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Abstract

Model refinement is an important step in the model implementation cycle that deals with adding details to an existing model. Several ways of implementing model refinement have been discussed in the literature, for rule-based models and for ODE models. We focus here on implementing model refinement in the framework of Petri nets, using the programming capabilities of colored Petri nets. We exemplify our strategy on a reaction-based model of the eukaryotic heat shock response. We conclude with an analysis of the initial and refined models, a proof that the two colored Petri net models we have built are bisimilar, and a discussion on how modeling biological systems with colored Petri nets scales with further expansions of the model.

Keywords: Quantitative model refinement, colored Petri nets, bisimilar, heat shock response.

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1 Introduction

One of the steps often required in modeling is model refinement, i.e. increasing the level of detail of a model to include more information. This process can be implemented either starting a new model from scratch, and doing all the model fitting steps, or start from an existing fitted model to which details are added in such a way that the model fit is preserved. The latter method is called *data refinement* and has been introduced in [3, 14] for rule-based models, and discussed in [6, 4] in the context of ODE models.

Throughout this paper we consider *reaction-based models* consisting of a list of reactions of the type $c_1A_1 + c_2A_2 + ... + c_nA_n \rightarrow c'_1B_1 + c'_2B_2 + ... + c'_mB_m$, with $m, n \geq 0$, where A_i, B_j are molecular species representing the reactants (substrate) and products of the reaction, respectively, and c_i, c'_j are the stoichiometric coefficients (multiplicities), with $1 \leq i \leq n, 1 \leq j \leq m$. The mathematical semantic for such a model can be defined both in terms of continuous mathematics or in terms of discrete mathematics.

A reaction-based model can be refined to incorporate more information regarding its reactants, a process called *data refinement*. In this paper we consider the implementation of data refinement as presented in [5]. The species of a model are considered to be either *atomic* or *complex*, where a complex species contains in its structure at least two (possibly identical) atomic species. Refinement can be done on atomic species only, and it implies replacing the species with several of its variants. The change propagates throughout the model to all complex species that contain the atomic species being refined. Depending on the composition of complex species, one small refinement of an atomic species can induce an explosion in the number of species in the refined model, and consequently in the number of reactions. For details on the size of this explosion, see [5].

We focus in this paper on a Petri net approach of refinement, with the goal of obtaining a compact representation of the refinement of a model. To this end, we use colored Petri nets, a variant of high-level Petri nets that are "programmable" by means of data types (color sets), variables and functions.

As proof of concept, we implement the refinement of a model of the eukaryotic heat shock response. We construct a Petri net model that we subsequently refine to include more biological details. The refinement of the model is compact; the structure of the Petri net (in terms of places, transitions and arcs connecting them) remains the same. All details that are added to the network are encoded by means of colors. Our focus is on the ability of the [colored] Petri net framework to scale up with model refinements.

The paper is organized as follows: we start with a short overview of the Petri net formalism and its use in modeling biological systems, in Section 2. We continue with the biological semantics of the eukaryotic heat shock re-

sponse, our case study, in Section 3. We also present here the molecular model for the heat shock response mechanism proposed in [15], and its refinement that accounts for the acetylation of one of the species, as introduced in [6]. In Section 4 we present our Petri net model for the heat shock response, and in Section 5 our modeling of its refinement as a colored Petri net. We prove that the two networks are bisimilar in Section 6, and draw some conclusions in Section 7.

2 Preliminaries on modeling with Petri nets

2.1 The Petri net formalism

Petri nets are a sound formalism for representing systems with concurrency and resource sharing. They can also be viewed as a simple, graphical modeling language represented as bipartite graphs. The language was defined by Carl Adam Petri with the purpose of describing chemical processes in [16]. Many extensions of Petri nets have been developed, with colored Petri nets being of particular interest for this paper. We consider the reader is familiar with the concepts of Petri nets and colored Petri nets; for details, we refer to [18, 19, 8].

Petri nets are represented as directed bipartite graphs, with four main components: places, transitions, arcs and tokens. *Places* are represented as circles, and they stand for the "states" of the system. *Transitions* are depicted as rectangles, and they stand for the transition of the system from one state to another. A transition has several pre-places and several post-places that are connected to it by arcs. *Arcs* represent the connection between places and transitions, and have an associated multiplicity, denoting how many elements of the preceding (following) place are consumed (produced). *Tokens* represent the quantities of species denoted by places (be it the number of particles or the concentration of a species).

Definition 1. *[13] A Petri net is a tuple* $N = (P, T, F, f, M_0)$ *where* P *is the finite set of places,* T *is the finite set of transitions,* $F \subseteq P \times T \cup T \times P$ *is the set of arcs,* $f : F \to \mathbb{N}$ *is the arc function assigning multiplicities to each arc, and* $M_0 : P \to \mathbb{N}$ *is the function assigning an initial marking of the network.*

Labeled Petri nets are Petri nets with a labeling of their transitions: $N = (P, T, F, f, L)$ where $L : T \to A$ assigns labels from the set A to each transition in T.

The colored counterpart of Petri nets has additional elements. *Color sets* are associated to places, and they represent data types by means of *colors*. *Variables* can be used to form complex *arc expressions* (the counterpart of

simple arc multiplicities), *functions*, and *guards* (conditions associated to transitions, that restrict the fireability of transitions to particular subsets of the colored tokens flowing from pre-places to transitions). Each place p contains a multiset of colored tokens with colors from the color set of p.

We use the following notations from [9, 12]: S_{MS} denotes the set of all multisets over a set S; $EXPR_S$ denotes the set of expressions over a set of typed variables S; the type of the values obtained when evaluating an expression $e \in EXPR_S$ is the type of the expression; b is a binding that maps each variable onto a value $b(v)$ which is of the same type as the variable; $t(b)$ is a transition instance with transition $t \in T$ and binding b; $p(c)$ is a place instance with $p \in P$ and $c \in C$; $I_P(p)$ ($I_T(t)$, resp.) denotes the place (transition, resp.) instances of a place $p \in P$ (transition $t \in T$, resp.); I_P (I_T, resp.) denotes the set of all instances of all places $p \in P$ (transitions $t \in T$, resp.); $f(x,y)\langle b \rangle\rangle\langle c \rangle$ denotes the number of tokens with color c that are present when evaluating arc expression $f(x,y)$ in binding b and $M(p)\langle c \rangle$ denotes the number of tokens with color c that are present in place p in marking M.

Definition 2. *[10] A colored Petri net is a tuple* $N = (P, T, F, \Sigma, V, C, G, f, M_0)$ *where* P *is the finite set of places,* T *is the finite set of transitions,* $F \subseteq P \times T \cup T \times P$ *is the set of arcs,* Σ *is the set of color sets,* V *is the set of typed variables with types from* Σ*,* $C : P \to \Sigma$ *is the color function assigning a color set to each place,* G *is the guard function,* $f : F \to EXPR_V$ *is the arc function assigning expressions over* V *to each arc such that the type of the arc expression is* $C(p)_{MS}$ *where* $p \in P$ *is the place connected to the arc, and* $M_0 : P \to EXPR_\emptyset$ *is the function assigning an initialization expression with type* $C(p)_{MS}$ *to each place* $p \in P$*.*

Each colored Petri net can be *unfolded* to a behaviorally equivalent standard Petri net representation ([9, 12]). We denote by $N^* = (P^*, T^*, F^*, f^*, M_0^*)$ the Petri net obtained by unfolding a colored Petri net $N = (P, T, F, \Sigma, V, C, G, f, M_0)$.

Definition 3. *[12] Given a colored Petri net* $N = (P, T, F, \Sigma, V, C, G, f, M_0)$*, its unfolded Petri net is denoted by* $N^* = (P^*, T^*, F^*, f^*, M_0^*)$*, where:* $P^* = I_P$*;* $T^* = I_T$*;* $F^* = \{(p(c), t(b)) \in P^* \times T^* \mid (f(p,t)\langle b \rangle\rangle\langle c \rangle > 0\} \cup \{(t(b), p(c)) \in T^* \times P^* \mid (f(t,p)\langle b \rangle\rangle\langle c \rangle > 0\}$*;* $f^*(p(c), t(b)) = (f(p,t)\langle b \rangle\rangle\langle c \rangle, \forall (p(c), t(b)) \in F^*$ *and* $f^*(t(b), p(c)) = f(t,p)\langle b \rangle\rangle\langle c \rangle, \forall (t(b), p(c) \in F^*$*;* $M_0^*(p(c)) = M_0(p)\langle c \rangle$*.*

2.2 Petri nets in biomodeling

One of the many applications of Petri nets is modeling biological systems. Such systems are bipartite, i.e. they consist of species and the interactions between them. Some of the interactions are independent, and could fire in

parallel, thus biological systems exhibit concurrent behavior. These characteristics make them suitable for modeling within the Petri nets formalism, as first proposed in [17]. Extensions of Petri nets allow modeling and simulation of both stochastic and continuous systems, integrating quantitative and qualitative analysis techniques, see [2].

The species in a biological reaction-based model can be represented as places in the Petri nets framework, and each reaction can be represented as a transition that has all substrates as pre-places, and all products as post-places, with the arc multiplicities given by the corresponding stoichiometric coefficients. For more details about modeling biological systems in the Petri net framework see [11].

The software we used to model our case study within the colored Petri nets framework is Snoopy [20]. We used the related tool Charlie to validate our implementations against some basic properties of the models.

3 Case study: the heat shock response

In this section, we briefly describe the regulatory mechanism of heat shock response and present a biochemical reactions model of this process, as proposed in [15]. We discuss the behavior of the system and the role of acetylation of one of the main actors driving the response.

3.1 A molecular model for the heat shock response

The heat shock response (HSR) is a highly conserved regulatory mechanism among eukaryotes, crucial for the survival of cells under stress conditions. At high temperatures proteins misfold and tend to form large aggregates, with destructive effects on the cell, leading to apoptosis. To counter this, cells produce heat shock proteins (hsp's), whose role is to assist misfolded proteins in their correct refolding.

During the response, heat shock factor (hsf) monomers in inactive state are transported to the nucleus of the cell, where they form trimers, hsf_3, and bind onto the promoter of the DNA heat shock genes (hse), expressing heat shock proteins (hsp). When the number of hsp's is sufficient, they will negatively regulate the reaction, binding to hsf active trimers and causing them to detach from DNA and dissociate into inactive monomers.

We consider the molecular model of the HSR proposed in [15]. The atomic species considered in the system are $\mathsf{hsf}, \mathsf{hse}, \mathsf{hsp}, \mathsf{prot}$, and mfp. The complex species and their composition are the following: $\mathsf{hsf}_2 = \{\mathsf{hsf}, \mathsf{hsf}\}$, $\mathsf{hsf}_3 = \{\mathsf{hsf}, \mathsf{hsf}, \mathsf{hsf}\}$, $\mathsf{hsf}_3\colon \mathsf{hse} = \{\mathsf{hsf}, \mathsf{hsf}, \mathsf{hsf}, \mathsf{hse}\}$, $\mathsf{hsp}\colon \mathsf{hsf} = \{\mathsf{hsf}, \mathsf{hsp}\}$, $\mathsf{hsp}\colon \mathsf{mfp} = \{\mathsf{hsp}, \mathsf{mfp}\}$.

The molecular model describing the heat shock response consists of 17

irreversible reactions, listed in Table 1. They cover the trimerization of heat shock factors in two steps, hsf_3 binding to heat shock elements, transcription of DNA and translation of hereby synthesized RNA into heat shock proteins. The negative regulation of the response is modeled with reactions 5-8, and degradation of hsp's is modeled with reaction 9. Protein misfolding and chaperon activity of hsp's are modeled through reactions 10-12.

3.2 A refinement of the HSR model

Acetylation of hsf's has a great influence on the heat shock response. A refinement of the model in [15] that considers hsf molecules as either acetylated or non-acetylated has been proposed in [6]. We consider the same refinement of the hsf molecules, but implement it differently, as we take into account the order of molecules in a compound.

More specifically, the atomic species hsf is replaced in the refined model with two of its variants: $\mathsf{hsf}^{(0)}$, a non-acetylated hsf molecule, and $\mathsf{hsf}^{(1)}$, an acetylated hsf molecule. The implicit assumption in [15] is that the order of the molecules in a compound does not matter, what matters is only the number of acetylated sites. We make instead the assumption that the order of molecules matters, a valid assumption since proteins have multiple binding sites and this could introduce ordering. Thus a dimer $\mathsf{hsf}^{(0)}\!:\!\mathsf{hsf}^{(1)}$ is different from $\mathsf{hsf}^{(1)}\!:\!\mathsf{hsf}^{(0)}$, although both dimers have one acetylated site. This small refinement induces an explosion of the model. Our refined model is fully listed in Table 2.

As opposed to the approach in [4], we consider that the number of acetylated sites is conserved by the reactions. For example, a reaction $\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)}$ will not appear in our refined model sincs it violates the conservation of acetylated sites constraint. One could think of this as a particular case of [4] where the reactions not present in the model have kinetic constant 0.

4 A Petri net model for the basic HSR model

We modeled the heat shock response model presented in [15] as a Petri net, following the standard methodology for modeling metabolic systems as Petri nets see [17]. The resulting network can be seen in Figure 2, and its Snoopy implementation is available at [1]. Throughout the paper we denote this network by $H_{bas} = (P, T, F, f_1, M_{0,1})$ for some initial marking $M_{0,1}$.

In order to validate our model, we simulated it with the numerical setup of [15] and checked that the continuous evolution of species concentrations is identical with the one reported in [15], data omitted here due to lack of space. We also checked that the P-invariants of H_{bas} correctly encode the

three mass conservation relations of the HSR model, see [15].

5 Colored Petri nets hide the combinatorial state space explosion for the refined HSR model

In this section we present our colored Petri net model of the refinement of the HSR model, and our modeling choices. One option of modeling the refinement of the HSR model in Table 2 is to use a standard Petri net. But this network will have a transition for each reaction, thus 77 transtions and 29 places, an explosion we avoid through the use of colors.

There are multiple ways of choosing color sets in a colored Petri net model of a biological system. Depending on the choice, additional transitions, guards or complicated functions may have to be introduced in the network, see [5]. For example, hsf dimers could be modeled as a place with an int color set with values {0,1,2} denoting the number of acetylated sites. They could also be modeled with an int color set with values {0,1,2,3} to account for the order of the acetylated sites. The same could be done with a compound color set $\{0,1\} \times \{0,1\}$.

We chose to model the hsf molecules as a place with a color set Monomer with values {0,1} denoting whether the molecule is acetylated (1) or not (0). hsf dimers are modeled as a Cartesian product of two hsf's, and hsf trimers are modeled as a Cartesian product of three hsf's. All complex species subject to refinement are modeled as Cartesian products of their atomic components. The atomic and complex species that are not refined have the default color set offered by Snoopy, Dot with a single color dot. This representation is very compact, and leaves the structure of the network unchanged when going from a standard Petri net representation to a colored Petri net representation.

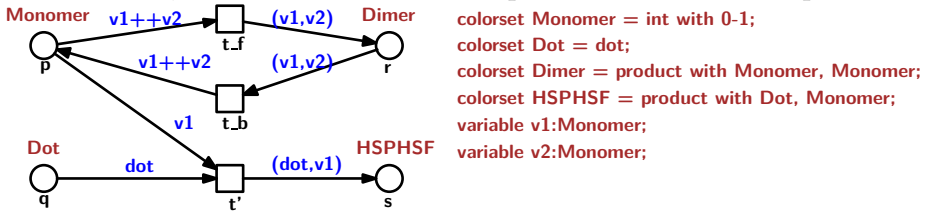
Our colored Petri net representation of the refined model is presented in Figure 3, and its Snoopy implementation is available at [1]. The structure of the network (places, transitions and the arcs connecting them) is the same as the one in the basic model. For this reason we will use the same sets of places, transitions and arcs in the definition of the refined network. The context will make it clear whether we are talking about the basic network or the refined one. We denote by $H_{ref} = (P, T, F, \Sigma, V, C, G, f_2, M_{0,2})$ our colored Petri net for the refined HSR model. The initial marking $M_{0,2}$ is defined so that Equation (1) holds for all $p \in P$.

$$\sum_{c \in C(p)} M_{0,2}(p)\langle c \rangle = M_{0,1}(p). \tag{1}$$

The entire complexity is encapsulated in the color sets of the places and

the arc expressions. To explain the choice of arc expressions, we first give the example of three reactions, and then give a general rule. We consider reactions $\mathsf{hsp} + \mathsf{hsf} \rightarrow \mathsf{hsp{:}\,hsf}$ and $2\,\mathsf{hsf} \rightleftarrows \mathsf{hsf}_2$. Their representation as a colored Petri net is shown in Figure 1. Places $\mathsf{p}, \mathsf{q}, \mathsf{r}, \mathsf{s}$ denote $\mathsf{hsf}, \mathsf{hsp}, \mathsf{hsf}_2$ and $\mathsf{hsp{:}\,hsf}$, respectively.

Figure 1: Example of a colored Petri net. The brown text on top of places represents the color set. The black text below places and transitions represents their name, and the blue text on top of arcs is the arc expression.



Reaction $\mathsf{hsp} + \mathsf{hsf} \rightarrow \mathsf{hsp{:}\,hsf}$ is refined into two reactions, see Table 2. The arc expression of arc $(\mathsf{q}, \mathsf{t}')$ is dot, meaning a token with color dot is consumed by reaction t'. Arc $(\mathsf{p}, \mathsf{t}')$ has arc expression $\mathsf{v1}$, a variable of type $\mathsf{Monomer}$. The variable can be bound to either value 0 or value 1. In the transition instance where $\mathsf{v1} = 0$, the product of transition t' is $(\mathsf{dot}, 0)$; thus this transition instance models the reaction $\mathsf{hsp} + \mathsf{hsf}^{(0)} \rightarrow \mathsf{hsp{:}\,hsf}^{(0)}$. Similarly, the transition instance where $\mathsf{v1}$ is bound to value 1 models reaction $\mathsf{hsp} + \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsp{:}\,hsf}^{(1)}$.

Reaction $2\,\mathsf{hsf} \rightleftarrows \mathsf{hsf}_2$ is refined into four reversible reactions, accounting for all possible combinations of acetylated and non-acetylated hsf's, see Table 2. The forward direction of the reaction is modeled by transition $\mathsf{t\_f}$, and the reverse direction is modeled by transition $\mathsf{t\_b}$ in Figure 1. Variables $\mathsf{v1}, \mathsf{v2}$ can be bound independently to values 0 or 1. The expression $\mathsf{v1} + +\mathsf{v2}$ denotes a multiset with variables $\mathsf{v1}$ and $\mathsf{v2}$. The arc expression $(\mathsf{v1}, \mathsf{v2})$ denotes a tuple of type Dimer, with the particular values of its components given by the values of variables $\mathsf{v1}$ and $\mathsf{v2}$. It is crucial for the components of a compound type to be explicitly referred in arc expressions, in order to satisfy the conservation of acetylated sites constraint and the ordering of molecules. Another crucial aspect to this end is that the arc expressions of arcs connecting a transition with its post-places use the variables of the arc expressions connecting the pre-places with the transition. Thus, the transition instance of $\mathsf{t\_f}$ with $\mathsf{v1} = 0$ and $\mathsf{v2} = 1$ uniquely represents reaction $\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsf}^{(0)}\mathsf{:}\,\mathsf{hsf}^{(1)}$ because the compound it produces, $(\mathsf{v1}, \mathsf{v2})$, is bound to $(0, 1)$. Similarly, the instance of $\mathsf{t\_b}$ where $\mathsf{v1}, \mathsf{v2}$ are bound to 1 and 0 respectively uniquely represents reaction $\mathsf{hsf}^{(1)}\mathsf{:}\,\mathsf{hsf}^{(0)} \rightarrow \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)}$ because it produces one $\mathsf{v1}$ and one $\mathsf{v2}$. The bindings of the variables $\mathsf{v1}, \mathsf{v2}$ to values $\{(0,0), (0,1), (1,0), (1,1)\}$ give all the variants that reaction $2\,\mathsf{hsf} \rightleftarrows \mathsf{hsf}_2$ is refined to.

As a general rule, the arc expression of an arc $a \in F$ connected to a place p that represents a species that is subject to refinement (hsf or a complex species containing hsf) uses variables. If p represents hsf, then the arc expression uses as many variables with type $C(p)$ as the multiplicity of arc a in H_{bas}: $f_2(a) = v_1 + + \ldots + + v_n$, where $v_i \in V$ with $\mathsf{type}(v_i) = C(p)$ and $n = f_1(a)$. If p denotes a complex species S, then the arc expression uses $f_1(a)$ ordered tuples of variables of types $C(q)$, where q is the place denoting hsf and values for places denoting atomic species that are contained in complex species S, e.g. $(\mathsf{dot}, \mathsf{v1})$ for $\mathsf{hsp}\colon \mathsf{hsf}$ or $(\mathsf{v1}, \mathsf{v2}, \mathsf{v3}, \mathsf{dot})$ for $\mathsf{hsf_3}\colon \mathsf{hse}$. With this construction of H_{ref} as a refinement of H_{bas}, the arc expressions obey the rule $\mid f_2(a) \mid = f_1(a)$ for all arcs $a \in F$, where $\mid f_2(a) \mid$ denotes the cardinality of arc expression $f_2(a)$.

We denote by $H_{unf} = (P^*, T^*, F^*, f_2^*, M_{0,2}^*)$ the standard Petri net obtained by unfolding H_{ref}. H_{unf} contains 29 places and 77 transitions (one for each reaction in Table 2), as opposed to 10 places and 17 transitions for the colored model. By definition of f_2^* as the equivalent of f_2 in the unfolded network, we have that $\sum_{\substack{q \in I_P(p) \\ q \in {}^\bullet t^*}} f_2^*(q, t^*) = \mid f_2(p, t) \mid, \ \forall t \in T, \ \forall p \in {}^\bullet t, \ \forall t^* \in I_T(t)$, thus

$$\sum_{\substack{q \in I_P(p) \\ q \in {}^\bullet t^*}} f_2^*(q, t^*) = f_1(p, t), \ \forall t \in T, \ \forall p \in {}^\bullet t, \ \forall t^* \in I_T(t) \tag{2}$$

6 Bisimilarity of the two Petri net models

Several equivalence criteria have been proposed for Petri nets, e.g. *bisimilarity, language (trace) equivalence*, and *reachability set equality*. In our case we cannot consider reachability set equality, since H_{unf} has a different number of places than H_{bas}. Instead, we will prove that the two are bisimilar. First, we recall the concept of bisimilarity in the context of standard labeled Petri nets, and then we extend the definition to bisimilarity between a labeled standard Petri net and a labeled colored Petri net. Finally, we prove the bisimilarity between our two Petri net models.

Definition 4. *[7] Given two labeled Petri nets* $N_1 = (P_1, T_1, F_1, f_1, M_{0,1}, L_1)$ *and* $N_2 = (P_2, T_2, F_2, f_2, M_{0,2}, L_2)$ *with* $L_1 : T_1 \to A$ *and* $L_2 : T_2 \to A$*, a binary relation* $R \subseteq \mathbb{N}^{P_1} \times \mathbb{N}^{P_2}$ *is a* bisimulation *if for all tuples* $(M_1, M_2) \in R$ *and for each label* $a \in A$*:*

1. *if* $M_1 \xrightarrow{a}_{N_1} M_1'$ *for some* M_1'*, then there is some* M_2' *such that* $M_2 \xrightarrow{a}_{N_2} M_2'$ *and* $(M_1', M_2') \in R$*;*
2. *if* $M_2 \xrightarrow{a}_{N_2} M_2'$ *for some* M_2'*, then there is some* M_1' *such that* $M_1 \xrightarrow{a}_{N_1} M_1'$ *and* $(M_1', M_2') \in R$*.*

Two labeled Petri nets N_1, N_2 are bisimilar *if there is a bisimulation relation R such that $(M_{0,1}, M_{0,2}) \in R$.*

We now introduce a labeling of the unfolded equivalent of a colored Petri net based on its original labeling.

Definition 5. *Consider a colored Petri net $N = (P, T, F, \Sigma, C, G, f, M_0)$ and its equivalent unfolded standard Petri net $N^* = (P^*, T^*, F^*, M_0^*)$. For any labeling $L : T \to A$ of N we define the* equivalent labeling of N^* *as the labeling $L^* : T^* \to A$ such that for all transitions $t \in T$ if $L(t) = a$, then all transitions $t' \in T^*$ such that $t' \in I_T(t)$ have the same label, $L^*(t') = a$.*

We next introduce a definition of bisimilarity between a standard and a colored Petri net.

Definition 6. *Given a labeled Petri net $N_1 = (P_1, T_1, F_1, f_1, M_{0,1}, L_1)$ and a labeled colored Petri net $N_2 = (P_2, T_2, F_2, \Sigma, C, G, f, M_{0,2}, L_2)$ with its corresponding unfolded Petri net with equivalent labelling, $N_2^* = (P_2^*, T_2^*, F_2^*, f_2^*, M_{0,2}^*, L_2^*)$ we say that N_1 and N_2 are* bisimilar *if there is a bisimulation relation $R \subseteq \mathbb{N}^{P_1} \times \mathbb{N}^{P_2^*}$ such that $(M_{0,1}, M_{0,2}^*) \in R$.*

We next prove that H_{bas} and H_{ref} are bisimilar. To this end, we label the two networks. Each transition in Figures 2 and 3 has a name written next to it, and moreover the transitions modeling the same reaction have the same name in the two models. We consider as labeling function of the two networks the function L that assigns to each transition its name as a label.

Theorem 1. *The Petri net H_{bas} developed for the basic HSR model with labeling L and the colored Petri net H_{ref} modeling the refined HSR with the same labeling L are bisimilar.*

Proof. The proof will use H_{unf}, the unfolded equivalent network of H_{ref}.

We define relation $R \subseteq \mathbb{N}^P \times \mathbb{N}^{P^*}$ such that:

$$(M_1, M_2) \in R \text{ iff } M_1(p) = \sum_{q \in I_P(p)} M_2(q), \ \forall p \in P, \tag{3}$$

where M_1 is a marking of H_{bas} and M_2 is a marking of H_{unf}.

We prove now that the first condition for R being a bisimulation relation holds: *for every $(M_1, M_2) \in R$ if $M_1 \xrightarrow{a}_{H_{bas}} M_1'$ for some M_1', then there exists some M_2' such that $M_2 \xrightarrow{a}_{H_{unf}} M_2'$ and $(M_1', M_2') \in R$;*

Let t_a denote the transition with label a in H_{bas} (by our labeling L, there is only one such transition). The pre-places $p \in {}^\bullet t_a$ of transition t_a in H_{ref} have $\sum_{q \in I_P(p)} M_2(q)$ elements, or by Equation (3) exactly $M_1(p)$ colored tokens. Since t_a is enabled by M_1 in H_{bas}, it is also enabled in H_{ref} because its pre-places are sufficiently marked and the color of tokens is not important

(as we consider all possible combinations of choosing colored tokens to enable a transition in H_{ref}, see Section 5). Let $t_a^* \in I_t(t_a)$ denote a transition that is enabled in H_{unf} by marking M_2.

M_1' and M_2' are computed as the standard update of a marking after firing a transition, as detailed in Equations (4), (5).

$$M_1'(p) = \begin{cases} M_1(p) - f_1(p,t_a) + f_1(t_a,p) & \text{if } p \in {}^\bullet t_a \cap t_a^\bullet \\ M_1(p) - f_1(p,t_a) & \text{if } p \in {}^\bullet t_a \setminus t_a^\bullet \\ M_1(p) + f_1(t_a,p) & \text{if } p \in t_a^\bullet \setminus {}^\bullet t_a \\ M_1(p) & \textit{otherwise} \end{cases} \tag{4}$$

$$M_2'(q) = \begin{cases} M_2(q) - f_2^*(q,t_a^*) + f_2^*(t_a^*,q) & \text{if } q \in {}^\bullet t_a^* \cap t_a^{*\bullet} \\ M_2(q) - f_2^*(q,t_a^*) & \text{if } q \in {}^\bullet t_a^* \setminus t_a^{*\bullet} \\ M_2(q) + f_2^*(t_a^*,q) & \text{if } q \in t_a^{*\bullet} \setminus {}^\bullet t_a^* \\ M_2(q) & \textit{otherwise} \end{cases} \tag{5}$$

Whenever a place $p \in P$ is a pre-(post-)place of t_a, some of its place instances are pre-(post-)places of the transition instance t_a^*. We sum over all place instances corresponding to places in P:

$$\sum_{q \in I_P(p)} M_2'(q) = \begin{cases} \sum\limits_{q \in I_P(p)} M_2(q) - \sum\limits_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} f_2^*(q,t_a^*) + \sum\limits_{\substack{q \in I_P(p) \\ q \in t_a^{*\bullet}}} f_2^*(t_a^*,q) & \text{if } p \in {}^\bullet t_a \cap t_a^\bullet \\ \sum\limits_{q \in I_P(p)} M_2(q) - \sum\limits_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} f_2^*(q,t_a^*) & \text{if } p \in {}^\bullet t_a \setminus t_a^\bullet \\ \sum\limits_{q \in I_P(p)} M_2(q) + \sum\limits_{\substack{q \in I_P(p) \\ q \in t_a^{*\bullet}}} f_2^*(t_a^*,q) & \text{if } p \in t_a^\bullet \setminus {}^\bullet t_a \\ \sum\limits_{q \in I_P(p)} M_2(q) & \textit{otherwise} \end{cases} \tag{6}$$

We next replace the partial sums in Equation (6) with their counterparts in Equations (2) and (3):

$$\sum_{q \in I_P(p)} M_2'(q) = \begin{cases} M_1(p) - f_1(p,t_a) + f_1(t_a,p) & \text{if } p \in {}^\bullet t_a \cap t_a^\bullet \\ M_1(p) - f_1(p,t_a) & \text{if } p \in {}^\bullet t_a \setminus t_a^\bullet \\ M_1(p) + f_1(t_a,p) & \text{if } p \in t_a^\bullet \setminus {}^\bullet t_a \\ M_1(p) & \textit{otherwise} \end{cases} \tag{7}$$

The right hand side of Equations (4) and (7) is identical, so by definition of relation R (Equation (3)) we conclude $(M_1', M_2') \in R$.

We prove now that the second condition for R being a bisimulation relation holds: *for every* $(M_1, M_1) \in R$, *if* $M_2 \xrightarrow{a}_{H_{unf}} M_2'$ *for some* M_2', *then there exists some* M_1' *such that* $M_1 \xrightarrow{a}_{H_{bas}} M_1'$ *and* $(M_1', M_2') \in R$.

By definition of R, $(M_1, M_2) \in R$ implies that whenever a transition t_a^* with label a is enabled by marking M_2 in H_{unf}, the transition t_a with

the same label a in H_{bas} is enabled, as its pre-places are sufficiently marked according to Equation (2). This is shown in (8).

$$M_1(p) = \sum_{q \in I_P(p)} M_2(q), \forall p \in P \Rightarrow M_1(p) \geq \sum_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} M_2(q), \forall p \in {}^\bullet t_a. \tag{8}$$

Equations (5) and (4) show how the markings of places change in the two networks when firing transitions t_a^* and t_a, respectively:

We substitute M_1 for its representation in relation to M_2, as given by Equation (3), in Equation (4):

$$M_1'(p) = \begin{cases} \sum_{q \in I_P(p)} M_2(q) - f_1(p, t_a) + f_1(t_a, p) & \text{if } p \in {}^\bullet t_a \cap t_a^\bullet \\ \sum_{q \in I_P(p)} M_2(q) - f_1(p, t_a) & \text{if } p \in {}^\bullet t_a \setminus t_a^\bullet \\ \sum_{q \in I_P(p)} M_2(q) + f_1(t_a, p) & \text{if } p \in t_a^\bullet \setminus {}^\bullet t_a \\ \sum_{q \in I_P(p)} M_2(q) & \textit{otherwise} \end{cases} \tag{9}$$

We next substitute Equation (2), where we consider t_a^* as the transition instance for the summation, in Equation (9):

$$M_1'(p) = \begin{cases} \sum\limits_{q \in I_P(p)} M_2(q) - \sum\limits_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} f_2^*(q, t_a^*) + \sum\limits_{\substack{q \in I_P(p) \\ q \in t_a^{*\bullet}}} f_2^*(t_a^*, q) & \text{if } p \in {}^\bullet t_a \cap t_a^\bullet \\ \sum\limits_{q \in I_P(p)} M_2(q) - \sum\limits_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} f_2^*(q, t_a^*) & \text{if } p \in {}^\bullet t_a \setminus t_a^\bullet \\ \sum\limits_{q \in I_P(p)} M_2(q) + \sum\limits_{\substack{q \in I_P(p) \\ q \in t_a^{*\bullet}}} f_2^*(t_a^*, q) & \text{if } p \in t_a^\bullet \setminus {}^\bullet t_a \\ \sum\limits_{q \in I_P(p)} M_2(q) & \textit{otherwise} \end{cases} \tag{10}$$

A place p is connected to t_a iff at least one of its instances is connected to t_a^*. We sum the markings M_1' in Equation (5) over all instances of places $p \in P$:

$$\sum_{q \in I_P(p)} M_2'(q) = \begin{cases} \sum\limits_{q \in I_P(p)} M_2(q) - \sum\limits_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} f_2^*(q, t_a^*) + \sum\limits_{\substack{q \in I_P(p) \\ q \in t_a^{*\bullet}}} f_2^*(t_a^*, q) & \text{if } p \in {}^\bullet t_a \cap t_a^\bullet \\ \sum\limits_{q \in I_P(p)} M_2(q) - \sum\limits_{\substack{q \in I_P(p) \\ q \in {}^\bullet t_a^*}} f_2^*(q, t_a^*) & \text{if } p \in {}^\bullet t_a \setminus t_a^\bullet \\ \sum\limits_{q \in I_P(p)} M_2(q) + \sum\limits_{\substack{q \in I_P(p) \\ q \in t_a^{*\bullet}}} f_2^*(t_a^*, q) & \text{if } p \in t_a^\bullet \setminus {}^\bullet t_a \\ \sum\limits_{q \in I_P(p)} M_2(q) & \textit{otherwise} \end{cases} \tag{11}$$

The right hand side of equations (10) and (11) is identical, so we can conclude that $(M_1', M_2') \in R$.

Relation R satisfies both conditions for being a bisimulation relation. By Equation (1) we have that $(M_{0,1}, M_{0,2}) \in R$. In conclusion, H_{bas} and H_{ref} are bisimilar.

□

7 Conclusions

We have developed two models for the heat shock response, using Petri nets and their colored extension as modeling frameworks. The first model contains 10 places and 17 transitions, corresponding to 10 species and 17 reactions, as in [15]. The second model contains the same number of places and transitions, but these stand for 29 species and 77 reactions modeling the refinement of the heat shock response that accounts for the acetylation of one of the main actors of the response. The complexity is hidden in the colors that each token in a place may have, but the representation is very compact (an important aspect when modeling large systems).

We introduced a notion of bisimilarity between a standard and a colored Petri net, and we proved that the two networks we have built are bisimilar. The construction of H_{ref} was done in a systematic way that makes it possible to generalize the method, and this is in the scope of a future paper.

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A The basic HSR molecular model

Table 1: The molecular model for the eukaryotic heat shock response proposed in [15].

1.	$2\,\mathsf{hsf} \rightleftarrows \mathsf{hsf}_2$	7.	$\mathsf{hsp} + \mathsf{hsf}_3 \to \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf}$
2.	$\mathsf{hsf} + \mathsf{hsf}_2 \rightleftarrows \mathsf{hsf}_3$	8.	$\mathsf{hsp} + \mathsf{hsf}_3\colon \mathsf{hse} \to \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf} + \mathsf{hse}$
3.	$\mathsf{hsf}_3 + \mathsf{hse} \rightleftarrows \mathsf{hsf}_3\colon \mathsf{hse}$	9.	$\mathsf{hsp} \to \emptyset$
4.	$\mathsf{hsf}_3\colon \mathsf{hse} \to \mathsf{hsf}_3\colon \mathsf{hse} + \mathsf{hsp}$	10.	$\mathsf{prot} \to \mathsf{mfp}$
5.	$\mathsf{hsp} + \mathsf{hsf} \rightleftarrows \mathsf{hsp}\colon \mathsf{hsf}$	11.	$\mathsf{hsp} + \mathsf{mfp} \rightleftarrows \mathsf{hsp}\colon \mathsf{mfp}$
6.	$\mathsf{hsp} + \mathsf{hsf}_2 \to \mathsf{hsp}\colon \mathsf{hsf} + \mathsf{hsf}$	12.	$\mathsf{hsp}\colon \mathsf{mfp} \to \mathsf{hsp} + \mathsf{prot}$

B The refined HSR molecular model

Table 2: The refinement of the molecular model proposed in [15].

Reaction in the basic model	Reactions in the refined model
$2\,\mathsf{hsf} \rightleftarrows \mathsf{hsf}_2$	$\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}$ $\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}$ $\mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}$ $\mathsf{hsf}^{(1)} + \mathsf{hsf}^{(1)} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}$
$\mathsf{hsf} + \mathsf{hsf}_2 \rightleftarrows \mathsf{hsf}_3$	$\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}$ $\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}$ $\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}$ $\mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}$ $\mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}$ $\mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}$ $\mathsf{hsf}^{(1)} + \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}$ $\mathsf{hsf}^{(1)} + \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}$
$\mathsf{hsf}_3 + \mathsf{hse} \rightleftarrows \mathsf{hsf}_3\mathsf{:hse}$	$\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hse}$ $\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hse}$ $\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hse}$ $\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hse}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hse}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hse}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hse}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)} + \mathsf{hse} \rightleftarrows \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hse}$
$\mathsf{hsf}_3\mathsf{:hse} \rightarrow \mathsf{hsf}_3\mathsf{:hse} + \mathsf{hsp}$	$\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(0)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hsf}^{(1)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(0)}\mathsf{:hse} + \mathsf{hsp}$ $\mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hse} \rightarrow \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hsf}^{(1)}\mathsf{:hse} + \mathsf{hsp}$
$\mathsf{hsp} + \mathsf{hsf} \rightleftarrows \mathsf{hsp}\mathsf{:hsf}$	$\mathsf{hsp} + \mathsf{hsf}^{(0)} \rightleftarrows \mathsf{hsp}\mathsf{:hsf}^{(0)}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} \rightleftarrows \mathsf{hsp}\mathsf{:hsf}^{(1)}$
$\mathsf{hsp} + \mathsf{hsf}_2 \rightarrow \mathsf{hsp}\mathsf{:hsf} + \mathsf{hsf}$	$\mathsf{hsp} + \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(0)} \rightarrow \mathsf{hsp}\mathsf{:hsf}^{(0)} + \mathsf{hsf}^{(0)}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)}\mathsf{:hsf}^{(1)} \rightarrow \mathsf{hsp}\mathsf{:hsf}^{(0)} + \mathsf{hsf}^{(1)}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)}\mathsf{:hsf}^{(0)} \rightarrow \mathsf{hsp}\mathsf{:hsf}^{(1)} + \mathsf{hsf}^{(0)}$

Table 2: The refinement of the model proposed in [15] - Continued

	$\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(1)}$
$\mathsf{hsp} + \mathsf{hsf}_3 \rightarrow$ $\mathsf{hsp} : \mathsf{hsf} + 2\,\mathsf{hsf}$	$\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + 2\,\mathsf{hsf}^{(0)}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + 2\,\mathsf{hsf}^{(1)}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + 2\,\mathsf{hsf}^{(0)}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + 2\,\mathsf{hsf}^{(1)}$
$\mathsf{hsp} + \mathsf{hsf}_3 : \mathsf{hse} \rightarrow$ $\mathsf{hsp} : \mathsf{hsf} + 2\,\mathsf{hsf} + \mathsf{hse}$	$\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + 2\,\mathsf{hsf}^{(0)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(0)} + 2\,\mathsf{hsf}^{(1)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(0)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + 2\,\mathsf{hsf}^{(0)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} : \mathsf{hsf}^{(1)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)} + \mathsf{hsf}^{(1)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(0)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(1)} + \mathsf{hsf}^{(0)} + \mathsf{hse}$ $\mathsf{hsp} + \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} : \mathsf{hsf}^{(1)} : \mathsf{hse} \rightarrow \mathsf{hsp} : \mathsf{hsf}^{(1)} + 2\,\mathsf{hsf}^{(1)} + \mathsf{hse}$
$\mathsf{hsp} \rightarrow \emptyset$	$\mathsf{hsp} \rightarrow \emptyset$
$\mathsf{prot} \rightarrow \mathsf{mfp}$	$\mathsf{prot} \rightarrow \mathsf{mfp}$
$\mathsf{hsp} + \mathsf{mfp} \rightleftarrows$ $\mathsf{hsp} : \mathsf{mfp}$	$\mathsf{hsp} + \mathsf{mfp} \rightleftarrows \mathsf{hsp} : \mathsf{mfp}$
$\mathsf{hsp} : \mathsf{mfp} \rightarrow$ $\mathsf{hsp} + \mathsf{prot}$	$\mathsf{hsp} : \mathsf{mfp} \rightarrow \mathsf{hsp} + \mathsf{prot}$

C Petri net for the basic HSR model

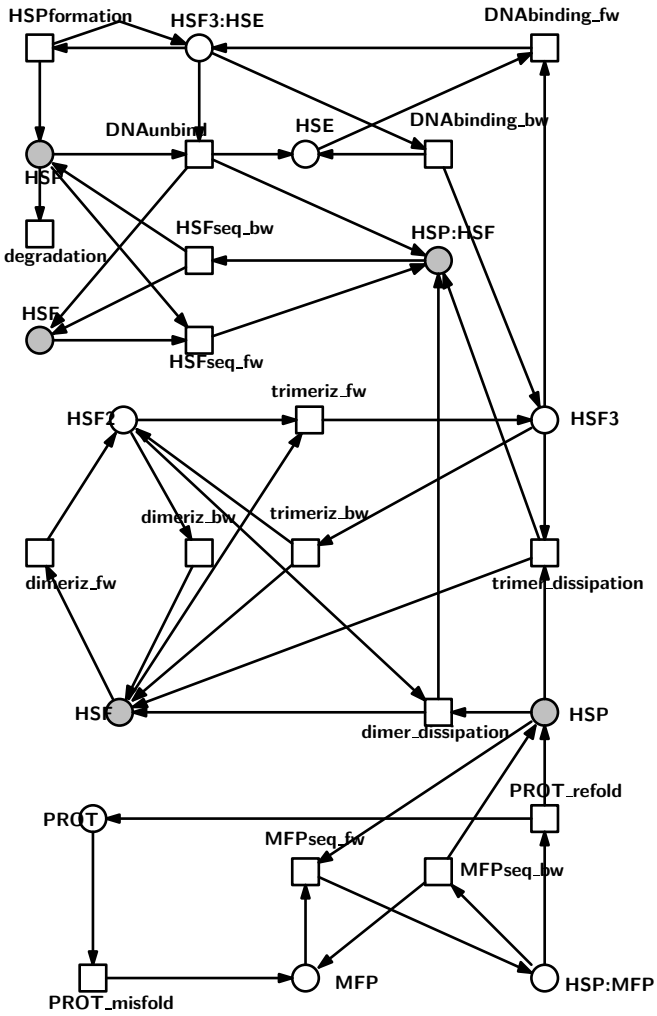

Figure 2: Snoopy representation of the basic heat shock response model

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D Colored Petri net for the refined HSR model

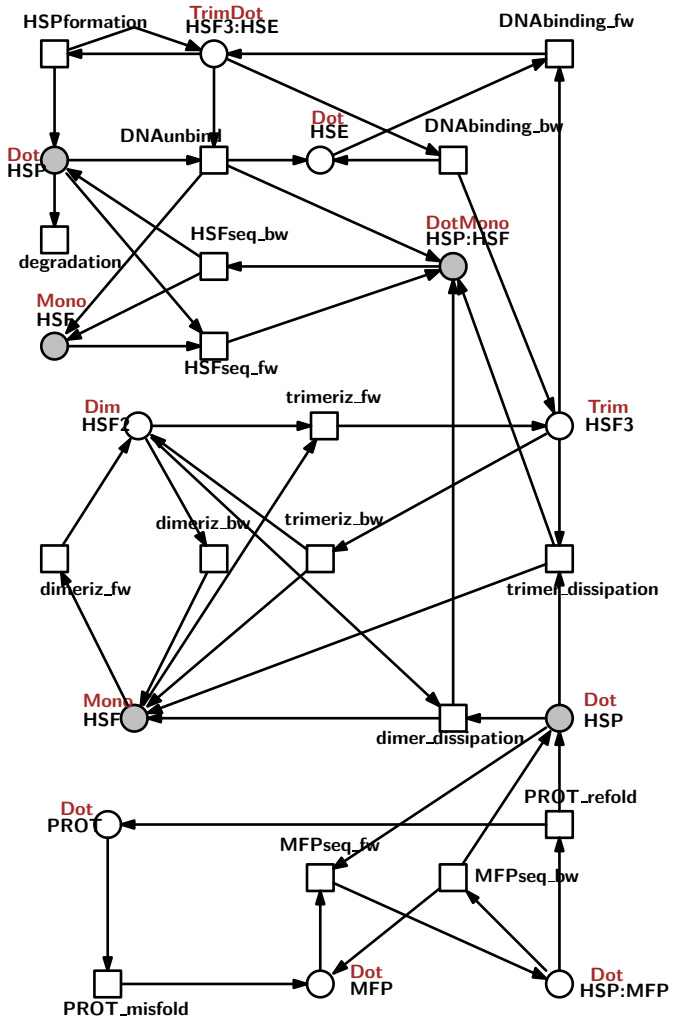

Figure 3: Snoopy representation of the refined heat shock response model. The network is similar to the basic model network. We include here the information about each place's color set (brown text next to each place, above the name of the place), and we omit all arc expressions, for readability reasons.

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