# Reachability Problems for Continuous Chemical Reaction Networks\*

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#### Abstract

Chemical reaction networks (CRNs) model the behavior of molecules in a well-mixed system. The emerging field of molecular programming uses CRNs not only as a descriptive tool, but as a programming language for chemical computation. Recently, Chen, Doty and Soloveichik introduced a new model of chemical kinetics, rate-independent continuous CRNs (CCRNs), to study the chemical computation of continuous functions. A fundamental question of a CRN is whether a state of the system is reachable through a sequence of reactions in the network. This is known as the reachability problem. In this paper, we investigate CCRN-REACH, the reachability problem for this model of chemical reaction networks. We show that, for continuous CRNs, constructing a path to a state of the network is computable in polynomial time. We also prove that a related problem, Sub-CCRN-REACH, is NP-complete.

#### 1 Introduction

Abstract chemical reaction networks (CRNs) model chemical interactions in a well mixed system. Informally, CRNs consist of a finite set of species of chemicals (usually written abstractly as capital letters; i.e., A, B, etc.) and a finite set of reactions between these species. A simple example is the CRN consisting of species A, B and C, with one reaction  $2A + B \xrightarrow{k} 2C$  (taking A to be the hydrogen molecule  $H_2$ , B to be the oxygen molecule  $O_2$ , and C to be the water molecule  $H_2O$ , this CRN models the formation of water molecules with kinetic rate constant k). CRNs have historically been used as a descriptive tool, allowing researchers to formally analyze

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the behavior of natural chemical systems. However, the field of molecular programming has recently brought CRNs to prominence as a programming language for chemical computation. Molecular programming, as the name suggests, is devoted to engineering complex computational systems from molecules. Recent work in this area has come to view abstract CRNs as a programming language to engineer "chemical software" [9, 18]. Exciting new developments have shown methods of converting arbitrary chemical reaction networks into computation using DNA strands [2, 4, 19]. Thus the programmable power of chemical reaction networks is no longer simply of theoretical interest. To achieve the goal of engineering large scale, robust chemical computation, tools to analyze CRNs will be vital.

There are many ways to define the behavior of abstract CRNs, the two most prominent being mass action kinetics and stochastic chemical reaction networks. Mass action kinetics was the first model to be studied extensively. It is a continuous, deterministic model of chemical reaction networks. Mass action kinetics is used to study systems with sufficiently large numbers of molecules so that the amount of a given molecule can be represented as a real-valued concentration. The dynamics of reactions under mass action kinetics are governed by deterministic differential equations. However, the deterministic mass action model is not well suited if the number of molecules of the system is low. Stochastic CRNs are widely used to analyze those systems with a relatively low number of molecules [16, 7]. The stochastic CRN model is discrete and non-deterministic. Unlike mass action, the amount of each species is represented as a non-negative integer, and the reactions of a system are modeled as Markov jump processes [8]. The stochastic model is closely related to many well-studied models of computation such as Vector Addition Machines [10], Petri Nets [6] and Population Protocols [1]. Recently, Chen, Doty and Soloveichik introduced a new model of chemical kinetics, rate-independent continuous CRNs (CCRNs) [3]. The CCRN model is continuous, dealing with real-valued concentrations of species, but, unlike the stochastic or mass action models, it is rate-free (reactions do not have any associated kinetic rate constant). Chen, Doty and Soloveichik used CCRNs to study which real valued functions  $f: \mathbb{R}^k \to \mathbb{R}$  were computable by a chemical reaction network. By being a rate-free model, it allows for the study of the computational power of large chemical systems relying on stoichiometry alone (i.e., without depending on specific rates of the reactions). This is important, as rate constants are hard to experimentally determine and vary under external factors such as temperature.

A fundamental question one can ask of a stochastic chemical reaction network is whether a particular state is reachable from a starting configuration; this is called the reachability problem. The reachability problem for stochastic CRNs is equivalent to an important problem in theoretical computer science, the Vector Addition System Reachability problem (VAS reachability) [5]. The VAS reachability problem was proven to be at least EXPSPACE-hard by Lipton in 1976 [14], before it was even proven decidable. In 1981, building on the work of Sacerdote and Tenney [17], Mayr proved the reachability problem was decidable [15]. Subsequently, Kosaraju [11] and Lambert [12] gave two additional proofs of the decidability of VAS Reachability. However, all proofs that the reachability problem is decidable were very difficult, until Lérôux [13] gave a greatly simplified proof. Unfortunately, we still do not know if this problem is decidable in any primitive recursive time bound.

In this paper, we investigate two variants of the reachability problem in the context of CCRNs. In section 3, we analyze the complexity of the direct analog of the reachability problem for CCRNs, the continuous chemical reaction network reachability problem (CCRN-REACH). Informally, the CCRN-REACH problem is: given a CCRN C and states  $\mathbf{c}$  and  $\mathbf{d}$ , output a path taking c to d, if one exists. To effectively compute CCRN-REACH, we will require the states to be over the rationals instead of over arbitrary reals. We show that, contrary to the difficulty of the VAS reachability problem, CCRN-REACH can be computed in polynomial time. In the process, we give new definitions and lemmas which we believe will be useful in further investigations of the continuous chemical reaction network model. In section 4, we define a problem closely related to the reachability problem, called the Sub-CCRN-REACH problem. Sub-CCRN-REACH asks if a path exists between two states using at most k of the reactions in the network. In contrast to the computational "ease" of CCRN-REACH, we show that Sub-CCRN-REACH is NP-complete.

### 2 Preliminaries

Throughout the remainder of this paper  $\|\cdot\|$  will be the max norm. Before proving the main theorem, we will review preliminary definitions and notations for continuous CRNs.

#### 2.1 Rate Independent Continuous CRNs

A continuous chemical reaction network (CCRN) is a pair  $C = (\Lambda, R)$ , where  $\Lambda$  is a finite set of species, and R is a finite set of reactions over  $\Lambda$ . We typically denote species by capital letters, so that  $\Lambda = \{A, B, ...\}$ . A reaction over the set of species  $\Lambda$  is an element  $\rho = (\mathbf{r}, \mathbf{p}) \in \mathbb{N}^{\Lambda} \times \mathbb{N}^{\Lambda}$ , where  $\mathbf{r}$  and  $\mathbf{p}$  specify the stoichiometry of the reactants and products, respectively. We require the net change  $\Delta \rho = \mathbf{p} - \mathbf{r}$  of a reaction  $\rho = (\mathbf{r}, \mathbf{p})$  to be nonzero. We will usually write a reaction using the "reactants, right arrow, products" notation; for example,  $\rho = A + B \to C$  (in this example  $\mathbf{r} = (1, 1, 0)$  and  $\mathbf{p} = (0, 0, 1)$ ). A reaction  $\rho = (\mathbf{r}, \mathbf{p})$  is catalytic if, for some species s,  $\mathbf{r}(s) = \mathbf{p}(s) \neq 0$  (for example,  $A + B \to A + C$ ). In this case, we call the species s a catalyst. Each CCRN  $C = (\Lambda, R)$  has an associated reaction

stoichiometry matrix  $\mathbf{M}$  specifying the net change of each species for every reaction. Formally,  $\mathbf{M}$  is a  $|\Lambda| \times |R|$  matrix over  $\mathbb{Z}$  such that  $\mathbf{M}(i,j)$  is the net change of the ith species for the jth reaction. Note that  $\mathbf{M}$  does not fully specify a CCRN C, since it does not identify catalytic reactions. A state of a CCRN  $C = (\Lambda, R)$  is a vector  $\mathbf{c} \in \mathbb{R}^{\Lambda}_{\geq 0}$  specifying the (nonnegative) concentration of each species. The support of a state  $\mathbf{c}$  is the set  $supp(\mathbf{c}) = \{s \in \Lambda \mid \mathbf{c}(s) > 0\}$  of all species with non-zero concentrations at  $\mathbf{c}$ . The support of a reaction  $\rho = (\mathbf{r}, \mathbf{p})$  is the set  $supp(\rho) = \{s \in \Lambda \mid \mathbf{r}(s) > 0\}$  of all reactants of  $\rho$ . A reaction  $\rho = (\mathbf{r}, \mathbf{p}) \in R$  is applicable at a state  $\mathbf{c}$  if  $supp(\mathbf{r}) \subseteq supp(\mathbf{c})$  (i.e., if the concentration of each reactant is non-zero at  $\mathbf{c}$ ). A flux vector  $\mathbf{u}$  is the set  $supp(\mathbf{u}) = \{\rho \in R \mid \mathbf{u}(\rho) > 0\}$ . A flux vector  $\mathbf{u}$  is a vector  $\mathbf{u}$  is the set  $supp(\mathbf{u}) = \{\rho \in R \mid \mathbf{u}(\rho) > 0\}$ . A flux vector  $\mathbf{u}$  is applicable at a state  $\mathbf{c}$  if the following conditions hold:

1. Every  $\rho \in supp(\mathbf{u})$  is applicable at  $\mathbf{c}$ .

2. 
$$\mathbf{c}(s) + \sum_{\rho \in R} \mathbf{u}(\rho) \Delta \rho(s) \ge 0$$
 for every  $s \in \Lambda$ .

If a flux vector  $\mathbf{u}$  is applicable at state  $\mathbf{c}$ , we can apply  $\mathbf{u}$  to  $\mathbf{c}$ , resulting in the state

$$\mathbf{c} * \mathbf{u} = \mathbf{c} + \sum_{\rho \in R} \mathbf{u}(\rho) \Delta \rho.$$

Equivalently,  $\mathbf{c} * \mathbf{u} = \mathbf{c} + \mathbf{M}\mathbf{u}$ . A flux vector sequence,  $\mathbf{U} = (\mathbf{u}_1, ..., \mathbf{u}_k)$  is a tuple of flux vectors. We apply a flux vector sequence  $\mathbf{U} = (\mathbf{u}_1, ..., \mathbf{u}_k)$  iteratively to a state  $\mathbf{c}$ ,

$$\mathbf{c} * \mathbf{U} = (\mathbf{c} * (\mathbf{u}_1, \dots, \mathbf{u}_{k-1})) * \mathbf{u}_k.$$

A flux vector sequence  $\mathbf{U} = (\mathbf{u}_1, ..., \mathbf{u}_k)$  is applicable at state  $\mathbf{c}$  if  $\mathbf{u}_i$  is applicable at  $(\mathbf{c} * (\mathbf{u}_1, ..., \mathbf{u}_{i-1}))$  for every  $1 < i \le k$ . If  $\mathbf{c}$  and  $\mathbf{d}$  are any states, we say that  $\mathbf{d}$  is reachable from  $\mathbf{c}$ , denoted  $\mathbf{c} \to^* \mathbf{d}$ , if there exists a flux vector sequence  $\mathbf{U}$  applicable at  $\mathbf{c}$  such that  $\mathbf{c} * \mathbf{U} = \mathbf{d}$ . We say that  $\mathbf{d}$  is reachable from  $\mathbf{c}$  in k steps, denoted  $\mathbf{c} \to^k \mathbf{d}$ , if there exists a flux vector sequence  $\mathbf{U} = (u_1, ..., u_k)$  applicable at  $\mathbf{c}$  such that  $\mathbf{c} * \mathbf{U} = \mathbf{d}$ . A reaction  $\rho \in R$  is eventually applicable from  $\mathbf{c}$  if there exists a state  $\mathbf{d}$  reachable from  $\mathbf{c}$  so that  $\rho$  is applicable at  $\mathbf{d}$ . A reaction is permanently inapplicable from  $\mathbf{c}$  if it is not eventually applicable from  $\mathbf{c}$ .

The following theorem, proven in [3], will be used in the proof of our first main theorem.

**Theorem 0.** If  $\mathbf{c} \to^* \mathbf{d}$ , then  $\mathbf{c} \to^{m+1} \mathbf{d}$  where m = |R| is the number of reactions.

## 3 The Reachability Problem for Continuous CRNs

Having defined the relevant concepts for continuous chemical reaction networks, we are now able to formally define our problem CCRN-REACH.

The Continuous CRN Reachability Problem. Given a continuous  $CRN \ C = (\Lambda, R)$  and two states  $\mathbf{c}$ ,  $\mathbf{d} \in \mathbb{Q}^{\Lambda}$ , output a flux vector sequence  $\mathbf{U}$  such that  $\mathbf{U}$  is applicable at  $\mathbf{c}$  and  $\mathbf{c} * \mathbf{U} = \mathbf{d}$ , if one exists; output "not reachable" otherwise.

Note that this problem becomes a trivial solution of a system of linear equations if we drop the requirement that the flux vector sequence must be applicable at **c**. We will prove that CCRN-REACH is computable in polynomial time. Intuitively, the dramatic difference in the computational difficulty between the VAS reachability problem (known to be at least EXPSPACE-hard) and CCRN-REACH is the additional flexibility given by the rational valued flux vectors. To compute CCRN-REACH, we show how to build a flux vector sequence lead from the starting state to a state of maximal support. This is only possible in the CCRN model of chemical reaction networks, which allows arbitrarily small additions via flux vectors. Once we are in such a maximal state we are able to get to the end state with the application of a single flux vector. To formalize this intuition, we will introduce several definitions and lemmas.

Fix a continuous CRN  $C = (\Lambda, R)$ .

**Definition.** Let **c** be a state, and  $\epsilon > 0$ . We say that a vector **u** is an  $\epsilon$ -max support flux vector of **c** if **u** satisfies the following:

- 1.  $\mathbf{u}$  is a flux vector that is applicable at  $\mathbf{c}$ .
- 2. for every flux vector  $\mathbf{v}$  applicable at  $\mathbf{c}$ , supp $(\mathbf{c} * \mathbf{v}) \subseteq supp(\mathbf{c} * \mathbf{u})$ .
- $3. \|\mathbf{u}\| \leq \epsilon.$

That is, a vector is an  $\epsilon$ -max support flux vector of a state  $\mathbf{c}$  if it is applicable at  $\mathbf{c}$  and maximally increases the support of  $\mathbf{c}$  while giving at most  $\epsilon$  flux to each reaction. We will show that  $\epsilon$ -max support flux vectors exist for every state and  $\epsilon > 0$ .

Let  $\epsilon > 0$ . We now construct a specific  $\epsilon$ -max support flux vector of  $\mathbf{c}$ , which we will henceforth call **the**  $\epsilon$ -max support flux vector of  $\mathbf{c}$ . Define  $App_{\mathbf{c}}$  to be the set of all applicable reactions at  $\mathbf{c}$ . Let  $\epsilon_{\mathbf{c}} = min\{\mathbf{c}(s) \mid s \in supp(\mathbf{c})\}$  (the lowest nonzero concentration of any species at state  $\mathbf{c}$ ),  $\Gamma_{\mathbf{c}} = max\{1, |\Delta \rho(s)| : \rho \in App_{\mathbf{c}}\}$ , and  $\delta_{\mathbf{c},\epsilon} = \frac{1}{\Gamma_{\mathbf{c}}|R|}min\{\frac{\epsilon_{\mathbf{c}}}{2}, \epsilon\}$ .

**Definition.** The  $\epsilon$ -max support flux vector of  $\mathbf{c}$  is the vector  $\mathbf{u}_{\mathbf{c},\epsilon}$  defined by

$$\mathbf{u}_{\mathbf{c},\epsilon}(\rho) = \begin{cases} \delta_{\mathbf{c},\epsilon}, & \text{if } \rho \in App_{\mathbf{c}} \\ 0, & \text{otherwise} \end{cases}$$

for every  $\rho \in R$ .

The following lemma shows that  $\mathbf{u}_{\mathbf{c},\epsilon}$  is a well defined  $\epsilon$ -max support flux vector of  $\mathbf{c}$ .

**Lemma 1.** Let  $\mathbf{c}$  be a state, and  $\epsilon > 0$ . Then  $\mathbf{u}_{\mathbf{c},\epsilon}$  is an  $\epsilon$ -max support flux vector of  $\mathbf{c}$ .

When the context is clear, we will refer to  $\mathbf{u}_{\mathbf{c},\epsilon}$  as the max support flux vector. The following observation can be easily seen from the definition of the max support flux vector.

**Observation 1.** The  $\epsilon$ -max support flux vector of  $\mathbf{c}$ ,  $\mathbf{u}_{\mathbf{c},\epsilon}$ , is computable in polynomial time in terms of  $(C, \mathbf{c}, \epsilon)$ .

Since  $\mathbf{u}_{\mathbf{c},\epsilon}$  is a flux vector applicable at  $\mathbf{c}$ , we are able to discuss the max support flux vector of the state  $(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})$ . For convenience, we will use the following notation:

- 1.  $\mathbf{u}_{\mathbf{c},\epsilon}^1 := \mathbf{u}_{\mathbf{c},\epsilon}$ .
- 2.  $\mathbf{u}_{\mathbf{c},\epsilon}^k := \text{the } \epsilon\text{-max support flux vector of the state } (\mathbf{c} * (\mathbf{u}_{\mathbf{c},\epsilon}^1, ..., \mathbf{u}_{\mathbf{c},\epsilon}^{k-1})).$

It is important to note that the vectors  $\mathbf{u}_{\mathbf{c},\epsilon}^i$  are distinct; in fact, the hope is that the set of applicable reactions grows with successive applications max support flux vectors.

**Definition.** Let  $\epsilon > 0$ , m = |R| + 1 and  $\gamma = \frac{\epsilon}{m}$ . The  $\epsilon$ -max support flux vector sequence of  $\mathbf{c}$ , denoted  $\mathbf{U}_{\mathbf{c},\epsilon}$ , is defined to be the sequence

$$\mathbf{U}_{\mathbf{c},\epsilon} = (\mathbf{u}_{\mathbf{c},\gamma}^1, \dots, \mathbf{u}_{\mathbf{c},\gamma}^m).$$

From Observation 1 it is clear that  $\mathbf{U}_{\mathbf{c},\epsilon}$  is computable in polynomial time in terms of  $(C, \mathbf{c}, \epsilon)$ .

**Observation 2.** For any state  $\mathbf{c}$  and any  $\epsilon > 0$ , the  $\epsilon$ -max support flux vector sequence of  $\mathbf{c}$  is a flux vector sequence that is applicable at  $\mathbf{c}$ . Moreover,  $\|\sum_{i=1}^{m} \mathbf{u}_{\mathbf{c},\gamma}^{i}\| \leq \epsilon$ .

*Proof.* This follows immediately from Lemma 1 and the choice of  $\gamma$ .

The choice of restricting the length of the flux vector  $\mathbf{U}_{\mathbf{c},\epsilon}$  to |R|+1 is not arbitrary. We will show that this is all that is required to get to the largest possible support of a state.

**Definition.** Let  $\mathbf{c}$  be a state and  $\epsilon > 0$ . We say that a state  $\mathbf{m}$  is an  $\epsilon$ -max support state of  $\mathbf{c}$  if, for every state  $\mathbf{d}$  that is reachable from  $\mathbf{c}$ ,  $supp(\mathbf{d}) \subseteq supp(\mathbf{m})$ .

Similar to our previous definitions, we now define the  $\epsilon$ -max support state of  ${\bf c}$  to be

$$\mathbf{m}_{\mathbf{c},\epsilon} := (\mathbf{c} * \mathbf{U}_{\mathbf{c},\epsilon}).$$

**Lemma 2.** If **c** is a state and  $\epsilon > 0$ , then  $\mathbf{m}_{\mathbf{c},\epsilon}$  is an  $\epsilon$ -max support state of **c**.

Since  $\epsilon$  was arbitrary in Lemma 2, we see that for every  $\epsilon, \epsilon' > 0$ ,  $supp(\mathbf{m}_{\mathbf{c},\epsilon}) = supp(\mathbf{m}_{\mathbf{c},\epsilon'})$ . Recall that a reaction  $\rho$  is eventually applicable from a state  $\mathbf{c}$  if  $\rho$  is applicable at some state  $\mathbf{d}$  that is reachable from  $\mathbf{c}$ . By Lemma 2, a reaction  $\rho$  is eventually applicable from a state  $\mathbf{c}$  if and only if  $\rho$  is applicable at  $\mathbf{m}_{\mathbf{c},\epsilon}$  for any  $\epsilon > 0$ . This allows us to compute all the permanently inapplicable reactions from  $\mathbf{c}$ , which will be vital in the algorithm computing CCRN-REACH.

**Observation 3.** The set of all permanently inapplicable reactions from  $\mathbf{c}$  is computable in polynomial time.

*Proof.* By Observation 1 we compute the 1-max support state of  $\mathbf{c}$ ,  $\mathbf{m}_{\mathbf{c},1}$ , and eliminate all reactions not applicable at  $\mathbf{m}_{\mathbf{c},1}$ .

We are now ready to prove our first main theorem.

Main Theorem 1. CCRN-REACH is computable in polynomial time.

*Proof.* Consider the following algorithm (Algorithm 1 below) deciding CCRN-REACH. From our previous observations, it is clear that the algorithm runs in polynomial time in terms of the input. We now prove that  $\mathbf{d}$  is reachable from  $\mathbf{c}$  if and only if the above algorithm outputs a flux vector sequence  $\mathbf{U}$  applicable at  $\mathbf{c}$  such that  $\mathbf{c} * \mathbf{U} = \mathbf{d}$ .

Assume that, on input  $C = (\Lambda, R)$ , **c** and **d**, the algorithm outputs a sequence of vectors **U**. Let R be the set of reactions left after exiting the loop (necessarily non-empty), and m = |R|. By the choice of  $\epsilon$  and Observation 2, for each  $\rho \in R$ ,

$$\sum_{i=1}^{m+1} \mathbf{u}_{\mathbf{c},\gamma}^{i}(\rho) < S(\rho),$$

where  $\mathbf{U}_{\mathbf{c},\epsilon} = (\mathbf{u}_{\mathbf{c},\gamma}^1, \dots, \mathbf{u}_{\mathbf{c},\gamma}^{m+1})$  (recall that  $\gamma = \frac{\epsilon}{m+1}$ ). Therefore, the vector  $\mathbf{v} = S - \mathbf{U}_{\mathbf{c},\epsilon}$  is a flux vector (in fact  $\mathbf{v}$  is strictly positive). Hence the output  $\mathbf{U} = (\mathbf{U}_{\mathbf{c},\epsilon}, \mathbf{v})$  is a flux vector sequence. By Observation 2,  $\mathbf{U}_{\mathbf{c},\epsilon}$  is applicable at  $\mathbf{c}$ . Upon exiting the loop we are guaranteed that any reactions remaining in R must be eventually applicable from  $\mathbf{c}$  using only the other

#### **Algorithm 1** CCRN-REACH on input $C = (\Lambda, R)$ , c, d

- 1: Eliminate from R all permanently inapplicable reactions from c
- 2: for each reaction  $\rho \in R$  do
- Compute a vector  $F_{\rho} \in \mathbb{Q}_{\geq 0}^{R}$  such that  $\mathbf{c} + \mathbf{M}F_{\rho} = \mathbf{d}$  and  $F_{\rho}(\rho) > 0$ , if one exists
- if no such vector exists, eliminate  $\rho$  from R, GOTO 1. 4:
- 5: end for
- 6: if  $R = \emptyset$ , output "not reachable"
- 7: otherwise define vector  $S \in \mathbb{Q}_{>0}^R$  as follows

8: for each 
$$\rho \in R$$
, set  $S(\rho) = \frac{1}{|R|} \sum_{i=1}^{|R|} F_i(\rho)$ 

- 9: Compute  $\epsilon=\frac{\min\{S(\rho)\}_{\rho\in R}}{2}$ 10: Compute the max support flux vector sequence  $\mathbf{U}_{\mathbf{c},\epsilon}$
- 11: Compute  $\mathbf{v} = S \mathbf{U}_{\mathbf{c},\epsilon}$
- 12: Output  $(\mathbf{U}_{\mathbf{c},\epsilon},\mathbf{v})$  (padded with 0s for eliminated reactions)

remaining reactions. Let  $\rho \in supp(\mathbf{v})$ . Then  $\rho \in R$ , and so  $\rho$  must be eventually applicable from  $\mathbf{c}$  using only reactions remaining in R. By Lemma 2,  $(\mathbf{c} * \mathbf{U}_{\mathbf{c},\epsilon}) = \mathbf{m}_{\mathbf{c},\epsilon}$  is a max support state, therefore  $\rho$  is applicable at  $(\mathbf{c}*\mathbf{U}_{\mathbf{c},\epsilon})$ . Since  $\rho$  was arbitrary,  $\mathbf{v}$  is applicable at  $(\mathbf{c}*\mathbf{U}_{\mathbf{c},\epsilon})$ , and so  $(\mathbf{U}_{\mathbf{c},\epsilon},\mathbf{v})$ is a flux vector sequence that is applicable at **c**. Finally, we have

$$\begin{split} \mathbf{c} * (\mathbf{U}_{\mathbf{c},\epsilon}, \mathbf{v}) &= \mathbf{c} + \mathbf{M}(\mathbf{U}_{\mathbf{c},\epsilon} + \mathbf{v}) \\ &= \mathbf{c} + \mathbf{M}S \\ &= \mathbf{c} + \mathbf{M} \frac{1}{|R|} \sum_{i=1}^{|R|} F_i(\rho) \\ &= \mathbf{c} + \frac{1}{|R|} \sum_{i=1}^{|R|} \mathbf{M} F_i(\rho) \\ &= \mathbf{c} + \frac{1}{|R|} \sum_{i=1}^{|R|} \mathbf{d} - \mathbf{c} \\ &= \mathbf{d}, \end{split}$$

where **M** is the stoichiometry matrix of  $C = (\Lambda, R)$ . Therefore if the algorithm outputs a vector sequence, then  $\mathbf{d}$  is reachable from  $\mathbf{c}$ .

For the other direction, assume that  $\mathbf{d}$  is reachable from  $\mathbf{c}$ . Then, by definition, there is a nonempty subset  $R' \subseteq R$  such that, for all  $\rho \in R'$ ,

- 1.  $\rho$  is eventually applicable from **c** using only reactions from R', and
- 2. there exists a vector  $F_{\rho}$  such that  $\mathbf{M}F_{\rho} = \mathbf{d} \mathbf{c}$  and  $F_{\rho}(\rho) > 0$ .

Therefore the algorithm will exit the loop with R nonempty, and output a flux vector sequence  $(\mathbf{U}_{\mathbf{c},\epsilon},\mathbf{v})$ . As we just shown,  $(\mathbf{U}_{\mathbf{c},\epsilon},\mathbf{v})$  applicable at  $\mathbf{c}$  such that  $\mathbf{c} * (\mathbf{U}_{\mathbf{c},\epsilon},\mathbf{v}) = \mathbf{d}$ .

## 4 The Subset Reachability Problem

Define the decision problem Sub-CCRN-REACH as follows,

The Continuous CRN Subset Reachability Problem. Given a continuous CRN  $C = (\Lambda, R)$ , states  $\mathbf{c}$ ,  $\mathbf{d}$  and integer k, accept if and only if there exists a path from  $\mathbf{c}$  to  $\mathbf{d}$  using only k reactions from R.

In contrast to the computational ease of CCRN-REACH, we give evidence that the related problem Sub-CCRN-REACH is quite difficult.

Main Theorem 2. Sub-CCRN-REACH is NP-complete.

*Proof.* From the proof that CCRN-REACH is computable in polynomial time, it is easy to see that Sub-CCRN-REACH is in NP. Simply guess a subset of k reactions and decide CCRN-REACH on the subset. We will reduce 3SAT to Sub-CCRN-REACH to show hardness.

Let  $\phi$  be a boolean formula on n variables  $x_1, \ldots, x_n$  with m clauses  $C_1, \ldots, C_m$ . Construct an equivalent CCRN  $C_{\phi} = (\Lambda_{\phi}, R_{\phi})$  and states  $\mathbf{c}_{\phi}$ ,  $\mathbf{d}_{\phi}$  as follows.

For each  $x_i$ , define three species  $S_i$ ,  $s_i$  and  $\bar{s}_i$ , and the following four reactions, where  $\emptyset$  is a null species (the reactants are being consumed without generating any products).

1. 
$$S_i \to s_i$$
 2.  $S_i \to \bar{s}_i$  3.  $s_i \to \emptyset$  4.  $\bar{s}_i \to \emptyset$ ,

For each clause  $C_j$  define one species  $T_j$ , and the following (catalytic) reactions

1. 
$$s_i \to s_i + T_j$$
, for every  $x_i$  in  $C_j$  2.  $\bar{s_i} \to \bar{s_i} + T_j$ , for every  $\bar{x_i}$  in  $C_j$ 

Define the start state  $\mathbf{c}_{\phi}$  to have a concentration of 1 for each species  $S_i$  and a concentration of 0 for all other species. Define the end state  $\mathbf{d}_{\phi}$  to have a concentration of 1 for each species  $T_j$ , and a concentration of 0 for all other species.

We now show that  $\phi \in 3SAT$  if and only if  $\mathbf{c}_{\phi} \to^* \mathbf{d}_{\phi}$  using exactly 2n + m reactions. Assume  $\phi \in 3SAT$ , let  $\mathbf{x}$  be any satisfying assignment. Define the flux vector  $\mathbf{u}_1$  by,

$$\mathbf{u}_1(\rho) = \begin{cases} 1 & \text{if } \rho = S_i \to s_i \text{ and } \mathbf{x}(x_i) = 1\\ 1 & \text{if } \rho = S_i \to \bar{s}_i \text{ and } \mathbf{x}(x_i) = 0\\ 0 & \text{otherwise.} \end{cases}$$

The flux vector  $\mathbf{u}_1$  transfers all of the concentration of  $S_i$  into either  $s_i$  or  $\bar{s}_i$ , depending on the satisfying assignment  $\mathbf{x}$ . The number of reactions given positive flux in  $\mathbf{u}_1$  is n. For each clause  $C_j$ , choose one variable  $x_{ij}$  or its negation that evaluates to true under  $\mathbf{x}$ . Define the flux vector  $\mathbf{u}_2$  by,

$$\mathbf{u}_{2}(\rho) = \begin{cases} 1 & \text{if } \rho = s_{i_{j}} \to s_{i_{j}} + T_{j} \text{ and } x_{i_{j}} \text{ is the chosen variable from } C_{j} \\ 1 & \text{if } \rho = s_{i_{j}}^{-} \to s_{i_{j}}^{-} + T_{j} \text{ and } x_{i_{j}}^{-} \text{ is the chosen variable from } C_{j} \\ 0 & \text{otherwise.} \end{cases}$$

Therefore  $\mathbf{u}_2$  only gives positive flux to m reactions, one for each clause in  $\phi$ . Finally, define the flux vector  $\mathbf{u}_3$  by,

$$\mathbf{u}_3(\rho) = \begin{cases} 1 & \text{if } \rho = s_i \to \emptyset \text{ and } \mathbf{x}(x_i) = 1\\ 1 & \text{if } \rho = \bar{s}_i \to \emptyset \text{ and } \mathbf{x}(x_i) = 0\\ 0 & \text{otherwise.} \end{cases}$$

The flux vector  $\mathbf{u}_3$  eliminates the concentrations of each species  $s_i$  or  $\bar{s}_i$  (only one of which has concentration 1). Clearly  $\mathbf{u}_3$  gives positive flux to only n reactions. Hence  $\mathbf{U} = (\mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3)$  gives positive flux to only 2n + m distinct reactions, and  $\mathbf{c}_{\phi} * \mathbf{U} = \mathbf{d}_{\phi}$ .

Assume  $\mathbf{c}_{\phi} * \mathbf{U} = \mathbf{d}_{\phi}$ . Since  $S_i$  has concentration 0 at  $\mathbf{d}$  at least one of the reactions  $S_i \to s_i$ ,  $S_i \to \bar{s}_i$  must be used, that is, at least n reactions. Similarly, since  $s_i$  and  $\bar{s}_i$  have concentration 0 at  $\mathbf{d}_{\phi}$ , at lest n must be used in any flux vector sequence. Since  $T_j$  has concentration 1 at  $\mathbf{d}_{\phi}$  at least one reaction of the form  $s_i \to s_i + T_j$  or  $\bar{s}_i \to \bar{s}_i + T_j$  must be used for each  $T_j$ , so at least m reactions. Hence  $\mathbf{U}$  must give positive flux to at least 2n+m reactions. In order to reach  $\mathbf{d}$  using the minimal number of reactions, 2n+m,  $\mathbf{U}$  must only give flux to one of  $S_i \to s_i$  or  $S_i \to \bar{s}_i$ . Let  $\mathbf{x}$  be the assignment of the variables  $(x_1, \ldots, x_n)$  given by

$$\mathbf{x}(x_i) = \begin{cases} 1 & \text{if } \mathbf{U}(S_i \to s_i) = 1\\ 0 & \text{otherwise.} \end{cases}$$

Since  $\mathbf{c}_{\phi} * \mathbf{U} = \mathbf{d}_{\phi}$ ,  $\mathbf{U}$  gives positive flux to  $s_i \to s_i + T_j$  or  $\bar{s}_i \to \bar{s}_i + T_j$  for each species  $T_j$  and some i. Therefore each clause  $C_j$  must be satisfiable under assignment  $\mathbf{x}$ . Hence, if  $\mathbf{c}_{\phi} \to^* \mathbf{d}_{\phi}$  using exactly 2n + m reactions, then  $\phi \in 3\mathrm{SAT}$ .

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## 5 Appendix

**Proof of Lemma 1.** First we show  $\mathbf{u}_{\mathbf{c},\epsilon}$  is a flux vector that is applicable at  $\mathbf{c}$ . It is clear that  $\mathbf{u}_{\mathbf{c},\epsilon}$  is a flux vector. It suffices to show that every reaction  $\rho \in supp(\mathbf{u}_{\mathbf{c},\epsilon})$  is applicable at  $\mathbf{c}$  and that  $(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon}) \in \mathbb{R}^{\Lambda}_{\geq 0}$ . From the definition of  $\mathbf{u}_{\mathbf{c},\epsilon}$ ,  $\mathbf{u}_{\mathbf{c},\epsilon}(\rho) > 0$  if and only if  $\rho \in App_{\mathbf{c}}$ . Therefore if  $\rho \in supp(\mathbf{u}_{\mathbf{c},\epsilon})$ , then  $\rho$  is applicable at  $\mathbf{c}$ . To complete the proof of item (1) we show  $\mathbf{c}*\mathbf{u}_{\mathbf{c},\epsilon}$  remains non-negative. Let  $s \in \Lambda$  be any species, and assume that the concentration of s at  $\mathbf{c}$  is greater than 0, i.e.,  $s \in supp(\mathbf{c})$ . By the definition of  $\mathbf{u}_{\mathbf{c},\epsilon}$ ,

$$|\sum_{\rho \in App_{\mathbf{c}}} \mathbf{u}_{\mathbf{c},\epsilon}(\rho) \Delta \rho(s)| \le \delta_{\mathbf{c},\epsilon} |R| \Gamma_{\mathbf{c}} \le \frac{\epsilon_{\mathbf{c}}}{2}$$

and therefore,

$$\begin{aligned} (\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})(s) &= \mathbf{c}(s) + \sum_{\rho \in R} \mathbf{u}_{\mathbf{c},\epsilon}(\rho) \Delta \rho(s) \\ &\geq \mathbf{c}(s) - |\sum_{\rho \in App_{\mathbf{c}}} \mathbf{u}_{\mathbf{c},\epsilon}(\rho) \Delta \rho(s)| \\ &\geq \epsilon_{\mathbf{c}} - \frac{\epsilon_{\mathbf{c}}}{2} \\ &> 0. \end{aligned}$$

Hence for every species  $s \in supp(\mathbf{c})$ ,  $(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})(s) > 0$ . Now assume  $s \notin supp(\mathbf{c})$ ; the concentration of s at  $\mathbf{c}$  is 0. As we have seen, the only reactions  $\rho$  such that  $\mathbf{u}_{\mathbf{c},\epsilon}(\rho) > 0$  are those reactions which are applicable at  $\mathbf{c}$ . By our assumption  $\mathbf{c}(s) = 0$ , any applicable reaction  $\rho$  at  $\mathbf{c}$  must have  $\Delta \rho(s) \geq 0$ . It is therefore clear that

$$(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})(s) \ge 0.$$

We now prove that, for every flux vector  $\mathbf{v}$  applicable at  $\mathbf{c}$ ,  $supp(\mathbf{c} * \mathbf{v}) \subseteq supp(\mathbf{c} * \mathbf{u})$ . Let  $s \in supp(\mathbf{c} * \mathbf{v})$ . We first assume that  $s \in supp(\mathbf{c})$ . We showed previously that if  $s \in supp(\mathbf{c})$ , then  $(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})(s) > 0$ . Hence  $s \in supp(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})$ . Now assume that  $s \notin supp(\mathbf{c})$ . As the concentration of s at  $\mathbf{c}$  is 0, any applicable reaction  $\rho$  at  $\mathbf{c}$  must have  $\Delta \rho(s) > 0$ . Since  $s \in supp(\mathbf{c} * \mathbf{v})$ , there must be at least one reaction  $\rho_s$  applicable at  $\mathbf{c}$  such that  $\Delta \rho_s(s) > 0$ . Since  $\rho_s$  is applicable at  $\mathbf{c}$ ,  $\mathbf{u}_{\mathbf{c},\epsilon}(\rho_s) = \delta_{\mathbf{c},\epsilon}$ . Thus

$$(\mathbf{c} * \mathbf{u}_{\mathbf{c},\epsilon})(s) = \mathbf{c}(s) + \sum_{\rho \in R} \mathbf{u}_{\mathbf{c},\epsilon}(\rho) \Delta \rho(s)$$

$$= |\sum_{\rho \in App_{\mathbf{c}}} \mathbf{u}_{\mathbf{c},\epsilon}(\rho) \Delta \rho(s)|$$

$$\geq \mathbf{u}_{\mathbf{c},\epsilon}(\rho_s) \Delta \rho_s(s)$$

$$\geq \delta_{\mathbf{c},\epsilon}$$

$$> 0.$$

Finally, it is immediate that  $\|\mathbf{u}_{\mathbf{c},\epsilon}\| \leq \epsilon$ .

**Proof of Lemma 2.** Let **d** be a state reachable from **c**. By Theorem 0, there exists a flux vector sequence of length m = |R| + 1 taking **c** to **d**, i.e.  $\mathbf{c} \to^m \mathbf{d}$ . By induction and use of Lemma 1, we see that for every state **d** such that  $\mathbf{c} \to^m \mathbf{d}$ ,  $supp(\mathbf{d}) \subseteq supp(\mathbf{m}_{\mathbf{c},\epsilon})$ .