Quantitative Model Refinement for Guarded Command Models

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Abstract. We consider in this paper the modeling of biological systems with guarded command models. We focus on the model refinement problem: to systematically add details to the variables of a model and thus, to dynamically specify a model at different levels of detail. We introduce a notion of refinement for guarded command models and prove that it is a natural extension of the model refinement concept for reaction-based models. We demonstrate these concepts with a a running example on the heat shock response.

1 Introduction

Advancement of technology and the abundance of experimental data together with the growing need to have a deeper understanding of the functions of a cell, have led to an increase in the size of bio-inspired models in the past years. That is why simulating and analysing large-scale models have become an interesting research topic, e.g. building a whole-cell [13] or organ model [2, 21]. Due to the computational complexity of such models the analysis often involves studying the sub-models of a larger model with different level of resolutions. This line of research opens the door to dealing with model refinement. Model refinement focuses on the step-wise construction of models, from small abstract models to large, detailed ones. This approach ensures model fit preservation at every step of the development, for more information see [8].

Various methods have been proposed to facilitate model refinement in different frameworks, e.g., ODE-based models [11], rule-based models [18], Petri nets [22], biochemical reaction networks [12], π-calculus [20]. The full structural refinement of a reaction-based model has been proposed in [11] and [8] introduced a sufficient condition for fit preserving of the model.

In [12] the authors implemented the definitions of [11] to build the refined model of the eukaryotic heat shock response mechanism in four different frameworks, i.e. ODE-based models, Petri net models, rule-based models and guarded command models. In this paper we focus on the guarded command models and specifically we provide the mathematical background to prove that the definition of refinement in the reaction-based framework can be extended to the one

of guarded command models. The concept of guarded command models was developed based on guarded command languages first introduced in [6]. Guarded command models are suitable for modelling dynamic systems with alternative and repetitive constructs which allow for a non-deterministic component in which the enabled activity is not utterly dependent on the initial input [6].

This paper is structured as follows, in Section 2 we provide the basic definitions and results related to the quantitative model refinement. In Section 3, we present the formal definitions related to guarded command models and in Section 4 we introduce the concept of refining a guarded command model and prove a theorem to show the compatibility of this new definition with the definition of refinement in the reaction-based formalism. We finally conclude with some discussions in Section 5.

2 Quantitative model refinement

Quantitative model refinement is an approach which focuses on preserving the quantitative behaviour of the models under study while introducing different level of details into the model.

Quantitative model refinement was introduced for rule-based models in [18, 5] and for reaction-based models in [17, 11]. In this section we present a quantitative refinement approach for reaction-based models first introduced by [8]. A *reaction-based model* M comprises *species* $\Sigma = \{A_1, \ldots, A_m\}$ and *reactions* $R = \{r_1, \ldots, r_n\}$, where reaction $r_j \in R$ are of the form:

$$r_j \ : \ s_{1,j}A_1 + \ldots + s_{m,j}A_m \xrightarrow{k_{r_j}} s'_{1,j}A_1 + \ldots + s'_{m,j}A_m, \tag{1}$$

where $s_{1,j}, \ldots, s_{m,j}, s'_{1,j}, \ldots, s'_{m,j} \in \mathbb{N}$ are the *stoichiometric coefficients* of r_j and $k_{r_j} \geq 0$ is the *kinetic rate constant* of reaction r_j. We denote by $r_j^{(1)} = [s_{1,j}, \ldots, s_{m,j}]$ the vector of stoichiometric coefficients on the left hand side of reaction r_j and by $r_j^{(2)} = [s'_{1,j}, \ldots, s'_{m,j}]$ the vector of stoichiometric coefficients on its right hand side. We also denote reaction r_j as $r_j^{(1)} \xrightarrow{k_{r_j}} r_j^{(2)}$.

In this approach all species are refined simultaneously. It means that every species in the initial model M is substituted by a non-empty set of species in its refined model M_R, based on a *species refinement relation* ρ.

Definition 1 ([8]). *Given two sets of species Σ and Σ', and a relation $\rho \subseteq \Sigma \times \Sigma'$, we say that ρ is a* species refinement relation *iff it satisfies the following conditions:*

1. *for each $A \in \Sigma$ there exists $A' \in \Sigma'$ such that $(A, A') \in \rho$;*
2. *for each $A' \in \Sigma'$ there exists* exactly one *$A \in \Sigma$ such that $(A, A') \in \rho$;*
3. *$\Sigma' = \bigcup_{A \in \Sigma} \rho(A)$.*

We denote $\rho(A) = \{A' \in \Sigma' \mid (A, A') \in \rho\}$. We say that all species $A' \in \rho(A)$ are siblings.

We next define the refinement of a vector (of stoichiometric coefficients), of a reaction, and of a reaction-based model.

Definition 2 ([8]). *Let $\Sigma = \{A_1, \ldots, A_m\}$ and $\Sigma' = \{A'_1, \ldots, A'_p\}$ be two sets of species, and $\rho \subseteq \Sigma \times \Sigma'$ a species refinement relation.*

1. *Let $\alpha = (\alpha_1, \ldots, \alpha_m) \in \mathbb{N}^{\Sigma}$ and $\alpha' = (\alpha'_1, \ldots, \alpha'_p) \in \mathbb{N}^{\Sigma'}$. We say that α' is a* ρ-refinement *of α, denoted $\alpha' \in \rho(\alpha)$, if*

$$\sum_{\substack{1 \le j \le p \\ A'_j \in \rho(A_i)}} \alpha'_j = \alpha_i, \text{ for all } 1 \le i \le m.$$

2. *Let r and r' be two reactions over Σ and Σ', resp.:*

$$r \; : \; s_1 A_1 + \ldots + s_m A_m \xrightarrow{k_r} s'_1 A_1 + \ldots + s'_m A_m;$$
$$r' : t_1 A'_1 + t_2 A'_2 + \ldots + t_p A'_p \xrightarrow{k'_r} t'_1 A'_1 + t'_2 A'_2 + \ldots + t'_p A'_p.$$

   We say that r' is a ρ-refinement *of r, denoted $r' \in \rho(r)$, if*

$$r'^{(1)} \in \rho(r^{(1)}) \text{ and } r'^{(2)} \in \rho(r^{(2)}).$$

3. *Let $M = (\Sigma, R)$ and $M' = (\Sigma', R')$ be two reaction-based models, and $\rho \subseteq \Sigma \times \Sigma'$ a species refinement relation. We say that M' is a* ρ-structural refinement of M, *denoted $M' \in \rho(M)$, if*

$$R' \subseteq \bigcup_{r \in R} \rho(r) \text{ and } \rho(r) \cap R' \neq \emptyset \; \forall r \in R.$$

   In case $R' = \bigcup_{r \in R} \rho(r)$, we say M' is the full structural ρ-refinement *of M.*

In the following example we provide a refinement of the heat shock response. The heat shock response is a highly conserved defence mechanism within a cell. Here we use the heat shock response model proposed in [19].

Example 1. The reactions provided in Table 1 describe the heat shock response process within a cell. When the cell is exposed to the stress the proteins start to misfold (reaction (10) in Table 1) which can eventually cause the cell death. To counter the misfolding of proteins the expression of heat shock proteins (hsp's), increases. Consequently hsp's bind to misfolded proteins and help assist them in their correct refolding (reactions (11),(12) in Table 1) thus preventing multi-protein aggregation and cell death. The trimers formed by hsf (reactions (1) and (2)) regulate the transcription of hsp-encoding genes and the subsequent synthesis of hsp (reactions (3) and (4)). The hsp's downregulate their expression levels by binding to $\mathsf{hsf_3}$:hse's, $\mathsf{hsf_3}$'s, $\mathsf{hsf_2}$'s and hsf's (reactions (5)-(8)) and breaking down the complexes, thus stopping the expression activity.

In this example we consider the refinement of hsf molecules as described in [11] which focuses on the acetylation status (ON/OFF) of hsf proteins. Protein

acetylation is to substitute a hydrogen atom by an acetyl group in a chemical compound and it is highly relevant to the heat shock response regulation [24]. We refine hsf to include two subtypes: $\mathsf{rhsf}^{(1)}$ where the K80 residue is acetylated and rhsf where it is not acetylated. To refine the other complexes including hsf, i.e. hsf_2, hsf_3 and $\mathsf{hsf}_3\colon\mathsf{hse}$, we count the number of hsf of the complex that have the K80 residue acetylated. The refinement is as follows:

- hsf is refined to $\{\mathsf{rhsf}, \mathsf{rhsf}^{(1)}\}$,
- a dimer molecule hsf_2 is refined to $\{\mathsf{rhsf}_2, {\mathsf{rhsf}_2}^{(1)}, {\mathsf{rhsf}_2}^{(2)}\}$,
- and a trimer molecule hsf_3 is refined to $\{\mathsf{rhsf}_3, {\mathsf{rhsf}_3}^{(1)}, {\mathsf{rhsf}_3}^{(2)}, {\mathsf{rhsf}_3}^{(3)}\}$,

where the superscript denotes the number of acetylated sites. This leads to an expansion of the model from 10 species and 17 irreversible reactions to 20 species and 55 irreversible reactions.

Table 1: The molecular model of the eukaryotic heat shock response proposed in [19].

No. Reaction	No. Reaction
(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) $\mathsf{hsp}\colon\mathsf{mfp} \to \mathsf{hsp} + \mathsf{prot}$

Table 2: The list of reactions for the refined heat shock response model. For an irreversible reaction k_i denotes its kinetic rate constant. For a reversible reaction k_i^+ and k_i^- denote the kinetic rate constants of its 'left-to-right' and 'right-to-left' directions, resp.

Reaction	Kinetic rate constants
$2\,\mathsf{rhsf} \leftrightarrows \mathsf{rhsf}_2$	k_1^+, k_1^-
$\mathsf{rhsf} + \mathsf{rhsf}^{(1)} \leftrightarrow {\mathsf{rhsf}_2}^{(1)}$	k_2^+, k_2^-
$2\mathsf{rhsf}^{(1)} \leftrightarrows {\mathsf{rhsf}_2}^{(2)}$	k_3^+, k_3^-
$\mathsf{rhsf} + \mathsf{rhsf}_2 \leftrightarrows \mathsf{rhsf}_3$	k_4^+, k_4^-
$\mathsf{rhsf}^{(1)} + \mathsf{rhsf}_2 \leftrightarrows {\mathsf{rhsf}_3}^{(1)}$	k_5^+, k_5^-
$\mathsf{rhsf} + {\mathsf{rhsf}_2}^{(1)} \leftrightarrows {\mathsf{rhsf}_3}^{(1)}$	k_6^+, k_6^-
$\mathsf{rhsf}^{(1)} + {\mathsf{rhsf}_2}^{(1)} \leftrightarrows {\mathsf{rhsf}_3}^{(2)}$	k_7^+, k_7^-
$\mathsf{rhsf} + {\mathsf{rhsf}_2}^{(2)} \leftrightarrows {\mathsf{rhsf}_3}^{(2)}$	k_8^+, k_8^-
$\mathsf{rhsf}^{(1)} + {\mathsf{rhsf}_2}^{(2)} \leftrightarrows {\mathsf{rhsf}_3}^{(3)}$	k_9^+, k_9^-
$\mathsf{rhsf}_3 + \mathsf{rhse} \leftrightarrows \mathsf{rhsf}_3\colon\mathsf{rhse}$	k_{10}^+, k_{10}^-

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Table 2 – *Continued from previous page*

Reaction	Kinetic rate constants
$\mathsf{rhsf_3}^{(1)} + \mathsf{rhse} \leftrightarrows \mathsf{rhsf_3}^{(1)}\mathsf{:rhse}$	k_{11}^+, k_{11}^-
$\mathsf{rhsf_3}^{(2)} + \mathsf{rhse} \leftrightarrows \mathsf{rhsf_3}^{(2)}\mathsf{:rhse}$	k_{12}^+, k_{12}^-
$\mathsf{rhsf_3}^{(3)} + \mathsf{rhse} \leftrightarrows \mathsf{rhsf_3}^{(3)}\mathsf{:rhse}$	k_{13}^+, k_{13}^-
$\mathsf{rhsf_3:rhse} \rightarrow \mathsf{rhsf_3:rhse} + \mathsf{rhsp}$	k_{14}
$\mathsf{rhsf_3}^{(1)}\mathsf{:rhse} \rightarrow \mathsf{rhsf_3}^{(1)}\mathsf{:rhse} + \mathsf{rhsp}$	k_{15}
$\mathsf{rhsf_3}^{(2)}\mathsf{:rhse} \rightarrow \mathsf{rhsf_3}^{(2)}\mathsf{:rhse} + \mathsf{rhsp}$	k_{16}
$\mathsf{rhsf_3}^{(3)}\mathsf{:rhse} \rightarrow \mathsf{rhsf_3}^{(3)}\mathsf{:rhse} + \mathsf{rhsp}$	k_{17}
$\mathsf{rhsp} + \mathsf{rhsf} \leftrightarrows \mathsf{rhsp:rhsf}$	k_{18}^+, k_{18}^-
$\mathsf{rhsp} + \mathsf{rhsf}^{(1)} \leftrightarrows \mathsf{rhsp:rhsf}^{(1)}$	k_{19}^+, k_{19}^-
$\mathsf{rhsp} + \mathsf{rhsf_2} \rightarrow \mathsf{rhsp:rhsf} + \mathsf{rhsf}$	k_{20}
$\mathsf{rhsp} + \mathsf{rhsf_2}^{(1)} \rightarrow \mathsf{rhsp:rhsf} + \mathsf{rhsf}^{(1)}$	k_{21}
$\mathsf{rhsp} + \mathsf{rhsf_2}^{(1)} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + \mathsf{rhsf}$	k_{22}
$\mathsf{rhsp} + \mathsf{rhsf_2}^{(2)} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + \mathsf{rhsf}^{(1)}$	k_{23}
$\mathsf{rhsp} + \mathsf{rhsf_3} \rightarrow \mathsf{rhsp:rhsf} + 2 * \mathsf{rhsf}$	k_{24}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(1)} \rightarrow \mathsf{rhsp:rhsf} + \mathsf{rhsf}^{(1)} + \mathsf{rhsf}$	k_{25}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(1)} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + 2 * \mathsf{rhsf}$	k_{26}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(2)} \rightarrow \mathsf{rhsp:rhsf} + 2\mathsf{rhsf}^{(1)}$	k_{27}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(2)} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + \mathsf{rhsf}^{(1)} + \mathsf{rhsf}$	k_{28}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(3)} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + 2\mathsf{rhsf}^{(1)}$	k_{29}
$\mathsf{rhsp} + \mathsf{rhsf_3:rhse} \rightarrow \mathsf{rhsp:rhsf} + 2\,\mathsf{rhsf} + \mathsf{rhse}$	k_{30}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(1)}\mathsf{:rhse} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + 2\,\mathsf{rhsf} + \mathsf{rhse}$	k_{31}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(1)}\mathsf{:rhse} \rightarrow \mathsf{rhsp:rhsf} + \mathsf{rhsf}^{(1)} + \mathsf{rhsf} + \mathsf{rhse}$	k_{32}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(2)}\mathsf{:rhse} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + \mathsf{rhsf}^{(1)} + \mathsf{rhsf} + \mathsf{rhse}$	k_{33}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(2)}\mathsf{:rhse} \rightarrow \mathsf{rhsp:rhsf} + 2\mathsf{rhsf}^{(1)} + \mathsf{rhse}$	k_{34}
$\mathsf{rhsp} + \mathsf{rhsf_3}^{(3)}\mathsf{:rhse} \rightarrow \mathsf{rhsp:rhsf}^{(1)} + 2\mathsf{rhsf}^{(1)} + \mathsf{rhse}$	k_{35}
$\mathsf{rhsp} \rightarrow \emptyset$	k_{36}
$\mathsf{rprot} \rightarrow \mathsf{rmfp}$	k_{37}
$\mathsf{rhsp} + \mathsf{rmfp} \leftrightarrows \mathsf{rhsp:rmfp}$	k_{38}^+, k_{38}^-
$\mathsf{rhsp:rmfp} \rightarrow \mathsf{rhsp} + \mathsf{rprot}$	k_{39}

This refinement can be described via the following species refinement relation:

$$\begin{aligned}\rho = \{&(\mathsf{hse}, \mathsf{rhse}), (\mathsf{hsp}, \mathsf{rhsp}), (\mathsf{prot}, \mathsf{rprot}), (\mathsf{mfp}, \mathsf{rmfp}), (\mathsf{hsp}\colon \mathsf{mfp}, \mathsf{rhsp}\colon \mathsf{rmfp}),\\ &(\mathsf{hsf}, \mathsf{rhsf}), (\mathsf{hsf}, \mathsf{rhsf}^{(1)}),\\ &(\mathsf{hsf}_2, \mathsf{rhsf}_2), (\mathsf{hsf}_2, \mathsf{rhsf}_2{}^{(1)}), (\mathsf{hsf}_2, \mathsf{rhsf}_2{}^{(2)}),\\ &(\mathsf{hsf}_3, \mathsf{rhsf}_3), (\mathsf{hsf}_3, \mathsf{rhsf}_3{}^{(1)}), (\mathsf{hsf}_3, \mathsf{rhsf}_3{}^{(2)}), (\mathsf{hsf}_3, \mathsf{rhsf}_3{}^{(3)}),\\ &(\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{hsp}\colon \mathsf{rhsf}), (\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{rhsp}\colon \mathsf{rhsf}^{(1)}),\\ &(\mathsf{hsf}_3\colon \mathsf{hse}, \mathsf{rhsf}_3\colon \mathsf{rhse}), (\mathsf{hsf}_3\colon \mathsf{hse}, \mathsf{rhsf}_3{}^{(1)}\colon \mathsf{rhse}), (\mathsf{hsf}_3\colon \mathsf{hse}, \mathsf{rhsf}_3{}^{(2)}\colon \mathsf{rhse}),\\ &(\mathsf{hsf}_3\colon \mathsf{hse}, \mathsf{rhsf}_3{}^{(3)}\colon \mathsf{rhse})\}.\end{aligned}$$

The full set of the refined reactions is given in Table 2.

3 Guarded command models

The notion of *Guarded command language (GCL)* was first introduced in [6] to capture the dynamics of alternative and repetitive constructs with a non-deterministic component in which the enabled activity is not utterly dependent on the initial input. Markov chains are excellent examples of such systems, for example *continuous time Markov chains (CTMC)* are often used to describe the population processes. In this case, the state of the system is a n-dimensional vector where the entry on ith position of the vector determines the population of type i of the model. Note that the changes of the population within a CTMC system is not deterministic and distinct results can be obtained in different runs of the system. Various formalisms have been proposed to model the dynamics of a *Markovian model*, e.g., stochastic Petri-nets [9], stochastic process algebra [3], guarded command models [7], etc. In what follows we introduce guarded command formalism.

3.1 Guarded command formalism

In this section we present the formal definition of a *guarded command model (GCM)* inspired by Dijkstra's GCL proposed in [6]. Guarded command models illustrate the dynamics of their underlying process by describing its state transition classes, i.e. partitions of the set of all transitions. In what follows we are presenting a description of such transitions which also have been adapted to develop the *PRISM language*, see [15].

Definition 3. *Let M be a population model with n* variables (species) *$s_1, \ldots, s_n$. The corresponding* state space *of M is $\mathbb{Z}^n_{>0}$ where $\mathbb{Z}$ is the set of integers. We also denote the ith state of the system with $s^i = (s^i_1, \ldots, s^i_n)$ where s^i_j stands for the value of the jth variables in the ith state of the system.*

In the following definition we introduce *guarded commands* which describe the behaviour of the system, i.e. how the system transits from one state to the other over time.

Definition 4. *Let M be a population model and S its corresponding state space. A* guarded command *over M is of form:*

$$[\mathsf{label}]\ \ \mathsf{guard} : \mathsf{rate} \rightarrow \mathsf{update},$$

where:

- label *is the label of the command,*
- guard *is a Boolean predicate over variables that indicates which transition is enabled in the current state, i.e. a command is enabled if the value of its corresponding* guard *is true, it is not enabled otherwise,*
- *If $G \subseteq S$ is the set of all states in which the* guard *is true, then* update *is a function $u : G \rightarrow S$,*
- *If $G \subseteq S$ is the set of all states in which the* guard *is true, then* rate *is a function $r : G \rightarrow \mathbb{R}_{\geq 0}$, where $\mathbb{R}$ is the set of real numbers.*

We call $G_M = (M, \Gamma_M)$ a guarded command model *where Γ_M is a set of guards over M.*

3.2 Guarded command implementation of a reaction-based model

In this section we propose the notion of the GCM *corresponding* to a reaction-based model. The following definition is adapted from [4].

Definition 5. *Let $M = (\Sigma, R)$ be a reaction-based model where Σ is the set of species and R is the set of reactions. We define the* corresponding GCM, *$G_M = (\sigma_M, \Gamma_M)$, as follows:*

- *$\sigma_M = \{a_i \mid A_i \in \Sigma\}$ is the set of variables of G_M; we denote by $N_{a_i} \in \mathbb{N}$ the upperbound for a_i;*
- *for any reaction $r \in R$ of the form:*

$$r \ : \ s_1 A_1 + \ldots + s_m A_m \xrightarrow{k_r} s'_1 A_1 + \ldots + s'_m A_m,$$

we write the corresponding guard, *$\gamma_r \in \Gamma_M$, as follows:*

$$[\gamma_r] \bigwedge_{i=1}^{m} (s_i \leq a_i \leq N_{a_i} - s'_i) \rightarrow k_r \prod_{i=1}^{m} a_i^{s_i} : \bigwedge_{i=1}^{m} (a'_i = a_i + s'_i - s_i).$$

We denote by Γ_M the set of guards of G_M.

Example 2. The guard corresponding to reaction (3) of Table 1 is expressed as follows:

$$[\gamma_3]\ \ \mathsf{hsf_3} \geq 1 \wedge \mathsf{hse} \geq 1 \wedge \mathsf{hsf_3{:}\,hse} \leq N - 1 \rightarrow \mathsf{hsf_3} * \mathsf{hse} * k_5 : \\ (\mathsf{hsf_3}' = \mathsf{hsf_3} - 1) \wedge (\mathsf{hse}' = \mathsf{hse} - 1) \wedge (\mathsf{hsf_3{:}\,hse}' = \mathsf{hsf_3{:}\,hse} + 1),$$

where N represents the upper bound for the level of $\mathsf{hsf_3{:}\,hse}$ in the system. The full GCM implementation of the heat shock response is presented in Table 3.

Table 3: The list of reactions for the basic GCM corresponding to HSR.

Guards
$[\gamma_1]$ $\mathsf{hsf} \geq 2 \wedge \mathsf{hsf}_2 \leq N_{\mathsf{hsf}_2} - 1 \rightarrow \mathsf{hsf} * \mathsf{hsf} * k_1 : (\mathsf{hsf}' = \mathsf{hsf} - 2) \wedge (\mathsf{hsf}_2{}' = \mathsf{hsf}_2 + 1)$
$[\gamma_2]$ $\mathsf{hsf}_2 \geq 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 2 \rightarrow \mathsf{hsf}_2 * k_2 : (\mathsf{hsf}' = \mathsf{hsf} + 2) \wedge (\mathsf{hsf}_2{}' = \mathsf{hsf}_2 - 1)$
$[\gamma_3]$ $\mathsf{hsf} \geq 1 \wedge \mathsf{hsf}_2 \geq 1 \wedge \mathsf{hsf}_3 \leq N_{\mathsf{hsf}_3} - 1 \rightarrow \mathsf{hsf} * \mathsf{hsf}_2 * k_3 :$ $(\mathsf{hsf}' = \mathsf{hsf} - 1) \wedge (\mathsf{hsf}_2{}' = \mathsf{hsf}_2 - 1) \wedge (\mathsf{hsf}_2{}' = \mathsf{hsf}_2 + 1)$
$[\gamma_4]$ $\wedge \mathsf{hsf}_3 \geq 1 \wedge \mathsf{hsf}_2 \leq N_{\mathsf{hsf}_2} - 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 1 \rightarrow \mathsf{hsf}_3 * k_4 :$ $(\mathsf{hsf}' = \mathsf{hsf} + 1) \wedge (\mathsf{hsf}_2{}' = \mathsf{hsf}_2 + 1) \wedge (\mathsf{hsf}_2{}' = \mathsf{hsf}_2 - 1)$
$[\gamma_5]$ $\mathsf{hsf}_3 \geq 1 \wedge \mathsf{hse} \geq 1 \wedge \mathsf{hsf}_3{:}\,\mathsf{hse} \leq N_{\mathsf{hsf}_3:\mathsf{hse}} - 1 \rightarrow \mathsf{hsf}_3 * \mathsf{hse} * k_5 :$ $(\mathsf{hsf}_3{}' = \mathsf{hsf}_3 - 1) \wedge (\mathsf{hse}' = \mathsf{hse} - 1) \wedge (\mathsf{hsf}_3{:}\,\mathsf{hse}' = \mathsf{hsf}_3{:}\,\mathsf{hse} + 1)$
$[\gamma_6]$ $\mathsf{hsf}_3{:}\,\mathsf{hse} \geq 1 \wedge \mathsf{hse} \leq N_{\mathsf{hse}} - 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 1 \rightarrow \mathsf{hsf}_3{:}\,\mathsf{hse} * k_6 :$ $(\mathsf{hsf}_3{}' = \mathsf{hsf}_3 + 1) \wedge (\mathsf{hse}' = \mathsf{hse} + 1) \wedge (\mathsf{hsf}_3{:}\,\mathsf{hse}' = \mathsf{hsf}_3{:}\,\mathsf{hse} - 1)$
$[\gamma_7]$ $\mathsf{hsf}_3{:}\,\mathsf{hse} \geq 1 \wedge \mathsf{hsp} \leq N_{\mathsf{hsp}} - 1 \wedge \mathsf{hsf}_3{:}\,\mathsf{hse} \leq N_{\mathsf{hsf}_3:\mathsf{hse}} - 1 \rightarrow \mathsf{hsf}_3 * k_7 :$ $(\mathsf{hsp}' = \mathsf{hsp} - 1)$
$[\gamma_8]$ $\mathsf{hsf} \geq 1 \wedge \mathsf{hsp} \geq 1 \wedge \mathsf{hsp}{:}\,\mathsf{hsf} \leq N_{\mathsf{hsf}_2} - 1 \rightarrow \mathsf{hsf} * \mathsf{hsp} * k_8 :$ $(\mathsf{hsf}' = \mathsf{hsf} - 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} - 1) \wedge (\mathsf{hsp}{:}\,\mathsf{hsf}' = \mathsf{hsp}{:}\,\mathsf{hsf} + 1)$
$[\gamma_9]$ $\mathsf{hsp}{:}\,\mathsf{hsf} \geq 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 1 \wedge \mathsf{hsp} \leq N_{\mathsf{hsp}} - 1 \rightarrow \mathsf{hsf} * \mathsf{hsp} * k_9 :$ $(\mathsf{hsf}' = \mathsf{hsf} - 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} - 1) \wedge (\mathsf{hsp}{:}\,\mathsf{hsf}' = \mathsf{hsp}{:}\,\mathsf{hsf} + 1)$
$[\gamma_{10}]$ $\mathsf{hsf}_2 \geq 1 \wedge \mathsf{hsp} \geq 1 \wedge \mathsf{hsp}{:}\,\mathsf{hsf} \leq N_{\mathsf{hsf}_2} - 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 1 \rightarrow \mathsf{hsf}_2 * \mathsf{hsp} * k_{10} :$ $(\mathsf{hsf}_2{}' = \mathsf{hsf}_2 - 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} - 1) \wedge (\mathsf{hsp}{:}\,\mathsf{hsf}' = \mathsf{hsp}{:}\,\mathsf{hsf} + 1) \wedge (\mathsf{hsf}' = \mathsf{hsf} + 1)$
$[\gamma_{11}]$ $\mathsf{hsf}_3 \geq 1 \wedge \mathsf{hsp} \geq 1 \wedge \mathsf{hsp}{:}\,\mathsf{hsf} \leq N_{\mathsf{hsf}_2} - 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 2 \rightarrow \mathsf{hsf}_3 * \mathsf{hsp} * k_{11} :$ $(\mathsf{hsf}_3{}' = \mathsf{hsf}_3 - 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} - 1) \wedge (\mathsf{hsp}{:}\,\mathsf{hsf}' = \mathsf{hsp}{:}\,\mathsf{hsf} + 1) \wedge (\mathsf{hsf}' = \mathsf{hsf} + 2)$
$[\gamma_{12}]$ $\mathsf{hsf}_3{:}\,\mathsf{hse} \geq 1 \wedge \mathsf{hsp} \geq 1 \wedge \mathsf{hsp}{:}\,\mathsf{hsf} \leq N_{\mathsf{hsf}_2} - 1 \wedge \mathsf{hsf} \leq N_{\mathsf{hsf}} - 2 \wedge$ $\mathsf{hse} \leq N_{\mathsf{hse}} - 1 \rightarrow \mathsf{hsf}_3 * \mathsf{hsp} * k_{12} : (\mathsf{hsf}_3{:}\,\mathsf{hse}' = \mathsf{hsf}_3{:}\,\mathsf{hse} - 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} - 1)$ $\wedge(\mathsf{hsp}{:}\,\mathsf{hsf}' = \mathsf{hsp}{:}\,\mathsf{hsf} + 1) \wedge (\mathsf{hsf}' = \mathsf{hsf} + 2) \wedge (\mathsf{hse}' = \mathsf{hse} + 2)$
$[\gamma_{13}]$ $\mathsf{hsp} \geq 1 \rightarrow \mathsf{hsp} * k_{13} : (\mathsf{hsp}' = \mathsf{hsp} - 1)$
$[\gamma_{14}]$ $\mathsf{prot} \geq 1 \wedge \mathsf{mfp} \leq N_{\mathsf{mfp}} - 1 \rightarrow \mathsf{prot} * k_{14} :$ $(\mathsf{prot}' = \mathsf{prot} - 1) \wedge (\mathsf{mfp}' = \mathsf{mfp} + 1)$
$[\gamma_{15}]$ $\mathsf{hsp} \geq 1 \wedge \mathsf{mfp} \geq 1 \wedge \mathsf{hsp}{:}\,\mathsf{mfp} \leq N_{\mathsf{hsp}:\mathsf{mfp}} - 1 \rightarrow \mathsf{hsp} * \mathsf{mfp} * k_{15} :$ $(\mathsf{hsp}' = \mathsf{hsp} - 1) \wedge (\mathsf{mfp}' = \mathsf{mfp} - 1) \wedge (\mathsf{hsp}{:}\,\mathsf{mfp}' = \mathsf{hsp}{:}\,\mathsf{mfp} + 1)$
$[\gamma_{16}]$ $\mathsf{hsp}{:}\,\mathsf{mfp} \geq 1 \wedge \mathsf{hsp} \leq N_{\mathsf{hsp}} - 1 \wedge \mathsf{mfp} \leq N_{\mathsf{prot}} - 1 \rightarrow \mathsf{hsp}{:}\,\mathsf{mfp} * k_{16} :$ $(\mathsf{hsp}{:}\,\mathsf{mfp}' = \mathsf{hsp}{:}\,\mathsf{mfp} + 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} + 1) \wedge (\mathsf{mfp}' = \mathsf{mfp} - 1)$
$[\gamma_{17}]$ $\mathsf{hsp}{:}\,\mathsf{mfp} \geq 1 \wedge \mathsf{hsp} \leq N_{\mathsf{hsp}} - 1 \wedge \mathsf{prot} \leq N_{\mathsf{prot}} - 1 \rightarrow \mathsf{hsp}{:}\,\mathsf{mfp} * k_{17} :$ $(\mathsf{hsp}{:}\,\mathsf{mfp}' = \mathsf{hsp}{:}\,\mathsf{mfp} + 1) \wedge (\mathsf{hsp}' = \mathsf{hsp} + 1) \wedge (\mathsf{prot}' = \mathsf{prot} - 1)$

4 Quantitative refinement for GCM models

In this section we introduce the quantitative model refinement for the guarded command models and we further prove that the corresponding GCM of a refined reaction-based model is equivalent to the GCM refinement of the basic model. In the next definition we propose an approach to refine a guard in a GCM. Our strategy is similar to the one of the refinement of reaction models. In this approach whenever there is a refined variable in a guard we replace that guard with

a set of guards considering all possible refinements whereas in the refinement of reaction networks we would replace each reaction involving any refined reactant by the corresponding set of all possible refined reactions.

Definition 6. *Let γ_r be a guard in a GCM $G = (\sigma, \Gamma)$, of the form*

$$[\gamma_r] \bigwedge_{i=1}^{m} (s_i \leq a_i \leq N_{a_i} - s'_i) \rightarrow k_r \prod_{i=1}^{m} a_i^{s_i} : \bigwedge_{i=1}^{m} (a'_i = a_i + s'_i - s_i)$$

and $\rho \subseteq \sigma \times \sigma'$ a refinement relation. We say γ'_r of the form

$$[\gamma'_r] \bigwedge_{i=1}^{p} (t_i \leq a_i \leq N_{a_i} - t'_i) \rightarrow k_r \prod_{i=1}^{p} a_i^{t_i} : \bigwedge_{i=1}^{p} (a'_i = a_i + t'_i - t_i)$$

is a ρ-refinement *of γ_r, denoted by $\gamma'_r \in \rho(\gamma_r)$, if ${\gamma'_r}^{(1)} \in \rho(\gamma_r^{(1)})$ and ${\gamma'_r}^{(2)} \in \rho(\gamma_r^{(2)})$, where:*

$$\gamma_r^{(1)} = (s_1, s_2, \ldots, s_m),\ \gamma_r^{(2)} = (s'_1, s'_2, \ldots, s'_m) \text{ and}$$
$${\gamma'_r}^{(1)} = (t_1, t_2, \ldots, t_p),\ {\gamma'_r}^{(2)} = (t'_1, t'_2, \ldots, t'_p).$$

We denote $\Gamma' = \{\gamma'_r \mid \gamma_r \in \Gamma\}$. We say that the GCM $G' = (\sigma', \Gamma')$ is the full structural ρ-refinement *of G.*

Example 3. The refined heat shock response model is built based on the approach of Definition 6 can be found in [1]. Due to lack of space we only include here the guards corresponding to the guard of Example 2:

$[\gamma_{19}]\, \mathsf{rhsf_3} \geq 1 \wedge \mathsf{rhse} \geq 1 \wedge \mathsf{rhsf_3{:}\,rhse} \leq N-1 \rightarrow \mathsf{rhsf_3} * \mathsf{rhse} * k_5 :$
$(\mathsf{rhsf_3}' = \mathsf{rhsf_3} - 1) \wedge (\mathsf{rhse}' = \mathsf{rhse} - 1) \wedge (\mathsf{rhsf_3{:}\,rhse}' = \mathsf{rhsf_3{:}\,rhse} + 1);$

$[\gamma_{20}]\, \mathsf{rhsf_3}^{(1)} \geq 1 \wedge \mathsf{rhse} \geq 1 \wedge \mathsf{rhsf_3}^{(1)}\mathsf{{:}\,rhse} \leq N-1 \rightarrow \mathsf{rhsf_3}^{(1)} * \mathsf{rhse} * k_5 :$
$(\mathsf{rhsf_3}^{(1)\prime} = \mathsf{rhsf_3}^{(1)} - 1) \wedge (\mathsf{rhse}' = \mathsf{rhse} - 1) \wedge (\mathsf{rhsf_3}^{(1)}\mathsf{{:}\,rhse}' = \mathsf{rhsf_3}^{(1)}\mathsf{{:}\,rhse} + 1);$

$[\gamma_{21}]\, \mathsf{rhsf_3}^{(2)} \geq 1 \wedge \mathsf{rhse} \geq 1 \wedge \mathsf{rhsf_3}^{(2)}\mathsf{{:}\,rhse} \leq N-1 \rightarrow \mathsf{rhsf_3}^{(2)}\mathsf{{:}\,rhse} * \mathsf{rhse} * k_5 :$
$(\mathsf{rhsf_3}^{(2)\prime} = \mathsf{rhsf_3}^{(2)} - 1) \wedge (\mathsf{rhse}' = \mathsf{rhse} - 1) \wedge (\mathsf{rhsf_3}^{(2)}\mathsf{{:}\,rhse}' = \mathsf{rhsf_3}^{(2)}\mathsf{{:}\,rhse} + 1);$

$[\gamma_{22}]\, \mathsf{rhsf_3}^{(3)} \geq 1 \wedge \mathsf{rhse} \geq 1 \wedge \mathsf{rhsf_3}^{(3)}\mathsf{{:}\,rhse} \leq N-1 \rightarrow \mathsf{rhsf_3}^{(3)}\mathsf{{:}\,rhse} * \mathsf{rhse} * k_5 :$
$(\mathsf{rhsf_3}^{(3)\prime} = \mathsf{rhsf_3}^{(3)} - 1) \wedge (\mathsf{rhse}' = \mathsf{rhse} - 1) \wedge (\mathsf{rhsf_3}^{(3)}\mathsf{{:}\,rhse}' = \mathsf{rhsf_3}^{(3)}\mathsf{{:}\,rhse} + 1).$

Definition 7. *Let $f : \Sigma \rightarrow \sigma$ and $g : \Sigma' \rightarrow \sigma'$ be two bijections and $\rho_1 \subseteq \Sigma \times \Sigma'$, $\rho_2 \subseteq \sigma \times \sigma'$ two refinement relations. We say that ρ_1 and ρ_2 are* equivalent *if and only if for any $A \in \Sigma$, $A' \in \Sigma'$, $(A, A') \in \rho_1$ iff $(f(A), g(A')) \in \rho_2$.*

Let M be a reaction-based model and G_M its corresponding GCM, in the following theorem we prove that the refinement of G_M as proposed in Definition 6 is equivalent to the corresponding GCM of full structural refined model of M. The result shows that by applying the refinement of Definition 6 we can successfully extend the concept of refinement from the reaction-based models to the guarded command models.

Theorem 1. *Let $M = (\Sigma, R)$ be a reaction-based model, $\rho \subseteq \Sigma \times \Sigma'$ a refinement relation, and $M_\rho = (\Sigma', R')$ the full structural ρ-refinemenet of M. Let $G_M = (\sigma, \Gamma)$ be the GCM corresponding to M and $G_{M_\rho} = (\sigma_\rho, \Gamma_\rho)$ the GCM corresponding to M_ρ. Then there exists a refinement relation $\rho' \subseteq \sigma \times \sigma'$ equivalent to ρ such that G_{M_ρ} is the ρ'-refinement of G_M.*

Proof. Let $\Sigma = \{A_1, \ldots, A_m\}$ and $\Sigma' = \{A'_{11}, \ldots, A'_{1k_1}, \ldots, A'_{m1}, \ldots, A'_{mk_m}\}$, such that $A'_{ij} \in \rho(A_i)$ for any $1 \leq i \leq m$ and $1 \leq j \leq k_i$. By Definition 5, $|\Sigma| = |\sigma|$ and $|\Sigma'| = |\sigma_\rho|$. Without loss of generality we assume $\sigma = \{a_1, \ldots, a_m\}$ and $\sigma_\rho = \{a'_{11}, \ldots, a'_{1k_1}, \ldots, a'_{m1}, \ldots, a'_{mk_m}\}$. We define bijections $f : \Sigma \to \sigma$ and $g : \Sigma' \to \sigma_\rho$ such that $f(A_i) = a_i$ and $g(A'_{ij}) = a'_{ij}$ for any $1 \leq i \leq m$ and $1 \leq j \leq k_i$. We define the refinement relation $\rho' \subseteq \sigma \times \sigma_\rho$ such that $a'_{ij} \in \rho'(a_i)$ for any $1 \leq i \leq m$ and $1 \leq j \leq k_i$. Hence by Definition 7, ρ and ρ' are equivalent refinement relations.

Let us denote the full structural ρ'- refinement of G_M by $G' = (\sigma_\rho, \Gamma')$. Let $\gamma_r \in \Gamma$ be the guard corresponding to reaction $r \in R$. Since ρ and ρ' are equivalent refinement relations, by Definition 2 we can conclude that for any $r' \in \rho(r)$, there is a $\gamma'_r \in \rho'(\gamma_r)$ and viceversa. This concludes the proof of the theorem.

5 Discussion

In recent years various studies have been conducted spinning around guarded command models and fuelled by the the development of PRISM (probabilistic model checker) software [15], see for example [10, 14, 4, 16, 23]. This paper provides a mathematical foundation for the practitioners who deal with the bio-inspired phenomena modelled within the guarded command framework and presents a different angle of these topics from the lens of model refinement which in turn can give a more detailed perspective and a deeper understanding of the topic under study.

This paper proposed a refinement method for guarded command models corresponding to the full structural refinement proposed in [11]. We proved that the GCM obtained by our method is also an implementation of the refined model of the basic GCM produced by the method of [11]. This gives an algorithm for refining guarded command models that preserves the refinement of reaction-based models.

We did not consider in this paper the numerical setup of guarded command models and the problem of how to set the numerical setup of the refined model in such a way that various properties between the starting and the refined model (such as model fit) are preserved. We plan to return to this issue in a separate study.

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