

# something something classification of realisability of integer hyperflows using petrinet reachability

Jakob L. Andersen, Sissel Banke, Rolf Fagerberg, Christoph Flamm, Daniel Merkle, Peter F. Stadler

**Abstract**—The abstract goes here.

**Index Terms**—Chemical reaction network, chemical pathway, Petri net.

## I. INTRODUCTION

- the reachability seems to be defined here <https://arxiv.org/abs/2211.12603>, with a PSPACE completeness proof
- chemical context

**C**OLLECTIONS of chemical reactions are important for many problems in biology, the environment, living cells, metabolic pathways in organisms, and synthesis, whether in lab or production, to name a few. Such collections of chemical reactions are usually called *Chemical Reaction Networks*. It is well known that they can be modelled as directed multi-hypergraphs [1]–[3]. In which each molecule is represented by a vertex, and each reaction is modelled by a directed hyperedge. In many of the aforementioned situations one is interested in reaction mechanisms in subnetworks that have a specific function. That could for example be for developing a synthesis plan or investigating a subnetwork of the metabolic network that has a distinct feature. These reaction mechanisms are often called *pathways*. Hence being able to specify and look for pathways in a network is a core objective in chemical modelling, exploration, and design.

In [3] it was discussed how to define a distinct feature in a chemical reaction network as a *chemical transformation motif* which has constraints on both input and output. Such a motif enumerates a collection of pathways which all meet the constraints of the motif. By formally defining a pathway as an integer hyperflow it allowed [3] to algorithmically (in

combination with ILP) enumerate these integer hyperflows. As the reader may know ILP is NP-hard in theory and also in the case of finding integer hyperflows in chemical reaction networks [?], but for many networks and pathways of practical interest current ILP solvers perform well [3]. The advantage of integer hyperflows, however, contradictory to real-valued hyperflows, is that they precisely specify the number of times each reaction must happen in order to perform a specific overall transformation, i.e., they define pathways. They do not, however, specify in which order the reactions must run such that the pathway use exactly the number of molecules that has been specified by the motif and not more, or if this is even possible. In some cases it is not, for example in Fig. 1 the pathway specified by the integer hyperflow has no order that allows it to happen without borrowing either  $C$  or  $D$ . As the number of enumerated integer hyperflows is a possibly large number it is not feasible to manually check them all for realisability, i.e., if the reactions can run as specified while only using the number of molecules specified by the motif. We will in this paper develop a method for determining just that. We propose to convert the integer hyperflow into a Petri net which will allow us to use Petri net methodology to express and decide whether integer hyperflows are realisable.

For flows that are realisable, we introduce the concept of a *realisability certificate* which demonstrates how the pathway can be executed. Furthermore, the realisability certificate gives the order in which the reactions in the pathway should occur, which not only is important in order to understand the mechanism of the pathway but is also necessary for computing atom traces using graph transformation rule composition [5]. Additionally, we study how non realisable integer hyperflows can be made realisable by various extensions of the integer hyperflow, for instance, by scaling the flow itself or borrowing additional molecules which are then returned. The latter is often called a network catalyst in chemistry.

The rest of this paper is organized as follows. Section 2 covers notation and definitions for directed multi-hypergraphs, an extension of a directed multi-hypergraph, the *extended hypergraph*, and Petri nets. Section 3 introduces the realisability question, as well as the method for converting the integer hyperflow into a Petri net, lastly it covers the realisability certificate. In Section 4 we study how non realisable flows can be made realisable by either scaling the flow or using network catalysts. It also covers when a flow can be made realisable and when it cannot.

We will throughout the paper use examples of both realisable and non realisable pathways from the formose and pentose phosphate chemistry, and we will also introduce

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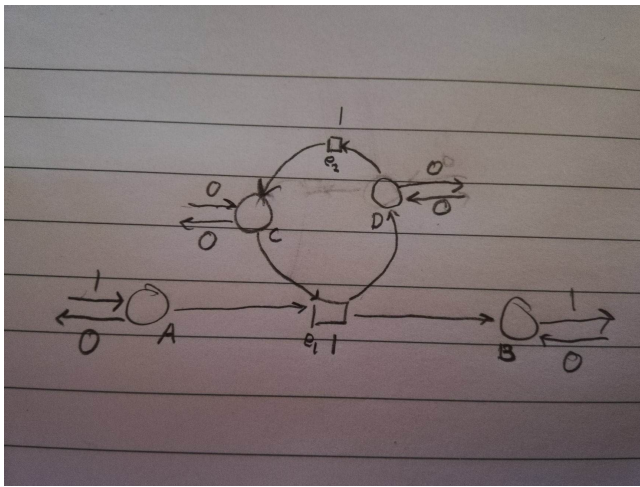


Fig. 1. Example of a flow that is not realisable in the strictest sense. Observe that the flow is indeed viable as it fulfils the flow conservation constraint. Furthermore notice that there is no input flow to neither  $C$  nor  $D$ , and therefore in the corresponding Petri net it will not be possible to fire either of  $e_1$  or  $e_2$  which is necessary for it to be realised. However, if  $C$  or  $D$  was borrowed the related flow with this borrowing would be realisable.

alternative pathways for both chemistries by either scaling a specific pathway by a factor or allowing network catalysts to be included in the pathway.

## II. PRELIMINARIES

- Make side-note on the trivial chemical P-invariant
- Make side-note on the connection between T-invariants
- decide on flow/hyperflow/pathway

### A. Chemical Reaction Networks and Pathways

Here we introduce the notation and definitions from [3] that is used within this paper.

A chemical reaction network can be modelled by a directed multi-hypergraph  $\mathcal{H} = (V, E)$ , where  $V$  is the set of vertices representing the molecules. The reactions are represented by the directed hyperedges  $E$ , where each edge  $e = (e^+, e^-)$  is an ordered pair of multisets of vertices, i.e.,  $e^+, e^- \subseteq V$ . We call  $e^+$  the *tail* of the edge  $e$ , and  $e^-$  the *head*. In the interest of conciseness we will refer to directed multi-hypergraphs simply as hypergraphs, directed hyperedges simply as edges, and chemical reaction networks as networks. For a multiset  $Q$  and an element  $q$  we use  $m_q(Q)$  to denote its multiplicity, i.e. the number of occurrences of  $q$  in  $Q$ . When denoting multisets we use the notation  $\{\{ \dots \}\}$ , e.g.,  $Q = \{\{a, a, b\}\}$  is a multiset with  $m_a(Q) = 2$  and  $m_b(Q) = 1$ . For a vertex  $v \in V$  and a set of edges  $A$  we use  $\delta_A^+(v)$  and  $\delta_A^-(v)$  to denote respectively the set of out-edges and in-edges of  $v$  contained in  $A$ , i.e., the edges in  $A$  that have  $v$  in their tail and  $v$  in their head, respectively.

In order to later define pathways we first introduce an extension of the network for representing input and output

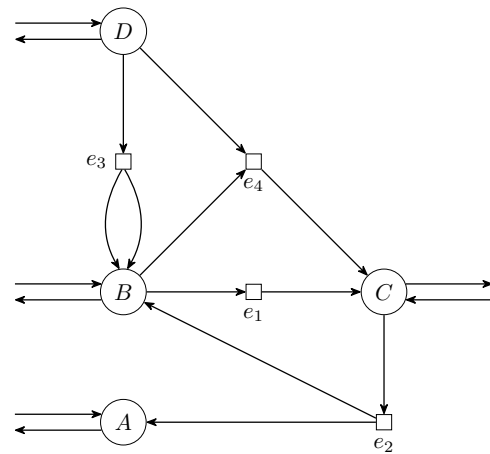


Fig. 2. Example extended hypergraph. The extended hypergraph consists of the vertices  $\{A, B, C, D\}$ , edges  $\{e_1, e_2, e_3, e_4\}$ , and half-edges. Throughout this paper we will represent directed hyperedges by boxes if they have more than one vertex in their head or tail.

Add stuff on multiplicities and edges from Figure 3 in the autocatalysis paper

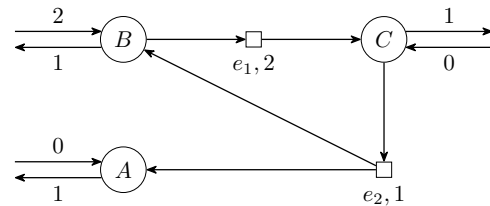


Fig. 3. Example integer hyperflow  $f$  on the example extended hypergraph in Fig. 2. The edges on which the flow is 0 have been omitted. In this hyperflow we, for example, have that  $f(e_B^-) = 2$ , i.e., the half edge into  $B$  has a flow 2,  $f(e_B^+) = 1$ , i.e., the half edge leaving  $B$  has a flow of 1,  $f(e_1) = 2$ , i.e., the edge  $e_1$  has a flow of 2, etc.

of compounds. Given a hypergraph  $\mathcal{H} = (V, E)$  we define the *extended hypergraph*  $\overline{\mathcal{H}}$  as

$$\begin{aligned} \overline{\mathcal{H}} &= (V, \overline{E}) \\ \overline{E} &= E \cup E^- \cup E^+ \\ E^- &= \{e_v^- = (\emptyset, \{\{v\}\}) \mid v \in V\} \\ E^+ &= \{e_v^+ = (\{\{v\}\}, \emptyset) \mid v \in V\} \end{aligned} \quad (1)$$

which has additional “half-edges”  $e_v^-$  and  $e_v^+$ , for each  $v \in V$ . An example of an extended hypergraph is presented in Fig. 2. These explicitly represent potential input and output channels to and from  $\mathcal{H}$ , i.e., what is called exchange reactions in metabolic networks.

In [3] it was proposed to model pathways in a network  $\mathcal{H}$  as an *integer hyperflow*. This is a function on its extended network  $f: \overline{E} \rightarrow \mathbb{N}_0$ , satisfying for each vertex  $v \in V$  the *flow conservation constraint*:

$$\sum_{e \in \delta_E^+(v)} m_v(e^+) f(e) - \sum_{e \in \delta_E^-(v)} m_v(e^-) f(e) = 0$$

Note in particular that  $f(e_v^-)$  is the input flow for a vertex  $v \in V$ , and the output flow is  $f(e_v^+)$ . An example of an integer hyperflow is given in Fig. 3.

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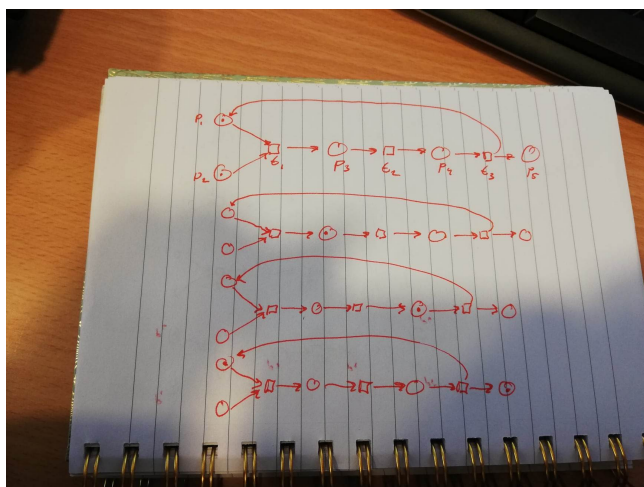


Fig. 4. Example firing sequence. In (a)  $P = \{p_1, p_2, p_3, p_4, p_5, p_6\}$ ,  $T = \{t_1, t_2, t_3\}$ ,  $F = \{(p_1, t_1), (p_2, t_1), (t_1, p_3), (p_3, t_2), (t_2, p_4), (p_4, t_3), (t_3, p_5), (t_3, p_6)\}$ , the weight on all arcs are 1 and the initial marking  $M_0 = (1, 1, 0, 0, 0, 0)$ . The firing sequence that leads to (d) is  $\sigma = t_1 t_2 t_3$ , which is illustrated through (a) to (d).

### B. Petri Nets

Another used method for analysing chemical reaction networks is that of Petri nets. Here one lets each molecule in the network be a place in the Petri net and each reaction be a transition [?], [?]. Even the stoichiometric matrix seen in chemistry has an equivalent in Petri net terminology called the incidence matrix [?]. We will in Section III present our method for transforming a hyperflow to a Petri net, and for that we will first introduce some notation. We primarily use the notation from [6], except arcs are weighted.

A *net* is a triple  $(P, T, W)$  with a set of places  $P$ , a set of transitions  $T$ , and an arc weight function  $W : (P \times T) \cup (T \times P) \rightarrow \mathbb{N}_0$ . A *marking* on such a net is a function  $M : P \rightarrow \mathbb{N}_0$  assigning a number of tokens to each place. With  $M_0$  we denote the empty marking, i.e.,  $M_0(p) = 0, \forall p \in P$ . A *Petri net* is then a pair  $(N, M_0)$  of a net  $N$  and an initial marking  $M_0$ .

We say that a transition  $t$  is enabled by the marking  $M$  if  $W(p, t) \leq M(p), \forall p \in P$ . When a transition  $t$  is enabled it can *fire*, resulting in a marking  $M'$ , denoted by  $M \xrightarrow{t} M'$  where  $M'(p) = M(p) - W(p, t) + W(t, p), \forall p \in P$ . A *firing sequence* is a sequence of firing transitions  $\sigma = t_1 t_2 \dots t_n$  such that  $M_0 \xrightarrow{t_1} M_1 \xrightarrow{t_2} M_2 \xrightarrow{t_3} \dots \xrightarrow{t_n} M_n$ , denoted by  $M_0 \xrightarrow{\sigma} M_n$ . In Fig. 4 we present an example of a firing sequence which in this instance is the sequence  $\sigma = t_1 t_2 t_3$ .

## III. REALISABILITY OF PATHWAYS

decide on integer hyperflow or pathway

In this section we describe how to model a flow on an extended hypergraph as a Petri net. We further define realisability of a pathway via Petri nets. Lastly we introduce the

realisability certificate which will work as an illustration of the firings needed to make the pathway in question realisable.

### A. Flows as Petri Nets

merge A and B

T-invariant

Let us start by defining how to convert a hypergraph  $\mathcal{H} = (V, E)$  directly to a net  $N = (P, T, W)$ . We do that by using the vertices  $V$  as the places  $P$ , the edges  $E$  as the transitions  $T$ , and defining the weight function from the incidence information: for each vertex/place  $v \in V$  and edge/transition  $e = (e^+, e^-) \in E$  let  $W(v, e) = m_v(e^+)$  and  $W(e, v) = m_v(e^-)$ . This conversion also works for extended hypergraphs, where the half-edges result in transitions with either an empty pre-set or post-set. The transitions corresponding to input reactions are thus always enabled.

Given a Petri net  $(N, M_0)$  with a net  $N$  obtained from an extended hypergraph and with the empty marking, we can now consider an arbitrary firing sequence also ending at the empty marking  $M_0 \xrightarrow{\sigma} M_0$ . From the transition sequence  $\sigma$  we can obtain the net flow  $f : \bar{E} \rightarrow \mathbb{N}_0$  simply by setting  $f(e)$  to be the number of occurrences of the transition  $e$  in the sequence  $\sigma$ . Note that if the firing sequence does not start or end in the empty marking the flow we define from it will not specify the in- or output flow, respectively. Furthermore, observe that the flow conservation constraint is satisfied due to the execution semantics of Petri nets.

A flow  $f$  on an extended hypergraph  $\mathcal{H} = (V, \bar{E})$  specifies how many times each reaction is carried out. As we wish to analyse each pathway in isolation we introduce the following conversion of  $(\mathcal{H}, f)$  to a Petri net  $(N, M_0)$ . Let  $(V, \bar{E}, W)$  be a net converted in the usual manner from  $\mathcal{H}$ , and  $N = (V \cup V_E, \bar{E}, W \cup W')$  be the extended net with the addition of places  $V_E$ , and related additions to weight function  $W'$ . For each edge  $e \in \bar{E}$  we add an extra place  $v_e \in V_E$  with connectivity  $W(v_e, e) = 1$ . We then create a Petri net  $(N, M_0)$  where the initial marking has  $M_0(v) = 0$  for places  $v \in V$ , and  $M_0(v_e) = f(e)$  for places  $v_e \in V_E$ . Thereby we limit each transition to be fired at most the number of times specified by the flow. Furthermore, any firing sequence  $M_0 \xrightarrow{*} M_0$ , ending in the empty marking, must use each transition exactly the number of times specified by the flow.

As an example of the method the hyperflow in Fig. 3 is converted to the Petri net in Fig. 5.

### B. Realisability of Pathways

A pathway is a specification of how many times each reaction must happen in order to perform a specific overall transformation. We are interested in whether a given pathway, represented by a flow  $f$ , on an extended hypergraph  $\mathcal{H} = (V, \bar{E})$ , is strict realisable. Meaning can we by the specification of the pathway and only with molecules in the exact quantities specified by the input flow, produce the number of molecules specified by the output flow, without leaving any waste in the system. Using the construction above, this translates to a reachability question on a Petri net: is there a firing sequence  $M_0 \xrightarrow{*} M_0$  on the Petri net constructed from  $(\mathcal{H}, f)$ ? For some

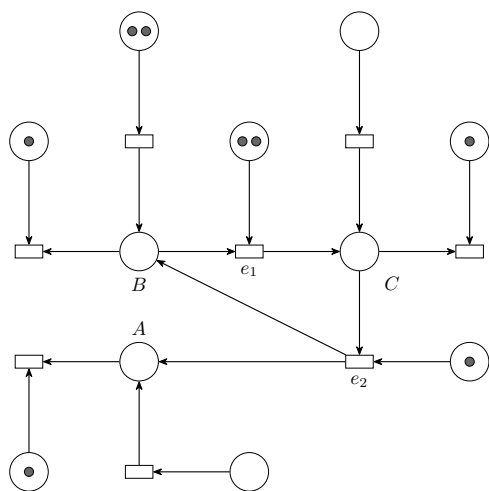


Fig. 5. The hyperflow from Fig. 3 converted to a Petri net.

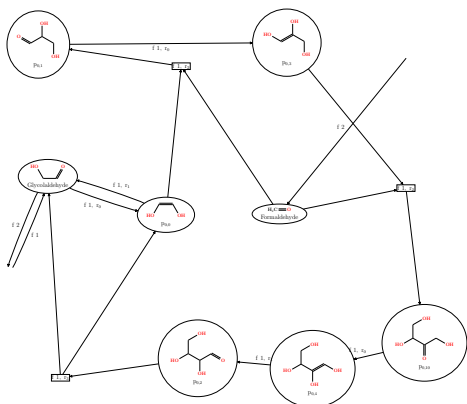


Fig. 6. An example of a hyperflow for the formose reaction which is realisable.

flows the answer is clearly no, as an example of this see Fig. 1. In this hyperflow as long as there is no flow entering either C or D it is impossible to realise the flow. For other flows there exists such a firing, for example, the flow presented in Fig. 3 is. Observe that the Petri net constructed from the integer hyperflow presented in Fig. 5 can reach the empty marking,  $M_0$ , by two different firing sequences one being  $e_1e_1e_2$  and the other being  $e_1e_2e_1$ . For a chemical example of a realisable flow see Fig. 6, which is made realisable by the firing sequence

### C. Realisability Certificate

In order to illustrate the firing sequence that shows that a flow is realisable we introduce the realisability certificate.

Given a Petri net with an initial marking  $M_0$  the realisability certificate is the occurrence net that results from an unfolding of the initial marking as done by [7].

would it be more correct to use the notion of a process?

Such an unfolding can lead to several different occurrence nets, we are interested in the one where following the longest path from each place leads to a transition  $t$  where  $t^\bullet = \emptyset$ . Note this unfolding leads to what [7] define as an occurrence net

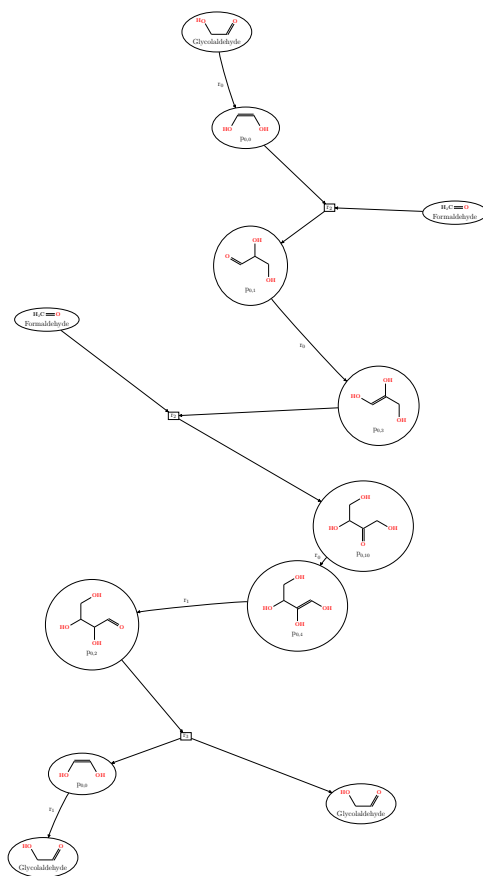


Fig. 7. The realisability certificate for the hyperflow in Fig. 6.

but is referred to by others [8] as a causal net. The unfolding also allows the token to be interpreted as individual tokens, such that they can be differentiated.

go back to this

This is also a necessity in order to trace atoms through graph transformation rule composition [5].

The realisability certificate specifies the order of the reactions, whereas the flow only specifies how many times each reaction must occur.

what do we want to say about the interpretation DAG?

The flow that we presented in Fig. 6 has the realisability certificate of Fig. 7. Which proves that the flow is indeed realisable, as we get a transition sequence that makes it realisable.

- Characterisation of pathways
  - realisable
  - borrow-realizable
  - scaling-realizable
- Defining the "interpretation"-DAG

## IV. EXTENDED FLOWS

As we have seen previously some flows are not strict realisable. However they do all have a related flow that is realisable. Here we present these extended flows, that can either be scaled realisable or borrow realisable, where a flow in some cases has a related flow that is scaled realisable, but always has a related flow that is borrow realisable.

write the firing sequence when the figure has been made

more references



### A. Scaled Realisable

**Definition IV.1** (Scaled Realisable). A flow  $f$  is scaled realisable, if there exists an integer  $k > 1$  such that the flow  $f \cdot k$  is realisable.

Asking if a flow  $f$  is scaled realisable corresponds to asking if  $k$  copies of  $f$  can be realised concurrently. This is of interest as in the real world, a pathway is often not just happening once, but multiple times. Therefore, even if the flow is not strict realisable, it still has value to consider if the scaled flow is. However not all flows are scaled realisable, for example the flow presented in Fig. 1 which was not strict realisable is also not scaled realisable. Observe this by seeing that no matter which integer we scale the flow by, we do not solve the problem that one of C and D is critical for the realisation of the flow. Furthermore there are specific flows for which we can prove that they are not scaled realisable. In order to do so, recall the procedure of graph traversal of a hypergraph.

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**Require:**  $\bar{H} = (V', \bar{E}'), S$   
**for all**  $s \in S$  **do**  
      $s.colour = black$   
**end for**  
**repeat**  
      $U \leftarrow$  all vertices in  $V$  that are not coloured black  
     **for all**  $v \in U$  **do**  
         **if**  $\exists (e^+, e^-) \in \bar{E} : v \in e^- : u.colour = black \ \forall u \in e^+$  **then**  
              $v.colour = black$   
         **end if**  
     **end for**  
**until** No node in  $U$  is coloured black

iff proof?

**Theorem IV.1.** Given a hyperflow  $f$  on an extended hypergraph  $\bar{H} = (V, \bar{E})$ , let  $\bar{H}' = (V', \bar{E}')$ , where  $\bar{E}' = suppE(f)$  and  $V' = suppV(f)$ . Denote by  $S$  the set  $\{v \in V : f(e_v^-) \neq 0\}$  and by  $T$  the set  $\{v \in V : f(e_v^+) \neq 0\}$ . If  $\exists v \in T : v \notin GT(\bar{H}', S)$  then the flow  $f$  is not scaled realisable.

*Proof.* A graph traversal of a hypergraph corresponds to having an infinite amount of flow into the source vertices, and no restrictions on the number of times an edge can be followed. Therefore if a vertex cannot be reached from the sources by a graph traversal, it cannot be reached in the stricter case, where the search is restricted by the flow specification.  $\square$

We present an example of a hyperflow that is proven to not be scaled realisable in Fig. 10. This example is a hyperflow constructed on a hypergraph that models the reactions seen in the pentose phosphate pathway. Fig 8 is an example of a hyperflow that is scaled realisable but not strict realisable. This flow is an alternative formose reaction. In order to see that this flow is indeed realisable, look to the realisability certificate of the flow in Fig. 9.

In the following subsection we will introduce the notion of borrow realisability. Here it is guaranteed that all flows have

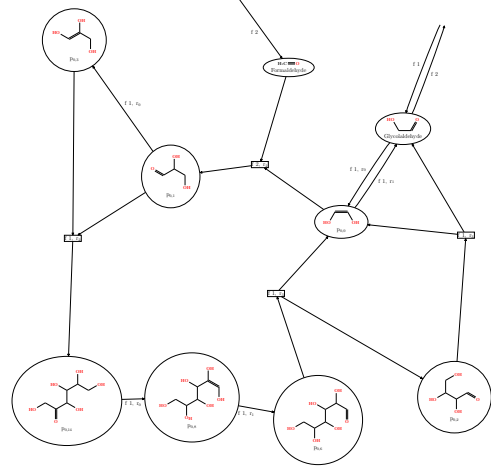


Fig. 8. An example of a hyperflow for the formose reaction which is not realisable but is scaled realisable by a factor 2.

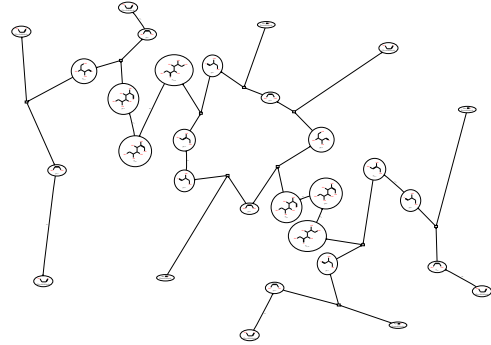


Fig. 9. The realisability certificate for the hyperflow in Fig. 8 when scaled by a factor 2, making it scaled realisable.

a related flow which is borrow realisable, contrary to scaled realisability.

### B. Borrow Realisable

**Definition IV.2** (Borrow Realisable). A flow  $f$  on an extended hypergraph  $H = (V, \bar{E})$  is borrow realisable if the related flow  $f'$  is realisable. Where  $f'$  is defined by

$$\begin{aligned} f'(e_v^-) &= b(v) + f(e_v^-) & \forall v \in V \\ f'(e_v^+) &= b(v) + f(e_v^+) & \forall v \in V \\ f'(e) &= f(e) & \forall e \in E \end{aligned}$$

and  $b: V \rightarrow \mathbb{N}_1$  is the borrow specification function.

We say that  $f'$  is the flow  $f$  where  $v \in V$  has been borrowed  $b(v)$  times. This allows for intermediary molecules of the pathway to be available in the environment, which we model by  $v \in V$ . Which corresponds to having additional I/O flow as specified by  $b$ . Furthermore, for a borrow specification  $b$  we define  $|b| = \sum_{v \in V} b(v)$ , i.e., the total count of molecules borrowed. The idea of borrowing tokens in the corresponding Petri net setting has been proposed earlier by [9, Proposition 10], in which a proof was also presented showing that such a borrowing always exists.

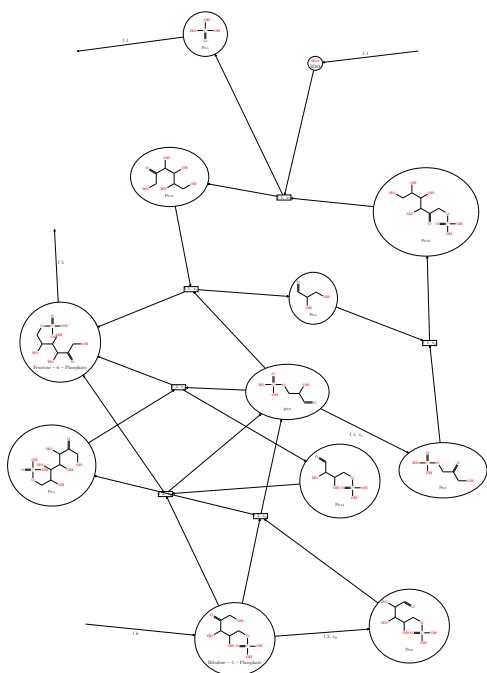


Fig. 10. An example of a hyperflow for the pentose phosphate pathway, which is neither realisable nor scaled realisable but is borrow realisable.

prove minimal amount of borrowed tokens needed for realisability

kom med eksemplerne

In Fig. 10 we present a flow that is neither strict realisable nor scaled realisable, we can however prove by creating the realisability certificate in Fig. 11 for the related flow that allows borrowing, that it is borrow realisable.

## V. “RESULTS”

- Atom tracing, connect to trace paper
- Formose for the scaling thingy
- PPP for stuff
- Pathway drawings vs. interpretation drawings

Here we present several examples of hyperflows that have first been modelled as Petri nets, which have then been unfolded from their initial marking in order to reach an interpretation DAG. All examples are based on chemical pathways.

## VI. CONCLUSION

The conclusion goes here.

## APPENDIX A FLOWS ON EXPANDED HYPERGRAPHS

elaborate

The hyperflows are actually found on what is called an expanded hypergraph [3]. Here the vertices are expanded as to allow for certain constraints on the *transit* edges, e.g. not allowing flow to exit the vertex the same way as it entered. However, in the case of scaled realisability, these constraints are too strict, as it does not allow the flow to be redistributed along the transit edges. This means that for most flows they are not scalable, when taking these constraints into account, but

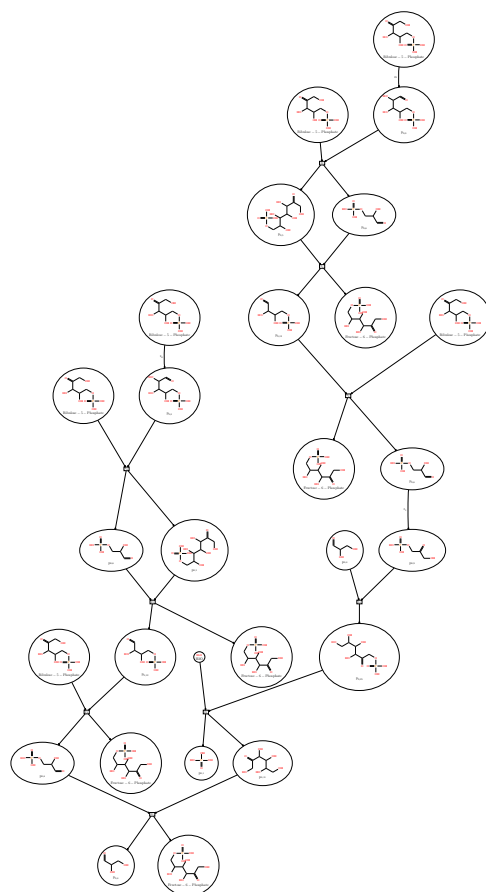


Fig. 11. The realisability certificate for the hyperflow in Fig. 10 where the molecule  $p_{\{0,4\}}$  is borrowed in order to make it borrow realisable.

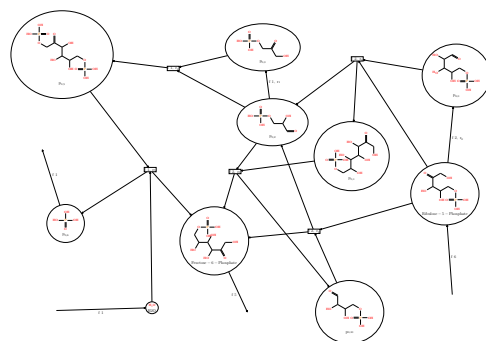


Fig. 12. An example of a hyperflow for the pentose phosphate pathway which is realisable.

when ignoring the transit edges the flow is scaled realisable. This comes down to the flow needing to be rerouted on the transit edges in order to be scaled realisable.

## ACKNOWLEDGMENT

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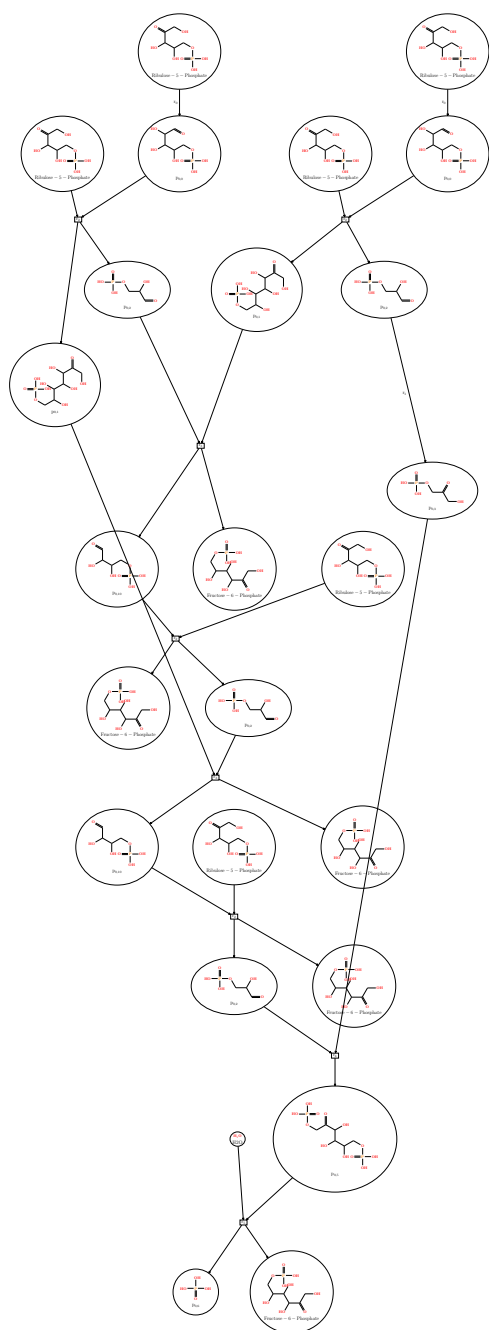


Fig. 13. The realisability certificate for the hyperflow in Fig. 12.

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