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Abstract. The paper offers an overview on recent techniques for representing Biological Pathways with Petri Nets and their extensions. The main focus is on the metabolic pathways and their representation by standard Petri Nets, self-modified Petri Nets and Colored (High Level) Petri Nets. Gene Regulatory Pathway and Message Massing Nets are also considered. All biological information are taken from the KEGG Database.

1 Introduction

In bioinformatics science a large and quickly increasing amount of genomic and protein sequence and structure data are getting available together with expression data. Interpreting such expression data, knowledge about actual or potential relationships between proteins, RNA and DNA is needed. Knowledge about proteins and their relation is provided in a number of metabolic databases containing the biochemical facts acquired over the past decades. As far as we know, no databases exist covering regulatory relationships in a range comparable to metabolic relationship in metabolic databases [8]. The need of facilitating static and dynamic analysis of pathways, merging information and unifying formalisms, Petri Net representation has been introduced by various authors. In this paper we present some of the suggested hypothesys to translate and/or represent a biological pathway taken from KEGG database into Petri Nets and we consider their weakness and strongness. We consider both static representation and kinetic one, analyzing which information can be immediately translated from KEGG, and which one must be retrieved from other sources. The paper treats in different sections the translation of the three kinds of biological pathways: metabolic, gene regulatory and message passing. Petri Net have been proposed for representing metabolic knowledge (Hofestädt and Thelen, 1998; Reddy et al., 1996) and for simulating dynamic behavior or reaction nets as an alternative to the use of systems based on differential equations.

2 Petri Nets

A Petri Net is an n-tuple $(\mathcal{P}, \mathcal{T}, \mathcal{A}, \mathcal{W}, \mathbf{m_0})$ where:

- $\mathcal{P}$ is the set of places, $\mathcal{P} = \{p_1, \ldots, p_N\}$
- $\mathcal{T}$ is the set of transitions, $\mathcal{T} = \{t_1, \ldots, t_M\}$
- $\mathcal{A}$ is the set of arcs $A = A_1 \cup A_2$, where $A_1 \subseteq P \times T$ and $A_2 \subseteq T \times P$
- $\mathcal{W}$ is a function from A to positive integer numbers set $\mathbb{N}$ which assigns to each arc a weight
- $\mathbf{m_0}$ is an N-dimensional vector of non negative integers which represents the initial *marking* of the net.

We call *input bag* $\mathbf{I_t}$ of the transition t the N-dimensional vector of non-negative integers in which the i-th position is 0 if $(p_i, t) \notin \mathcal{A}$ and is $\mathcal{W}(p_i, t)$ otherwise. We call *output bag* $\mathbf{O_t}$ of the transition t the N-dimensional vector of non negative integers in which the i-th position is 0 if $(t, p_i) \notin \mathcal{A}$ and is $\mathcal{W}(t, p_i)$ otherwise. The transition t with input bag $\mathbf{I}$ is *enabled* by the marking $\mathbf{m} = (m_1, \ldots, m_N)$ if for all $i = 1, \ldots, N$ we have that $m_i \geq I_i$. If a transition t is enabled then it can *fire* and, as consequence, the net marking changes from $\mathbf{m}$ to $\mathbf{m'}$ as follows:

$$\mathbf{m'} = \mathbf{m} - \mathbf{I_t} + \mathbf{O_t}$$

where $\mathbf{I_t}$ and $\mathbf{O_t}$ are the input and the output bag of the transition.

Note that a marking can enable zero, one or more transitions. In the first case we say that the net is *dead*, in the second case we are sure that the only transition enabled will fire, in the third case we say that the enabled transitions are in *conflict*. Some ways to treat transition conflicts are:

- general non-determinism;
- a hierarchy among transitions can be defined to recover determinism;
- if S is a set of conflicting transitions a probability can be associated to each element of S;
- in Stochastic Petri Net a random firing time is associated to each transition; to allow a simple state representation, the random variable representing the transition firing rate is exponentially distributed.

We call *reachability set* (or *space of the states*) of the net the set of all possible markings of the network, starting from the initial marking $\mathbf{m_0}$. The reachability set can be infinite. It is known that, in general, the problem of deciding if a state is part of the reachability set of a net is NP-hard. We call incidence matrix the $N \times M$ matrix which has a row for each transition, and a column for each place. The row associated to the transition t is the vector $\mathbf{O_t} - \mathbf{I_t}$ which basically represents the marking change in the net due to the firing of the transition t. We call structural analysis of the net, an analysis which does not require the building of the reachability set and which is independent from the initial marking. Two basic results from the structural analysis are interesting. A T-Invariant is an M dimensional vector in which each component represents the number of times that a transition should fire to take the network from a state $\mathbf{m}$ back to the state $\mathbf{m}$. Note that the existence of a T-invariant does not mean that there actually exists a firing sequence that will allow the net to cycle in a state. A T-invariant $\mathbf{T}$ can be calculated from the incidence matrix $\mathbf{A}$ in this way:

$$\mathbf{A^T T} = \mathbf{0}.$$

Another important invariant is the S-invariant which is a N dimension vector; an S-invariant $\mathbf{S}$ is calculated as:

$$\mathbf{AS} = \mathbf{0}.$$

If an S-invariant with all positive components exists, then the net is called *conservative*, it means that the weighted sum of the tokens for each marking of the reachability set is costant. In modelling biological networks we will see that this appears to be similar to the conservation law in chemistry, so we expect to work with conservative networks.

Petri Net extensions The basic model of Petri Net can be extended to obtain more complex and expressive formalisms. The first extension introduces the use of inhibitors arcs which allows the representation of a situation when the presence of one or more token in a place inhibits the firing of a transition. With this extension the Petri Net expressive power reaches the Turing Machine one, and the reachability problem (is a marking reachable from a given initial state?) is, in the general case, equivalent to the halting problem of the Turing Machine [7].

Another important extension is the introduction of classes of tokens; in this case we call the model *Colored Petri Net*. The idea is to assign to each token a *color* and to label the arcs of the net with conditions regarding this colors. Colored Petri Nets are difficult to analyze, but are often used for simulation purposes.

3 Biological Pathways

There are three kinds of pathways that can be represented by Petri Nets: the metabolic pathways classified in KEGG database with *Metabolism* and the regulatory pathways classified in KEGG database with *Environmental Information Processing* and *Cellular Processes* and finally gene regulatory pathways. These three classes of pathways are quite different, an example of the first one is shown in figure 1, while in figure 2 is shown an example of the second one.

Figure 1 represents some molecules which are transformed in others by chemical reactions catalyzed by one or more enzymes. This kind of diagrams does not explain why something happens but that it can happen. In figure 2, on the other hand, the main focus is on what the cell is doing; some molecules regulate and react to internal or external input. This requires different ways of modelling with Petri Nets: for example in message passing pathways, the inhibition actions performed by some proteins can be modelled with inhibitor arcs in the corresponding Petri Net. This is not needed in metabolic pathways where, on the other hand, we could be more interested in paying attentions on kinetic aspects.

3.1 Representing a chemical reaction catalyzed by an enzyme

The easiest way to represent a bio-chemical reaction is to consider each component of the substrate as a place of the Petri Net, each enzyme another place, and

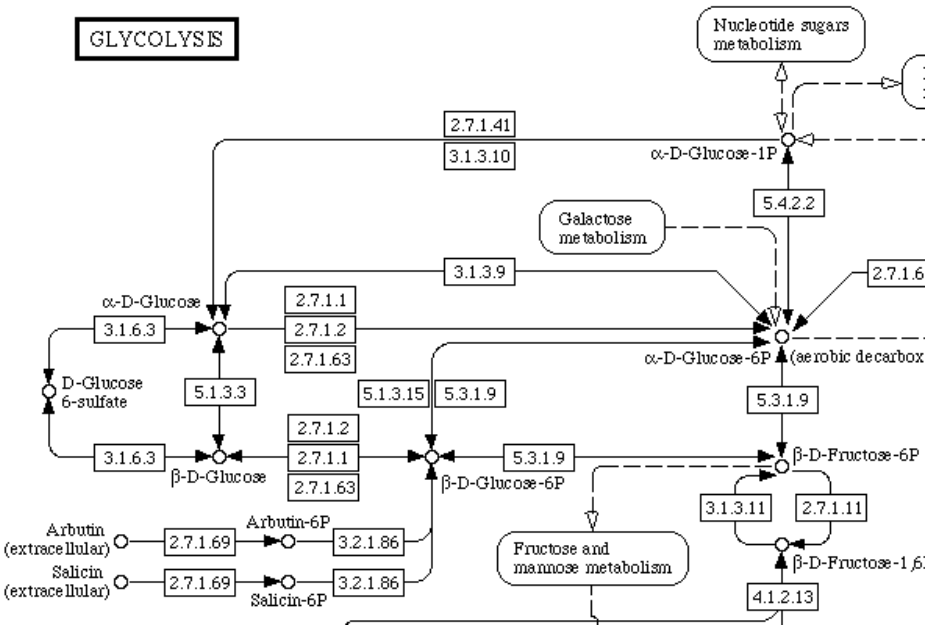

Fig. 1. Part of the glycolysis pathway (metabolic) taken from KEGG database
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the products other places. A transition represents the chemical reaction. Let us consider in the example found in KEGG database for the Glycolysis Pathway, the reaction showed in figure 3: Following the notes about enzyme 3.1.6.3 on the KEGG web page, we can obtain details about the reaction, namely:

$$\text{D-glucose 6-sulfate} + \text{H2O} = \text{D-glucose} + \text{sulfate}$$

where the substrate is D-glucose 6-sulfate and water, and the product is D-glucose and sulfate.

Then we can associate the Petri Net of figure 4. Observe that the enzyme place is connected to the transition with a double arrow: this must be read, following the standard Petri Nets specification, as a one way arrow from the place to the transition and another one way arrow from the transition to the place, in fact an enzyme is not *consumed* by a reaction. In the KEGG diagram the presence of H_2O and sulfate is not important, so the net of figure 4 can be simplified omitting two places.

As observed for example in [6] a reversible reaction can occur in two ways. The enzyme catalyzes the reaction from the higher concentration rate to the lower one. So for dynamic (simulation) purposes a quantitative approach in necessary. Finally, as observed in [4] kinetic has a great matter; most reactions follow the

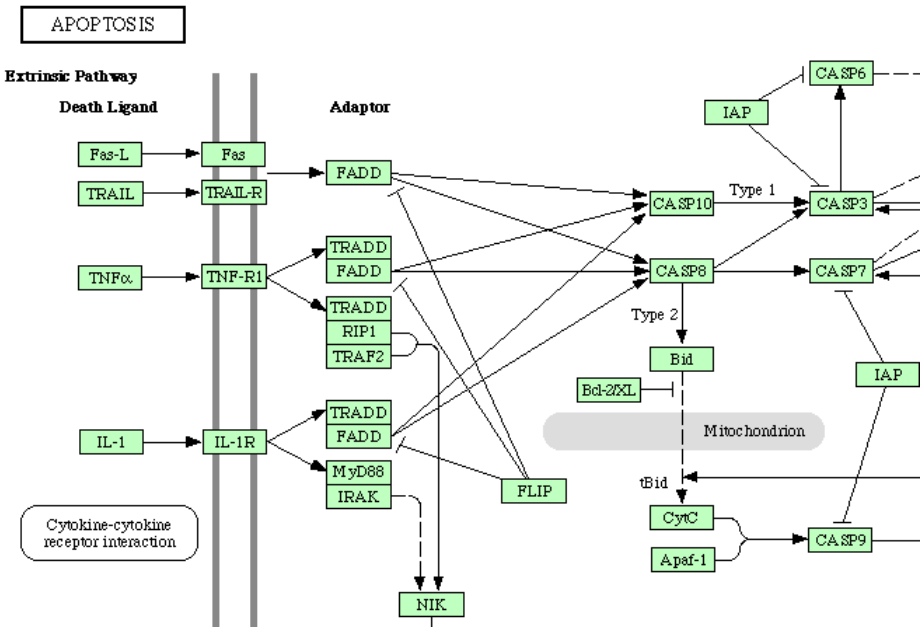

Fig. 2. Part of the apoptosis pathway take from KEGG database

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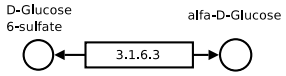

Fig. 3. Example of a biochemical reaction in the Glycolysis Pathway.

Michaelis-Menten scheme:

$$V = -\frac{dS}{dT} = \frac{V_{max} \cdot S}{S + K_m}$$

where V_{max} is the maximum reaction rate of the hydrolysis, S the substrate concentration, K_m the Michaelis constant. V_{max} and K_m characterize the interactions of the enzyme with its substrate.

The time feature can be represented by assigning a firing time to the transition. In [2] a stochastic approach with bounded random variables is used. To represent the quantitative feature in [6] the self-modified Petri Nets are used. This extention allows the modeler to set the arc weight as a function of the state of the network. In this way it is possible to change the network behavior depending on the reagents concentration.

Let us consider the example in [6] with a reaction where for each element of the substrate we obtain two elements of the product. The reaction is catalyzed by

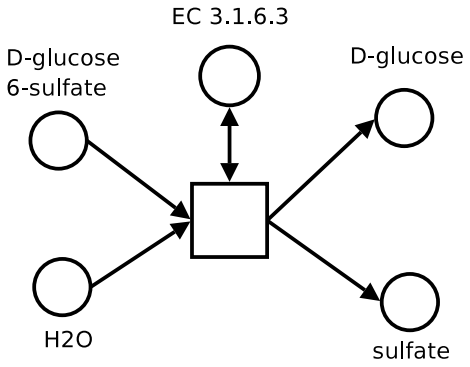

Fig. 4. Petri net associated to the biochemical reaction of Fig. 3

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an enzyme, and the concentration of the enzyme influences the reaction speed. Assuming a costant speed for the firing transition or measuring the speed with the number of firings, we are able to model the speed of the reaction (see figure 5).

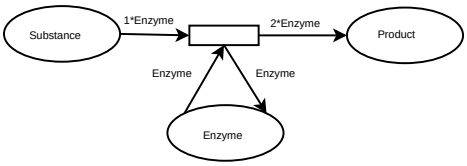

Fig. 5. Petri net associated to a catalyzed biochemical reaction. In this model Substance, Product and Enzyme are not the name of the places, but variables which represent the number of tokens in the place. Note that the arcs are labelled with functions of the variable Enzyme (self-modified Petri Net)

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3.2 Representing a whole metabolic pathway or more merge metabolic pathways

A metabolic pathway is usually quite complex and difficult to represent with Petri Nets, first of all because it seems that a KEGG diagram carries more information than what it actually displays. We focus our attention on these problems:

P1: In figure 6 we show two different situations which can not be distinguished in a KEGG graphical diagram. In the first case we have a reaction with one

substrate and two products, while in the second case we have a substrate which allows two possible reactions and this leads to a conflict. To understand which is the correct model of the reaction we have to consult the KEGG database and look for the chemical reaction.

P2: Most of the reactions catalyzed by an enzyme are reversible. Representing a reaction and its inverse with a Petri Net could give a dynamic behavior where the cell keeps looping in producing and destroying the same molecules which is biologically without sense. In [2] the authors point out that this kind of incongruence can be solved with an appropriate resolution of transition conflicts.

P3: When we represent a metabolic pathway, the same molecules can be found in different positions: are the same molecules in the cells represented in the same place? The topic is considered in [9] and the authors show that the answer is not unique because it depends on the location of the molecules: for instance the ATP pools inside and outside the mitochondrion in a cell are different and their relative concentrations are determined through a selective transport process. In [2] the authors use for their examples different Petri Net places for each reaction (so they introduce ATP1, ATP2, ...). This can be done without specific problems for *ubiquitous* molecules such as ADP, ATP, NAD+, Pi, NADH because they are found in sufficiently large amounts in almost all organisms[1].

P4: Metabolic pathways are complex systems whose components and reagents strongly interact. For example the product of a reaction which is part of a pathway, could be used as substrate of another reaction of the same pathway or as substrate of a reaction of another pathway. When we represent this situation with a Petri Net we have a conflict between transitions. Solving these conflicts can be difficult and different approaches can lead to different analysis on the net.

P5: In nature the fact that something can happen does not mean that it is relevant for the behavior of a system. For example if a reaction happens in a direction much more faster than the inverse, the effect of the inverse is unimportant. This means that the structural analysis or an analysis which does not consider the kinetic factor can lead to wrong results. Unluckily formal studies of Petri Nets which are able to represent kinetic factors (such as Timed Petri Nets or self-modified Petri Nets) are not easy, even if they are still useful for simulation purposes.

Problem P1 is easily resolved, and we already described the solution. We present some models used for metabolic pathways representation and we study them related to the problems P2, P3, P4, P5.

Low level and high level Petri Nets In the literature two levels of qualitative representation with PN are considered: a low level representation (introduced

[1] It has not be found a complete list of ubiquitous molecules, and it's not clear if in the KEGG database is somehow possible to retrieve the location of a molecule

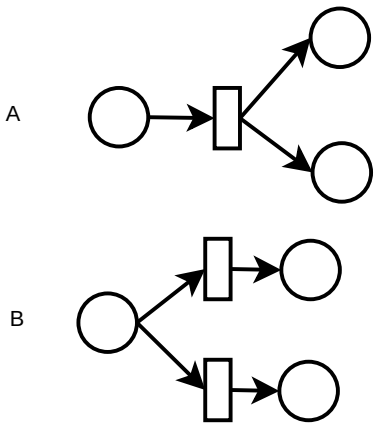

Fig. 6. Petri net associated to two different situations in the pathway. **A**: A reaction gives two products. **B**: From a substrate there are two possibles reactions, this leads to a conflict. Usually the state of cell, and the concentration of the substrate or enzyme determines which transition will fire. From a metabolic pathway KEGG diagram it's possible to understand which model is correct by the information stored in the database, i.e. the chemical reaction.

with the articles [5] and [9]) and a more recent high level one (for example [2]). Basically the low level representation does not consider the reverse reactions and does not resolve conflicts, but it is useful for the study of invariants. In the high level representation Colored Petri Nets are used; these will be harder to study but can give a great help for simulation purposes. Introducing colors on tokens allows us to give roles to substances which are chemically indistinguishable. This enables the modeler to separate different branches of the compound pathway and to distinguish among molecules on the same place according to their origin and destination reaction. Thus we resolve problems P2 and P4.

Assume for example that the process α obtains C from A in this way: $A \rightarrow B \rightarrow C$ and the process β obtains E from D in the following way: $D \rightarrow B \rightarrow E$. Suppose that the cell is in a state which requires to obtain C, then the metabolism starts producing B. Now we have a conflict which is not immediately resolved by low level Petri Net; a way to do it, without using high level net, is introducing state places which tell us if we are working for the process α or β (see figure 7). The main disadvantage of this approach is that the introduction of state places seems not to be easily computable.

As already said, the other way to solve conflicts is the use of high lever Petri Nets. After building the low level net, conflict places must be found and an appropriate actions must be taken. By definition a *conflict place* is a place p with more than one output transition and all of these are enabled if p carries a suitable token. We can now fall in three different cases:

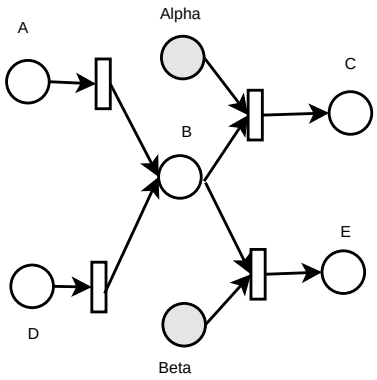

Fig. 7. Petri net with the use of states to solve conflicts.

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1. All but one alternative paths starting from p end up again at p without any lasting marking change.
2. The alternative pathways belong to different metabolisms.
3. The alternative pathways belong to the same metabolism.

In the first case (not really frequent) we can just ignore the conflict. In the second and third case we use colors and guards on the net to discriminate the right path.

Conflicts with paths belonging to different or same metabolisms We can treat the second and third case in the same way considering merge places, as we will see later. Now consider for example the Glycolysis and the Pentose Phosphate pathways; From KEGG diagrams we can obtain the low level net shown in figure 8.

The Glycolysis pathway is: Glucose → Glucose-6-phosphate → Fructose-6-Phosphate, while the Pentose Phosphate pathway is: Glucose → Glucose-6-Phosphate → Ribulose-5-phosphate. The high level approach to solve the conflict is to assign a color to the Glucose-6-Phosphate molecules assigned to the Phosphoglucose Isomerase, call it C, and another one for the Glucose-6-Phosphate molecules assigned to the G6P oxidation reactions. In figure 9 it is shown the high level net: the guard $[x <> C]$ prevents tokens of color C to be consumed by the oxidation reactions G6P.

One difficult in catching the conflicts for merged pathways occurs when two pathways produce the same molecules. As already said, we don't know from KEGG graph the physical location of those molecules, if they are far there's no conflict and they can just be represented as distinct places. On the other hand the approach used in [2] is to consider them as unique *merged* place. Doing this it could happen that the tokens which arrive to the place are already colored,

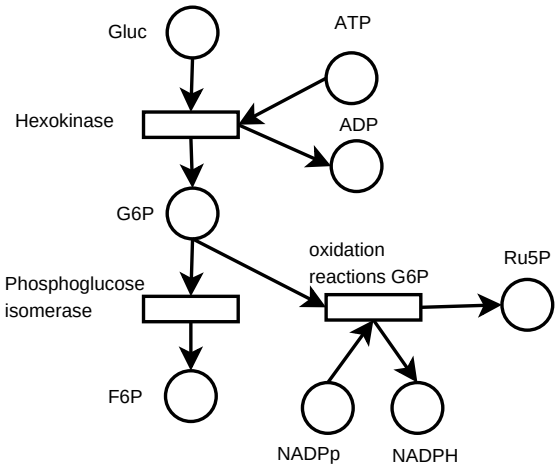

Fig. 8. Conflict in Glycolysis and Pentose Phosphate pathways. Enzymes places are omitted and used as labels near the transitions.

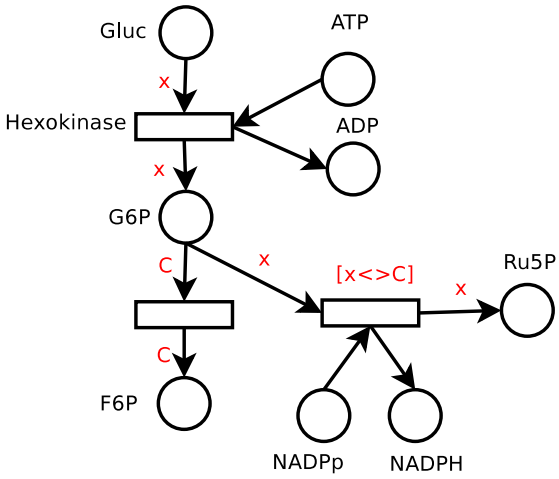

Fig. 9. Conflict in Glycolysis and Pentose Phospate pathways solved with High Level Net. C represents the color assigned to G6P destinated to the Glycolysis, x represents a generic color (C or some other)

and the conflict does not exist, or the tokens which arrive to the place are not yet colored. In the latter case we have to introduce a new color in order to solve the conflict. In figure 10 an example is shown.

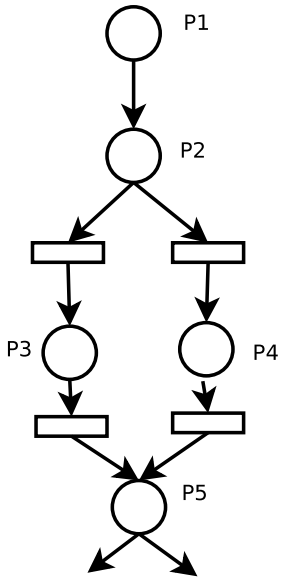

Fig. 10. Example of solving conflict using color tokens. The conflict in place P_2 has to be solved by the introduction of a new color, whereas the conflict in place P_5 is already resolved by the colors introduced before. This is a simple example, but the algorithm of color assignments, not yet coded as far as we know, would not be easy because of the complexity of metabolic net.

Adding quantitative approach and reverse reactions We have seen how we can obtain a qualitative Petri Net (eventually colored) given a KEGG diagram, and we pointed out which information can not be obtained by the network representation. Now we have to consider the quantitative approach (see problems P5, P2) and the reverse reactions. This two topics are put together because the quantitative approach seen with self-modified Petri Nets, already solve the problem of reverse reactions. Anyway in [2] it is solved by the introduction of reverse transitions and some guards or reductions to avoid meaningless loops. It's not clear what is *meaningless* by the authors. It seems that it's not something which can be taken out from the KEGG description or just the reaction knowledge, and anyway no general algorithm is given.

4 Analysis on metabolic pathways

As usual in this kind of studies, the analysis issues become harder to treat as the model becomes more expressive. On a Petri Net representation of a metabolic pathway we can do three kinds of analysis:

– finding T-Invariant

– finding S-Invariant
– finding steady state

Basically the non zero components S-Invariant is a validator of the net: a conservative measure of tokens in places means that conservation law is respected. We allow zero components for the ubiquitous molecules whenever they are considered by the modeler infinite in the system. The presence of T-Invariants signals to the analyst the potential loops among cell metabolisms and this is biologically of great interest. A complete analysis of S-Invariant and T-Invariant of glycolysis can be found in [9] although its conclusions are confuted by [2] where high level nets carry slightly different results. The use of high level net makes more difficult the discovery of T-Invariant: the net must be divided in subnetworks depending on the assigned colors (again a general algorithm is not explicit) and the usual algebraic approach is then applied.

A metabolic pathway is said to persist in a *steady state* if the concentrations of all internal substances have reached a dynamic equilibrium: for each internal metabolite, the total rate of its consumption equals that of its production. The only available approach in this case is to extend the model with quantitative information, and apply simulation [2].

5 Gene Regulatory networks

We start this paragraph with a quotation taken from [1]:

> Gene Regulatory Networks are sometimes interpreted as the on-off switches of a cell, operating at the gene level. They dynamically orchestrate the level of expression for each gene in the genome by controlling whether and how vigorously the gene will be transcribed into RNA. Each RNA transcript then functions as the template for the synthesis of a specific protein by the translation process. This gene products may act as transcript factors which regulate the expression of other genes.

To represent Gene Regulation Processes first we have to introduce the notions of positive control and negative control. Both positive and negative controls can be either inducible or repressible. When the activator enables the transcription process we talk of *positive control*, when an effector element, called *inducible enzyme*, enables the transcription process we talk of *inducible positive control*. In this case the effector element activates the activator element to obtain a protein complex which enables the transcription process. The associated net can be seen in figure 11.

The positive control can be also repressive, that is the effector element will repress the transcription process. The catalytic element is inducible for the transcription process until the effector element will appear, so the effector element, in the model, will inactivate the activator (see figure 12).

The negative control is slightly more difficult to represent. In the inducible negative control the transcription of the genes in the operon does not take place

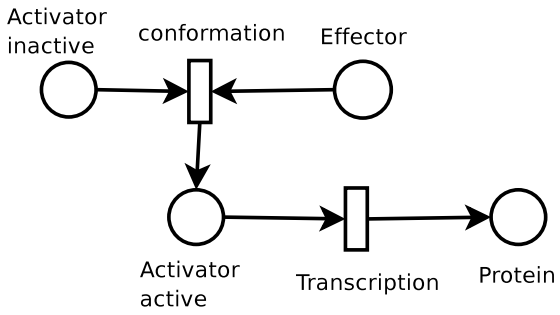

Fig. 11. Positive Control in Gene Regulatory Network: Petri Net Associated.

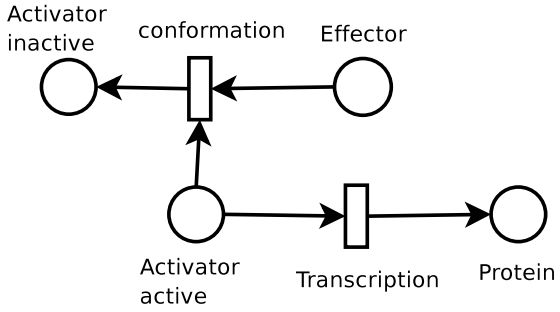

Fig. 12. Repressive Positive Control in Gene Regulatory Network: Petri Net Associated.

because a produced protein binds with the operon and keeps it inactive. If an inducer molecule is present, it binds with the repressor and change its conformation so that it can not repress the transcription. See figure 13.

Last case is the repressive negative control. Here the operon normally takes place. Repressor proteins are produced by a regulator gene but they are unable to bind to the operator in their normal conformation. However certain molecules called corepressors can bind to the repressor protein and change its conformation so that it can bind to the operon. The activated repressor protein binds to the operon and prevents transcription. See figure 14[2].

Sometime, to represent Gene Regulatory Network, Petri Net with inhibitor arcs are used. The idea is very simple, the inhibitor active place simply inhibits the transcription transition so that the protein is not transcripted. This approach is useful because it simplifies the network but, on the other hand, the on/off representation that we obtain is not realistic. In fact, especially for simu-

[2] The presented net is slightly different from the one presented on [6] because we think it is wrong (probably due to some typos)

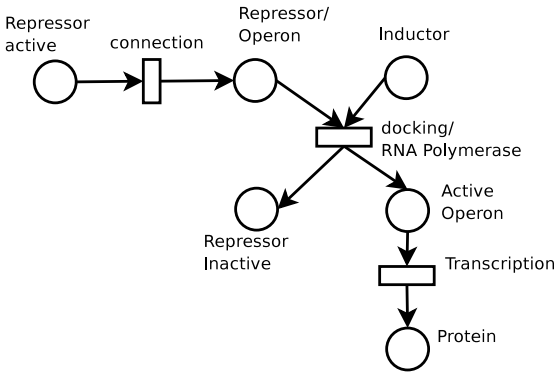

Fig. 13. Negative Control in Gene Regulatory Network: Petri Net Associated.

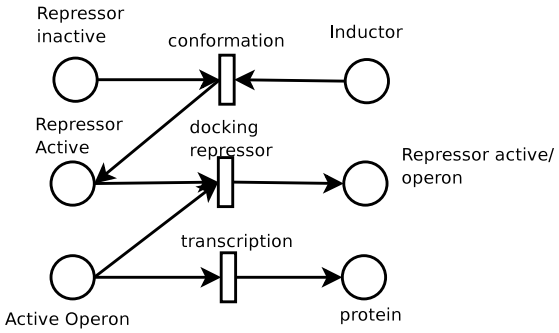

Fig. 14. Repressive Negative Control in Gene Regulatory Network: Petri Net Associated.

lation purposes, the transcription is not inhibited completely by the presence of the repressor, but its rate is changed. For example, if the concentration of the inhibitor molecules is low, the transcription (in a negative control) keeps going on, but at lower rate.

6 Message Passing Networks

A message passing network is one of the type shown in figure 2. In [6] the authors claim that this Petri Net representation is easy: It suffices to represent uptake of metabolites by a cell with a transition without incoming arcs, and substance leaving a cell with a transition without outgoing arcs. On the other hand, in the article [3] the authors point out that the translation is not simple as could be seen at first. Even if previous rules keep hanging, some problems arise especially due to the KEGG diagrams ambiguities. In particular, one of the

main problems is the activation action: when a molecule activates two or more receptor in a KEGG diagram, is it done simultaneously (one transition in the net) or alternatively (one transition for receptor)? See an example in figure 15. The opposite problem is for the activation (is a substance enough, or every substance with an arc reaching the receptor is needed?). For the authors there's not a clear solution, and for the presented example they refer to a informal description of the apoptosis without giving any algorithmic computation to obtain the Petri Net.

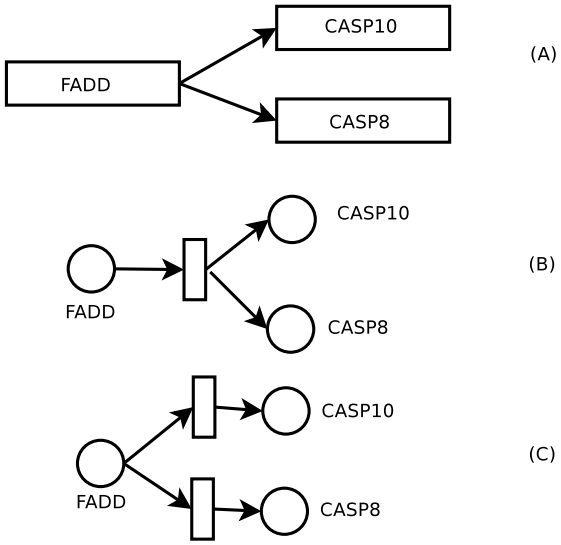

Fig. 15. Ambiguous translation of KEGG diagram about a message passing pathway into Petri Net. In (A) we can see part of the apoptosis pathway (see figure 2), in (B) a translation with synchronism and in (C) a translation without synchronism. This kind of ambiguity is raised in [3].

7 Automatic calculation from Biological Pathways in KEGG Diagrams to Petri Net

The problem of translating a KEGG diagram for a biological pathway into a Petri Net in an algorithmic way is not directly treated in any of the paper found. In [1] the authors introduce the language BioPNML (based on XML) which can represent a biological pathway based on Petri Nets. They also claim that the BioPNML net description can be obtained from a KEGG diagram XML representation, but no algorithm for such transformation is given. Moreover, some information they associate to a BioPNML description (e.g. the kinetic

behavior of reactions) cannot be deduced from a KEGG diagram. This suggests that they do not have an automatic way to transform from XML-KEGG to BioPNML.

We considered three kinds of biological pathways:

- Metabolic Pathways
- Gene Regulation Pathways
- Message Passing Pathways

In [6] for the first time (as far as we know) a quantitative approach is suggested; not only it represents the biological behavior of a cell in a realistic way, but it also represents the three kind of networks with the same formalism, eventually allowing the modeler to merge them together. This feature is obtained by the use of Self-modifying Petri Nets and the introduction of firing time semantics. Probably this aspect should be analyzed more deeply because some problems arise depending on the choice of the firing semantics, see [7]: an *atomic firing* is chemically associate to the idea that a compound of the substrate is available for all competing reactions, the faster one take it *after* its firing time and atomically gives the product(s); in a *nonatomic firing* semantic, a transition removes the compounds of the substrate as soon as it is enabled and gives the product after the firing time. The nonatomic firing semantics looks more suitable for representing chemical reactions, but some static analysis problems should then be treated.

On the other hand it appears that an automatic translation from KEGG formalism to self-modified Petri Nets is not possible, because some information are missing. We did not investigate on an algorithmic procedure taking KEGG information and merging it with other information (maybe coming from other databases, or natural laws) to have the translation, anyway this is not explicit in the papers.

For metabolic pathways it is possible an automatic translation for qualitative analyzes. The lack of this kind of analysis is basically that they usually consider on/off processes which are unusual in nature. However they have been successfully used in [9] where low level Petri Nets are used to study structural properties of metabolic pathways and in [2] where a high level Petri Net formalism is introduced and used to refine the analysis of [9]. For high level Petri Nets there is not (as far as we know) an explicit algorithm to associate colors to tokens, and to study the structural properties of the network. In [2] the use of high level Petri Net is showed by an example.

In message passing networks, enzymes activate some reactions and inhibit other ones; from a qualitative point of view, the translation in Petri Nets with inhibitor arcs is immediate. In [3] some problems are presented due to KEGG ambiguity; in our opinion these kind of problems are more related to computer science than biology. If the enzyme A activates reaction α then we put an arc from place A to α, while if it inhibits the reaction β we put an inhibitory arc from A to β. If A is either activated and inhibited we can choose a priority, or use a quantitative model (such as self-modified Petri Nets without inhibition

arcs) to study the kinetic behavior although this information are not available directly from KEGG database.

For gene regulatory networks we presented a possible translation without the use of inhibitor arcs; If we want a qualitative model, we can just think that an enzyme inhibition or activation for message passing could be associated to inhibitors or activation of operon. In [10] an interesting analysis for gene regulatory pathways is presented with a model which can be easily translated in Petri Nets with inhibitor arcs, but the reference database is not KEGG.

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