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# Equivalences in multi-valued asynchronous models of regulatory networks

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**Abstract** Multi-valued network models can be described by their topology and a set of parameters capturing the effects of the regulators for each component. Dynamics can then be derived and represented as state transition systems. Different network models may lead to the same transition system, meaning dynamics analysis of a representative model covers a larger class of models. While rather clear in the Boolean case, the properties contributing to this effect become more involved for multi-valued models. We analyse these properties and present a mathematical description of the resulting model equivalence classes.

## 1 Introduction

Boolean and multi-valued network models have long since shown their worth in providing insights into complex systems, e.g., in the context of molecular networks [1]. System components are represented as variables with a finite value range, e.g., Boolean variables, and component interactions are captured in a directed (multi-)graph. Logical parameters then determine the value evolution of each component over time depending on the values of its regulators. Utilizing some update strategy leads to a transition system describing the evolution of the system state. We focus on the (unitary) asynchronous update allowing only one component value change per transition and only by absolute value one [2]. In particular for describing biological systems, this yields realistic trajectories.

Analysis of such transition systems can be hard due to non-determinism of the dynamics. In biological applications, one often has to compare transition systems of many models since data uncertainty may result in several models consistent with the data. In this context, it is an interesting observation that different models may give rise to the same state transition system. For Boolean networks this phenomenon has been investigated and is directly related to superfluous edges, meaning edges without detectable dynamical effect, in the graph capturing the network topology (see e.g. [3]). In the multi-valued setting however, not only existence but also strength of a regulatory effect can be captured in the model. This allows for models differing both in topology and parametrization to generate the same transition system, even if only functional edges are considered.

In this paper, we clarify the reasons leading to different models exhibiting the same dynamics. We also determine a representative for each class of models sharing the same transition system and propose a procedure for testing whether two model belong to the same class.

## 2 Background

We start by introducing the relevant notions, with a simple illustrative example given in Fig. 3.

A multi-valued regulatory multi-graph is a triple  $G = (V, E, \rho)$  where:

- $V = \{1, \dots, n\}$  with  $n \in \mathbb{N}^+$  is a set of *components*,
- $\rho : V \rightarrow \mathbb{N}^+$  assigns the maximal *activity level* to a component,
- $E \subseteq V \times \mathbb{N}^+ \times V$ ,  $n \leq \rho(u)$  for all  $(u, n, v) \in E$ , is a set of *regulations*.

We denote  $\mathcal{G}$  the set of multi-valued regulatory graphs.

The function  $\theta : V \times V \rightarrow 2^{\mathbb{N}^+}$  giving the *thresholds* of all edges between two vertices is defined as  $\theta(u, v) = \{n \mid (u, n, v) \in E\}$  where  $u, v \in V$ . Note that  $\theta(u, v) = \emptyset$  if there is no edge from  $u$  to  $v$ .

### 2.1 Discrete kinetic parameters

As the range of values for each component is finite, we can describe the set of all possible configurations of the system, called *state space*  $S = \prod_{v \in V} [0, \rho(v)]$ . Note that the state space is shared among the graphs that have the same function  $\rho$  and thus also the same  $V$ . We will use  $\mathcal{G}_\rho = \{(V, E, \rho') \mid \rho = \rho'\}$  to refer to the class of graphs that share the state space.

The set  $S$  represents all the qualitatively different configurations of a system. However, each component is dependent only on the values of its regulators. An equivalence class on  $S$  w.r.t. regulation of a component  $v \in V$  is called the regulatory context. To define the relevant notions we first describe the *activity interval* of a regulator. For formal reasons we consider an extended threshold function  $\tilde{\theta}$  with  $\tilde{\theta}(u, v) = \theta(u, v) \cup \{0, \rho(u) + 1\}$  for all  $u, v \in V$ . Then

$$I_v^u = \{[j, k] \mid j, k \in \tilde{\theta}(u, v), j < k, \neg(\exists l \in \tilde{\theta}(u, v)(j < l < k))\} \quad (1)$$

is the set of activity intervals of  $u$  in regulation of  $v$ . Here, the intuition is that the regulator effect of  $u$  on  $v$  is constant in each of the intervals of  $I_v^u$ . Note that  $\bigcup I_v^u = [0, \rho(u)]$ , even in the case that there is no edge from  $u$  to  $v$ .

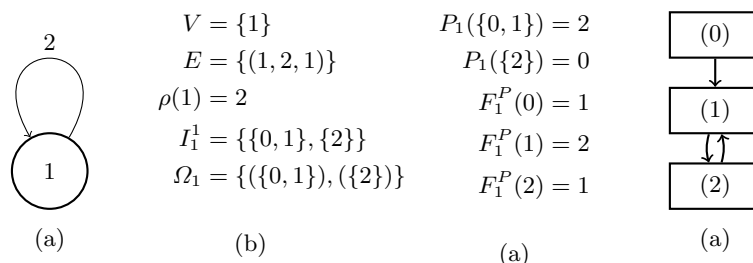


Figure 3: (a) A regulatory graph with a single node. (b) Properties of the network. (c) A single non-canonical parametrization and the respective update function. (d) The transition system based on the update function  $F^P$ .

The set of regulatory contexts of  $v$  is then denoted and defined  $\Omega_v = \prod_{u \in V} I_v^u$ . For each  $v \in V$ , a regulatory context  $\omega \in \Omega_v$  is a  $|V|$ -tuple where  $\omega_u$  is the activity interval  $I_v^u$  for each  $u \in V$ .

The dynamics of the regulatory graph are given via integral values, called *logical parameter*, assigned to each context. We use a *parametrization function*  $P_v : \Omega_v \rightarrow [0, \rho(v)]$  for each  $v \in V$ . The parametrization of a regulatory network  $G \in \mathcal{G}$  is then a tuple  $P = (P_1, \dots, P_{|V|})$ . Lastly, we denote  $\mathcal{P}_G$  the set of all parametrizations of the regulatory graph  $G$ , called the *parametrization space*.

## 2.2 Asynchronous transition systems

Having a regulatory graph  $G = (V, E, \rho)$  and a parametrization  $P \in \mathcal{P}_G$  we can fully describe its dynamical behaviour as a *transition system* over its state space  $S$ . This is a directed graph  $(S, \rightarrow)$  where  $\rightarrow \subset S \times S$  is the *transition relation*. As mentioned, we are interested in asynchronous dynamics which means that the transition relation is non-deterministic.

First  $P$  is converted into a so-called *update function*  $F^P = (F_v^P)_{v \in V}$  where  $F_v^P : S \rightarrow [0, \rho(v)]$  for all  $v \in V$ . Here we exploit the fact that for each  $s \in S$  and for each  $v \in V$  there exists a context  $\omega \in \Omega_v$  such that  $s \in \prod_{u \in V} \omega_u$ . To simplify the notation we will further write  $s \in \omega$  instead of  $s \in \prod_{u \in V} \omega_u$ . For every  $v \in V$  we obtain the function  $F^P : S \rightarrow S$  from a parametrization  $P_v$  as

$$F_v^P(s) = \begin{cases} s_v + 1, & \text{if } s_v < P_v(\omega), s \in \omega, \\ s_v, & \text{if } s_v = P_v(\omega), s \in \omega, \\ s_v - 1, & \text{if } s_v > P_v(\omega), s \in \omega. \end{cases} \quad (2)$$

Having  $F^P$ , we now assign each parametrized regulatory graph a transition system via the function  $T_G : \mathcal{P}_G \rightarrow \{(S, \rightarrow)\}$  where  $T_G(P) = (S, \rightarrow)$  such that

$$\forall v \in V, \forall s \in S (s \rightarrow s[v/n] \iff (F_v^P(s) = n \wedge F_v^P(s) \neq s_v)), \quad (3)$$

with  $x[i/k]$  denoting that in the vector  $x$ , the  $i$ -th value is substituted for  $k$ .

In the following, we will compare the resulting transitions systems generated by regulatory graphs with the same state space, i.e., those in  $\mathcal{G}_\rho$  for some  $\rho$ . We denote this set of transition systems  $\mathcal{T}_\rho = \{(S, \rightarrow) \mid T_G(P) = (S, \rightarrow), G \in \mathcal{G}_\rho, P \in \mathcal{P}_G\}$ .

## 3 Equivalence classes of parametrizations

We now investigate the cases where different parametrized regulatory graphs generate the same transition system. From (3) it is clear that two functions  $F^{P_1} \neq F^{P_2}$  will lead to distinct transition systems, while coinciding functions  $F^{P_1}, F^{P_2}$  lead to the same dynamics. We therefore focus on describing the situations where for  $P_1 \neq P_2$  we still have  $F^{P_1} = F^{P_2}$ .

Considering the simple example in Fig. 2a. We see that replacing  $P_1(\{2\}) = 0$  by  $P_1(\{2\}) = 1$  still yields  $F_1(2) = 1$  and therefore the transition system remains

the same. This illustrates that, other than in the Boolean case, information on parameter values may get lost when deriving the update function. In Fig. 2a we have a case where the parameter value lies outside its context and by incremental change we leave the context even before the value can be attained.

We now define the notion of a *canonical* parametrization that prohibits such effects. Observe that a value change in  $v$  can cause the change of context only if  $v$  regulates itself. Therefore we say that  $P \in \mathcal{P}_G$  is *canonical* if and only if

$$\forall v \in V, \forall \omega \in \Omega_v, \omega_v = [j, k) ((P_v(\omega) \geq j - 1) \wedge (P_v(\omega) \leq k)). \quad (4)$$

We also denote  $\dot{\mathcal{P}}_G \subseteq \mathcal{P}_G$  the subset of canonical parametrizations in  $\mathcal{P}_G$ .

We can obtain a clear correspondence between  $P$  and  $F^P$  if all the contexts contain just a single state, so that no ambiguities are introduced in (2). This partition is achieved when only considering *complete* graphs. For clarity we add that  $(V, E, \rho) \in \mathcal{G}$  is complete if and only if for all  $u, v \in V$  and every  $n \in [1, \rho(u)]$  the edge  $(u, n, v)$  is in  $E$ . This gives us the following theorem:

**Theorem 1.** *For each  $G = (V, E, \rho) \in \mathcal{G}$  it holds that if  $G$  is complete then  $T_G$  defines a bijection between  $\dot{\mathcal{P}}_G$  and  $\mathcal{T}_\rho$ .*

*Proof.* Let  $T_G(P) = (S, \rightarrow)$  for some complete  $G = (V, E, \rho) \in \mathcal{G}$  such that  $P \in \dot{\mathcal{P}}_G$ . The one-to-one correspondence between  $F^P$  and  $(S, \rightarrow)$  immediately follows from (3). We therefore need to show that there is also such a correspondence between  $P$  and  $F^P$ .

First, it is important to note that if the graph is complete, each regulatory context depicts only a single configuration. This follows since if  $G$  is complete then by (1) we have:

$$\forall v \in V (\Omega_v = \prod_{u \in V} \{[0, 1), [1, 2), \dots, [\rho(u), \rho(u) + 1)\}).$$

Since each context is a singleton, each component can only adopt one value. Now, canonicity requires that the parameter of the context differs from that value only by 1. Therefore we have only three options for the parameter value. More precisely, by substituting (4) we have

$$\forall v \in V, \forall s \in S (s_v - 1 \leq P_v(\{s\}) \leq s_v + 1).$$

Then in such a case, (2) can be written as

$$F_v^P(s) = \begin{cases} s_v + 1, & \text{if } s_v + 1 = P_v(\{s\}), \\ s_v, & \text{if } s_v = P_v(\{s\}), \\ s_v - 1, & \text{if } s_v - 1 = P_v(\{s\}), \end{cases}$$

from which we immediately see that  $F_v^P(s) = P_v(\{s\})$ . Thus we can write (3) as

$$\forall v \in V, \forall s \in S (s \rightarrow s[v/n] \iff P_v(\{s\}) = n \wedge P_v(\{s\}) \neq s_v).$$

□

Based on this theorem, we can consider a complete graph with canonical parametrization as a representative of a class of models with the same behaviour. Now we show that it is possible to convert any graph with some parametrization into a complete graph with canonical parametrization, while keeping the dynamics unchanged.

First, we focus on the *canonization* function  $Can : \{(G, P) \mid G \in \mathcal{G}, P \in \mathcal{P}_G\} \rightarrow \{(G, \dot{P}) \mid G \in \mathcal{G}, \dot{P} \in \dot{\mathcal{P}}_G\}$ . To define  $Can(G, P) = (G, \dot{P})$  we proceed as follows. For each component  $v \in V$  and for each regulatory context  $\omega \in \Omega_v$  with  $\omega_v = [j, k)$  we construct  $\dot{P}$  as follows:

$$\dot{P}_v(\omega) = \begin{cases} j - 1, & \text{if } P_v(\omega) < j - 1 \\ k, & \text{if } P_v(\omega) > k \\ P_v(\omega), & \text{otherwise} \end{cases} .$$

The goal is to avoid that the parameter value cannot be reached in one transition from any state in the context, since this allows effects as illustrated in Fig. 3 to occur. We now prove that this procedure indeed yields a canonical parametrization for any regulatory graph that shares the transition system with the original one.

**Lemma 1.** *Canonization is correct. For all  $G \in \mathcal{G}$  and all  $P \in \mathcal{P}_G$  it holds that if  $Can(G, P) = (G, \dot{P})$  then  $\dot{P}$  is canonical.*

*Proof.* Consider some  $Can(G, P) = (G, \dot{P})$  and assume  $P$  is not canonical, since otherwise  $P$  and  $\dot{P}$  coincide by definition. There are two cases for  $P$  to be considered. The first option is that

$$\exists v \in V, \exists \omega \in \Omega_v, \omega_v = [j, k)(P_v(\omega) < j - 1)$$

but then  $\dot{P}_v(\omega) = j - 1$ , so  $\dot{P}$  is canonical. The second case

$$\exists v \in V, \exists \omega \in \Omega_v, \omega_v = [j, k)(P_v(\omega) > k)$$

can be treated analogously.  $\square$

**Lemma 2.** *Canonization is conservative. For all  $G \in \mathcal{G}$  and all  $P \in \mathcal{P}_G$  it holds that if  $Can(G, P) = (G, \dot{P})$  then  $T_G(P) = T_G(\dot{P})$ .*

*Proof.* Recall that the transition systems  $T_G(P)$  and  $T_G(\dot{P})$  are fully defined by  $F^P$  and  $F^{\dot{P}}$ , respectively. We therefore need to show that  $F^P = F^{\dot{P}}$ .

For all  $v \in V$  and for all  $\omega \in \Omega_v$  the value  $\dot{P}_v(\omega)$  is set based on one of the three cases in the definition. First consider the case that  $P_v(\omega) < j - 1, \omega_v = [j, k)$ . We have  $\omega_v = [j, k)$  and therefore for all  $s \in \omega$  it holds that  $s_v > j - 1$ . This means that

$$\forall s \in \omega (P_v(\omega) < s_v \wedge \dot{P}_v(\omega) < s_v)$$

and therefore for each  $s \in \omega$  we have  $F_v^P(s) = s_v - 1 = F_v^{\dot{P}}(s)$ .

The case that  $P_v(\omega_v) > k, \omega_v = [j, k)$  can be treated analogously.

The third case is that we have  $P_v(\omega_v) = \dot{P}_v(\omega_v)$  and thus by definition  $F_v^P(s) = F_v^{\dot{P}}(s)$  for any  $s \in \omega_v$ .  $\square$

Now, we extend the topology of a graph using the *completion* function  $Comp : \{(G, P) \mid G \in \mathcal{G}, P \in \mathcal{P}_G\} \rightarrow \{(\hat{G}, \hat{P}) \mid \hat{G} \in \mathcal{G}, \hat{P} \in \mathcal{P}_{\hat{G}}\}$ . If  $G$  is complete, we map  $(G, P)$  to itself. For an incomplete  $G = (V, E, \rho)$  and some  $P \in \mathcal{P}_G$  we consider the non-empty set of missing edges  $\hat{E} = \{(u, n, v) \mid u, v \in V, n \in [1, u], (u, n, v) \notin E\}$ . Assume that the set of all possible edges has some ordering. We extend the graph  $G$  to  $\hat{G}$  such that  $\hat{G} = (V, E \cup \{min(\hat{E})\}, \rho)$ .

To extended the parametrization  $\hat{P}$  to the new topology we observe that  $\hat{G}$  gives rise to new contexts that were obtained by partitioning some context of  $G$  into two. To preserve the dynamical behaviour we simply assign the parameter value of the original context to both resulting new contexts. Formally, we define two assisting variables  $n_-, n_+ \in \tilde{\theta}(\hat{u}, \hat{v})$  that denote the closest lower and higher thresholds to  $\hat{n}$  that is already in  $E$ , i.e.,

$$\neg(\exists m \in \theta(\hat{u}, \hat{v})(n_- < m < n)) \wedge \neg(\exists m \in \theta(\hat{u}, \hat{v})(n < m < n_+)).$$

For each  $v \in V$  and for each  $\hat{\omega} \in \hat{\Omega}_v$  we then create  $\hat{P}$  as

$$\hat{P}_v(\hat{\omega}) = \begin{cases} P_v(\hat{\omega}) & \text{if } v \neq \hat{v} \vee (\omega_{\hat{u}} = [j, k] \wedge (j \neq n_- \vee k \neq n_+)) \\ P_v(\hat{\omega}[\hat{u}/[n_-, n_+]]) & \text{otherwise} \end{cases}$$

We now prove that for an incomplete regulatory graph we can use the completion procedure to add a new edge while retaining the dynamics.

**Lemma 3.** *Completion is sound. For all  $G \in \mathcal{G}$  and all  $P \in \mathcal{P}_G$  it holds that if  $Comp(G, P) = (\hat{G}, \hat{P})$  then  $\hat{G} \in \mathcal{G}$  and  $\hat{P} \in \mathcal{P}_{\hat{G}}$ .*

*Proof.* For  $G \in \mathcal{G}$ , denote  $(\hat{u}, \hat{n}, \hat{v})$  the newly added edge in  $\hat{G}$ . We have  $\hat{u}, \hat{v} \in V$  and  $\hat{n} \in \rho(\hat{u})$ . By definition of  $\mathcal{G}$  we have that if  $(V, E, \rho) \in \mathcal{G}$  then  $(V, E \cup \{(\hat{u}, \hat{n}, \hat{v})\}, \rho) \in \mathcal{G}$ .

The variables  $n_-, n_+$  exist since 0 is always a possible choice for  $n_-$  and  $\rho(\hat{u}) + 1$  for  $n_+$ . For any  $m \in \theta(u, \hat{v})$  we know that  $(0 < m < \rho(\hat{u}) + 1)$ .

From (1) we know that the only change occurs in the interval  $I_{\hat{v}}^{\hat{u}}$ . We therefore only need to show that  $\hat{P}_{\hat{v}}$  is extended to the corresponding contexts. Since  $n_-, n_+$  exist, for any  $\omega \in \Omega_{\hat{v}}$  we have that  $\omega_{\hat{u}} \in \{i_1, \dots, [n_-, n_+], \dots, i_k\}$ . Therefore, for any  $\hat{\omega} \in \hat{\Omega}_{\hat{v}}$ , we also have  $\hat{\omega}[\hat{u}/[n_-, n_+]] \in \Omega_{\hat{v}}$ . Thus  $\hat{P}_{\hat{v}}$  is defined on the whole  $\hat{\Omega}_v$  for each  $v \in V$ .  $\square$

**Lemma 4.** *Completion is conservative. For each  $G \in \mathcal{G}$  and for each  $P \in \mathcal{P}_G$  it holds that if  $Comp(G, P) = (\hat{G}, \hat{P})$  then  $T_G(P) = T_{\hat{G}}(\hat{P})$ .*

*Proof.* We have that  $P$  differs from  $\hat{P}$  only in a context  $\hat{\omega} \in \hat{\Omega}_{\hat{v}}$  with  $\hat{\omega} = [j, k]$  where either  $j = n_-$  or  $k = n_+$ .

Assume there exists some  $s \in \hat{\omega}$  for which  $F_{\hat{v}}^P(s) \neq F_{\hat{v}}^{\hat{P}}(s)$ . We know that  $[j, k] \subset [n_-, n_+)$  and therefore  $s \in \hat{\omega}[\hat{u}/[n_-, n_+]]$ . This implies that also  $\hat{P}_{\hat{v}}(\hat{\omega}_{\hat{v}}) \neq P_{\hat{v}}(\hat{\omega}[\hat{u}/[n_-, n_+]])$ , which contradicts the definition of  $\hat{P}$ .

We therefore have that  $F^P(s) = F^{\hat{P}}(s)$ .  $\square$

Since the completion procedure adds only one edge at the time, we need to repeat the procedure. This is captured in the following Lemma.

**Lemma 5.** *For  $G \in \mathcal{G}$  and  $P \in \mathcal{P}_G$ , consider the recursive sequence  $Comp(G, P)$ ,  $Comp(Comp(G, P)), \dots$ .*

*This sequence converges to a fixed point  $(G^c, P^c)$  and  $G^c$  is complete.*

*Proof.* The set  $\hat{E}$  of missing edges in  $G$  is finite as  $V$  is finite. For each  $v \in V$  also  $[1, \rho(v)]$  is finite. In each iterative use of  $Comp$  the size of  $\hat{E}$  is decremented by one. The recursive sequence becomes constant, when  $\hat{E}$  is empty, signifying a fixed point  $(G^c, P^c)$  of  $Comp$ . By definition,  $G^c$  is complete.  $\square$

Combining all the statements above, we arrive at our final theorem:

**Theorem 2.** *Let  $G, G' \in \mathcal{G}$ ,  $P \in \mathcal{P}_G$ , and  $P' \in \mathcal{P}_{G'}$  and denote  $Comp^*(G, P)$  and  $Comp^*(G', P')$  the fixed points derived from iterating  $Comp$  starting in  $(G, P)$  resp.  $(G', P')$ .*

*Then  $T_G(P) = T_{G'}(P')$  if and only if  $Can(Comp^*(G, P)) = Can(Comp^*(G', P'))$ .*

*Proof.* We now know that  $Can(Comp^*(G, P))$  and  $Can(Comp^*(G', P'))$  are canonical and complete. The equivalence follows from  $T_G$  being a bijection, as proven in Theorem 1.  $\square$

## 4 Conclusion

In the setting of multi-valued networks, both different topologies and different parametrizations do not necessarily lead to distinct dynamics. We have shown how such networks can be grouped into classes according to their transition systems, provided an explicit description of a representative of such a class and a procedure to identify this representative for an arbitrary network. The procedure highlights two key aspects, namely the resolution of the state space via the regulatory contexts and the parameter values related to self-regulation.

Our method for identifying the classes is not efficient in application, since it relies on construction of a complete graph. In future work, we would like to be able to identify, for each class of models that share the transition system, a representative that is minimal in some sense, and to provide the respective reduction. In the boolean case one does so by removing superfluous regulations. However in the multi-valued graph it is not so easy to recognize when an edge is superfluous and it may be that different order of reduction will yield different results. A fruitful strategy could be to eliminate edges without dynamical impact as can be read off of the parameter values and then focus on components carrying loops, aiming at eliminating as many loops as possible.

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