

Observational Equivalences in a Bio-Inspired Formalism Involving Mobility and Lifetimes

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ABSTRACT

We use membrane systems to define a formalism inspired by cell biology in which mobility and timing are explicitly specified. In order to reason about the behaviours of complex biological systems, we introduce several observational equivalences over mobile membranes with lifetimes. These equivalences based on observations correspond to several combinations of mobility operations that can be performed, timing aspects of the objects involved in mobility and their explicit positions inside membranes. Various relationships between these observational equivalences are proved.

Categories and Subject Descriptors

F.4 [Computation by Abstract Devices]: Models of Computation, Modes of Computation

General Terms

Theory

Keywords

mobility, lifetimes, equivalences

1. TIMING ASPECTS IN CELL MOVEMENTS

Inspired by the compartments of biological cells and their movement, we have defined a rule-based model of mobile membranes [4]. The structure of the cell is represented by a set of hierarchically embedded regions, each one delimited by a surrounding boundary (called membrane), and all of them contained inside an external special membrane called *skin*. A membrane without other membranes inside is called elementary. The molecular species (ions, proteins, agents, etc.) floating inside cellular compartments are represented by multisets of objects described by means of symbols or strings over a given alphabet. Chemical reactions (e.g. $H_2 + O \rightarrow H_2O$) are represented by evolution rules that operate on multisets of objects written as $H^2 + O \rightarrow H_2O$,

meaning that we have two objects H and an object O producing an object H_2O . The biologically inspired rules we use in this paper are endocytosis (moving an elementary membrane inside a neighbouring membrane), exocytosis (moving an elementary membrane outside the membrane where it is placed), and elementary division (dividing an elementary membrane).

Timing is an important aspect in biological systems: evolution of real systems frequently involves various temporal interdependence among components [12]. We consider lifetimes associated to objects (as done in [3]), and use a global clock to simulate the passage of time. The endocytosis and exocytosis rules work whenever the involved membranes “agree” on the movement by using dual objects a and \bar{a} in the involved membranes. An object a marks the active part of the movement (is ready to interact when its lifetime reaches 0), while an object \bar{a} marks the passive part (is ready to interact during its entire lifetime).

DEFINITION 1. A system of mobile membranes with lifetimes is a construct

$$\Pi_t = (O_t, H, \mu, w_{t,1}, \dots, w_{t,n}, R_t), \text{ where:}$$

1. $n \geq 1$ (the degree of the system);
2. $O_t = O \times \mathbb{N}$ is a set of objects with lifetimes, where O is an alphabet (its elements are called objects), and (a, t_a) represents an object a and its lifetime $t_a \geq 0$;
3. H is a finite set of labels for membranes;
4. $\mu \subset H \times H$ is the membrane structure, a tree-like structure in which $(i, j) \in \mu$ denotes that the membrane labelled by j is inside the membrane labelled by i ;
5. $w_{t,1}, w_{t,2}, \dots, w_{t,n}$ are multisets over O_t describing the initial multisets of objects with their lifetimes placed in the n regions of μ ;
6. The finite set R_t contains the rules for mobile membranes [4], where lifetimes for objects are added, and rules used to manipulate the lifetimes of objects. The rules of R_t have the following forms, where $(a, 0), (a, t_a), (a, t_a - 1), (\bar{a}, t_{\bar{a}}), (c, t_c), (b, t_b) \in O_t$ and $h, m \in H$:

$$(a) [(a, 0)]_h [(\bar{a}, t_{\bar{a}})]_m \rightarrow [(c, t_c)]_h [(b, t_b)]_m; \text{ (endo)} \\ \text{an elementary membrane } h \text{ containing } (a, 0) \text{ enters the adjacent membrane } m \text{ containing } (\bar{a}, t_{\bar{a}}); \\ (a, 0) \text{ and } (\bar{a}, t_{\bar{a}}) \text{ are rewritten to } (c, t_c) \text{ and } (b, t_b), \\ \text{respectively;}$$

- (b) $[[(a, 0)]_h (\bar{a}, t_{\bar{a}})]_m \rightarrow [(c, t_c)]_h [(b, t_b)]_m$; (exo) an elementary membrane h containing $(a, 0)$ exits the parent membrane m containing $(\bar{a}, t_{\bar{a}})$; $(a, 0)$ and $(\bar{a}, t_{\bar{a}})$ are rewritten to (c, t_c) and (b, t_b) , respectively;
- (c) $[(a, 0)]_h \rightarrow [(c, t_c)]_h [(b, t_b)]_h$; (elementary division) if containing $(a, 0)$, a membrane h is divided into two membranes with the same label h , and $(a, 0)$ is rewritten to (b, t_b) and (c, t_c) .
- (d) $(a, t_a) \rightsquigarrow (a, t_a - 1)$; (lifetime decrementing)
- (e) $(a, 0) \rightsquigarrow \varepsilon$, for $(a, 0) \in O_t$. (object degradation)

In terms of computation, we are working with membrane configurations. A computation is performed in the following way: starting from an initial configuration of the system, the evolution takes place by applying sequentially rules from the set R_t . A rule is applicable to a membrane configuration when all the involved objects and membranes appearing in its left hand side are available. When a membrane is divided, then all its inner objects are replicated in the two new membranes. When there is no rule from R_t applicable, then a lifetime decreasing step is performed using the rules (d) and (e): all the objects from a current configuration have either their lifetimes decreased by one or are eliminated from the system (depending on the value of their lifetime).

DEFINITION 2. The set $\mathcal{M}(\Pi_t)$ of membrane configurations M in a system Π_t is inductively defined as follows:

- if $i \in H$ denotes the label of an elementary membrane and u_t is a multiset over O_t , then $\langle i; u_t \rangle \in \mathcal{M}(\Pi_t)$ is an elementary membrane configuration;
- if $M_1, \dots, M_n \in \mathcal{M}(\Pi_t)$, $n \geq 1$, $i \in H$ and u_t is a multiset over O_t , then $\langle i; u_t, M_1 \parallel \dots \parallel M_n \rangle \in \mathcal{M}(\Pi_t)$ is a composite membrane configuration. $M_1 \parallel M_2$ denotes two membrane configurations M_1 and M_2 placed in parallel using the parallel composition operator \parallel .

DEFINITION 3. For a membrane system Π_t , we say that a membrane configuration M reduces to another membrane configuration N if there exists a rule in R_t applicable to membrane configuration M such that we can obtain membrane configuration N . We denote by \rightarrow^n (\rightsquigarrow^n) a sequence of $n \geq 1$ reductions \rightarrow (time steps \rightsquigarrow), and by \rightarrow^* (\rightsquigarrow^*) the reflexive and transitive closure of \rightarrow (\rightsquigarrow).

Using commutativity and associativity of parallel composition, we can identify large populations in which elements are commuted. Membrane systems with the same structure and commuted components are identified. This is expressed by means of an equivalence relation \equiv defined as the smallest congruence such that the following laws hold:

$$\frac{M \parallel Q \equiv N \parallel Q}{(M \parallel N) \parallel Q \equiv M \parallel (N \parallel Q)} \quad \begin{array}{l} \text{(Par Comm)} \\ \text{(Par Assoc)} \end{array}$$

Due to the strong relationship established between mobile ambients and mobile membranes [1], it results that the structural congruence \equiv over mobile membranes is decidable.

2. OBSERVATIONAL EQUIVALENCES

Process calculi can be used to describe biological systems at different levels of abstraction. Two systems are deemed equivalent when they “have the same observed behaviour”. Bisimulation congruences of a very simple formalism are used in [15] to reduce the size of a model of the lactose operon regulation. In [11], bisimulations are used to compare the evolution of biological systems described in κ -calculus [8]. Using process calculi like mobile ambients [6] and $tD\pi$ -calculus [7], the authors use bisimulations over membranes to reduce the size and compare behaviours of complex biological systems in which mobility is involved [4].

Membrane systems are closed to automata [14], and two membrane systems are said to be equivalent whenever they have the same input/output behaviour with respect to the external world, regardless their evolution. The idea underlying observational equivalence is that two systems are equivalent when no observation can distinguish them. In process calculi, various observational equivalences are used to equate systems which behave in the same way according to specific assumptions [5, 13]. The simplest equivalence that can be defined and used in our framework to compare two evolving systems is given by $M \rightsquigarrow^* N$ denoting the fact that given a membrane configuration M to which no rule from R_t is applicable, there are performed a number of \rightsquigarrow steps until a rule from R_t is applicable.

DEFINITION 4. A reduction equivalence \mathcal{S} is a symmetric binary relation over membrane configurations such that, for all $(M, N) \in \mathcal{S}$, if $M \rightsquigarrow^* M'$, then there exists N' such that $N \rightsquigarrow^* N'$ and $(M', N') \in \mathcal{S}$.

Reduction bisimilarity is the union of all reduction bisimulations. Two membrane configurations are reduction bisimilar, denoted $M \sim N$, if and only if $(M, N) \in \mathcal{S}$ for some reduction bisimulation \mathcal{S} .

Note that \sim is an equivalence relation (\sim is reflexive, symmetric & transitive), and the largest reduction bisimulation.

In this paper we connect our approach to process calculi, in which several bisimulations involving mobility are already defined [7, 13]. Using mobile membranes, we are interested either in explicit locations, lifetimes of evolution, mobility objects, or in combinations of these concepts. Thus we define several equivalences, showing that some of them are finer than others, and that some of them are incomparable. Defining several equivalences, we offer flexibility in selecting the right one when verifying biological systems and comparing them. We present five observational equivalences forming a lattice (see Figure 1), and use them to compare systems of mobile membranes with lifetimes.

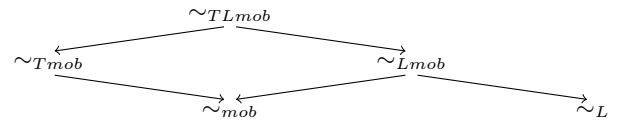


Figure 1: Five bisimulations and their relationships

To avoid ambiguity, in what follows we consider that the objects involved in mobility, namely endocytosis and exocytosis rules, belong to the sets of objects O_{exo} and O_{endo} , respectively, such that O_{exo} and O_{endo} are subsets of O_t and $O_{endo} \cap O_{exo} = \emptyset$.

In what follows, $x \in \{endo, exo\}$ represents the possible

movements, u'_t, u''_t arbitrary multisets of objects with lifetimes, M, M' configurations, and $m \in H$ a membrane label.

2.1 Mobility and Location Observational Equivalences

There are mainly three observational coordinates in systems of mobile membranes with lifetimes: one involves the mobility operations that can be performed, another is given by the position (explicit location) inside a membrane, and a third one is given by timing aspects. Following [13], two membrane configurations are observational bisimilar if they satisfy the same observation predicates and, by performing a reduction, can evolve to membrane configurations that are still observational bisimilar. Two systems are equivalent if an observer cannot distinguish their behaviour.

We clarify first what is observable. To emphasise the mobility aspects, the objects involved in endocytosis and exocytosis rules are observable. In what follows, $M_0 \parallel \dots \parallel M_i$, $i \geq 0$ stands for the parallel composition of zero or more membrane configurations. The predicate $\downarrow_{x(a)}$ means that an object a performs a movement $x \in \{endo, exo\}$.

DEFINITION 5. A mobility observation predicate $\downarrow_{x(a)}$ is defined by the rule $M \downarrow_{x(a)}$ iff $M \equiv \langle m; (a, t_a) \uplus u'_t, N_0 \parallel \dots \parallel N_k \parallel M_0 \parallel \dots \parallel M_i$, where $a \in O_x$.

DEFINITION 6. A mobility observational bisimulation \mathcal{S} is a reduction equivalence over membrane configurations such that, for all $(M, N) \in \mathcal{S}$, if $M \downarrow_{x(a)}$, then $N \downarrow_{x(a)}$ for any mobility observation predicate $\downarrow_{x(a)}$.

Mobility observational bisimilarity is the union of all mobility observational bisimulations. Two membrane configurations are mobility observational bisimilar, denoted $M \sim_{mob} N$, if and only if $(M, N) \in \mathcal{S}$ for some mobility observational bisimulation \mathcal{S} .

Note that \sim_{mob} is an equivalence, and the largest mobility observational bisimulation.

EXAMPLE 1. Following an example of [2], we consider a molecule infected by a virus that offers the possibility to molecules like CD8 and CD4 to read and initiate the signalling pathways for the destruction sequence before the newly created viruses are released. The information \bar{b} about the infecting virus is displayed by the infected cell for a short period of time (until the lifetime of object \bar{b} reaches 0). The lifetime 20 of the object \bar{b} restricts the amount of time to wait for an interaction with a T cell.

An interaction between the infected cell and either CD8 or CD4 takes place if these contain an object $b \in O_{endo}$ is present. By considering the configurations:

$$M_1 = \langle cell; (\bar{b}, 20), M \parallel \langle virus; u'_t \rangle \parallel \langle CD8; (b, 13) \rangle$$

$$M_2 = \langle cell; (\bar{b}, 20), M \parallel \langle virus; u'_t \rangle \parallel \langle CD4; (b, 14) \rangle$$

it results that $M_1 \downarrow_{endo(b)}$, $M_2 \downarrow_{endo(b)}$, $M_1 \downarrow_{endo(\bar{b})}$ and $M_2 \downarrow_{endo(\bar{b})}$ hold, and thus $M_1 \sim_{mob} M_2$.

Due to the connection between mobile membranes and mobile ambients [1], we define an observational bisimulation that is similar to the bisimulation defined for mobile ambients in [9], being able to distinguish only locations.

DEFINITION 7. A located observation predicate $\downarrow_{@m}$ is defined by the rule: $M \downarrow_{@m}$ iff $M \equiv \langle m; u_t, N_0 \parallel \dots \parallel N_k \parallel M_0 \parallel \dots \parallel M_i$.

DEFINITION 8. A located observational bisimulation \mathcal{S} is a reduction equivalence over membrane configurations such that, for all $(M, N) \in \mathcal{S}$, if $M \downarrow_{@m}$, then $N \downarrow_{@m}$ for any located observation predicate $\downarrow_{@m}$.

Located observational bisimilarity is the union of all located observational bisimulations. Two membrane configurations are located observational bisimilar, denoted $M \sim_L N$, if and only if $(M, N) \in \mathcal{S}$ for some located observational bisimulation \mathcal{S} .

Note that \sim_L is an equivalence, and the largest located observational bisimulation.

\sim_{mob} and \sim_L are the coarsest equivalences of this paper, in the sense that the observer is restricted to observe only movement objects \sim_{mob} or the label of membranes in \sim_L .

It is rather natural to strengthen the observing power of the previous defined observations:

DEFINITION 9. A located mobility observation predicate $\downarrow_{x(a)@m}$ is defined by the rule $M \downarrow_{x(a)@m}$ iff $M \equiv \langle m; (a, t_a) \uplus u'_t, N_0 \parallel \dots \parallel N_k \parallel M_0 \parallel \dots \parallel M_i$, where $a \in O_x$.

The observational bisimulation \sim_{Lmob} is defined in the same way as the observational bisimulation \sim_{mob} given above. This bisimulation compares membrane configurations by looking also at the label of the membrane containing an object that facilitates a movement, and it is of interest when tracing the movements of certain membranes. Note that \sim_{Lmob} is an equivalence relation, and the largest located mobility observational bisimulation.

In what follows, for simplicity, we use \mathcal{O} for the operational semantics induced by the observational equivalences $\sim_{\mathcal{O}}$ (e.g., we use mob to stand for \sim_{mob}). We define a pre-order relation \preceq over observational equivalences to say that the first observational equivalence makes at least the same number of identifications as the second. This means that the first observational equivalence (the coarsest) can equate more processes than the second observational equivalence (the finest). For the sake of notation, $\mathcal{O} \preceq \mathcal{O}'$ is used instead of $\sim_{\mathcal{O}} \preceq \sim_{\mathcal{O}'}$. Also, $\mathcal{O} \prec \mathcal{O}'$ if $\mathcal{O} \preceq \mathcal{O}'$ and $\mathcal{O}' \not\preceq \mathcal{O}$. The difference in the observation power between equivalences comes from the definition of observations.

PROPOSITION 1 ($mob \prec Lmob$).

1. $mob \preceq Lmob \Leftrightarrow \forall M, N$, if $M \sim_{Lmob} N$ then $M \sim_{mob} N$;
2. $Lmob \not\preceq mob \Leftrightarrow \exists M, N$, if $M \sim_{mob} N$ then $M \not\sim_{Lmob} N$.

The first part of the above result holds, since the located mobility observation can distinguish in both membrane configurations the same object a placed inside the same membrane m facilitating a movement. Thus the mobility observation has the same observations for the object a in both membrane configurations, and so $M \downarrow_{x(a)@m}$ implies $M \downarrow_{x(a)}$.

For the second part we give the following counterexample: take two membrane configurations M and N , and an object $\bar{a} \in O_{exo}$ s.t. $M = \langle l; (\bar{a}, t_{\bar{a}}) \uplus u'_t \rangle$ and $N = \langle k; (\bar{a}, t_{\bar{a}}) \uplus u'_t \rangle$ with $l \neq k$. Both $M \downarrow_{exo(\bar{a})}$ and $N \downarrow_{exo(\bar{a})}$ hold, and thus the two membrane configurations are mobility observational equivalent: $M \sim_{mob} N$. However $M \downarrow_{exo(\bar{a})@l}$ and $N \downarrow_{exo(\bar{a})@k}$ also hold, and $l \neq k$; therefore $M \not\sim_{Lmob} N$.

2.2 Timed Observational Equivalences

In what follows we deal also with the timed features for systems of mobile membranes with lifetimes, and consider also as observable the values of the lifetimes.

DEFINITION 10. A *timed mobility observation predicate* $\downarrow_{x(a)}^{t_a}$ is defined by the rule $M \downarrow_{x(a)}^{t_a}$ iff $M \equiv \langle m; (a, t_a) \uplus u_t', N_0 \parallel \dots \parallel N_k \parallel M_0 \parallel \dots \parallel M_i, \text{ where } a \in O_x.$

The timed mobility bisimulation \sim_{Tmob} is defined in the same way as the mobility bisimulation \sim_{mob} , where in Definition 6, we replace the reduction equivalence condition if $M \rightsquigarrow^* \rightarrow M'$, then $\exists N'$ s.t. $N \rightsquigarrow^* \rightarrow N'$ and $(M', N') \in \mathcal{S}$. by if $M \rightsquigarrow^* \rightarrow M'$, then $\exists N'$ s.t. $N \rightsquigarrow^n \rightarrow N'$ and $(M', N') \in \mathcal{S}$. Replacing $*$ by n means that both membrane configuration M and N have to perform the same number n of lifetime decreasing steps, before performing a reduction step, instead of performing arbitrary number $*$ of lifetime decreasing steps, before performing a reduction step.

Note that \sim_{Tmob} is an equivalence relation, and the largest timed mobility observational bisimulation.

PROPOSITION 2 ($mob \prec Tmob$).

1. $mob \preceq Tmob \Leftrightarrow \forall M, N, \text{ if } M \sim_{Tmob} N \text{ then } M \sim_{mob} N;$
2. $Tmob \not\preceq mob \Leftrightarrow \exists M, N, \text{ if } M \sim_{mob} N \text{ then } M \not\sim_{Tmob} N.$

We extend the timed mobility observation with positioning awareness as in located observation.

DEFINITION 11. A *timed mobility located observation predicate* $\downarrow_{x(a)@m}^{t_a}$ is defined by the rule $M \downarrow_{x(a)@m}^{t_a}$ iff $M \equiv \langle m; (a, t_a) \uplus u_t', N_0 \parallel \dots \parallel N_k \parallel M_0 \parallel \dots \parallel M_i, \text{ where } a \in O_x.$

The bisimulation \sim_{TLmob} , in terms of timing, location and mobility, is defined in the same way as the bisimulation \sim_{Tmob} . This bisimulation compares membrane configurations by looking at the objects that facilitates a movement, their positions, and also their lifetimes. It is of interest when tracing the membranes movements in time and space. Note that \sim_{TLmob} is an equivalence relation, and the largest timed located mobility observational bisimulation.

PROPOSITION 3 ($Lmob \prec TLMob$).

1. $Lmob \preceq TLMob \Leftrightarrow \forall M, N, \text{ if } M \sim_{TLMob} N \text{ then } M \sim_{Lmob} N;$
2. $TLMob \not\preceq Lmob \Leftrightarrow \exists M, N, \text{ if } M \sim_{Lmob} N \text{ then } M \not\sim_{TLMob} N.$

PROPOSITION 4 ($Tmob \prec TLMob$).

1. $Tmob \preceq TLMob \Leftrightarrow \forall M, N, \text{ if } M \sim_{TLMob} N \text{ then } M \sim_{Tmob} N;$
2. $TLMob \not\preceq Tmob \Leftrightarrow \exists M, N, \text{ s.t. if } M \sim_{Tmob} N \text{ then } M \not\sim_{TLMob} N.$

For all observational equivalences defined above:

PROPOSITION 5. *The observational equivalence is strictly finer than reduction equivalence.*

PROPOSITION 6. *Structural congruence implies observational equivalence.*

3. CONCLUSION

The paper focuses on timing, mobility and locations for mobile membranes with lifetimes. Several observational equivalences are defined, and their distinguishing power is reflected by several relationships between them. The discriminating power of the defined equivalences is given by the used sets of observation predicates. The existence of this family of equivalences allows to select the right observational equivalence (as done in this paper for simple biological systems), providing a flexible tool for studying and comparing biological systems involving lifetimes, mobility and locations. We have omitted an example and more details due to page limit.

As future work, we are interested in theoretical investigation of other behavioural equivalences and their applicability to systems biology, thinking to behavioural equivalences like trace equivalences and testing equivalences. Trace equivalences are used to compare in two labelled transition systems the traces obtained by concatenating the labels of the transitions of each possible execution path. Testing equivalences require observer processes: two processes are equivalent if they interact similarly with all the observer processes composed in parallel with each of them.

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