A Novel Variant of Tissue P Systems for the Modelling of Biochemical Systems

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Summary. In the last decade, different computing paradigms and modelling frameworks for the description and simulation of biochemical systems have been proposed. Here, we consider membrane systems, in particular, tissue P systems and τ-DPP, for the development of a novel variant of membrane systems with dimensions associated to the volumes involved in the structure and to the molecular species occurring inside the system. Moreover, this variant allows the communication of molecules among non adjacent membranes arranged in a hybrid structure, that is, organised in a tissue-like fashion where nodes can have a complex internal structure. The features presented in the new variant of P systems can be used to describe, among others, reaction-diffusion systems, where molecules are involved in chemical reactions and move among membranes and their movements depend on the free space of the volumes, or systems where exist privileged pathways between membranes, which are inspired to the role of microtubule in protein transport within the intracellular space. We conclude presenting two test cases of biochemical systems in which the features of the new variant are suitable for the modelling, and we discuss about the modelling power and the possible developments of this work.

1 Introduction

Membrane systems, also known as P systems, introduced in [17], are one of the computation models inspired by the structure and the functioning of living cells presented in the recent years. The basic model consists of a hierarchical structure composed by several membranes, embedded into a main membrane called the *skin*. Membranes divide the space into *regions*, that contain some *objects* (represented by symbols over an alphabet) and *evolution rules*.

The current variants of membrane systems used in the modelling of biochemical systems provide a description where membranes can contain up to an infinite number of molecules because the sizes of the structure components and of the objects involved are not considered. Moreover, the communication channels are limited to adjacent membranes. In particular, in the framework of tree-like P systems, the communication is permitted from/to a membrane to/from another one immediately inside or outside the first one. On the other hand, working with tissue P systems (or tP systems), communication of objects is achieved using the "synapses" defined among nodes. In addition, either variant of P systems use only a tree-like or a tissue-like structure, while hybrid structures are not considered. For instance, the description of tissues where nodes have a complex internal structure or tree-like systems with membranes enclosing a tissue are not allowed. There exist other works on P systems which use different strategies to represent the structure and the communication channels, like *Hyperdag P systems* [16], or variants applied to the economic processes [19].

In this paper, we present a novel variant of P systems where we exploit tP systems [15] to describe the topological organisation of the membranes and to denote the possible communication channels of the system. Furthermore, for the description of the dynamics, we consider τ-DPP, presented in [7]. Within the framework of τ-DPP, the probabilities are associated to the rules, following the method introduced by Gillespie in [10]. In particular, τ-DPP extends the tau-leaping procedure [5] in order to quantitatively simulate the behaviour of complex biological and chemical systems, embedded in membrane structures composed by different volumes.

Starting from the structure of tP systems and the description of the dynamics provided by τ-DPP, we introduce a variant of tP systems with dimensions associated to membranes and objects, representing respectively, the "size" of the volume where the computation occurs and the amount of volume occupied by objects. Both the dimensions of membranes and objects are useful to describe any real system where it is important to avoid the infinite accumulation of objects inside the system membranes. The structure of a modelled system is independent from the communication channels among membranes, that is, two different graphs are used to denote the topology of the membranes involved in the system structure and the connections among membranes for the communication of objects. Moreover, the structure of the system can be hybrid, as mentioned above, and the communication can be performed between non adjacent membranes, to denote privileged pathways between membranes. This formalism takes inspiration from a specific component of living cells, microtubules; in particular, the formalism can reproduce their role as intracellular "highways" for the transport of other cellular components, such as vesicles and proteins [24].

The paper is organised as follows: in Section 2 we will recall the basic notions of membrane systems, tP systems and τ-DPP variants; in Section 3 we will introduce the novel variant of tP systems with membranes and objects dimensions; in Section 4 we will present some test cases of biochemical systems defined using the new

variant; finally in Section 5 we will discuss the modelling power of our variant of membrane systems and we will conclude with some possible future developments for this work.

2 Membrane systems

In this section we describe the framework of membrane systems [18], recalling their basic notions and definitions. We then present tissue P systems, a variant consisting of a set of several cells connected through protein channels [15]. Finally, we describe τ-DPP, a computational method introduced in [7], used to describe and perform stochastic simulations of complex biological or chemical systems.

2.1 Basic notions of P systems

P systems, or membrane systems, have been introduced in [17] as a class of unconventional computing devices of distributed, parallel and nondeterministic type, inspired by the compartmental structure and the functioning of living cells.

In order to define a basic P system, three main parts need to be introduced: the *membrane structure*, the *objects* and the *rules*.

The *membrane structure* defines the topological and hierarchical organisation of a system consisting of distinct compartments. The definition of membrane structure is given through a set of membranes with a distinct label (usually numbers), hierarchically organised inside a unique membrane, named *skin membrane*. Among others, a representation of a membrane structure is given by using a string of square parentheses.

In particular, each membrane identifies a *region*, delimited by the membrane itself and any other adjacent membrane possibly present inside it. The number of membranes in a membrane structure is called the *degree* of the P system. The whole space outside the skin membrane is called the *environment*.

The internal state of a P system is described by the *objects* (represented by symbols taken from an alphabet V) occurring inside the membranes. In order to denote the presence of multiple copies of the same object inside a membrane, multisets are usually used.

The objects inside the membranes of a P system are transformed by means of *evolution rules*. These are multiset rewriting rules of the form $r_i : u \rightarrow v$, where u and v are multisets of objects. The meaning of the generic rule i is that the multiset u is modified into the multiset v.

Moreover, it is possible to associate a target to v, representing the membrane where the multiset v is placed when the rule is applied. There are three different types of target. If the target is *here*, then the object remains in the region where the rule is executed (usually, this target label is omitted in the systems description). If the target is *out*, then the object is sent out from the membrane containing the rule and placed to the outer region (the environment in the case of skin membrane).

Finally, if the target is in_j, where j is a label of a membrane, then the object is sent into the membrane labelled with j. It is possible to apply this kind of rule, only if the membrane j is placed immediately inside the membrane where the rule is executed.

Starting from an initial configuration (described by a membrane structure containing a certain number of objects and a fixed set of rules), and letting the system evolve, a computation is obtained. A universal clock is assumed to exist: at each step, all rules in all regions are simultaneously applied to all objects which can be the subjects of evolution rules. So doing, the rules are applied in a maximal parallel manner, hence the membranes evolve simultaneously. If no further rule can be applied, the computation halts. The result of a computation is the multiset of objects contained into a previously specified *output membrane* or the environment.

For a complete and extensive overview of P systems, we refer the reader to [18], and to the P Systems Web Page (`http://ppage.psystems.eu`).

2.2 tP Systems

The basic definition of P systems consists of a membrane structure organised in a tree-like structure. In [15], *tP systems* were defined to describe a tissue-like architecture, where cells are placed in the nodes of a (directed) graph, and objects are communicated along the edges of the graph. These communication channels are called synapses. Moreover, the communication of objects is achieved both in a replicative and non-replicative manner, that is, the objects are sent to all the adjacent cells or to only one adjacent cell, respectively.

In general, the structure of a tP system is composed by elementary membranes, namely, each node of the system is represented by a membrane that does not contain other membranes. Furthermore, the communication of objects is allowed, as in standard P systems, only to/from adjacent membranes.

Tissue P systems have been further elaborated, for example in [9] and [20], with recent results about both theoretical properties [1] and applications [13]. The variants of tP systems considered in the literature essentially differ in the mechanisms used to communicate objects between cells. For instance, particular sets of communication rules (i.e., symport and antiport rules) can be assigned to the edges of the graph that defines the structure of the tissue, in order to model the existence of communication channels among the cells [12, 9].

Alternatively, there are evolution-communication tP systems (adopting the terminology introduced in [6]), where the objects produced by particular transformations occurring inside the cells are nondeterministically propagated from one place to another one [14, 2].

2.3 τ-DPP

We recall now the basic definition of the stochastic simulation technique called τ-DPP [7], where the probabilities are associated to the rules, following the method

introduced by Gillespie in [10]. The aim of τ-DPP is to extend the single-volume algorithm of tau-leaping [5], in order to simulate multi-volume systems, where the distinct volumes are arranged according to a specified hierarchy. The structure of the system is required to be kept fixed during the evolution; note that the framework of membrane system we consider satisfies this requirement. Hence, the spatial arrangement of P system is exploited in the τ-DPP description. In particular, τ-DPP has been defined starting from a variant of P systems called dynamical probabilistic P systems (DPP). DPP, presented in [23], exploit the membrane structure of P systems and associate probabilities with the rules, such values vary (dynamically), according to a prescribed strategy, during the evolution of the system. They have been introduced to take into account the stochasticity of the modelled systems and to probe different levels of parallelism of the rules executions. For the formal definitions of DPP and examples of simulated systems, we refer the reader to [22, 21, 4, 3].

There is a difference between these two membrane systems variants: DPP provides only a qualitative description of the analysed system, that is, "time" is not associated to the evolution steps, while τ-DPP is able to give a quantitative description tracing the time-stream of the evolution.

The τ-DPP approach is designed to share a common time increment among all the membranes, used to accurately extract the rules that will be executed in each compartment (at each step). This improvement is achieved using, inside the membranes of τ-DPP, a modified tau-leaping algorithm, which gives the possibility to simulate the time evolution of every volume as well as that of the entire system.

The internal behaviour of the membranes is therefore described by means of a modified tau-leaping procedure. The original method, first introduced in [11], is based on the stochastic simulation algorithm (SSA) presented in [10]. These approaches are used to describe the behaviour of chemical systems, computing the probabilities of the reactions placed inside the system and the length of the step (at each iteration), according to the current system state. While SSA is proved to be equivalent to the Chemical Master Equation (CME), therefore it provides the exact behaviour of the system, the tau-leaping method describes an approximated behaviour with respect to the CME, but it is faster for what concerns the computational time required.

To describe the correct behaviour of the whole system, all the volumes evolve in parallel, through a strategy used to compute the probabilities of the rules (and then, to select the rules that will be executed), and to choose the "common" time increment that will be used to update the system state. The method applied for the selection of the time step length is the following. Each membrane independently computes a candidate time increment (exploiting the tau-leaping procedure), based on its internal state. The smallest time increment among all membranes is then selected and used to describe the evolution of the whole system, during the current iteration. Since all volumes *locally* evolve according to the same time increment, τ-DPP is able to correctly work out the *global* dynamics of the system. Moreover, using the "common" time increment inside the membranes, it is possible to manage

the communication of objects among them. This is achieved because the volumes are naturally *synchronised* at the end of each iterative step, when all the rules are executed.

3 The new variant

In this Section we will present the new variant of tissue P systems, based on the structure definition of basic tP systems and the dynamics description of τ-DPP, in which nodes can have a complex structure hierarchically organised in a tree-like structure. Moreover, in this new variant we will consider dimensions both for membranes and objects, and the rules defined inside each membrane will be enabled only in the case there is sufficient space, for instance, to "create" new objects or to send objects to other membranes. The dimensions considered here can be used in the modelling of biochemical systems where diffusive processes play an important role in the system dynamics and it is important to avoid the unlimited accumulation of objects in a region of finite size.

In order to correctly describe the hierarchy of complex nodes of the system we first need a directed graph representing the topology of the membranes. In particular, undirected edges indicate that the two membranes are placed on the same level (as in the first definition of tP systems). On the other hand, directed edges denote that the target membrane is contained inside the source membrane.

Another directed graph is needed to represent the communication channels among the membranes. Clearly, the arrows of the edges indicate the direction of the (permitted) flow of objects among membranes. Note that, the communication graph can contain edges which are not indicated inside the structure graph. The meaning of these particular edges is to represent communication channels that connect non adjacent membranes. Thanks to these arcs it is possible to create privileged pathways of communication between membranes.

Considering its properties, this new variant can be used to represent (among the other real life systems) reaction-diffusion systems [8], mathematical models which capture the dynamics of a set of substances involved in a number of chemical reactions, considering both the temporal and spatial dimension. In this case, the membrane structure can be used to represent a reaction volume as a sum of a number of finite size subvolumes and the communication graph will describe the diffusion among the considered regions.

3.1 Definition

A tP systems with dimension associated with objects and membranes is defined as

$$\Pi = (\mathcal{V}, \mathcal{T}_G, \mathcal{C}_G, \mathcal{S}, \mathcal{M}, \mathcal{R}, \mathcal{C}, \mathcal{D}_X, \mathcal{D}_V),$$

where:

- $\mathcal{V} = \{V_0, \ldots, V_N\}$ is the set of the volumes V_i of the system, $N \in \mathbb{N}$;
- $\mathcal{T}_G = (\mathcal{V}, A_\mathcal{T})$ is a directed graph representing the topological arrangement of the volumes in $\mathcal{V}$ and $A_\mathcal{T}$ is the set of the arcs $(\mathcal{V}_l, \mathcal{V}_k)$ which describes the inclusion structure of the volumes. It is useful to define the set of the volumes enclosed in V_i as $a_\mathcal{T}(V_i) = \{V_l \; s.t. \; V_l \in \mathcal{V}, \; (V_i, V_l) \in A_\mathcal{T}\}$;
- $\mathcal{C}_G = (\mathcal{V}, A_\mathcal{C})$ is a directed graph representing the connections (channels of communication) among the volumes in $\mathcal{V}$ and $A_\mathcal{C}$ is the set of the arcs $(\mathcal{V}_l, \mathcal{V}_k)$ which describes the existing connections;
- $\mathcal{S} = \{X_1, \ldots, X_M\}$ is the set of molecular species, $M \in \mathbb{N}$, that is, the alphabet of the system;
- $\mathcal{M} = \{M_0, \ldots, M_N\}$, is the set of the multisets occurring inside the membranes $V_0, \ldots, V_N$, representing the internal state of the volumes. The multiset M_i $(0 \leq i \leq N)$ is defined over $\mathcal{S}^*$;
- $\mathcal{R} = \{R_0, \ldots, R_N\}$ is the set of the sets of rules defined in volumes $V_0, \ldots, V_N$, respectively. A rule can be of internal or of communication type (as described below);
- $\mathcal{C} = \{C_0, \ldots, C_N\}$ is the set of the sets of stochastic constants associated to the rules defined in volumes $V_0, \ldots, V_N$.
- $\mathcal{D}_X = \{D_{X_1}, \ldots, D_{X_M}\}$, with $D_{X_j} \in \mathbb{R}^+$, is the set of the dimensions of the molecular species $X_1, \ldots, X_M$, respectively.
- $\mathcal{D}_V = \{D_{V_0}, \ldots, D_{V_N}\}$, with $D_{V_i} \in \mathbb{R}^+$, is the set of the dimensions of the volume $V_0, \ldots, V_N$, respectively.

The multiset M_i, describing the state of volume V_i $(i = 0, \ldots, N)$, is defined as $M_i = (m_0, \ldots, m_M)$ where m_j denotes the number of molecules of the species X_j occurring inside V_i $(j = 0, \ldots, M)$.

Given the internal state M_i of a membrane V_i together with the species volumes in $\mathcal{D}_X$, it is possible to define the occupied volume in V_i as:

$$O(V_i) = \sum_{j=1}^{M} (m_j \cdot D_{X_j}) + \sum_{V_l \in a_\mathcal{T}(V_i)} D_{V_l} \tag{1}$$

Hence, it is possible to define the value of the *free space* in V_i as:

$$F(V_i) = D_{V_i} - O(V_i) \tag{2}$$

Note that, at each rule execution, the free space value has to be updated as $F(V_i) = F(V_i) - \sum_{j=1}^{M} \beta_j \cdot D_{X_j}$ where β_j are the stoichiometric coefficients of the chemical species occurring in the right-hand side of the executed rule.

The sets $R_0, \ldots, R_N$ define the rules occurring inside the membranes of the system. There are two different kind of rules which can be defined inside the volumes V_i: internal and communication rules. Internal rules are used to modify (evolve) the objects involved in their left-hand sides; communication rules send to other membranes the objects occurring in their left-hand sides without modifying them.

Internal rules have the general form $\alpha_1 X_1 + \alpha_2 X_2 + \cdots + \alpha_M X_M \rightarrow \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_M X_M$. Moreover, an internal rule is enabled inside V_i if $F(V_i) - \sum_{j=1}^{M} \beta_j \cdot D_{X_j} \geq 0$. On the contrary, a communication rule, having the general form $\alpha_1 X_1 + \alpha_2 X_2 + \cdots + \alpha_M X_M \rightarrow (\beta_{1,1} X_1 + \cdots + \beta_{M,1} X_M, tgt_1) + (\beta_{1,2} X_1 + \cdots + \beta_{M,2} X_M, tgt_2) + \cdots + (\beta_{1,N} X_1 + \cdots + \beta_{M,N} X_M, tgt_N)$ is enabled inside membrane V_i if, for each volume V_{tgt_k}, $F(V_{tgt_k}) - \sum_{j=1}^{M} \beta_{j,k} D_{X_j} \geq 0$. Note that, communication rules send objects to target volumes which are always different from the source volume.

The sets of stochastic constants $C_0, \ldots, C_N$, associated to the sets of rules $R_0, \ldots, R_N$, are needed to compute the probabilities of the rule applications (also called propensity functions), along with a combinatorial function depending on the left-hand side of the rule [10].

In order to obtain a correct description of the system dynamics, we need to check if a rule r_μ (internal or communicating) is applicable. Therefore, we need to compute the effect of a rule on the free space of the volume affected by the rule. It is clear that a rule can be executed only if the free space of the volume, after the rule application, is greater or equal to zero. The rule applicability is computed differently for internal and communication rules. Given an internal rule occurring inside volume V_i, we need to check if:

$$F(V_i) - \sum_{j=1}^{M} (\beta_j \cdot D_{X_j}) \geq 0$$

For what concerns a communication rule r_μ, we need to check the free space of the targets indicated by the rule:

$$\forall\ tgt_l \text{ of } r_\mu,\ F(V_{tgt_l}) - \sum_{j=1}^{M} (\beta_j \cdot D_{X_j}) \geq 0$$

where the values β_j are the stoichiometric coefficients of the molecular species associated with V_{tgt_l}.

Note that, using a modified version of the tau-leaping algorithm to describe the behaviour of the system, at each iteration step, a number of rules is applied in parallel. Hence, the applicability of the parallel execution of the rules has to be verified in order to update the state of the system.

3.2 The algorithm

We now describe the algorithm used to simulate the evolution of the entire system. Each step is executed *independently* and *in parallel* within each volume V_i ($i = 0, \ldots, N$) of the system. In the following description, the algorithm execution naturally proceeds according to the order of instructions, when not otherwise specified by means of "go to" commands.

Step 1. Initialisation: load the description of volume V_i, which consists of the initial quantities of all object types, the set of rules and their respective stochastic constants, the volume and the objects dimensions.

Step 2. Compute the initial free space of the volume V_i using Equation 2.

Step 3. Compute the propensity function a_μ of each rule $r_\mu \in R_i$, where $\mu = 1, \ldots, l$, and evaluate the sum of all the propensity functions in V_i, $a_0 = \sum_{\mu=1}^{l} a_\mu$. If $a_0 = 0$, then `go to` *step 4*, otherwise `go to` *step 6*.

Step 4. Set τ_i, the length of the step increment in volume V_i, to ∞.

Step 5. Wait for the communication of the smallest time increment $\tau_{min} = \min\{\tau_0, \ldots, \tau_N\}$ among those generated independently inside all volumes $V_0, \ldots, V_N$, during the current iteration, then `go to` *step 14*.

Step 6. Generate the step size τ_i according to the internal state, and select the way to proceed in the current iteration (i.e. SSA-like evolution, tau-leaping evolution with non-critical reactions only, or tau-leaping evolution with non-critical reactions and one critical reaction), using the selection procedure defined in [5].

Step 7. Wait for the communication of the smallest time increment $\tau_{min} = \min\{\tau_0, \ldots, \tau_N\}$ among those generated independently inside all volumes, during the current iteration.

Step 8. According to the evolution strategy of the current iteration:

- if the evolution is SSA-like and the value $\tau_i = \tau_{SSA}$ generated inside the volume is greater than τ_{min}, then `go to` *step 9*;
- if the evolution is SSA-like and $\tau_i = \tau_{SSA}$ is equal to τ_{min}, then `go to` *step 12*;
- if the evolution is tau-leaping with non-critical reactions plus one critical reaction, and $\tau_i = \tau_{nc1c}$ is equal to τ_{min}, then `go to` *step 13*;
- if the evolution is tau-leaping with non-critical reactions plus one critical reaction and $\tau_i = \tau_{nc1c}$ is greater than τ_{min}, then `go to` *step 14*;
- if the evolution is tau-leaping with non-critical reactions only ($\tau_i = \tau_{nc}$), then `go to` *step 14*.

Step 9. Compute $\tau_{SSA} = \tau_{SSA} - \tau_{min}$.

Step 10. Wait for possible communication of objects from other volumes, by means of communication rules. If some object is received, then `go to` *step 16*, otherwise `go to` *step 11*.

Step 11. Set $\tau_i = \tau_{SSA}$ for the next iteration, then `go to` *step 7*.

Step 12. Using the SSA strategy [10], extract the rule that will be applied in the current iteration, then `go to` *step 15*.

Step 13. Extract the critical rule that will be applied in the current iteration.

Step 14. Extract the set of non-critical rules that will be applied in the current iteration.

Step 15. Check if the execution of the selected rules (considering all the volumes) leads to an unfeasible state, namely, there are negative amounts of molecules, or if there is not enough space either inside the volume V_i (for internal rules) or inside the target volumes (for communication rules). If one of these conditions

is satisfied, reduce τ_{min} by half and send the new value to the other membranes, then `go to` *step 8*.

Step 16. If a new value of τ_{min} reduced by half is received, then `go to` *step 8*, otherwise `go to` *step 17*.

Step 17. Update the internal state by applying the extracted rules (both internal and communication) to modify the current number of objects, then check for objects (possibly) received from the other volumes, and finally update the value of the free space $F(V_i)$.

Step 18. If the termination criteria is satisfied, then finish, otherwise `go to` *step 3*.

The algorithm described above is based on the τ-DPP procedure presented in [7], this new version is obtained by considering the dimensions of the objects and membranes and checking if the execution of the selected rules leads to unfeasible states of the system. The original τ-DPP algorithm has been modified to take into account the dimensions of volumes and objects, while the other features introduced in the new variant of tP systems were already (implicitly) considered in the algorithm.

The algorithm begins by loading the initial conditions of the membrane. The next operation consists in the calculation of the free space of the volume and in the computation of the propensity functions (and their sum a_0) in order to check if, inside the membrane, it is possible to execute some reaction. If the sum of the propensity functions is zero, then the value of τ is set to ∞ and the membrane waits for the communication of the smallest τ computed among the other membranes (τ_{min}) in order to synchronise with them; then, it checks if it is the target of some communication rule applied inside the other volumes. These operations are needed in order to properly update the internal state of the membrane.

On the other hand, if the sum of the propensity functions is greater than zero, the membrane will compute a τ value based only on its internal state, following the first part of the original tau-leaping procedure [5]. Besides this operation, the membrane selects the kind of evolution for the current iteration (like the computation of τ, this procedure is executed independently from the other volumes).

The algorithm proceeds to *step 7*, where the membrane receives the smallest τ value computed by the volumes. This will be the common value used to update the state of the entire system. It is necessary to proceed inside every membrane using the same time increment, in order to manage the communication of objects.

At this stage, the membrane knows the length of the time step and the kind of evolution to perform. The next step consists in the extraction of the rules that will be applied in the current iteration. In order to properly extract the rules, several conditions need to be checked.

In the case the membrane is evolving using the SSA strategy: if τ_{min} is the value generated inside itself, then it is possible to extract the rule, otherwise the execution of the rule is not allowed, because the step is "too short". In the next stage, the membrane verifies for possible incoming objects, to update its internal state according to the communication rules (possibly) executed inside other

regions. Finally, if its state is changed (according to some internal or communication rule), then the membrane, in the successive iteration, will compute a new value of τ. On the contrary, the value of the time increment will be the result of the application of *step 9*.

If the evolution strategy corresponds to a tau-leaping step with the application of a set of non-critical reactions and one critical reaction, the algorithm verifies if the value of τ computed by the membrane is equal to τ_{min}. If this is true, the membrane selects the set of non-critical reactions to execute as well as the critical reaction. The execution of the critical reaction is allowed because, here τ_{min} represents the time needed to execute it. Otherwise, the application of the critical reaction is forbidden and the membrane will execute non-critical reactions only.

If the membrane is following the tau-leaping strategy with the execution of non-critical reactions only, τ_{min} is used to extract the rules (from the set of non-critical) to apply in the current iteration.

In the next step, the algorithm checks if the execution of the rules selected inside all volumes of the system leads to negative amounts of the molecular quantities or if the entire set of rules is enabled, that is, the effects of the rules application result in positive values of the free space of each volume. If these conditions are not satisfied, then the set of selected rules cannot be executed, therefore, the value of τ is reduced by half and the algorithm goes back to *step 8* in order to select a new (possibly smaller) set of rules. On the contrary, if the conditions on the set of rules are satisfied, then the system can be updated. Here, every membrane executes the selected rules and updates its state and free space according to both internal and communication rules. This step is executed in parallel inside every membrane, therefore it is possible to correctly manage the "passage" of objects and to synchronise the volumes.

The last step checks if the termination criterion is satisfied in order to stop the simulation. Here, conditions for the termination of the execution are related to the time of the simulation, to the number of iteration executed or to the absence of free space.

4 Test cases

In this section we will present two test cases showing how the properties introduced in the variant of tP systems presented here are useful to describe systems in which the dynamics is influenced by objects and volume size and by the presence of privileged paths for objects movement.

4.1 A reaction-diffusion system

We consider the membrane system Π_1, represented in Fig. 1, where;

- $\mathcal{V} = \{V_0, \ldots, V_9\}$;

- $\mathcal{T}_G = (\mathcal{V}, A_\mathcal{T})$, $A_\mathcal{T} = \{(V_0, V_1), (V_0, V_2), (V_0, V_3), (V_0, V_4), (V_0, V_5), (V_0, V_6), (V_0, V_7), (V_0, V_8), (V_0, V_9)\}$;
- $\mathcal{C}_G = (\mathcal{V}, A_\mathcal{C})$, $A_\mathcal{C} = \{(V_0, V_1), (V_1, V_0), (V_0, V_2), (V_2, V_0), (V_0, V_3), (V_3, V_0), (V_0, V_7), (V_7, V_0), (V_0, V_8), (V_8, V_0), (V_0, V_9), (V_9, V_0), (V_1, V_2), (V_2, V_1), (V_1, V_4), (V_4, V_1), (V_1, V_5), (V_5, V_1), (V_2, V_3), (V_3, V_2), (V_2, V_4), (V_4, V_2), (V_2, V_5), (V_5, V_2), (V_2, V_6), (V_6, V_2), (V_3, V_5), (V_5, V_3), (V_3, V_6), (V_6, V_3), (V_4, V_5), (V_5, V_4), (V_4, V_7), (V_7, V_4), (V_4, V_8), (V_8, V_4)$ $(V_5, V_6), (V_6, V_5), (V_5, V_7), (V_7, V_5), (V_5, V_8), (V_8, V_5), (V_5, V_9), (V_9, V_5), (V_7, V_8), (V_8, V_7), (V_8, V_9), (V_9, V_8)\}$;
- $\mathcal{S} = \{X_1, X_2, X_3\}$;
- $\mathcal{M} = \{M_0, \ldots, M_9\}$, $M_0 = \{X_1^{100}\}$, $M_1 = \{X_1^5, X_2^3\}$, $M_2 = \{X_1^5, X_2^3\}$, $M_3 = \{X_1^5, X_2^3\}$, $M_4 = \{X_2^3\}$, $M_5 = \{X_2^3\}$, $M_6 = \{X_2^3\}$, $M_7 = \{X_2^3\}$, $M_8 = \{X_2^3\}$, $M_9 = \{X_2^3\}$;
- $\mathcal{R} = \{R_0, \ldots, R_7\}$, $R_0 = \{r_{0,0}, \ldots, r_{0,2}\}$, $R_1 = \{r_{1,0}, \ldots, r_{1,3}\}$, $R_2 = \{r_{2,0}, \ldots, r_{2,5}\}$, $R_3 = \{r_{3,0}, \ldots, r_{3,3}\}$, $R_4 = \{r_{4,0}, \ldots, r_{4,5}\}$, $R_5 = \{r_{5,0}, \ldots, r_{5,8}\}$, $R_6 = \{r_{6,0}, \ldots, r_{6,5}\}$, $R_7 = \{r_{7,0}, \ldots, r_{7,5}\}$, $R_8 = \{r_{8,0}, \ldots, r_{8,6}\}$, $R_9 = \{r_{9,0}, \ldots, r_{9,4}\}$
- $\mathcal{C} = \{C_0, \ldots, C_9\}$, $c_{i,j} = 1$ $\forall i \in \{0, \ldots, 9\}, j \in \mathbb{N}$
- $\mathcal{D}_X = \{1, 1, 1\}$;
- $\mathcal{D}_V = \{200, 10, 10, 10, 10, 10, 10, 10, 10, 10\}$

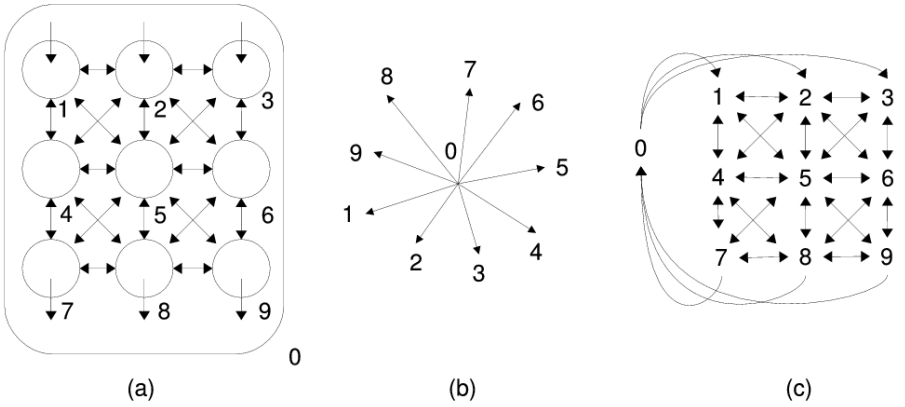

Fig. 1. A membrane system, Π_1, inspired to a reaction volume composed by a number of subvolumes. a) Graphical representation, in which the arrows indicate the communication possibilities; b) topological structure $\mathcal{T}_G$, note that arcs between adjacent nodes are not drawn for clarity; c) communication channels $\mathcal{C}_G$ of the system.

Π_1 can be seen as a reaction-diffusion system composed by 9 regions with the same dimension, $V_1 = V_2 = \cdots = V_9$, enclosed in the environment V_0 (the set of its rules is listed in Tab. 1). The communication possibilities within the regions represent the free diffusion of molecules from the environment to the "top" of the

Table 1. Rules of the membrane system Π_1. The constants of the rules of Π_1 are all set to 1.

Reaction	**Reaction**
$r_{0,0} : X_1 \to (X_1, 1)$	$r_{5,5} : X_1 \to (X_1, 7)$
$r_{0,1} : X_1 \to (X_1, 2)$	$r_{5,6} : X_1 \to (X_1, 8)$
$r_{0,2} : X_1 \to (X_1, 3)$	$r_{5,7} : X_1 \to (X_1, 9)$
$r_{1,0} : X_1 \to (X_1, 2)$	$r_{5,8} : X_1 + X_2 \to (X_1 + X_3, 5)$
$r_{1,1} : X_1 \to (X_1, 4)$	$r_{6,0} : X_1 \to (X_1, 2)$
$r_{1,2} : X_1 \to (X_1, 5)$	$r_{6,1} : X_1 \to (X_1, 3)$
$r_{1,3} : X_1 + X_2 \to (X_1 + X_3, 1)$	$r_{6,2} : X_1 \to (X_1, 5)$
$r_{2,0} : X_1 \to (X_1, 1)$	$r_{6,3} : X_1 \to (X_1, 8)$
$r_{2,1} : X_1 \to (X_1, 3)$	$r_{6,4} : X_1 \to (X_1, 9)$
$r_{2,2} : X_1 \to (X_1, 4)$	$r_{6,5} : X_1 + X_2 \to (X_1 + X_3, 6)$
$r_{2,3} : X_1 \to (X_1, 5)$	$r_{7,0} : X_1 \to (X_1, 0)$
$r_{2,4} : X_1 \to (X_1, 6)$	$r_{7,1} : X_1 \to (X_1, 4)$
$r_{2,5} : X_1 + X_2 \to (X_1 + X_3, 2)$	$r_{7,2} : X_1 \to (X_1, 5)$
$r_{3,0} : X_1 \to (X_1, 2)$	$r_{7,3} : X_1 \to (X_1, 4)$
$r_{3,1} : X_1 \to (X_1, 5)$	$r_{7,4} : X_1 \to (X_1, 8)$
$r_{3,2} : X_1 \to (X_1, 6)$	$r_{7,5} : X_1 + X_2 \to (X_1 + X_3, 7)$
$r_{3,3} : X_1 + X_2 \to (X_1 + X_3, 3)$	$r_{8,0} : X_1 \to (X_1, 0)$
$r_{4,0} : X_1 \to (X_1, 1)$	$r_{8,1} : X_1 \to (X_1, 4)$
$r_{4,1} : X_1 \to (X_1, 2)$	$r_{8,2} : X_1 \to (X_1, 5)$
$r_{4,2} : X_1 \to (X_1, 5)$	$r_{8,3} : X_1 \to (X_1, 6)$
$r_{4,3} : X_1 \to (X_1, 7)$	$r_{8,4} : X_1 \to (X_1, 7)$
$r_{4,4} : X_1 \to (X_1, 8)$	$r_{8,5} : X_1 \to (X_1, 9)$
$r_{4,5} : X_1 + X_2 \to (X_1 + X_3, 4)$	$r_{8,6} : X_1 + X_2 \to (X_1 + X_3, 8)$
$r_{5,0} : X_1 \to (X_1, 1)$	$r_{9,0} : X_1 \to (X_1, 0)$
$r_{5,1} : X_1 \to (X_1, 2)$	$r_{9,1} : X_1 \to (X_1, 5)$
$r_{5,2} : X_1 \to (X_1, 3)$	$r_{9,2} : X_1 \to (X_1, 6)$
$r_{5,3} : X_1 \to (X_1, 4)$	$r_{9,3} : X_1 \to (X_1, 8)$
$r_{5,4} : X_1 \to (X_1, 6)$	$r_{9,4} : X_1 + X_2 \to (X_1 + X_3, 9)$

reaction volume, regions $\{V_1, V_2, V_3\}$, within the 9 regions of the reaction volume itself and from the "bottom", $\{V_7, V_8, V_9\}$, to the environment. Three types of objects of the same dimension are included in the system. X_1 is initially placed outside of the system and once it enters in the reaction volume drives the production of X_3 starting from X_2.

Note that in this example we structured the reaction volume in 9 regions to simplify the description. However, a system analogue to Π_1 with an appropriate number of volumes of the appropriate size can be used to model the entrance of a molecular signal in a cell leading to the activation of a biochemical reaction in the different regions of the cell itself.

In this context the concepts of size and free space play a key role avoiding the unlimited accumulation of objects within a particular volume. Moreover, the use of two distinct graphs to capture the membranes structure and the communication within the system enables the representation of adjacent membranes that do not

communicate, like in the case of $\{V_4, V_5, V_6\}$ that are adjacent to V_0 but do not communicate with it.

In order to clarify how the algorithm handles the checking for the free space during the rules execution, let us consider the potential situation in V_1 at the first step of computation. At this point we have $M_1 = \{X_1^5, X_2^3\}$ and hence the free space is $F(V_1) = 10 - (5 + 3) = 2$. Let us imagine that a τ has been selected such that the set of enabled rules includes $12 \cdot r_{0,0}, 2 \cdot r_{1,0}, 2 \cdot r_{1,1}, 2 \cdot r_{1,2}$, that is $12 \cdot X_1$ should enter and $6 \cdot X_1$ should exit. This situation leads to a negative value of the free space, since $2 < (12-6)$. The value of τ will be updated such that $\tau' = \tau/2$ and let us consider that the new set of enabled rules includes $4 \cdot r_{0,0}, 1 \cdot r_{1,0}, 1 \cdot r_{1,1}, 1 \cdot r_{1,2}$, that is $4 \cdot X_1$ should enter and $3 \cdot X_1$ exit; assuming that there is free space in the target volumes $\{V_2, V_4, V_6\}$ the rules will be executed since $2 \geq 1$.

4.2 A system with preferential communication pathways

In the following example we show how the communication between not adjacent membranes can be used to represent privileged pathways for the communication of objects. We consider the membrane system Π_2, represented in Fig. 2, where:

- $\mathcal{V} = \{V_0, \ldots, V_7\}$;
- $\mathcal{T}_G = (\mathcal{V}, A_\mathcal{T})$, $A_\mathcal{T} = \{V_1 \subset V_0, (V_2, V_3) \subset V_1, (V_4, V_5) \subset V_3, (V_6, V_7) \subset V_5\}$;
- $\mathcal{C}_G = (\mathcal{V}, A_\mathcal{C})$, $A_\mathcal{C} = \{(V_0, V_1), (V_1, V_0), (V_1, V_2), (V_1, V_3), (V_3, V_1), (V_3, V_2), (V_3, V_4), (V_3, V_5), (V_5, V_3), (V_5, V_4), (V_5, V_6), (V_5, V_7), (V_7, V_5), (V_6, V_7)\}$;
- $\mathcal{S} = \{X_1, X_2\}$;
- $\mathcal{M} = \{M_0, \ldots, M_7\}$, $M_0 = \{X_1^{20}, X_2^{20}\}$, $M_3 = M_4 = \ldots = M_7 = \emptyset$;
- $\mathcal{R} = \{R_0, \ldots, R_7\}$, $R_0 = \{r_{0,0}, r_{0,1}\}$, $R_1 = \{r_{1,0}, \ldots, r_{1,4}\}$, $R_2 = \{r_{2,0}\}$, $R_3 = \{r_{3,0}, \ldots, r_{3,2}, \ldots, r_{3,4}\}$, $R_4 = \{r_{4,0}\}$, $R_5 = \{r_{5,0}, \ldots, r_{5,4}\}$, $R_6 = \{r_{6,0}\}$, $R_7 = \{r_{7,0}, \ldots, r_{7,4}\}$
- $\mathcal{C} = \{C_0, \ldots, C_7\}$, $c_{i,j} = 1 \ \forall i \in \{0, \ldots, 7\}, j \in \mathbb{N}$
- $\mathcal{D}_X = \{1, 1\}$;
- $\mathcal{D}_V = \{200, 100, 4, 50, 4, 25, 4, 10\}$

Π_2 is a simplified version of a "cellular" system which describes the "movement" of molecules X_1 and X_2 from the "extracellular space", V_0, to the "nucleus", V_7, of the "cell", represented by the volumes $\{V_1, \ldots, V_7\}$, passing through nested regions of the "cytoplasm", $\{V_1, V_3, V_5\}$, and "microtubules", $\{V_2, V_4, V_6\}$. The rules, listed in Tab. 2, represent the diffusion of X_1 and X_2 through the considered regions. Note that, only X_2 can enter in microtubule region and once it enters in a microtubule region, its movement is possible only towards the nucleus. Conversely, in the other regions, the diffusion is enabled in both direction for both molecules X_1 and X_2.

Hence, it is easy to predict that the evolution of the system will be characterised by a faster movement of molecules of type X_2 from the extracellular space to the nucleus, since they will take advantage from the presence of microtubules that constitute a privileged path towards V_7.

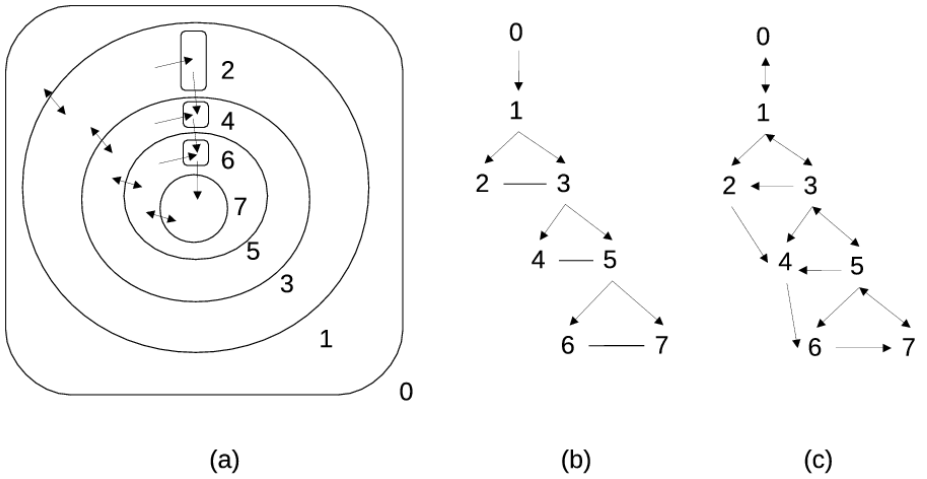

Fig. 2. A membrane system, Π_1, with communication channels between not adjacent membranes. a) Graphical representation, in which the arrows indicate the communication possibilities; b) topological structure $\mathcal{T}_G$; c) communication channels $\mathcal{C}_G$ of the system.

Table 2. Rules of the membrane system Π_2. The constants of the rules of Π_2 are all set to 1.

Reaction
$r_{0,0} : X_1 \to (X_2, 1)$
$r_{0,1} : X_2 \to (X_2, 1)$
$r_{1,0} : X_1 \to (X_1, 0)$
$r_{1,1} : X_2 \to (X_2, 0)$
$r_{1,2} : X_1 \to (X_1, 2)$
$r_{1,3} : X_1 \to (X_1, 3)$
$r_{1,4} : X_2 \to (X_2, 3)$
$r_{2,0} : X_1 \to (X_1, 4)$
$r_{3,0} : X_1 \to (X_1, 1)$
$r_{3,1} : X_2 \to (X_2, 1)$

Reaction
$r_{3,2} : X_1 \to (X_1, 4)$
$r_{3,3} : X_1 \to (X_1, 5)$
$r_{3,4} : X_2 \to (X_2, 5)$
$r_{4,0} : X_1 \to (X_1, 6)$
$r_{5,1} : X_1 \to (X_1, 3)$
$r_{5,2} : X_2 \to (X_2, 3)$
$r_{5,3} : X_1 \to (X_1, 6)$
$r_{5,4} : X_1 \to (X_1, 7)$
$r_{5_5} : X_2 \to (X_2, 7)$
$r_{6,0} : X_2 \to (X_1, 7)$

5 Discussion and future developments

In this paper we presented a new variant of P systems inspired to tP systems and τ-DPP. The novel properties consist in the representation of the membranes structure and the communication within the system with two distinct directed graphs, the possibility to define tissue-like structure where nodes have a complex internal architecture, the association of a size to objects and membranes and the consequent handling of the free space during the system evolution with a new version of the τ-DPP simulation technique.

The introduction of the new properties enables the formalism to be used to model a number of real systems in which, first of all, the unlimited accumulation

of objects within membranes is not possible or, in other words, in which the free space within regions is a critical resource for the system dynamics. In the first test case we shown how the formalism can be used to model a reaction-diffusion system, using the membranes to divide a reaction volume in a series of sub-volumes of finite size.

Moreover, the use of two distinct graphs for describing the membranes structure and the communication within the system provides a formalism with a strong expressive power: indeed it is possible to have communication channels between membranes that are not adjacent and, conversely, it is possible that adjacent membranes do not communicate. The first possibility allows the creation of preferential paths of communication; this feature has been used in the second test case to reproduce the role of microtubules in the protein transport within cells. On the contrary, the second communication strategy has been used to model the first test case. Finally, as already stated above, membranes can have a complex structure hierarchically organised in a tree-like structure (this feature has been used in both test cases).

As a future improvement of this work, we plan to better characterise and study the role of space occupation and diffusion of molecules among the volumes of the modelled systems. Furthermore, the simulation algorithm can be optimised in order to obtain a more efficient procedure and, otherwise, alternative strategies for the rules selection and to handle the rules applicability can be tested.

As a development of the proposed work, we are also studying the computational power of this new variant of P systems, in order to prove if it is computationally (Turing) complete.

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