

# Causal Static Analysis for Brane Calculi

Chiara Bodei, Roberta Gori, Francesca Levi

*Dip. di Informatica, Università di Pisa, Via Pontecorvo, 3 - Pisa, Italy*  
*{chiara.bodei, roberta.gori, francesca.levi}@unipi.it*

---

## Abstract

We present here a static analysis, based on *Abstract Interpretation* [8], obtained by defining an abstract version of the causal semantics for the Mate/Bud/Drip (MBD) version of Brane Calculi [7], proposed by Busi [6]. Our analysis statically approximates the dynamic behaviour of MBD systems. More precisely, the analysis is able to describe the essential behaviour of the represented membranes, in terms of their possible interactions. Furthermore, our analysis is able to statically capture the possible causal dependencies among interactions, whose determination can be exploited to better understand the modelled biological phenomena. Finally, we apply our analysis to an abstract specification of the receptor-mediated endocytosis mechanism.

*Keywords:* Causality, Abstract Interpretation, Brane Calculi

---

## 1. Introduction

In Systems Biology, understanding the causal relationships among the actions performed by a system is a relevant issue. Determining which events are necessary for another event to occur is in general essential in biology, to capture the overall emerging behaviour of a complex system. Causal information can be exploited in several ways. For instance, knowing the order of some events may limit the size of the system to be explored. Only the events that may have an impact on the phenomenon of interest deserve our attention. Also, in drug research, e.g. determining the chemical species that are involved in causing a pathological phenomenon, can help in identifying possible drug targets.

In her seminal work [6], Nadia Busi formally addresses causality in a bio-inspired process algebraic framework. More precisely, she proposes a causal semantics for the Mate/Bud/Drip (MBD) fragment of Brane Calculi [7]. Brane calculi [7] have been introduced to more closely model the behaviour of dynamic and nested membranes. As

a consequence, these calculi are useful for modelling and reasoning about a large class of biological systems.

In [6], different kinds of causal dependencies are taken into account, including the subtle ones, due to the membrane structure and to the specific MBD primitives.

Causality is embedded in the semantics, as follows. Each reduction step is annotated with a fresh cause name and with a set of causes names that represent the previous reactions on which the current step depends. Extracting causal information from a complex system is in this way less difficult than in the case of standard semantics. Nevertheless, it is still not cost-effective, because the causal transition system that describes its dynamic behaviour is usually quite huge (or even infinite), and computationally demanding to be investigated. Due to the intrinsic complexity of biological systems, the computational cost is particularly high.

A typical way to reduce the computational cost of dynamic investigation is resorting to *static analysis* techniques. Fostering some ideas presented in [3], we therefore propose a static analysis for the causal MBD, based on *Abstract Interpretation* [8] techniques. The analysis relies on the definition of an abstract version of the causal semantics of [6], and provides two related results: an *abstract state* and a *causality relation*. The abstract state describes the possible hierarchical structures of membranes, and the processes that may be associated to each membrane, while the causality relation describes the possible causal dependencies among reduction steps. Both the abstract state and the causality relation are statically computed by collecting the information from the abstract causal semantics of the system that we want to analyse. What we obtain is a *safe* over-approximation of the causal behaviour. This means that all the events that the analysis does not predict will never happen, while all the events that the analysis predicts may happen, i.e. they are only possible. Therefore, in particular, we can predict that a particular reduction step *does not causally depend* on another one. The analysis has polynomial complexity, thus being quite efficient.

Our static analysis can be seen as a further level of abstraction in modelling a biological system, and can be exploited accordingly. It can be used to perform a preliminary investigation of the systems of interest. The analysis results may contribute to *dry lab* activities, by giving some insights on which *in silico* experiments may be more promising to be performed.

*Related work.* Static analysis avoids a full exploration of the potential concrete behaviour of a system, by keeping the computational costs low, but still offering accurate and useful information. Many static analysis techniques ([20, 11, 2, 21]) have been applied to biologically-oriented calculi (see [14] for a nice survey on calculi for biology), to make predictions about systems. These techniques compute over-approximate information

on the possible structure of the states that can be reached from the initial one. As a consequence, this approach guarantees invariant properties, showing that certain events will not happen in each state of the transition system, but it hardly captures causality aspects.

The first attempt [22] of statically addressing causality has been made for Bioambients [26], another compartment-based process calculus. In [22], the authors introduce a context-dependent *Control Flow Analysis* (CFA), together with three auxiliary analyses, which are able to increase the precision of the over-approximation, and to capture causality information for the action capabilities. The contextual CFA introduced in [3] for Brane calculi exploits some causality information to reduce the degree of approximation. As a result, the analysis is able to partly reflect the causal dependencies discussed in [6], giving some causal structure to the usually flat CFA results. Nevertheless, the gain in precision is paid in computational terms: the presented analysis is rather expensive.

The approaches based on the abstraction of the transition system are able to address causality and even more general temporal properties. The flow sensitive pathway analysis in [23] (for BioAmbients) focusses on the way the configurations are reachable, by approximating the sequential order of the transitions that lead to a given configuration. The approximation, given in terms of a finite automaton, faithfully embeds the causal orderings underlying the possible dynamic evolutions of the analysed systems. The analysis establishes also that a transition step does not causally depend on another one. The analyses in [12, 13], based on Abstract Interpretation techniques, still applied to Bioambients, rely instead on the definition of an abstract version of the transition system. The technique supports the validation of important causality properties such as the check-point one, showing when an event is necessary for another one to happen. This approach is more expensive from a computational point of view and costly like the one in [23].

In all the above mentioned papers, though, abstraction techniques are applied to the standard interleaving semantics and causality information is extracted only in an indirect way. Causal dependencies are mainly derived by observing the possible modifications of the nesting hierarchy, due to interactions, and to the possible sequences of transitions.

The main advantage of the analysis presented here is that causality is embedded in the concrete semantics, on which the abstraction is built on. As a consequence, besides the possible hierarchies of membranes, we can *directly* obtain the possible causal dependencies between interactions, which are an over-approximation of the actual dynamic ones.

The idea of including causal information inside an interleaving semantics, through relabelling of transitions, dates back to the late '80s and '90s (see [16, 5, 9] to cite only a few). The interested process calculi were CCS [18] and  $\pi$ -calculus [19]. In [6], this

approach has been adapted to the MBD fragment of Brane calculi, thus paving the way for our abstraction. Causality issues have been addressed also in [15], starting from [9], in the framework of Beta Binders [25], another bio-inspired language, in which processes are enveloped inside boxes representing the borders of biological entities.

*Overview.* The rest of the paper is organised as follows. In Section 2, we recall the standard MBD semantics, in Section 3, we present the causal semantics for MBD, while in Section 4, we introduce the analysis. In Section 5, our analysis is applied to an abstract specification of the receptor-mediated endocytosis mechanism. Some concluding remarks can be found in Section 6. Proofs of theorems and lemmata presented throughout the paper are collected in Appendix A.

This article is the full and revised version of the extended abstract published in [4]. More precisely, the new contributions of this paper with respect to [4] are:

- the treatment of the full MBD calculus, including the replication construct. The resulting static analysis is more complex and requires the introduction of a certain number of new features;
- the introduction of several examples and explanations to better illustrate the causal semantics and our analysis;
- the presentation of a new example to test our analysis in the biological systems setting;
- the inclusion of extended definitions, results and proofs.

## 2. An Overview on the MBD Part of Brane Calculi

Brane Calculi [7] are a family of calculi based on a set of primitives inspired by biological membrane interactions. The membrane interactions are explicitly described by means of a set of interaction capabilities. The actions of the MBD fragment are inspired by membrane fusion and splitting. Because membrane fission is an uncontrollable process that can split a membrane at an arbitrary place, it is replaced by two simpler operations: *budding*, which is splitting off one internal membrane, and *dripping*, which consists in splitting off zero internal membranes. Membrane fusion, or merging, is called *mating*.

We introduce the syntax and the interleaving semantics for MBD, considering a *labelled version* of the calculus. As usual in static analysis, labels are exploited to support the abstraction and *do not affect* the dynamic semantics of the calculus. Specifically,

$P, Q$	$::= \diamond \mid P \circ Q \mid !P \mid \sigma(P)^\Gamma$	systems <b>Sys</b>
$\sigma, \tau$	$::= 0 \mid \sigma \mid \tau \mid !\sigma \mid a^\lambda.\sigma$	membrane processes <b>Proc</b>
$a, b$	$::= \mathbf{mate}_n \mid \overline{\mathbf{mate}}_n \mid \mathbf{bud}_n \mid \overline{\mathbf{bud}}_n(\sigma) \mid \mathbf{drip}(\sigma)$	actions <b>Act</b>

Table 1: Syntax of Labelled MBD.

the labels are used in both the definitions of the causal semantics and of the analysis (presented in Sections 3 and 4, respectively).

A membrane system consists of nested membranes, where each membrane has associated a membrane process. The syntax of labelled MBD is described in Table 1, where  $n$  is taken from a countable set  $\mathcal{N}$  of names, and where we write  $P \in \mathbf{Sys}$  for *systems*,  $\sigma \in \mathbf{Proc}$  for *membrane processes*, and  $a \in \mathbf{Act}$  for *actions*. Each membrane is annotated with a *membrane label*  $\Gamma \in \widehat{\mathbf{Lab}}_{\mathcal{M}}$  and each action is annotated with a *process label*  $\lambda \in \mathbf{Lab}_{\mathcal{P}}$ .

We therefore need two distinct sets of labels. We have the set of *process labels*  $\mathbf{Lab}_{\mathcal{P}}$ , ranged over by  $\alpha, \beta, \gamma \dots$ , that is partitioned, i.e. is obtained by the disjoint union of countable sets  $\mathbf{Lab}_{\mathcal{P}_i}$  (formally  $\mathbf{Lab}_{\mathcal{P}} = \uplus_{i=1}^{\omega} \mathbf{Lab}_{\mathcal{P}_i}$ ). Moreover, given a countable set of basic labels  $\mathbf{Lab}_{\mathcal{M}}$ , we have the associated set of *membrane labels*  $\widehat{\mathbf{Lab}}_{\mathcal{M}}$ , ranged over by  $\Delta, \Gamma, \Psi \dots$ , defined as the least set such that: (i)  $\mathbf{Lab}_{\mathcal{M}} \subseteq \widehat{\mathbf{Lab}}_{\mathcal{M}}$ ; and (ii) if  $\Gamma, \Delta \in \widehat{\mathbf{Lab}}_{\mathcal{M}}$  and  $\lambda, \mu \in \mathbf{Lab}_{\mathcal{P}}$ , then  $\mathbf{mate}(\Gamma, \Delta, \lambda, \mu)$ ,  $\mathbf{bud}(\Gamma, \Delta, \lambda, \mu)$ ,  $\mathbf{drip}(\Gamma, \lambda) \in \widehat{\mathbf{Lab}}_{\mathcal{M}}$ .

The structure of a system consists of an empty system (denoted by  $\diamond$ ), the parallel composition of two systems (denoted by the operator  $\circ$ ), and the parallel composition of an unbounded number of systems (denoted by the replication operator  $!$ ). The system  $\sigma(P)^\Gamma$  describes a *membrane*, decorated by label  $\Gamma^1$  that contains the system  $P$  and that performs the *membrane process*  $\sigma$ , describing its interaction capabilities.

The term  $0$  denotes the empty membrane process, the operator  $\mid$  denotes the parallel composition of two processes, and the operator  $!$  denotes the replication of a process. The construct  $a^\lambda.\sigma$  defines a sequential process that executes an action  $a$ , decorated by label  $\lambda$ , and then behaves as the process  $\sigma$ . We adopt standard syntactical abbreviations:  $a^\lambda$  stands for  $a^\lambda.0$ ,  $(P)^\Gamma$  stands for  $0(P)^\Gamma$ , and  $\sigma(\diamond)^\Gamma$  is a shorthand for  $\sigma(\diamond)^\Gamma$ .

As we have already mentioned, the labels will be exploited in our version of the causal semantics of MBD. More in details, the process labels related to the actions that interact in a reaction are used to generate the *fresh cause name* associated to

---

<sup>1</sup>For brevity, from now on, we will usually write membrane  $\Gamma$ , instead of membrane labelled by  $\Gamma$ .

$P \circ Q \equiv Q \circ P$	$\sigma   \tau \equiv \tau   \sigma$
$P \circ (Q \circ R) \equiv (P \circ Q) \circ R$	$\sigma   (\tau   \rho) \equiv (\sigma   \tau)   \rho$
$P \circ \diamond \equiv P$	$\sigma   0 \equiv \sigma$
$! \diamond \equiv \diamond$	$!0 \equiv 0$
$!(P \circ Q) \equiv !P \circ !Q$	$!(\sigma   \tau) \equiv !\sigma   !\tau$
$!!P \equiv !P$	$!!\sigma \equiv !\sigma$
$!P \equiv \mathbf{relab}(P) \circ !P$	$!\sigma \equiv \mathbf{relab}(\sigma)   !\sigma$
$P \equiv Q \Rightarrow P \circ R \equiv Q \circ R$	$\sigma \equiv \tau \Rightarrow \sigma   \rho \equiv \tau   \rho$
$P \equiv Q \Rightarrow !P \equiv !Q$	$\sigma \equiv \tau \Rightarrow !\sigma \equiv !\tau$
$P \equiv Q \wedge \sigma \equiv \tau \Rightarrow \sigma \langle P \rangle^\Gamma \equiv \tau \langle Q \rangle^\Gamma$	$\sigma \equiv \tau \Rightarrow a^\lambda . \sigma \equiv a^\lambda . \tau$
$0 \langle \rangle^\Gamma \equiv \diamond$	

Table 2: Structural Congruence for (Well Labelled) MBD.

the corresponding reduction step. To this aim, we require that systems are *well labelled*, i.e. that all process labels  $\lambda \in \mathbf{Lab}_{\mathcal{P}}$  occurring in the system are distinct. In the following, we therefore consider only well labelled systems and membrane processes.

The semantics of the calculus is given in terms of a transition system on well labelled systems, defined up to *structural congruence* and *reduction rules*. The structural congruence on systems and membrane processes is the least congruence satisfying the clauses in Table 2. The definition is standard except for the rules that model the unfolding of replication (both for systems and membrane processes) that are adapted in order to preserve well labelling. The new system (process, respectively) introduced by replication is suitably *relabelled*, using *fresh* process labels. Formally, given a system  $P$ ,  $\mathbf{relab}(P)$  denotes a relabelled version of  $P$ , where each process label  $\lambda \in \mathbf{Lab}_{\mathcal{P}_i}$  is replaced by a label  $\mu$  such that  $\mu \in \mathbf{Lab}_{\mathcal{P}_i}$  (i.e.  $\lambda$  and  $\mu$  belong to the same partition of  $\mathbf{Lab}_{\mathcal{P}}$ ). Similarly, we define  $\mathbf{relab}(\sigma)$  for a process  $\sigma$ .

The reduction rules given in Table 3 complete the definition of the semantics. Besides the standard reduction rule for congruence (STRUCT), and the contextual rules to propagate reductions across parallel composition (PAR) and membrane nesting (BRANE), there are the axioms specific of the MBD fragment.

Rule (MATE) models the fusion of two parallel membranes, labelled by  $\Delta$  and  $\Gamma$ , which exercise the actions  $\mathbf{mate}_n^\lambda$  and  $\overline{\mathbf{mate}}_n^\mu$ , respectively. The membrane introduced by the fusion takes the label  $\mathbf{mate}(\Delta, \Gamma, \lambda, \mu)$  and has associated the parallel composition of the residual processes of the two membranes. In the rule (BUD), a membrane labelled by  $\Gamma$  expels a child membrane labelled by  $\Delta$ , by performing the actions  $\overline{\mathbf{bud}}_n^\mu(\rho)$  and  $\mathbf{bud}_n^\lambda$ , respectively. The membrane  $\Delta$  is wrapped inside a new membrane with label

$\text{(PAR)} \frac{P \rightarrow Q}{P \circ R \rightarrow Q \circ R} \qquad \text{(BRANE)} \frac{P \rightarrow Q}{\sigma(P)^\Gamma \rightarrow \sigma(Q)^\Gamma}$ $\text{(STRUCT)} \frac{P \equiv P' \wedge P' \rightarrow Q' \wedge Q' \equiv Q}{P \rightarrow Q}$
$\text{(MATE)} \quad \text{mate}_n^\lambda . \sigma   \sigma_0(P)^\Delta \circ \overline{\text{mate}}_n^\mu . \tau   \tau_0(Q)^\Gamma \rightarrow \sigma   \sigma_0   \tau   \tau_0(P \circ Q)^{\text{mate}(\Delta, \Gamma, \lambda, \mu)}$ $\text{(BUD)} \quad \overline{\text{bud}}_n^\mu(\rho) . \tau   \tau_0(\text{bud}_n^\lambda . \sigma   \sigma_0(P)^\Delta \circ Q)^\Gamma \rightarrow \rho   (\sigma   \sigma_0(P)^\Delta)^{\text{bud}(\Delta, \Gamma, \lambda, \mu)} \circ \tau   \tau_0(Q)^\Gamma$ $\text{(DRIP)} \quad \text{drip}^\lambda(\rho) . \sigma   \tau(P)^\Delta \rightarrow \rho   \text{drip}^\lambda(\rho) \circ \sigma   \tau(P)^\Delta$

Table 3: Reduction Semantics for (Well Labelled) MBD.

$\text{bud}(\Delta, \Gamma, \lambda, \mu)$  and has associated the membrane process  $\rho$ . Finally, in the rule (DRIP), a membrane labelled by  $\Delta$ , by performing the action  $\text{drip}^\lambda(\rho)$ , creates a new empty membrane, labelled by  $\text{drip}(\Delta, \lambda)$ , which has associated the membrane process  $\rho$ .

### 3. Causal Semantics for MBD

In this section, we introduce a simplified version of the causal semantics of [6], adapted for dealing with well labelled systems and for simplifying the abstract version of the semantics. Before introducing the causal semantics, we briefly recall the discussion, presented in [6], on the causal dependencies arising in MBD, and on the way these dependencies can be expressed by the causal semantics of the calculus.

#### 3.1. Causality in MBD

In [6], Busi describes and classifies different kinds of causal dependencies arising in MBD. As in all process algebras, we can find the standard *structural causality*, due to the prefix structure of terms and the *synchronisation causality*, due to the synchronisation of complementary actions.

Furthermore, there are the causal dependencies coming from the membrane structure and due to the MBD primitives. In particular, the *mate reaction* introduces a quite subtle kind of causality, called *environment causality*. The fusion of two membranes modifies indeed the environment, so that the interaction possibilities of their child membranes may result increased. More in details, after the fusion of two membranes it is possible that: (i) two child membranes become siblings and, therefore, can perform a mate reaction that was not possible before; and (ii) a child membrane can move out from the

parent membrane, by performing a bud reaction that was not possible before. Hence, such interactions of the child membranes *causally depend* on the mate realised by the parent membranes. On the contrary, a drip reaction realised by a child membrane can be considered *causally independent* from the mate operation, because it can be executed regardless of the fact that the fusion of the parent membranes has been performed.

We present some illustrative examples, taken from [6], of these kinds of causality. The first example illustrates both *structural* and *synchronisation causality*.

In all the examples, to obtain a more precise approximation, we assume a particular labelling for the initial (well labelled) systems<sup>2</sup>. In particular, we assume that all the process labels belong to different subsets of  $\text{Lab}_{\mathcal{P}}$ , and that all the membrane labels belong to the set of basic membrane labels  $\text{Lab}_{\mathcal{M}}$ .

**Example 1** (Structural and Synchronisation Causality). *The following system illustrates both forms of causality,*

$$P_1 = \text{drip}^\lambda(\sigma_1).\text{mate}_n^\nu.\text{drip}^\mu(\tau_1)\langle\!\rangle^\Delta \circ \text{drip}^\beta(\sigma_2).\overline{\text{mate}}_n^\delta.\text{drip}^\kappa(\tau_2)\langle\!\rangle^\Gamma.$$

The system is given by the parallel composition of two membranes  $\Delta$  and  $\Gamma$ . The first one has associated the process  $\text{drip}^\lambda(\sigma_1).\text{mate}_n^\nu.\text{drip}^\mu(\tau_1)$ , while the second one the process  $\text{drip}^\beta(\sigma_2).\overline{\text{mate}}_n^\delta.\text{drip}^\kappa(\tau_2)$ . Initially, both membranes can perform a drip reaction. Membrane  $\Delta$  may fire the action  $\text{drip}^\lambda(\sigma_1)$ , thus leading to the creation of a new membrane, which has associated the process  $\sigma_1$ . Similarly, membrane  $\Gamma$  may fire the action  $\text{drip}^\beta(\sigma_2)$ , thus leading to the creation of a new membrane, which has associated the process  $\sigma_2$ . The two drip reactions can be exercised in any order, and therefore, they are causally independent.

$$P_1 \xrightarrow{\text{drip}} \xrightarrow{\text{drip}} P'_1 = \sigma_1\langle\!\rangle^{\Phi_1} \circ \sigma_2\langle\!\rangle^{\Phi_2} \circ \text{mate}_n^\nu.\text{drip}^\mu(\tau_1)\langle\!\rangle^\Delta \circ \overline{\text{mate}}_n^\delta.\text{drip}^\kappa(\tau_2)\langle\!\rangle^\Gamma.$$

After the execution of the two drip reactions (for readability, we annotate the transitions with the kind of the corresponding interaction), the two new created membranes are labelled by  $\Phi_1 = \text{drip}(\Delta, \lambda)$  and  $\Phi_2 = \text{drip}(\Gamma, \beta)$ , respectively. Furthermore, the membrane  $\Delta$  has associated the process  $\text{mate}_n^\nu.\text{drip}^\mu(\tau_1)$ , while the membrane  $\Gamma$  to the process  $\overline{\text{mate}}_n^\delta.\text{drip}^\kappa(\tau_2)$ . The two membranes  $\Delta$  and  $\Gamma$  are now ready to realise a mate reaction on  $n$ , by firing the actions  $\text{mate}_n^\nu$  and  $\overline{\text{mate}}_n^\delta$ , respectively. Due to the prefix structure of membrane processes, the two co-actions causally depend on the previously occurred drip reactions. As a consequence, the mate reaction on  $n$  causally depends on

---

<sup>2</sup>We refer the reader to the analysis of the systems presented in the Examples 8, 9 and 10.



both the previous drip reactions.

$$P_1 \xrightarrow{\text{mate}_n} P_2'' = \sigma_1(\mathbb{O})^{\Phi_1} \circ \sigma_2(\mathbb{O})^{\Phi_2} \circ (\text{drip}^\mu(\tau_1) | \text{drip}^\kappa(\tau_2))(\mathbb{O})^\Pi.$$

Finally, the membrane  $\Pi = \text{mate}(\Delta, \Gamma, \nu, \delta)$ , resulting from the fusion, has associated the process  $\text{drip}^\mu(\tau_1) | \text{drip}^\kappa(\tau_2)$ . As before, the two drip reactions can be exercised in any order, and thus they are causally independent. However, they both causally depend on the previous mate reaction on  $n$  and, in turn, also on the drip reactions that caused the mate. In particular, the more recent reaction (the mate on  $n$ ) represents what we will call their immediate cause.

In the next examples, we focus on *environment causality*, by discussing the effect of a mate reaction on the future interactions (mate and bud) of the child membranes.

**Example 2** (Environment Causality 1). *The following system illustrates the dependence of a mate reaction between two membranes from a previous mate reaction, which leads the two merging membranes to be siblings,*

$$P_2 = \text{mate}_n^\nu(\text{mate}_m^\mu | \text{mate}_o^\zeta)(\mathbb{O})^\Theta \circ \overline{\text{mate}}_o^\beta(\mathbb{O})^\Phi)^\Delta \circ \overline{\text{mate}}_n^\delta(\overline{\text{mate}}_m^\lambda(\mathbb{O})^\Psi)^\Gamma.$$

The system is composed by the two parallel membranes  $\Delta$  and  $\Gamma$ , the first one has associated the process  $\text{mate}_n^\nu$ , and the other one  $\overline{\text{mate}}_n^\delta$ . The membrane  $\Delta$  contains two child membranes  $\Theta$  and  $\Phi$ , while the membrane  $\Gamma$  only contains the child membrane  $\Psi$ . Initially, the two top level membranes can realise a mate reaction on  $n$  (by firing the corresponding actions  $\text{mate}_n^\nu$  and  $\overline{\text{mate}}_n^\delta$ ). At the same time, also the two membranes  $\Theta$  and  $\Phi$  can realise a mate reaction on  $o$  (by firing the corresponding actions  $\text{mate}_o^\zeta$  and  $\overline{\text{mate}}_o^\beta$ ). Therefore, the mate reactions on  $n$  and on  $o$  are causally independent. Actually, the membranes  $\Delta$  and  $\Gamma$  are initially siblings at top level, as well as the membranes  $\Theta$  and  $\Phi$  are initially siblings, inside the membrane  $\Delta$ .

On the contrary, the membranes  $\Theta$  and  $\Psi$  are willing to realise a mate reaction on  $m$ , by performing the actions  $\text{mate}_m^\mu$  and  $\overline{\text{mate}}_m^\lambda$ , respectively, but they cannot interact, because, initially, they are not siblings. Since the membranes  $\Theta$  and  $\Psi$  become siblings only after the fusion of the parent membranes  $\Delta$  and  $\Gamma$ , we can conclude that the mate reaction on  $m$  causally depends on the mate reaction on  $n$ ,

As an example, we present the computation in which the first mate interaction is that on  $n$ , the second one is on  $m$ , and the third one is on  $o$ .

$$P_2 \xrightarrow{\text{mate}_n} P_2' = ((\text{mate}_m^\mu | \text{mate}_o^\zeta)(\mathbb{O})^\Theta \circ \overline{\text{mate}}_o^\beta(\mathbb{O})^\Phi \circ \overline{\text{mate}}_m^\lambda(\mathbb{O})^\Psi)^\Pi.$$

The membrane resulting from the mate reaction on  $n$  is labelled by  $\Pi = \mathbf{mate}(\Delta, \Gamma, \nu, \delta)$ . After the fusion of the parent membranes, the mate reaction on  $m$  becomes possible,

$$P'_2 \xrightarrow{\mathbf{mate}_m} P''_2 = ((\mathbf{mate}_o^\zeta(\emptyset))^{\Pi_1} \circ \overline{\mathbf{mate}_o^\beta(\emptyset)^\Phi})^\Pi.$$

The membrane resulting from the mate reaction on  $m$  is labelled by  $\Pi_1 = \mathbf{mate}(\Theta, \Psi, \mu, \lambda)$ . The last reaction is the mate on  $o$ ,

$$P''_2 \xrightarrow{\mathbf{mate}_o} P'''_2 = ((\emptyset)^{\Pi_2})^\Pi$$

where the new resulting membrane is labelled by  $\Pi_2 = \mathbf{mate}(\Pi_1, \Phi, \zeta, \beta)$ . It should be clear that the mate reaction on  $o$  could have been performed before, because it does not depend on any other reaction.

**Example 3** (Environment Causality 2). The following system illustrates the dependence of a bud reaction from a previous mate reaction, which made parent-child the two interacting membranes.

$$P_3 = \mathbf{mate}_n^\nu | \overline{\mathbf{bud}_m^\lambda(\rho_1)} | (\mathbf{bud}_m^\mu(\emptyset)^\Theta \circ \mathbf{bud}_o^\zeta(\emptyset)^\Phi)^\Delta \circ \overline{\mathbf{mate}_n^\delta} | \overline{\mathbf{bud}_o^\beta(\rho_2)}(\emptyset)^\Gamma.$$

As in Example 2, the system is composed by two parallel membranes  $\Delta$  and  $\Gamma$  that are ready to interact, performing a mate reaction on  $n$ . Here, the membrane  $\Delta$  contains two child membranes  $\Theta$  and  $\Phi$  that are both willing to realise a bud reaction.

The child membrane  $\Theta$  can perform an action  $\mathbf{bud}_m^\mu$ , to which the parent membrane  $\Delta$  can immediately offer the corresponding action  $\overline{\mathbf{bud}_m^\lambda(\rho_1)}$ . Therefore, the bud reaction on  $m$  can be performed independently from the mate reaction on  $n$ .

On the contrary, the child membrane  $\Phi$  offers an action  $\mathbf{bud}_o^\zeta$ , but it cannot interact with its parent membrane  $\Delta$  that does not offer the corresponding co-action. After the fusion of the parent membranes  $\Delta$  and  $\Gamma$ , the bud reaction on  $o$  becomes possible, because the newly created membrane inherits the action  $\overline{\mathbf{bud}_o^\beta(\rho_2)}$  from membrane  $\Gamma$ . Therefore, we can conclude that the bud reaction on  $o$  causally depends on the mate reaction on  $n$ .

As an example, we present the computation in which the first reaction is the mate reaction on  $n$ , the second one is the bud reaction on  $o$  and the third one is the bud reaction on  $m$ .

$$P_3 \xrightarrow{\mathbf{mate}_n} P'_3 = (\overline{\mathbf{bud}_m^\lambda(\rho_1)} | \overline{\mathbf{bud}_o^\beta(\rho_2)}) | (\mathbf{bud}_m^\mu(\emptyset)^\Theta \circ \mathbf{bud}_o^\zeta(\emptyset)^\Phi)^\Pi.$$

The membrane resulting from the mate on  $n$  reaction is labelled by  $\Pi = \mathbf{mate}(\Delta, \Gamma, \nu, \delta)$ . Due to the previous mate reaction on  $n$ , the bud reaction on  $o$  becomes possible,

$$P'_3 \xrightarrow{\text{bud}_o} P''_3 = \rho_2(\langle \langle \rangle \rangle^\Phi)^{\Psi_1} \circ \overline{\text{bud}}_m^\lambda(\rho_1)(\langle \langle \rangle \rangle^\Theta)^\Pi.$$

The new membrane created by the bud reaction is labelled by  $\Psi_1 = \text{bud}(\Phi, \Pi, \zeta, \beta)$ . The last reaction is the bud reaction on  $m$ ,

$$P''_3 \xrightarrow{\text{bud}_m} P'''_3 = \rho_2(\langle \langle \rangle \rangle^\Phi)^{\Psi_1} \circ \rho_1(\langle \langle \rangle \rangle^\Theta)^{\Psi_2} \circ \langle \langle \rangle \rangle^\Pi,$$

where the new resulting membrane is labelled by  $\Psi_2 = \text{bud}(\Theta, \Pi, \mu, \lambda)$ . It should be clear the bud on  $m$  could have been performed before, because it does not depend on any other reaction.

The causal semantics for MBD in [6] is based on the idea of annotating each reduction step with the following causal information:

- a *fresh name*  $k$  in a set of causes  $\mathcal{K}$  that represents the name associated to the reaction;
- a set of causes  $H \subseteq \mathcal{K}$  that includes the names associated to the already occurred reactions, which represent the *immediate causes* of the current reaction.

Note that the set of all the causes of a reduction step can be obtained by transitive closure of the immediate causal relation. Moreover, the syntax of the calculus is enriched with causal information, to propagate the cause name associated to each reduction step to the next interactions that may causally depend on it. Finally, further causes, called *internal* and *external* causes, respectively, are introduced to handle environment causality dependencies, as the ones illustrated in the Examples 2 and 3.

### 3.2. The Causal Semantics Revised

We simplify and adapt the causal semantics in [6], to make the definition of its abstract version easier. The main difference consists in the construction of the fresh cause names associated to each reduction step. In our semantics, the *cause name*  $k$ , associated to a given reaction step, is obtained by using the process labels related to the involved actions: the labels of the two co-actions for the mate and bud interactions, and a single label for the drip interaction. The well labelling condition of systems guarantees that  $k$  is *fresh*.

In [6], decorated cause are specifically introduced to capture the *environment causality*, due the fusion of two membranes, in a way that will be made clear in the following. We just adapt the original definition of decorated causes, by deriving it from our definition of cause names.

$$\begin{array}{ll}
\tilde{P}, \tilde{Q} & ::= \diamond \mid \tilde{P} \circ \tilde{Q} \mid !\tilde{P} \mid \tilde{\sigma}(\tilde{P})^\Gamma & \text{systems with causes } \widetilde{\text{Sys}} \\
\tilde{\sigma}, \tilde{\tau} & ::= 0 \mid \tilde{\sigma} \mid \tilde{\tau} \mid !\tilde{\sigma} \mid (K, I, E) :: a^\lambda.\sigma & \text{membrane processes with causes } \widetilde{\text{Proc}}
\end{array}$$

Table 4: Syntax of MBD with Causes, where  $a \in \text{Act}$  is defined as in Table 1.

**Definition 1.** Let  $\mathcal{K}$  be the set of cause names defined as follows,

$$\mathcal{K} = \text{Lab}_{\mathcal{P}} \cup (\text{Lab}_{\mathcal{P}} \times \text{Lab}_{\mathcal{P}})^3.$$

The derived set of decorated causes is defined as follows,

$$\mathcal{K}^\pm = \{k^x \mid k \in \mathcal{K}, x \in \{+, -\}\}.$$

For simplicity, when a set of causes (or, similarly, a set of decorated causes) is a singleton, we omit the surrounding parentheses.

The causal information that we will use to annotate membrane processes is subdivided into three parts: the set of *immediate* cause names, followed by the set of *internal* decorated causes, and by the set of *external* decorated causes.

**Definition 2.** We define  $\widehat{\mathcal{K}}$ , ranged over by triples like  $(K, I, E)$ , as follows

$$\widehat{\mathcal{K}} = \wp(\mathcal{K}) \times \wp(\mathcal{K}^\pm) \times \wp(\mathcal{K}^\pm)^4.$$

In [6], internal and external causes come with different subscripts, and can therefore be merged in one single set, together with immediate causes. For the sake of clarity, we prefer instead to distinguish them in simple, internal and external causes, respectively.

We now define the MBD calculus with causes by introducing the causal information in well labelled systems and membrane processes. The syntax of *systems with causes*  $\widetilde{\text{Sys}}$  and of *membrane processes with causes*  $\widetilde{\text{Proc}}$  is defined in Table 4, where  $(K, I, E) \in \widehat{\mathcal{K}}$ . The causal information  $(K, I, E)$  is recorded in front of each sequential processes, associated to a membrane.

In a sequential process with causes  $(K, I, E) :: a^\lambda.\sigma$ , the component  $K$  represents the set of *immediate causes* of the process, while the components  $I$  and  $E$  report sets of decorated causes representing its *internal* and *external* causes, respectively. Decorated causes are specifically introduced to handle *environment causality* and, therefore, to treat

<sup>3</sup>We assume the set  $\mathcal{K}$  disjoint from the name set  $\mathcal{N}$ .

<sup>4</sup>Here and afterwards,  $\wp(S)$  denotes the power set of the set  $S$ .

the causal dependencies originated by the fusion of two membranes. More in details, they are used to assign the cause associated to the mate of two membranes to the future mate and bud interactions of the child membranes, provided that such interactions have become possible as a consequence of the fusion of the parent membranes. Intuitively, in a decorated cause  $h^x$  the cause name  $h$  refers to a previously occurred mate reaction, while the sign  $x \in \{-, +\}$  is used to distinguish one membrane that has merged from the other one. More precisely, an internal cause  $h^x \in I$  says that the membrane, which has associated the process  $a^\lambda.\sigma$ , was a child membrane of one of the two membranes that realised the mate associated to  $h$ , and, in particular, the one associated to the sign  $x$ . Similarly, an external cause  $h^x \in E$  says that the process  $a^\lambda.\sigma$  derives from one of the two membranes that realised the mate associated to  $h$ , and, in particular, the one associated to the sign  $x$ .

By suitably combining the internal and external causes of two membranes that want to realise a mate or a bud reaction, we can determine whether such interaction is a consequence of a previous mate reaction. The use of internal and external causes can be completely understood in the following, once the semantic rules have been defined in Table 5, by looking at the examples presented in Section 3.3.

For simplicity, we omit the empty causal information represented by a triple  $(\emptyset, \emptyset, \emptyset)$  in front of sequential membrane processes. By abuse of notation, a labelled process (labelled system, respectively) can be interpreted, when required, as a process with empty causes (a system with empty causes, respectively).

The causal semantics is given in terms of the causal transition relation  $\xrightarrow{k;H}$ , where  $\tilde{P} \xrightarrow{k;H} \tilde{Q}$  denotes that the system  $\tilde{P}$  performs an action, associated with the fresh cause name  $k \in \mathcal{K}$ , and with the set of *immediate causes*  $H \subseteq \mathcal{K}$ .

We first introduce two auxiliary operators. The first operator distributes the causal information on sequential membrane processes and on systems.

**Definition 3.** *Given a triple  $(K, I, E) \in \widehat{\mathcal{K}}$ , the operator  $(K, I, E) \triangleright$  is inductively defined on membrane processes  $\widetilde{\text{Proc}}$ , and on systems with causes  $\widetilde{\text{Sys}}$  as follows,*

$$\begin{aligned}
(K, I, E) \triangleright 0 &= 0 \\
(K, I, E) \triangleright \tilde{\sigma} | \tilde{\tau} &= (K, I, E) \triangleright \tilde{\sigma} \mid (K, I, E) \triangleright \tilde{\tau} \\
(K, I, E) \triangleright !\tilde{\sigma} &= !(K, I, E) \triangleright \tilde{\sigma} \\
(K, I, E) \triangleright (K', I', E') :: a^\lambda.\sigma &= (K \cup K', I \cup I', E \cup E') :: a^\lambda.\sigma \\
(K, I, E) \triangleright \diamond &= \diamond \\
(K, I, E) \triangleright (\tilde{P} \circ \tilde{Q}) &= (K, I, E) \triangleright \tilde{P} \circ (K, I, E) \triangleright \tilde{Q} \\
(K, I, E) \triangleright !\tilde{P} &= !(K, I, E) \triangleright \tilde{P} \\
(K, I, E) \triangleright \tilde{\sigma} (\tilde{P})^\Gamma &= ((K, I, E) \triangleright \tilde{\sigma}) (\tilde{P})^\Gamma.
\end{aligned}$$

The following auxiliary operator is used to combine sets of decorated causes, according to their sign.

**Definition 4.** The function  $\otimes : \wp(\mathcal{K}^\pm) \times \wp(\mathcal{K}^\pm) \rightarrow \wp(\mathcal{K})$  is defined as follows,

$$Y_1 \otimes Y_2 = \{k \mid k^x \in Y_1, k^y \in Y_2, \text{ with } x, y \in \{+, -\}, x \neq y\}.$$

Note that, due to the subdivision of the cause set in three parts,  $\otimes$  plays the role of the several operators used to combine causes in [6].

The causal transition system is defined up to causal structural congruence (which is the trivial adaptation of the one presented in Table 2) and to causal reduction rules, obtained by decorating the rules of Table 3 with information on causes. Table 5 presents the causal version of the MBD axioms, and includes the obvious adaptation of the rules (PAR), (BRANE) and (STRUCT) in Table 3.

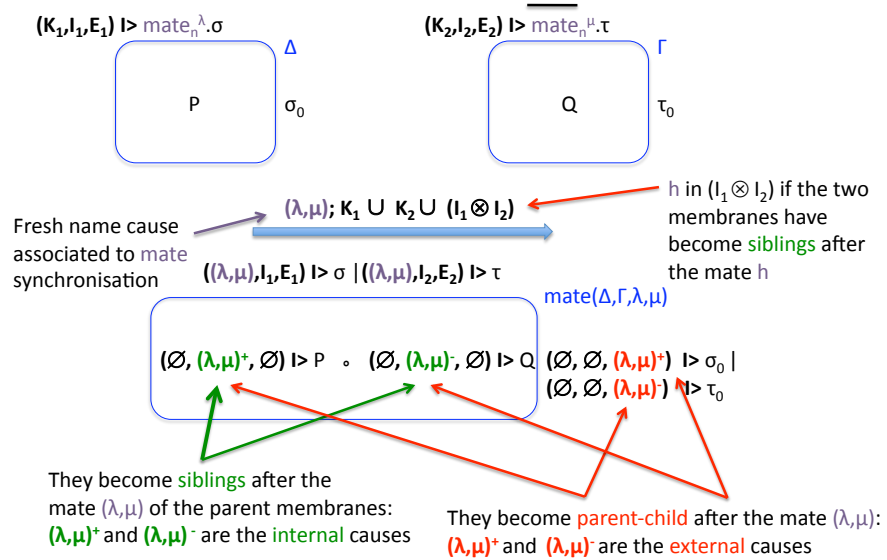


Figure 1: Illustration of the (MATE<sub>c</sub>) Rule (where tildes are omitted for simplicity in systems and membrane processes.)

- In the rule (MATE<sub>c</sub>) (illustrated in Figure 1), two membranes  $\Delta$  and  $\Gamma$  realise a fusion, by synchronising on actions  $\text{mate}_n^\lambda$  and  $\overline{\text{mate}}_n^\mu$ , respectively. The reduction step is associated to the *fresh cause name*  $k$  derived from the process labels  $\lambda$  and  $\mu$ . Moreover, it has, in the set of *immediate causes*, the immediate causes of both actions ( $K_1$  and  $K_2$ , respectively), and all the causes  $h \in I_1 \otimes I_2$ , derived by combining the internal causes of both actions ( $I_1$  and  $I_2$ , respectively). Actually, if  $h^x \in I_1$  and  $h^y \in I_2$ , with  $x \neq y$ , then the two membranes  $\Delta$  and  $\Gamma$  have become siblings as a consequence of the mate reaction associated to cause  $h$ . Therefore, the mate reaction associated to  $k$  *causally depends* on the one associated to  $h$ .

The information on causes is propagated into the resulting system with causes as follows. Both continuations of mate and co-mate have  $k$  as immediate cause, and inherit the internal and external causes from the previous action. Both *internal* and *external causes* related to cause  $k$  are introduced to propagate the cause  $k$  to the future mate and bud interactions of the child membranes. More in details, the child membranes coming from the membrane  $\Delta$  ( $\Gamma$ , respectively) take internal cause  $k^+$  ( $k^-$ , respectively). These causes are defined *internal*, because they concern the membranes inside the merging membranes.

Finally, external causes are assigned to the remaining subprocesses coming from the two merging membranes. Again, cause  $k^+$  is propagated in the subprocess coming from the membrane  $\Delta$ , while  $k^-$  is propagated in the subprocess coming from the membrane  $\Gamma$ . These causes are called *external*, because they concern the sequential processes associated to the merging membranes.

- In the rule (BUD<sub>c</sub>), a membrane  $\Gamma$  expels a child membrane  $\Delta$ , by synchronising on actions  $\text{bud}_n^\lambda$  and  $\overline{\text{bud}}_n^\mu(\rho)$ , respectively. The reduction step is associated to the *fresh cause name*  $k$ , derived as in rule (MATE<sub>c</sub>). The set of *immediate causes* contains the immediate causes of both actions, and the causes  $h \in E_1 \otimes I_2$ , derived by combining the external causes of the cobud ( $E_1$ ) and the internal causes of the bud action ( $I_2$ ). Actually, if  $h^x \in E_1$  and  $h^y \in I_2$ , with  $x \neq y$ , then the movement of the child membrane  $\Delta$  out from the parent membrane  $\Gamma$  has become possible after the execution of the mate reaction  $h$ . Hence, the bud reaction associated to  $k$  *causally depends* on the mate reaction associated to  $h$ . Propagation of causes in the resulting system is obtained as follows. The continuations of the two actions acquire causes as in Rule (MATE<sub>c</sub>). The new membrane enclosing the membrane  $\Delta$  has associated the process  $\rho$ , which has  $k$  as immediate cause and inherits, from the cobud, the internal causes  $I_1$ , needed to control the possible future mate interactions of the new membrane.

- In the rule ( $\text{DRIP}_c$ ), a membrane  $\Delta$  splits off an empty membrane, performing an action  $\text{drip}^\lambda(\rho)$ . The reduction step is associated to the *fresh cause name*  $\lambda$ , and to the set of *immediate causes* of the drip action. Differently from the previous cases, a drip reaction is causally independent from the previously mate reactions realised by the parent membranes. The continuation of the drip action has immediate cause  $\lambda$  and inherits internal and external causes from the drip action. The new membrane has associated the process  $\rho$ , which acquires the causes from the drip action as done in rule ( $\text{BUD}_c$ ).

$ \begin{array}{c} (\text{PAR}_c) \frac{\tilde{P} \xrightarrow{k;H} \tilde{Q}}{\tilde{P} \circ \tilde{R} \xrightarrow{k;H} \tilde{Q} \circ \tilde{R}} \quad (\text{BRANE}_c) \frac{\tilde{P} \xrightarrow{k;H} \tilde{Q}}{\tilde{\sigma}(\tilde{P})^\Gamma \xrightarrow{k;H} \tilde{\sigma}(\tilde{Q})^\Gamma} \\ (\text{STRUCT}_c) \frac{\tilde{P} \equiv \tilde{P}' \wedge \tilde{P}' \xrightarrow{k;H} \tilde{Q}' \wedge \tilde{Q}' \equiv \tilde{Q}}{\tilde{P} \xrightarrow{k;H} \tilde{Q}} \end{array} $
$ \begin{array}{c} (\text{MATE}_c) \quad ((K_1, I_1, E_1) :: \text{mate}_n^\lambda.\sigma)   \tilde{\sigma}_0(\tilde{P})^\Delta \circ ((K_2, I_2, E_2) :: \overline{\text{mate}_n^\mu}.\tau)   \tilde{\tau}_0(\tilde{Q})^\Gamma \\ \quad \xrightarrow{k; K_1 \cup K_2 \cup (I_1 \otimes I_2)} \\ ((k, I_1, E_1) \triangleright \sigma)   ((\emptyset, \emptyset, k^+) \triangleright \tilde{\sigma}_0)   ((k, I_2, E_2) \triangleright \tau)   \\ ((\emptyset, \emptyset, k^-) \triangleright \tilde{\tau}_0)   ((\emptyset, k^+, \emptyset) \triangleright \tilde{P} \circ (\emptyset, k^-, \emptyset) \triangleright \tilde{Q})^{\Psi_m} \\ (\text{BUD}_c) \quad ((K_1, I_1, E_1) :: \overline{\text{bud}_n^\mu}(\rho).\tau)   \tilde{\tau}_0   ((K_2, I_2, E_2) :: \text{bud}_n^\lambda.\sigma)   \tilde{\sigma}_0(\tilde{P})^\Delta \circ \tilde{Q}  ^\Gamma \\ \quad \xrightarrow{k; K_1 \cup K_2 \cup (E_1 \otimes I_2)} \\ ((k, I_1, \emptyset) \triangleright \rho)   ((k, I_2, E_2) \triangleright \sigma)   \tilde{\sigma}_0(\tilde{P})^\Delta  ^{\Psi_b} \circ ((k, I_1, E_1) \triangleright \tau)   \tilde{\tau}_0(\tilde{Q})^\Gamma \\ (\text{DRIP}_c) \quad ((K, I, E) :: \text{drip}^\lambda(\rho).\sigma)   \tau(\tilde{P})^\Delta \\ \quad \xrightarrow{\lambda; K} \\ ((\lambda, I, \emptyset) \triangleright \rho)   \langle \diamond \rangle^{\Psi_d} \circ ((\lambda, I, E) \triangleright \sigma)   \tilde{\tau}(\tilde{P})^\Delta \end{array} $
<p>where <math>k = (\lambda, \mu)</math>, <math>\Psi_m = \text{mate}(\Delta, \Gamma, \lambda, \mu)</math>, <math>\Psi_b = \text{bud}(\Delta, \Gamma, \lambda, \mu)</math>, and <math>\Psi_d = \text{drip}(\Delta, \lambda)</math></p>

Table 5: Causal Reduction Semantics of MBD.

Given a system  $P$ , its causal semantics is defined as a *Labelled Transition System*



(LTS), obtained by transitive closure starting from the system with empty causes, corresponding to  $P$ . Given  $P \in \mathbf{Sys}$ ,  $\widetilde{LTS}(P)$  denotes the LTS  $(X, \rightarrow, P)$ , where: (i)  $X \subseteq \widetilde{\mathbf{Sys}}$  is the set of reachable systems with causes; (ii)  $\rightarrow \subseteq \widetilde{\mathbf{Sys}} \times (\mathcal{K}, \wp(\mathcal{K})) \times \widetilde{\mathbf{Sys}}$  is the causal reduction relation defined by the rules in Table 5; (iii)  $P$  is the initial system with empty causes.

In the following, using a standard notation, we denote the reflexive and transitive closure of the causal transition relation  $\xrightarrow{k;H}$  with  $\longrightarrow_*$ , and, analogously, the transitive closure after  $n$  steps with  $\longrightarrow_n$ .

Starting from the causal semantics, it is easy to retrieve the standard interleaving semantics, by just removing the causes in membrane processes and systems. To this aim, we need the following auxiliary function, which represents the adaptation of the function *DropCause* in [6] to our version of the semantics.

**Definition 5.** *The function DropCause is defined inductively on membrane processes with causes Proc and on systems with causes Sys as follows,*

$$\begin{aligned}
\text{DropCause}(0) &= 0 \\
\text{DropCause}(\tilde{\sigma}|\tilde{\tau}) &= \text{DropCause}(\tilde{\sigma})|\text{DropCause}(\tilde{\tau}) \\
\text{DropCause}(!\tilde{\sigma}) &= !\text{DropCause}(\tilde{\sigma}) \\
\text{DropCause}((K, I, E) :: a^\lambda.\sigma) &= a^\lambda.\sigma \\
\text{DropCause}(\diamond) &= \diamond \\
\text{DropCause}(\tilde{P} \circ \tilde{Q}) &= \text{DropCause}(\tilde{P}) \circ \text{DropCause}(\tilde{Q}) \\
\text{DropCause}(!\tilde{P}) &= !\text{DropCause}(\tilde{P}) \\
\text{DropCause}(\tilde{\sigma}(|\tilde{P}|)^\Gamma) &= \text{DropCause}(\tilde{\sigma})(|\text{DropCause}(\tilde{P})|)^\Gamma
\end{aligned}$$

Now, we can state a correspondence theorem, similar to the one in [6]. The proof is analogous and it is therefore omitted.

**Theorem 1.** *Let  $\tilde{P} \in \widetilde{\mathbf{Sys}}$  a system with causes. The following properties hold:*

- if  $\tilde{P} \xrightarrow{k;H} \tilde{P}'$  then  $\text{DropCause}(\tilde{P}) \longrightarrow \text{DropCause}(\tilde{P}')$ ;
- if  $\text{DropCause}(\tilde{P}) \longrightarrow Q$ , then there exists a system with causes  $\tilde{Q}$ , a cause name  $k$  and a set of causes  $H$  such that  $\tilde{P} \xrightarrow{k;H} \tilde{Q}$  and  $Q = \text{DropCause}(\tilde{Q})$ .

### 3.3. Semantics at work

We now revisit the previously introduced examples, by discussing their causal semantics. We will show that the causal semantics captures the causal dependencies, already described in the Examples 1, 2 and 3.

**Example 4.** We consider the system  $P_1$ , introduced in Example 1,

$$P_1 = \mathbf{drip}^\lambda(\sigma_1).\mathbf{mate}_n^\nu.\mathbf{drip}^\mu(\tau_1)\langle\langle\rangle\rangle^\Delta \circ \mathbf{drip}^\beta(\sigma_2).\overline{\mathbf{mate}}_n^\delta.\mathbf{drip}^\kappa(\tau_2)\langle\langle\rangle\rangle^\Gamma.$$

As an example, we show the causal version of the computation there illustrated.

$$\begin{aligned} P_1 &\xrightarrow{h_1;\emptyset} \xrightarrow{h_2;\emptyset} \tilde{P}_1' = && (h_1, \emptyset, \emptyset) :: \sigma_1\langle\langle\rangle\rangle^{\Phi_1} \circ (h_2, \emptyset, \emptyset) :: \sigma_2\langle\langle\rangle\rangle^{\Phi_2} \circ \\ &&& (h_1, \emptyset, \emptyset) :: \mathbf{mate}_n^\nu.\mathbf{drip}^\mu(\tau_1)\langle\langle\rangle\rangle^\Delta \circ \\ &&& (h_2, \emptyset, \emptyset) :: \overline{\mathbf{mate}}_n^\delta.\mathbf{drip}^\kappa(\tau_2)\langle\langle\rangle\rangle^\Gamma \\ \tilde{P}_1' &\xrightarrow{h_3;\{h_1, h_2\}} \tilde{P}_1'' = && (h_1, \emptyset, \emptyset) :: \sigma_1\langle\langle\rangle\rangle^{\Phi_1} \circ (h_2, \emptyset, \emptyset) :: \sigma_2\langle\langle\rangle\rangle^{\Phi_2} \circ \\ &&& (h_3, \emptyset, \emptyset) :: \mathbf{drip}^\mu(\tau_1)|(h_3, \emptyset, \emptyset) :: \mathbf{drip}^\kappa(\tau_2)\langle\langle\rangle\rangle^\Pi \\ \tilde{P}_1'' &\xrightarrow{h_4;\{h_3\}} \xrightarrow{h_5;\{h_3\}} \tilde{P}_1''' = && (h_1, \emptyset, \emptyset) :: \sigma_1\langle\langle\rangle\rangle^{\Phi_1} \circ (h_2, \emptyset, \emptyset) :: \sigma_2\langle\langle\rangle\rangle^{\Phi_2} \circ \\ &&& (h_4, \emptyset, \emptyset) :: \tau_1\langle\langle\rangle\rangle^{\Phi_3} \circ (h_5, \emptyset, \emptyset) :: \tau_2\langle\langle\rangle\rangle^{\Phi_4} \circ \langle\langle\rangle\rangle^\Pi \end{aligned}$$

where

$h_1 = \lambda, h_2 = \beta, h_3 = (\nu, \delta), h_4 = \mu, h_5 = \kappa$ , and

$\Phi_1 = \mathbf{drip}(\Delta, \lambda), \Phi_2 = \mathbf{drip}(\Gamma, \beta), \Pi = \mathbf{mate}(\Delta, \Gamma, \nu, \delta), \Phi_3 = \mathbf{drip}(\Pi, \mu), \Phi_4 = \mathbf{drip}(\Pi, \kappa)$ .

Causal annotations make it possible to derive the causal dependencies among the different reactions.

- The drip reaction, realised by membrane  $\Delta$ , is associated to the fresh cause name  $h_1$ , while the one realised by the membrane  $\Gamma$  is associated to  $h_2$ . In both cases, the reactions have empty sets of immediate causes. As a consequence, the continuation of action  $\mathbf{drip}^\lambda(\sigma_1)$  (associated to membrane  $\Delta$ ) acquires  $h_1$  as immediate cause, while the continuation of action  $\mathbf{drip}^\beta(\sigma_2)$  (associated to membrane  $\Gamma$ ) acquires  $h_2$ . The newly created membranes are decorated by labels  $\Phi_1$  and  $\Phi_2$ , respectively.
- The mate reaction on  $n$ , realised by membranes  $\Delta$  (by firing the action  $\mathbf{mate}_n^\nu$ ) and  $\Gamma$  (by firing the co-action  $\overline{\mathbf{mate}}_n^\delta$ ), is associated to the fresh cause name  $h_3$ , and has as immediate causes the set  $\{h_1, h_2\}$ . This set is the union of the immediate causes of the corresponding mate and comate actions. The fusion introduces a new membrane labelled by  $\Pi$ , which has associated the parallel composition of the residual processes of both membranes. The continuation of both mate and comate actions acquire  $h_3$  as immediate cause.

- Finally, the membrane  $\Pi$  can perform two drip reactions. The reaction corresponding to the execution of the action  $\mathbf{drip}^\mu(\tau_1)$  is associated to the fresh cause name  $h_4$ , and leads to the creation of the new membrane labelled by  $\Phi_3$ . Instead, the reaction corresponding to the execution of  $\mathbf{drip}^\kappa(\tau_2)$  is associated to  $h_5$ , and leads to the creation of the new membrane labelled by  $\Phi_4$ . In both cases, the set of immediate causes is  $\{h_3\}$ .

Note that the mate reaction on  $n$  (associated to  $h_3$ ) is the immediate cause of both drip reactions associated to  $h_4$  and  $h_5$ . The set of all causal dependencies can be obtained by transitive closure of the immediate causal relation. The other computations are similar.

**Example 5.** We consider the system  $P_2$ , introduced in Example 2,

$$P_2 = \mathbf{mate}'_n(\mathbf{mate}^\mu_m | \mathbf{mate}^\zeta_o)^\Theta \circ \overline{\mathbf{mate}}^\beta_o(\Phi)^\Delta \circ \overline{\mathbf{mate}}^\delta_n(\overline{\mathbf{mate}}^\lambda_m(\Psi)^\Gamma).$$

As an example, we show the causal version of the computation there illustrated. The other computations are similar.

$$\begin{aligned} P_2 \xrightarrow{h_1; \emptyset} \tilde{P}_2' &= (((\emptyset, h_1^+, \emptyset) :: \mathbf{mate}^\mu_m | (\emptyset, h_1^+, \emptyset) :: \mathbf{mate}^\zeta_o)^\Theta \circ \\ &\quad (\emptyset, h_1^+, \emptyset) :: \overline{\mathbf{mate}}^\beta_o(\Phi)^\Delta \circ (\emptyset, h_1^-, \emptyset) :: \overline{\mathbf{mate}}^\lambda_m(\Psi)^\Gamma)^\Pi \\ \tilde{P}_2' \xrightarrow{h_2; \{h_1\}} \tilde{P}_2'' &= (((\emptyset, h_1^+, h_2^+) :: \mathbf{mate}^\zeta_o)^\Pi \circ (\emptyset, h_1^+, \emptyset) :: \overline{\mathbf{mate}}^\beta_o(\Phi)^\Delta)^\Pi \xrightarrow{h_3; \emptyset} ((\Pi)^\Pi)^\Pi \end{aligned}$$

where

$$\begin{aligned} h_1 &= (\nu, \delta), \quad h_2 = (\mu, \lambda), \quad h_3 = (\zeta, \beta), \quad \text{and} \\ \Pi &= \mathbf{mate}(\Delta, \Gamma, \nu, \delta), \quad \Pi_1 = \mathbf{mate}(\Theta, \Psi, \mu, \lambda), \quad \Pi_2 = \mathbf{mate}(\Pi_1, \Phi, \zeta, \beta). \end{aligned}$$

Causal annotations make it possible to derive the causal dependencies among the different reactions.

- The mate reaction on  $n$ , realised by membranes  $\Delta$  and  $\Gamma$ , is associated to the fresh cause name  $h_1$ . The set of immediate causes is empty. Internal causes related to  $h_1$  are propagated into the processes associated to the child membranes of the membrane  $\Pi$  resulting from the fusion. In particular, the membranes  $\Theta$  and  $\Phi$ , which were child membranes of membrane  $\Delta$ , acquire internal cause  $h_1^+$ . Analogously, the membrane  $\Psi$ , which was the child membranes of membrane  $\Gamma$ , acquires internal cause  $h_1^-$ . Internal causes are used to assign the cause  $h_1$ , associated to the mate on  $n$ , to the future interactions of the child membranes.

- The mate reaction on  $m$ , realised by membranes  $\Psi$  and  $\Theta$ , is associated to the fresh cause name  $h_2$ . The set of immediate causes  $\{h_1\}$  is derived by combining the internal causes of the mate ( $h_1^+$ ) and comate ( $h_1^-$ ). The signs of decorated causes show that the two membranes  $\Theta$  and  $\Psi$  have become siblings as a consequence of the mate reaction on  $n$ .
- Finally, the mate reaction on  $o$ , realised by membranes  $\Pi_1$  and  $\Phi$ , is associated to the fresh cause name  $h_3$ . In this case, differently from the previous one, the set of immediate causes is empty. The mate and the comate indeed carry the same internal cause  $h_1^+$ , thus revealing that the two membranes were siblings also before the mate reaction on  $n$ .

**Example 6.** We consider the system  $P_3$ , introduced in Example 3,

$$P_3 = \text{mate}_n^\nu | \overline{\text{bud}}_m^\lambda(\rho_1) | (\text{bud}_m^\mu(\emptyset)^\Theta \circ \text{bud}_o^\zeta(\emptyset)^\Phi)^\Delta \circ \overline{\text{mate}}_n^\delta | \overline{\text{bud}}_o^\beta(\rho_2) | \emptyset^\Gamma.$$

We show the causal version of the computation there illustrated. The other computations are similar.

$$\begin{aligned} P_3 \xrightarrow{h_1; \emptyset} \tilde{P}_3' &= (\emptyset, \emptyset, h_1^+) :: \overline{\text{bud}}_m^\lambda(\rho_1) | \\ & (\emptyset, \emptyset, h_1^-) :: \overline{\text{bud}}_o^\beta(\rho_2) | ((\emptyset, h_1^+, \emptyset) :: \text{bud}_m^\mu(\emptyset)^\Theta \circ (\emptyset, h_1^+, \emptyset) :: \text{bud}_o^\zeta(\emptyset)^\Phi)^\Pi \\ \tilde{P}_3' \xrightarrow{h_2; \{h_1\}} \tilde{P}_3'' &= (h_2, \emptyset, \emptyset) :: \rho_2(\emptyset)^\Phi \Psi_1 \circ (\emptyset, \emptyset, h_1^+) :: \overline{\text{bud}}_m^\lambda(\rho_1) | ((\emptyset, h_1^+, \emptyset) :: \text{bud}_m^\mu(\emptyset)^\Theta)^\Pi \\ \tilde{P}_3'' \xrightarrow{h_3; \emptyset} \tilde{P}_3''' &= (h_2, \emptyset, \emptyset) :: \rho_2(\emptyset)^\Phi \Psi_1 \circ (h_3, \emptyset, \emptyset) :: \rho_1(\emptyset)^\Theta \Psi_2 \circ \emptyset^\Pi \end{aligned}$$

where

$$\begin{aligned} h_1 &= (\nu, \delta), \quad h_2 = (\zeta, \beta), \quad h_3 = (\mu, \lambda), \quad \text{and} \\ \Pi &= \text{mate}(\Delta, \Gamma, \nu, \delta), \quad \Psi_1 = \text{bud}(\Phi, \Pi, \zeta, \beta), \quad \Psi_2 = \text{bud}(\Theta, \Pi, \mu, \lambda). \end{aligned}$$

Causal annotations make it possible to derive the causal dependencies among the different reactions.

- The mate reaction on  $n$ , realised by membranes  $\Delta$  and  $\Gamma$ , is modelled as in Example 5. Internal and external causes related to cause name  $h_1$  are propagated into the resulting system, to propagate the effect of the fusion. More precisely, the processes associated to the membranes  $\Theta$  and  $\Phi$ , which were child membranes of membrane  $\Delta$ , acquire internal cause  $h_1^+$ . In addition, the residual processes derived from the two membranes  $\Gamma$  and  $\Delta$  acquire external causes. The process in parallel with the mate takes  $h_1^+$ , while the process in parallel with the comate takes  $h_1^-$ .

- The bud reaction on  $o$  realised by membranes  $\Pi$  and  $\Phi$  is associated to the fresh cause name  $h_2$  and has set of immediate causes  $\{h_1\}$ . The immediate causes are derived by combining the external causes of the cobud ( $h_1^+$ ) and the internal causes of the bud ( $h_1^-$ ). The decorated causes show that the bud reaction on  $o$  has become possible as a consequence of the mate reaction on  $n$ .
- Finally, the bud reaction on  $m$ , realised by membranes  $\Pi$  and  $\Theta$ , is associated to the fresh cause name  $h_3$ , and has the set of immediate causes empty. Differently from the previous case, both the bud and the cobud carry the same decorated cause  $h_1^+$ , thus showing that the bud reaction on  $m$  was possible also before the mate reaction on  $n$ .

## 4. The Abstraction

The analysis computes a description of the structure of all the derivatives of the initial system, together with a description of the possible causal dependencies among reaction steps. Following the *Abstract Interpretation* approach, the analysis relies on the definition of an abstract version of the causal semantics, in which systems with causes are represented by *abstract states*. More precisely, an abstract state provides information on the possible hierarchical structure of membranes, and on the processes with causes that may be associated to each membrane. The abstract causal semantics is described by abstract causal transitions among abstract states. The analysis result is calculated by collecting the information from the abstract causal semantics, describing the approximated behaviour of the system that we want to analyse. We prove that the analysis is a *safe over-approximation* of the concrete causal behaviour.

### 4.1. Abstract Causal Semantics

#### 4.1.1. Abstract MBD with Causes

The first thing we need to abstract are labels, whose treatment deserves some attention because of replication. The unfolding of replication may indeed lead to an infinite number of process and membrane labels. Therefore, to guarantee that the analysis can be computed in a finite number of steps, we need to have an *abstraction of labels* (both for membrane processes and membranes), able to keep the set of abstract labels finite.

As far as the process labels are concerned, we consider the equivalence classes induced by the partition of  $\mathbf{Lab}_{\mathcal{P}}$ .

**Definition 6.** *The set of abstract process labels is defined as  $\mathbf{Lab}_{\mathcal{P}}^{\circ} = \mathbf{Lab}_{\mathcal{P}} / \equiv$  (ranged over by  $\lambda^{\circ}, \beta^{\circ}, \mu^{\circ}$ ), where for  $\lambda, \mu \in \mathbf{Lab}_{\mathcal{P}}$ , we have  $\lambda \equiv \mu$  if and only if  $\lambda, \mu \in \mathbf{Lab}_{\mathcal{P}_i}$ , for some  $i$ . In the following,  $\lambda^{\bullet}$  denotes the abstract version of  $\lambda \in \mathbf{Lab}_{\mathcal{P}}$ .*

Note that  $\lambda^\circ$  denotes a generic abstract process label, while  $\lambda^\bullet$  exactly denotes the abstract version of the process label  $\lambda$  (i.e. the equivalence class of  $\lambda$ ).

As far as membrane labels are concerned, we first introduce the abstract version of the set of basic membrane labels  $\text{Lab}_M^\circ = \text{Lab}_M \cup \{\@\}$ , where the special symbol  $\@$  represents the outermost membrane.

**Definition 7.** *The set of abstract membrane labels  $\widehat{\text{Lab}}_M^\circ$ , ranged over by  $\Gamma^\circ, \Delta^\circ, \dots$ , is defined as the least set such that: (i)  $\text{Lab}_M^\circ \subseteq \widehat{\text{Lab}}_M^\circ$ ; and (ii) if  $\Gamma^\circ, \Delta^\circ \in \widehat{\text{Lab}}_M^\circ$  then  $\text{mate}(\Gamma^\circ, \Delta^\circ), \text{bud}(\Gamma^\circ, \Delta^\circ), \text{drip}(\Gamma^\circ) \in \widehat{\text{Lab}}_M^\circ$ .*

Nevertheless, since interactions between membranes may introduce arbitrarily nested membrane labels (e.g.  $\text{mate}(\text{bud}(\text{drip}(\Gamma^\circ), \Delta^\circ), \Psi^\circ)$ ), the approximation introduced by  $\widehat{\text{Lab}}_M^\circ$  may not suffice to assure the finiteness of the analysis.

We therefore introduce a further abstraction. Intuitively, it is possible to choose a fixed level of nesting depth  $d$ . All the abstract membrane labels with depth no greater than  $d$  can be recorded, while all the labels with depth greater than  $d$  are approximated with the new special labels:  $\text{mate}(\top, \top)$ ,  $\text{bud}(\top, \top)$  and  $\text{drip}(\top)$ .

**Definition 8.** *The set of abstract membrane labels parametric with respect to  $d$  with  $d \in \mathbb{N}^+$  is defined as follows,*

$$\widehat{\text{Lab}}_M^d = \{\Delta^\circ \mid \Delta^\circ \in \widehat{\text{Lab}}_M^\circ \text{ and } \text{depth}(\Delta^\circ) \leq d\} \cup \{\text{mate}(\top, \top), \text{bud}(\top, \top), \text{drip}(\top)\}$$

where given  $\Delta^\circ \in \widehat{\text{Lab}}_M^\circ$ ,

$$\text{depth}(\Delta^\circ) = \begin{cases} 1 & \text{if } \Delta^\circ \in \text{Lab}_M^\circ, \\ 1 + \max(\text{depth}(\Gamma^\circ), \text{depth}(\Psi^\circ)) & \text{if } \Delta^\circ \in \{\text{mate}(\Gamma^\circ, \Psi^\circ), \text{bud}(\Gamma^\circ, \Psi^\circ)\}, \\ 1 + \text{depth}(\Gamma^\circ) & \text{if } \Delta^\circ = \text{drip}(\Gamma^\circ) \end{cases}$$

According to the previous definition, e.g.  $\text{depth}(\text{mate}(\text{bud}(\text{drip}(\Gamma^\circ), \Delta^\circ), \Psi^\circ)) = 4$ .

We can now formalise the relation between membrane labels  $\widehat{\text{Lab}}_M$  and abstract membrane labels  $\widehat{\text{Lab}}_M^d$ , by introducing the abstract version of a membrane label  $\Delta$ , denoted by  $\Delta^\bullet$ <sup>5</sup>.

**Definition 9.** *For  $\Delta \in \widehat{\text{Lab}}_M$ , we define  $\Delta^\bullet$  as follows.*

- $\Delta \in \text{Lab}_M \Rightarrow \Delta^\bullet = \Delta$ ;

---

<sup>5</sup>For simplicity we omit the explicit indication of the parameter  $d$ .

$P^\circ, Q^\circ ::= \diamond \mid P^\circ \circ Q^\circ \mid !P^\circ \mid \sigma^\circ(P^\circ)^{\Gamma^\circ}$	abstract systems $\mathbf{Sys}^\circ$
$\sigma^\circ, \tau^\circ ::= 0 \mid \sigma^\circ \mid \tau^\circ \mid !\sigma^\circ \mid a^{\lambda^\circ}.\sigma^\circ$	abstract membrane processes $\mathbf{Proc}^\circ$
$\tilde{P}^\circ, \tilde{Q}^\circ ::= \diamond \mid \tilde{P}^\circ \circ \tilde{Q}^\circ \mid !\tilde{P}^\circ \mid \tilde{\sigma}^\circ(\tilde{P}^\circ)^{\Gamma^\circ}$	abstract systems with causes $\widetilde{\mathbf{Sys}}^\circ$
$\tilde{\sigma}^\circ, \tilde{\tau}^\circ ::= 0 \mid \tilde{\sigma}^\circ \mid \tilde{\tau}^\circ \mid !\tilde{\sigma}^\circ \mid$ $(K^\circ, I^\circ, E^\circ) ::= a^{\lambda^\circ}.\sigma^\circ$	abstract membrane processes with causes $\widetilde{\mathbf{Proc}}^\circ$

Table 6: Syntax of Abstract MBD and Abstract MBD with Causes, where  $a \in \mathbf{Act}$  is defined as in Table 1.

- $\Delta = \#(\Gamma, \Psi, \lambda, \mu)$  with  $\# \in \{\text{mate}, \text{bud}\} \Rightarrow \Delta^\bullet = \begin{cases} \#(\Gamma^\bullet, \Psi^\bullet) & \text{if } \text{depth}(\#(\Gamma^\bullet, \Psi^\bullet)) \leq d \\ \#(\top, \top) & \text{otherwise} \end{cases}$
- $\Delta = \text{drip}(\Gamma, \lambda) \Rightarrow \Delta^\bullet = \begin{cases} \text{drip}(\Gamma^\bullet) & \text{if } \text{depth}(\text{drip}(\Gamma^\bullet)) \leq d \\ \text{drip}(\top) & \text{otherwise} \end{cases}$

At last, we have all the ingredients to define the abstract version of MBD with and without causes.

Starting from the abstraction of process labels described above, the abstract version of causes and of decorated causes is easily obtained from the concrete one, by replacing process labels with abstract process labels. Formally, we define the set of *abstract cause names* as

$$\mathcal{K}^\circ = \mathbf{Lab}_p^\circ \cup (\mathbf{Lab}_p^\circ \times \mathbf{Lab}_p^\circ)$$

and the derived set of *abstract decorated causes* as

$$\mathcal{K}^{\pm\circ} = \{k^{\circ x} \mid k^\circ \in \mathcal{K}^\circ, x \in \{+, -\}\}.$$

The information on causes associated to membrane processes is modelled by a triple  $(K^\circ, I^\circ, E^\circ)$ , where  $K^\circ$  is the set of abstract *immediate causes*, while  $I^\circ$  and  $E^\circ$  are the sets of abstract decorated causes representing *internal* and *external* causes, respectively. In the abstract case, we therefore adopt the following set

$$\widehat{\mathcal{K}}^\circ = \wp(\mathcal{K}^\circ) \times \wp(\mathcal{K}^{\pm\circ}) \times \wp(\mathcal{K}^{\pm\circ}).$$

The syntax of *abstract systems*  $\mathbf{Sys}^\circ$ , and that of *abstract membrane processes*  $\mathbf{Proc}^\circ$ , (reported in the first part of Table 6), is obtained from the concrete syntax in Table 1, while the syntax of *abstract systems with causes*  $\widetilde{\mathbf{Sys}}^\circ$ , and that of *membrane processes with causes*  $\widetilde{\mathbf{Proc}}^\circ$ , (reported in the second part of Table 6), is obtained from the concrete syntax in Table 4. In both cases, the abstract versions are obtained by replacing process

and membrane labels with abstract process and membrane labels, respectively, and, elements of  $\widehat{\mathcal{K}}$  with the corresponding abstract elements of  $\widehat{\mathcal{K}}^\circ$ .

Note that any concrete element has a corresponding abstract version. For instance, any membrane process  $\sigma \in \mathbf{Proc}$  has a corresponding abstract version, denoted by  $\sigma^\bullet \in \mathbf{Proc}^\circ$ , obtained by replacing each process label  $\lambda$ , and each membrane label  $\Delta$ , with their abstract versions  $\lambda^\bullet$  and  $\Delta^\bullet$ , respectively. Similarly, each process  $P \in \mathbf{Sys}$  has a corresponding abstract process  $P^\bullet \in \mathbf{Sys}^\circ$ . Then, we denote with  $k^\bullet$  the abstract version of a cause name  $k$ , obtained by replacing each process label  $\lambda$  with its abstract version  $\lambda^\bullet$ . Using an analogous notation, we use  $K^\bullet$  ( $Y^\bullet$ , respectively) for denoting the abstract version of the set of causes  $K$  (of the set of decorated causes  $Y$ , respectively). Finally, we use  $\tilde{P}^\bullet$  ( $\tilde{\sigma}^\bullet$ , respectively) to indicate the abstract version of the system with causes  $\tilde{P}$  (process with causes  $\tilde{\sigma}$ , respectively), obtained by extending the previous definitions.

In the following, we also use the operators  $\mathbf{lab} : \widetilde{\mathbf{Sys}}^\circ \rightarrow \wp(\mathbf{Lab}_p^\circ)$ , and  $\mathbf{lab} : \widetilde{\mathbf{Proc}}^\circ \rightarrow \wp(\mathbf{Lab}_p^\circ)$ , to denote the set of abstract process labels  $\mathbf{lab}(P^\circ)$  ( $\mathbf{lab}(\tilde{\sigma}^\circ)$ , respectively) occurring in the process  $\tilde{P}^\circ$  ( $\tilde{\sigma}^\circ$ , respectively).

In the abstract framework, we further use some operators that are the obvious adaptations of the ones given in the causal semantics. To combine sets of abstract decorated causes, we introduce the operator  $\otimes : \wp(\mathcal{K}^{\pm^\circ}) \times \wp(\mathcal{K}^{\pm^\circ}) \rightarrow \wp(\mathcal{K}^\circ)$ , that adapts the corresponding concrete operator of Definition 4. Moreover, we assume to have the operator  $\triangleright$  that adapts the concrete operator  $\triangleright$  of Definition 3. Finally, for simplicity, as in the concrete case, we omit the empty triple  $(\emptyset, \emptyset, \emptyset)$  in front of abstract sequential membrane processes.

#### 4.1.2. Abstract States

We now introduce the abstract states that are used to represent approximate information about systems with causes, in the abstract causal semantics. An abstract state reports information about membrane hierarchy, and about processes with causes associated to each membrane. Formally, an *abstract state* is defined as a function that, for each abstract membrane label  $\Delta^\circ$ , returns: (a) a set of abstract membrane labels representing the membranes that *may* be child membranes of membrane  $\Delta^\circ$ ; and (b) a set of *abstract sequential membrane processes with causes* representing the processes that *may* be associated to membrane  $\Delta^\circ$ . The component (b) is described by what we call a *configuration*.

**Definition 10** (Configurations). *Let  $C^\circ \subseteq \widetilde{\mathbf{Proc}}^\circ$  be a set of abstract membrane processes with causes s.t., for each  $\tilde{\sigma}^\circ \in C^\circ$ , we have  $\tilde{\sigma}^\circ = (K^\circ, I^\circ, E^\circ) :: a^{\lambda^\circ}.\tau^\circ$ . We say that  $C^\circ$  is a configuration iff, for each  $(K_1^\circ, I_1^\circ, E_1^\circ) :: a^{\lambda^\circ}.\tau^\circ, (K_2^\circ, I_2^\circ, E_2^\circ) :: a^{\lambda^\circ}.\tau^\circ \in C^\circ$  then*



$K_1^\circ = K_2^\circ$ ,  $I_1^\circ = I_2^\circ$  and  $E_1^\circ = E_2^\circ$ . We use  $\mathcal{C}^\circ$  for the set of configurations.

**Definition 11** (Abstract States). An abstract state is a partial function  $S^\circ : \widehat{\text{Lab}}_{\mathcal{M}}^d \rightarrow \wp(\widehat{\text{Lab}}_{\mathcal{M}}^d) \times \mathcal{C}^\circ$ . We use  $\mathcal{S}^\circ$  for the set of abstract states.

An abstract state  $S^\circ$  can be alternatively described by

$$\bigcup_{\Gamma^\circ \in \text{dom}(S^\circ)} \{(\Gamma^\circ, (M^\circ, C^\circ)) \mid S^\circ(\Gamma^\circ) = (M^\circ, C^\circ)\}$$

i.e. by the set of pairs  $(\Gamma^\circ, (M^\circ, C^\circ))$ , given by the set of abstract membrane labels  $M^\circ$  and the configuration  $C^\circ$ , associated to  $\Gamma^\circ$ .

In standard *Abstract Interpretation* style, the abstract states have to be equipped with an approximation order (denoted by  $\sqsubseteq^\circ$ ) that allows us to compare two approximations in terms of precision. Thus,  $S_1^\circ \sqsubseteq^\circ S_2^\circ$  says that the abstract state  $S_1^\circ$  is more precise than the abstract state  $S_2^\circ$  or, analogously that  $S_2^\circ$  *safely approximates*  $S_1^\circ$ . The definition of the approximation order on abstract states relies on a corresponding approximation order on configurations (denoted by  $\sqsubseteq_C$ ).

**Definition 12** (Approximation Orders). Let  $C_1^\circ, C_2^\circ \in \mathcal{C}^\circ$  be two configurations and let  $S_1^\circ, S_2^\circ \in \mathcal{S}^\circ$  be two abstract states.

- We say that  $C_1^\circ \sqsubseteq_C C_2^\circ$  if and only if, for each  $(K_1^\circ, I_1^\circ, E_1^\circ) :: a^{\lambda^\circ}.\tau^\circ \in C_1^\circ$  there exists a  $(K_2^\circ, I_2^\circ, E_2^\circ) :: a^{\lambda^\circ}.\tau^\circ \in C_2^\circ$  such that  $K_1^\circ \subseteq K_2^\circ$ ,  $I_1^\circ \subseteq I_2^\circ$  and  $E_1^\circ \subseteq E_2^\circ$ .
- We say that  $S_1^\circ \sqsubseteq^\circ S_2^\circ$  if and only if  $\text{dom}(S_1^\circ) \subseteq \text{dom}(S_2^\circ)$  and, for each  $\Delta^\circ \in \text{dom}(S_1^\circ)$  we have  $S_1^\circ(\Delta^\circ) = (M_1^\circ, C_1^\circ)$  and  $S_2^\circ(\Delta^\circ) = (M_2^\circ, C_2^\circ)$  with  $M_1^\circ \subseteq M_2^\circ$  and  $C_1^\circ \sqsubseteq_C C_2^\circ$ .

Given the previous orders, we also derive the corresponding least upper bounds (l.u.b.), as expected. The l.u.b. over configurations  $\mathcal{C}^\circ$  and over abstract states  $\mathcal{S}^\circ$  are denoted by  $\sqcup_C$  and  $\sqcup^\circ$ , respectively.

Abstract states are used to approximate the systems with causes. To formally relate systems with causes and abstract states, we introduce several auxiliary functions.

First of all, we define a *translation function*  $t^\circ : \widehat{\text{Lab}}_{\mathcal{M}}^d \times \widetilde{\text{Sys}}^\circ \rightarrow \mathcal{S}^\circ$ , which returns an abstract state, describing an abstract system with causes  $\tilde{P}^\circ$ , with respect to an abstract membrane  $\Delta^\circ$  (representing the enclosing membrane). The resulting abstract state contains the information on the parent-relation between membranes, and on the set of sequential processes with causes associated to each membrane, assuming that

$\tilde{P}^\circ$  is enclosed inside the membrane  $\Delta^\circ$ . The translation function on abstract systems with causes is defined in Table 7 and uses an auxiliary translation function on abstract membrane processes with causes  $t^\circ : \widetilde{\text{Proc}}^\circ \rightarrow \mathcal{C}^\circ$ <sup>6</sup>. The description of an abstract process with causes is simply a set of abstract sequential membrane processes with causes, i.e. a configuration.

$$\begin{aligned}
t^\circ(\Delta^\circ, \diamond) &= \{(\Delta^\circ, (\emptyset, \emptyset))\} \\
t^\circ(\Delta^\circ, \tilde{P}^\circ \circ \tilde{Q}^\circ) &= t^\circ(\Delta^\circ, \tilde{P}^\circ) \sqcup^\circ t^\circ(\Delta^\circ, \tilde{Q}^\circ) \\
t^\circ(\Delta^\circ, !\tilde{P}^\circ) &= t^\circ(\Delta^\circ, \tilde{P}^\circ) \\
t^\circ(\Delta^\circ, \tilde{\sigma}^\circ(\tilde{P}^\circ)\Gamma^\circ) &= \{(\Delta^\circ, (\{\Gamma^\circ\}, \emptyset))\} \sqcup^\circ t^\circ(\Gamma^\circ, \tilde{P}^\circ) \sqcup^\circ \{(\Gamma^\circ, (\emptyset, t^\circ(\tilde{\sigma}^\circ)))\} \\
t^\circ(0) &= \emptyset \\
t^\circ(\tilde{\sigma}^\circ|\tilde{\tau}^\circ) &= t^\circ(\tilde{\sigma}^\circ) \sqcup_C t^\circ(\tilde{\tau}^\circ) \\
t^\circ(!\tilde{\sigma}^\circ) &= t^\circ(\tilde{\sigma}^\circ) \\
t^\circ((K^\circ, I^\circ, E^\circ) :: a^{\lambda^\circ}.\sigma^\circ) &= \{(K^\circ, I^\circ, E^\circ) :: a^{\lambda^\circ}.\sigma^\circ\}
\end{aligned}$$

Table 7: Translation Functions for Abstract Systems and Processes with Causes.

Based on the translation function, it is immediate to derive a corresponding *abstraction function*, which relates systems with causes with abstract states. The abstraction function, for each system with causes, returns the abstract state that is the *best approximation*. Intuitively, the best approximation is the *most precise* (with respect to the order  $\sqsubseteq^\circ$ ) abstract state that *safely represents* the information contained in the system.

**Definition 13** (Abstraction function). *We define  $\alpha_{\widetilde{\text{Sys}}} : \widetilde{\text{Sys}} \rightarrow \mathcal{S}^\circ$  such that for  $\tilde{P} \in \widetilde{\text{Sys}}$ ,  $\alpha_{\widetilde{\text{Sys}}}(\tilde{P}) = t^\circ(@, \tilde{P}^\bullet)$ .*

The best approximation  $\alpha_{\widetilde{\text{Sys}}}(\tilde{P})$  of a system with causes  $\tilde{P}$  is obtained, by applying the translation function  $t^\circ$  to its abstract version (denoted by  $\tilde{P}^\bullet$ ), with respect to the abstract membrane label representing the outermost membrane (denoted by @).

Note that the previously introduced notions can be used to formalise the notion of safe approximation between abstract states and system with causes. Specifically, an abstract state  $S^\circ$  *safely approximates* the system with causes  $\tilde{P}$  if and only if  $\alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^\circ S^\circ$ .

Finally, we derive the corresponding abstraction and concretisation functions that constitute a *Galois connection* [8]. The *abstraction function*  $\bar{\alpha}$  computes the best approximation of a set of systems with causes, by taking the l.u.b. of the best abstraction

<sup>6</sup>For simplicity, we use  $t^\circ$  for both abstract systems with causes and membrane processes.

of each system contained in the set. The *concretisation function*  $\bar{\gamma}$  reports the set of systems with causes safely approximated by an abstract state.

**Definition 14.** We define the abstraction and concretisation functions  $\bar{\alpha} : \wp(\widetilde{\mathbf{Sys}}) \rightarrow \mathcal{S}^\circ$  and  $\bar{\gamma} : \mathcal{S}^\circ \rightarrow \wp(\widetilde{\mathbf{Sys}})$  functions as follows,

1. for  $X \in \wp(\widetilde{\mathbf{Sys}})$ ,  $\bar{\alpha}(X) = \bigsqcup_{\tilde{P} \in X} \alpha_{\widetilde{\mathbf{Sys}}}^\circ(\tilde{P})$ ;
2. for  $S^\circ \in \mathcal{S}^\circ$ ,  $\bar{\gamma}(S^\circ) = \{\tilde{P} \mid \alpha_{\widetilde{\mathbf{Sys}}}^\circ(\tilde{P}) \sqsubseteq^\circ S^\circ\}$ .

**Theorem 2.** The pair of functions  $(\bar{\alpha}, \bar{\gamma})$  in Definition 14 is a Galois connection between  $(\wp(\widetilde{\mathbf{Sys}}), \subseteq)$  and  $(\mathcal{S}^\circ, \sqsubseteq^\circ)$ .

The proof of Theorem 2 can be found in Appendix A.

#### 4.1.3. Abstract LTS

The abstract causal semantics is given in terms of the causal transition relation  $\xrightarrow[k^\circ; H^\circ]{}_\circ$  among abstract states, where  $k^\circ \in \mathcal{K}^\circ$  is the *abstract cause* name (not necessarily fresh) describing the reaction, while  $H^\circ \subseteq \mathcal{K}^\circ$  is the set of abstract *immediate causes*. The abstract transitions are obtained by introducing inference rules for abstract states that model the possible membrane interactions (mate, bud and drip).

To obtain a more precise approximation of the possible interactions, we exploit a relation between abstract process labels, recording pairs of sequential processes that never occur in parallel on the same membrane, in any possible execution. This relation is reminiscent of the approximation of the possible membrane incompatibilities, presented in [3]. More in details, the incompatibility between membrane processes is expressed by a suitable *incompatibility relation*, which is a symmetric relation on the set of abstract process labels  $\text{Lab}_P^\circ$ . If a pair  $(\lambda^\bullet, \mu^\bullet) \in R^\circ$  is included in the incompatibility relation  $R^\circ$ , then two sequential processes  $a^\lambda.\tau$  and  $b^\mu.\sigma$  can never appear in parallel on the same membrane, during the execution. Due to this relation, in the abstract version of the rule mate, we gain precision, when determining the set of sequential membrane processes with causes that may be associated to the resulting fused membrane. In the following, we use  $\mathcal{I}^\circ$  for the set of incompatibility relations.

The incompatibility relation is statically extracted, by analysing the syntax of the abstract system with causes  $\tilde{P}^\bullet$  we want to examine. The goal of the definition is to calculate pairs of abstract process labels that are incompatible in  $\tilde{P}$ , and in any derivative of  $\tilde{P}$ . To this aim, it is important to rely on the information on the possible number of occurrences of the abstract process labels appearing in the abstract system with causes  $\tilde{P}^\bullet$ . To represent occurrence counting information, we adopt a rather simple domain of abstract multiplicity  $\{1, \omega\}$ , where 1 stands for one occurrence, while  $\omega$  indicates more

than one occurrence. The occurrence counting information is provided by the following auxiliary partial function.

**Definition 15** (Occurrence Counting). *The partial function  $\text{oc}_{\tilde{P}^\circ} : \text{Lab}_{\tilde{P}^\circ} \rightarrow \{1, \omega\}$  is defined as follows, for  $\lambda^\circ \in \text{lab}(\tilde{P}^\circ)$ ,*

$$\text{oc}_{\tilde{P}^\circ}(\lambda^\circ) = \begin{cases} 1 & \text{if } \exists! \text{ occurrence } \lambda^\circ \text{ in } \tilde{P}^\circ, \text{ not under the scope of the replication!} \\ \omega & \text{otherwise} \end{cases}$$

Note that for each abstract process label  $\lambda^\bullet$  the function  $\text{oc}_{\tilde{P}^\bullet}(\lambda^\bullet)$  reports the possible number of occurrences of the process label  $\lambda$  appearing in  $\tilde{P}$ , and in any derivative of  $\tilde{P}$ .

The definition of the incompatibility relation for abstract systems with causes is provided by the function  $\text{rel}^\circ : \widetilde{\text{Sys}}^\circ \rightarrow \mathcal{I}^\circ$ , presented in Table 8, relying, in turn, on two further auxiliary functions  $\text{rel}^\circ : \widetilde{\text{Proc}}^\circ \rightarrow \mathcal{I}^\circ$  and  $\text{rel}^\circ : \text{Act} \rightarrow \mathcal{I}^{\circ 7}$ .

In looking at the definition, recall that abstract membrane processes may be interpreted, when required, as processes with empty causes. The intuition is that each label which occurs only once is incompatible with itself, and with all the labels which occur in the membrane process it prefixes.

Before the introduction of our abstract semantics, we need to introduce some auxiliary operators. The first operator, given an abstract membrane  $\Delta^\circ$ , and an abstract state  $S^\circ$ , returns the set of membrane labels, whose membranes are possible parents of  $\Delta^\circ$ . We define  $\text{parent} : \mathcal{S}^\circ \times \widehat{\text{Lab}}_{\mathcal{M}}^d \rightarrow \wp(\widehat{\text{Lab}}_{\mathcal{M}}^d)$  as follows,

$$\text{parent}(S^\circ, \Delta^\circ) = \{\Gamma^\circ \mid S^\circ(\Gamma^\circ) = (M^\circ, C^\circ) \text{ and } \Delta^\circ \in M^\circ\}.$$

This operator can be also used to establish if two membranes are possible siblings, by checking whether they share the same parent.

The second operator, given an incompatibility relation  $R^\circ$ , a process label  $\lambda^\circ$ , and a configuration  $C^\circ$ , returns only the sequential membrane processes in  $C^\circ$  that are compatible with  $\lambda^\circ$ , according to  $R^\circ$ . We define  $\text{comp} : \mathcal{I}^\circ \times \text{Lab}_{\tilde{P}^\circ} \times \mathcal{C}^\circ \rightarrow \mathcal{C}^\circ$  as follows,

$$\text{comp}(R^\circ, \lambda^\circ, C^\circ) = \{(K^\circ, I^\circ, E^\circ) :: a^{\mu^\circ}.\sigma^\circ \in C^\circ \mid (\mu^\circ, \lambda^\circ) \notin R^\circ\}.$$

Finally, the last operators  $\triangleright_C$  and  $\triangleright_S$  propagate the causal information, given by a triple  $(K^\circ, I^\circ, E^\circ) \in \widehat{\mathcal{K}}^\circ$ , both to configurations and to the set of configurations associated to a set of abstract membrane labels  $M^\circ$  in an abstract state  $S^\circ$ . We have

$$\begin{aligned} (K^\circ, I^\circ, E^\circ) \triangleright_C C^\circ &= \{(K^\circ, I^\circ, E^\circ) \triangleright \tilde{\sigma}^\circ \mid \tilde{\sigma}^\circ \in C^\circ\} \\ (K^\circ, I^\circ, E^\circ) \triangleright_S (M^\circ, S^\circ) &= \bigsqcup_{\Delta^\circ \in M^\circ} \{(\Delta^\circ, (\emptyset, (K^\circ, I^\circ, E^\circ) \triangleright_C C_1^\circ)) \mid S^\circ(\Delta^\circ) = (M_1^\circ, C_1^\circ)\}. \end{aligned}$$

---

<sup>7</sup>For simplicity, we overload the function name  $\text{rel}^\circ$ .

$rel^\circ(!\tilde{Q}^\circ) = rel^\circ(\diamond) = \emptyset$ $rel^\circ(\tilde{Q}_1^\circ \circ \tilde{Q}_2^\circ) = rel^\circ(\tilde{Q}_1^\circ) \cup rel^\circ(\tilde{Q}_2^\circ)$ $rel^\circ(\tilde{\sigma}^\circ(\tilde{Q}^\circ)^{\Gamma^\circ}) = rel^\circ(\tilde{Q}^\circ) \cup rel^\circ(\tilde{\sigma}^\circ)$ $rel^\circ(0) = rel^\circ(!\tilde{\sigma}^\circ) = \emptyset$ $rel^\circ(\tilde{\sigma}^\circ \tilde{\tau}^\circ) = rel^\circ(\tilde{\sigma}^\circ) \cup rel^\circ(\tilde{\tau}^\circ)$ $rel^\circ((K^\circ, I^\circ, E^\circ) :: a^{\lambda^\circ}.\sigma^\circ) = \begin{cases} rel^\circ(a) \cup rel^\circ(\sigma^\circ) \cup L^\circ & \text{if } \text{oc}_{\tilde{p}^\circ}(\lambda^\circ) = 1 \\ rel^\circ(a) \cup rel^\circ(\sigma^\circ) & \text{if } \text{oc}_{\tilde{p}^\circ}(\lambda^\circ) = \omega \end{cases}$ <p>where <math>L^\circ = \{(\lambda^\circ, \lambda^\circ)\} \cup \{(\lambda^\circ, \mu^\circ) \mid \mu^\circ \in \text{lab}(\sigma^\circ)\}</math></p> $rel^\circ(a) = \begin{cases} \emptyset & \text{if } a \in \{\text{mate}_n, \overline{\text{mate}_n}, \text{bud}_n\}, \\ rel^\circ(\rho^\circ) & \text{if } a \in \{\text{bud}_n(\rho^\circ), \text{drip}(\rho^\circ)\} \end{cases}$
--

Table 8: Incompatibility Relation with respect to  $\text{oc}_{\tilde{p}^\circ}$ .

We can now present the abstract inference rules, reported in Tables 9 and 10, where we write  $R^\circ \vdash S_1^\circ \xrightarrow{k^\circ; H^\circ} S_2^\circ$  to denote a transition from the abstract state  $S_1^\circ$  to the abstract state  $S_2^\circ$ , given an *incompatibility relation*  $R^\circ \in \mathcal{I}^\circ$ . We insist, in particular, on the abstract version of the inference rule (MATE<sub>c</sub>), because it is the more delicate and complex rule.

The Rule (MATE<sub>c</sub><sup>°</sup>), in Table 9, models the fusion of two membranes ( $\Delta^\circ$  and  $\Gamma^\circ$ ) that *may* synchronise on actions  $\text{mate}_n^{\lambda^\circ}$  and  $\overline{\text{mate}_n^{\mu^\circ}}$ . This requires that: (i) the abstract membranes  $\Delta^\circ$  and  $\Gamma^\circ$  are reported as possible siblings (having a common parent membrane  $\Phi^\circ$ ); (ii) the configurations  $C_1^\circ$  and  $C_2^\circ$ , describing the processes associated to  $\Delta^\circ$  and  $\Gamma^\circ$ , respectively, include the actions *mate* and *comate*.

The abstract reaction step is associated to the cause name  $k^\circ$  and to the set of abstract immediate causes, computed as in the concrete case, by using the abstract version of the  $\otimes$  operator.

The resulting abstract state enriches the starting abstract state  $S^\circ$  with information reporting the effects of the possible fusion of the two membranes  $\Delta^\circ$  and  $\Gamma^\circ$ , in particular on the membrane possibly resulting from the fusion. This membrane is described by the abstract membrane label  $\Psi^\circ$ , obtained by approximating the label  $\text{mate}(\Delta^\circ, \Gamma^\circ)$ , according to its depth. Moreover, we have the following.

$(\text{MATE}_c^\circ)$	$\begin{aligned} & \Phi^\circ \in \text{parent}(S^\circ, \Delta^\circ) \cap \text{parent}(S^\circ, \Gamma^\circ), \\ & S^\circ(\Delta^\circ) = (M_1^\circ, C_1^\circ), \quad S^\circ(\Gamma^\circ) = (M_2^\circ, C_2^\circ), \\ & (K_1^\circ, I_1^\circ, E_1^\circ) :: \text{mate}_n^{\lambda^\circ} \cdot \sigma^\circ \in C_1^\circ, \quad (K_2^\circ, I_2^\circ, E_2^\circ) :: \overline{\text{mate}}_n^{\mu^\circ} \cdot \tau^\circ \in C_2^\circ \end{aligned}$ <hr style="border: 0.5px solid black;"/> $R^\circ \vdash S^\circ \xrightarrow{k^\circ; K_1^\circ \cup K_2^\circ \cup (I_1^\circ \otimes I_2^\circ)} S^\circ \sqcup^\circ \{(\Phi^\circ, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (M_1^\circ \cup M_2^\circ, C^\circ))\} \sqcup^\circ (\emptyset, k^{\circ+}, \emptyset) \triangleright_S (M_1^\circ, S^\circ) \sqcup^\circ (\emptyset, k^{\circ-}, \emptyset) \triangleright_S (M_2^\circ, S^\circ)$ <p style="margin-top: 10px;">where <math>k^\circ = (\lambda^\circ, \mu^\circ)</math> and <math>\Psi^\circ = \begin{cases} \text{mate}(\Delta^\circ, \Gamma^\circ) &amp; \text{if } \text{mate}(\Delta^\circ, \Gamma^\circ) \in \widehat{\text{Lab}}_{\mathcal{M}}^d, \\ \text{mate}(\top, \top), &amp; \text{otherwise,} \end{cases}</math></p> $C^\circ = \begin{aligned} & t^\circ((k^\circ, I_1^\circ, E_1^\circ) \triangleright \sigma^\circ) \sqcup_C (\emptyset, \emptyset, k^{\circ+}) \triangleright_C \text{comp}(R^\circ, \lambda^\circ, C_1^\circ) \sqcup_C \\ & t^\circ((k^\circ, I_2^\circ, E_2^\circ) \triangleright \tau^\circ) \sqcup_C (\emptyset, \emptyset, k^{\circ-}) \triangleright_C \text{comp}(R^\circ, \mu^\circ, C_2^\circ). \end{aligned}$
-------------------------	--

Table 9: Abstract Causal Semantics: the  $(\text{MATE}_c)$  rule.

- The abstract membrane  $\Psi^\circ$  is added as a possible child of the membrane  $\Phi^\circ$ , common parent of the two membranes  $\Delta^\circ$  and  $\Gamma^\circ$ .
- The membrane  $\Psi^\circ$  inherits all the possible child membranes of  $\Delta^\circ$  and  $\Gamma^\circ$ , which thus become possible children of  $\Psi^\circ$ .
- The membrane processes with causes associated to  $\Psi^\circ$  are described by the configuration  $C^\circ$ , which contains a set of sequential processes with causes, inherited from the configurations of both membranes  $\Delta^\circ$  and  $\Gamma^\circ$ . As a consequence, the configuration  $C^\circ$  contains the translation of the continuations of the mate and of the comate actions, respectively. In addition, it contains the membrane processes with causes that may run in parallel with the action  $\text{mate}_n^{\lambda^\circ}$  ( $\overline{\text{mate}}_n^{\mu^\circ}$ , respectively), associated to  $\Delta^\circ$  (to  $\Gamma^\circ$ , respectively). In both cases, the set of membrane processes is computed starting from the corresponding configurations ( $C_1^\circ$  and  $C_2^\circ$ , respectively), and by filtering out the incompatible sequential membrane processes, according to the relation  $R^\circ$ .
- Finally, the abstract cause name  $k^\circ$  related to the mate, and the corresponding external and internal causes ( $k^{\circ+}$  and  $k^{\circ-}$ ) are propagated, as in the concrete case.

(BUD <sub>c</sub> <sup>°</sup> )	$\begin{aligned} & \Phi^\circ \in \text{parent}(S^\circ, \Gamma^\circ), \Gamma^\circ \in \text{parent}(S^\circ, \Delta^\circ), \\ & S^\circ(\Gamma^\circ) = (M_1^\circ, C_1^\circ), S^\circ(\Delta^\circ) = (M_2^\circ, C_2^\circ), \\ & (K_1^\circ, I_1^\circ, E_1^\circ) :: \overline{\text{bud}}_n^{\mu^\circ}(\rho^\circ) \cdot \tau^\circ \in C_1^\circ, (K_2^\circ, I_2^\circ, E_2^\circ) :: \text{bud}_n^{\lambda^\circ} \cdot \sigma^\circ \in C_2^\circ \end{aligned}$
	$R^\circ \vdash S^\circ \xrightarrow{k^\circ; K_1^\circ \cup K_2^\circ \cup (E_1^\circ \otimes I_2^\circ)} S^\circ \sqcup^\circ \{(\Phi^\circ, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (\Delta^\circ, t^\circ((k^\circ, I_1^\circ, \emptyset) \triangleright \rho^\circ)))\}$ $\sqcup^\circ \{(\Delta^\circ, (\emptyset, t^\circ((k^\circ, I_2^\circ, E_2^\circ) \triangleright \sigma^\circ)))\}$ $\sqcup^\circ \{(\Gamma^\circ, (\emptyset, t^\circ((k^\circ, I_1^\circ, E_1^\circ) \triangleright \tau^\circ)))\}$
	<p>where <math>k^\circ = (\lambda^\circ, \mu^\circ)</math> and <math>\Psi^\circ = \begin{cases} \text{bud}(\Delta^\circ, \Gamma^\circ) &amp; \text{if } \text{bud}(\Delta^\circ, \Gamma^\circ) \in \widehat{\text{Lab}}_{\mathcal{M}}^d, \\ \text{bud}(\top, \top), &amp; \text{otherwise.} \end{cases}</math></p>
(DRIP <sub>c</sub> <sup>°</sup> )	$\begin{aligned} & \Gamma^\circ \in \text{parent}(S^\circ, \Delta^\circ), S^\circ(\Delta^\circ) = (M^\circ, C^\circ), \\ & (K^\circ, I^\circ, E^\circ) :: \text{drip}^{\lambda^\circ}(\rho^\circ) \cdot \sigma^\circ \in C^\circ \end{aligned}$
	$R^\circ \vdash S^\circ \xrightarrow{\lambda^\circ; K^\circ} S^\circ \sqcup^\circ \{(\Gamma^\circ, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (\emptyset, t^\circ((\lambda^\circ, I^\circ, \emptyset) \triangleright \rho^\circ)))\} \sqcup^\circ$ $\{(\Delta^\circ, (\emptyset, t^\circ((\lambda^\circ, I^\circ, E^\circ) \triangleright \sigma^\circ)))\}$
	<p>where <math>\Psi^\circ = \begin{cases} \text{drip}(\Delta^\circ) &amp; \text{if } \text{drip}(\Delta^\circ) \in \widehat{\text{Lab}}_{\mathcal{M}}^d, \\ \text{drip}(\top), &amp; \text{otherwise.} \end{cases}</math></p>

Table 10: Abstract Causal Semantics: the (BUD<sub>c</sub>) and the (DRIP<sub>c</sub>) rules.

The rules (BUD<sub>c</sub><sup>°</sup>) and (DRIP<sub>c</sub><sup>°</sup>), in Table 10, are derived from the concrete versions by applying similar techniques. Note that, in both cases, the inference rules do not depend on the incompatibility relation  $R^\circ$ .

As in the concrete case, the abstract causal semantics of a system  $P$  is defined as an *abstract Labelled Transition System (LTS)*, obtained by starting from its best approximation  $\alpha_{\text{sys}}^\sim(P)$ . The abstract transition relation  $\rightarrow_\circ$  is derived, by applying the abstract inference rules of Tables 9 and 10, with respect to the incompatibility relation  $\text{rel}^\circ(P^\bullet)$ , calculated for the abstract version of  $P$ . For  $P \in \mathbf{Sys}$ , we use  $\widehat{\text{LTS}}^\circ(P)$  to denote the *abstract LTS*  $(X^\circ, \rightarrow_\circ, \alpha_{\text{sys}}^\sim(P))$ , where: (i)  $X^\circ \subseteq \mathcal{S}^\circ$  is the set of reachable abstract states; (ii)  $\rightarrow_\circ \subseteq \mathcal{S}^\circ \times (\mathcal{K}^\circ, \wp(\mathcal{K}^\circ)) \times \mathcal{S}^\circ$  is the abstract causal transition relation

@	$\Delta, \Gamma$	
$\Delta$		$\text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)$
$\Gamma$		$\text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}_n^{\delta^\bullet}}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$

Table 11: Abstract State  $\alpha_{\widetilde{\text{sys}}}(P_1)$  of Example 7.

defined by the inference rules in Tables 9 and 10, with respect to the incompatibility relation  $\text{rel}^\circ(P^\bullet)$ ; and (iii)  $\alpha_{\widetilde{\text{sys}}}(P)$  is the initial abstract state. Note that the system  $P$  is interpreted, as in the concrete case, as a system with empty causes.

We now illustrate the abstract causal semantics, by means of an example. In this example, as well as in the ones presented in Section 4.3, we assume that the depth parameter  $d$ , used to approximate membrane labels, is equal to 3.

**Example 7.** *We consider the system introduced in Examples 1 and 4,*

$$P_1 = \text{drip}^\lambda(\sigma_1).\text{mate}_n^\nu.\text{drip}^\mu(\tau_1)\langle\!\langle\Delta\rangle\!\rangle \circ \text{drip}^\beta(\sigma_2).\overline{\text{mate}_n^\delta}.\text{drip}^\kappa(\tau_2)\langle\!\langle\Gamma\rangle\!\rangle.$$

The abstract causal semantics of  $P_1$  is computed starting from the initial state that is the best approximation  $\alpha_{\widetilde{\text{sys}}}(P_1)$  (depicted in Table 11). For each abstract membrane label, the table gives the set of possible child membranes (on the second column) and the configuration (on the third one). For instance, the first line must be read as: the abstract membranes  $\Delta$  and  $\Gamma$ , may<sup>8</sup> appear at top level (as their parent is the outermost membrane  $\textcircled{\Delta}$ ). The second line must be read instead as: the membrane  $\Delta$  does not include any membrane, but it may have associated the processes  $\text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)$ . Similarly, the third line must be read as: the membrane  $\Gamma$  does not include any membrane, but it may have associated the processes  $\text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}_n^{\delta^\bullet}}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$ .

To apply the inference rules of Tables 9 and 10, first, we have to calculate the incompatibility relation  $\text{rel}^\circ(P_1^\bullet)$  for the abstract version of  $P_1$ . We obtain

$$\text{rel}^\circ(P_1^\bullet) = \{ (\lambda^\bullet, \nu^\bullet), (\lambda^\bullet, \mu^\bullet), (\mu^\bullet, \nu^\bullet), (\beta^\bullet, \delta^\bullet), (\beta^\bullet, \kappa^\bullet), (\delta^\bullet, \kappa^\bullet), \\ (\lambda^\bullet, \lambda^\bullet), (\nu^\bullet, \nu^\bullet), (\mu^\bullet, \mu^\bullet), (\beta^\bullet, \beta^\bullet), (\delta^\bullet, \delta^\bullet), (\kappa^\bullet, \kappa^\bullet) \}$$

where

$$P_1^\bullet = \text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)\langle\!\langle\Delta\rangle\!\rangle \circ \text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}_n^{\delta^\bullet}}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)\langle\!\langle\Gamma\rangle\!\rangle.$$

The incompatibility relation  $\text{rel}^\circ(P_1^\bullet)$  is defined according to the definition presented in Table 8. Since the abstract system with causes  $P_1^\bullet$  does not contain any occurrence

---

<sup>8</sup>May and not *must* since this is an over-approximation.



@	$\Delta, \Gamma, \Phi_1^\bullet, \Phi_2^\bullet,$	
$\Delta$		$\text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet),$ $(h_1^\bullet, \emptyset, \emptyset) :: \text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)$
$\Gamma$		$\text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}}_n^{\delta^\bullet}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet),$ $(h_2^\bullet, \emptyset, \emptyset) :: \overline{\text{mate}}_n^{\delta^\bullet}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$
$\Phi_1^\bullet = \text{drip}(\Delta)$		$(h_1^\bullet, \emptyset, \emptyset) :: \sigma_1^\bullet$
$\Phi_2^\bullet = \text{drip}(\Gamma)$		$(h_2^\bullet, \emptyset, \emptyset) :: \sigma_2^\bullet$

Table 12: Abstract State  $S_{1,1}^\circ$ , where  $h_1^\bullet = \lambda^\bullet$  and  $h_2^\bullet = \beta^\bullet$ .

of replication, the number of occurrences of each abstract process label in the system is equal to 1. As a consequence, the pairs of incompatible labels can be simply extracted from the structure of the processes associated to membranes. From the process  $\text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)$ , we extract the pairs  $(\lambda^\bullet, \nu^\bullet)$ ,  $(\lambda^\bullet, \mu^\bullet)$ ,  $(\mu^\bullet, \nu^\bullet)$ ,  $(\lambda^\bullet, \lambda^\bullet)$ ,  $(\nu^\bullet, \nu^\bullet)$ , and  $(\mu^\bullet, \mu^\bullet)$ . Similarly, from the process  $\text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}}_n^{\delta^\bullet}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$ , we extract  $(\beta^\bullet, \delta^\bullet)$ ,  $(\beta^\bullet, \kappa^\bullet)$ ,  $(\delta^\bullet, \kappa^\bullet)$ ,  $(\beta^\bullet, \beta^\bullet)$ ,  $(\delta^\bullet, \delta^\bullet)$ , and  $(\kappa^\bullet, \kappa^\bullet)$ . Nothing can be said, instead, on the incompatibility between process labels occurring on membrane  $\Delta$  with respect to the ones occurring on membrane  $\Gamma$ . Actually, due to membrane fusion, it can happen that these processes may end up in parallel, associated to the same membrane.

To illustrate the abstract semantics, we present now the abstract version of the initial part of the computation presented in Example 4, by showing the reached abstract states. Specifically, we focus on the computation in which the system exercises the two drip reactions, realised by the membranes  $\Gamma$  and  $\Delta$ , and then the mate reaction on  $n$  realised by the membranes  $\Gamma$  and  $\Delta$ . In the abstract case we have,

$$\alpha_{\widetilde{\text{Sys}}}(P_1) \xrightarrow{h_1^\bullet; \emptyset} \circ \xrightarrow{h_2^\bullet; \emptyset} \circ S_{1,1}^\circ \xrightarrow{h_3^\bullet; \{h_1^\bullet, h_2^\bullet\}} \circ S_{1,2}^\circ$$

where the abstract states  $S_{1,1}^\circ$  and  $S_{1,2}^\circ$  are depicted in Tables 12 and 13, respectively. Moreover, the abstract cause names are defined as  $h_1^\bullet = \lambda^\bullet$ ,  $h_2^\bullet = \beta^\bullet$ , and  $h_3^\bullet = (\nu^\bullet, \delta^\bullet)$ .

The abstract state  $S_{1,1}^\circ$  is obtained by applying the rule  $(\text{DRIP}_c^\circ)$ , which models the two drip reactions realised by membranes  $\Delta$  and  $\Gamma$ . The abstract reaction steps are associated to cause names  $h_1^\bullet$  and  $h_2^\bullet$ , respectively, and have an empty set of immediate causes, as in the concrete case. The drip reactions introduce the new membranes  $\Phi_1^\bullet = \text{drip}(\Delta)$  and  $\Phi_2^\bullet = \text{drip}(\Gamma)$ , respectively, which reside at top level. The causes related to  $h_1^\bullet$  and  $h_2^\bullet$  are propagated as in the concrete case.

According to the membranes hierarchy expressed in  $S_{1,1}^\circ$ , the membranes  $\Delta$  and  $\Gamma$  may be siblings and may be ready to exercise the actions *mate* and *comate*, respectively.

@	$\Delta, \Gamma, \Phi_1^\bullet, \Phi_2^\bullet, \Pi^\bullet$	
$\Delta$		$\text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet),$ $(h_1^\bullet, \emptyset, \emptyset) :: \text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)$
$\Gamma$		$\text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}}_n^{\delta^\bullet}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet),$ $(h_2^\bullet, \emptyset, \emptyset) :: \overline{\text{mate}}_n^{\delta^\bullet}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$
$\Phi_1^\bullet = \text{drip}(\Delta)$		$(h_1^\bullet, \emptyset, \emptyset) :: \sigma_1^\bullet$
$\Phi_2^\bullet = \text{drip}(\Gamma)$		$(h_2^\bullet, \emptyset, \emptyset) :: \sigma_2^\bullet$
$\Pi^\bullet = \text{mate}(\Delta, \Gamma)$		$(h_3^\bullet, \emptyset, \emptyset) :: \text{drip}^{\mu^\bullet}(\tau_1^\bullet),$ $(h_3^\bullet, \emptyset, \emptyset) :: \text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$

Table 13: Abstract State  $S_{1,2}^\circ$ , where  $h_1^\bullet = \lambda^\bullet, h_2^\bullet = \beta^\bullet, h_3^\bullet = (\nu^\bullet, \delta^\bullet)$ .

Therefore, by applying the rule ( $\text{MATE}_c^\circ$ ), we derive the abstract state  $S_{1,2}^\circ$ . The abstract reaction step is associated to cause names  $h_3^\bullet$ , and has  $\{h_1^\bullet, h_2^\bullet\}$  as the set of immediate causes, derived as in the concrete case from the immediate causes of the mate and comate actions. The newly created membrane  $\Pi^\bullet = \text{mate}(\Delta, \Gamma)$  is placed at top level, i.e. at the same level of the membranes  $\Delta$  and  $\Gamma$ . The causes related to cause name  $h_3^\bullet$  are propagated as in the concrete case.

It is worth discussing in more details the crucial role of the incompatibility relation  $\text{rel}^\circ(P_1^\bullet)$  in the rule ( $\text{MATE}_c^\circ$ ). The information on incompatible pairs of labels is fundamental indeed to reduce the loss of information due to the approximation. In particular, the incompatibility relation is used to determine the configuration of the new membrane  $\Pi^\bullet$ , resulting from the fusion of the two membranes  $\Delta$  and  $\Gamma$ .

The membrane  $\Pi^\bullet$  inherits all the sequential membrane processes that are compatible with the label  $\nu^\bullet$  of the mate action, from the configuration describing membrane  $\Delta$  (reported in Table 12). Given that  $(\lambda^\bullet, \nu^\bullet), (\nu^\bullet, \nu^\bullet) \in \text{rel}^\circ(P_1^\bullet)$ , the membrane  $\Pi^\bullet$  does not inherit any process from the configuration describing  $\Delta$ . The incompatibility relation guarantees that these processes can never run on membrane  $\Delta$ , in parallel with the mate action, in any possible execution of the system  $P_1$ .

Analogously, the membrane  $\Pi^\bullet$  does not inherit any process from the configuration describing  $\Gamma$  (reported in Table 12), since all those processes are incompatible with the label  $\delta^\bullet$  of the comate action. The incompatibility relation guarantees that these processes can never be associated to the membrane  $\Gamma$ , in parallel with the comate action, in any possible execution of the system  $P_1$ .

As a consequence, the configuration describing the membrane  $\Pi^\bullet$  (reported in Table 13) contains the sequential processes with causes corresponding to the continuation of the mate and comate actions, only. In conclusion, due to the use of the incompat-

ibility relation, the membrane  $\Pi^\bullet$  does not acquire the two drip actions as well as the mate and comate actions from the membranes  $\Delta$  and  $\Gamma$ . Note that these actions can never indeed be associated with the membrane resulting from the mate reaction between the membrane  $\Delta$  and  $\Gamma$ , in any possible execution of the system  $P_1$ .

#### 4.2. Causal Analysis

The analysis provides: (i) an *abstract state* describing the possible structure of all the derivatives of the initial system, and (ii) a description of the set of the *possible causal dependencies* between reaction steps. Both kinds of information are derived from the abstract causal LTS describing the approximate behaviour of the system that we want to analyse. The abstract state is obtained by considering the l.u.b. of all the abstract states that can be reached, while the abstract causal dependencies are collected by considering the causal annotations that decorate the abstract transition steps.

Causal dependencies are formally described by relations in the set of *causality relations*, defined as  $\mathcal{D}^\circ = \wp(\mathcal{K}^\circ \times \mathcal{K}^\circ)$ . If the pair  $(k^\circ, h^\circ)$  belongs to a causality relation, then the reaction step associated to the abstract cause name  $k^\circ$  may causally depend on a reaction step associated to  $h^\circ$ . The set of all the causes associated to a reaction step can be obtained by transitive closure of the immediate causal relation. Hence,  $\text{closure}(D^\circ)$  stands for the transitive closure of a causality relation  $D^\circ \in \mathcal{D}^\circ$ .

**Definition 16** (The Analysis). *We define a function  $\mathcal{A}^\circ : \mathbf{Sys} \rightarrow \mathcal{S}^\circ \times \mathcal{D}^\circ$  such that for  $P \in \mathbf{Sys}$  with  $\widetilde{LTS}^\circ(P) = (X^\circ, \rightarrow_\circ, \alpha_{\widetilde{\mathbf{Sys}}}^\circ(P))$ , we have  $\mathcal{A}^\circ(P) = (S^\circ, D^\circ)$  where*

- $S^\circ = \sqcup_{S^{\circ'} \in X^\circ} S^{\circ'}$  is the abstract state,
- $D^\circ = \text{closure}(\{(k^\circ, h^\circ) \mid h^\circ \in H^\circ, S_1^\circ \xrightarrow{k^\circ; H^\circ} S_2^\circ \in \rightarrow_\circ\})$  is the causality relation.

##### 4.2.1. Properties of the Analysis

We show that the analysis of a system is a *safe approximation* of the concrete causal behaviour. The main theorem is based on two auxiliary properties.

The first lemma presents the properties of the incompatibility relation, defined in Table 8. The result states that, for any abstract system with causes  $\tilde{P}^\bullet$ , any pair of abstract process labels such that  $(\lambda^\bullet, \mu^\bullet) \in \text{rel}^\circ(\tilde{P}^\bullet)$ , are incompatible in  $\tilde{P}$ , and in any derivative of  $\tilde{P}$ .

**Lemma 1.** *Given  $\tilde{P} \in \widetilde{\mathbf{Sys}}$ , if  $(\lambda^\bullet, \mu^\bullet) \in \text{rel}^\circ(\tilde{P}^\bullet)$ , then two sequential membrane processes  $(K, I, E) :: a^\lambda.\tau$  and  $(K_1, I_1, E_1) :: b^\mu.\sigma$  do not occur in parallel on the same membrane, in any  $\tilde{P}'$  such that  $\tilde{P} \longrightarrow_* \tilde{P}'$ .*

The next result relates concrete reduction steps of the causal semantics with abstract transition steps. More precisely, the property relates the reaction steps of a system with causes  $\tilde{P}_1$  with the ones of an abstract state  $S_1^\circ$  that *safely approximates*  $\tilde{P}_1$  ( $\alpha_{\widetilde{\text{Sys}}}(\tilde{P}_1) \sqsubseteq^\circ S_1^\circ$ ). We have that each reaction step of  $\tilde{P}_1$  is *safely approximated* by a reaction step of  $S_1^\circ$ . In particular, if the concrete reaction step is decorated by the cause  $k$ , and by the set of immediate causes  $H$ , then the abstract one is decorated by the abstract version of  $k$  ( $k^\bullet$ ), and by a set of abstract immediate causes  $H^\circ$  that approximates  $H$ . Formally, for each  $h \in H$ , it must be the case that  $h^\bullet \in H^\circ$  (or, analogously,  $H^\bullet \subseteq H^\circ$ ).

**Lemma 2.** *Let  $\tilde{P}_1 \in \widetilde{\text{Sys}}$  be a system with causes and let  $S_1^\circ \in \mathcal{S}^\circ$  be an abstract state such that  $\alpha_{\widetilde{\text{Sys}}}(\tilde{P}_1) \sqsubseteq^\circ S_1^\circ$ . For each  $\tilde{P}_1 \xrightarrow{k;H} \tilde{P}_2$ , there exists  $\text{rel}^\circ(\tilde{P}^\bullet) \vdash S_1^\circ \xrightarrow{k^\bullet;H^\circ} S_2^\circ$ , where  $\alpha_{\widetilde{\text{Sys}}}(\tilde{P}_2) \sqsubseteq^\circ S_2^\circ$  and  $H^\bullet \subseteq H^\circ$ , for each  $\tilde{P}$  such that  $\tilde{P} \rightarrow_* \tilde{P}_1$ .*

The main theorem shows that the analysis of a system *safely approximates* its concrete causal behaviour, described by the causal LTS. Thus, the result states that: (i) each derivative of the initial system is *safely approximated* by the abstract state computed by the analysis; and (ii) each causal dependency arising in the concrete causal semantics is reflected by a corresponding abstract causal dependency. As in the abstract case, to capture all causal dependencies, we need to apply the transitive closure of the immediate causal dependencies. Therefore,  $\text{closure}(D)$  stands for the transitive closure of a relation  $D \in \wp(\mathcal{K} \times \mathcal{K})$ .

**Theorem 3 (Safety).** *Let  $P \in \text{Sys}$  be a system with  $\widetilde{\text{LTS}}(P) = (X, \rightarrow, P)$  and  $D = \text{closure}(\{(k, h) \mid h \in H, \tilde{Q}_1 \xrightarrow{k;H} \tilde{Q}_2 \in \rightarrow\})$ . If  $\mathcal{A}^\circ(P) = (S^\circ, D^\circ)$ , then we have:*

1.  $\bar{\alpha}(X) \sqsubseteq^\circ S^\circ$ ;
2.  $(k^\bullet, h^\bullet) \in D^\circ$  for each  $(k, h) \in D$ .

The proofs of Lemmata 1 and 2, and that of Theorem 3 can be found in the Appendix A.

#### 4.2.2. Complexity

We discuss the complexity of our approach. As a measure of complexity of our analysis, we consider the maximal number of steps necessary to reach a fix point of the computation of  $\mathcal{A}^\circ(P)$ , in the worst case. Let  $P$  be a well labelled system, let  $m$  be the number of different subprocesses running on the membranes of  $P$  (i.e. the number of different process labels in the system  $P$ ), and  $n$  be the number of different membrane labels appearing in  $P$ .

First, we compute an upper bound to the maximal number of different abstract membrane labels that can be introduced by the analysis. Such upper bound depends on the chosen depth level  $d$ . Since the membrane label constructor `mate` and `bud` are binary, while `drip` is unary, we have that, for  $d = 2$ , the maximal number of abstract membrane labels is  $(n + 2(n^2) + n) \approx \mathcal{O}(n^2)$ . Similarly, for  $d = 3$ , we have  $(n^2 + 2(n^2 \cdot n^2) + n^2) \approx \mathcal{O}(n^4)$  and for  $d = 4$ , we have  $(n^4 + 2(n^4 \cdot n^4) + n^4) \approx \mathcal{O}(n^8)$ . A further generalisation allows us to derive that the maximal number of abstract membrane labels is  $\mathcal{O}(n^{2^{(d-1)}})$ , for a given  $d$ .

We can now count the number of different abstract causes names that can be generated. They are  $m$  for the unary causes and  $m^2$  for binary causes. Therefore, the number of different abstract causes names that can be generated is  $\mathcal{O}(m^2)$ .

Now for each abstract membrane label, in the worst case, our analysis adds (i) one new abstract label as a child, or, (ii) a new subprocess as a running process, or, (iii) one new internal or external cause to a subprocess. Note that the immediate cause is just one and that is univocally determined, when introducing the related subprocess on the membrane. Hence, in the worst case, the complexity of our analysis amounts to  $n^{2^{(d-1)}}(n^{2^{(d-1)}} + m + (m^2 + m^2 + m) \cdot m) \approx \mathcal{O}(n^{2^d} + n^{2^{(d-1)}}m^3)$ . This assures us that our analysis is *polynomial* in the number of different membranes and subprocesses of the analysed system  $P$ .

### 4.3. Our Analysis at work

We now show the application of the analysis to the systems introduced in the examples in Section 3<sup>9</sup>. Since the analysis safely approximates the causal behaviour (as stated by Theorem 3), it can be applied to prove that a reaction *does not causally depend* on another one.

**Example 8.** *We consider the system presented in Examples 4 and 7,*

$$P_1 = \mathbf{drip}^\lambda(\sigma_1).\mathbf{mate}_n^\nu.\mathbf{drip}^\mu(\tau_1)\langle\!\rangle^\Delta \circ \mathbf{drip}^\beta(\sigma_2).\overline{\mathbf{mate}}_n^\delta.\mathbf{drip}^\kappa(\tau_2)\langle\!\rangle^\Gamma.$$

*In Example 7, we have illustrated the abstract causal semantics of the system, representing part of an abstract computation. We recall that the abstract causal semantics of  $P_1$  is calculated starting from the abstract state  $\alpha_{\overline{\text{sys}}}(P_1)$ , which represents the best approximation of  $P_1$  (depicted in Table 11). Furthermore, the abstract inference rules are applied using the incompatibility relation  $\text{rel}^\circ(P_1^\bullet)$ , there illustrated.*

---

<sup>9</sup>We recall that, as in Example 7, we assume that the depth parameter, used to abstract membrane labels, is  $d = 3$ .

The analysis of  $P_1$  is performed as follows. The abstract state is computed by collecting the information on all the abstract states that can be obtained from the abstract state  $\alpha_{\widetilde{\text{sys}}}(P_1)$ , by applying the abstract inference rules with respect to  $\text{rel}^\circ(P_1^\bullet)$ . Moreover, the causality relation is derived by considering the transitive closure of the causal dependencies, associated to all abstract transition steps.

As a result of the analysis, we have  $\mathcal{A}^\circ(P_1) = (S_1^\circ, D_1^\circ)$ , where

- $S_1^\circ$  is the abstract state, illustrated in Table 14. For clarity, the membrane hierarchy described by the second column is also depicted in the tree in Figure 2, where the nodes represent the membrane labels and the edges represent the inclusion relation.
- $D_1^\circ = \text{closure}(\{(h_3^\bullet, h_1^\bullet), (h_3^\bullet, h_2^\bullet), (h_4^\bullet, h_3^\bullet)(h_5^\bullet, h_3^\bullet)\})$  is the causality relation.

As expected, the abstract state  $S_1^\circ$  safely approximates the abstract states of the abstract computation, described in Example 7, in particular, the abstract states  $\alpha_{\widetilde{\text{sys}}}(P_1)$ ,  $S_{1,1}^\circ$  and  $S_{1,2}^\circ$ , illustrated in Tables 11, 12 and 13, respectively. Analogously, the causality relation  $D_1^\circ$  contains the causal dependencies  $(h_3^\bullet, h_1^\bullet)$  and  $(h_3^\bullet, h_2^\bullet)$ , derived from the causal annotations of the computation illustrated in Example 7.

In addition, the abstract state  $S_1^\circ$  contains the information on the abstract membrane label  $\Phi_3^\bullet$ , introduced by the two drip reactions realised by  $\Pi^\bullet$ . We recall that, in the causal semantics of system (illustrated in Example 4), the execution of the two drip reactions, realised by  $\Pi$ , introduces two new membrane labels  $\Phi_3 = \text{drip}(\Pi, \mu)$  and  $\Phi_4 = \text{drip}(\Pi, \kappa)$ . The membrane label  $\Phi_3$  is related to the execution of  $\text{drip}^\mu(\tau_1)$ , while the membrane label  $\Phi_4$  is related to the execution of  $\text{drip}^\kappa(\tau_2)$ . In the abstract setting, due to the abstraction of labels, the membrane labels  $\Phi_3$  and  $\Phi_4$  are represented by the same abstract membrane  $\Phi_3^\bullet = \text{drip}(\Pi^\bullet)$ . As a consequence, the abstract state  $S_1^\circ$  predicts that the processes  $\tau_1^\bullet$  and  $\tau_2^\bullet$  may be associated to the same membrane  $\Phi_3^\bullet$ .

The causality relation  $D_1^\circ$  reports the possible causal dependencies among the reactions steps. Due to the over-approximation this information establishes that

- both the drip reactions, associated to causes  $h_1^\bullet$  and  $h_2^\bullet$ , do not causally depend on any other reaction,
- the mate reaction on  $n$ , associated to cause  $h_3^\bullet$ , does not causally depend on the drip reactions associated to causes  $h_4^\bullet$  and  $h_5^\bullet$ ,
- the drip reactions, associated to causes  $h_4^\bullet$  and  $h_5^\bullet$ , do not causally depend on each other.

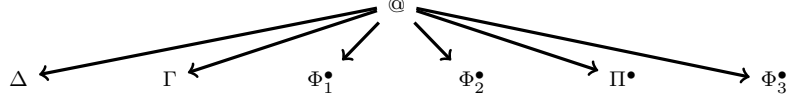


Figure 2: The Membrane Hierarchy Tree of  $S_1^\circ$ .

@	$\Delta, \Gamma, \Phi_1^\bullet, \Phi_2^\bullet, \Pi^\bullet, \Phi_3^\bullet$	
$\Delta$		$\text{drip}^{\lambda^\bullet}(\sigma_1^\bullet).\text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet),$ $(h_1^\bullet, \emptyset, \emptyset) :: \text{mate}_n^{\nu^\bullet}.\text{drip}^{\mu^\bullet}(\tau_1^\bullet)$
$\Gamma$		$\text{drip}^{\beta^\bullet}(\sigma_2^\bullet).\overline{\text{mate}_n^{\delta^\bullet}}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet),$ $(h_2^\bullet, \emptyset, \emptyset) :: \overline{\text{mate}_n^{\delta^\bullet}}.\text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$
$\Phi_1^\bullet = \text{drip}(\Delta)$		$(h_1^\bullet, \emptyset, \emptyset) :: \sigma_1^\bullet$
$\Phi_2^\bullet = \text{drip}(\Gamma)$		$(h_2^\bullet, \emptyset, \emptyset) :: \sigma_2^\bullet$
$\Pi^\bullet = \text{mate}(\Delta, \Gamma)$		$(h_3^\bullet, \emptyset, \emptyset) :: \text{drip}^{\mu^\bullet}(\tau_1^\bullet),$ $(h_3^\bullet, \emptyset, \emptyset) :: \text{drip}^{\kappa^\bullet}(\tau_2^\bullet)$
$\Phi_3^\bullet = \text{drip}(\Pi^\bullet)$		$(h_4^\bullet, \emptyset, \emptyset) :: \tau_1^\bullet, \quad (h_5^\bullet, \emptyset, \emptyset) :: \tau_2^\bullet$

Table 14: Abstract State  $S_1^\circ$  of Example 8, where  $h_1^\bullet = \lambda^\bullet, h_2^\bullet = \beta^\bullet$ , and  $h_3^\bullet = (\nu^\bullet, \delta^\bullet), h_4^\bullet = \mu^\bullet, h_5^\bullet = \kappa^\bullet$ .

In addition, the abstract state described by Table 14 provides information on the possible hierarchy of membranes, and on the processes that may be associated to each membrane, as explained in Example 7. This information can be exploited to prove invariant properties that hold in any system with causes that can be reached from the system  $P_1$ , as in other related approaches [20, 11, 2, 21]. Here, for instance, we can observe that the membranes  $\Delta, \Gamma, \Phi_1, \Pi, \Phi_2$  and  $\Phi_3$  may appear at top level, while they cannot be included inside any other membrane. Moreover, the membrane  $\Pi$  resulting from the mate reaction of membranes  $\Delta$  and  $\Gamma$  does not include any membrane, but it may have associated the processes  $(h_3, \emptyset, \emptyset) :: \text{drip}^\mu(\tau_1)$  and  $(h_3, \emptyset, \emptyset) :: \text{drip}^\kappa(\tau_2)$ .

In Example 7, we have discussed the use of the incompatibility relation in the computation of the analysis of  $P_1$ , in particular in the rule  $(\text{MATE}_c^\circ)$ . Note that, without this information, the membrane  $\Pi^\bullet = \text{mate}(\Delta, \Gamma)$  would have inherited all the membrane processes with causes contained in the configurations of membranes  $\Delta$  and  $\Gamma$  (described by the second and third line in Table 14). This would have lead us to predict that the membrane  $\Pi^\bullet$  could realise the two drip reactions, as well as a mate reaction with itself. As a consequence, an infinite number of membrane labels would be generated. Even if

such infinite number of membrane labels will be approximated using the parameter  $d$ , a serious loss in precision will be introduced, both on the membrane hierarchy and on the causality relation.

**Example 9.** We consider the system introduced in Example 5,

$$P_2 = \text{mate}_n^\nu(\text{mate}_m^\mu | \text{mate}_o^\zeta(\emptyset)^\ominus \circ \overline{\text{mate}_o^\beta(\emptyset)^\Phi})^\Delta \circ \overline{\text{mate}_n^\delta(\overline{\text{mate}_m^\lambda(\emptyset)^\Psi})^\Gamma}.$$

In this case the incompatibility relation  $\text{rel}^\circ(P_2^\bullet)$  is

$$\text{rel}^\circ(P_2^\bullet) = \{(\nu^\bullet, \nu^\bullet), (\mu^\bullet, \mu^\bullet), (\zeta^\bullet, \zeta^\bullet), (\beta^\bullet, \beta^\bullet), (\delta^\bullet, \delta^\bullet), (\lambda^\bullet, \lambda^\bullet)\}$$

The analysis of  $P_2$  is computed starting from the initial state that is the best approximation (depicted in Figure 15), using the incompatibility  $\text{rel}^\circ(P_2^\bullet)$ .

@	$\Delta, \Gamma,$	
$\Delta$	$\Theta, \Phi$	$\text{mate}_n^{\nu^\bullet}$
$\Gamma$	$\Psi$	$\overline{\text{mate}_n^{\delta^\bullet}}$
$\Theta$		$\text{mate}_m^{\mu^\bullet}, \text{mate}_o^{\zeta^\bullet}$
$\Phi$		$\overline{\text{mate}_o^{\beta^\bullet}}$
$\Psi$		$\overline{\text{mate}_m^{\lambda^\bullet}}$

Table 15: Abstract State  $\alpha_{\widetilde{\text{Sys}}}(P_2)$ .

The result of our analysis for  $P_2$  is  $\mathcal{A}^\circ(P_2) = (S_2^\circ, D_2^\circ)$ , where  $S_2^\circ$  is the abstract state illustrated in Table 16 and  $D_2^\circ = \{(h_2^\bullet, h_1^\bullet)\}$  is the causality relation. As before, the membrane hierarchy, expressed in the first two columns of state  $S_2^\circ$ , is also depicted in Figure 3, for clarity. Note that membranes  $\Pi_3^\circ$  and  $\Pi_4^\circ$  are introduced by abstract computations different from the one described in the Example 5, i.e. they abstract the two alternative computations, in which the mate on  $o$  is performed before the mate on  $m$ .

The causality relation  $D_2^\circ$  allows us to prove that the mate reaction on  $n$  (associated to cause  $h_1^\bullet$ ) and the mate on  $o$  (associated to  $h_3^\bullet$ ) do not causally depend on any other reaction. Moreover, the mate reaction on  $m$  (associated to  $h_2^\bullet$ ) does not causally depend on the mate reaction on  $o$ .

**Example 10.** We consider the system introduced in Example 6,

$$P_3 = \text{mate}_n^\nu | \overline{\text{bud}_m^\lambda(\rho_1)}(\text{bud}_m^\mu(\emptyset)^\ominus \circ \text{bud}_o^\zeta(\emptyset)^\Phi)^\Delta \circ \overline{\text{mate}_n^\delta} | \overline{\text{bud}_o^\beta(\rho_2)}(\emptyset)^\Gamma.$$

In this case incompatibility relation  $\text{rel}^\circ(P_3^\bullet)$  is



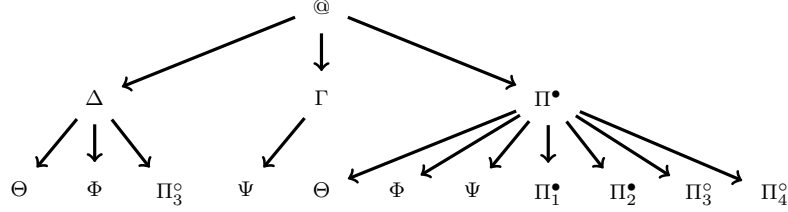


Figure 3: The Membrane Hierarchy Tree of  $S_2^\circ$ .

@	$\Delta, \Gamma, \Pi^\bullet$	
$\Delta$	$\Theta, \Phi, \Pi_3^\circ$	$\text{mate}_n^{\nu^\bullet}$
$\Gamma$	$\Psi$	$\overline{\text{mate}}_n^{\delta^\bullet}$
$\Theta$		$(\emptyset, h_1^{\bullet+}, \emptyset) :: \text{mate}_m^{\mu^\bullet},$ $(\emptyset, h_1^{\bullet+}, \emptyset) :: \text{mate}_o^{\zeta^\bullet}$
$\Phi$		$(\emptyset, h_1^{\bullet+}, \emptyset) :: \overline{\text{mate}}_o^{\beta^\bullet}$
$\Psi$		$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_m^{\lambda^\bullet}$
$\Pi^\bullet = \text{mate}(\Delta, \Gamma)$	$\Theta, \Phi, \Psi, \Pi_1^\bullet, \Pi_2^\bullet, \Pi_3^\circ, \Pi_4^\circ$	
$\Pi_1^\bullet = \text{mate}(\Theta, \Psi)$		$(\emptyset, h_1^{\bullet+}, h_2^{\bullet+}) :: \text{mate}_o^{\zeta^\bullet}$
$\Pi_2^\bullet = \text{mate}(\Pi_1^\bullet, \Phi)$		
$\Pi_3^\circ = \text{mate}(\Theta, \Phi)$		$(\emptyset, h_1^{\bullet+}, h_3^{\bullet+}) :: \text{mate}_m^{\mu^\bullet}$
$\Pi_4^\circ = \text{mate}(\Pi_3^\circ, \Psi)$		

Table 16: Abstract State  $S_2^\circ$  of Example 9, where  $h_1^\bullet = (\nu^\bullet, \delta^\bullet)$ ,  $h_2^\bullet = (\mu^\bullet, \lambda^\bullet)$ , and  $h_3^\bullet = (\zeta^\bullet, \beta^\bullet)$ .

$$\text{rel}^\circ(P_3^\bullet) = \{(\nu^\bullet, \nu^\bullet), (\lambda^\bullet, \lambda^\bullet), (\mu^\bullet, \mu^\bullet), (\zeta^\bullet, \zeta^\bullet), (\delta^\bullet, \delta^\bullet), (\beta^\bullet, \beta^\bullet)\}.$$

The analysis of  $P_3$  is computed starting from the initial state that is the best approximation (depicted in Figure 17), using the incompatibility  $\text{rel}^\circ(P_3^\bullet)$ .

The result of our analysis for  $P_3$  is  $\mathcal{A}^\circ(P_3) = (S_3^\circ, D_3^\circ)$ , where  $S_3^\circ$  is the abstract state illustrated in Table 18 and  $D_3^\circ = \{(h_2^\bullet, h_1^\bullet)\}$  is the causality relation. As before, the membrane hierarchy, expressed in the first two columns of state  $S_3^\circ$ , is also depicted in Figure 4, for clarity.

The causality relation  $D_3^\circ$  allows us to prove that the mate reaction on  $n$  (associated to cause name  $h_1^\bullet$ ) and the bud reaction on  $m$  (associated to  $h_3^\bullet$ ) do not causally depend

@	$\Delta, \Gamma$	
$\Delta$	$\Theta, \Phi$	$\text{mate}_n^{\nu^\bullet}, \overline{\text{bud}}_m^{\lambda^\bullet}(\rho_1^\bullet)$
$\Gamma$		$\overline{\text{mate}}_n^{\delta^\bullet}, \overline{\text{bud}}_o^{\beta^\bullet}(\rho_2^\bullet)$
$\Theta$		$\text{bud}_m^\mu$
$\Phi$		$\text{bud}_o^\zeta$

Table 17: Abstract State  $\alpha_{\widetilde{\text{sys}}}(P_3)$ .

on any other reaction. Moreover, the bud reaction on  $o$  (associated to  $h_2^\bullet$ ) does not causally depend on the bud reaction on  $m$ .

@	$\Delta, \Gamma, \Pi^\bullet, \Psi_1^\bullet, \Psi_2^\bullet, \Psi_3^\circ$	
$\Delta$	$\Theta, \Phi$	$\text{mate}_n^{\nu^\bullet}, \overline{\text{bud}}_m^{\lambda^\bullet}(\rho_1^\bullet)$
$\Gamma$		$\overline{\text{mate}}_n^{\delta^\bullet}, \overline{\text{bud}}_o^{\beta^\bullet}(\rho_2^\bullet)$
$\Theta$		$(\emptyset, h_1^{\bullet+}, \emptyset) :: \text{bud}_m^\mu$
$\Phi$		$(\emptyset, h_1^{\bullet+}, \emptyset) :: \text{bud}_o^\zeta$
$\Pi^\bullet = \text{mate}(\Delta, \Gamma)$	$\Theta, \Phi$	$(\emptyset, \emptyset, h_1^{\bullet-}) :: \overline{\text{bud}}_o^{\beta^\bullet}(\rho_2^\bullet),$ $(\emptyset, \emptyset, h_1^{\bullet+}) :: \overline{\text{bud}}_m^{\lambda^\bullet}(\rho_1^\bullet)$
$\Psi_1^\bullet = \text{bud}(\Phi, \Pi^\bullet)$	$\Phi$	$(h_2^\bullet, \emptyset, \emptyset) :: \rho_2^\bullet$
$\Psi_2^\bullet = \text{bud}(\Theta, \Pi^\bullet)$	$\Theta$	$(h_3^\bullet, \emptyset, \emptyset) :: \rho_1^\bullet$
$\Psi_3^\circ = \text{bud}(\Delta, \Theta)$	$\Theta$	$(h_3^\bullet, \emptyset, \emptyset) :: \rho_1^\bullet$

Table 18: Abstract State  $S_3^\circ$  of Example 10, where  $h_1^\bullet = (\nu^\bullet, \delta^\bullet)$ ,  $h_2^\bullet = (\zeta^\bullet, \beta^\bullet)$ , and  $h_3^\bullet = (\mu^\bullet, \lambda^\bullet)$ .

**Impact of a different choice of depth parameter** We now briefly discuss what would happen, if we chose  $d = 2$  as maximal depth of a membrane label. In this case, we would have a unique abstract label, say  $\Psi^\circ = \text{bud}(\top, \top)$ , for describing both the abstract membrane labelled  $\Psi_1^\bullet$  and  $\Psi_2^\bullet$ , obtained by the previous analysis. Therefore, the lines for  $\Psi_1^\bullet$  and  $\Psi_2^\bullet$  should be replaced by the following single line:

$\Psi^\circ$	$\Phi, \Theta$	$(h_2^\bullet, \emptyset, \emptyset) :: \rho_2^\bullet, (h_3^\bullet, \emptyset, \emptyset) :: \rho_1^\bullet$
--------------	----------------	--

As a consequence, this would introduce an approximation in the description of the topology of the systems. For instance, according to the analysis, the membrane processes  $\rho_1^\bullet$  and  $\rho_2^\bullet$  could run in parallel on the same membrane, even though this behaviour does not

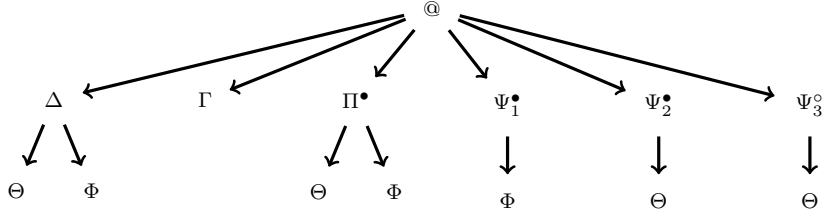


Figure 4: The Membrane Hierarchy Tree of  $S_3^\circ$ .

correspond to any concrete behaviour. On the contrary, in this case, we would obtain the same causality information, i.e. the same set of causal dependencies  $D_3^\circ$ .

The previous examples show that our analysis is able to capture the possible causal dependencies in a very precise way. For all these systems indeed, the causality relation reported by the analysis exactly contains the causal dependencies that may arise in the dynamic behaviour (illustrated in Examples 4, 5 and 6). This precision could not have been obtained without using the incompatibility relation in the inference rule ( $\text{MATE}_c^\circ$ ). As far as the system of Example 4 is concerned, the role of the incompatibility relation is widely discussed in Examples 7 and 8. Similar considerations also hold for the analysis of the other systems of Examples 5 and 6. Hence, our approach is able to handle all kinds of causality that may appear in MBD, included the critical environment causality.

## 5. Biological Applications

We illustrate our approach by applying it to the MDB specification of the process known as *receptor-mediated endocytosis*, a very general mechanism that allows living cells to transport specific substances (ligands) from the external environment to the cytoplasm.

The general process, depicted in Figure 5, consists of various steps and involves the formation of vesicles. The first step occurs on the outer side of the cell membrane and is represented by the binding between the ligands and a set of specialised molecules (*receptors*) embedded in the cell membrane. The formation of the *ligand-receptor complex* (LR) triggers further events close to the inner side of the cell membrane: first, one molecule of the AP-2 complex binds to each LR complex, thus allowing the binding with a protein called Clathrin. These molecules elicit the invagination of the part of the cell membrane that resides close to the receptors, and eventually leads to the formation of a vesicle, which contains the LR complex and is coated by an external layer of AP-2

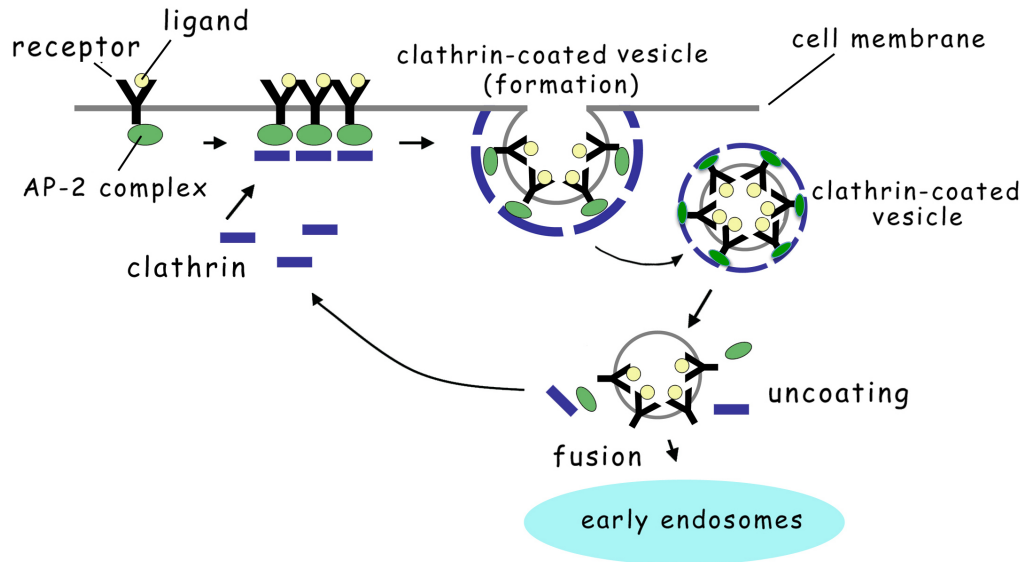


Figure 5: The Receptor-mediated Endocytosis.

and Clathrin molecules. This vesicle moves along the cytoplasm towards other vesicles (*Endosomes*). Finally, the vesicle coalesces with the Endosome (fusion) immediately after the dissociation of the external AP-2-Clathrin coat (uncoating).

We model, in particular, the process used by cells to acquire additional Low Density Lipoprotein (LDL, or “bad”) *cholesterol*, by removing it from the bloodstream. Therefore, our ligand is given by LDL particles. We also provide a pathological version of the process, which arises in the presence of the genetic disorder called Familial Hypercholesterolemia. Our analysis provides a safe over-approximation of the causal behaviour of both versions of the process, giving some insights on the biological phenomenon under investigation. In this example, we consider  $d = 7$  as the maximal depth of abstract membrane labels. Our analysis results can be exploited to prove when a reaction step does not causally depend on another one.

As expected, we model compartments and multi-protein complexes as membranes, and we render chemical reactions, by exploiting the membrane fusion and splitting primitives of MDB calculus. For simplicity, we do not explicitly model the binding process between AP2 and Clathrin, but we directly specify the AP-2-Clathrin complex behaviour. The corresponding causality dependencies are not crucial and can be left out. Alternatively, we could have used a sequential process to subdivide the binding in steps.

Anyway, we choose to give an abstract model of the pathway: in particular, we abstract on the bind & release operations of molecules on membrane surfaces. For a more faithful model of the LDL Degradation pathway, see the one presented in [27], where the full calculus is exploited, with recursion in place of replication.

The system that models the previously described *receptor-mediated endocytosis*, in absence of diseases, is specified as follows:

$$\begin{aligned}
P &= \text{Ligand} | \text{Cell} \\
\text{Ligand} &= \text{mate}_{\text{lig-rec}}^\nu (\text{mate}_{\text{recept}}^\mu (\mathbb{1})^\ominus)^\Delta \\
\text{Cell} &= \overline{\text{mate}}_{\text{lig-rec}}^\delta \cdot \tau_1 | \overline{\text{bud}}_{\text{ligand}}^\lambda (\rho_1) (\text{Receptor} \circ \text{Ap2-Clathrin} \circ \text{Endosome})^\Gamma \\
\text{Receptor} &= \overline{\text{mate}}_{\text{recept}}^\beta \cdot \overline{\text{mate}}_{\text{ap2-clathrin}}^\eta (\text{bud}_{\text{ap2-clathrin}}^\theta (\mathbb{1})^\Xi)^\Sigma \\
\text{Ap2-Clathrin} &= \text{mate}_{\text{ap2-clathrin}}^\zeta | \overline{\text{bud}}_{\text{ap2-clathrin}}^\xi (\text{mate}_{\text{free}}^\kappa) \cdot \text{mate}_{\text{endo}}^\pi (\mathbb{1})^\Omega \\
\text{Endosome} &= \overline{\text{mate}}_{\text{free}}^\zeta \cdot \overline{\text{mate}}_{\text{endo}}^\varepsilon \cdot \tau_2 (\mathbb{1})^\Upsilon.
\end{aligned}$$

The system describes a pathway, i.e. a sequence of reactions, that have to take place in order for the cell to bind with the early endosomes. More in details, the first mate interaction (on the actions  $\text{mate}_{\text{lig-rec}}^\nu$  and  $\overline{\text{mate}}_{\text{lig-rec}}^\delta$ ), between the *Ligand* and *Cell* membranes, leads to the first binding between the ligands and a set of receptors, located in the cell, driven by the second mate interaction (on  $\text{mate}_{\text{recept}}^\mu$  and  $\overline{\text{mate}}_{\text{recept}}^\beta$ ). At this point, the action  $\overline{\text{bud}}_{\text{ligand}}^\lambda (\rho_1)$  is associated to the newly created membrane. This action models the possibility that the binding between the *Ligand* and *Receptor* is not stable, thus allowing *Ligand* to unbind from the *Cell*. Note that the instability does never occur in absence of diseases. Therefore, in this model, the newly created membrane can only perform a bud interaction (on  $\text{bud}_{\text{ap2-clathrin}}^\theta$  and  $\overline{\text{bud}}_{\text{ap2-clathrin}}^\xi (\text{mate}_{\text{free}}^\kappa)$ ) between the membranes *Ap2-Clathrin* and *Receptor*, by producing the Clathrin-coated vesicle. Finally, we have two additional mate interactions. The first one (on  $\text{mate}_{\text{free}}^\kappa$  and  $\overline{\text{mate}}_{\text{free}}^\zeta$ ) models the uncoating of the external AP-2-Clathrin coat, while the second one (on  $\text{mate}_{\text{endo}}^\pi$  and  $\overline{\text{mate}}_{\text{endo}}^\varepsilon$ ) models the vesicle coalescence with the Endosome.

The analysis of  $P$  is described by the causality relation

$$D_1^\circ = \text{closure}(\{(h_2^\bullet, h_1^\bullet), (h_3^\bullet, h_2^\bullet), (h_4^\bullet, h_3^\bullet), (h_5^\bullet, h_4^\bullet), (h_6^\bullet, h_5^\bullet)\})$$

and by the abstract state  $S_1^\circ$  shown in Table 19.

Information on the possible causality dependencies of the pathway can be inferred from the causal dependencies in  $D_1^\circ$ . In particular, we have that the reaction associated to the cause name  $h_1^\bullet$  does not depend on any other reaction. Moreover, the analysis shows that the reaction associated to  $h_2^\bullet$  may depend only on the reaction associated to  $h_1^\bullet$ . Therefore, the binding leading to the ligand-receptor complex does not depend on any other reactions. Similarly, the binding of the ligand-receptor complex with the complex AP2-Clathrin (reaction associated to  $h_3^\bullet$ ) does not depend on actions such as the production of the Clathrin-coated vesicle (associated to  $h_4^\bullet$ ), the dissociation of the external AP2-Clathrin coat, the so called uncoating (associated to  $h_5^\bullet$ ), or the coalescing with the Endosome (associated to  $h_6^\bullet$ ). The production of the Clathrin-coated vesicle (associated to  $h_4^\bullet$ ) does not depend on the dissociation of the external AP2-Clathrin coat (associated to  $h_5^\bullet$ ) or on the coalescing with the Endosome (associated to  $h_6^\bullet$ ). Finally, the dissociation of the external AP2-Clathrin coat (associated to  $h_5^\bullet$ ) is not causally dependent from the fusion with the Endosome (associated to  $h_6^\bullet$ ). It is worth noting that the previously described causal dependencies are fully coherent with the pathway structure of the system  $P$ .

We now present a pathological version of the above process that models the effects of the hereditary disorder called Familial Hypercholesterolemia. This disorder is due to a genetic defect in the LDL receptor proteins that makes it difficult to remove LDL from the blood, thus increasing the risk of cardiovascular disease. In this case, the receptor is not longer able to form a stable binding with the ligand.

We model this phenomenon by introducing a defective receptor, called *DefReceptor*, which allows the ligand to unbind after binding. The new system  $P'$  extends  $P$ , by introducing the membrane *DefReceptor* inside the membrane  $Cell'$ , a revised version of the membrane  $Cell$  of system  $P$ . Hence, system  $P'$  now models two alternative behaviours: the healthy one and the ill one. More precisely, such kinds of behaviour are modelled using two pathways that become alternative after the binding between the *Ligand* and the  $Cell$ . Indeed, either the *Ligand* binds with a healthy *Receptor*, and it evolves into the sequence of reactions already discussed for system  $P$ , or the *Ligand* binds with a *DefReceptor* and the newly created binding between  $Cell$  and *Ligand* is undone, by letting the *Ligand* exit from the  $Cell$ .

@	$\Delta, \Gamma, \Pi^\circ$	
$\Delta$	$\Theta$	$\text{mate}_{lig-rec}^{\nu^\bullet}$
$\Gamma$	$\Sigma, \Omega, \Upsilon$	$\overline{\text{mate}}_{lig-rec}^{\delta^\bullet} \cdot \tau_1^\bullet, \overline{\text{bud}}_{ligand}^\lambda(\rho_1^\bullet)$
$\Theta$		$(\emptyset, h_1^{\bullet+}, \emptyset) :: \text{mate}_{recept}^\mu$
$\Sigma$	$\Xi$	$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{recept}^\beta \cdot \overline{\text{mate}}_{ap2-clathrin}^\eta$
$\Omega$		$(\emptyset, h_1^{\bullet-}, \emptyset) :: \text{mate}_{ap2-clathrin}^\varsigma$ $(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{bud}}_{ap2-clathrin}^\xi(\text{mate}_{free}^\kappa) \cdot \text{mate}_{endo}^\pi$
$\Upsilon$		$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{free}^\zeta \cdot \overline{\text{mate}}_{endo}^\varepsilon \cdot \tau_2^\bullet$
$\Xi$		$(\emptyset, \{h_2^{\bullet-}, h_3^{\bullet-}, h_5^{\bullet+}\}, \emptyset) :: \overline{\text{bud}}_{ap2-clathrin}^\theta$
$\Pi^\circ = \text{mate}(\Delta, \Gamma)$	$\Theta, \Sigma, \Omega, \Upsilon, \Pi_1^\circ,$ $\Pi_2^\circ, \Phi^\circ, \Pi_3^\circ, \Pi_4^\circ$	$(h_1^\bullet, \emptyset, \emptyset) :: \tau_1^\bullet, (\emptyset, \emptyset, h_1^{\bullet-}) :: \overline{\text{bud}}_{ligand}^\lambda(\rho_1^\bullet)$
$\Pi_1^\circ = \text{mate}(\Theta, \Sigma)$	$\Xi$	$(h_2^\bullet, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{ap2-clathrin}^\eta$
$\Pi_2^\circ = \text{mate}(\Omega, \Pi_1^\circ)$	$\Xi$	$(\emptyset, h_1^{\bullet-}, h_3^{\bullet+}) :: \overline{\text{bud}}_{ap2-clathrin}^\xi(\text{mate}_{free}^\kappa) \cdot \text{mate}_{endo}^\pi$ $(h_5^\bullet, h_1^{\bullet-}, h_3^{\bullet+}) :: \text{mate}_{endo}^\pi$
$\Phi^\circ = \text{bud}(\Xi, \Pi_2^\circ)$	$\Xi$	$(h_4^\bullet, h_1^{\bullet-}, \emptyset) :: \text{mate}_{free}^\kappa$
$\Pi_3^\circ = \text{mate}(\Phi^\circ, \Upsilon)$		$(h_5^\bullet, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{endo}^\varepsilon \cdot \tau_2^\bullet$
$\Pi_4^\circ = \text{mate}(\Pi_2^\circ, \Pi_3^\circ)$		$(h_6^\bullet, h_1^{\bullet-}, \emptyset) :: \tau_2^\bullet$

Table 19: Abstract State  $S_1^\circ$ , where  $h_1^\bullet = (\nu^\bullet, \delta^\bullet), h_2^\bullet = (\mu^\bullet, \beta^\bullet), h_3^\bullet = (\varsigma^\bullet, \eta^\bullet), h_4^\bullet = (\theta^\bullet, \xi^\bullet), h_5^\bullet = (\kappa^\bullet, \zeta^\bullet)$ , and  $h_6^\bullet = (\varepsilon^\bullet, \pi^\bullet)$ .

$P' = \text{Ligand} | \text{Cell}'$

$\text{Ligand} = \text{mate}_{lig-rec}^{\nu^\bullet} (\text{mate}_{recept}^\mu \langle \rangle^\Theta)^\Delta$

$\text{Cell}' = \overline{\text{mate}}_{lig-rec}^{\delta^\bullet} \cdot \tau_1^\bullet | \overline{\text{bud}}_{ligand}^\lambda(\rho_1) (\text{Receptor} \circ \text{Ap2-Clathrin} \circ \text{Endosome} \circ \text{DefReceptor})^\Gamma$

$\text{Receptor} = \overline{\text{mate}}_{recept}^\beta \cdot \overline{\text{mate}}_{ap2-clathrin}^\eta (\text{bud}_{ap2-clathrin}^\theta \langle \rangle^\Xi)^\Sigma$

$\text{DefReceptor} = \overline{\text{mate}}_{recept}^\sigma \cdot \text{bud}_{ligand}^\iota \langle \rangle^\Lambda$

$\text{Ap2-Clathrin} = \text{mate}_{ap2-clathrin}^\varsigma | \overline{\text{bud}}_{ap2-clathrin}^\xi(\text{mate}_{free}^\kappa) \cdot \text{mate}_{endo}^\pi \langle \rangle^\Omega$

$\text{Endosome} = \overline{\text{mate}}_{free}^\zeta \cdot \overline{\text{mate}}_{endo}^\varepsilon \cdot \tau_2^\bullet \langle \rangle^\Upsilon$ .

The analysis of the system  $P'$  is described by the causality relation

$$D_2^\circ = \text{closure}(\{(h_2^\bullet, h_1^\bullet), (h_3^\bullet, h_2^\bullet), (h_4^\bullet, h_3^\bullet), (h_5^\bullet, h_4^\bullet), (h_6^\bullet, h_5^\bullet), (h_7^\bullet, h_1^\bullet), (h_8^\bullet, h_7^\bullet)\}),$$

and by the abstract state  $S_2^\circ$ , depicted in Table 20. Besides the causality dependencies of the original system  $P$ , the analysis includes the possible causal dependencies introduced

by the binding with a defective receptor. The causal dependencies in  $D_2^\circ$  guarantee that the binding of the ligand-receptor complex with the complex AP2-Clathrin (reaction associated to cause name  $h_3^\bullet$ ) the production of the Clathrin-coated vesicle (associated to  $h_4^\bullet$ ), the dissociation of the external AP2-Clathrin coat (associated to  $h_5^\bullet$ ), and, finally, the coalescing with the Endosome (associated to  $h_6^\bullet$ ) *do not depend* on the binding between the ligand and the defective receptor (associated to  $h_7^\bullet$ ), and on the exit of the ligand from the cell (associated to  $h_8^\bullet$ ) and vice versa. Note that this results are totally coherent with the fact that two pathways are alternative: if the binding between ligand and receptor is not stable, the receptor-mediated endocytosis cannot be completed successfully.

@	$\Delta, \Gamma, \Pi^\circ$	
$\Delta$	$\Theta$	$\overline{\text{mate}}_{\text{lig-rec}}^{\nu^\bullet}$
$\Gamma$	$\Sigma, \Omega, \Upsilon, \Lambda$	$\overline{\text{mate}}_{\text{lig-rec} \cdot \tau_1}^{\delta^\bullet}, \overline{\text{bud}}_{\text{ligand}}^{\lambda^\bullet}(\rho_1^\bullet)$
$\Theta$		$(\emptyset, h_1^{\bullet+}, \emptyset) :: \overline{\text{mate}}_{\text{recept}}^{\mu^\bullet}$
$\Sigma$	$\Xi$	$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{recept}}^{\beta^\bullet} \cdot \overline{\text{mate}}_{\text{ap2-clathrin}}^{\eta^\bullet}$
$\Omega$		$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{ap2-clathrin}}^{\varsigma^\bullet}$ $(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{bud}}_{\text{ap2-clathrin}}^{\xi^\bullet}(\overline{\text{mate}}_{\text{free}}^{\kappa^\bullet}) \cdot \text{mate}_{\text{endo}}^{\pi^\bullet}$
$\Upsilon$		$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{free}}^{\zeta^\bullet} \cdot \overline{\text{mate}}_{\text{endo}}^{\varepsilon^\bullet} \cdot \tau_2^\bullet$
$\Lambda$		$(\emptyset, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{recept}}^{\sigma^\bullet} \cdot \overline{\text{bud}}_{\text{ligand}}^{\iota^\bullet}$
$\Xi$		$(\emptyset, \{h_2^{\bullet-}, h_3^{\bullet-}, h_5^{\bullet+}\}, \emptyset) :: \overline{\text{bud}}_{\text{ap2-clathrin}}^{\theta^\bullet}$
$\Pi^\circ = \text{mate}(\Delta, \Gamma)$	$\Theta, \Sigma, \Omega, \Upsilon, \Pi_1^\circ, \Pi_2^\circ, \Phi^\circ, \Pi_3^\circ, \Pi_4^\circ, \Pi_5^\circ, \Phi_1^\circ$	$(h_1^\bullet, \emptyset, \emptyset) :: \tau_1^\bullet, (\emptyset, \emptyset, h_1^{\bullet-}) :: \overline{\text{bud}}_{\text{ligand}}^{\lambda^\bullet}(\rho_1^\bullet)$
$\Pi_1^\circ = \text{mate}(\Theta, \Sigma)$	$\Xi$	$(h_2^\bullet, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{ap2-clathrin}}^{\eta^\bullet}$
$\Pi_2^\circ = \text{mate}(\Omega, \Pi_1^\circ)$	$\Xi$	$(\emptyset, h_1^{\bullet-}, h_3^{\bullet+}) :: \overline{\text{bud}}_{\text{ap2-clathrin}}^{\xi^\bullet}(\overline{\text{mate}}_{\text{free}}^{\kappa^\bullet}) \cdot \text{mate}_{\text{endo}}^{\pi^\bullet}$ $(h_4^\bullet, h_1^{\bullet-}, h_3^{\bullet+}) :: \overline{\text{mate}}_{\text{endo}}^{\pi^\bullet}$
$\Phi^\circ = \text{bud}(\Xi, \Pi_2^\circ)$	$\Xi$	$(h_4^\bullet, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{free}}^{\kappa^\bullet}$
$\Pi_3^\circ = \text{mate}(\Phi^\circ, \Upsilon)$		$(h_5^\bullet, h_1^{\bullet-}, \emptyset) :: \overline{\text{mate}}_{\text{endo}}^{\varepsilon^\bullet} \cdot \tau_2^\bullet$
$\Pi_4^\circ = \text{mate}(\Pi_2^\circ, \Pi_3^\circ)$		$(h_6^\bullet, h_1^{\bullet-}, \emptyset) :: \tau_2^\bullet$
$\Pi_5^\circ = \text{mate}(\Theta, \Lambda)$		$(h_7^\bullet, h_1^{\bullet-}, \emptyset) :: \overline{\text{bud}}_{\text{ligand}}^{\iota^\bullet}$
$\Phi_1^\circ = \text{bud}(\Pi_5^\circ, \Pi)$	$\Pi_5^\circ$	$(h_8^\bullet, \emptyset, \emptyset) :: \rho_1^\bullet$

Table 20: Abstract State  $S_1^\circ$ , where  $h_1^\bullet = (\nu^\bullet, \delta^\bullet)$ ,  $h_2^\bullet = (\mu^\bullet, \beta^\bullet)$ ,  $h_3^\bullet = (\varsigma^\bullet, \eta^\bullet)$ ,  $h_4^\bullet = (\theta^\bullet, \xi^\bullet)$ ,  $h_5^\bullet = (\kappa^\bullet, \zeta^\bullet)$ ,  $h_6^\bullet = (\varepsilon^\bullet, \pi^\bullet)$ ,  $h_7^\bullet = (\mu^\bullet, \sigma^\bullet)$ ,  $h_8^\bullet = (\iota^\bullet, \lambda^\bullet)$ .

The whole LDL Degradation pathway, expressed in BioAmbients [26], is statically



analysed also in [24, 23]. The contextual Control Flow Analysis in [24] describes the possible hierarchies of the nested ambient, but it is not able to capture causal information about the sequential order of transitions. Instead, in [23], an additional flow sensitive pathway analysis is able to safely approximate the set of possibly infinite sequential behaviours that occur at run-time. As a consequence, the analysis can indirectly capture some causality aspects in the setting of the LDL Degradation pathway. More precisely, the analysis can state which reactions cannot arise.

## 6. Conclusions

Developing abstract models to reason about complex biological systems is one of the main tasks of System Biology. Explicitly including causality in these models can contribute to better understand the relationships among the different activities occurring in biological systems. The causal semantics in [6] for the MBD part of Brane Calculi [7] meets this need, but leads to quite big causal transition systems, computationally demanding to explore. Our *Abstract Interpretation*-based analysis for approximating the causal semantics in [6] cuts the computational cost of dynamic investigation: its complexity is indeed polynomial.

Our static analysis can be used to efficiently predict the causal dependencies among membranes interactions and, therefore, to understand the causal behaviour of the analysed systems. Because of over-approximation, the analysis introduces some imprecision, but on the safe side. It can never happen that a causal dependency arises, at run time, between two reaction steps, if the analysis does not report it. As a consequence, the analysis can be applied to show that a reaction step *does not* depend on another one.

Our abstraction is able to reflect all the kinds of causality (discussed in [6]) that may arise in MBD, included the environment causality, which is peculiar of the membrane interactions. Any membrane fusion is indeed able to modify the environment of membranes (and their hierarchy), and to cause further interactions not possible before the fusion. We have applied our analysis to the simple systems presented in [6], which model critical situations from a causality point of view. The causal dependencies reported by the analysis of these systems turned out to be very precise with respect to the dynamic ones. We have also applied our approach to an MBD specification of the receptor-mediated endocytosis mechanism.

The main novelty of our approach is that the abstraction techniques are applied to the causal semantics of [6], rather than to the standard interleaving semantics. As a consequence, the possible causal dependencies are directly obtained by collecting the immediate causal transition relation, for any abstract computation. Therefore, our analysis is more efficient with respect to the alternative approaches relying on the definition

of an abstract transition system, as the ones for Bioambients presented in [12, 13, 23]. Other related analysis techniques ([20, 11, 2, 21]) provide relevant information on the structure of the configurations that can be reached, but they do not directly capture causality aspects.

We plan to apply our approach to other biological case studies in which causality can help in identifying chains of causally related interactions. Furthermore, our static analysis can be exploited to study static causal properties, and, therefore, to obtain useful insights on membrane interactions. In future work, we also intend to extend our causal analysis to the full Brane calculus [7]. Finally, there are other biologically-oriented calculi potentially of interest for our approach, such as an extension [17] of  $\kappa$ -calculus [10], the Calculus of Looping Sequences [1], and Beta Binders [25], whose causality issues have been addressed in [15].

- [1] R. Barbuti, G. Caravagna, A. Maggiolo-Schettini, P. Milazzo, and G. Pardini. The Calculus of Looping Sequences. In *Proc. of Formal Methods for Computational Systems Biology (SFM'08)*, Lecture Notes in Computer Science, volume 5016, 387–423, Springer, 2008.
- [2] C. Bodei. Control Flow Analysis for Beta-binders with and without Static Compartments. In *Theoretical Computer Science* 410(33-34): 3110-3127, Elsevier, 2009.
- [3] C. Bodei and L. Brodo. Brane Calculi Systems: A Static Preview of their Possible Behaviour. In *Proc. of Membrane Computing and Biologically Inspired Process Calculi (MeCBIC'11)*, CoRR abs/1108.3429, 2011.
- [4] C. Bodei, R. Gori, F. Levi. An Analysis for Causal Properties of Membrane Interactions. In *Proc. of the 4th International Workshop on Interactions between Computer Science and Biology (CS2Bio'13)*, Electronic Notes in Theoretical Computer Science 299: 15-31 (2013).
- [5] M. Boreale, D. Sangiorgi: A Fully Abstract Semantics for Causality in the Pi-Calculus. In *Proc. of Symposium on Theoretical Aspects of Computer Science (STACS'95)*, Lecture Notes in Computer Science, volume 900, pp. 243-254, 1995.
- [6] N. Busi. Towards a Causal Semantics for Brane Calculi. In *What is it About Government that Americans Dislike*, pp. 1945–1965, University Press, 2007.
- [7] L. Cardelli. Brane Calculi - Interactions of Biological Membranes. In *Proc. of Computational Methods in Systems Biology (CMSB'04)*, Lecture Notes in Computer Science, volume 3082, pp. 257–280, 2005.

- [8] P. Cousot and R. Cousot. Abstract Interpretation: A Unified Lattice Model for Static Analysis of Programs by Construction or Approximation of Fixpoints. In *Proc. of Fourth ACM Symp. Principles of Programming Languages (POPL'77)*, pp. 238–252, 1977.
- [9] P. Degano and C. Priami. Non Interleaving Semantics for Mobile Processes. In *Theoretical Computer Science* 216(1-2): 237-270, 1999.
- [10] V. Danos and C. Laneve. Graphs for Core Molecular Biology. In *Proc. of Computational Methods in Systems Biology (CMSB'03)*, Lecture Notes in Computer Science, volume 2602, pp. 34–46, 2003, Springer.
- [11] R. Gori and F. Levi. A New Occurrence Counting Analysis for BioAmbients. In *Proc. of Asian Symposium on Programming Languages and Systems (APLAS'05)*, Lecture Notes in Computer Science, volume 3780, pp. 381-400, 2005.
- [12] R. Gori and F. Levi. An Analysis for Proving Temporal Properties of Biological Systems. In *Proc. of Asian Symposium on Programming Languages and Systems (APLAS'06)*, Lecture Notes in Computer Science, volume 4279, pp. 234–252, 2006.
- [13] R. Gori and F. Levi. Abstract Interpretation Based Verification of Temporal Properties for BioAmbients, *Information and Computation*(8): 869-921, 2010.
- [14] M.L. Guerriero and D. Prandi and C. Priami and P. Quaglia. Process Calculi Abstractions for Biology. In *Algorithmic Bioprocesses Natural Computing Series*, pp 463-486, Springer, 2009
- [15] M.L. Guerriero and C. Priami. Causality and Concurrency in Beta-binders. In *TR-01-2006 The Microsoft Research - University of Trento Centre for Computational and Systems Biology*, 2006.
- [16] A. Kiehn. Proof Systems for Cause Based Equivalences. In *Proc. of Mathematical Foundations of Computer Science (MFCS'93)*, Lecture Notes in Computer Science, volume 711, pp. 547-556, Springer, 1993.
- [17] C. Laneve and F. Tarissan. A Simple Calculus for Proteins and Cells, In *Theoretical Computer Science*, volume 404 (1-2): 127-141, Elsevier, 2008.
- [18] R. Milner. A Calculus of Mobile Processes (I and II). In *Information and Computation*, 100(1):1-77, 1992.

- [19] R. Milner. *Communication and concurrency*. Prentice-Hall, London, 1989.
- [20] H. R. Nielson, F. Nielson and H. Pilegaard. Spatial Analysis of BioAmbients. LNCS 69-83 In *Proc. of Static Analysis Symposium (SAS'04)*, Lecture Notes in Computer Science, volume 3148, pp. 69–83, Springer, 2004.
- [21] F. Nielson, H. Riis Nielson, C. Priami, and D. Schuch da Rosa. Control Flow Analysis for BioAmbients. In *Proc. of Workshop on Concurrent Models in Molecular Biology (BioConcur'03)*, Electronic Notes in Theoretical Computer Science, volume 180(3), pp. 65–79, Elsevier, 2003.
- [22] H. Pilegaard, F. Nielson, H. Riis Nielson. Context Dependent Analysis of BioAmbients. In *Proc. of Emerging Aspects of Abstract Interpretation*, 2006.
- [23] H. Pilegaard, F. Nielson, H. Riis Nielson. Pathway Analysis for BioAmbients. In *The Journal of Logic and Algebraic Programming* 77(1-2): 92-130, Elsevier, 2008.
- [24] H. Pilegaard, F. Nielson, H. Riis Nielson. Static Analysis of a Model of the LDL Degradation Pathway. In *Simulation and Verification of Dynamic Systems*, Dagstuhl Seminar Proceedings, 2006
- [25] C. Priami and P. Quaglia. Beta Binders for Biological Interactions. In *Proc. of Computational Methods in Systems Biology (CMSB'04)*, Lecture Notes in Computer Science, volume 3082, pp. 20–33, Springer, 2005.
- [26] A. Regev, E.M. Panina, W. Silverman, L. Cardelli, and E.Y. Shapiro. BioAmbients: An Abstraction for Biological Compartments. In *Theoretical Computer Science* 325(1): 141-167, Elsevier, 2004.
- [27] N. Busi, C. Zandron. Modeling and Analysis of Biological Processes by Mem(brane) Calculi and Systems. In *Proc. of the Winter Simulation Conference (WSC 2006)*, pp. 1646-1655, 2006.

## Appendix A. Appendix: the Formal Proofs

*Proof of Theorem 2.* We have to prove that the pair of functions  $(\bar{\alpha}, \bar{\gamma})$  of Definition 14 is a Galois connection.

- $\bar{\alpha} : \wp(\widetilde{\text{Sys}}) \rightarrow \mathcal{S}^\circ$  and  $\bar{\gamma} : \mathcal{S}^\circ \rightarrow \wp(\widetilde{\text{Sys}})$  are obviously monotone.

- for each  $X \in \wp(\widetilde{\text{Sys}})$ , we have to prove that  $\bar{\gamma}(\bar{\alpha}(X)) \supseteq X$ . We have  $\bar{\alpha}(X) = \bigsqcup_{\tilde{P} \in X}^{\circ} \alpha_{\widetilde{\text{Sys}}}(\tilde{P})$  and, therefore,  $\bar{\gamma}(\bar{\alpha}(X)) = \{\tilde{P} \mid \alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^{\circ} \bigsqcup_{\tilde{P} \in X}^{\circ} \alpha_{\widetilde{\text{Sys}}}(\tilde{P})\}$ . We recall that  $\bigsqcup^{\circ}$  stands for the least upper bound on the  $\mathcal{S}^{\circ}$  domain. Hence, for each  $\tilde{P} \in X$ , we have that  $\alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^{\circ} \bigsqcup_{\tilde{P} \in X}^{\circ} \alpha_{\widetilde{\text{Sys}}}(\tilde{P})$ . We can then conclude that  $X \subseteq \bar{\gamma}(\bar{\alpha}(X))$ .
- for  $S^{\circ} \in \mathcal{S}^{\circ}$ , we have to prove that  $\bar{\alpha}(\bar{\gamma}(S^{\circ})) \sqsubseteq^{\circ} S^{\circ}$ . We have  $\bar{\gamma}(S^{\circ}) = \{\tilde{P} \mid \alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^{\circ} S^{\circ}\}$ , and, therefore,  $\bar{\alpha}(\bar{\gamma}(S^{\circ})) = \bigsqcup_{\{\tilde{P} \mid \alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^{\circ} S^{\circ}\}}^{\circ} \alpha_{\widetilde{\text{Sys}}}(\tilde{P})$ .  
Now it can be easily seen that  $\bigsqcup_{\{\tilde{P} \mid \alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^{\circ} S^{\circ}\}}^{\circ} \alpha_{\widetilde{\text{Sys}}}(\tilde{P}) \sqsubseteq^{\circ} S^{\circ}$ , because, by definition,  $\bigsqcup^{\circ}$  is the least upper bound on  $\mathcal{S}^{\circ}$ .

□

*Proof of Lemma 1.* We prove it by induction on the number of transition steps necessary to obtain  $\tilde{P}'$  from system  $\tilde{P}$ , i.e.  $\tilde{P} \rightarrow_n \tilde{P}'$ .

( $n = 0$ .) Assume, by contradiction, that there exists a  $(\lambda^{\bullet}, \mu^{\bullet}) \in \text{rel}^{\circ}(\tilde{P}^{\bullet})$  such that the two sequential processes labelled  $\lambda$  and  $\mu$  run in parallel on the same membrane of  $\tilde{P}$ . By definition of  $\text{rel}^{\circ}$ , there are two cases:

- $\lambda^{\bullet} = \mu^{\bullet}$ . We have two further cases: either (i) a process labelled  $\lambda$  was under the scope of a replication operator in  $\tilde{P}$  or, (ii) a process labelled  $\lambda$  was not under the scope of a replication operator in  $\tilde{P}$ . In case (i), by definition,  $\text{oc}_{\tilde{P}^{\bullet}}(\lambda^{\bullet}) = \omega$  since  $\lambda^{\bullet}$  occurs under the scope of a replication operator. This leads to a contradiction, because the pair  $(\lambda^{\bullet}, \mu^{\bullet})$  is introduced in  $\text{rel}^{\circ}(\tilde{P}^{\bullet})$  if and only if  $\text{oc}_{\tilde{P}^{\bullet}}(\lambda^{\bullet}) = 1$ . In case (ii) we assume that the processes  $(K, I, E) :: a^{\lambda}.\tau$  and  $(K_1, I_1, E_1) :: b^{\mu}.\sigma$  run in parallel in  $\tilde{P}$ . Also in this case, by definition,  $\text{oc}_{\tilde{P}^{\bullet}}(\lambda^{\bullet})$  must be  $\omega$  because  $\tilde{P}^{\bullet}$  contains at least two processes labelled  $\lambda^{\bullet}$ . This leads to a contradiction, because the pair  $(\lambda^{\bullet}, \mu^{\bullet})$  is introduced in  $\text{rel}^{\circ}(\tilde{P}^{\bullet})$  if and only if  $\text{oc}_{\tilde{P}^{\bullet}}(\lambda^{\bullet}) = 1$ .
- $\lambda^{\bullet} \neq \mu^{\bullet}$ . In this case, we have a process with causes  $(K, I, E) :: a^{\lambda}.\tau$  in  $\tilde{P}$ . By definition,  $(\lambda^{\bullet}, \mu^{\bullet}) \in \text{rel}^{\circ}(\tilde{P}^{\bullet})$  if and only if  $\mu^{\bullet} \in \text{lab}(\tau^{\bullet})$ ,  $\text{oc}_{\tilde{P}^{\bullet}}(\mu^{\bullet}) = 1$  and  $\text{oc}_{\tilde{P}^{\bullet}}(\lambda^{\bullet}) = 1$ . From  $\mu^{\bullet} \in \text{lab}(\tau^{\bullet})$ , we have that  $\lambda^{\bullet}$  and  $\mu^{\bullet}$  belong to the same sequential process. We have a contradiction because there are at least two processes labelled  $\mu^{\bullet}$  in  $\tilde{P}^{\bullet}$ : one in  $\tau^{\bullet}$ , and the other one (we have assumed) running in parallel with  $(K, I, E) :: a^{\lambda}.\tau$ . This allows us to conclude that if  $(\lambda^{\bullet}, \mu^{\bullet}) \in \text{rel}^{\circ}(\tilde{P}^{\bullet})$ , then there are not processes labelled  $\mu^{\bullet}$  that can run in parallel with the process labelled  $\lambda^{\bullet}$ .

( $n > 0$ .) We assume that the claim holds for a process  $\tilde{P}'$  obtained in  $n$  transition steps from  $\tilde{P}$ , i.e.  $\tilde{P} \rightarrow_n \tilde{P}'$  and we prove it for  $\tilde{P}''$  such that  $\tilde{P}' \xrightarrow{k;H} \tilde{P}''$ . Note that the only rule that deserves our attention is the Rule (Mate<sub>c</sub>) in Table 5, since this is the only rule that enriches the number of processes running in parallel on a membrane. More precisely, the Rule (Mate<sub>c</sub>) allows processes that run on the two membranes that are going to fuse, to run together in parallel on the same newly created membrane, as a result of the fusion. Without loss of generality, we assume that the membranes that are going to perform the fusion occur at top level and that the system is  $\tilde{P}' = ((K_1, I_1, E_1) :: \text{mate}_n^\pi.\sigma) | \tilde{\sigma}_0(\tilde{P})^\Delta \circ ((K_2, I_2, E_2) :: \overline{\text{mate}}_n^\psi.\tau) | \tilde{\tau}_0(\tilde{Q})^\Gamma$  and  $\tilde{P}'' = ((k, I_1, E_1) \triangleright \sigma) | ((\emptyset, \emptyset, k^+) \triangleright \tilde{\sigma}_0) | ((k, I_2, E_2) \triangleright \tau) | ((\emptyset, \emptyset, k^-) \triangleright \tilde{\tau}_0) | ((\emptyset, k^+, \emptyset) \triangleright \tilde{P} \circ (\emptyset, k^-, \emptyset) \triangleright \tilde{Q})^\Psi$ . Note that since no other membranes of the system would be involved by the application of the Rule (Mate<sub>c</sub>), our simplification does not impact on the result.

We have to prove that it cannot be the case that if  $(\lambda^\bullet, \mu^\bullet) \in \text{rel}^\circ(\tilde{P}^\bullet)$ , then the two sequential processes  $(K_3, I_3, E_3) :: a^\lambda.\tau_1$  and  $(K_4, I_4, E_4) :: b^\mu.\sigma_1$  occur in parallel on the membrane. Since, by induction, the claim holds for the process  $\tilde{P}'$ , the case we have to prove is the one in which  $(K_3, I_3, E_3) :: a^\lambda.\tau_1$  and  $(K_4, I_4, E_4) :: b^\mu.\sigma_1$  run in parallel on the same membrane  $\Psi_m$  and, more in details, when  $\tilde{\tau}_0 = (K_3, I_3, E_3) :: a^\lambda.\tau_1$  or  $((k, I_2, E_2) \triangleright \tau) = (K_3, I_3, E_3) :: a^\lambda.\tau_1$  and  $\tilde{\sigma}_0 = (K_4, I_4, E_4) :: b^\mu.\sigma_1$  or  $((k, I_1, E_1) \triangleright \sigma) = (K_4, I_4, E_4) :: b^\mu.\sigma_1$ , or vice versa. Now, we first assume that  $\tilde{\tau}_0 = (K_3, I_3, E_3) :: a^\lambda.\tau_1$ . Note that this leads to a contradiction, because, by definition  $(\lambda^\bullet, \mu^\bullet) \in \text{rel}^\circ(\tilde{P}^\bullet)$  if and only if  $\mu^\bullet \in \text{lab}(\tau_1^\bullet)$ ,  $\text{oc}_{\tilde{P}^\bullet}(\mu^\bullet) = 1$  and  $\text{oc}_{\tilde{P}^\bullet}(\lambda^\bullet) = 1$ . Hence, in this case, we have that there exists a process labelled  $\mu^\bullet$  as subprocess of  $\tau_1$ . This leads to a contradiction, since  $\text{oc}_{\tilde{P}^\bullet}(\mu^\bullet) = 1$ . This allows us to conclude that no process labelled  $\mu^\bullet$  can be a subprocess of the sequential process  $\sigma_1$  or  $\sigma$ , as it was initially assumed. A similar reasoning allows us to exclude the case where  $((k, I_2, E_2) \triangleright \tau) = (K_3, I_3, E_3) :: a^\lambda.\tau_1$ .

This concludes the proof. □

*Proof of Lemma 2.* The proof is by cases depending on the rule applied to obtain the transition  $\tilde{P}_1 \xrightarrow{k;H} \tilde{P}_2$ .

**(Mate<sub>c</sub>)** In this case there exists a membrane  $\Sigma$  of  $\tilde{P}_1$  that encloses the two parallel membranes  $\Gamma$  and  $\Delta$ . More precisely,  $\Sigma$  contains  $((K_1, I_1, E_1) :: \text{mate}_n^\lambda.\sigma) | \tilde{\sigma}_0(\tilde{P})^\Delta \circ ((K_2, I_2, E_2) :: \overline{\text{mate}}_n^\mu.\tau) | \tilde{\tau}_0(\tilde{Q})^\Gamma$ . By applying the Rule (Mate<sub>c</sub>) in Table 5, we obtain a system  $\tilde{P}_2$ , where, instead of  $\Gamma$  and  $\Delta$  in  $\Sigma$ , there is the newly created

membrane  $\Psi_m = \text{mate}(\Delta, \Gamma, \lambda, \mu)$ , obtained as follows  $((k, I_1, E_1) \triangleright \sigma) | ((\emptyset, \emptyset, k^+) \triangleright \tilde{\sigma}_0) | ((k, I_2, E_2) \triangleright \tau) | ((\emptyset, \emptyset, k^-) \triangleright \tilde{\tau}_0) | ((\emptyset, k^+, \emptyset) \triangleright \tilde{P} \circ (\emptyset, k^-, \emptyset) \triangleright \tilde{Q})^{\Psi_m}$ . More in details, by applying the Rule  $(\text{Mate}_c)$ ,  $\tilde{P}_1 \xrightarrow{k;H} \tilde{P}_2$  with  $k = (\lambda, \mu)$ ,  $H = K_1 \cup K_2 \cup (I_1 \otimes I_2)$  and  $\Psi_m = \text{mate}(\Delta, \Gamma, \lambda, \mu)$ .

We now want to prove that we can “mimic” this transition step in the abstract setting, starting from the state  $S_1^\circ$ , and using the abstract version of the  $(\text{Mate}_c)$ , i.e. Rule  $(\text{Mate}_c^\circ)$  in Table 9.

Since  $S_1^\circ$  is such that  $\alpha_{\text{sys}}(\tilde{P}_1) \sqsubseteq^\circ S_1^\circ$ , by definition of  $\alpha_{\text{sys}}(\tilde{P}_1)$ , and by definition of the order  $\sqsubseteq^\circ$ , we can be sure that  $\Sigma^\bullet \in \text{parent}(S_1^\circ, \Delta^\bullet) \cap \text{parent}(S_1^\circ, \Gamma^\bullet)$ . Moreover,  $S_1^\circ(\Delta^\bullet) = (M_1^\circ, C_1^\circ)$ ,  $S_1^\circ(\Gamma^\bullet) = (M_2^\circ, C_2^\circ)$ ,  $(K_1^\circ, I_1^\circ, E_1^\circ) :: \text{mate}_n^{\lambda^\bullet} \cdot \sigma^\bullet \in C_1^\circ$ , and  $(K_2^\circ, I_2^\circ, E_2^\circ) :: \overline{\text{mate}}_n^{\mu^\bullet} \cdot \tau^\bullet \in C_2^\circ$  with  $K_1^\bullet \subseteq K_1^\circ, I_1^\bullet \subseteq I_1^\circ, E_1^\bullet \subseteq E_1^\circ$ , and  $K_2^\bullet \subseteq K_2^\circ, I_2^\bullet \subseteq I_2^\circ, E_2^\bullet \subseteq E_2^\circ$ . Consider now any  $\tilde{P}$  such that  $\tilde{P} \xrightarrow{k_1;H_1} \tilde{P}_1$  and let us apply  $(\text{MATE}_c^\circ)$  to  $S_1^\circ$  with respect to  $\text{rel}^\circ(P^\bullet)$ . First note that such transition  $\text{Mate}_c^\circ$  is decorated with  $(\lambda^\bullet, \mu^\bullet); K_1^\circ \cup K_2^\circ \cup (I_1^\circ \otimes I_2^\circ)$ . Moreover, note that  $k = (\lambda, \mu)$ . Hence, we have that  $k^\bullet = (\lambda^\bullet, \mu^\bullet)$ , and, also, since  $K_i^\bullet \subseteq K_i^\circ, I_i^\bullet \subseteq I_i^\circ$  and  $E_i^\bullet \subseteq E_i^\circ$  for  $i \in \{1, 2\}$ , by monotonicity of the  $\otimes$  operator, we have that  $(K_1 \cup K_2 \cup (I_1 \otimes I_2))^\bullet \subseteq K_1^\bullet \cup K_2^\bullet \cup (I_1^\bullet \otimes I_2^\bullet) \subseteq K_1^\circ \cup K_2^\circ \cup (I_1^\circ \otimes I_2^\circ)$ . Therefore, we can conclude that  $\text{rel}^\circ(\tilde{P}^\bullet) \vdash S_1^\circ \xrightarrow{k^\bullet;H^\circ} S_2^\circ$ , with  $H^\bullet \subseteq H^\circ$ . We now have to relate  $\tilde{P}_2$  and  $S_2^\circ$ , as required by the claim of the theorem.

By definition of Rule  $(\text{MATE}_c^\circ)$ , we know that  $S_2^\circ$  is as follows

$$S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi^\bullet\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (M_1^\circ \cup M_2^\circ, C^\circ))\} \sqcup^\circ \\ (\emptyset, k^{\bullet+}, \emptyset) \triangleright_S (M_1^\circ, S_1^\circ) \sqcup^\circ (\emptyset, k^{\bullet-}, \emptyset) \triangleright_S (M_2^\circ, S_1^\circ)$$

where  $k^\bullet = (\lambda^\bullet, \mu^\bullet)$  and

$\Psi^\circ = \text{mate}(\Delta^\bullet, \Gamma^\bullet)$  if  $\text{mate}(\Delta^\bullet, \Gamma^\bullet) \in \widehat{\text{Lab}}_{\mathcal{M}}^d$ ,  $\Psi^\circ = \text{mate}(\top, \top)$ , otherwise,

$$C^\circ = t^\circ((k^\bullet, I_1^\circ, E_1^\circ) \triangleright \sigma^\bullet) \sqcup_C (\emptyset, \emptyset, k^{\bullet+}) \triangleright_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \lambda^\bullet, C_1^\circ) \sqcup_C \\ t^\circ((k^\bullet, I_2^\circ, E_2^\circ) \triangleright \tau^\bullet) \sqcup_C (\emptyset, \emptyset, k^{\bullet-}) \triangleright_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \mu^\bullet, C_2^\circ).$$

We are then left to prove that  $\alpha_{\text{sys}}(\tilde{P}_2) \sqsubseteq^\circ S_2^\circ$ . Let us call  $N_1$  the membrane labels occurring at top level inside membrane  $\Delta$ , and  $N_2$  the membrane labels occurring at top level inside membrane  $\Gamma$  in  $\tilde{P}_1$ . Let  $\tilde{P}_3 = (k, I_1, E_1) \triangleright \sigma | ((\emptyset, \emptyset, k^+) \triangleright \tilde{\sigma}_0) | ((k, I_2, E_2) \triangleright \tau) | ((\emptyset, \emptyset, k^-) \triangleright \tilde{\tau}_0) | ((\emptyset, k^+, \emptyset) \triangleright \tilde{P} \circ$

$(\emptyset, k^-, \emptyset) \triangleright \tilde{Q})^{\Psi_m}$ . Since, by hypothesis,  $\alpha_{\widetilde{\text{sys}}}(\tilde{P}_1) \sqsubseteq^\circ S_1^\circ$ , we have,

$$\begin{aligned} \alpha_{\widetilde{\text{sys}}}(\tilde{P}_2) &\sqsubseteq^\circ S_1^\circ \sqcup^\circ t^\circ(\Sigma^\bullet, \tilde{P}_3^\bullet) \\ &\sqsubseteq^\circ S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi_m^\bullet\}, \emptyset))\} \sqcup^\circ \{(\Psi_m^\bullet, (N_1^\bullet \cup N_2^\bullet, C'^\circ))\} \sqcup^\circ \\ &\quad \bigsqcup_{\Delta_n^\circ \in N_1^\bullet} t^\circ((\emptyset, k^{\bullet+}, \emptyset) \triangleright \tilde{\sigma}_n(\tilde{P}_n) \Delta_n^\circ) \bigsqcup_{\Gamma_n^\circ \in N_2^\bullet} t^\circ((\emptyset, k^{\bullet-}, \emptyset) \triangleright \tilde{\tau}_n(\tilde{Q}_n) \Gamma_n^\circ) \end{aligned}$$

where  $C'^\circ = t^\circ(((k^\bullet, I_1^\bullet, E_1^\bullet) \triangleright \sigma^\bullet) | ((\emptyset, \emptyset, k^{\bullet+}) \triangleright \tilde{\sigma}_0^\circ) | ((k^\bullet, I_2^\bullet, E_2^\bullet) \triangleright \tau^\bullet) | ((\emptyset, \emptyset, k^{\bullet-}) \triangleright \tilde{\tau}_0^\circ))$ . Note that  $\Psi_m^\bullet = \text{mate}(\Delta, \Gamma, \lambda, \mu)^\bullet = \Psi^\circ$ . Moreover, since  $\alpha_{\widetilde{\text{sys}}}(P_1) \sqsubseteq^\circ S_1^\circ$ ,  $N_1^\bullet \subseteq M_1^\circ$  and  $N_2^\bullet \subseteq M_2^\circ$ . Hence, by definition of  $\sqsubseteq^\circ$ , we have that

$$\begin{aligned} \alpha_{\widetilde{\text{sys}}}(\tilde{P}_2) &\sqsubseteq^\circ S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (M_1^\circ \cup M_2^\circ, C'^\circ))\} \\ &\quad \bigsqcup_{\Delta_n^\circ \in M_1^\circ} \{(\Delta_n^\circ, (\emptyset, (\emptyset, k^{\bullet+}, \emptyset) \triangleright_C C_1^\circ)) | S_1^\circ(\Delta_n^\circ) = (M_3^\circ, C_1^\circ)\} \\ &\quad \bigsqcup_{\Gamma_n^\circ \in M_2^\circ} \{(\Gamma_n^\circ, (\emptyset, (\emptyset, k^{\bullet-}, \emptyset) \triangleright_C C_2^\circ)) | S_1^\circ(\Gamma_n^\circ) = (M_4^\circ, C_2^\circ)\} \\ &= S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (M_1^\circ \cup M_2^\circ, C'^\circ))\} \\ &\quad \sqcup^\circ (\emptyset, k^{\bullet+}, \emptyset) \triangleright_S (M_1^\circ, S_1^\circ) \sqcup^\circ (\emptyset, k^{\bullet-}, \emptyset) \triangleright_S (M_2^\circ, S_1^\circ) \end{aligned}$$

Note that last equality holds by definition of the  $\triangleright_S$  operator.

We are now left to prove that  $C'^\circ \sqsubseteq_C C^\circ$ . Recall that, on the one hand, we have that

$$\begin{aligned} C^\circ &= t^\circ((k^\bullet, I_1^\circ, E_1^\circ) \triangleright \sigma^\bullet) \sqcup_C (\emptyset, \emptyset, k^{\bullet+}) \triangleright_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \lambda^\bullet, C_1^\circ) \\ &\quad \sqcup_C t^\circ((k^\bullet, I_2^\circ, E_2^\circ) \triangleright \tau^\bullet) \sqcup_C (\emptyset, \emptyset, k^{\bullet-}) \triangleright_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \mu^\bullet, C_2^\circ). \end{aligned}$$

On the other hand, we have that

$$\begin{aligned} C'^\circ &= t^\circ(((k^\bullet, I_1^\bullet, E_1^\bullet) \triangleright \sigma^\bullet) | ((\emptyset, \emptyset, k^{\bullet+}) \triangleright \tilde{\sigma}_0^\circ) | ((k^\bullet, I_2^\bullet, E_2^\bullet) \triangleright \tau^\bullet) | ((\emptyset, \emptyset, k^{\bullet-}) \triangleright \tilde{\tau}_0^\circ)) \\ &= t^\circ((k^\bullet, I_1^\bullet, E_1^\bullet) \triangleright \sigma^\bullet) \sqcup_C t^\circ((\emptyset, \emptyset, k^{\bullet+}) \triangleright \tilde{\sigma}_0^\circ) \\ &\quad \sqcup_C t^\circ((k^\bullet, I_2^\bullet, E_2^\bullet) \triangleright \tau^\bullet) \sqcup_C t^\circ((\emptyset, \emptyset, k^{\bullet-}) \triangleright \tilde{\tau}_0^\circ) \end{aligned}$$

Since  $I_i^\bullet \subseteq I_i^\circ$  and  $E_i^\bullet \subseteq E_i^\circ$  for  $i \in \{1, 2\}$ , we have that  $t^\circ(((k^\bullet, I_1^\bullet, E_1^\bullet) \triangleright \sigma^\bullet) \sqsubseteq_C t^\circ((k^\bullet, I_1^\circ, E_1^\circ) \triangleright \sigma^\bullet)$  and  $t^\circ((k^\bullet, I_2^\bullet, E_2^\bullet) \triangleright \tau^\bullet) \sqsubseteq_C t^\circ((k^\bullet, I_2^\circ, E_2^\circ) \triangleright \tau^\bullet)$ . The last step consists in proving that  $t^\circ((\emptyset, \emptyset, k^{\bullet+}) \triangleright \tilde{\sigma}_0^\circ) \sqsubseteq_C (\emptyset, \emptyset, k^{\bullet+}) \triangleright_C \text{comp}(R^\circ, \lambda^\bullet, C_1^\circ)$  and, analogously,  $t^\circ((\emptyset, \emptyset, k^{\bullet-}) \triangleright \tilde{\tau}_0^\circ) \sqsubseteq_C (\emptyset, \emptyset, k^{\bullet-}) \triangleright_C \text{comp}(R^\circ, \mu^\bullet, C_2^\circ)$ . It is worth noting that  $t^\circ(\tilde{\sigma}_0^\circ) \sqsubseteq_C C_1^\circ$ . Note that, by Theorem 1, if  $(\xi^\bullet, \nu^\bullet) \in \text{rel}^\circ(\tilde{P}^\bullet)$ , then the two sequential processes labelled  $\xi$  and  $\nu$  cannot run in parallel (on the same membrane)  $\tilde{P}_1$ . This is because, by hypothesis,  $\tilde{P}_1$  is a derivative of  $\tilde{P}$ . Hence, by definition of  $\text{comp}$ ,  $t^\circ(\tilde{\sigma}_0^\circ) \sqsubseteq_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \lambda^\bullet, C_1^\circ)$ . Moreover, by definition of  $\triangleright_C$ ,  $t^\circ((\emptyset, \emptyset, k^{\bullet+}) \triangleright \tilde{\sigma}_0^\circ) \sqsubseteq_C (\emptyset, \emptyset, k^{\bullet+}) \triangleright_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \lambda^\bullet, C_1^\circ)$ . With the same argument, we show that  $t^\circ((\emptyset, \emptyset, k^{\bullet-}) \triangleright \tilde{\tau}_0^\circ) \sqsubseteq_C (\emptyset, \emptyset, k^{\bullet-}) \triangleright_C \text{comp}(\text{rel}^\circ(\tilde{P}^\bullet), \mu^\bullet, C_2^\circ)$ . Since  $\sqcup_C$  is the least upper bound, we can conclude that  $C'^\circ \sqsubseteq_C C^\circ$ .



**(Bud<sub>c</sub>)** In this case there exists a membrane  $\Sigma$  of  $\tilde{P}_1$  that encloses a membrane  $\Gamma$  obtained as follows  $((K_1, I_1, E_1) :: \overline{\text{bud}}_n^\mu(\rho).\tau)|\tilde{\tau}_0(|((K_2, I_2, E_2) :: \text{bud}_n^\lambda.\sigma)|\tilde{\sigma}_0(|\tilde{P}|^\Delta \circ \tilde{Q})|)^\Gamma$ . By applying the Rule (Bud<sub>c</sub>) in Table 5, we obtain a system  $\tilde{P}_2$ , where, the membranes inside  $\Sigma$  are modified as follows:  $((k, I_1, \emptyset) \triangleright \rho)|((k, I_2, E_2) \triangleright \sigma)|\tilde{\sigma}_0(|\tilde{P}|^\Delta)^\Psi_b \circ ((k, I_1, E_1) \triangleright \tau)|\tilde{\tau}_0(|\tilde{Q}|)^\Gamma$ . More in details, by applying the Rule (Bud<sub>c</sub>),  $\tilde{P}_1 \xrightarrow{k;H} \tilde{P}_2$  with  $k = (\lambda, \mu)$ ,  $H = K_1 \cup K_2 \cup (E_1 \otimes I_2)$  and  $\Psi_b = \text{bud}(\Delta, \Gamma, \lambda, \mu)$ .

We now want to prove that we can “mimic” this transition step in the abstract setting, starting from the state  $S_1^\circ$  of the claim, and by using the abstract version of the Rule (Bud<sub>c</sub>), i.e. the Rule (Bud<sub>c</sub><sup>°</sup>) in Table 10.

Since  $S_1^\circ$  is such that  $\alpha_{\text{sys}}(\tilde{P}_1) \sqsubseteq^\circ S_1^\circ$ , by definition of  $\alpha_{\text{sys}}(\tilde{P}_1)$ , and by definition of the order  $\sqsubseteq^\circ$ , we can be sure that  $\Sigma^\bullet \in \text{parent}(S_1^\circ, \Gamma^\bullet)$ ,  $\Gamma^\bullet \in \text{parent}(S_1^\circ, \Delta^\bullet)$ ,  $S_1^\circ(\Gamma^\bullet) = (M_1^\circ, C_1^\circ)$ ,  $S_1^\circ(\Delta^\bullet) = (M_2^\circ, C_2^\circ)$ ,  $(K_1^\circ, I_1^\circ, E_1^\circ) :: \overline{\text{bud}}_n^\mu(\rho^\bullet).\tau^\bullet \in C_1^\circ$ ,  $(K_2^\circ, I_2^\circ, E_2^\circ) :: \text{bud}_n^\lambda.\sigma^\bullet \in C_2^\circ$  with  $K_1^\bullet \subseteq K_1^\circ, I_1^\bullet \subseteq I_1^\circ, E_1^\bullet \subseteq E_1^\circ$  and  $K_2^\bullet \subseteq K_2^\circ, I_2^\bullet \subseteq I_2^\circ, E_2^\bullet \subseteq E_2^\circ$ .

Consider now any  $\tilde{P}$  such that  $\tilde{P} \xrightarrow{k_1;H_1} \tilde{P}_1$  and let us apply (BUD<sub>c</sub><sup>°</sup>) to  $S_1^\circ$  w.r.t.  $\text{rel}^\circ(P^\bullet)$ .

First, note that such transition Bud<sub>c</sub><sup>°</sup> is decorated with  $(\lambda^\bullet, \mu^\bullet); K_1^\circ \cup K_2^\circ \cup (E_1^\circ \otimes I_2^\circ)$ . Furthermore, note that  $k = (\lambda, \mu)$ , and, hence,  $k^\bullet = (\lambda^\bullet, \mu^\bullet)$ . Moreover, since  $K_i^\bullet \subseteq K_i^\circ, I_i^\bullet \subseteq I_i^\circ$ , and  $E_i^\bullet \subseteq E_i^\circ$  for  $i \in \{1, 2\}$ , by monotonicity of the  $\otimes$  operator, we have that  $(K_1 \cup K_2 \cup (E_1 \otimes I_2))^\bullet \subseteq K_1^\bullet \cup K_2^\bullet \cup (E_1^\bullet \otimes I_2^\bullet) \subseteq K_1^\circ \cup K_2^\circ \cup (E_1^\circ \otimes I_2^\circ)$ .

Hence, we can conclude that  $\text{rel}^\circ(\tilde{P}^\bullet) \vdash S_1^\circ \xrightarrow{k^\bullet;H^\circ} S_2^\circ$  with  $H^\bullet \subseteq H^\circ$ . We now have to relate  $\tilde{P}_2$  and  $S_2^\circ$  as required by the claim of the theorem.

By definition of Rule (BUD<sub>c</sub><sup>°</sup>), we know that  $S_2^\circ$  is as follows

$$S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (\Delta^\bullet, t^\circ((k^\bullet, I_1^\circ, \emptyset) \triangleright \rho^\bullet)))\} \sqcup^\circ \{(\Delta^\bullet, (\emptyset, t^\circ((k^\bullet, I_2^\circ, E_2^\circ) \triangleright \sigma^\bullet)))\} \sqcup^\circ \{(\Gamma^\bullet, (\emptyset, t^\circ((k^\bullet, I_1^\circ, E_1^\circ) \triangleright \tau^\bullet)))\}$$

where  $k^\bullet = (\lambda^\bullet, \mu^\bullet)$  and

$\Psi^\circ = \text{bud}(\Delta^\bullet, \Gamma^\bullet)$  if  $\text{bud}(\Delta^\bullet, \Gamma^\bullet) \in \widehat{\text{Lab}}_{\mathcal{M}}^d$ ,  $\Psi^\circ = \text{bud}(\top, \top)$ , otherwise.

We are then left to prove that  $\alpha_{\text{sys}}(\tilde{P}_2) \sqsubseteq^\circ S_2^\circ$ . Let

$$\tilde{P}_3 = ((k, I_1, \emptyset) \triangleright \rho)|((k, I_2, E_2) \triangleright \sigma)|\tilde{\sigma}_0(|\tilde{P}|^\Delta)^\Psi_b \circ ((k, I_1, E_1) \triangleright \tau)|\tilde{\tau}_0(|\tilde{Q}|)^\Gamma.$$

Since, by hypothesis,  $\alpha_{\widetilde{\text{sys}}}(\tilde{P}_1) \sqsubseteq^\circ S_1^\circ$ , we have that

$$\begin{aligned} \alpha_{\widetilde{\text{sys}}}(\tilde{P}_2) &\sqsubseteq^\circ \\ &S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi_b^\bullet\}, \emptyset))\} \sqcup^\circ \{(\Psi_b^\bullet, (\Delta^\bullet, t^\circ((k^\bullet, I_1^\bullet), \emptyset) \triangleright \rho^\bullet))\} \sqcup^\circ \\ &\{(\Delta^\bullet, (\emptyset, t^\circ((k^\bullet, I_2^\bullet), E_2^\bullet) \triangleright \sigma^\bullet))\} \sqcup^\circ \{(\Gamma^\bullet, (\emptyset, t^\circ((k^\bullet, I_1^\bullet), E_1^\bullet) \triangleright \tau^\bullet))\} \end{aligned}$$

Note that  $\Psi_b^\bullet = \text{bud}(\Delta, \Gamma, \lambda, \mu)^\bullet = (\Delta^\bullet, \Gamma^\bullet) = \Psi^\circ$ . Moreover, since  $I_i^\bullet \subseteq I_i^\circ$  and  $E_i^\bullet \subseteq E_i^\circ$ , for  $i \in \{1, 2\}$ , we can conclude that

$$\begin{aligned} \alpha_{\widetilde{\text{sys}}}(\tilde{P}_2) &\sqsubseteq^\circ \\ &S_1^\circ \sqcup^\circ \{(\Sigma^\bullet, (\{\Psi^\circ\}, \emptyset))\} \sqcup^\circ \{(\Psi^\circ, (\Delta^\bullet, t^\circ((k^\bullet, I_1^\circ), \emptyset) \triangleright \rho^\bullet))\} \sqcup^\circ \\ &\{(\Delta^\bullet, (\emptyset, t^\circ((k^\bullet, I_2^\circ), E_2^\circ) \triangleright \sigma^\bullet))\} \sqcup^\circ \\ &\{(\Gamma^\bullet, (\emptyset, t^\circ((k^\bullet, I_1^\circ), E_1^\circ) \triangleright \tau^\bullet))\} \\ &\sqsubseteq^\circ S_2^\circ. \end{aligned}$$

**(Drip<sub>c</sub>)** In this case, the proof can easily be obtained from the one for Bud<sub>c</sub>. □

*Proof of Theorem 3.* The proof is obtained by reasoning by induction on the number of transition steps necessary to obtain  $P'$  from  $P$ , i.e.  $P \longrightarrow_n P'$  with  $P' \in X$ , by applying Lemma 2, to relate each concrete transition step of the causal semantics to its corresponding abstract one. Then, we apply Definition 14 and 16, to obtain the claim. □