

# Generation and revision of Delayed Biological Regulatory Systems

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**Abstract.** The modeling of biological systems relies on background knowledge, deriving either from literature and/or the analysis of biological observations. But with the development of high-throughput data, there is a growing need for methods that automatically generate (resp. revise) admissible models with regard to initial (resp. additional) observations provided by biologists. Our research aims at providing a logical approach to generate (resp. to revise) biological regulatory networks thanks to time series data, i.e., gene expression data depending on time. In this paper, we propose a new methodology for models expressed through a timed extension of the Process Hitting framework (which is a restriction, well suited for biological systems, of networks of synchronized timed automata). The revision methods we introduce aim to make the minimum amount of modifications (addition/deletion of actions between biological components) to a given input model so that the resulting model is the most consistent as possible with the observed data. The originality of our work relies in the integration of quantitative time delays directly in our learning approach. Finally, we show the benefits of such automatic approaches on dynamical biological models. In order to exhibit the scalability of our contribution, we conduct benchmarks on the DREAM4 datasets, a popular reverse-engineering challenge, and discuss the computational performances of our algorithm.

**Keywords:** network construction, network revision, dynamic modelisation, biological regulatory networks, time-varying genetic networks, Process Hitting

## 1 Introduction

With both the spread of numerical tools in every part of daily life and the development of NGS methods (New Generation Sequencing methods), like DNA microarrays in biology, a large amount of time series data is now produced every

day, every minute, every second [16]. This means that the number of experiments - and corresponding data - led on a biological system grows drastically. The newly produced data - as long as the associated noise does not raise an issue with regard to the precision and relevance of the corresponding information - can give us some new insights on the behavior of a system. This justifies the urge to design efficient revision methods that are able to update previous knowledge on a model with regard to additional information. In other words, there is a strong need for automatic methods that update a given model so that the dynamics of the model is consistent with given observations and a set of criteria (for example, minimize the number of modifications).

Network completion has been the subject of numerous recent works. In [3], the authors targeted the completion of stationary Boolean networks. This method has been further refined along the years. Latest works [18] focus on completion in Time Varying Genetic Networks. These are networks whose topology does not change through time, but the nature of the interactions (activation, inhibition, or no interaction) between components may change at some (finite number of) time points. The completion approach (which, in these authors' papers, refers to both addition and deletion of interactions, making it a synonym of revision) has been successfully applied to biological case-studies, for example the DREAM4 Challenge [20], and the implementation has been improved through heuristics [19]. The method however is limited to acyclic networks.

Logical-based approaches may be also fruitful to network revision. It has been successfully applied to causal networks [15] and molecular networks represented with the SBGN-AF language [26].

Despite being a proper research area, revision is strongly connected to model inference. Starting from an empty model, revision may indeed be used to model from gene expression data. On the reverse, existing inference algorithms may be an inspiration for new revision methodologies. In particular, Answer Set Programming (ASP), a form of declarative programming that has been successively used in many knowledge representation and reasoning tasks [21,4,5] has been proven useful for network reconstruction [9] and inference of metabolic networks [25].

To our knowledge, no works have been led so far in the field of revision of timed models, without any restriction on the structure of the network.

In this paper, we aim to provide a logical approach to tackle the revision of qualitative models of biological dynamic systems, like gene regulatory networks. In our context, we assume the set of interacting components as fixed and we consider potential additions/deletions of interactions between components. The main originality of our work is that we address this problem in a timed setting, with quantitative delays potentially occurring between the moment an interaction activated and the moment its effect is visible. It allows for example to catch delays between the activation of a gene, and the moment the concentration of a gene reaches a qualitative threshold.

During the past decade, there has been a growing interest for the hybrid modeling of gene regulatory networks with delays. These hybrid approaches consider

various modeling frameworks. In [17], the authors hybrid Petri nets: the advantage of hybrid with regard to discrete modeling lies in the possibility of capturing biological factors, e.g., the delay for the transcription of RNA polymerase. The merits of other hybrid formalisms in biology have been studied, for instance timed automata [24] and hybrid automata [2]. Finally, in [8], the authors investigate a direct extension of the discrete René Thomas’ modeling approach by introducing quantitative delays. These delays represent the compulsory time for a gene to turn from a discrete qualitative level to the next (or previous) one. They exhibit the advantage of such a framework for the analysis of mucus production in the bacterium *Pseudomonas aeruginosa*. The approach we propose in this paper inherits from this idea that some models need to capture these timing features.

In order to address the formal checking of dynamical properties within very large BRNs, we previously introduced in [22] a new formalism, named the “*Process Hitting*” (PH), to model concurrent systems having components with a few qualitative levels. Being a particular restriction of asynchronous automata networks or safe Petri nets, Process Hitting can be applied to complex dynamical systems with a very large number of interacting components, where each of these components can be described with a few internal states. In this paper, following recent works enriching (by adding priorities) the expressivity of PH while preserving its efficiency [12], we extend PH with quantitative timing features and exhibit efficient ASP-based approaches to perform network revision.

As readers may not be familiar with PH, we briefly introduce it in section 2, then give in section ?? some preliminary insights about recent translation of PH into ASP presented in [6]. All theoretical and practical notions are then settled to introduce our timed extension of PH, and related completion algorithm in section 3. Then we illustrate the merits of our approach in section ?? by first applying it on a simplified model of mammalian circadian clock [7], then discussing the practical results on a range of benchmarks from bioinformatics literature. Finally, in section 5, we summarize our contribution and give some perspectives for future works.

## 2 Process Hitting

Definition 1 introduces the Process Hitting (PH) framework [22] which allows to model a finite number of local levels, called *processes*, grouped into a finite set of components, called *sorts*. A process is noted  $a_i$ , where  $a$  is the sort’s name, and  $i$  is the process identifier within sort  $a$ . At any time, exactly one process of each sort is *active*, and the set of active processes is called a *state*.

The concurrent interactions between processes are defined by a set of *actions*. Each action is responsible for the replacement of one process by another of the same sort conditioned by the presence of at least one other process in the current state. A normal action is denoted by  $a_i \rightarrow b_j \uparrow b_k$ , which is read as  $a_i$  *hits*  $b_j$  to make it *bounce* to  $b_k$ , where  $a_i$ ,  $b_j$ ,  $b_k$  are processes of sorts  $a$  and  $b$ , called respectively *hitter*, *target* and *bounce* of the action. We also call a *self-*

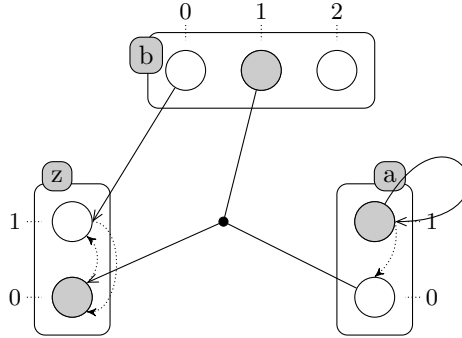
*hit* any action whose hitter and target sorts are the same, that is, of the form:  $a_i \rightarrow a_i \uparrow a_k$ . The original Process Hitting framework contains only actions with one hitter but it should be noted that during these last years it was gradually enriched with new type of sorts like cooperative sorts and new actions like plural actions [11] (at least 2 hitters), actions with priority [13] and actions with delay.

The PH is therefore a restriction of asynchronous automata, where each transition changes the local state of exactly one automaton, and is triggered by the local states of at most two distinct automata. This restriction in the form of the actions was chosen to permit the development of efficient static analysis methods based on abstract interpretation [23].

**Definition 1 (Process Hitting).** A Process Hitting is a triple  $(\Sigma, \mathcal{L}, \mathcal{H}_p)$  where:

- $\Sigma = \{a, b, \dots\}$  is the finite set of sorts;
- $\mathcal{L} = \prod_{a \in \Sigma} \mathcal{L}_a$  is the set of states where  $\mathcal{L}_a = \{a_0, \dots, a_{l_a}\}$  is the finite set of processes of sort  $a \in \Sigma$  and  $l_a$  is a positive integer, with  $a \neq b \Rightarrow \mathcal{L}_a \cap \mathcal{L}_b = \emptyset$ ;
- $\mathcal{H}_p = \{ A \rightarrow b_j \uparrow b_k \text{ with } A \in \mathcal{L}^\diamond \wedge b \in \Sigma \wedge b_j \neq b_k \wedge \text{if } b_j \in A \Rightarrow A = b_j \}$  is the finite set of actions. With  $\mathcal{L}^\diamond$  the set of all the sub-states of  $\mathcal{L}$ .

*Example 1.* The figure 1 represents a  $\mathcal{PH}(\Sigma, \mathcal{L}, \mathcal{H})$  with three sorts ( $\Sigma = \{a, b, c\}$ ) and:  $\mathcal{L}_a = \{a_0, a_1\}$ ,  $\mathcal{L}_b = \{b_0, b_1\}$ ,  $\mathcal{L}_z = \{z_0, z_1, z_2\}$ .



**Fig. 1.** A PH model example with three sorts:  $a$ ,  $b$  and  $z$  ( $a$  is either at level 0 or 1,  $b$  at either level 0, 1 or 2 and  $z$  at either level 0, or 1). Boxes represent the *sorts* (network components), circles represent the *processes* (component levels), and the 3 *actions* that model the dynamic behavior are depicted by pairs of arrows in solid and dotted lines. A self-action:  $a_1 \rightarrow a_1 \uparrow a_0$ , a mono-action:  $b_0 \rightarrow z_1 \uparrow z_0$  and plural action  $a_0 \wedge b_1 \rightarrow z_0 \uparrow z_1$ . The grayed processes stand for the possible initial state:  $\langle a_1, b_1, z_0 \rangle$ .

A state of a given PH consists in a set of active processes containing a single process of each sort. The active process of a given sort  $a \in \Sigma$  in a state  $s \in \mathcal{L}$  is noted  $s[a]$ . For any given process  $a_i$  we also note:  $a_i \in s$  if and only if  $s[a] = a_i$ .

The dynamic of the PH networks is performed thanks to the actions. Indeed, the transition from one state  $s_1$  to its successor  $s_2$  is done when there is a playable action (definition 4) at  $s_1$ . After each transition only one sort, or one component, changes its level from one process to another.

In some dynamics it is crucial to have information about the delays between two events (two states of a PH). Classic actions cannot exhibit this information: we just know chronology, i.e., that the state  $s_2$  will be after  $s_1$  in the next step but it is not possible to know chronometry, i.e., how much time this transition takes to occur. We propose to add the delay in the action attributes which is responsible of the transition between the two states. That means that this action needs to be played during a specific time so that the system does not change its state (Definition 2).

**Definition 2 (Timed action).** Let  $\mathcal{PH} = (\Sigma, \mathcal{L}, \mathcal{H})$  be a process hitting and  $\mathcal{L}^\circ$  be the set of all the sub-states of  $\mathcal{L}$ . A timed action of  $\mathcal{PH}$  is a action with a delay  $D$ :  $A \xrightarrow{D} b_i \uparrow b_j$  where  $D \in \mathbb{R}^+$ ,  $A \in \mathcal{L}^\circ$ , and  $b_i, b_j$  where  $b_i \neq b_j$  are two processes of the target sort  $b$ . If  $b_i \in A$ ,  $A = b_i$ .

To model biological networks, we used the PH framework with timed actions (Definition 3). Indeed, in the biological models that we studied we need to present not only the cooperation between the components to influence another one (action), but also the time that this action need to take place (delays).

**Definition 3 (Process Hitting with Timed Actions).** A Process Hitting with timed actions is a triple  $(\Sigma, \mathcal{L}, \mathcal{H}_{tp})$  where:

- $\Sigma = \{a, b, \dots\}$  is the finite set of sorts;
- $\mathcal{L} = \prod_{a \in \Sigma} \mathcal{L}_a$  is the set of states where  $\mathcal{L}_a = \{a_0, \dots, a_{l_a}\}$  is the finite set of processes of sort  $a \in \Sigma$  and  $l_a$  is a positive integer, with  $a \neq b \Rightarrow \mathcal{L}_a \cap \mathcal{L}_b = \emptyset$ ;
- $\mathcal{H}_{tp} = \{A \xrightarrow{D} b_j \uparrow b_k \mid A \in \mathcal{L}^\circ, b_j \neq b_k, b_i \in A \Rightarrow A = b_j\}$  is the finite set of timed actions.

Duration of actions can now be represented in a Process Hitting model thanks to timed actions. Note that if all actions delays are set to 1 it is equivalent to Process Hitting without delays (original PH). The way these new actions should be used is described as follows.

**Definition 4 (Playable timed action).** Let  $\mathcal{PH} = (\Sigma, \mathcal{L}, \mathcal{H}_{tp})$  be a PH with timed actions and  $s \in \mathcal{L}$  a state of PH. We say that the action  $h = A \xrightarrow{D} b_i \uparrow b_j$  is playable in state  $s$  if and only if  $A \subseteq s$  and  $b_i \in s$ .

Even if there already exists a few hybrid formalisms, we chose to propose this extension of the PH framework for several reasons. First, PH is a general framework that, although it was mainly used for biological networks, allows to represent any kind of dynamical models, and converters to several other representations are available. Although an efficient dynamical analysis already exists for this framework, based on an approximation of the dynamics, it is interesting

to identify its limits (especially the fact that previous studies were focusing only on discrete, not timed, dynamics) and compare them to the approach we present later in this paper. Finally, the particular form of the actions in a PH model allows to easily represent them in ASP, with one fact per action, as described in the next section. Other representations may have required supplementary complexity; for instance, a labeling would be required if actions could be triggered by a variable number of processes. We now show how to represent the previous definitions through ASP.

### 3 Revision of PH networks

#### 3.1 Algorithm

In this section we propose an algorithm to construct and/or revise Process Hitting models. We assume that new observation data are provided as a *chronogram* of size  $T$ : the value of each variable is given for each time step  $t$ ,  $0 \leq t \leq T$ , through a time interval discretization. This algorithm takes as input a Process Hitting and a chronogram of genes evolutions of this network. Knowing the genes' influences (or assuming all possible influences), this algorithm will complete the input network by adding the delayed actions that could have realized the changes observed in the chronogram. Algorithm 1 shows the pseudo code of our algorithm. If the observations are perfect, it will generate all possible actions that can realize each change observed. Because of the delayed semantics, it is not possible to decide whether an action is correct or not. But we can output the minimal sets of actions necessary to realize the changes observed. If the observations are not perfect, we can merge actions by replacing the one that only differs by the delay by one action whose delay is the average one. The intuition is that, in practice, if there are enough observations, the delay of those actions should tend to the real value.

**Theorem 1 (Completeness).** *Let  $PH$  be a Process Hitting,  $C$  be a chronogram of the genes of  $PH$  and  $A$  be the set of actions of  $PH$  that realized the chronogram  $C$ . Let  $PH'$  be a Process Hitting and  $A'$  be the set of actions of  $PH'$  such that  $A' \subseteq A$ . Given  $PH'$  and  $C$  as input, Algorithm 1 (without step 2) is complete: it will output a set of process hitting  $S$ , such that  $\exists PH'' \in S$  with  $A''$  the set of actions of  $PH''$  such that  $A'' = A' \cup A$ .*

*Proof.* Let us suppose that the algorithm is not complete, then there is an action  $a \in A$  that realized  $C$  and  $a \notin A''$ . After step 1.2,  $PH''$  contains all actions that can realized each gene change. Here there is no action  $a \in A$  that realized  $C$  which is not generated by the algorithm, so  $a \in A''$ . Then it implies that at step 3, the action  $a$  is removed from  $A''$ . But since  $a$  realized one the change of  $C$  and  $a$  is generated at step 1, then it will be present in one of the minimal subset of actions. And  $a$  will be in one of the network outputted by the algorithm.  $\square$

**Theorem 2 (Complexity).** *Let  $PH$  be a Process Hitting,  $S$  be the number of sorts of  $PH$  and  $P$  be the maximal number of processes of a sort of  $PH$ .*

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**Algorithm 1** PH-Completion( $PH, Chronogram, Influences, indegree$ )
 

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- INPUT: a Process Hitting  $PH$ , a chronogram  $C$  of the genes evolution of  $PH$ , the genes influences and a maximal action in-degree  $i$ .
- Let  $A := \emptyset$
- Step 1: For each time where a gene  $G$  changes its value from  $P$  to  $P'$  in  $C$ :
  - Let  $D$  be the delay since the last time a gene has changed.
  - Generate all actions with delay  $D$  which involve all subsets of size  $i$  of the genes  $S_1, \dots, S_n$  having an influence on  $G$ :

$$a := action(S_1, P_1, \dots, S_n, P_n, G, P, P', D)$$

- Add all action  $a$  in  $A$
  - Step 2 (optional): Merge each action with the same hitters,  $S_1, P_1, \dots, S_n, P_n$  and the same target,  $G, P, P'$ , into one action where the delay is the average.
  - Step 3: Generate  $S$  the set of all subsets of actions of  $A$  that realize  $C$  such that:
    - $A$  is minimal:
 
$$\forall A \in S, \nexists A' \in S, A' \subset A$$
    - Atmost one delay per action:  $\forall h \in A$ , where  $h = A \xrightarrow{D} b_j \uparrow b_k$ ,  $\nexists h' \in A$ , such that  $h' = A \xrightarrow{D'} b_j \uparrow b_k$ ,  $D \neq D'$ .
  - OUTPUT:  $S$  a set of completed Process Hittings that realize the chronogram.
-

Let  $C$  be a chronogram of the genes of  $PH$  over  $T$  units of time, such that  $c$  is the number of gene change of  $C$ . The memory use of our algorithm belongs to  $O(T \times P \times i^S \times 2^{T \times P \times i^S})$  that is bound by  $O(T \times P^{S+1} \times 2^{T \times P^{S+1}})$ . The complexity of completing  $PH$  by generating actions from the observations of  $C$  with Algorithm 1 belongs to  $O(c \times i^S + (T \times P \times i^S)^2 + 2^{2 \times T \times P \times i^S} + c \times 2^{T \times P \times i^S})$  that is bound by  $O(2^{3 \times T \times P^{S+1}})$ .

*Proof.* Let  $i$  be the maximal indegree of an action in  $PH$ ,  $0 \leq i \leq P$ . Let  $p$  be a process of  $PH$  and  $n$  be the number of sorts that can influence  $p$ . There is  $i^S$  possible combinations of those process that can hit  $p$ , each of those can form an action. There is  $P$  process and at most  $T$  possibles delay, so that there are  $T \times P \times i^S$  possibles actions, thus at step 1, the memory of our algorithm is bound by  $O(T \times P \times i^S)$ , which belongs to  $O(T \times P^{S+1})$  since  $0 \leq i \leq P$ . Generating all minimal subsets of actions  $A$  of  $PH'$  that realize  $C$  can require to generate at most  $2^{T \times P \times i^S}$  set of rules. Thus, the memory of our algorithm belongs to  $O(T \times P \times i^S \times 2^{T \times P \times i^S})$  and is bound by  $O(T \times P^{S+1} \times 2^{T \times P^{S+1}})$ .

Merging the actions at step 2 is polynomial in the number of actions and the complexity of this operation belongs to  $O((T \times P \times i^S)^2)$ . The complexity of this algorithm belongs to  $O(c \times i^S + (T \times P \times i^S)^2)$ . Since  $0 \leq i \leq P$  and  $0 \leq c \leq T$  the complexity of Algorithm 1 is bound by  $O(T \times P^S + (T \times P \times P^S)^2) = (T \times P^S + T^2 \times P^{2S+2})$ .

Generating all minimal subsets of actions  $A$  of  $PH'$  that realize  $C$  can require to generate at most  $2^{T \times P \times i^S}$  set of rules. Each set has to be compared with the others to keep only the minimal ones, which costs  $O(2^{2 \times T \times P \times i^S})$ . Furthermore, each set of actions has to realize each change of  $C$ , it requires to check  $c$  changes and it costs  $O(c \times 2^{T \times P \times i^S})$ . Finally, the total complexity of completing  $PH$  by generating actions from the observations of  $C$  belongs to  $O(c \times i^S + (T \times P \times i^S)^2 + 2^{2 \times T \times P \times i^S} + c \times 2^{T \times P \times i^S})$  that is bound by  $O(T \times P^S + (T \times P^{S+1})^2 + 2^{2 \times T \times P^{S+1}} + T \times 2^{T \times P^{S+1}})$   $\square$

## 4 Algorithm simulation

In this section we demonstrate how our methode permits to generate a  $PH$  model coherent to the set of biological regulatory time series data given as an input.

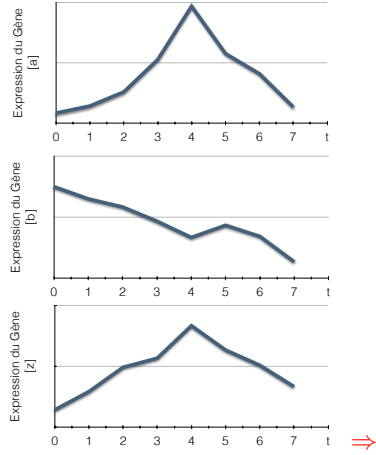
First, the method uses discretised observations as an input, thus it is necessary to use an other method which transforms the analogic time series data to discretised time series data.

## 5 Conclusion and perspectives

In this paper, we proposed an approach to automatically infer timed models of Process Hitting from time series data (expressed as chronograms). To do so, we implemented our algorithm in ASP. We illustrated the applicability and limits of the method through various benchmarks. This opens the way to promising

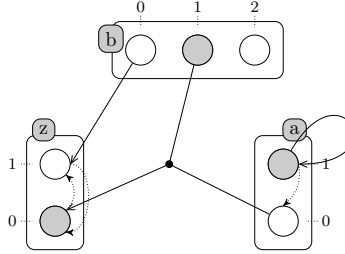


Observations:



Process

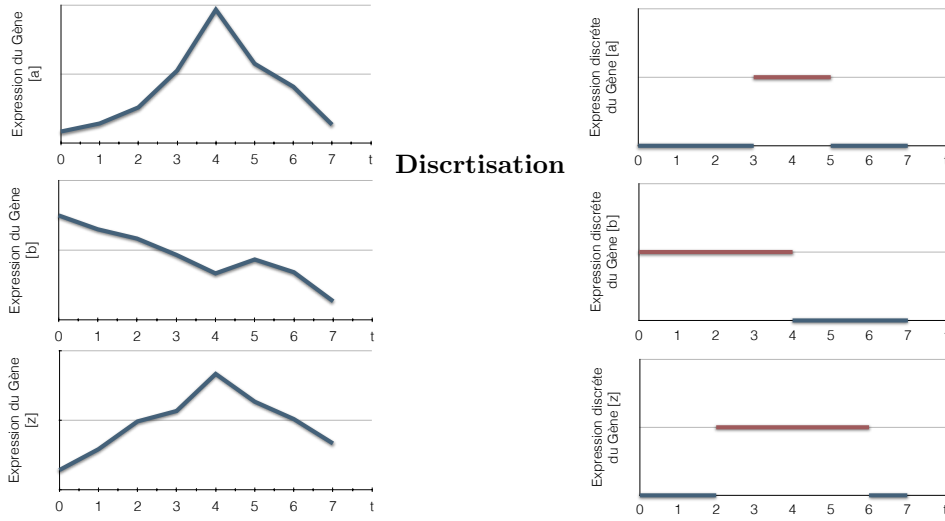
Hitting:



applications in the connection between biologists and computer scientists. Further works will now consist in discussing the kind of information one can get on timed Process Hitting by analyzing the associated untimed model. We also plan to improve our implementation to make it robust against noisy data.

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