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# A notion of biological diagnosability inspired by the notion of opacity in systems security

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**Abstract.** A formal model for diagnostics of biological systems modelled as P systems is presented. We assume the presence of some biologically motivated changes (frequently pathological) in the systems behavior and investigate when these changes could be diagnosed by an external observer by exploiting some techniques originally developed for reasoning on system security.

## 1. Introduction

In the last few years people have become aware that biological processes can be described by using means originally developed by to model systems of interacting components. This permits simulation of system behaviour and verification of properties. P systems were introduced by Păun [10] as distributed parallel computing devices inspired by the structure and the functioning of a living cell. Given its biological inspirations, P systems can be suitably used for describing biological processes.

In this paper we show how semantics based techniques can be used to diagnose pathological behaviours of biological systems described by P systems. We consider the variant of P systems with *promoters* and *inhibitors* [4], we assume the semantics of P systems given in [1] and we formalize a notion of diagnosable system property. To do so we exploit techniques originally developed for reasoning on systems security. Many of these techniques are based on a concept of *non-interference* [9, 17, 18], in which systems are considered to be secure if from observations of their public activities no information about private activities can be deduced. This approach has found many reformulations. We exploit here one of its more general reformulations known as *opacity* [5].

We motivate the use of diagnosis with an example of signal transduction pathway modulating cell proliferation, namely the signalling pathway induced by the Epidermal Growth Factor Receptor (EGFR).

## 2. P Systems and the P Algebra

We recall the definition of P systems [10, 12] and of the P Algebra [1, 2]. The class of P systems we consider includes rule promoters and inhibitors [4].

### 2.1. P Systems with Promoters and Inhibitors

A P system consists of a *hierarchy of membranes*, each of them containing a multiset of *objects*, representing molecules, a set of *evolution rules*, representing chemical reactions, and possibly other membranes. Each evolution rule consists of two multisets of objects, describing the reactants and the products of the chemical reaction. A rule in a membrane can be applied only to objects in the same membrane. Some objects produced by the rule remain in the same membrane, others are sent *out* of the membrane, others are sent *into* the inner membranes (assumed to exist) which are identified by their labels. In the original definition of P systems, rules are applied with *maximal parallelism*, namely it cannot happen that a rule is not applied when the objects needed for its triggering are available. However, other forms of parallelism have been considered with different aims (see e.g. [3, 7, 8]). Here, we assume that at each step at least one evolution rule in the whole system is applied, and also that more than one rule and several occurrences of the same rule can be applied at the same step (to different objects). In other words, we assume that at each step a multiset of evolution rule instances is non-deterministically chosen and applied in each membrane, such that in the whole system at least one rule is applied. This is a general form of parallelism that is better suited than the maximal one to describe events in biological systems.

In P systems with promoters and inhibitors an evolution rule in a membrane may have some *promoters* and some *inhibitors*. Promoters are objects that are required to be present and inhibitors are objects that are required to be absent in the membrane $m$ in order to enable the application of the rule. Promoters will be denoted simply as objects, namely $a, b, c, \ldots$, while inhibitors will be denoted as objects preceded by a negation symbol, namely $\neg a, \neg b, \neg c, \ldots$. We denote with $\mathcal{D}_V$ the set of all possible promoters and inhibitors symbols that can be obtained from an alphabet $V$, namely $\mathcal{D}_V = V \cup \neg V$. Given a set of promoter and inhibitor symbols $D$, we denote with $D^+$ and $D^-$ the sets of objects containing all the objects occurring in $D$ as promoters and all the objects occurring in $D$ as inhibitors, respectively. We remark that $D^+$ and $D^-$ are sets of objects, hence elements on $D^-$ will not be preceded by $\neg$. Moreover, with $\neg D$ we denote the set obtained by transforming each promoter in $D$ into an inhibitor and viceversa. As an example, if $D = \{a, \neg b, \neg c, d\}$ we have $D^+ = \{a, d\}$, $D^- = \{b, c\}$ and $\neg D = \{\neg a, b, c, \neg d\}$.

We assume that all evolution rules have the following form, where $u, v_h, v_o, v_1, \ldots, v_n$ are multisets of objects, $\{l_1, \ldots, l_n\}$ is a set of membrane labels in $\mathbb{N}$, and $D$ is a set of promoters and inhibitors:

$$u \to (v_h, here)(v_o, out)(v_1, in_{l_1}) \ldots (v_n, in_{l_n})|_D \,.$$

A rule can be applied only if requirements expressed by $D$ are satisfied. When a rule is applied, the multiset of objects $u$ is replaced by $v_h$, multiset $v_o$ is sent to the parent membrane, and each $v_i$ is sent to inner membrane $l_i$. Promoters are not consumed by the application of the corresponding evolution rule and a single occurrence of a promoter may enable the application of more than one rule in each evolution step. Similarly, a single occurrence of an inhibitor forbids the application of all the evolution rules in which it appears. We assume that the set of promoters and inhibitors $D$ of an evolution rule does not contain the same object both as a promoter and as an inihibitor, namely $D^+ \cap D^- = \varnothing$, and that consumed objects $u$ are not mentioned among inhibitors, namely $u \cap D^- = \varnothing$.

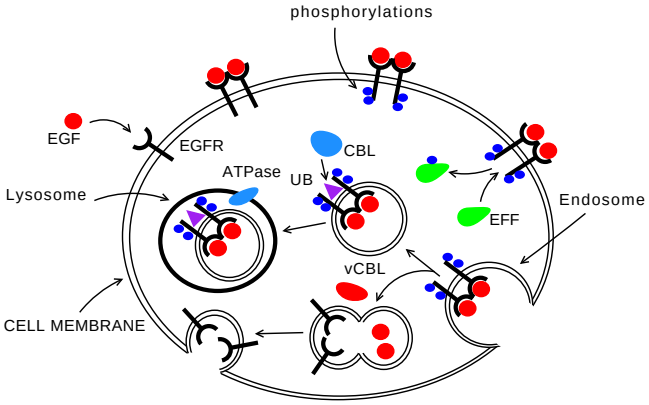


Figure 1. The first steps of the EGF pathway and the effect of the vCBL virus.

**Definition 2.1.** A *P System* $\Pi$ is a tuple $(V, \mu, w_1, \ldots, w_n, R_1, \ldots, R_n)$ where:

- $V$ is an *alphabet* whose elements are called *objects*;
- $\mu \subset \mathbb{N} \times \mathbb{N}$ is a *membrane structure*, such that $(l_1, l_2) \in \mu$ denotes that the membrane labeled by $l_2$ is contained in the membrane labeled by $l_1$;
- $w_j$ with $1 \leq j \leq n$ are multisets of objects in $V$ associated with the membranes $1, \ldots, n$ of $\mu$;
- $R_j$ with $1 \leq j \leq n$ are finite sets of *evolution rules* associated with the membranes $1, \ldots, n$ of $\mu$.

## 2.2. Running Example

We show a P system model of a biological system we use in the following to present the notions we introduce. The biological system we consider is the network of protein interactions known as *EGFR pathway*. We consider the first steps of the pathway and the effect on such steps of a viral infection.

Signal transduction is a process by which a cell converts one kind of signal, typically a protein that may be present in the environment, into another. In order to be able to recognize that signal proteins are available in the environment, a cell exposes some receptor proteins on its external membrane. A complex signal transduction cascade, that modulates cell proliferation, survival, adhesion, migration and differentiation, is based on a family of receptors called epidermal growth factor receptors (EGFRs). These receptors are located on the cell surface and are activated by the binding with a specific ligand (epidermal growth factor, EGF) to form a ligand-receptor complex (Fig. 1). Subsequently, two complexes bind to form a dimer and this stimulates intracellular phosphorylation which activates signalling proteins. These activated signalling proteins (effector proteins, EFFs) initiate several signal transduction cascades (not shown in Fig. 1), leading to DNA synthesis and cell proliferation. After the activation of effector proteins, ligand-receptor dimers are internalized in endosomes. In a normal process an enzyme, known as CBL, is involved: CBL binds an ubiquitin protein to the dimer (ubiquitination). The ubiquitin protein targets the dimers for lysosomal degradation (see Fig. 1).

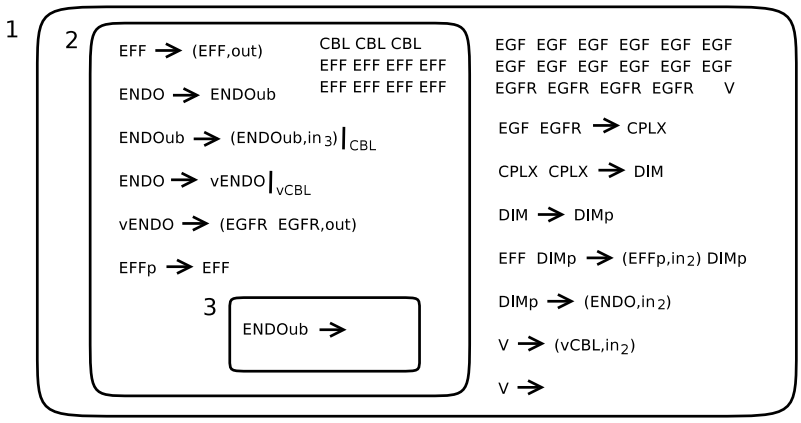


Figure 2. A P system modeling the considered biological system.

Many types of oncogenic viruses exploit the EGFR signalling cascade by manipulating its components. When the vCBL, the viral oncogenic form of CBL, is present, EGFRs might also be recycled to the cellular membrane, thus promoting cellular proliferation (see Fig. 1).

The P system model of the considered biological system is shown in Fig. 2. In the figure, labels $here$ in evolution rules are omitted. Membrane 1 models the external membrane of the cell and the external environment. Initially, it contains some objects modelling EGF and EGFR proteins and a special object $V$. Membrane 2 models the internal part of the cell, that initially contains objects modelling CBL enzymes and effector proteins. Finally, membrane 3 models the lysosome, initially empty.

Evolution rules model the events that may happen in the system. Rules in membrane 1 model the first steps of the pathway, with $CPLX, DIM$ and $DIMp$ describing ligand-receptor complexes, dimers and active dimers, resp. An active dimer might transform an effector $EFF$, sent out by the first rule of membrane 2, into its activated form $EFFp$ that is sent back into membrane 2. The active dimer might also be internalized as an endosome modelled by $ENDO$. Rules involving $V$ model the possibility for the cell to become infected by vCBL, that is the result of a non-deterministic choice. Rules in membrane 2 model the steps of the pathway that occur inside the cell, where $ENDOub$ and $vENDO$ model the ubiquitinated and the virus-influenced endosomes, respectively. Note that $CBL$ and $vCBL$ act as promoters in the rules in which they are involved. One might give $vCBL$ a stronger effect by using it also as inhibitor of endosome ubiquitination, namely by adding inhibitor $\neg vCBL$ to rule $ENDO \rightarrow ENDOub$. This would completely stop normal endosome degradation in case of virus infection.

## 2.3. The P Algebra: Syntax and Semantics

In this section we recall the *P Algebra*, the algebraic notation of P Systems we have introduced in [1], with slight modifications.We assume $V$ to be an alphabet of objects and we adopt the usual string notation to represent multisets of objects in $V$. For instance, to represent $\{a, a, b, b, c\}$ we may write either $aabbc$, or $a^2b^2c$, or $(ab)^2c$. We denote with $\mathsf{Set}(u)$ the support of multiset $u$, namely the set of all the objects occurring in $u$. We denote multiset (and set) union as string concatenation, hence we write $u_1u_2$ for $u_1 \cup u_2$. Moreover, we shall write $u(a)$ for the number of occurrences of $a$ in multiset

$u$. For the sake of legibility, we shall write $u \rightarrow v_h v_o\{v_{l_i}\}|_D$ for the generic evolution rule $u \rightarrow (v_h, here)(v_o, out)(v_1, in_{l_1}) \ldots (v_n, in_{l_n})|_D$.

The abstract syntax of the P Algebra is defined as follows.

**Definition 2.2. (P Algebra)**
The abstract syntax of *membrane contents* $c$, *membranes* $m$, and *membrane systems* $ms$ is given by the following grammar, where $l$ ranges over $\mathbb{N}$ and $a$ over $V$:

$$\begin{aligned} c &::= (\varnothing, \varnothing) \mid (u \rightarrow v_h v_o\{v_{l_i}\}|_D, \varnothing) \mid (\varnothing, a) \mid c \cup c \\ m &::= [_l\, c\, ]_l \\ ms &::= ms \mid ms \mid \mu(m, ms) \mid F(m) \end{aligned}$$

A membrane content $c$ represents a pair $(\mathcal{R}, u)$, where $\mathcal{R}$ is a set of evolution rules and $u$ is a multiset of objects. A membrane content is obtained through the union operation $\_ \cup \_$ from constants representing single evolution rules and single objects, and can be plugged into a membrane with label $l$ by means of the operation $[_l\, \_\, ]_l$ of membranes $m$. Hence, given a membrane content $c$ representing the pair $(\mathcal{R}, u)$ and $l \in \mathbb{N}$, $[_l\, c\, ]_l$ represents the membrane having $l$ as label, $\mathcal{R}$ as evolution rules and $u$ as objects.

Membrane systems $ms$ have the following meaning: $ms_1 \mid ms_2$ represents the juxtaposition of $ms_1$ and $ms_2$, $\mu(m, ms)$ represents the hierarchical composition of $m$ and $ms$, namely the containment of $ms$ in $m$, and $F(m)$ represents a *flat membrane*, namely it states that $m$ does not contain any child membrane. Juxtaposition is used to group sibling membranes, namely membranes all having the same parent in a membrane structure. This operation allows hierarchical composition $\mu$ to be defined as a binary operator on a single membrane (the parent) and a juxtaposition of membranes (all the children).

Note that every P system has a corresponding membrane system in the P algebra, and that there exist membrane systems which do not correspond to any P system.

In what follows we will often write $[\![_l\, c\, ]\!]_l$ for $F([_l\, c\, ]_l)$. We shall also often write $(\mathcal{R}, u)$ where $\mathcal{R} = \{r_1, \ldots, r_n\}$ is a set of rules and $u = o_1 \ldots o_m$ a multiset of objects rather than $(r_1, \varnothing) \cup \ldots \cup (r_n, \varnothing) \cup (\varnothing, o_1) \cup \ldots \cup (\varnothing, o_m)$. Moreover, we shall often omit parentheses around membrane contents.

Let us consider again the P system model of EGFR signalling pathway given in Fig. 2. The corresponding P algebra term is the following:

$$\mu\Big(\quad [_1\, \mathcal{R}_1\, ,\, EGF^{12}\, EGFR^4\, V\, ]_1 \quad , \quad \mu\Big(\quad [_2\, \mathcal{R}_2\, ,\, CBL^3\, EFF^8\, ]_2 \quad , \quad [\![_3\, \mathcal{R}_3\, ,\, \varnothing\, ]\!]_3 \quad \Big) \quad \Big)$$

where $\mathcal{R}_1$,$\mathcal{R}_2$ and $\mathcal{R}_3$ are the rules of membrane 1, 2 and 3, resp., as in Fig. 2.

The semantics of the P Algebra is given as a labelled transition system (LTS). In this paper labels of the LTS are slightly richer with respect to what defined in [1, 2]. In particular, we include in labels some information on the internal configuration and on the internal causes of the transition that can be observed from outside. This information reflects the fact that it is usually possible to observe something on the internal behavior of a biological system (such as the expression of some genes, the presence of some molecules, etc...). More precisely, given an alphabet $V$, we assume that the internal information of a membrane to be exposed in a transition label is an element of $\Gamma_V$, that is the set of all tuples $(u, v, D, I, O^{\uparrow}, O^{\downarrow})$ where $u, v, I, O^{\uparrow} \in V^*$, $D \in \mathcal{D}_V$ and $O^{\downarrow} \in \mathbb{N} \times V^*$. In what follows we will write $\Gamma$ in place of $\Gamma_V$ if the alphabet is clear from the context.

Labels of the LTS can be of the following forms:

- $(u, v, v', D, I, O^{\uparrow}, O^{\downarrow})$, describing a computation step performed by a membrane content $c$, where:

- $u$ is the multiset of objects consumed by the application of evolution rules in $c$, as it results from the composition, by means of $\_ \cup \_$, of the constants representing these evolution rules.
- $v$ is the multiset of objects in $c$ offered for the application of the evolution rules, as it results from the composition, by means of $\_ \cup \_$, of the constants representing these objects. When operation $[_l \_]_l$ is applied to $c$, it is required that $v$ and $u$ coincide.
- $v'$ is the multiset of objects in $c$ that are not used to apply any evolution rule and, therefore, are not consumed, as it results from the composition, by means of $\_ \cup \_$, of the constants representing these objects.
- $D$ is a set of promoters and inhibitors required to be present and absent, respectively, by the application of evolution rules in $c$. More precisely, $D^-$ contains all the inhibitors of the applied evolution rules in $c$, whereas $D^+$ is a subset of the promoters of those rules. Such a subset contains only those objects that are not present in the multiset of objects of $c$.
- $I$ is the multiset of objects received as input from the parent membrane and from the child membranes.
- $O^\uparrow$ is the multiset of objects sent as an output to the parent membrane.
- $O^\downarrow$ is a set of pairs $(l_i, v_{l_i})$ describing the multiset of objects sent as an output to each child membrane $l_i$.

- $(o, \mathcal{I}^\downarrow, I^\uparrow, O^\uparrow, O^\downarrow, app)$, describing a computation step performed by a membrane $m$, where: $o$ is a set containing only the pair $(l, \gamma)$ where $\gamma \in \Gamma$ is the information on the internal causes of the transition performed by membrane $m$, $\mathcal{I}^\downarrow$ is a set containing only the pair $(l, I)$ where $l$ is the label of $m$ and $I$ is the multiset of objects received by $m$ as input from the parent membrane, $I^\uparrow$ is the multisets of objects received from the child membranes of $m$, and $O^\uparrow$ and $O^\downarrow$ are as in the previous case. Finally, $app \in \{0, 1\}$ is equal to 0 if no rule has been applied in $m$ in the described computation step, and it is equal to 1 otherwise.

- $(o, \mathcal{I}^\downarrow, O^\uparrow, app)$, describing a computation step performed by a membrane system $ms$, where $O^\uparrow$ and $app$ are as in the previous cases, and $o$ and $\mathcal{I}^\downarrow$ differ with respect to the previous case because they can contain more than one pair $(l, I)$ and $(l, \gamma)$, respectively.

For the sake of legibility, in transitions with labels of the first form we shall write the first four elements of the label under the arrow denoting the transition and the other elements over the arrow. Similarly, in transitions of the second and third forms we shall write $o$ under the arrow. Now, LTS transitions are defined through SOS rules [13]. We give here a very short explanation of such rules. Please, refer to [1] for more details.

We start by giving in Fig. 3 the transition rules for membrane contents. Rule $(mc1_n)$ describes $n$ simultaneous applications of an evolution rule for any $n \in \mathbb{N}$. Rule $(mc2)$ describes the case in which an evolution rule is not applied because a subset $D'$ of the promoters and inhibitors in $D$ it requires to be present and absent, respectively, are assumed not to satisfy the requirements. Rules $(mc3), (mc4)$ and $(mc5)$ describe the transitions performed by membrane contents consisting of a single object and the transitions performed by an empty membrane content.

Rule $(u1)$ describes the behaviour of a union of membrane contents. In this transition rule we use some auxiliary notations. We assume a function Objects from membrane contents to multisets of objects

$$\frac{I \in V^* \qquad n \in \mathbb{N}}{(u \to v_h v_o\{v_{l_i}\}|_D, \varnothing) \xrightarrow[u^n,\varnothing,\varnothing,D]{I,v_o^n,\{(l_i,v_{l_i}^n)\}} (u \to v_h v_o\{v_{l_i}\}|_D, I v_h^n)} \quad (mc1_n)$$

$$\frac{I \in V^* \qquad D' \subseteq \neg D \qquad D' \neq \varnothing}{(u \to v_h v_o\{v_{l_i}\}|_D, \varnothing) \xrightarrow[\varnothing,\varnothing,\varnothing,D']{I,\varnothing,\varnothing} (u \to v_h v_o\{v_{l_i}\}|_D, I)} \quad (mc2)$$

$$\frac{I \in V^*}{(\varnothing, a) \xrightarrow[\varnothing,a,\varnothing,\varnothing]{I,\varnothing,\varnothing} (\varnothing, I)} \quad (mc3) \qquad \frac{I \in V^*}{(\varnothing, a) \xrightarrow[\varnothing,\varnothing,a,\varnothing]{I,\varnothing,\varnothing} (\varnothing, Ia)} \quad (mc4)$$

$$\frac{I \in V^*}{(\varnothing, \varnothing) \xrightarrow[\varnothing,\varnothing,\varnothing,\varnothing]{I,\varnothing,\varnothing} (\varnothing, I)} \quad (mc5)$$

$$\frac{\begin{array}{c} x_1 \xrightarrow[u_1,v_1,v_1',D_1]{I_1,O_1^\uparrow,O_1^\downarrow} y_1 \qquad x_2 \xrightarrow[u_2,v_2,v_2',D_2]{I_2,O_2^\uparrow,O_2^\downarrow} y_2 \\ (D_1^- \cup D_2^-) \cap \mathsf{Set}(v_1 v_1' v_2 v_2') = \varnothing \qquad D_1 \cap \neg D_2 = \varnothing \qquad D = (D_1 D_2) \setminus \mathsf{Set}(v_1 v_1' v_2 v_2') \end{array}}{x_1 \cup x_2 \xrightarrow[u_1u_2,v_1v_2,v_1'v_2',D]{I_1 I_2, O_1^\uparrow O_2^\uparrow, O_1^\downarrow \cup_{\mathbb{N}} O_2^\downarrow} y_1 \cup y_2} \quad (u1)$$

Figure 3. Transition rules for membrane contents and unions of membrane contents.

such that $\mathsf{Objects}((\mathcal{R}, u)) = u$. Moreover, given two sets $O_1^\downarrow$ and $O_2^\downarrow$ representing two outputs to inner membranes, we write $O_1^\downarrow \cup_{\mathbb{N}} O_2^\downarrow$ to denote the set $\{(l, uv) \,|\, (l, u) \in O_1^\downarrow \wedge (l, v) \in O_2^\downarrow\} \cup \{(l, u) \,|\, (l, u) \in O_1^\downarrow \wedge \nexists v.(l, v) \in O_2^\downarrow\} \cup \{(l, v) \,|\, (l, v) \in O_2^\downarrow \wedge \nexists u.(l, u) \in O_1^\downarrow\}$.

Now, we have to give transition rules for individual membranes, juxtaposition and hierarchical compositions. The labels of the transitions obtained from these rules contain information on the internal behaviour of membranes. Such information is a set of elements, each denoted $\gamma$, that can be obtained from the label of the transition performed by the content of each membrane. In particular, the part of the membrane content transition label that could be used as information on the internal behaviour consists of the objects that were contained in the membrane before performing the transition (by distinguishing between those that have been consumed by some evolution rule during the transition and those that have not been consumed), the set of promoters and inhibitors that have been used, and the information on the objects received and sent by the membrane.

In Fig. 4 we give transition rules for individual membranes, juxtaposition and hierarchical composition. Rules $(m1)$ and $(m2)$ describe the transitions performed by a membrane with label $l$. In particular, $(m1)$ describes the case in which no objects are received as an input from the external membrane, while $(m2)$ describes the case in which a multiset of objects $I_1 \neq \varnothing$ is received. In these rules $app$ is set to zero if no evolution rule is applied ($u = \varnothing$), and it is set to one if at least one rule is applied ($u \neq \varnothing$). Rule $(fm1)$ allows us to infer the behaviour of a flat membrane $[\![_l\, c]\!]_l = F([_l\, c]_l)$ from the behaviour of membrane $[_l\, c]_l$. Rule $(jux1)$ allows us to infer the behaviour of a juxtaposition of two membrane structures from the behaviours of the two structures. Finally, rule $(h1)$ describes the behaviour of a hierarchical composition of membranes. In this rule we assume $\doteq$ to be an equivalence relation on sets of

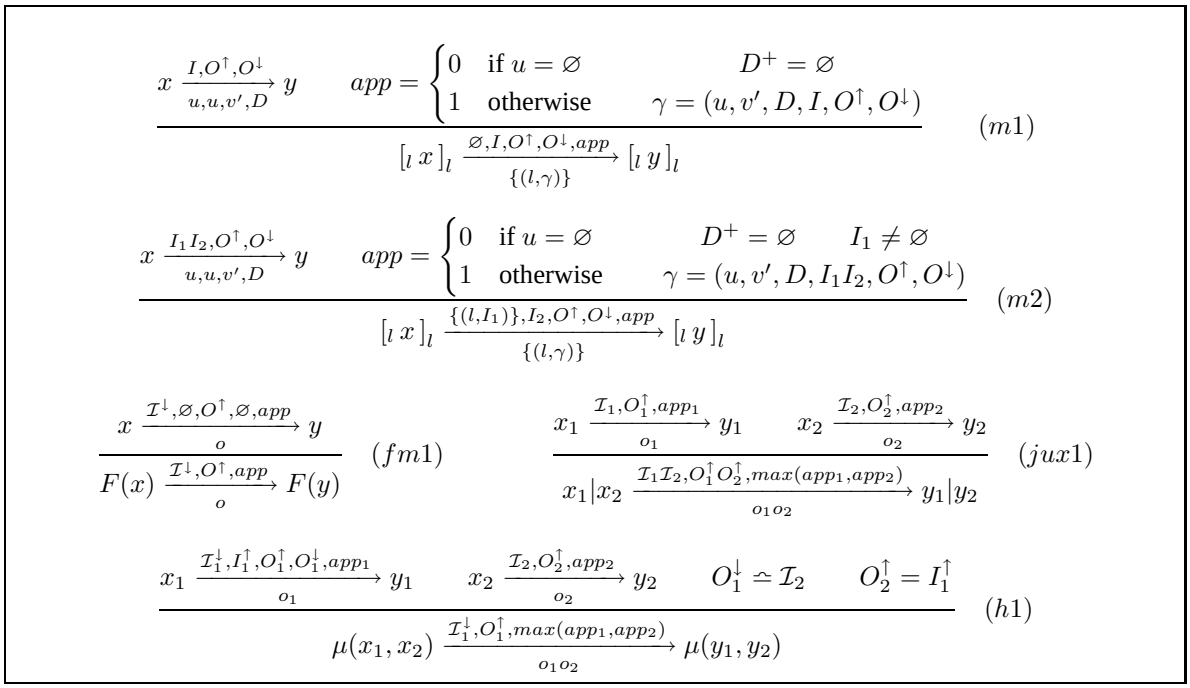


Figure 4. Rules for individual membranes and hierarchical composition of membranes

pairs $(l, u)$ with $l \in \mathbb{N}$ and $u \in V^*$, such that, given two such sets $\mathcal{I}_1$ and $\mathcal{I}_2$, then $\mathcal{I}_1 \backsimeq \mathcal{I}_2$ holds if and only if $(\mathcal{I}_1 \setminus \{(l, \varnothing) \mid l \in \mathbb{N}\}) = (\mathcal{I}_2 \setminus \{(l, \varnothing) \mid l \in \mathbb{N}\})$. In the last two rules $app$ is set to one if at least one $app_1$ and $app_2$ is equal to one, namely $app = max(app_1, app_2)$. This means that at least one rule has been applied in the whole composition.

We conclude by defining a *system trace* as a sequence of internal information given by an execution of a P Algebra term. We assume that the system can send objects out of the outmost membrane, but cannot receive objects from outside. This requirement corresponds to the fact that in a P system objects cannot be received by the outmost membrane from the external environment. Note that executions containing steps in which no rule is applied, namely those with 0 as last element of the label, are not considered.

**Definition 2.3. (Trace)**
A *trace* of a membrane system $ms$ with alphabet $V$ is a (possibly infinite) sequence $w$ such that, for any $O_i^{\uparrow}$ and $ms_i$ with $i \in \mathbb{N}^+$

either $w = o_1....o_n$ and $ms \xrightarrow[o_1]{\varnothing,O_1^{\uparrow},1} ms_1 \xrightarrow[o_2]{\varnothing,O_2^{\uparrow},1} \dots \xrightarrow[o_n]{\varnothing,O_n^{\uparrow},1} ms_n \xrightarrow[o]{\varnothing,O^{\uparrow},1}\!\!\!\!\!\!\diagup$,

or $w = o_1 o_2 o_3....$ and $ms \xrightarrow[o_1]{\varnothing,O_1^{\uparrow},1} ms_1 \xrightarrow[o_2]{\varnothing,O_2^{\uparrow},1} ms_2 \xrightarrow[o_3]{\varnothing,O_3^{\uparrow},1} ....$ .

We denote with $\mathcal{T}$ the set of all traces.

## 3. Security concepts as diagnostic concepts

We use the semantics of the P Algebra to define diagnosable properties or activities of the corresponding P systems. From now on we will assume that properties of interest cannot be observed directly. We will consider them to be diagnosable if they can be deduced by observing other, for an external observer visible, system activities. In other words, a property is diagnosable if considering it as a private property, the corresponding system is not secure as their presence can be discovered by an intruder observing the system activities. Hence, there is a direct connection between diagnosability and systems security.

We recall one of the most general security concepts called opacity [5]. By means of opacity many other security concepts can be modelled [6], and moreover opacity can be defined independently of systems constructors and operations since it exploits only the corresponding LTS. Opacity is based on concepts of observations and of predicates over system traces. In order to define the notion of observation in the transition rules we introduce a notion of *observation function*.

**Definition 3.1.** Given a set of observables $\Theta$, an *observation function* is any function $\mathcal{O} : \mathcal{T} \to \Theta^*$.

In general, different types of observation functions can be used, but here we consider only *static observations*. This means that an observation of a trace is given by the observations of each of its actions separately, namely if $w = o_1 o_2 \ldots . o_n$ then $\mathcal{O}(w) = \mathcal{O}(o_1)\mathcal{O}(o_2)\ldots .\mathcal{O}(o_n)$. Opacity is defined for an arbitrary predicate $\phi$ over sequences of system actions. Roughly, the observer cannot deduce validity of $\phi$ if there are two traces $w, w'$ such that $\phi(w), \neg\phi(w')$ and the the sequences cannot be distinguished by the observer, namely $\mathcal{O}(w) = \mathcal{O}(w')$.

**Definition 3.2.** A predicate $\phi$ over system traces is *opaque* w.r.t. the observation function $\mathcal{O}$ and P system $\Pi$ if for every trace $w$ of $\Pi$ such that $\phi(w)$ holds, there exists a trace $w'$ such that $\neg\phi(w')$ holds and $\mathcal{O}(w) = \mathcal{O}(w')$.

By predicate $\phi$ we can express various types of properties, starting from simple ones (e.g. traces contain a particular element) to more sophisticated ones.

**Example 3.1.** Let us consider again the P system model of the EGFR pathway. A property of interest on the behavior of the modelled system is the infection of the cell by the vCBL virus. Such a property can be expressed as a predicate $\phi$ on execution traces $w$ of the P system model as follows:

$$\phi(w) \text{ holds iff } \left\{\left(1, \gamma_1\right), \left(2\,,\ (u, v\, vCBL, D, I, O^{\uparrow}, O^{\downarrow})\right), \left(3, \gamma_3\right)\right\} \in w\,.$$

Let us assume that what is observable is the presence of the ubiquitinated endosome in the lysosome. This is modelled by the following observation function:

$$\mathcal{O}_1(o) = \begin{cases} LYSO & \text{if } \left(3, (u\, ENDOub, v, D, I, O^{\uparrow}, O^{\downarrow})\right) \in o \\ \lambda & \text{otherwise} \end{cases}$$

In this case we have that predicate $\phi$ is opaque. For every trace in which the $vCBL$ virus occurs inside membrane 2 ($\phi$ is true) there are different kinds of behaviour. In the first kind the phosphorilated dimers ($DIMp$) remain on the cell membrane and they continue to send signalling proteins ($EFFp$) inside the cell. In this case no endosome is sent to the lysosome (there are no $LYSO$ observations). In a

second kind of behaviour a phosphorilated complex is taken by an endosome, but it is not destroyed because of the presence of $vCBL$ and the $EGFR$ receptors are recycled. Also in this case there are no $LYSO$ observations. The opacity of $\phi$ derives from the fact that the above first kind of behaviour can be expressed also by a cell without $vCBL$ virus. That is there exists a trace for which $\phi$ is false with the same observable behaviour. The same happens when the endosome is destroyed.

In general, opacity is undecidable, as stated by the following theorem.

**Theorem 3.1.** Opacity is undecidable for P systems.

**Proof:**
We reduce opacity to the Post correspondence problem. Let us consider two finite lists $u_1, \ldots, u_N$ and $v_1, \ldots, v_N$ of words over some alphabet $A$ having at least two symbols. Let us consider P system which randomly outputs through the outmost membrane objects $b_1, \ldots b_N$. Let $o_i$ be elements of traces such that $\big(1, (u, v, D, I, b_i, O^{\downarrow})\big) \in o_i$. Let $\mathcal{O}$ be such that it hides everything, namely it maps everything to $\epsilon$, for $\epsilon \in \Theta$. Let $\phi(w)$ hold if for $w = o_{i_1} \ldots o_{i_K}$ we have $u_{i_1} \ldots u_{i_K} \neq v_{i_1} \ldots v_{i_K}$. The opacity of $\phi$ would mean that there exists another trace $w' = o_{j_1} \ldots o_{j_K}$ such that $\neg\phi(w')$ holds, but this would imply $u_{j_1} \ldots u_{j_K} = v_{j_1} \ldots v_{j_K}$, namely a solution of the Post correspondence problem. □

Now we define diagnosability as a property dual to opacity. Labels of LTSs defined in the previous section carry complex information about systems state and activity. We exploit observation functions to express what can be really observed by an external observer from systems behavior.

**Definition 3.3.** A predicate $\phi$ over system traces is *diagnosable* w.r.t diagnoser defined by $\mathcal{O}$ and P system $\Pi$ if the predicate $\phi$ is not opaque w.r.t. the observation function $\mathcal{O}$ and P system $\Pi$, namely there exists a trace $w$ such that $\phi(w)$ holds and there is no trace $w'$ such that $\neg(w')$ holds and $\mathcal{O}(w) = \mathcal{O}(w')$.

In other words a diagnosable property $\phi$ with respect to $\mathcal{O}$ is such that there exists a sequence $w$ of system activities such that $\phi(w)$ holds and also $\phi(w')$ holds for every trace such that $\mathcal{O}(w) = \mathcal{O}(w')$.

**Example 3.2.** Let us consider again the P system model of the EGFR pathway and the predicate $\phi$ as in Ex. 3.1. Let us assume that what is observable are the phosphorilation of an effector protein, the creation of an endosome and the presence of a ubiquitinated endosome in the lysosome. This can be modelled by the following observation function:

$$\mathcal{O}_2(o) = \begin{cases} PH & \text{if } \big(1, (u, v, D, I \cup \{(2, EFFp)\}, O^{\uparrow}, O^{\downarrow})\big) \in o \\ ENDO & \text{if } \big(1, (u, v, D, I \cup \{(2, ENDO)\}, O^{\uparrow}, O^{\downarrow})\big) \in o \\ LYSO & \text{if } \big(3, (u\, ENDOub, v, D, I, O^{\uparrow}, O^{\downarrow})\big) \in o \\ \lambda & \text{otherwise} \end{cases}$$

In this case we have that predicate $\phi$ is diagnosable because there exists a trace $w$ which verifies it and there is not a trace $w'$ which does not and such that $\mathcal{O}(w) = \mathcal{O}(w')$. First of all note that the only possible looping situation in the system can be due to recurrent phosphorilations and de-phosphorilations of effector proteins $EFF$. In these cases we obtain infinite traces and inifinite sequences of observations (as phosphorilation of $EFF$ is observable). Finite traces (and observations) occur when all the phosphorilated dimers $DIMp$ sooner or later are taken by endosomes and then destroyed by a lysosome. Let us

now consider only the finite traces, in particular those traces in which, in presence of $vCBL$, a $DIMp$ is taken by an endosome ($ENDO$ observation) and the $EGFR$ receptors are recycled. In this case there would be an occurrence of $ENDO$ that is not followed by $LYSO$. Hence, when the virus is present we may have finite traces with more $ENDOs$ than $LYSOs$. In the case in which $vCBL$ is absent, in each finite trace in which $DIMp$ is taken by an endosome it is always destroyed by a lysosome, namely an observation $ENDO$ is always followed by a $LYSO$. Thus, a finite trace $w$, such that $\neg\phi(w)$, in which we can observe more $ENDOs$ than $LYSOs$ does not exist.

**Theorem 3.2.** Diagnosability is undecidable for P systems.

**Proof:**
Follows from undecidability of opacity. □

Diagnosability as it is defined in Definition 3.3 might be considered too weak. It is required that there exists a computation with a property of interest such that there cannot be another computation without that property which is indistinguishable for an observer from the first one. Hence, to diagnose the property a diagnoser needs to force the system to perform the particular computation having the above property, and this might not be an easy task. To overcome this problem we propose strong diagnosability.

**Definition 3.4.** A predicate $\phi$ over system traces is *strongly diagnosable* with respect to diagnoser defined by $\mathcal{O}$ and P system $\Pi$ if there exists a trace $w$ such that $\phi(w)$ holds and for every trace $w$ such that $\phi(w)$ holds there is no trace $w'$ such that $\neg\phi(w')$ holds and $\mathcal{O}(w) = \mathcal{O}(w')$.

With respect to diagnosability, in strong diagnosability *all* traces which satisfy the property allow the property to be diagnosed. Note that the concept of strong diagnosability is analogous to the concept of simple visibility introduced in [11] in the framework of digital forensis investigations.

**Example 3.3.** Let us consider again the P system model of the EGFR pathway and the predicate $\phi$ as in Ex. 3.1 and Ex. 3.2. Let us assume that what is actually observable in this case is the presence of the $vCBL$ virus. This can be modelled by the following observation function:

$$\mathcal{O}_3(o) = \begin{cases} vCBL & \text{if } \big(2, (u, v\, vCBL, D, I, O^{\uparrow}, O^{\downarrow})\big) \in o \\ \lambda & \text{otherwise} \end{cases}$$

In this case we have that predicate $\phi$ is obviously strongly diagnosable.

**Theorem 3.3.** Strong diagnosability is undecidable for P systems.

**Proof:**
The proof is similar to that of Theorem 3.1, but with $\phi(w)$ that holds if for $w = o_{i_1} \dots o_{i_K}$ we have $u_{i_1} \dots u_{i_K} = v_{i_1} \dots v_{i_K}$. Since strong diagnosability requires that there exists a trace $w$ such that $\phi(w)$ holds (that is a solution of the Post correspondence problem) it follows that it is undecidable. □

We consider some restrictions under which the introduced properties of opacity and diagnosability become decidable. First of all, let us consider the notions of *initial* opacity, *initial* diagnosability, and strong *initial* diagnosability. In the definition of these variants, we assume that the P system may have several different initial states (represented as a set of membrane systems $\{ms_1, \dots, ms_n\}$. In particular, we consider a notion of *extended trace* in which traces of a P system are associated with their initial state.

**Definition 3.5. (Extended trace)**
An *extended trace* of a set of membrane systems $\{ms_1, \ldots, ms_n\}$ is a pair $(ms_i, w)$, with $1 \leq i \leq n$, such that $w$ is a trace of $ms_i$.

Given a set of extended traces $ET$, let $sup(ET)$ be the set of all membrane systems mentioned in $ET$ (called *support* of $ET$), namely $sup(ET) = \{ms \mid (ms, w) \in ET\}$. Similarly, we denote with $tr(ET)$ the set of traces obtained by removing from each extended trace the reference to its initial state, namely $tr(ET) = \{w \mid (ms, w) \in ET\}$. We say that a set of extended traces is *complete* if for every $ms \in sup(ET)$ and every trace $w$ that can be obtained from the semantics of membrane system $ms$, we have that $(ms, w) \in ET$. With use extended traces in new variants of opacity and diagnosability.

**Definition 3.6.** Given a complete set of extended traces $ET$, a predicate $\phi$ over $tr(ET)$ is *initial opaque/ initial diagnosable/strongly initial diagnosable* with respect to observation function $\mathcal{O}$ if and only if $\phi$ is opaque/diagnosable/strongly diagnosable, respectively, and there exists a predicate $\psi$ over membrane systems such as for every $(ms, w) \in ET$, it holds $\phi(w) = \psi(ms)$.

The introduced variants of opacity and diagnosability deal with properties of the behaviour which depend tightly on the initial state of the system. In the context of system security the notion of initial opacity has been introduced to deal, for instance, with secrecy protocols in which the secrecy of some information during the execution is ensured by the correct distribution of private keys in the initial state.

Note that, our definition of initial opacity is more general than that given in [5] on Petri Nets [14]. In [5] initial states of a system are different markings of the same net. Here, by the definition of extended trace, we allow initial states to be completely different membrane systems. In practice, initial states constituting the support of an extended trace will often have the same membrane structure and the same evolution rules, but different objects. However, we do not add this requirement here.

In the context of biological systems the notions of initial diagnosability can be used to discover the presence of some pathological entity at the beginning the evolution of a system, by analysing the dynamics of the system itself. For example, let us consider two initial states for our model of the EGFR pathway, the first obtained by removing object $V$ from membrane 1, and the second in which $V$ is replaced by $vCBL$ (the virus) in membrane 2. Property $\phi$ of Ex. 3.1 holds only on traces starting from the second initial state. Hence, being able to diagnose $\phi$ by observing the behaviour of the system (as in Ex. 3.2 and 3.3) gives information about the presence of the virus in the initial state. In the EGFR model with two initial states we have that $\phi$ is initial diagnosable and strongly initial diagnosable, if the observation functions of Ex. 3.2 and 3.3, resp., are considered.

We give a decidability result on the variants of opacity and diagnosability, that is based on the finiteness of the semantics of membrane systems. A membrane system $ms$ has a finite semantics if the LTS obtained by the given inference rules and rooted in $ms$ can reach a finite number of states. We consider here only transitions of the form $\xrightarrow[o]{\varnothing, O^{\uparrow}, 1}$, namely those in which at least one rule has been applied.

**Theorem 3.4.** Initial opacity, initial diagnosability and strong initial diagnosability are decidable for every complete set of extended traces $ET$ such that $sup(ET)$ is finite if the semantics of each $ms \in sup(ET)$, restricted to transitions of the form $\xrightarrow[o]{\varnothing, O^{\uparrow}, 1}$, is finite.

**Proof:**
In order to prove that initial opacity, initial diagnosability and strong initial diagnosability are decidable,

we follow the approach used to prove Th. 7 of [6] (that, in turn, is based on Th. 3.3 of [5]). The idea is to reduce the three properties to regular language inclusion problems. W.r.t. the proofs in [6, 5], here we deal with possibly infinite traces, hence we shall reduce the three properties to $\omega$-regular language inclusion problems (see [16, 15] for an introduction to $\omega$-languages and $\omega$-automata). Let us consider $\omega$-automata with Büchi acceptance condition, and let us denote with $L(A)$ the ($\omega$-regular) language accepted by $\omega$-automaton $A$. Let the alphabets of the $\omega$-automata we are going to construct consist of a set of observables $\Theta$ and of a special symbol $\epsilon \notin \Theta$. We also assume $\phi, \psi, \mathcal{O}$ and $ET$ to be as in Def. 3.6.

Let us construct an $\omega$-automaton from the semantics of each $ms \in \sup(ET)$ (that is a finite LTS) as follows: the set of states of the automaton is the same as that of the LTS, and the LTS contains a transition $ms_1 \xrightarrow[o]{\varnothing, O^{\uparrow}, 1} ms_2$ if and only if the $\omega$-automaton contains a transition from $ms_1$ to $ms_2$ with label $\mathcal{O}(o)$. In addition, let the $\omega$-automaton contain a self-looping $\epsilon$-transition from each state $ms'$ such as in the LTS we have $ms' \xrightarrow[o]{\varnothing, O^{\uparrow}, 1}\!\!\!\!\!\!/\;\;$. Moreover, let all the states of the obtained $\omega$-automaton to be final.

Now, let us consider an $\omega$-automaton $A_1$ constructed by connetting, with an $\epsilon$-transition, a fresh initial state with every $ms \in sup(ET)$ such that $\psi(ms)$ holds. Moreover, let us consider another $\omega$-automaton $A_2$ constructed by connetting, with an $\epsilon$-transition, a fresh initial state with every $ms \in sup(ET)$ such that $\neg\psi(ms)$ holds. It is easy to see that $\phi$ is initial opaque if and only if $L(A_1) \subseteq L(A_2)$, that it is initial diagnosable if and only if $L(A_1) \not\subseteq L(A_2)$, and that it is strongly initial diagnosable if and only if $L(A_1) \neq \varnothing$ and $L(A_1) \cap L(A_2) = \varnothing$. All these properties are decidable for $\omega$-regular languages. □

We remark that the model of the EGFR pathway we have given has a finite semantics. We have that the initial diagnosability and strong inital diagnosability of $\phi$ (as defined in example 3.1) with respect to suitable observation functions in a EGFR model with two initial states are decidable (and actually hold).

The decidability of the initial variants of opacity and diagnosability is based on a semantical requirement on membrane systems, namely finiteness of the semantics. Consequently, such a decidability result is meaningful only if the finiteness of the semantics of a P system is decidable. We can prove that this is the case for P systems with rules without promoters and inhibitors. For P systems with promoters and inhibitors, we shall rather give a sufficient condition that ensures finiteness of the semantics. Both these results are based on a translation of P systems without promoters and inhibitors into Petri Nets [14].

Let us recall the definition of Petri Nets with weighted arcs. A *net* is a triple $N = (P, T, W)$ such that $P$ is a finite set of *places*, $T$ is a finite set of *transitions* and $W : (T \times P) \cup (P \times T) \to \mathbb{N}$ is the *weight function* of $N$. A *marking* of a net $N$ is a multiset of places. Given a marking $M$ and a place $p$, we write $M(p)$ for the number of occurrences of $p$ in $M$. The dynamics of a net consists of steps from one marking to another, in which the latter is determined by the transitions of the net. As in [5], we allow here a multiset of simultaneously occurring transitions can be performed at each step. Given a multiset of transitions $U$ and a place $p$, let $pre_N(U)(p)$ and $post_N(U)(p)$ be defined as follows:

$$pre_N(U)(p) = \textstyle\sum_{t \in U} U(t) \cdot W(p,t) \qquad post_N(U)(p) = \textstyle\sum_{t \in U} U(t) \cdot W(t,p)$$

where $U(t)$ is the number of occurrences of $t$ in $U$. We say that a multiset of transitions $U$ is *enabled* at a marking $M$ if $\forall p \in P. M(p) \geq pre_N(U)(p)$. If $U$ is enabled, it can be executed (or fired) leading to marking $M'$ s.t. $M'(p) = M(p) - pre_N(U)(p) + post_N(U)(p)$, for every $p \in P$. A *step* of the execution of a net $N$ from a marking $M$ to another consists in the firing of a non-empty multiset of transitions.

Let us now give a translation of membrane systems without promoters and inhibitors into Petri Nets. For the sake of simplicity, we give the translation of P systems, rather than of membrane systems.

**Definition 3.7.** Given a P system $\Pi = (V, \mu, w_1, \ldots, w_n, R_1, \ldots, R_n)$, its translation into Petri Net $N_\Pi = (P, T, W)$ is such that $P = V \times \{1, \ldots, n\}$ and $T = R_1 \cup \ldots \cup R_n$. Moreover, $W$ is such that for every $1 \leq j \leq n$ and every $r = u \rightarrow v_h v_o \{v_{l_i}\}$ in $R_j$ (hence in $T$), the following axioms hold:

$$\forall a \in u. W((a,j),r) = u(a) \qquad \forall a \in v_h. W(r,(a,j)) = v_h(a)$$
$$\forall a \in v_o. W(r,(a,k)) = v_o(a) \text{ if } (k,j) \in \mu \qquad \forall a \in v_{l_i}. W(r,(a,i)) = v_{l_i}(a) \text{ if } (j,i) \in \mu$$

and $W$ gives 0 otherwise. The initial marking $M_\Pi$ of the net is such that $M_\Pi((a,i)) = w_i(a)$, with $1 \leq i \leq n$ and $a \in V$.

**Proposition 3.1.** Let $ms$ be a membrane system without promoters and inhibitors corresponding to a P system $\Pi$. It holds that $ms \xrightarrow[o]{\varnothing, O^{\uparrow}, 1} ms'$ if and only if $N_\Pi$ performs a step from $M_\Pi$ to $M'$, with $ms'$ corresponding to a P system $\Pi'$, with $N_\Pi = N_{\Pi'}$ and $M' = M_{\Pi'}$.

**Proof:**
Follows immediately from the definition of the translation of P systems into Petri Nets and from the fact that the considered kinds of parallelism in Petri Nets and membrane systems coincide. □

We are now ready to give our decidability results on the finiteness of the semantics of a membrane system which are necessary to ensure that the decidability result in Theorem 3.4 actually holds.

**Theorem 3.5.** The finiteness of the semantics of a membrane system without promoters and inhibitors is decidable.

**Proof:**
Follows from the translation into Petri Nets, and the fact that the finiteness of the set of reachable markings in a Petri Net is decidable, through the standard coverability tree construction [14]. □

**Theorem 3.6.** Given a membrane system $ms$, let $ms'$ be obtained by removing promoters and inhibitors from the evolution rules of $ms$. If $ms'$ has a finite semantics, then $ms$ has a finite semantics as well.

**Proof:**
Follows from the fact that promoters and inhibitors are restrictions on the applicability of rules. Hence, transitions in the semantics of $ms$ are a subset of those in the semantics of $ms'$. □

The proofs of the last two theorems exploit techniques developed to decide the finiteness of the semantics of Petri Nets. Similar techniques could be developed for membrane systems. This could allow a stronger result on membrane systems with promoters and inhibitors to be obtained.

# 4. Conclusions

We have proposed and investigated notions of diagnosability of pathological changes in the behaviour of biological systems by taking inspiration from notions of systems security. Moreover, we have shown applications of such notions on a P system model of the EGFR signalling pathway.

Diagnosability notions are in general undecidable. However, we have considered classes of properties and systems for which such notions are decidable. In particular, we have considered a form of diagnosability in which properties on the behaviour can be reduced to properties on the initial states, and we have shown that for systems with a finite semantics such a form of diagnosability is decidable.

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