanisms, both based on the same nine elementary reactions, have been proposed for the reaction (Park *et al.*, 1999; Aghalayam *et al.*, 2000).

The stoichiometric expressions for the overall reaction of concern and the nine elementary reactions, yielding the two available mechanisms, are given below (Park *et al.*, 1999; Aghalayam *et al.*, 2000).

Overall reaction: $\Sigma \quad 2H_2 + O_2 \rightleftharpoons 2H_2O$

Elementary reactions: E

(1) $O_2 + 2\ell \rightleftharpoons 2O\ell$
(2) $H_2 + 2\ell \rightleftharpoons 2H\ell$
(3) $H\ell + O\ell \rightleftharpoons OH\ell + \ell$
(4) $OH\ell + H\ell \rightleftharpoons H_2O\ell + \ell$
(5) $2OH\ell \rightleftharpoons H_2O\ell + O\ell$
(6) $H_2O\ell \rightleftharpoons H_2O + \ell$
(7) $OH\ell \rightleftharpoons OH + \ell$
(8) $H\ell \rightleftharpoons H + \ell$
(9) $O\ell \rightleftharpoons O + \ell$

In the above expressions, ℓ stands for an active site on the catalyst.

Algorithms RPIMSG and RPISSG together with their subsidiary algorithms of our P-graph-based approach have identified the 7 combinatorially feasible reaction pathways in the search space containing $(3^9 - 1) = 19{,}682$ combinations of the 9 elementary reactions. Fig. 2 displays combinatorially feasible reaction pathways 1 through 7 that have been generated.

The feasibility of the 7 combinatorially feasible pathways can be determined in two ways. One is through the determination of stoichiometric numbers for each combinatorially feasible pathway by linear programming (LP) subject to the molar-balance constraints involving all participating chemical and active species. If the pathway fails to satisfy the constraints, it is infeasible: it does not yield the solution. The other is through the generation of feasible pathways directly from the maximal structure (maximal reaction network) by means of algorithm PBT. The outcomes are that combinatorially feasible pathways 1, 2, and 5 are identified as feasible independent pathways 1, 2, and 3, respectively, and combinatorially feasible pathways 3 and 7 are identified as feasible, acyclic combined pathways 4 and 5, respectively. Table 1 lists all these feasible pathways.

Combinatorially feasible pathways 4 and 6 are infeasible pathways: Each of them includes a cyclic loop thereby violating Axiom (R5). Pathway 4 contains a loop consisting of the set of elementary-reaction steps, (3←), (4→) and (5←); and pathway 6, contains a loop consisting of the steps, (3→), (4←) and (5→). Table 1 indicates that independent pathways 2 and 3 are identical to those identified by (Park *et al.*, 1999) as well as by (Aghalayam *et al.*, 2000). Independent pathway 1 and combined pathways 4 and 5, however, have been unknown hitherto. Apparently, elementary reactions (7), (8), and (9) are redundant; this has been confirmed by repeating the solution with elementary reactions (1) through (6) only, which has yielded the same results as those obtained with the 9 elementary reactions.

It is worth mentioning that each of the 2 initiation steps should preferably be expressed in 2 steps, for instances, $H_2 + \ell \rightleftharpoons H_2\ell$ and $H_2\ell + \ell \rightleftharpoons 2H\ell$, rather than in 1 step as originally given.

Upon supplementing the opposite step to each reaction step, the five feasible pathways in Table 1 give rise to the five stoichiometrically exact and thus valid mechanisms. Merely, 0.01 second is required to determine all the five feasible mechanisms on a modest-size PC (Pentium III, 700 MHz, 256 MB RAM).

2. Nitrogen-Oxide Reduction

Nitric oxides (NO_x) and sulfur dioxide (SO_2) are the major air pollutants in the flue gas of fossil-fuel combustion that should be prevented from entering

Table 1 Five resultant feasible pathways and the corresponding stoichiometric numbers for the reaction between H_2 and O_2 on platinum catalysts: Note that the positive sign indicates the forward step; and the negative sign, the reverse step

Elementary reactions		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Independent pathways	Pathway 1	1	2		4	-2	2			
	Pathway 2*	1	2	2	2		2			
	Pathway 3*	1	2	4		2	2			
Acyclic combined pathways	Pathway 4	1	2	1	3	-1	2			
	Pathway 5	1	2	3	1	1	2			

*Park *et al.* (1999) and Aghalayam *et al.* (2000)

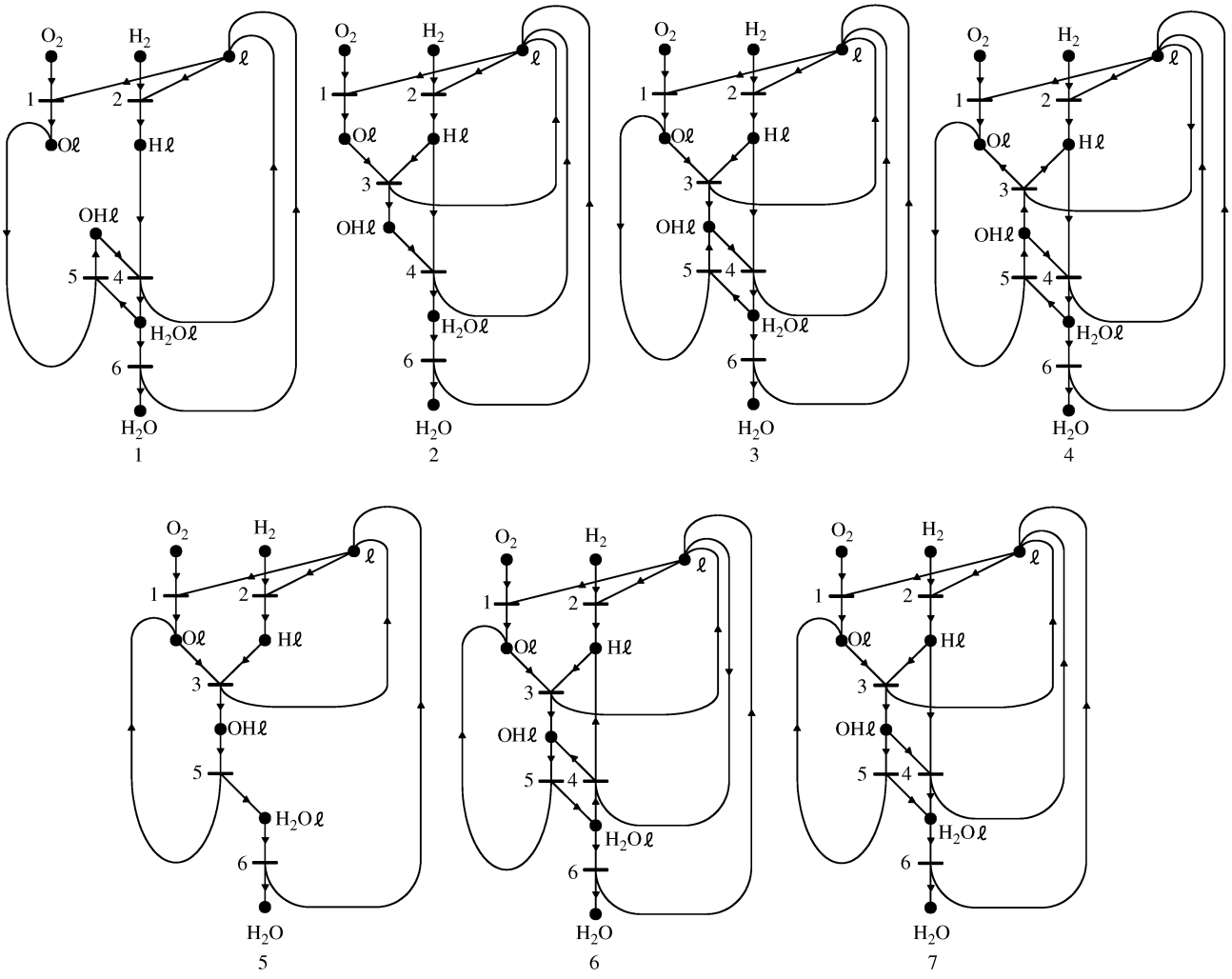

Fig. 2 Combinatorially feasible pathways for the catalytic reaction between H_2 and O_2 on platinum.

into the atmosphere. Once in the atmosphere, these pollutants affect not only human health, but also the ecosystem. They generate acid rain and urban smog and cause depletion of the ozone. One of the most common means of minimizing NO_x, or more specifically NO_2, is through its reduction with carbon monoxide (CO) over the transition metal catalyst. The recent regulatory emphasis on reducing NO_x and CO emissions from automobile exhausts has promoted the development of catalysts for the reaction between NOx and CO to produce CO_2 and NO or N_2; specifically, NO is the product of NO_2 partial reduction, which can undergo further reduction to N_2 (Wickham and Koel, 1988; Banse *et al.*, 1989; Koebel *et al.*, 2001).

The partial reduction of NO_2 by CO, whose overall reaction is designated as d_1: $NO_2 + CO \rightleftharpoons NO$

Table 2 Overall reaction and plausible elementary reactions in the mechanisms of partial reduction of NO_2 to NO by CO on platinum catalyst at temperatures below 400 K (Case 1) and overall reaction and plausible elementary reactions in the mechanisms of reduction of NO to N_2 by CO at temperatures below and above 400 K (Case 2) on platinum catalyst; ℓ denotes an active site on the catalyst

Case 1. (A) (Wickham, and Koel, 1988) (B) (current work)			Case 2. (Banse *et. al*., 1989)		
Overall reaction			Overall reaction		
d_1: $NO_2 + CO$	$\rightleftharpoons$	$NO + CO_2$	d_2: $2NO + 2CO$	$\rightleftharpoons$	$N_2 + 2CO_2$
Elementary reactions			Elementary reactions		
(A) (1) $NO_2 + 2\ell$	$\rightleftharpoons$	$NO\ell + O\ell$	(B) (1) $NO_2 + 2\ell$	$\rightleftharpoons$	$NO\ell + O\ell$
(2) $NO\ell$	$\rightleftharpoons$	$NO + \ell$	(2) $NO\ell$	$\rightleftharpoons$	$NO + \ell$
(3) $CO + \ell$	$\rightleftharpoons$	$CO\ell$	(3) $CO + \ell$	$\rightleftharpoons$	$CO\ell$
(4) $CO\ell + O\ell$	$\rightleftharpoons$	$CO_2 + 2\ell$	(4) $CO\ell + O\ell$	$\rightleftharpoons$	$CO_2 + 2\ell$
(5) $NO_2 + \ell$	$\rightleftharpoons$	$NO_2\ell$	(5) $NO_2 + \ell$	$\rightleftharpoons$	$NO_2\ell$
(6) $CO\ell + NO_2\ell$	$\rightleftharpoons$	$CO_2 + NO + 2\ell$	(6) $CO\ell + NO_2\ell$	$\rightleftharpoons$	$CO_2 + NO + 2\ell$
(7) $CO\ell + NO\ell$	$\rightleftharpoons$	$CO_2 + N\ell + \ell$	(7) $CO\ell + NO\ell$	$\rightleftharpoons$	$CO_2 + N\ell + \ell$
(8) $NO\ell + \ell$	$\rightleftharpoons$	$N\ell + O\ell$	(8) $2N\ell$	$\rightleftharpoons$	$N_2 + 2\ell$
			(9) $NO\ell + \ell$	$\rightleftharpoons$	$N\ell + O\ell$

$+ CO_2$ is listed as Case 1 of Table 2. Wickham and Koel (1988) have proposed a mechanism for this overall reaction involving 6 elementary reactions listed in Set (A) of Case 1 in Table 2, which include the dissociation of NO_2 and a bimolecular reaction between co-adsorbed NO_2 and CO, at temperatures below 400 K. They have derived the rate law from this mechanism.

Based on their studies on transient kinetics, Banse *et al*. (1989) have proposed a mechanism comprising 9 elementary reactions, involving a dissociative reaction, for further reduction of NO to N_2 by CO, thus yielding the overall reaction, d_2: $2NO + 2CO \rightleftharpoons N_2 + 2CO_2$. These elementary reactions are listed in Case 2 of Table 2.

The overall reaction, d_2, proceeds even at temperatures below 400 K. It is, therefore, highly plausible that some of the elementary reactions, not involving N_2, participate in the pathway leading to d_1. By including 2 such elementary reactions, the current work proposes a set of 8 elementary reactions for d_1; it is listed as Set (B) of case 1 in Table 2.

(i)Catalytic Partial Reduction of NO_2 to NO by CO (d_1: $NO_2 + CO \rightleftharpoons NO + CO_2$)

When applied to Set (A) of Case 1 in Table 2, algorithm RPISSG and its subsidiary algorithms have yielded from the maximal structure generated by algorithm RPIMSG, which is illustrated in Fig. 3, all five combinatorially feasible reaction networks illustrated in Fig. 4. Note that algorithms RPIMSG and RPISSG collectively reduce the search space containing $(3^6 - 1) = 728$ combinations of the six elementary

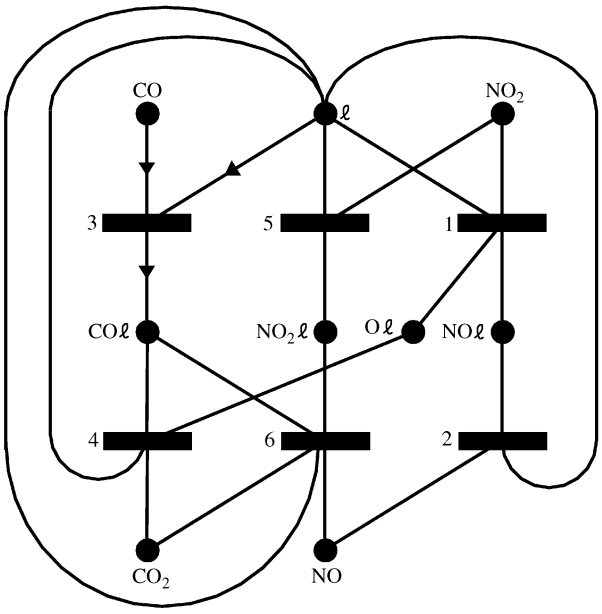

Fig. 3 P-graph representation of the maximal structure for the partial reduction of NO_2 to NO by CO at temperatures below 400 K; Set (A) of Case 1 in Table 2

reactions to only five combinatorially feasible pathways. Moreover, algorithm PBT, together with the subsidiary algorithms (Fan *et a*l., 1999, 2002), recover directly from the search space 3 feasible solutions, thereby showing that combinatorially feasible pathways 1 and 3 are in fact feasible independent pathways 1 and 2, respectively; the former corresponds to a dissociative NO_2 mechanism, and the latter, to a bimolecular reaction between co-adsorbed NO_2 and CO (Wickham and

Table 3 Three feasible reaction pathways and the corresponding stoichiometric numbers for catalytic partial reduction of NO_2 by CO to NO on platinum catalyst at temperatures below 400 K obtained from the 6 element reactions in Set (A) of Case 1 in Table 2 (Wickham, and Koel, 1988): Note that the positive numbers indicate the forward step; and the negative numbers, the reverse step

Elementary reactions		(1)	(2)	(3)	(4)	(5)	(6)
Independent pathways	Pathway 1	1	1	1	1		
	Pathway 2			1		1	1
Acyclic combined pathway	Pathway 3*	1	1	2	1	1	1

*Wickham and Koel (1988)

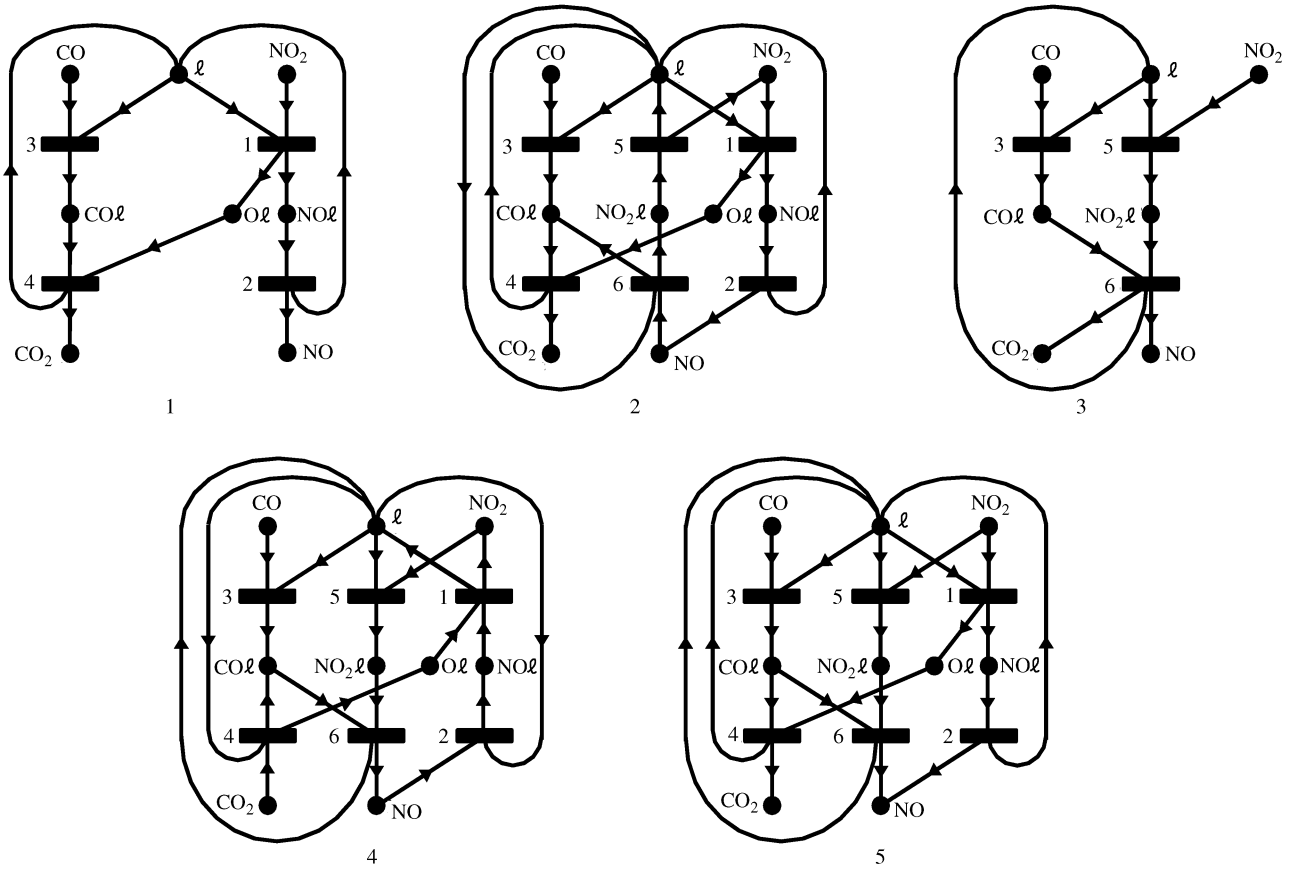

Fig. 4 P-graph representation of the combinatorially feasible reaction networks for the partial reduction of NO_2 to NO by CO at temperatures below 400 K; Set (A) of Case 1 in Table 2

Koel, 1988). Algorithm PBT, together with the subsidiary algorithms, also identifies combinatorially feasible pathway 5 as feasible acyclic combined pathway 3. It is worth noting that combinatorially feasible pathways 2 and 4 are infeasible because each of them contains a cyclic loop; this renders them infeasible in view of Axiom (R5). Given in Table 3 are the three resultant feasible pathways and the corresponding stoichiometric numbers by which each elementary reaction is to be multiplied. Upon supplementing the opposite step to each reaction step, the three feasible pathways give rise to three stoichiometrically exact and thus valid mechanisms. In fact, the mechanism resulting from pathway 3, which is an acyclic combined pathway, is identical to that proposed by (Wickham and Koel, 1988). All the results for Set (A) of Case 1 in Table 3 have been obtained on a PC (Pentium-III, 550MHz, 256MB RAM) with a computational time of less than 0.1 second.

Suppose that the feasible pathways for overall reaction d_1 are determined for the eight elementary reactions in Set (B) of Case 1 in Table 2 on the bases of the aforementioned rationale proposed in the current work. For these eight elementary reactions combinatorially feasible networks or pathways numbering 43 are identified via algorithms RPIMSG and RPISSG. In parallel, algorithms RPIMSG and PBT,

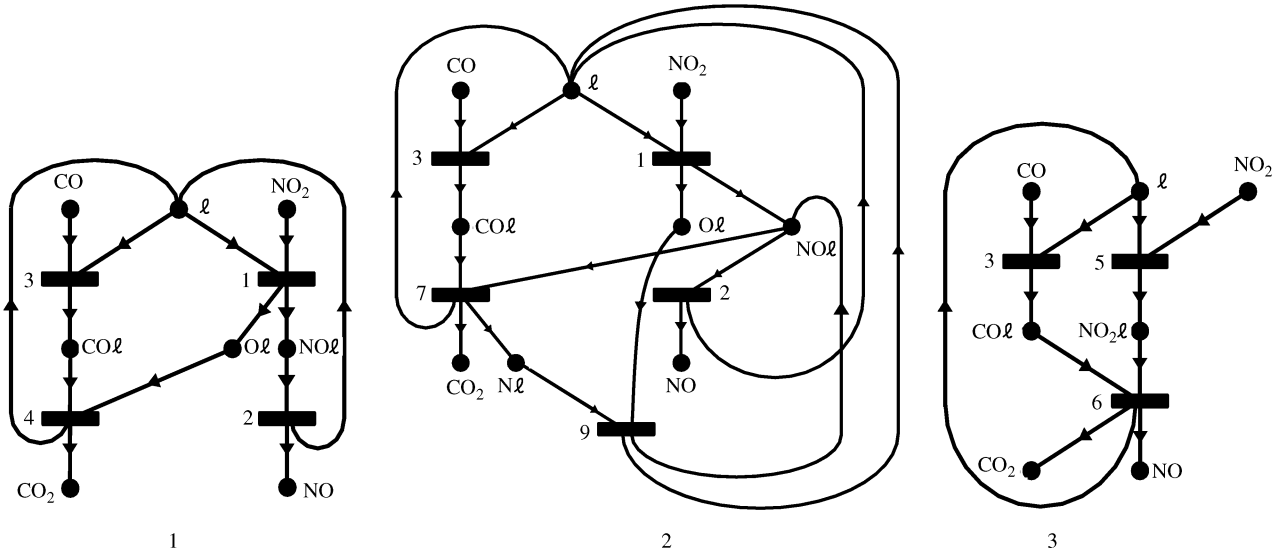

Fig. 5 P-graph representation of the feasible independent reaction pathways for the catalytic partial reduction of NO_2 to NO by CO at temperatures below 400 K; Set (B) of Case 2 in Table 2

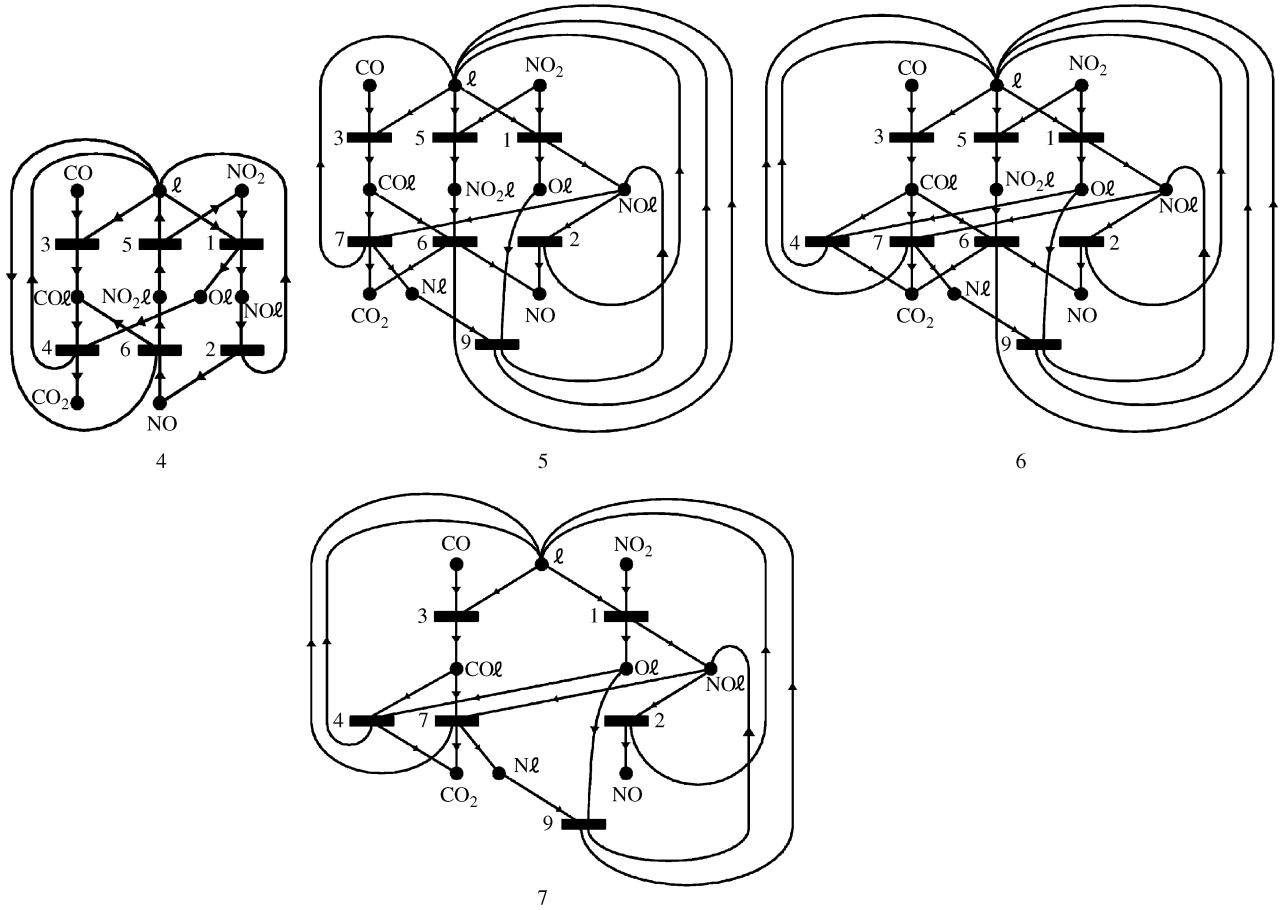

Fig. 6 P-graph representation of the feasible combined acyclic reaction pathways for the catalytic partial reduction of NO_2 to NO by CO at temperatures below 400 K; Set (B) of Case 2 in Table

together with the subsidiary algorithms, generate the three feasible independent and four feasible acyclic combined pathways illustrated in Figs. 5 and 6, respectively. Given in Table 4 are these seven feasible pathways and the corresponding stoichiometric numbers by which the corresponding elementary re-

Table 4 Seven feasible reaction pathways and the corresponding stoichiometric numbers for catalytic partial reduction of NO_2 by CO to NO on platinum catalyst at temperature below 400 K obtained from the 9 element reactions in Set (B) of Case 1 in Table 2 with the forward steps indicated by the positive numbers and the reverse steps indicated by the negative numbers

Elementary reactions		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Independent pathways	Pathway 1	1	1	1	1				
	Pathway 2	1	1	1				1	-1
	Pathway 3			1		1	1		
Acyclic combined pathways	Pathway 4	2	2	2	1			1	-1
	Pathway 5*	1	1	2	1	1	1		
	Pathway 6	1	1	2		1	1	1	-1
	Pathway 7	2	2	3	1	1	1	1	-1

*Wickham and Koel (1988)

actions are multiplied. Naturally, the three feasible pathways based on Set (A) of Case 1 in Table 3 are a subset of the seven feasible pathways based on Set (B) of Case 1 in Table 4. All the results have been obtained on the same PC used for Set (A) Case 1 with a computational time of also less than 0.1 second.

(ii) Further Catalytic Reduction of NO to N_2 by CO (d_2: $2NO + 2CO \rightleftharpoons N_2 + 2CO_2$)

The two consecutive reactions, d_1 and d_2, reduce NO_2 to N_2 by CO via the partial reduction to NO. Banse *et al*. (1989) have proposed a mechanism comprising nine elementary reactions including a dissociative reaction for d_2 under a wide range of reacting conditions; see Case 2 in Table 2. Fig. 7 illustrates the maximum structure generated by algorithms RPIMSG from these elementary reactions from which 37 combinatorially feasible reaction networks have been recovered by algorithm RPISSG. Note that these algorithms reduce the search space of $(3^9 - 1) = 19{,}682$ combinations of the nine elementary reactions to only 37 combinatorially feasible combinations, i.e., networks, of the elementary-reaction steps.

Algorithm PBT, together with the subsidiary algorithms, yields directly from maximal structure 6 feasible independent pathways and 11 feasible acyclic combined pathways; these 17 feasible pathways are given in Table 5. Note that feasible pathway 1 involves the bimolecular reaction, and feasible pathway 2, the dissociative reaction as reported by Banse *et al*. (1989). All the results for d_2 have been obtained on the same PC as used for d_1 with a computational time of less than 0.1 second.

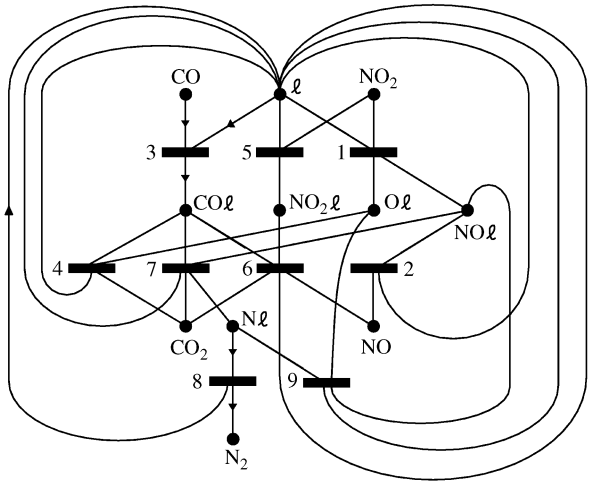

Fig. 7 P-graph representation of the maximal structure for the reduction of NO to N_2 by CO; Case 2 in Table 2

IV. METHABOLIC REACTION: ETHANOL PRODUCTION BY YEAST

Ethanol production by yeast is one of the most, if not the most, ubiquitous biochemical processes. Our P-graph-based approach is applied to the *in silico* model of metabolism involved in ethanol production by yeast. Nevertheless, the approach's implementation needs to be aided by flux balance analysis (FBA) based on linear programming for determining the overall reaction, which is often unknown a priori for a biochemical, or metabolic reaction (Lee *et al*., 2003; Lee *et al*., 2005).

(i) In Silico Representation of Yeast Metabolic Network

Figure 8 depicts an overview of the metabolic network of the *in silico* model. This network incorporates 48 metabolites (6 extracellular metabolites and 42 intermediates) and 50 metabolic reactions (see Table 6). Embedded in the metabolic network are the glycolytic pathway, the pentose phosphate

Table 5 Seventeen feasible reaction pathways and the corresponding stoichiometric numbers for catalytic reduction of NO to N_2 by CO on platinum catalyst obtained from the 9 element reactions in Case 2 in Table 2 (Banse *et al*., 1989) with the forward steps indicated by the positive signs and the reverse steps indicated by the negative signs

Elementary reactions		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Independent pathways	Pathway 1*		-2	2				2	1	
	Pathway 2*		-2	2	2				1	2
	Pathway 3	-2	-4	2		2	2		1	2
	Pathway 4	2		2	4	-2	-2		1	2
	Pathway 5	2		2	2	-2	-2	2	1	
	Pathway 6	2		2		-2	-2	4	1	-2
Acyclic combined pathways	Pathway 7	-1	-3	2	1	1	1		1	2
	Pathway 8		-2	2	1			1	1	1
	Pathway 9	-1	-3	2		1	1	1	1	1
	Pathway 10	-2	-8	6	2	2	2	2	3	4
	Pathway 11	2		2	3	-2	-2	1	1	1
	Pathway 12	2		2	1	-2	-2	3	1	-1
	Pathway 13	1	-1	2	1	-1	-1	2	1	
	Pathway 14	1	-1	2		-1	-1	3	1	-1
	Pathway 15	4	-2	6	2	-4	-4	8	3	-2
	Pathway 16	1	-1	2	3	-1	-1		1	2
	Pathway 17	2	-4	6	6	-2	-2	2	3	4

*Banse *et al.* (1989)

pathway (PPP), the tricarboxylic acid (TCA) cycle, glyoxylate shunt, and the energy and redox metabolisms, along with the necessary transport reactions for extracellular metabolites. In addition, growth is quantified by a biomass equation derived from the drain of biosynthetic precursors (11 intermediates) into yeast biomass with their appropriate ratios.

Of extra cellular metabolites, glucose is regarded as the only carbon source consumed through the system while metabolic products, i.e., ethanol and acetate, and biomass, are allowed to be secreted or accumulated. The consumption of oxygen and carbon dioxide are unconstrained, and they are allowed to accumulate as needed; however, all the intermediates are equally constrained. Fueling of the metabolic network is rendered possible by a constrained amount of glucose (< 10 mmol/g DCW · h) signifying limited substrate availability, along with unconstrained uptake/secretion routes for inorganic phosphate, oxygen and carbon dioxide. (Note: g DCW stands for grams dry cell weight.)

Based on the hypothesis that biological functions in the cell evolve optimally under the given environmental conditions (Bialy, 2001and Edwards *et al*., 2002), the cell behavior can be predicted under various culture conditions by means of FBA. Thus, a variety of scenarios or cases representing different culture conditions can be considered for physiologically meaningful results by setting some of the fluxes as the desired targets (objective functions) within the defined system.

When applied to the aforementioned *in silico* model of yeast metabolism involved in ethanol production (Cakir *et al*., 2004), our P-graph-based approach in conjunction with FBA identifies multiple flux distributions (MFD) and multiple metabolic pathways (MMP) as delineated in what follows.

(ii) Maximization of Ethanol Production

Herein, the ethanol production is set as the desired target to be maximized within the defined system under highly oxygen-limited or anaerobic conditions. Under these conditions, the use of non-growing cells is assumed for the production of metabolic products to obtain the maximum possible yield. The objective function to be maximized in FBA is the ethanol production, which can be achieved through the dissimilation of pyruvate initiated by its conversion into acetaldehyde through reaction *PDC* (see Fig. 8). The theoretical maximum ethanol production rate of 20 mmol/g DCW · h has been obtained in the absence of cell growth with software MetaFluxNet for implementing FBA (Lee *et al*., 2003). The resultant flux distribution given in Table 7 leads to the net reaction balance, 10.0 GLCxt → 20.0 ETHxt + 20.0 CO_2. The flux distribution can be

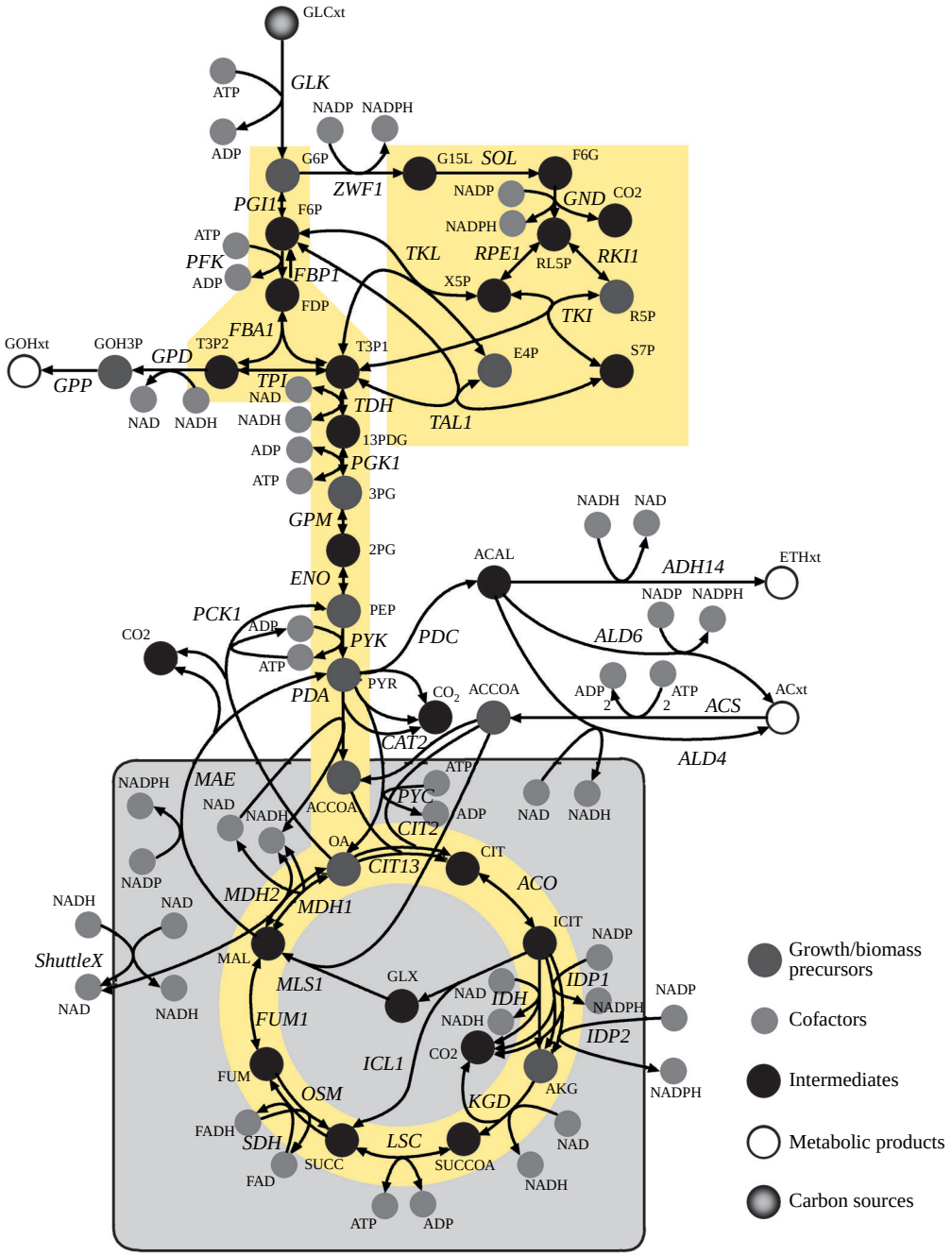

Fig. 8 Overview of the metabolic network of yeast model (Cakir *et al*., 2004)

normalized by the glucose uptake rate of 10 mmol/g DCW · h, thus resulting in the overall reaction,

$$\text{GLCxt} \rightarrow 2\ \text{ETHxt} + 2\ \text{CO}_2\text{xt},$$

representing the external state, which is indicated by xt.

On the basis of the above overall reaction, three feasible metabolic pathways have been recovered via algorithms RPIMSG and PBT for metabolic-pathway identification (MPI) from the metabolic reactions in the yeast network model. Subsequently, the corresponding 3 flux distributions, given in Table 7, are obtained through the FBA of each of the 3 feasible metabolic pathways. Note that the fluxes are distributed mainly through the glycolytic pathway in all the metabolic pathways; however, they involve distinctly different bypasses through the pathway. All the results have been obtained on a PC (Pentium IV, 3.2 GHz, 2 GB RAM) in less than 1 second.

Table 6 Metabolic reactions for the central metabolism of yeast

Name	Reaction
Substrate uptake	
GLK	GLCxt + ATP -> G6P + ADP
Glycolysis and gluconeogenesis	
PGI1	G6P <-> F6P
PFK	F6P + ATP -> FDP + ADP
FBP1	FDP -> F6P
FBA1	FDP <-> T3P2 + T3P1
TPI	T3P2 <-> T3P1
TDH	T3P1 + NADcyt <-> 13PDG + NADHcyt
PGK1	13PDG + ADP <-> 3PG + ATP
GPM	3PG <-> 2PG
ENO	2PG <-> PEP
PYK	PEP + ADP -> PYR + ATP
GPD	DHAP + NADHcyt -> GOH3P + NADcyt
GPP	GOH3P -> GOHxt
PDC	PYR -> ACAL + CO_2
ADH1,4	ACAL + NADHcyt -> ETOHxt + NADcyt
ALD6	ACAL + NADPcyt -> ACxt + NADPHcyt
ALD4	ACAL + NADmit -> ACxt + NADHmit
ACS	ACxt + 2 ATP -> ACCOAcyt + 2ADP
PDA	PYR + NADmit -> ACCOAmit + NADHmit + CO_2
PYC	PYR + ATP + CO_2 -> OAC + ADP
PCK1	OAC + ATP -> PEP + ADP + CO_2
Pentose Phosphate Pathway	
ZWF1	G6P + NADPcyt -> G15L + NADPHcyt
SOL	G15L -> P6G
GND	P6G + NADPcyt -> RL5P + NADPHcyt + CO_2
RKI1	RL5P <-> R5P
RPE1	RL5P <-> X5P
TKI	R5P + X5P <-> S7P + T3P1
TAL1	S7P + T3P1 <-> F6P + E4P
TKL	X5P + E4P <-> F6P + T3P1
Citric Acid Cycle	
CIT2	OA + ACCOAmit -> CIT
ACO	CIT <-> ICIT
IDH	ICIT + NADmit -> AKG + NADHmit + CO_2
IDP1	ICIT + NADPmit -> AKG + NADPHmit + CO_2
IDP2	ICIT + NADPcyt -> AKG + NADPHcyt + CO_2
KGD	AKG + NADmit -> SUCCOA + NADHmit + CO_2
LSC	SUCCOA + ADP <-> SUCC + ATP
SDH	SUCC + FAD -> FUM + FADH
OSM	FUM + FADH -> SUCC + FAD
FUM1	FUM <-> MAL
MDH1	MAL + NADmit <-> OA + NADHmit
MAE	MAL + NADPmit -> PYR + CO_2 + NADPHmit
CAT2	ACCOAcyt -> ACCOAmit
ShuttleX	NADHcyt + NADmit -> NADcyt + NADHmit

Note: -> indicates an irreversible step.
<-> indicates a reversible step.
xt represents the external state, i.e., the cell's surrounding environment.

Table 6 Metabolic reactions for the central metabolism of yeast (continued)

Name	Reaction
Glyoxlyate shunt	
CIT2	OA + ACCOAcyt -> CIT
ICL1	ICIT -> GLX + SUCC
MLS1	GLX + ACCOAcyt -> MAL
MDH2	MAL + NADmit <-> OA + NADHcyt
Oxidative phosphorylation	
NADHX	12 ADP + 10 NADHmit + 5 O_2 -> 12 ATP + 10 NADmit
FADHX	12 ADP + 10 $FADH_2$ + 5 O_2 -> 12 ATP + 10 FAD
MAINT	ATP -> ADP
Biomass formation	
BIOMASS	3 ACCOAmit + 24 ACCOAcyt + 11 AKG + 3 E4P + 6 3PG + GOH3P + 6 PEP + 18 PYR + 3 R5P + 25 G6P + 10 OA + 16 NADcyt + 6 NADmit + 90 NADPHcyt + 22 NADPHmit + 254 ATP -> 10000 Biomass + 90 NADPcyt + 16 NADHcyt + 6 NADHmit + 22 NADPmit + 254 ADP

Note: -> indicates an irreversible step.
<-> indicates a reversible step.
xt represents the external state, i.e., the cell's surrounding environment.

Table 7 Resultant multiple flux distributions (unit: mmol/g DCW · h) for the case of maximization of ethanol production and the corresponding stoichiometric numbers

Flux	Multiple flux distributions*			Normalized flux distributions		
	Solution1	Solution2	Solution3	Solution1	Solution2	Solution3
GLK	10	10	10	1	1	1
PGI1	10	10	10	1	1	1
PFK	10	30	10	1	3	1
FBP1		20			2	
FBA1	10	10	10	1	1	1
TPI	10	10	10	1	1	1
TDH	20	20	20	2	2	2
PGK1	20	20	20	2	2	2
GPM	20	20	20	2	2	2
ENO	20	20	20	2	2	2
PYK	20	20	40	2	2	4
GPD						
GPP						
PDC	20	20	20	2	2	2
ADH1,4	20	20	20	2	2	2
ALD6						
ALD4						
ACS						
PDA						
PYC			20			2
PCK1			20			2
ZWF1						
SOL						
GND						

*Net reaction balance: 10.0 GLCxt → 20.0 ETHxt + 20.0 CO_2
Corresponding overall reaction: GLCxt → 2 ETHxt + 2 CO_2

Table 7 Resultant multiple flux distributions (unit: mmol/g DCW · h) for the case of maximization of ethanol production and the corresponding stoichiometric numbers (continued)

Flux	Multiple flux distributions*			Normalized flux distributions		
	Solution1	Solution2	Solution3	Solution1	Solution2	Solution3
RKI1						
RPE1						
TKI						
TAL1						
TKL						
CIT2						
ACO						
IDH						
IDP1						
IDP2						
KGD						
LSC						
SDH						
OSM						
FUM1						
MDH1						
MAE						
CAT2						
ShuttleX						
NADHX						
FADHX						
MAINT	20			2		
BIOMASS						

*Net reaction balance: 10.0 GLCxt → 20.0 ETHxt + 20.0 CO_2
Corresponding overall reaction: GLCxt → 2 ETHxt + 2 CO_2

V. DISCUSSION AND CONCLUDING REMRAKS

The exceptional efficacy of our graph-theoretic approach based on P-graphs for identifying the pathways of catalytic or metabolic reactions are amply demonstrated with one metabolic and two catalytic reactions, all of which are of practical as well as theoretical importance. Nevertheless, the approach's efficacy can be further enhanced.

It has been demonstrated that our P-graph-based approach is highly amenable to the parallel mode of computing (Varga *et al.*, 1995; Friedler *et al*., 1996). Algorithm PBT preserves the useful property of conventional branch-and-bound of being suitable for parallel implementation. Specifically, all sub-problems in the branches of an enumeration tree in algorithm PBT can be segmented to generate master-slave architecture; subsequently, they can be solved separately in the multi-processor or parallel computing environment. It is highly likely that the P-graph-based approach is also amenable to the grid mode of computing because of the similarity between the parallel and grid modes of computing. Certainly, these modes of computing can profoundly increase the computational speed of the approach.

The recently completed effort by resorting to our P-graph-based method in conjunction with the LP-based flux balanced analysis (FBA) is the complementary identification of the multiple flux distribution (MFD) in metabolic flux analysis and the multiple metabolic pathways (MMP) in structural pathway analysis of the *in silico E. coli* model containing 50 metabolic reactions (Cakir *et al.*, 2004). Moreover, our effort is being extended to models containing as many as 300 and even 700 metabolic reactions.

Moreover, we are determining exhaustively catalytic pathways, which are feasible for ethylene hydrogenation of ethane on platinum by means of our P-graph-based approach. Unlike the well-known pathways involving a single class of active sites and 7 elementary reactions, these novel pathways involve two classes of active sites and 14 elementary reactions (Davis and Davis, 2003).

REFERENCES

Anton, A. B., and Cadogan, D. C., 1991, "Kinetics of

Water Formation On Pt(111)," *Journal of Vacuum Science and Technology A*, pp. 1890-1897.

Aghalayam, P., Park, Y. K., and Vlachos, D. G., 2000, "Construction and Optimization of Complex Surface-Reaction Mechanisms," *AIChE Journal*, Vol. 46, pp. 2017-2029.

Aris, R., 1965, *Introduction to the Analysis of Chemical Reactors*, Prentice-Hall, Englewood Cliffs, NJ, USA, pp. 7-14.

Banse, B. A., Wickham, D. T., and Koel, B. E., 1989, "Transient Kinetic Studies of the Catalytic Reduction of NO by CO on Platinum," *Journal of Catalysis*, Vol. 119, pp. 238-248.

Baily, H., 2001, " Living on the Edges," *Nature Biotechnology*, Vol. 19, pp. 111-112.

Balakos, M. -W., and Chuang, S. -S. -C., 1995, "Dynamic and LHHW Kinetic Analysis of Heterogeneous Catalytic Hydroformylation," *Journal of Catalysis*, Vol. 151, pp. 266-278.

Berry, R. -S., Rice, S. -A., Ross, J., 1980, *Physical Chemistry*, Wiley & Sons, NY, USA, p. 1176.

Blázsik, Z., Imreh, B., 1996, "A Note on Connection Between PNS and Set Covering Problems," *Acta Cybernetica*, Vol. 12, pp. 309-312.

Boudart, M., and Djega-Mariadassou, G., 1984, *Kinetics of Heterogeneous Catalytic Reactions*, Princeton University Press, Princeton, NJ, USA, pp. 87-89.

Cakir, T., Kirdar, B., and Ulgen, K. O., 2004, "Metabolic Pathway Analysis of Yeast Strengthens the Bridge between Transcriptomics and Metabolic Networks," *Biotechnology and Bioengineering*, Vol. 86, pp. 251-260.

Davis, M. -E., and Davis, R. -J., 2003, *Fundamentals of Chemical Reaction Engineering*, McGraw Hill, New York, USA, pp. 252-253.

Edwards, J. S., Covert, M., and Palsoon, B., 2002, "Metabolic Modeling of Microbes: the Flux-Balance Approach," *Environmental Microbiology*, Vol. 4, pp. 133-140.

Fan L. T., Bertok B., and Friedler F., 1999, "Combinatorial Framework for the Systematic Generation of Reaction Pathways," *AIChE Annual Meeting*, Dallas, TX, USA.

Fan, L. T., Bertok, B., Friedler, F., and Shafie, S., 2001, "Mechanisms of Ammonia-Synthesis Reaction Revisited with the Aid of a Novel Graph-Theoretic Method for Determining Candidate Mechanisms in Deriving the Rate Law of a Catalytic Reaction," *Hungarian Journal of Industrial Chemistry*, Vol. 29, pp. 71-80.

Fan, L. T., Bertok, B., and Friedler, F., 2002, "A Graph-Theoretical Method to Identify Candidate Mechanisms for Deriving the Rate Law of a Catalytic Reaction," *Computers and Chemistry*, Vol. 26, pp. 265-292.

Friedler, F., Fan, L.-T., and Imreh, B., 1998, "Process Network Synthesis: Problem Definition," *Networks*, Vol. 28, pp.119-124.

Friedler, F., Tarjan, K., Huang, Y. -W., and Fan, L. -T., 1992, "Combinatorial Algorithms for Process Synthesis," *Chemical Engineering. Science*. Vol. 47, pp. 1973-1988.

Friedler, F., Tarjan, K., Huang, Y. -W., and Fan, L. -T., 1993, "Graph-Theoretic Approach to Process Synthesis: Polynomial Algorithm for Maximal Structure Generation," *Computers Chemical Engineering*, Vol. 17, pp. 929-942.

Friedler, F., Varga, J. -B., and Fan, L. -T., 1995, "Decision-Mapping: A Tool for Consistent and Complete Decisions in Process Synthesis," *Chemical Engineering Science*, Vol. 50, pp. 1755-1768.

Friedler, F., Varga, J. -B., Feher, E., and Fan, L. -T., 1996, "Combinatorially Accelerated Branch-and-Bound Method for Solving the MIP Model of Process Network Synthesis," *State of the Art in Global Optimization*, C. -A. Floudas and P. -M. Pardalos, eds., Kluwer Academic Publishers, Norwell, MA, USA, pp. 609-626.

Hanson, F. V., and Boudart, M., 1978, "The Reaction between H_2 and O_2 over Supported Platinum Catalysts," *Journal of Catalysis*, Vol. 53, pp. 56-67.

Happel, J., 1986, *Isotopic Assessment of Heterogeneous Catalysis*, Academic Press, Orlando, FL, USA.

Happel, J., 1988, "Kinetic Studies on the Mechanism of Catalytic Ethene Oxidation," *Journal of Catalysis*, Vol. 109, pp. 236-237.

Happel, J., and Sellers, P. -H., 1982, "Multiple Reaction Mechanisms in Catalysis," *Industrial and Engineering Chemistry Fundamentals*, Vol. 21, pp. 67-76.

Happel, J., and Sellers, P. -H., 1983, "Analysis of the Possible Mechanisms for a Catalytic Reaction System," *Advances in Catalysis*, Vol. 32, pp. 273-323.

Happel, J., and Sellers, P. -H., 1990, "Mechanistic Study of Chemical Reaction Systems" *Industrial and Engineering Chemistry Research*, Vol. 29, pp. 1057-1064.

Hei, M. -J., 1997, "Catalytic Energetics and Its Applications," *Master Thesis*, Xiamen University, Xiamen, People's Republic of China.

Horiuti, J., 1973, "Theory of Reaction Rates as Based on the Stoichiometric Number Concept," *Annals of the New York Academy of Science*, Vol. 213, pp. 5-30.

Koebel, M., Elsener, M., and Madia, G., 2001, "Reaction Pathways in the Selective Catalytic Reduction Process with NO and NO_2 at Low Temperatures," *Industrial and Engineering Chemistry Research*, Vol. 40, pp. 52-59.

Lee, D. -Y., Yun, H., Lee, S. Y., and Park, S., 2003, "MetaFluxNet: The Management of Metabolic Reaction Information and Quantitative Metabolic

Flux Analysis," *Bioinformatics*, Vol. 19, pp. 2144-2146.

Lee, D. -Y., Fan, L. T., Park, S., Lee, S. Y., Shafie, S., Bertok, B., and Friedler, F., 2005, "Complementary Identification of Multiple Flux Distributions and Multiple Metabolic Pathways," *Metabolic Engineering*, Vol. 7, pp. 182-200.

Park, Y. K., Aghalayam, P., and Vlachos, D. G., 1999, "A Generalized Approach for Predicting Coverage-Dependent Reaction Parameters of Complex Surface Reactions: Application of H_2 Oxidation over Platinum," *Journal of Physical Chemistry*, Vol. 103, pp. 8101-8107.

Peters, M. S., Timmerhaus, K. D., and West, R. E., 2003, *Algorithmic Flowsheet Generation. In: Plant Design and Economics for Chemical Engineers*, McGraw-Hill, New York, USA, pp. 158-188.

Ross, J., 1993, "On the Concept of Stoichiometry of Reaction Mechanisms Comment" *Journal of Physical Chemistry*, Vol. 97, pp. 2798.

Seo, H., Lee, D. -Y., Park, S., Fan, L. T., Shafie, S., Bertok, B., and Friedler, F., 2001, "Graph-Theoretical Identification of Pathways for Biochemical Reactions," *Biotechnology Letters*, Vol. 23, pp. 1551-1557.

Seressiotis A., and Bailey, J. -E., 1988, "An Artificially Intelligent Software System for the Analysis and Synthesis of Metabolic Pathways," *Biotechnology and Bioengineering*, Vol. 31, pp. 587-602.

Temkin, M. -I., 1971, "The Kinetics of Steady-State Complex Reactions," *International Chemical Engineering*, Vol. 11, pp. 709-717.

Temkin, M. I., 1979, "The Kinetics of Some Industrial Heterogeneous Catalytic Reactions," *Advances in Catalysis*, Vol. 28, pp. 173-291.

Varga, J. B., Friedler, F., and Fan, L. T., 1995, "Parallelization of the Accelerated Branch-and-Bound Algorithm of Process Syntheses: Application in Total Flowsheet Synthesis," *Acta Chimica Slovenica*, Vol. 42, pp. 15-20.

Wickham, D. T., and Koel, B. E., 1988. "Steady-State Kinetics of the Catalytic Reduction of Nitrogen Dioxide by Carbon Monoxide on Platinum," *Journal of Catalysis*, Vol. 114, pp. 207-216.

Manuscript Received: Jul. 07, 2005
and Accepted: Aug. 02, 2005