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On modularity and persistence of chemical reaction networks

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***Abstract*— In this paper we exploit the notion of State Machine Decomposable Petri nets (SMD nets), in order to enforce persistence of chemical reaction networks described by ODEs. Persistence is, in this context, the property that all chemical species are guaranteed to be asymptotically available if present at initial time.**

***Index Terms*— Chemical Reaction Networks, Petri Nets, Persistence, Liveness, Siphon, Modularity**

I. Introduction

Comprehension of cell life at the molecular level entails the dissection and qualitative understanding of complex networks of chemical reactions which, overall, regulate growth, metabolism, differentiation, death and reproduction of individual cells. The intricate machinery which biologists gradually uncover easily resembles the size and complexity of electronic circuitry, and it is believed that a true comprehension, as well as sharper synthetic capabilities in this respect, will only be achievable once quantitative models of the underlying chemical mechanism become available. Even in this case, however, a deeper understanding of the working principles underlying the network's lay out will only be accessible provided that analytical tools will join simulation and computational ones in explaining how and when robustness arises as a result of network topology, how are dynamics and ultimately functionality of a cell subsystem affected by structure and uncertainty in the models.

It is worth recalling that there is no general agreement over which modeling framework should be adopted in order to model biochemical systems. Several options are indeed possible, ranging from purely qualitative discrete models, such as Logic Petri Nets, to more quantitative ones, both in a discrete and continuous framework, such as Stochastic Timed Petri Nets (STPN), as well as Ordinary Differential Equations or even PDEs in case effects of stochastic fluctuations or diffusion are taken into account. While relationships and analogies between different formalisms are obviously expected, sometimes contrasting results are found and it is an interesting issue to better understand the links between the different models and, on a case by case basis, clarify which methods provides more reliable predictions.

II. Background on chemical reaction networks and Petri nets

This paper studies the structure of chemical reaction networks and their dynamical behavior on the basis of purely topological considerations. From a mathematical point of view, a chemical reaction network is a couple $(\mathcal{S}, \mathcal{R})$, where $\mathcal{S} = \{S_1, S_2, \ldots, S_n\}$ is a finite set of species ($n \in \mathbb{N}$), and $\mathcal{R}$ is a set of chemical reactions, viz. $\mathcal{R} = \{R_1, R_2, \ldots, R_m\}$. In turn, each chemical reaction is specified as follows:

$$R_i : \sum_{j=1}^{n} \alpha_{ij} S_j \;\rightarrow\; \sum_{j=1}^{n} \beta_{ij} S_j \qquad i = 1 \ldots m \qquad (1)$$

for some positive integer coefficients α_{ij}, β_{ij}. For the i-th reaction, *reactants* are the species with $\alpha_{ij} > 0$ and *products* those for which $\beta_{ij} > 0$. A very natural way to represent chemical reaction networks structure is by means of Petri Nets. A Petri Net is in fact a weighted bipartite graph, viz. a graph with two kinds of nodes P and T, (called places and transitions) such that $P \cap T = \emptyset$ and two kinds of weighted directed arcs, viz. arcs linking places to transitions, and transitions to places, denoted respectively Pre and $Post$. In particular, species can be associated to places of the graph and transitions to reactions. Each non-zero coefficient at the left-hand side of a chemical reaction corresponds to an arc of equal weight from the corresponding species to the transition associated to that chemical reaction. Similarly, each term at the right-hand side of a chemical reaction corresponds to a weighted arc which leaves the associated transition and reaches the designated species. In addition to this structure, a Petri Net can be made into a discrete-event system by considering a certain number of tokens associated to each place of the net, (at each given instant in time), which defines the so called *marking*. The net is then able to evolve according to the *firing rule* which specifies, among all transitions, which one are enabled and which one are not (viz. which have the potential to occur). In perfect analogy to chemical reactions, only those transitions whose input places have a number of tokens at least equal to the weight of the corresponding input arcs are enabled. Once an enabled transition takes place, the marking changes and a number of tokens equal to the weight of the corresponding arc is subtracted from each input place; at the same time, a number of tokens equal to the weight of the corresponding arc is added to each output place. Indeed, interpreting tokens as molecules of chemical species, this dynamic evolution rule precisely mimics what happens in reality.

In the past decades, many powerful tools have been developed for the analysis of the dynamics of various kinds of Petri Nets. A specially interesting line of research, is that

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of identifying meaningful classes of Petri Nets which, by their very structure, enjoy some guaranteed dynamical properties, or allow for tighter and simpler algorithmic checks of them. One remarkable idea, in this respect, is to define families of Petri Nets which can be decomposed into simpler networks (or taking instead a bottom-up approach) which result from the union of such simpler building blocks, [7], [6], [2], [5], [3]. Indeed, *modularity* of biological networks, not only is a convenient way to analyze complexity, but it is generally believed to be a prerequisite for evolution and robustness, (though not unanimous definition of *module* has been identified, see for instance [10]).

Our goal in this paper is to show why, as it is apparent from the example Sections in [1], many relevant examples of reaction networks arising in biochemistry have the remarkable property that all of its chemical species do not asymptotically disappear (precise definitions will be found later).

To this end, the notion of *subnet* is crucial. Its introduction however requires additional notations which are explained in the rest of this Section. For a given $p \in P$ or a given $t \in T$ we define

1) $\bullet t := \{p \in P : (p,t) \in Pre\}$, the set of input places of a transition (for CRN the reactants of a reaction);
2) $t\bullet := \{p \in P : (t,p) \in Post\}$, the set of output places of a transition (for CRN the products of a reaction);
3) $\bullet p := \{t \in T : (t,p) \in Post\}$, the set of input transitions of a place (the reactions which produce a given species);
4) $p\bullet := \{t \in T : (p,t) \in Pre\}$, the set of output transitions of a place (the reactions which need a given species).

The notation is easily extended to subsets of P and T: i.e for $\Pi \subset P$ we denote by $\bullet\Pi := \bigcup_{p\in\Pi} \bullet p$.

With this notation, a *subnet* of a given Petri Net $N := (P, T, Pre, Post)$ is a quadruple $\hat{N} := (\hat{P}, \hat{T}, \hat{Pre}, \hat{Post})$ which satisfies the following conditions:

1) $\hat{P} \subseteq P$ and $\hat{T} \subseteq T$;
2) $\bullet\hat{P} = \hat{P}\bullet = \hat{T}$ (where $\bullet$ refers to the network N);
3) $\hat{Pre} = Pre \cap (\hat{P} \times \hat{T})$ and $\hat{Post} = Post \cap (\hat{T} \times \hat{P})$.

The atomic structure of molecules is reflected in the topology of the network by the simple observation that complex CRN can often be decomposed into the union of subnetworks, each one corresponding to a specific atom, or to a molecule which, within the considered network, behaves as an indecomposable particle.

Let us consider, as an illustrative example, the double-phosphorilation and de-phosphorilation network which was also analyzed in [1]. We recall one plausible hypothesis of its constitutive reactions below:

$$S_0 + E \leftrightarrow ES_0 \rightarrow S_1 + E \leftrightarrow ES_1 \rightarrow S_2 + E$$

$$S_2 + F \leftrightarrow FS_2 \rightarrow S_1 + F \leftrightarrow FS_1 \rightarrow S_0 + F$$

where we used a standard convention that double arrows denote reversible reactions, viz. reactions which may take place in both directions, and hence should be listed twice if one were to adopt the formalism described so far. Also, instead of writing $C_1 \rightarrow C_2$ and $C_2 \rightarrow C_3$ we simply use the chained expression $C_1 \rightarrow C_2 \rightarrow C_3$. Hence, the set of species and reactions are respectively given by

$$\mathcal{S} = \{S_0, S_1, S_2, E, F, ES_0, ES_1, FS_2, FS_1\}$$

$$\mathcal{R} = \{R_1, R_{-1}, R_2, R_3, R_{-3}, R_4, R_5, R_{-5}, R_6, R_7, R_{-7}, R_8\}.$$

The associated Petri Net, which is shown in Fig. 1, can be decomposed as the union of three conservative subnetworks, those shown in Fig. 2.

A special kind of decomposition which was first introduced in [9] and has attracted a lot of attention in the past, is obtained when each of the individual subnetworks is a *strongly connected state machine*. We recall for the sake of completeness that a network $N = (P, T, Pre, Post)$ is a

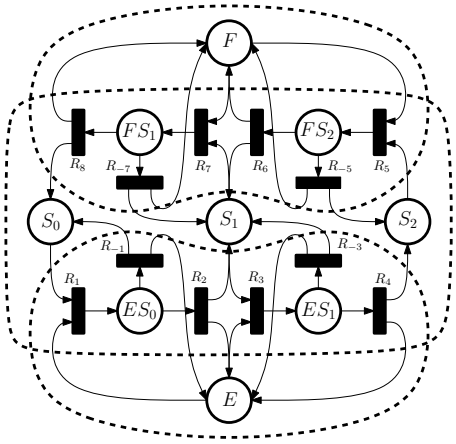

Fig. 1. Petri net associated to the double-phosphorilation double-dephosphorilation chemical reaction network

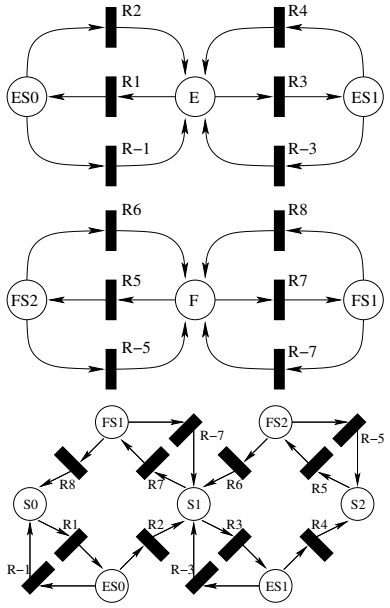

Fig. 2. Elementary reaction networks associated to a double phosphorilation enzymatic reaction

state machine if for all $t \in T$, $|\bullet t| = 1$ and $|t \bullet| = 1$ and the weights of the corresponding arcs are unitary, viz. there exists a unique input and a unique output place for each transition of the network, and these are connected through arcs of multiplicity 1. On its own, this is an elementary net, not very likely to show up in any meaningful chemical reaction networks, however, concurrent composition of such networks provides a rich source of examples, especially in biochemistry.

Definition. *A Petri Net $N = (P, T, Pre, Post)$ is called* State Machine Decomposable*, (SMD for short), if there exist subnetworks $N_i = (P_i, T_i, Pre_i, Post_i)$, $i = 1, \ldots, N$, such that $P = \bigcup_{i=1}^{N} P_i$ and $T = \bigcup_{i=1}^{N} T_i$, moreover, each N_i is a* strongly connected state machine.

III. Persistence of Chemical Reaction Networks

In [1], criteria were developed to study the *persistence* of closed chemical reaction networks. This property, originally introduced in the ecology literature, amounts to asymptotic non-extinction of all species involved in a certain ecosystem. In this context it translates into the important feature that, for a certain closed reaction network, none of the chemicals present at initial time tends to disappear. For networks modeled by means of ODEs, this amount to the following condition:

$$\forall\, x \in \text{int}(\mathbb{R}^n_{\geq_0}) \quad \omega(x) \cap \partial\mathbb{R}^n_{\geq_0} = \emptyset.$$

where $\omega(x)$ denotes the ω-limit set of the solution initiated at x. The sufficient and necessary conditions therein presented proved to be useful in several practical examples, included some of rather high dimensionality. The criteria, which for the sake of completeness will be later recalled, are stated in the language of Petri Nets, and make use of notions which are introduced below.

While for general Petri Nets these assumptions need not be fulfilled, we show that the underlying atomic structure of biochemical networks frequently leads to automatic enforcement the conditions requested.

Definition. *A set of places $\Sigma \subseteq P$ is called a siphon for a network $N = (P, T, Pre, Post)$ if $\bullet\Sigma \subseteq \Sigma\bullet$. A siphon is called minimal, if no proper subset is also a siphon.*

Let us organize the coefficients of a chemical reaction network into a matrix (the so called incidence or stoichiometry matrix, respectively in the language of Petri Nets and CRN Theory). In particular, we let $\Gamma_{ij} := \beta_{ji} - \alpha_{ji}$, for $i = 1 \ldots m$ and $j = 1 \ldots n$.

Definition. *A non-negative integer row vector c, is called a P-semiflow if it satisfies $c \cdot \Gamma = 0$. Its support is given by $\sigma(c) := \{i : c_i > 0\}$.*

Physically P-semiflows correspond to linear conservation laws of the network. A network which admits a P-semiflow, whose support coincides with the set of all places is called *conservative*. Dually, we may define:

Definition. *A non-negative integer column vector w, is called a T-semiflow if it satisfies $\Gamma \cdot w = 0$. Its support is given by $\sigma(w) := \{i : w_i > 0\}$.*

A network admitting a T-semiflow whose support coincides with the set of all transitions is called *consistent*.

According to [1], a siphon which contains the support of a P-semiflow is called *structurally non-emptiable*, since the presence of a conservation law prevents concentrations in the siphon from asymptotically vanishing. The main result in [1] was indeed to show that, under mild assumptions on the expression of reaction rates, *a conservative network whose siphons are all structurally non-emptiable is also persistent*. Moreover, consistency of the network is necessary for persistence to hold.

We show next that for SMD networks structural non-emptiability of P-semiflows is fulfilled under some relatively mild topological assumptions, thus justifying a prevalence of biochemical examples for which persistence can be ensured by the criterion developed in [1]. Indeed, all networks in [1] can be understood in terms of our main result.

In order to state it concisely we recall some useful notions. In particular, a finite sequence of alternating transitions and places $t_1 p_1 t_2 p_2 \ldots t_n$ is a tt-path provided that (t_i, p_i) and (p_i, t_{i+1}) are arcs in N for all $i = 1, \ldots, n-1$. Given two subnets N_a and N_b, we say that a path $t_1 p_1 t_2 p_2 \ldots t_n$ is a *crossing path* between N_a and N_b provided that $\{t_1, p_1, t_2, p_2, \ldots t_n\} \subset (T_a \cup P_a) \cap (T_b \cup P_b)$, (meaning that each node in the path belongs to both subnets) and $\bullet t_1 \cap (N_a \backslash N_b)$ and $\bullet t_1 \cap (N_b \backslash N_a)$ are both non-empty, as well as, $t_n \bullet \cap (N_a \backslash N_b)$ and $t_n \bullet \cap (N_b \backslash N_a)$. These 4 sets are respectively denoted as the input and output places of the path relative to the subnetworks N_a and N_b.

We associate to an SMD network an undirected graph which reflects the structure of the network according to the following rules: the nodes of the graph are the subnetworks N_i, $i = 1 \ldots N$. An undirected edge between N_i and N_j exists if and only if $N_i \cap N_j \neq \emptyset$ (meaning that the two networks have at least some transition in common). Hence $\mathcal{G} = (\mathcal{N}, \mathcal{E})$ with $\mathcal{N} = \{N_i, i = 1 \ldots N\}$ and $\mathcal{E} = \{\{N_i, N_j\} : N_i \cap N_j \neq \emptyset, i \neq j\}$.

Definition. We say that an SMD Petri Net has tree like structure, provided the associated undirected graph (defined above) is a connected tree.

Definition. We say that an SMD Petri Net ($N = \bigcup_i N_i$) is *overlap compatible* (OC) if for every ordered pair (N_i, N_j) of distinct subnetworks and every pair of crossing paths p_a and p_b between them, there always exists an input place in common among the two.

Theorem The following facts are equivalent for a state machine decomposable network N with tree structure and

satisfying the OC condition:

1) Σ is a minimal siphon;
2) $\sigma(c) = \Sigma$ for some P-semiflow c of minimal support.

Proof. Let $N = (P, T, Pre, Post)$ be a state machine decomposable Petri Net, and $N_i = (P_i, T_i, Pre_i, Post_i)$ with $i = 1 \dots N$ the corresponding cover. In particular, for each $t \in T$, the set $\bullet t \cap P_i$ is either empty or a singleton. Let $\Sigma \subset P$ be a minimal siphon and consider the associated bipartite subgraph, G_Σ, as defined by $\Sigma, \bullet\Sigma$, and their incident edges, viz. arcs in Pre and $Post$ which connect elements of Σ and $\bullet\Sigma$ only. Obviously G_Σ is (weakly) connected, (otherwise each of its connected components would in turn be a siphon, thus violating minimality). Moreover, there exists a map $\pi : \bullet\Sigma \to \Sigma$, such that $\pi(t) \in \bullet t$ (this kind of map is sometimes called an allocation) and

$$f_\pi(\Sigma) := \bigcup_{p \in \Sigma} \bigcup_{t \in \bullet p} \{\pi(t)\} \tag{2}$$

by definition of siphon, fulfills the inclusion:

$$f_\pi(\Sigma) \subseteq \Sigma. \tag{3}$$

Notice that f_π is monotone with respect to its argument, viz. $S_1 \subseteq S_2 \Rightarrow f_\pi(S_1) \subseteq f_\pi(S_2)$. Moreover, $\pi(t) \in \bullet t$ implies $\pi(t)\bullet \supseteq \{t\}$. As a consequence, for any $S \subset P$ we have the following inclusion:

$$f_\pi(S)\bullet = \bigcup_{p \in S} \bigcup_{t \in \bullet p} \pi(t)\bullet \supseteq \bigcup_{p \in S} \bigcup_{t \in \bullet p} \{t\} = \bigcup_{p \in S} \bullet p = \bullet S. \tag{4}$$

By virtue of equation (4), applied with $S = f_\pi(\Sigma)$, and recalling (3) we have $\bullet f_\pi(\Sigma) \subseteq f_\pi(f_\pi(\Sigma))\bullet \subseteq f_\pi(\Sigma)\bullet$. Hence $f_\pi(\Sigma)$ is also a siphon, and by minimality of Σ, we necessarily have $\Sigma = f_\pi(\Sigma)$. This implies, that G_Σ is indeed strongly connected (besides being connected which was shown before).

Let us consider now the following recursion:

$$\begin{aligned} \Sigma_0(q) &= \{q\} \\ \Sigma_{k+1}(q) &= \Sigma_k(q) \cup f_\pi(\Sigma_k(q)). \end{aligned} \tag{5}$$

Clearly, for each $q \in \Sigma$, $\Sigma_k(q) \subset \Sigma$, moreover, by construction $\bullet\Sigma_k(q) \subseteq \Sigma_{k+1}(q)\bullet$, so that indeed $\bigcup_{k \in \mathbb{N}} \Sigma_k(q)$ is a siphon (included in Σ), and by minimality of Σ:

$$\bigcup_{k \in \mathbb{N}} \Sigma_k(q) = \Sigma$$

Notice that these conclusions hold for an arbitrary choice of π (besides being true for each q in Σ).

Consider now the (bipartite) subgraph $\tilde{G}_\Sigma(\pi)$ of G_Σ defined according to the following rules:

1) same set of vertices of G_Σ, namely Σ and $\bullet\Sigma$
2) same set of arcs of type $t \to p$, for $p \in \Sigma$ and $t \in \bullet\Sigma$, viz. $(\Sigma \times \bullet\Sigma) \cap Post$
3) all arcs of type $p \to t$ satisfying $p = \pi(t)$.

Notice that iteration (5) propagates backwards, along edges of $\tilde{G}_\Sigma(\pi)$, the set of nodes controllable to q in k steps. By the previous considerations, $\tilde{G}_\Sigma(\pi)$ is also strongly connected, regardless of π.

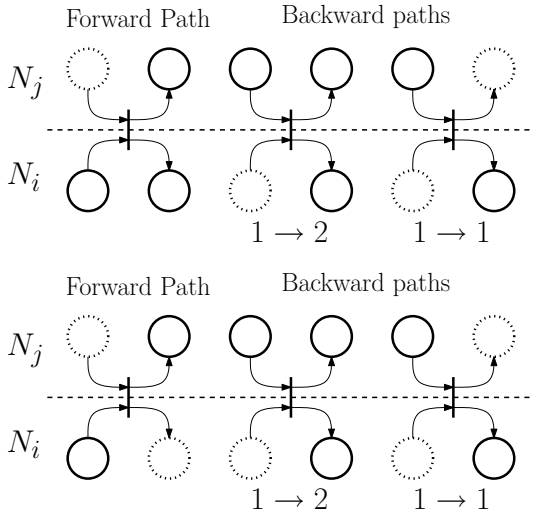

Fig. 3. Incompatibility of scenarios with $1 \to 2$ and $1 \to 1$ crossing paths

We claim that each transition $t \in \Sigma\bullet$ has exactly one input and one output place. Hence Σ is the support of the P-semiflow which has 1s for all entries which belong to Σ and zeros elsewhere.

If $\Sigma \subset P_i$ for some $i \in \{1, \dots, N\}$, meaning that all of its places are nodes of a single subnetwork, then there is nothing left to prove, as, by strong connectedness of each N_i, we have indeed $\Sigma = P_i$.

Next we show by contradiction that the case of siphons not contained in a single subnetwork is indeed to be excluded. If this were not the case $\tilde{G}_\Sigma(\pi)$ must contain at least one crossing path of N. Moreover, by the tree structure assumption, for each crossing path from subnetwork N_i to N_j contained in $\tilde{G}_\Sigma(\pi)$ there must exist at least one crossing path in the opposite direction, viz. from N_j to N_i, which is again contained in $\tilde{G}_\Sigma(\pi)$. We say that a crossing path (crossing from N_i to N_j) is of type $l \to m$ with $l, m \in \{1, 2\}$ if l input places and m output places belong to Σ.

Notice that, by construction, crossing paths contained in $\tilde{G}_\Sigma(\pi)$ can be only of 2 different types: $1 \to 2$ or $1 \to 1$. It is straightforward to verify from Fig. 3 that both scenarios are not consistent with the OC assumption (indeed none of the input places of such forward and backward paths can be in common). In the figure a dashed input node stands for a place not in Σ, a solid one for a place contained in Σ. Hence, non-existence of crossing paths in $\tilde{G}_\Sigma(\pi)$ contradicts the fact that Σ is not contained in a single subnetwork. This shows how the vector $c := [c_p]_{p \in P}$ defined according to the rule $c_p = 1$ if $p \in \Sigma$ and 0 if $p \notin \Sigma$, is indeed a P-semiflow for the network. It is also of minimal support since any other P-semiflow has a support which is trivially also a siphon and hence minimality of Σ as a siphon precludes existence of siphons with smaller support.

We show next the converse implication. Namely every minimal P-semiflow has a support which is also a minimal

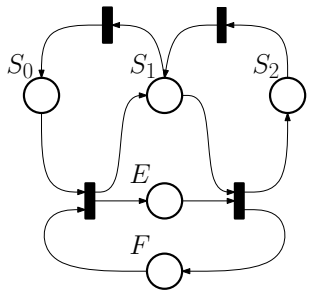

Fig. 4. An SMD network with emptiable siphons

siphon. Let c be a P-semiflow of minimal support; hence its support is also trivially a siphon. Every siphon contains a minimal siphon, which is also the support of a P-semiflow by the implication $1 \Rightarrow 2$ which we completed above. Hence, necessarily, the support of c is a minimal siphon, otherwise minimality of c as a P-semiflow would be violated).

IV. Examples and Counter-examples

A. SMD networks with emptiable siphons

We show, first of all, that minimal siphons in State Machine Decomposable nets need not be support of P-semiflows. In particular, if the OC condition is not fulfilled it may well occur that siphons do not contain the support of any P-semiflow. Consider the following reaction network:

$$S_0 + F \to S_1 + E \to S_2 + F$$

$$S_2 \to S_1 \to S_0$$

whose associated Petri net is shown in Fig. 4. This is given by the composition of two strongly connected state machines, respectively comprising species $\{S_0, S_1, S_2\}$ and $\{E, F\}$. It is straightforward to verify that $\{F, S_1, S_2\}$ is a minimal siphon for the net in question, but it does not contain the support of any P-semiflow. Indeed, the only conservation laws of the Petri Net in Fig. 4 are those corresponding to the supports of the individual state machines, namely:

$$S_0 + S_1 + S_2 = const., \qquad E + F = const.$$

We show below, that the associated ODE may fail to be persistent. Let us first write equations for the reaction network under consideration by assuming mass-action kinetics. This yields:

$$\begin{array}{rcl} \dot{S}_0 &=& -k_1 F \cdot S_0 + k_4 S_1 \\ \dot{S}_1 &=& -k_4 S_1 - k_2 E \cdot S_1 + k_3 S_2 + k_1 F \cdot S_0 \\ \dot{S}_2 &=& -k_3 S_2 + k_2 E \cdot S_1 \\ \dot{E} &=& -k_2 E \cdot S_1 + k_1 F \cdot S_0 \\ \dot{F} &=& -k_1 F \cdot S_0 + k_2 E \cdot S_1. \end{array} \tag{6}$$

As remarked above there are two conservation laws. Let $x = [S_0, S_1, S_2, E, F]'$ be the state of system (6); we consider the equilibrium $x_e = [1, 0, 0, 1, 0]'$. Linearizing around x_e yields the system:

$$\dot{\partial x} = \begin{bmatrix} 0 & k_4 & 0 & 0 & -k_1 \\ 0 & -k_2 - k_4 & k_3 & 0 & k_1 \\ 0 & k_2 & -k_3 & 0 & 0 \\ 0 & -k_2 & 0 & 0 & k_1 \\ 0 & k_2 & 0 & 0 & -k_1 \end{bmatrix} \partial x \doteq A\, \partial x$$

Simple inspection of matrix A shows that:

$$\text{sp}(A) = \{0\} \cup \text{sp} \begin{bmatrix} -k_2 - k_4 & k_3 & k_1 \\ k_2 & -k_3 & 0 \\ k_2 & 0 & -k_1 \end{bmatrix}$$

where the eigenvalue in 0 has multiplicity 2 and is in agreement with the 2 conservation laws exhibited by the reaction network. Notice that the 3×3 minor in the previous equation is a Metzler matrix. Hence its asymptotic stability can be checked by establishing negativity of its dominant eigenvalue. Indeed, provided $k_4 > k_2$ we have:

$$[1, 1, 1]' \begin{bmatrix} -k_2 - k_4 & k_3 & k_1 \\ k_2 & -k_3 & 0 \\ k_2 & 0 & -k_1 \end{bmatrix} = [k_2 - k_4, 0, 0] \prec 0$$

which proves negativity of Perron-Frobenius eigenvalue. Hence, the equilibrium x_e is locally asymptotically stable relative to its stoichiometry class (indeed, due to conservation laws, it can only attract initial conditions which belong to the same stoichiometry class). This, of course, contradicts persistence as x_e is a locally attractive equilibrium point which belongs to the boundary of the positive orthant.

B. Liveness and Persistence

One property which is central in studies dealing with Petri Nets and also in the quest for a modular approach to their investigation is the notion of Liveness (see [5], [7], [6]). This property amounts, for a given Petri Net, to the possibility of executing any transition, from an arbitrary reachable state through a suitable firing sequence. It is a *behavioral* property, viz. it not only depends upon the topology of the network, but also on the initial marking that it is considered. Moreover, the property is in general non monotone with respect to the marking itself (adding tokens to a live network need not preserve liveness), so that it seems difficult to expect a tight relation between Liveness and Persistence. While it is not known whether Liveness implies Persistence for Chemical Reaction Networks with Mass-Action Kinetics, it is relatively easy to show that for networks with arbitrary kinetics (for instance satisfying some simple monotonicity conditions), this implication fails to hold. Consider the following reversible reaction:

$$2A + B \leftrightarrow A + 2B. \tag{7}$$

The associated Petri Net is conservative, with a unique P-semiflow $[1, 1]$, consistent, with T-semiflow $[1, 1]'$ and has 2 minimal siphons, $\{A\}$ and $\{B\}$ respectively. Moreover, it is a live network, provided it is initialized with at least 3 tokens (this can be verified straightforwardly by constructing the reachable graph). When equations are written assuming

mass-action kinetics it turns out to be a persistent network irrespectively of the parameters. We show that, assuming different type or rates, the network indeed violates persistence. In particular, assuming reaction rates of the following type:

$$R_1(A,B) = k_1 AB^2 \qquad R_{-1}(A,B) = k_{-1}A^2B, \tag{8}$$

we obtain the following systems of differential equations:

$$\begin{array}{rcl} \dot{A} & = & -R_1(A,B) + R_{-1}(A,B) \\ \dot{B} & = & R_1(A,B) - R_{-1}(A,B). \end{array} \tag{9}$$

Denoting by c_0 the conserved total amount of A and B, viz. $c = A(t) + B(t) = A(0) + B(0)$ we are able to bring down dimension by 1 and study the following scalar differential equation:

$$\begin{array}{rcl} \dot{A} & = & -k_1 A \cdot (c-A)^2 + k_{-1}A^2(c-A) \\ & = & A \cdot (c-A) \cdot (-k_1 c + k_1 A + k_{-1}A) \end{array} \tag{10}$$

on the interval $A \in [0, c]$. Therefore, in each non-trivial stoichiometry class we have 3 equilibria: $A = 0$, $A = c$ and $A = k_1 c/(k_1 + k_{-1})$. In particular, for $A \in (0, k_1 c/(k_1 + k_{-1}))$ we have $\dot{A} < 0$, while for $A \in (k_1 c/(k_1 + k_{-1}), c)$ we have $\dot{A} > 0$ showing indeed that the two equilibria at the boundary are asymptotically stable, while the equilibrium in the interior is unstable, regardless of parameters values. Indeed, with this choice of rates the reaction network is never persistent.

C. Mitogen Activated Protein Kinase cascade

As an example of application of our Main Result we illustrate the decomposition of a MAPK cascade; this is one of the most studied signaling pathways in molecular biology and is involved in many vital activities of living cells. In particular we consider a network involving three phosphorilation steps, of which the first one is a single phosphorilation, and the two following ones are double-phosphorilations of the type exemplified earlier. The structure of the network is given below:

$$\begin{array}{l} E + S \leftrightarrow ES \rightarrow S_p \\ F + S_p \leftrightarrow FS_p \rightarrow F + S \\ S_p + R \leftrightarrow S_pR \rightarrow S_p + R_p \leftrightarrow S_pR_p \rightarrow S_p + R_{pp} \\ G + R_{pp} \leftrightarrow GR_{pp} \rightarrow G + R_p \leftrightarrow GR_p \rightarrow G + R \\ R_{pp} + Q \leftrightarrow R_{pp}Q \rightarrow R_{pp} + Q_p \leftrightarrow R_{pp}Q_p \rightarrow R_{pp} + Q_{pp} \\ H + Q_{pp} \leftrightarrow HQ_{pp} \rightarrow H + Q_p \leftrightarrow HQ_p \rightarrow H + Q. \end{array} \tag{11}$$

The names of species have been chosen according to the convention that each "$_p$" subscript denotes the presence of a phosphate group attached to the corresponding chemical species. This is an SMD network, with tree-like structure. In particular, it can be decomposed into 7 state machines; each one of them corresponds to the conservation law of a different kind of species, namely E, F, S, R, G, Q, H. The state machine decomposition and the corresponding tree-like structure are shown in Fig. 5. Notice that the overall network satisfies the Overlap Compatibility condition. Therefore, the Main Result applies and structural non-emptiability of siphons can be concluded. This, in turn, implies persistence of the network according to the Theorem in [1].

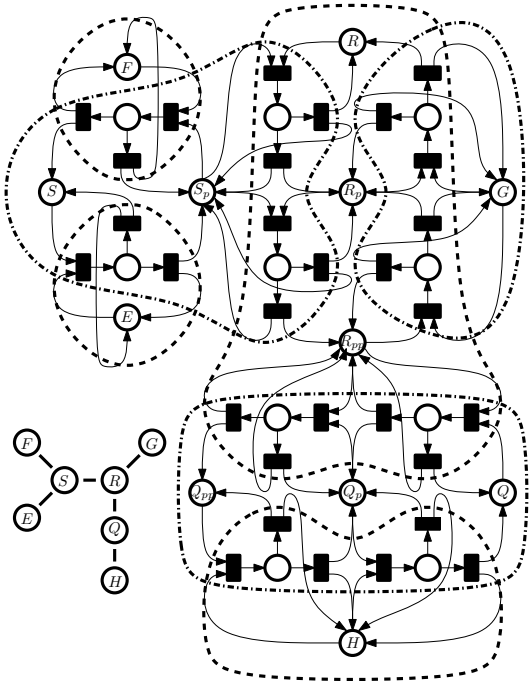

Fig. 5. SM decomposition for the MAPK cascade network

V. Conclusions

We derived a sufficient condition which allows to conclude structural non-emptiability of siphons for SMD Petri Nets which are composed according to some special overlapping rule. The condition is then illustrated on a non-trivial example of chemical reaction network arising in biochemistry.

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