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Abstract

Reaction systems are a formal framework for modeling processes driven by biochemical reactions. They are based on the mechanisms of facilitation and inhibition. A main assumption is that if a resource is available, then it is present in sufficient amounts and as such, several reactions using the same resource will not compete concurrently against each other; this makes reaction systems very different as a modeling framework than traditional frameworks such as ODEs or continuous time Markov chains. We construct in this paper a reaction systems model for the heat shock response in such a way that its (qualitative) behavior correlates well with the quantitative behavior of the corresponding ODE model. We discuss two different approaches for building the model. We conclude with a discussion on the expressivity of reaction systems as compared to that of ODE-based models.

Keywords: Reaction systems; heat shock response; quantitative model; qualitative model; model comparison.

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1 Introduction

Reaction systems (RS in short) are a formal framework for modeling processes driven by biochemical reactions. They were introduced in [2], see also [1] and references therein. The fundamental idea in this framework is that biochemical reactions are based on the mechanisms of *facilitation* and *inhibition*. A reaction is modeled as a triplet: a set of reactants, a set of inhibitors, and a set of products. A reaction can take place in a given state if all its reactants are present in that state and none of its inhibitors; when triggered, the reaction creates its products. Two major assumptions in reaction systems set them apart from standard methods for biomodeling (such as ordinary differential equations, stochastic processes, Petri nets, and process algebra):

- *The threshold assumption:* if a resource is present, then it is present in a "sufficient amount" and it will not cause any conflict between several reactions needing that resource. In other words, several reactions needing the same reactant will not be in conflict.

- *No permanency:* an entity will vanish from the current state unless it is produced by one of the reactions enabled in that state.

We construct in this paper an RS model for the molecular heat shock response introduced in [6]. Our focus is on building the model in such a way that a number of properties of the ODE-based model of [6] for the heat shock response are preserved: mass-conservation, steady state configuration with and without stress, behavior under continuous stress. The challenge here is that these properties are essentially numerical, correlating well to numerical experimental data and knowledge, whereas the RS framework is qualitative, as shown by the threshold assumption. Moreover, special attention has to be given to overcoming the no permanency assumption to make sure that, e.g., a gene is not removed from the system, even when no gene activity has occurred. We first take the straightforward approach of building the RS model through translating the reactants/products from the molecular model to an RS with the same reactants/products and no inhibitors. It turns out however that the resulting RS model leads to a behavior that is very different than that of the ODE-based model. We show however that an RS model can be built in a different way, qualitatively replicating the numerical behavior of the ODE model.

The paper is structured as follows. In Section 2 we introduce some basics of modeling with ODEs and some basic notions of reaction systems. In Section 3 we introduce our molecular model for the heat shock response and discuss some of the numerical properties of its corresponding mass-action-based ODE model. In Section 4 we build a direct translation of the molecular model to an RS model with no inhibitors and look at some of its interactive processes. In Section 5 we build a different RS model whose interactive processes correlate well with the numerical behavior of the ODE model. We conclude with some discussion in Section 6.

2 Preliminaries

2.1 Reaction-based molecular models and their ODE-based representation

Biochemical networks can be represented as reaction-based molecular models. Such models consist of sets of coupled chemical reactions describing the system of interest; the reactions can be reversible or irreversible. Formally, the fundamental constituents of a model M are represented by a set of species $\Sigma = \{S_i \mid 1 \leq i \leq m\}$ and a set of reactions $\{R_j \mid 1 \leq j \leq n\}$, where n and m are nonnegative integers.

An irreversible reaction R_j, $1 \leq j \leq n$, is formalized as a rewriting rule as follows:

$$R_j \ : \ c_{1,j}S_1 + c_{2,j}S_2 + \ldots + c_{m,j}S_m \xrightarrow{k_j} c'_{1,j}S_1 + c'_{2,j}S_2 + \ldots + c'_{m,j}S_m.$$

A reversible reaction can be written in the following form:

$$R_j \ : \ c_{1,j}S_1 + c_{2,j}S_2 + \ldots + c_{m,j}S_m \underset{k_j^-}{\overset{k_j^+}{\rightleftarrows}} c'_{1,j}S_1 + c'_{2,j}S_2 + \ldots + c'_{m,j}S_m.$$

The nonnegative integers k_j and k_j^-, k_j^+ represent the *kinetic rate constants* of an irreversible, respectively reversible reaction R_j. The coefficients $c_{1,j}, \ldots, c_{m,j}, c'_{1,j}, \ldots, c'_{m,j}$ are positive integers characterizing the stoichiometry of the reaction. The stoichiometric coefficient of species S_i in reaction R_j is defined by: $n_{i,j} = c'_{i,j} - c_{i,j}$.

The reactant species, found on the left-hand side of the reaction, are called *substrates*, while the species produced, occurring on the right-hand side, are referred to as *products*. A species $c_{i,j} = 0$ ($c'_{i,j} = 0$, resp.) can be omitted from the left-hand (right-hand, resp.) side of the reaction corresponding to the null coefficient. A reversible reaction can always be regarded as a pair of two irreversible reactions, see [3].

The *molecularity* of a reaction R_j is defined by the following sum: $\sum_{i=1}^{m} c_{i,j}$. One generally considers systems comprising reactions of a molecularity of at most two. Reactions exhibiting a molecularity of three are very infrequent due to the high improbability of a simultaneous collisions between three molecules leading to the formation of a complex. Reactions with a molecularity greater than three are completely disregarded due to the impossibility of collision between more than three molecules synchronously, see [5].

A molecular model M can be represented as a mathematical model in various manners, following a continuous or discrete time evolution, based on continuous or discrete species variables. A common representation is based on ordinary differential equations (ODEs) and the principle of mass-action, see [4].

To each species S_i, $1 \leq i \leq m$, one associates a time-dependent function: $[S_i] : \mathbb{R}_+ \to \mathbb{R}_+$, representing the concentration of the species over time. Therefore, the evolution of the system is described by a system of differential equations of the following form:

$$\frac{d[S_i]}{dt} = -\sum_{j=1}^{n} \left(k_j c_{i,j} \prod_{l=1}^{m} [S_l]^{c_{l,j}} \right) + \sum_{j=1}^{n} \left(k_j c'_{i,j} \prod_{l=1}^{m} [S_l]^{c'_{l,j}} \right), \quad 1 \leq i \leq m.$$

Such systems of ODEs can be rarely solved analytically, but many numerical methods for analyzing them exist. In particular, a numerical integration of the ODE system is interpreted as a numerical simulation of the corresponding molecular model.

2.2 Reaction systems

Reaction systems have been introduced in [2] as a formal framework for the analysis of biochemical networks. A biochemical reaction in this framework is based on a finite set of reactants and it is triggered provided that all the reactants involved in that particular reaction are *present* in a given state and all of its inhibitors are *absent*, see [8].

We recall in this section the basic definitions we need throughout the paper. For more details we refer to [2, 8].

Definition 1. [2] A reaction is a triplet of non-empty, finite sets: $a = (R_a, I_a, P_a)$, where $R_a \cap I_a = \emptyset$, $I_a, P_a \neq \emptyset$. The sets R_a, I_a, P_a stand for the set of *reactants*, *inhibitors*, *products* of a, respectively. Given a set S, if R_a, I_a, $P_a \subseteq S$, then a is a reaction in S. The set of reactions in S is denoted by *rac*(S).

Definition 2. [2] Let A be a set of reactions, T a finite set, and $a \in A$.

(i) The *result* of a on T, denoted $res_a(T)$, is

$$res_a(T) = \begin{cases} P_a, & \text{if } R_a \subseteq T \text{ and } I_a \cap T = \emptyset \\ \emptyset, & \text{otherwise.} \end{cases}$$

(ii) The result of A on T, denoted $res_A(T)$, is

$$res_A(T) = \bigcup_{a \in A} res_a(T).$$

Definition 3. [2] A reaction system (RS in short) is defined as an ordered pair $\mathcal{A} = (S, A)$, where S is a finite set and $A \subseteq$ *rac*(S). The set S is called the *background* (set) of A.

Definition 4. [2] Let $\mathcal{A}$ be a reaction system. An interactive process in $\mathcal{A}$ is a pair $\pi = (\gamma, \delta)$, where $\gamma = C_0, C_1, ..., C_n, \delta = D_1, D_2, ..., D_n \subseteq S$, $n \geq 1$, with $D_1 = \mathit{res}_{\mathcal{A}}(C_0)$ and, for each $1 < i \leq n$, $D_i = \mathit{res}_{\mathcal{A}}(C_{i-1} \cup D_{i-1})$.

The sequences γ and δ are the *context sequence* of π, *con*(π), and the *result sequence* of π, *res*(π), resp. The *state sequence* of π is $\tau = W_0, W_1, ..., W_n$, where $W_i = C_i \cup D_i$, for all $i \in \{0, ..., n\}$ and $W_0 = C_0$. W_0 is the *initial state* of π, init(π), and W_n is the *final state* of π, fst(π).

Definition 5. Let $\mathcal{A} = (S, A)$ be a reaction system and $C \subseteq S$. We say that $D \subseteq S$ is a *steady state* of $\mathcal{A}$ for context C if $\mathit{res}_{\mathcal{A}}(C \cup D) = D$.

3 A molecular model for the heat shock response

The heat shock response in eukaryotes is a fundamental, well conserved defense mechanism, which allows the cell to react to environmental stressors such as elevated temperatures. The increase of temperature in the environment causes proteins in the cell to misfold and build up large conglomerates that ultimately result in cell death. The key elements for the heat shock response mechanism are the heat shock proteins(hsp), which operate as molecular chaperones for misfolded proteins (mfp), facilitating their refolding process. The response is regulated by the transactivation of the hsp-encoding genes. Gene transcription is mediated by heat shock factors (hsf), which, under stress, dimerize (hsf_2), subsequently trimerize (hsf_3) and then bind to a promoter-site of the hsp-encoding gene, the heat shock-element (hse). As soon as trimers are bound, protein synthesis is activated and new hsp molecules are produced. When the level of hsp is sufficiently uplifted, hsp synthesis is turned off, see [6, 7]. Heat shock proteins sequestrate hsf molecules, hence promoting DNA binding. When the temperature is elevated, proteins in the cell (prot) tend to misfold, causing hsp: hsf complexes to break up. The heat shock response is switched on again, facilitating hsp synthesis, see [6]. We list in Table 1 the reactions of the molecular model in [6].

A mathematical model is associated with the molecular model in Table 1. The mathematical model consists in a mass-action-based system of ODEs, see [4] for a brief discussion on the principle of mass-action. We refer to [6] for the system of ODEs and the numerical setup of the ODE model.

For a constant temperature of $37°C$ the model reaches a steady state where most hsf's are bound in a complex hsp: hsf, most hse's are available for binding to trimers and there are very few misfolded proteins. For a constant temperature of $42°C$ the model reaches a steady state different from the one at $37°C$ in that the level of misfolded proteins, in both forms mfp and hsp: mfp are relatively high. Upon removal of the stress and return to $37°C$, the model returns to the basal values attained under a constant temperature of $37°C$. For a more detailed discussion about the steady states of the model and numerical simulations we refer to [6].

Table 1: The molecular model for the eukaryotic heat shock response proposed in [6].

Reaction	Reaction
$2\,\mathsf{hsf} \leftrightarrows \mathsf{hsf}_2$	$\mathsf{hsp} + \mathsf{hsf}_3 \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf}$
$\mathsf{hsf} + \mathsf{hsf}_2 \leftrightarrows \mathsf{hsf}_3$	$\mathsf{hsp} + \mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf} + \mathsf{hse}$
$\mathsf{hsf}_3 + \mathsf{hse} \leftrightarrows \mathsf{hsf}_3\colon \mathsf{hse}$	$\mathsf{hsp} \rightarrow \emptyset$
$\mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsf}_3\colon \mathsf{hse} + \mathsf{hsp}$	$\mathsf{prot} \rightarrow \mathsf{mfp}$
$\mathsf{hsp} + \mathsf{hsf} \leftrightarrows \mathsf{hsp}\colon \mathsf{hsf}$	$\mathsf{hsp} + \mathsf{mfp} \leftrightarrows \mathsf{hsp}\colon \mathsf{mfp}$
$\mathsf{hsp} + \mathsf{hsf}_2 \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + \mathsf{hsf}$	$\mathsf{hsp}\colon \mathsf{mfp} \rightarrow \mathsf{hsp} + \mathsf{prot}$

Table 2: The simplified molecular model for the eukaryotic heat shock response.

Reaction		Reaction	
$3\,\mathsf{hsf} \leftrightarrows \mathsf{hsf}_3$	(1)	$\mathsf{hsp} + \mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf} + \mathsf{hse}$	(6)
$\mathsf{hsf}_3 + \mathsf{hse} \rightarrow \mathsf{hsf}_3\colon \mathsf{hse}$	(2)	$\mathsf{prot} \rightarrow \mathsf{mfp}$	(7)
$\mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsf}_3\colon \mathsf{hse} + \mathsf{hsp}$	(3)	$\mathsf{hsp} + \mathsf{mfp} \rightarrow \mathsf{hsp}\colon \mathsf{mfp}$	(8)
$\mathsf{hsp} + \mathsf{hsf} \leftrightarrows \mathsf{hsp}\colon \mathsf{hsf}$	(4)	$\mathsf{hsp}\colon \mathsf{mfp} \rightarrow \mathsf{hsp} + \mathsf{prot}$	(9)
$\mathsf{hsp} + \mathsf{hsf}_3 \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf}$	(5)		

4 From the molecular model to a reaction system model: a direct translation

In this section, we formulate a reaction systems model for the heat shock response, based on the mechanisms of facilitation and inhibition. We use a direct translation approach, i.e. we translate each reaction in the molecular model to a reaction in the corresponding reaction system. We disregard in the current model the reaction $\mathsf{hsp} \rightarrow \emptyset$ in Table 1 due to its very low reaction rate in the ODE model; similarly, we ignore reactions $\mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsf} + \mathsf{hse}$ and $\mathsf{hsp}\colon \mathsf{mfp} \rightarrow \mathsf{hsp} + \mathsf{mfp}$. We also disregard the dimer form hsf_2 of hsf; indeed, the dimer is only a transient state from hsf to hsf_3 and their levels remain insignificant regardless of the stress. The simplified molecular model for the heat shock response is in Table 2.

4.1 The first reaction system model

We describe first a simple method for translating a set of molecular reactions to a reaction system. Consider a molecular reaction $A + B \rightarrow C$. We define its sets of reactants and of products to be $R = \{A, B\}$ and $P = \{C\}$, resp., i.e., all species

Table 3: The direct translation of the biochemical reactions of the simplified model of the heat shock response to a reaction system.

Reaction in chemical network	Reaction in reactions system	
$3\,\mathsf{hsf} \leftrightarrow \mathsf{hsf}_3$	$(\{\mathsf{hsf}\}, \{\mathsf{d_I}\}, \{\mathsf{hsf}_3\})$	(i)
	$(\{\mathsf{hsf}_3\}, \{\mathsf{d_I}\}, \{\mathsf{hsf}\})$	(ii)
$\mathsf{hsf}_3 + \mathsf{hse} \rightarrow \mathsf{hsf}_3\colon \mathsf{hse}$	$(\{\mathsf{hsf}_3, \mathsf{hse}\}, \{\mathsf{d_I}\}, \{\mathsf{hsf}_3\colon \mathsf{hse}\})$	(iii)
$\mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsf}_3\colon \mathsf{hse} + \mathsf{hsp}$	$(\{\mathsf{hsf}_3\colon \mathsf{hse}\}, \{\mathsf{d_I}\}, \{\mathsf{hsf}_3\colon \mathsf{hse}, \mathsf{hsp}\})$	(iv)
$\mathsf{hsp} + \mathsf{hsf} \leftrightarrow \mathsf{hsp}\colon \mathsf{hsf}$	$(\{\mathsf{hsp}, \mathsf{hsf}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}\colon \mathsf{hsf}\})$	(v)
	$(\{\mathsf{hsp}\colon \mathsf{hsf}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}, \mathsf{hsf}\})$	(vi)
$\mathsf{hsp} + \mathsf{hsf}_3 \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + 2\,\mathsf{hsf}$	$(\{\mathsf{hsp}, \mathsf{hsf}_3\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{hsf}\})$	(vii)
$\mathsf{hsp} + \mathsf{hsf}_3\colon \mathsf{hse} \rightarrow \mathsf{hsp}\colon \mathsf{hsf} + \mathsf{hse} + 2\,\mathsf{hsf}$	$(\{\mathsf{hsp}, \mathsf{hsf}_3\colon \mathsf{hse}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{hsf}, \mathsf{hse}\})$	(viii)
$\mathsf{prot} \rightarrow \mathsf{mfp}$	$(\{\mathsf{prot}\}, \{\mathsf{d_I}\}, \{\mathsf{mfp}\})$	(ix)
$\mathsf{hsp} + \mathsf{mfp} \rightarrow \mathsf{hsp}\colon \mathsf{mfp}$	$(\{\mathsf{hsp}, \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}\colon \mathsf{mfp}\})$	(x)
$\mathsf{hsp}\colon \mathsf{mfp} \rightarrow \mathsf{hsp} + \mathsf{prot}$	$(\{\mathsf{hsp}\colon \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}, \mathsf{prot}\})$	(xi)

on the left-hand side, right-hand side, resp., of the reaction; we use R and P in our definition of the corresponding reaction system. As the molecular reaction above does not specify any variable explicitly inhibiting it, for the corresponding RS reaction we set no inhibitor for any of the reactions; to comply with the restriction that the set of inhibitors is non-empty, we use the standard approach of setting $I = \{\mathsf{d_I}\}$, with $\mathsf{d_I}$ a dummy variable. The case of reversible molecular reactions is handled analogously, provided that we first replace it with two irreversible molecular reactions, standing for the two directions of the original reaction, and then define their correspondents in a reaction system as above.

Using this method we construct the direct translation of the heat shock response model in Table 2 to an RS model. We only discuss the construction for one reaction; the others are treated analogously. Consider as an example reaction $\mathsf{hsf}_3 + \mathsf{hse} \rightarrow \mathsf{hsf}_3\colon \mathsf{hse}$ modeling DNA binding by the hsf trimer.

Its correspondent in the reaction system can be defined as follows. The set of reactants consists of the species on the left hand side of the reaction, i.e., $R = \{\mathsf{hsf}_3, \mathsf{hse}\}$. Its set of products consists of the set of species on the right hand side of the reaction, i.e., $P = \{\mathsf{hsf}_3\colon \mathsf{hse}\}$. As discussed before, we set $I = \mathsf{d_I}$. This reaction is presented as reaction (iii) in Table 3. The full RS model obtained as a result is given in Table 3.

4.2 Interactive processes in the first model

We analyze in this subsection the dynamics of the reaction system in terms of interactive processes and compare it with that of the corresponding ODE model.

Note that in the ODE model the temperature was taken into account through the temperature dependent protein misfolding rate constant. Since our construction only translates the reactions and not their quantitative values, the effect of the temperature on the model is lost in the translation.

In our first interactive process we start from an initial state consisting of a minimal set of species needed in the heat shock response model: hsf, hse, and prot; all other species and complexes can be obtained in the molecular model (as well as in the ODE model) starting from these main ingredients. Thus, let the initial context of our reaction system be $C_0 = \{\mathsf{hsf}, \mathsf{prot}, \mathsf{hse}\}$. Throughout this interactive process all subsequent contexts are empty: $C_i = \emptyset$, for all $i \geq 1$.

The only reactions triggered in this state are (i) and (ix). Therefore, $D_1 = \mathit{res}_{\mathcal{A}}(C_0) = \{\mathsf{hsf}_3, \mathsf{mfp}\}$. In state D_1, the only reaction triggered is (ii) and as a result $D_2 = \{\mathsf{hsf}\}$. In state D_2, the only reaction triggered is (i) and as a result $D_3 = \{\mathsf{hsf}_3\}$. In state D_3, the only reaction triggered is (ii) and as a result $D_4 = \{\mathsf{hsf}\}$. Consequently, for every $k \geq 1$, $D_{2k} = \{\mathsf{hsf}\}$ and $D_{2k+1} = \{\mathsf{hsf}_3\}$. This interactive process is represented in Table 4.

The prediction of the RS model is thus that the model will enter into a loop of length two when starting from $\{\mathsf{hsf}, \mathsf{prot}, \mathsf{hse}\}$, for an empty context. This is in contradiction with the prediction of the ODE model, which shows the system converging to a steady state at $37°C$.

Table 4: An interactive process for the direct translation of the simplified model of the heat shock reponse for the first setting.

State	C_i	D_i	W_i	r_i
0	$\{\mathsf{hsf}, \mathsf{prot}, \mathsf{hse}\}$	$\emptyset$	$\{\mathsf{hsf}, \mathsf{prot}, \mathsf{hse}\}$	{(i), (ix)}
1	$\emptyset$	$\{\mathsf{hsf}_3, \mathsf{mfp}\}$	$\{\mathsf{hsf}_3, \mathsf{mfp}\}$	{ (ii) }
2	$\emptyset$	$\{\mathsf{hsf}\}$	$\{\mathsf{hsf}\}$	{ (i) }
3	$\emptyset$	$\{\mathsf{hsf}_3\}$	$\{\mathsf{hsf}_3\}$	{ (ii) }
4	$\emptyset$	$\{\mathsf{hsf}\}$	$\{\mathsf{hsf}\}$	{ (i) }

For our second interactive process, the initial state consists of all species included in the $37°C$ steady-state of the ODE model: $C_0 = \{\mathsf{hse}, \mathsf{hsp}{:}\,\mathsf{hsf}, \mathsf{prot}\}$. The interactive process starting from this state and using an empty context is represented in Table 5. Thus, the prediction of the RS model is that $D_{2k-1} = D_5$ and $D_{2k} = D_6$, for all $k \geq 3$. This again shows a contradiction with the ODE model.

Indeed, starting from an initial state corresponding to the $37°C$ steady state of the ODE model, the RS model eventually enters into a loop of length 2.

Table 5: An interactive process for the direct translation of the simplified model of the heat shock response for the second setting.

State	C_i	D_i	W_i	r_i
0	$\{\mathsf{hse}, \mathsf{hsp}\colon \mathsf{hsf}, \mathsf{prot}\}$	$\emptyset$	$\{\mathsf{hse}, \mathsf{hsp}\colon \mathsf{hsf}, \mathsf{prot}\}$	(vi) , (ix)
1	$\emptyset$	$\{\mathsf{hsp}, \mathsf{hsf}, \mathsf{mfp}\}$	$\{\mathsf{hsp}, \mathsf{hsf}, \mathsf{mfp}\}$	(i), (v), (x)
2	$\emptyset$	$\{\mathsf{hsf}_3, \mathsf{hsp}\colon \mathsf{hsf}, \mathsf{hsp}\colon \mathsf{mfp}\}$	$\{\mathsf{hsf}_3, \mathsf{hsp}\colon \mathsf{hsf}, \mathsf{hsp}\colon \mathsf{mfp}\}$	(ii), (vi), (xi)
3	$\emptyset$	$\{\mathsf{hsp}, \mathsf{hsf}, \mathsf{prot}\}$	$\{\mathsf{hsf}, \mathsf{hsp}\}$	(i), (v), (ix)
4	$\emptyset$	$\{\mathsf{hsf}_3, \mathsf{hsp}\colon \mathsf{hsf}, \mathsf{mfp}\}$	$\{\mathsf{hsf}_3, \mathsf{hsp}\colon \mathsf{hsf}, \mathsf{mfp}\}$	(ii), (vi)
5	$\emptyset$	$\{\mathsf{hsf}, \mathsf{hsp}\}$	$\{\mathsf{hsf}, \mathsf{hsp}\}$	(i), (v)
6	$\emptyset$	$\{\mathsf{hsf}_3, \mathsf{hsp}\colon \mathsf{hsf}\}$	$\{\mathsf{hsf}_3, \mathsf{hsp}\colon \mathsf{hsf}\}$	(ii), (vi)
7	$\emptyset$	$\{\mathsf{hsp}, \mathsf{hsf}\}$	$\{\mathsf{hsp}, \mathsf{hsf}\}$	(i), (v)

5 A second reaction system model for heat shock response

We introduce in this section a second RS model for the heat shock response. Our strategy this time is completely different than in the last section: we will formulate a number of essential properties of the heat shock response model and build the RS model to satisfy them. These properties will be achieved in the RS model only through the mechanism of inhibition, whereas they are emerging in the ODE model through a 'game of numbers', i.e., through the numerical values of the kinetic rate constants.

We introduce two new resources, nostress and stress, to model the system in the absence and the presence of the heat shock, resp., mirroring the behavior of the ODE model for temperature values of $37°C$ and $42°C$, resp.

We build the model so that the following properties hold in any state W of the reaction system $\mathcal{A}$, where either $\mathsf{stress} \in W$, or $\mathsf{nostress} \in W$, but not both:

P1. *mass-conservation of* hse: if $\{\mathsf{hse}, \mathsf{hsf}_3\colon \mathsf{hse}\} \cap W \neq \emptyset$, then $\{\mathsf{hse}, \mathsf{hsf}_3\colon \mathsf{hse}\} \cap res_{\mathcal{A}}(W) \neq \emptyset$;

P2. *a single form of* hse: if $\{\mathsf{hse}, \mathsf{hsf}_3\colon \mathsf{hse}\} \not\subseteq W$, then $\{\mathsf{hse}, \mathsf{hsf}_3\colon \mathsf{hse}\} \not\subseteq res_{\mathcal{A}}(W)$;

P3. *mass-conservation of* prot: if $\mathsf{prot} \in W$, then $\mathsf{prot} \in res_{\mathcal{A}}(W)$;

P4. *misfolded proteins must be addressed*: if $\mathsf{mfp} \in W$, then $\{\mathsf{mfp}, \mathsf{hsp}\colon \mathsf{mfp}\} \cap \mathit{res}_{\mathcal{A}}(W) \neq \emptyset$;

P5. *a single form of* hsf: let $\mathsf{HSF} = \{\mathsf{hsf}, \mathsf{hsf_3}, \mathsf{hsf_3}\colon \mathsf{hse}, \mathsf{hsp}\colon \mathsf{hsf}\}$; if $|W \cap \mathsf{HSF}| \leq 1$, then $|\mathit{res}_{\mathcal{A}}(W) \cap \mathsf{HSF}| \leq 1$;

P6. *stability of* $\mathsf{hsp}\colon \mathsf{hsf}$ *in the absence of stress*: if $\mathsf{nostress}, \mathsf{hsp}\colon \mathsf{hsf} \in W$, then $\mathsf{hsp}\colon \mathsf{hsf} \in \mathit{res}_{\mathcal{A}}(W)$.

Our main challenge is in building an RS model that captures qualitatively a behavior driven by numerical competition on resources, *in the absence* of an explicit mechanism for concurrency. Since our model consists of only unary and binary reactions, our main observation is that we can capture the competition between two binary molecular reactions using resources $\{A, B_1\}$ and $\{A, B_2\}$, resp., in terms of a preference (*binding affinity*) of A over, say, B_1, rather than B_2. We can formulate these relationships in the form of a dominance graph, where the graph nodes represent the molecular reactions (we indicate by '+' the left-to-right direction of a reversible reaction and by '-' the reverse direction) and a directed edge $u \to v$ indicates that u, v compete on the same resource and u is favoured over v. We build the dominance graph for the molecular model in Table 2 based on the following assumptions:

- hsf has a higher affinity for hsp than for another hsf (edge $4^+ \to 1^+$);
- $\mathsf{hsf_3}$ has a higher affinity to bind to hsp, than to break into hsf monomers or to interact with hse (edges $5 \to 1^-$ and $5 \to 2$);
- $\mathsf{hsf_3}$ has a higher affinity to bind to hse, than to break into hsf monomers (edge $2 \to 1^-$);
- $\mathsf{hsf_3}\colon \mathsf{hse}$ has a higher affinity to interact with hsp than to promote gene transcription (edge $6 \to 3$);
- hsp has a higher affinity for mfp than for hsf, $\mathsf{hsf_3}$, $\mathsf{hsf_3}\colon \mathsf{hse}$ (edges $8 \to 4^+$, $8 \to 5$, $8 \to 6$);

The resulting dominance graph for the heat shock response model is shown in Figure 1.

5.1 Building the second model

We discuss now the construction of the RS model going through the reaction of the simplified molecular model in Table 2 one by one. The corresponding RS reactions are in Table 6. In the following we extend the terminology of 'enabled reactions' to the molecular model in Table 2; we will say that a molecular reaction is enabled in the current state W of our RS system, if all its reactants are in W.

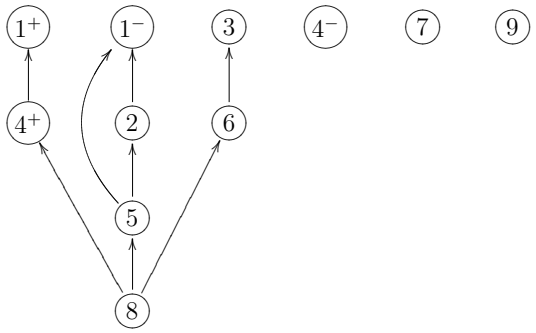

Figure 1: The reaction dominance graph of the simplified heat shock response model. The node labels refer to the molecular reactions in Table 2. We indicate with a directed edge $u \to v$ the property that u is favoured over v.

Molecular reaction (1^+) is modeled through the RS reaction (10), where hsp is indicated as an inhibitor, as suggested by the edge $4^+ \to 1^+$. Note however based on Figure 1 that reaction (1^+) is enabled also when (8) is enabled, since in this case (4^+) is disabled. In other words, (1^+) is enabled in the presence of hsp, mfp, with no inhibitor. This leads to formulating the RS reaction (11).

Molecular reaction (1^-) is modeled through the RS reaction (12), where hse, hsp are indicated as inhibitors, as suggested by edges $5 \to 1^-$ and $2 \to 1^-$. Similarly, as above, we note based on Figure 1 that if (8) is enabled, i.e., if hsp and mfp are in the current state, then (5) is disabled and so, in this case only reaction (2) supersedes (1^-). This leads to formulating the RS reaction (13).

Molecular reaction (2) is modeled through the RS reactions (14) and (15). The reasoning in this case is similar to that corresponding to (1^+). Additionally however, we need to introduce several other RS reactions to make sure that, in case (14) and (15) are disabled in the current state, hse is not lost, as required by property **P1**. In other words, this is analogous to building the RS correspondent of a molecular reaction hse $\to$ hse that in the dominance graph would have an incoming edge from node 2. With a similar reasoning as above, this leads to adding the RS reaction (16): hse is preserved unless hsf_3 is present, when (2) is enabled. Moreover, based on the graph in Figure 1, we note that if (5) is enabled, i.e., if hsf_3 and hsp were in the current state, but not mfp, then (2) is disabled, i.e., the molecular reaction hse $\to$ hse would be enabled. This leads to introducing the RS reaction (17).

Molecular reaction (3) is modeled through the RS reactions (18) and (19). The reasoning in this case is similar to that corresponding to (1^+).

Modeling molecular reactions (4^+), (5) and (6) are all similar. They are modeled through the RS reactions (20), (23), and (24), resp. We only note that when writing (23) we took into account **P5** and excluded hsf from the result of the RS reaction, in slight disagreement with the molecular reaction (5).

To model the molecular reaction (4^-) we took into account **P6** and formulated it through RS reactions (21) and (22), depending on whether stress or nostress are in the current state.

Molecular reaction (7) is modeled through RS reactions (25) and (26), where we also took into account **P3**.

Molecular reaction (8) is modeled through RS reaction (27) and (28), where we also took into account **P4**.

Finally, molecular reaction (9) is modeled in a straightforward way through RS reaction (29). The complete list of reactions of the RS model for heat shock response is given in Table 6.

Table 6: The list of reactions of the second reaction system model for heat shock response.

Reaction		Reaction	
$(\{\mathsf{hsf}\}, \{\mathsf{hsp}\}, \{\mathsf{hsf_3}\})$	(10)	$(\{\mathsf{hsp}, \mathsf{hsf}\}, \{\mathsf{mfp}\}, \{\mathsf{hsp}\colon \mathsf{hsf}\})$	(20)
$(\{\mathsf{hsf}, \mathsf{hsp}, \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsf_3}\})$	(11)	$(\{\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{stress}\}, \{\mathsf{nostress}\}, \{\mathsf{hsp}, \mathsf{hsf}\})$	(21)
$(\{\mathsf{hsf_3}\}, \{\mathsf{hse}, \mathsf{hsp}\}, \{\mathsf{hsf}\})$	(12)		
$(\{\mathsf{hsf_3}, \mathsf{hsp}, \mathsf{mfp}\}, \{\mathsf{hse}\}, \{\mathsf{hsf}\})$	(13)	$(\{\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{nostress}\}, \{\mathsf{stress}\}, \{\mathsf{hsp}\colon \mathsf{hsf}\})$	(22)
$(\{\mathsf{hsf_3}, \mathsf{hse}\}, \{\mathsf{hsp}\}, \{\mathsf{hsf_3}\colon \mathsf{hse}\})$	(14)	$(\{\mathsf{hsp}, \mathsf{hsf_3}\}, \{\mathsf{mfp}\}, \{\mathsf{hsp}\colon \mathsf{hsf}\})$	(23)
$(\{\mathsf{hsf_3}, \mathsf{hse}, \mathsf{hsp}, \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsf_3}\colon \mathsf{hse}\})$	(15)	$(\{\mathsf{hsp}, \mathsf{hsf_3}\colon \mathsf{hse}\}, \{\mathsf{mfp}\}, \{\mathsf{hsp}\colon \mathsf{hsf}, \mathsf{hse}\})$	(24)
$(\{\mathsf{hse}\}, \{\mathsf{hsf_3}\}, \{\mathsf{hse}\})$	(16)	$(\{\mathsf{prot}, \mathsf{stress}\}, \{\mathsf{nostress}\}, \{\mathsf{prot}, \mathsf{mfp}\})$	(25)
$(\{\mathsf{hse}, \mathsf{hsf_3}, \mathsf{hsp}\}, \{\mathsf{mfp}\}, \{\mathsf{hse}\})$	(17)	$(\{\mathsf{prot}, \mathsf{nostress}\}, \{\mathsf{stress}\}, \{\mathsf{prot}\})$	(26)
$(\{\mathsf{hsf_3}\colon \mathsf{hse}\}, \{\mathsf{hsp}\}, \{\mathsf{hsf_3}\colon \mathsf{hse}, \mathsf{hsp}\})$	(18)	$(\{\mathsf{hsp}, \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}\colon \mathsf{mfp}\})$	(27)
$(\{\mathsf{hsf_3}\colon \mathsf{hse}, \mathsf{hsp}, \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsf_3}\colon \mathsf{hse}, \mathsf{hsp}\})$	(19)	$(\{\mathsf{mfp}\}, \{\mathsf{hsp}\}, \{\mathsf{mfp}\})$	(28)
		$(\{\mathsf{hsp}\colon \mathsf{mfp}\}, \{\mathsf{d_I}\}, \{\mathsf{hsp}, \mathsf{prot}\})$	(29)

Our following result shows that the resulting model satisfies properties **P1-P6**.

Theorem 1. *The reaction system in Table 6 satisfies properties* **P1-P6**.

Proof. To prove **P1**, note that if $\mathsf{hse} \in W$, then either (14), (15), (16), or (17) are enabled, all leading to a state containing hse or $\mathsf{hsf_3}\colon \mathsf{hse}$. If $\mathsf{hsf_3}\colon \mathsf{hse} \in W$, then the same argument holds, noting that either (18), or (19), or (24) are enabled.

To prove **P2** we first observe that there is no reaction with both hse and $\mathsf{hsf_3}\colon \mathsf{hse}$ in its list of products. To prove that the model satisfies the property it is enough to show that no two reactions, one having hse, the other having $\mathsf{hsf_3}\colon \mathsf{hse}$

in its list of products, are enabled simultaneously. The reactions having hse in their list of products are (16), (17) and (24); those having hsf_3: hse in their list of products are (14), (15), (18), and (19). Reaction (16) cannot be enabled simultaneously with either (14) or (15) because hsf_3 is an inhibitor for (16) and it is a reactant for the others. Also, if (16) were enabled simultaneously with (18) or (19), then hse, hsf_3: hse $\in W$, a contradiction with the hypothesis of **P2**. Similar arguments show that (17) and (24) cannot be enabled simultaneously with (14), (15), (18), and (19).

To prove **P3** note that the only reactions involving prot are (25) and (26), that exactly one of them is triggered if stress $\in W$ or nostress $\in W$ but not both, and that both have prot in their list of products.

To prove **P4**, it is enough to observe that if mfp, hsp $\in W$, then (27) is enabled, while if mfp $\in W$ and hsp $\notin W$, then (28) is enabled.

We prove now **P5**. First, it is easy to see that if $W \cap \mathsf{HSF} = \emptyset$, then $res_{\mathcal{A}}(W) \cap \mathsf{HSF} = \emptyset$. Second, note that there is no reaction with more than one element of HSF in its set of products. If hsf $\in W$, then the reactions that may be enabled are (10), (11), (20); no two of them can be enabled simultaneously. If $\mathsf{hsf}_3 \in W$, then the reactions that may be enabled are (12), (13), (14), (15), (17), and (23); of these, only (17) and (23) can be enabled simultaneously, but the products of (17) do not include any element from HSF. If hsf_3: hse $\in W$, then the reactions that may be enabled are (18), (19), and (24); no two of them can be enabled simultaneously. If hsp: hsf $\in W$, then the reactions that may be enabled are (21) and (22), which cannot be enabled simultaneously.

Property **P6** follows from reaction (22). □

5.2 Interactive processes in the second model

We analyze here the interactive processes of the second RS model of the heat shock response and compare it with the results previously attained in the ODE model of [6]. Taking into account the qualitative nature of our model, by the presence of a resource in the environment, except for stress and nostress, conforming to the *threshold assumption*, we assume that there is a sufficient amount of the respective resource in the environment.

Similarly as in the case of our first reaction systems model, we start our first interactive process from an initial state consisting of a minimal set of species needed in the heat shock response model: hsf, hse, and prot. To draw a parallel with the numerical simulations of the ODE model at $37°C$, the subsequent contexts of our reaction system consists of the resource nostress. The result is shown in Table 7. The result shows that the reaction system in this case enters into a steady state, that is similar to the steady state of the ODE model in the absence of stress.

Our next interactive process follows the behavior of the RS model when the context introduces stress in every state, corresponding to the situation when the temperature is set to $42°C$ in the ODE model. As the initial state we take the

Table 7: An interactive process of the second RS model for heat shock response, in the absence of stress. The first column of the table represents the state of the system, C_i is the context given to the system in state i, $D_i = res_{\mathcal{A}}(C_{i-1} \cup D_{i-1})$ and $W_i = C_i \cup D_i$. The last column provides the list of the reactions triggered in each state.

State	C_i	D_i	W_i	r_i
0	{hsf, prot, hse, nostress}	$\emptyset$	{hsf, prot, hse, nostress}	(10),(16),(26)
1	{nostress}	{hsf_3, prot, hse}	{hsf_3, prot, hse, nostress}	(14), (26)
2	{nostress}	{hsf_3: hse, prot}	{hsf_3: hse, prot, nostress}	(18), (26)
3	{nostress}	{hsp, hsf_3: hse, prot}	{hsp, hsf_3: hse, prot, nostress}	(24), (26)
4	{nostress}	{hsp: hsf, hse, prot}	{hsp: hsf, hse, prot, nostress}	(16),(22),(26)
5	{nostress}	{hsp: hsf, hse, prot}	{hsp: hsf, hse, prot, nostress}	(16),(22),(26)

steady state achieved in the previous interactive process: {hse, prot, hsp: hsf}. The result is shown in Table 8. We note that also in this case the system is reaching a steady state, similar to the steady state of the ODE model for a temperature of $42°C$.

In our final interactive process we start from the steady state achieved in the previous one and consider the case when the context consists in all subsequent state of only nostress. This corresponds to a case when the ODE model is stabilized at $42°C$, followed then by a temperature of $37°C$. The result is shown in Table 9. The model reaches again a steady state, the same as that reached in the first interactive process. The situation is similar to that of the ODE model, where upon removal of the stress, the model eventually returns to its basal physiological values.

6 Discussion

We investigated in this paper the ability of the reaction system framework to capture the behavior of a molecular model for the heat shock response. We focused on emulating the behavior of the corresponding mass-action ODE model for the heat shock response. Whereas the ODE model is driven by the numerical values of its kinetic constants, the reaction system framework only allows the specification of logical dependencies in terms of facilitators and inhibitors. Moreover, its two fundamental principles, the non-permanency of resources and the uncompetitive triggering of reactions, make the reaction system framework fundamentally

Table 8: An interactive process of the second reaction system model for heat shock response at $42°C$

State	C_i	D_i	W_i	r_i
0	{hse, prot, hsp: hsf, stress}	$\emptyset$	{hse, prot, hsp: hsf, stress}	(16),(21),(25)
1	{stress}	{hse, hsp, hsf, prot, mfp}	{hse, hsp, hsf, prot, mfp, stress}	(11),(16), (25),(27)
2	{stress}	{prot, mfp, hsp: mfp, hsf_3, hse}	{prot, mfp, hsp: mfp, hsf_3, hse, stress}	(14),(25), (28), (29)
3	{stress}	{hsp, prot, mfp, hsf_3: hse}	{hsp, prot, mfp, hsf_3: hse, stress}	(19), (25),(27)
4	{stress}	{hsp, prot, mfp, hsf_3: hse, hsp: mfp}	{hsp, prot, mfp, hsf_3: hse, hsp: mfp, stress}	(19),(25),(27) ,(29)
5	{stress}	{hsp, prot, mfp, hsf_3: hse, hsp: mfp}	{hsp, prot, mfp, hsf_3: hse, hsp: mfp, stress}	(19),(25),(27) ,(29)

Table 9: Interactive process for the recovery (at $37°C$) of the second reaction system model after several steps of heat shock (at $42°C$). The process starts from the steady state obtained in Table 8.

State	C_i	D_i	W_i	r_i
0	{hsp, prot, hsf_3: hse, mfp, hsp: mfp, nostress}	$\emptyset$	{hsp, prot, hsf_3: hse, mfp, hsp: mfp, nostress}	(19),(26),(27), (29)
1	{nostress}	{hsp, prot, hsp: mfp, hsf_3: hse}	{hsp, prot, hsp: mfp, hsf_3: hse, nostress}	(24),(26),(29)
2	{nostress}	{hse, hsp, hsp: hsf, prot}	{hse, hsp, hsp: hsf, prot, nostress}	(16),(22),(26)
3	{nostress}	{hse, prot, hsp: hsf}	{hse, prot, hsp: hsf, nostress}	(16),(22),(26)
4	{nostress}	{hse, prot, hsp: hsf}	{hse, prot, hsp: hsf, nostress}	(16),(22),(26)

different than that of the ODE-based modeling.

Our first approach, where each molecular reaction would be directly translated to a reaction system with no inhibitors failed to reproduce the biological knowledge about the heat shock response and the behavior of the ODE model. The *non-permanency principle* of the reaction systems has a major role in the behavior of the reaction system being different than that of the ODE model. For example, the heat shock element hse is lost in an interactive process in any state where reaction (iii) is not triggered; this is in disagreement with the common intuition that a gene promoter is not lost when there is no gene binding activity; it is also in disagreement with the ODE model, where the total amount of heat shock element, either in the form of hse , or as hsf_3: hse, is conserved. The solution here, that we implement in our second reaction system model, is to have several rules making sure that hse is involved in at least one reaction regardless of the context, and thus preserved throughout the interactive process.

The *threshold assumption* of the reaction systems also plays a major role in the disagreement between the models. This is seen, e.g., in the treatment of proteins in the two models. While the ODE model exhibits a *gradual* misfolding (and refolding) of prot, in the RS model *all* proteins (prot) are converted into mfp's in a single step.

Another weakness of the RS model obtained through the direct translation is that it does not take into consideration the main driving factor of the heat shock response: the temperature.

Our second RS model was successful in emulating the behavior of the ODE model. To achieve this, we developed an approach where we capture the affinity of a species for another species through carefully selected inhibitors rather than kinetic constants as in the ODE model. We also focused on a number of properties, including mass conservation, that the RS model should satisfy. Our approach might be possible to generalize for arbitrary molecular models consisting of unary and binary molecular reactions. How much a-priori knowledge about the model, beyond the list of its molecular reactions, is needed, as well as how well the procedure scales up with the size of the model appear as interesting questions, worthy of further attention.

The reaction system framework forces the modeler to make explicit a number of assumptions about the model, that in other framework are typically hidden in some numerical values. Moreover, the explicit list of inhibitors is shedding light into the causality relations between the various reactions in the system. This kind of insight is highly valuable and may be very difficult to obtain through other frameworks, either from the presentation of the model, or from numerical simulations.

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