

Process Algebra with Hooks for Models of Pattern Formation

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Abstract

We introduce Process Algebra with Hooks (PAH). In PAH processes represent different layers of abstraction, from biochemistry to tissue, and special synchronisations via hook actions ensure consistency between these abstractions. There is an explicit representation of geometrical space and the algebra has a stochastic semantics based on functional rates of reactions.

Keywords: process algebra, labelled transition system, pattern formation, geometrical space

1 Introduction

Deep analogies appear to exist between software and biochemical processes, leading to several modelling approaches based on the abstractions of *molecule-as-process*, *species-as-process* or *pathway-as-process* [3]. Existing formalisms have been applied to the modelling of biological systems, such as π -calculus [17,15] and PEPA [10,2], while new ones have been developed for this specific purpose, such as Beta-Binders [14], Bio-PEPA [6], κ -calculus [8], BIOCHAM [4]. Attention has also turned to spatial aspects of behaviour, and there are several approaches that take space into account, usually in the form of topological locations [5,16].

Following this flow of research, we consider models that include a geometrical notion of space [9]. Here we present *process algebra with hooks* (PAH),

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a process algebra designed to capture essential features of models of pattern formation. Our approach is inspired by mathematical models of pattern formation that have their roots in the early work on morphogenesis of Turing [18]. Turing supported the hypothesis that, given an area with identical and uniformly distributed cells, patterns of different phenotypes arise due only to the diffusion and the local reactive activity of the molecules present in the cells. These ideas inspired new models that today are validated by increasing experimental evidence [12]. Additionally, Turing introduced the term *morphogen*, a special molecule whose concentration determines the phenotype of a region in space. Today, we know that this phenotype depends usually on the *absolute* concentration [11] of morphogens and in some cases on the *relative* concentration [13].

Following these concepts, in PAH we use processes to represent different layers of abstraction, e.g. from biochemistry to tissue. A bottom-up synchronisation of these layers via actions called *hooks* ensures the consistency of the abstractions. Moreover, an explicit notion of geometrical space is embedded in the algebra. Other features are borrowed from Bio-PEPA, such as multi-way synchronisation, functional rates and parsimony of the syntax. In this paper we focus mainly on the multi-layer aspect of PAH, rather than the spatial aspect.

Finally, using PAH we produce a *temporary labelled transition system* (temporary LTS), that we call temporary to emphasise that it is not intended to be used directly. The labels on the transitions present actions from every layer of abstraction, so they require to be filtered, to select the layer of abstraction that we are interested in. Eventually, we aim to use action based relations such as a probabilistic version of bisimulation to test whether two systems with different biochemistries form the same set of patterns.

In summary the contributions of this paper are the following:

- syntax of labelled transition semantics of a process algebra featuring geometrical position and layers of abstraction with a biochemical layer being the lowest;
- extensible activities acting on two layers of abstraction;
- actions that include spatial position in Cartesian coordinates or represent transport between positions;
- a listen operator for synchronising processes at different layers of abstraction;
- examples including a model of tissue behaviour that is determined by biochemical reactions involving two positions;
- extension to stochastic labelled transition systems.

The paper is organised as follows. In Section 2 we introduce PAH by

examples, before presenting the formal syntax and semantics in Section 3. In Section 4 we show how to model the biochemical layer in PAH, while an example of the use of PAH is in Section 5. We conclude with discussion related work in Section 6 and conclusions and future work in Section 7. The interested reader will find the stochastic semantics is in Appendix A, additional formal definitions in Appendix B and the details of our formalisation of functional rates in Appendix C.

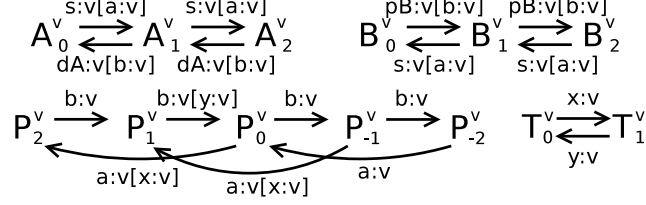
2 Process Algebra with Hooks by Examples

Example 1. Using the *process as level of concentration* abstraction, let M_i^v ($i = 0, \dots, 3$) be the process representing the morphogen M at a position v in space, with concentration level i . Moreover, let T_0^v and T_1^v be processes at a higher layer, representing the possible states (the phenotypes) of the tissue T at position v . Consider the following graphical representation of concurrent processes M_0^v and T_0^v , where arrows represent actions that the processes can perform:

$$M_0^v \begin{array}{c} \xrightarrow{a:v} \\ \xleftarrow{b:v} \end{array} M_1^v \begin{array}{c} \xrightarrow{a:v[x:v]} \\ \xleftarrow{b:v[y:v]} \end{array} M_2^v \begin{array}{c} \xrightarrow{a:v} \\ \xleftarrow{b:v} \end{array} M_3^v \quad T_0^v \begin{array}{c} \xrightarrow{x:v} \\ \xleftarrow{y:v} \end{array} T_1^v$$

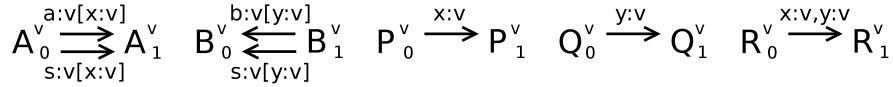
Actions $a:v$ and $b:v$ represent biochemical reactions that increase or decrease, respectively, the concentration of M at position v . The state of T changes when the absolute concentration of M passes a threshold. In this case, the action $x:v$ denotes T_0^v becoming T_1^v , when M_1^v becomes M_2^v ; and conversely T_1^v becomes T_0^v with a $y:v$ action when M_2^v becomes (by a $b:v$) M_1^v . It is important to note that tissue layer actions $x:v$ and $y:v$ synchronise only with *some* instances of biochemical layer actions $a:v$ and $b:v$. These instances represent a concentration threshold and are represented by the different notation $a:v[x:v]$ and $b:v[y:v]$. $x:v$ and $y:v$ are called *hooks*, because they link actions on different layers of abstraction bottom-up. $a:v$ and $x:v$ are indeed the same action, interpreted from two different layers of abstraction. They carry different but complementary pieces of information: $a:v$ means the biochemical reaction $R_{a:v}$ has happened, while $x:v$ means a change at the tissue layer has been triggered. Note, we do not represent the execution of $a:v[x:v]$ as an interleaving of the action names $a:v$ and $x:v$. Instead, $a:v[x:v]$ generates a single transition of the form $M_1^v \triangleleft_{x:v,y:v} T_0^v \xrightarrow{a:v,x:v[x:v]} M_2^v \triangleleft_{x:v,y:v} T_1^v$, which carries the entire information of what happened. The *listen* operator $\triangleleft_{x:v,y:v}$ composes processes on different layers of abstraction that can synchronise on actions in the set $\{x:v, y:v\}$. This operator is not commutative: the process on the left is at a lower layer of abstraction.

Example 2. More complex relations between biochemistry and tissue can be described. In this example, the state change of T is triggered when the concentration of morphogen A surpasses the concentration of morphogen B. We define additional *utility process* P_i to represent the difference between the concentration levels of A and B.



A can degrade ($dA:v$), B can be produced ($pB:v$), while both A and B can synchronise ($s:v$) so that a level of B is converted into a level of A. P_i^v represents the difference $A-B$, while $a:v$ and $b:v$ actions represent events that make this difference increase by two and decrease by one respectively. An example of a transition is $((A_1^v \boxtimes_{s:v} B_2^v) \triangleleft_{a:v,b:v} P_{-1}^v) \triangleleft_{x:v,y:v} T_0^v \xrightarrow{s:v,a:v,x:v[a:v,x:v]} ((A_2^v \boxtimes_{s:v} B_1^v) \triangleleft_{a:v,b:v} P_1^v) \triangleleft_{x:v,y:v} T_1^v$. The parallel operator \boxtimes composes processes at the same layer of abstraction that can synchronise on actions in the set $\{s:v\}$.

Example 3. If a layer of abstraction triggers more than one hook, the resulting set of hooks can be caught *in sequence* by multiple listeners or *in parallel* by a single listener. Consider the following processes:



Given these processes, two possible examples of transitions are $((A_0^v \boxtimes_{s:v} B_1^v) \triangleleft_{x:v} P_0^v) \triangleleft_{y:v} Q_0^v \xrightarrow{s:v,x:v,y:v[x:v,y:v]} ((A_1^v \boxtimes_{s:v} B_0^v) \triangleleft_{x:v} P_1^v) \triangleleft_{y:v} Q_1^v$ and $(A_0^v \boxtimes_{s:v} B_1^v) \triangleleft_{x:v,y:v} R_0^v \xrightarrow{s:v,x:v,y:v[x:v,y:v]} (A_1^v \boxtimes_{s:v} B_0^v) \triangleleft_{x:v,y:v} R_1^v$, which represent hook synchronisations in sequence and in parallel respectively.

Example 4. The positioning of hooks on actions at the biochemical layer simplifies the construction of utility processes and is particularly useful when geometrical space is considered as a grid of locations. Let A_n^e denote the process representing a concentration level n of species A at position e . Concentration can migrate to and from the position e and many different transport actions will have the same effect of lowering or increasing the concentration at one position in space, as shown in the diagram in Figure 1. For example, A can decrease a level of concentration, from A_n^e to A_{n-1}^e , through a transport action of the form $t:(e \rightarrow s)$, $s \in \{b, d, f, h\}$. t is the action name, and e and s are positions. $(e \rightarrow s)$ denotes transport from position e to position s . At position s , a process A_m^s will synchronise and become A_{m+1}^s . If we want to

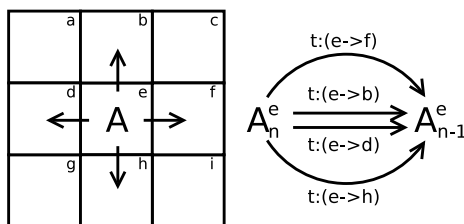


Fig. 1. Example 4: graphical representation of transport actions of process A_n^e .

denote that a threshold is crossed when passing from level n to $n - 1$ of A at e , we can add a hook to the four transport actions, that for example become $t:(e \rightarrow s)[y:v]$.

As an aid to the reader, we conclude this introduction with an explanation of the terminology of actions and their composition. So far, we have been using actions of the kind $a:v[x:v]$ or $b:v$. a , b and x are *action names*, v is a location and the compositions of action names and locations, e.g. $b:v$, are called *actions*. A set of actions $\{a:v, b:s, \dots\}$ is called an *activity*. In fact, processes can perform only what we call an *extensible activity*, written $\mathcal{A}[\mathcal{H}]$, where \mathcal{A} and \mathcal{H} are activities. If \mathcal{H} is empty, a short hand notation for $\mathcal{A}[\mathcal{H}]$ is \mathcal{A} . To simplify the notation, we omit the curly brackets $\{$ and $\}$ when this does not generate ambiguity. Finally, when we write $a:v[x:v]$ we mean the extensible activity composed of two activities, both singletons, while when we write $b:v$ we mean the extensible activity composed of two activities, where the first is a singleton and the second is empty and so omitted.

3 Process Algebra with Hooks

Process algebras afford a richer modelling and analysis paradigm than traditional differential equations by offering formal, executable models as well as comparison of models by relations, e.g. simulation and bisimulation.

In this paper we present a new process algebra, PAH. Due to space limitations we concentrate here on the syntax, semantics and examples of use. While we do not define relations here, the reader should bear in mind our overarching motivation for this algebra is comparing systems with different underlying biochemistries.

The distinctive features of the syntax are: extensible activities, acting on two layers of abstraction, actions that include spatial position or transport between positions and a listen operator that synchronises processes at different layers of abstraction. In addition, there are the standard operators such as parallel composition, prefix and choice.

We now define PAH formally.

Syntax of PAH. The syntax of PAH is defined as:

$$\begin{aligned}
 S &::= nil \mid \mathcal{L}'[\mathcal{L}''].C^v \mid S + S & P &::= P \underset{\mathcal{L}}{\boxtimes} P \mid P \underset{\mathcal{L}'}{\triangleleft} C^v \mid C^v \\
 \mathcal{L} &::= \emptyset \mid \mathcal{L}' & \mathcal{L}' &::= a:m \mid a:m, \mathcal{L}' & \mathcal{L}'' &::= \emptyset \mid a:m \\
 m &::= v \mid (v \rightarrow v) & v &::= (z, z, z) & C^v &\triangleq S
 \end{aligned}$$

where:

- $S \in \mathbb{P}_s$ and $P \in \mathbb{P}_m$ are respectively the *sequential component*, used to represent the behaviour of biochemical species or of higher layers of abstraction, and the *model component*, that represents the state of the model. \mathbb{P}_s is the set of sequential components while \mathbb{P}_m is the set of model components. C^v is a constant, with $C^v \in \mathbb{P}_c \subseteq \mathbb{P}_m$, where \mathbb{P}_c is the set of constants. Sequential and model components are in general referred to as components or *processes* and form the set of processes $\mathbb{P} = \mathbb{P}_m \cup \mathbb{P}_s$;
- $a \in \mathbb{A}$, $\mathbb{A} = \{a, b, c, \dots\}$, is an action name belonging to \mathbb{A} ;
- $a:m \in Act$, $Act = \{a:m_1, b:m_2, c:m_3, \dots\}$, is an action belonging to the set of actions Act . A set of actions $\mathcal{A} \subseteq Act$ is also called an *activity*;
- m is either the position v used to identify the spatial position in three Cartesian coordinates (z, z, z) , $z \in \mathbb{Z}$, of a constant or an action, or the pair of positions $(v \rightarrow v)$ of transport actions;
- nil is the deadlock process. $\mathcal{L}, \mathcal{L}', \mathcal{L}''$ are sets of actions ($\mathcal{L}, \mathcal{L}', \mathcal{L}'' \subseteq Act$), \mathcal{L}' is a non empty set and \mathcal{L}'' is either empty or a singleton set;
- $\mathcal{L}'[\mathcal{L}''] \in Ext$, $Ext = \{\mathcal{A}[\mathcal{H}] \mid \mathcal{A}, \mathcal{H} \subseteq Act\}$, is an *extensible activity* belonging to the set of extensible activities Ext . Given $\mathcal{A}[\mathcal{H}] \in Ext$, \mathcal{A} is a set of *regular actions* and \mathcal{H} is a set of *hooks*.
- $\mathcal{A}[\mathcal{H}].C^v$ is the prefix of an extensible activity to a constant;
- $S + S$ is the choice between sequential components;
- $P \underset{\mathcal{L}}{\boxtimes} P$ is the cooperation of model components, synchronising on the actions in \mathcal{L} ;
- $P \underset{\mathcal{L}'}{\triangleleft} C^v$ is the cooperation of model components synchronising between layers of abstraction on the actions in \mathcal{L} . Process C^v is a *listener* of actions in P , which it can synchronise with or ignore;
- $C^v \triangleq S$ is a constant definition. The sequential component S captures the behaviour of the constant C^v .

Given $\mathcal{A}[\mathcal{H}] \in Ext$, if $\mathcal{H} = \emptyset$, $\mathcal{A}[\mathcal{H}]$ can be written \mathcal{A} .

Semantics of PAH. The semantics of PAH is given by a *temporary LTS* $\mathfrak{L}_u = (\mathbb{P}_m, Act, \rightarrow_u)$, where \mathbb{P}_m is the set of model components, Act is the set of actions and \rightarrow_u is a transition relation such that $\rightarrow_u \subseteq \mathbb{P}_m \times Ext \times \mathbb{P}_m$. \mathfrak{L}_u is defined by the following derivation rules:

Prefix

$$\frac{}{\mathcal{A}[\mathcal{H}].C^v \xrightarrow{\mathcal{A}[\mathcal{H}]} C^v}, \quad \mathcal{A}[\mathcal{H}] \in Ext$$

Choice Left

$$\frac{S_1 \xrightarrow{\mathcal{A}[\mathcal{H}]} C_3^v}{S_1 + S_2 \xrightarrow{\mathcal{A}[\mathcal{H}]} C_3^v}$$

Cooperation Left

$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{H}]} P_3}{P_1 \underset{\mathcal{L}}{\boxtimes} P_2 \xrightarrow{\mathcal{A}[\mathcal{H}]} P_3 \underset{\mathcal{L}}{\boxtimes} P_2}, \quad \mathcal{A} \cap \mathcal{L} = \emptyset$$

Regular Cooperation

$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{E}]} P_3 \quad P_2 \xrightarrow{\mathcal{B}[\mathcal{F}]} P_4}{P_1 \underset{\mathcal{L}}{\boxtimes} P_2 \xrightarrow{\mathcal{A} \cup \mathcal{B}[\mathcal{E} \cup \mathcal{F}]} P_3 \underset{\mathcal{L}}{\boxtimes} P_4}, \quad \mathcal{A} \cap \mathcal{B} \cap \mathcal{L} \neq \emptyset$$

Hook Synchronisation

$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{E}]} P_2 \quad C_1^v \xrightarrow{\mathcal{B}[\mathcal{F}]} C_2^v}{P_1 \underset{\mathcal{L}}{\triangleleft} C_1^v \xrightarrow{\mathcal{A} \cup \mathcal{B}[\mathcal{E} \cup \mathcal{F}]} P_2 \underset{\mathcal{L}}{\triangleleft} C_2^v}, \quad \mathcal{B}[\mathcal{F}] \text{ cond}$$

$\mathcal{B}[\mathcal{F}] \text{ cond}$: given $C_1^v \triangleq \mathcal{B}_1[\mathcal{F}_1].C_1^v + \mathcal{B}_2[\mathcal{F}_2].C_2^v + \dots + \mathcal{B}_n[\mathcal{F}_n].C_n^v$, let \mathcal{B} be a \mathcal{B}_i in $\mathcal{B}_1, \mathcal{B}_2, \dots, \mathcal{B}_n$ such that $\mathcal{B}_i \subseteq \mathcal{E}$ and $\mathcal{B}_i \subseteq \mathcal{L}$ (i.e. $\mathcal{B}_i \subseteq \mathcal{E} \cap \mathcal{L}$) and there is no \mathcal{B}_j in $\mathcal{B}_1, \mathcal{B}_2, \dots, \mathcal{B}_n$ with larger cardinality than \mathcal{B}_i such that $\mathcal{B}_j \subseteq \mathcal{E} \cap \mathcal{L}$. We define this formally in Definition B.1.

As an example of hook synchronisation, consider the following sequential components, where positions are omitted to improve readability:

$$\begin{aligned} A &\triangleq x[a].A & B &\triangleq x[b].B & C &\triangleq x[c].C \\ Q_0 &\triangleq a.Q_1 + a, b.Q_2 + a, b, d.Q_3 \end{aligned}$$

The transition $(A \underset{x}{\boxtimes} B \underset{x}{\boxtimes} C) \underset{a, b, c}{\triangleleft} Q_0 \xrightarrow{x, a, b[a, b, c]} (A \underset{x}{\boxtimes} B \underset{x}{\boxtimes} C) \underset{a, b, c}{\triangleleft} Q_2$, is performed because, although $\{a\} \neq \{x\}$ and $\{a\} \subseteq \{a, b, c\} \cap \{a, b, c\}$, Q_0 cannot become Q_1 because $\{a, b\} \neq \{x\}$, $\{a, b\} \subseteq \{a, b, c\} \cap \{a, b, c\}$ and $|\{a, b\}| > |\{a\}|$. Then Q_0 can become Q_2 , because although $|\{a, b, d\}| > |\{a, b\}|$, we also have that $\{a, b, d\} \not\subseteq \{a, b, c\} \cap \{a, b, c\}$.

Well-formed PAH model. We now introduce additional definitions, necessary to define a well-formed PAH model.

Definition 3.1 *Biochemical Species.* The set *Species* is the set of biochemical

species. Every biochemical species $S \in \text{Species}$ is associated with one or more constants, the *biochemical processes*, which represent different levels of concentration for S .

Definition 3.2 *Functions species and level.* “species: $\mathbb{P}_c \rightarrow \text{Species}$ ” is the function that given a constant C^v returns the species S it is associated with. If C^v is not associated with a biochemical species, $\text{species}(C^v)$ returns \perp . Similarly, “level: $\mathbb{P}_c \rightarrow \mathbb{N}$ ”, is the function that converts processes in their corresponding level of concentration. In analogy with the species function, $\text{level}(C^v)$ returns \perp if C^v is not associated with a biochemical species.

Definition 3.3 *Biochemical Actions.* The set $\text{BioAct} \subseteq \text{Act}$ is the set of biochemical actions.

Definition 3.4 *Well formed PAH model.* A PAH model is well formed if the following conditions are met:

- in the sequential component $\mathcal{A}[\mathcal{H}].C^v$, if \mathcal{A} contains a biochemical action $a:m$, then $\mathcal{A} = \{a:m\}$;
- species consistency, i.e. if a constant C_1^v changes to C_2^v after executing an extensible activity $\mathcal{A}[\mathcal{H}]$, then $\text{species}(C_1^v) = \text{species}(C_2^v)$;
- hooks never contain biochemical actions;
- the lowest layer of abstraction contains biochemical processes and there is only one process for each species in the model.

We define this formally in Definition B.2.

Filtered LTS. The LTS \mathfrak{L}_u is called temporary because it is not intended to be used directly. Given a transition $P \xrightarrow{\mathcal{A}[\mathcal{H}]} Q$, the label $\mathcal{A}[\mathcal{H}]$ has to be filtered, removing the hooks and filtering the set of regular actions \mathcal{A} . In particular, \mathcal{A} contains several actions, but they might be just the same action, seen from different layers of abstraction. In the *filtered* system, depending on which layer of abstraction is to be considered, only those actions belonging to that layer will be kept on the label.

The following curried function is used to filter the temporary LTS:

$$\text{filter} : 2^{\text{Act}} \longrightarrow (2^{\mathbb{P}_m \times \text{Ext} \times \mathbb{P}_m} \longrightarrow 2^{\mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{P}_m})$$

Given a set of actions \mathcal{T} , which contains actions relative to a specific layer of abstraction, the function $\text{filter}(\mathcal{T})$ replaces each transition $(P, \mathcal{A}[\mathcal{H}], Q)$ with a transition (P, \mathcal{B}, Q) , where \mathcal{B} is the set intersection of \mathcal{T} and \mathcal{A} . If such intersection is empty, \mathcal{B} is equal to $\{\tau\}$, where τ is the hidden action. Function filter is defined formally in Definition B.3.

Definition 3.5 *Filtered LTS.* Given a temporary LTS $\mathfrak{L}_u = (\mathbb{P}_m, \text{Act}, \rightarrow_u)$ and a set of actions \mathcal{T} , the *filtered* LTS $\mathfrak{L}_p = (\mathbb{P}_m, \text{Act}, \rightarrow_p)$, with $\rightarrow_p \subseteq \mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{P}_m$, is given by $(\mathbb{P}_m, \text{Act}, \text{filter}(\mathcal{T})(\rightarrow_u))$.

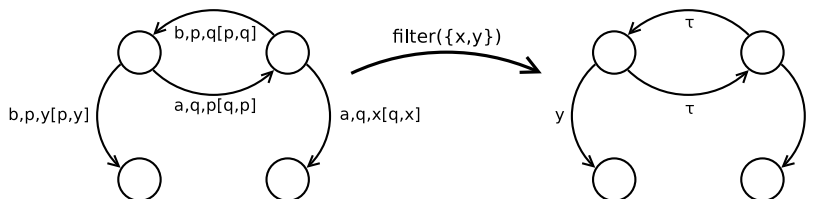


Fig. 2. A temporary labelled transition system (left) is filtered, removing hooks and labels that are not in the set $\{x, y\}$ (right).

An example of LTS filtering is shown in Figure 2.

Stochastic semantics. We aim to formalise models of pattern formation where patterns arise due to biochemical reactions and diffusion. In order to provide accurate quantitative predictions, we developed a stochastic semantics for PAH, based on functional rates. This means that we can derive rates for the transitions of the LTS from arbitrary kinetics laws. The interested reader can find the stochastic semantics of PAH in Appendix A.

4 Abstraction of Biochemistry

PAH has been designed to model biochemical interactions localised in space, using the *processes as levels of concentration* abstraction. The concentration of each molecule S is divided in N_S levels ($N_S + 1$ with 0), with a common step size or granularity h . S has a maximum concentration M_S , with $h = M_S/N_S$. Given two consecutive levels n and $n + 1$, a concentration in the range $(h \cdot n, h \cdot (n + 1)]$ is represented by the discrete level $n + 1$. As a consequence, 0 is not considered a level, but it represents the absence of concentration.

Geometrical space is divided into *slots* of the same shape and volume, in a grid-like manner, where each slot is identified by a position $v = (i, j, k)$, with $(i, j, k) \in \mathbb{Z}^3$. Slots are rectangular parallelepipeds with edges of length Δx , Δy and Δz . Given an origin of Cartesian axes $(0,0,0)$, the Cartesian position of a corner of a slot is given by $(i \cdot \Delta x, j \cdot \Delta y, k \cdot \Delta z)$. For example, with respect to the dimension x , boundaries of slot i are at positions $i \cdot \Delta x$ and $(i + 1) \cdot \Delta x$. Each species S is identified by a position v of the slot where it is located, written as S^v . The concentration of a species is considered uniformly distributed within a slot.

Biochemical reactions are identified by a name $a \in \mathbb{A}$ and by a position v where it takes place, or a transition between positions $v \rightarrow v'$ if it is a transport reaction.

We formalise the concentration of a species S^v using $N_S + 1$ constant processes $S_0^v, S_1^v, \dots, S_{N_S}^v$, which represent different levels of concentration of S^v and from which the concentration can be computed simply by $\text{level}(S_n^v) \cdot h$. We use one process to represent a concentration level for each location where a species S can be present.

5 A more detailed example

Consider a portion of tissue, divided into two adjacent slots with positions v and s respectively. In these slots, two species A and B can be produced or can degrade, A can turn into B and B into A. Moreover, A and B can migrate freely between the two slots. To indicate, for example, molecule A in slot v we use the notation A^v . In chemical form, the reactions of the system, and corresponding actions, are ($i, j \in \{v, s\}, i \neq j$):

Reaction	Chemical	Action	Reaction	Chemical	Action
R_1 :	$\rightarrow A^i$	$r1:i$	R_5 :	$A^i \rightarrow B^i$	$r5:i$
R_2 :	$A^i \rightarrow$	$r2:i$	R_6 :	$B^i \rightarrow A^i$	$r6:i$
R_3 :	$\rightarrow B^i$	$r3:i$	R_7 :	$A^i \rightarrow A^j$	$tA:(i \rightarrow j)$
R_4 :	$B^i \rightarrow$	$r4:i$	R_8 :	$B^i \rightarrow B^j$	$tB:(i \rightarrow j)$

We use process M_i^j to indicate that a species $M \in \{A, B\}$ at position j has a concentration level $i \in \{0, 1, 2\}$. In this example we want to express that an action happens at the tissue layer, when both A and B reach level two. We use an utility process P_i^j ($j \in \{v, s\}, i \in \{0, 1, 2\}$), which counts how many A or B are at level two in position j . P_0^j denotes none of them, P_1^j denotes one of them and P_2^j means both. Finally, we use a process T_i^j to represent the state of the slot (tissue layer) in position j , which can be *inactive* (T_0^j) or *active* (T_1^j). For $i, j \in \{v, s\}, i \neq j$, the PAH model presents the following constant definitions:

$$\begin{aligned}
 A_0^i &\triangleq r1:i.A_1^i + r6:i.A_1^i + tA:(j \rightarrow i).A_1^i \\
 A_1^i &\triangleq r1:i[p:i].A_2^i + r6:i[p:i].A_2^i + r2:i.A_0^i + r5:i.A_0^i + tA:(j \rightarrow i)[p:i].A_2^i + \\
 &tA:(i \rightarrow j).A_0^i \\
 A_2^i &\triangleq r2:i[q:i].A_1^i + r5:i[q:i].A_1^i + tA:(i \rightarrow j)[q:i].A_1^i \\
 B_0^i &\triangleq r3:i.B_1^i + r5:i.B_1^i + tB:(j \rightarrow i).B_1^i \\
 B_1^i &\triangleq r3:i[p:i].B_2^i + r5:i[p:i].B_2^i + r4:i.B_0^i + r6:i.B_0^i + tB:(j \rightarrow i)[p:i].B_2^i + \\
 &tB:(i \rightarrow j).B_0^i \\
 B_2^i &\triangleq r4:i[q:i].B_1^i + r6:i[q:i].B_1^i + tB:(i \rightarrow j)[q:i].B_1^i \\
 P_0^i &\triangleq p:i.P_1^i \quad P_2^i \triangleq q:i[y:i].P_1^i \\
 P_1^i &\triangleq q:i.P_0^i + q:i, p:i[\emptyset].P_1^i + p:i[x:i].P_2^i \\
 T_0^i &\triangleq x:i.T_1^i \quad T_1^i \triangleq y:i.T_0^i
 \end{aligned}$$

The initial state of the model is given by the following model component:

$$\begin{aligned}
 &(((A_0^v \boxtimes_{r5:v, r6:v} B_0^v) \triangleleft_{p:v, q:v} P_0^v) \triangleleft_{x:v, y:v} T_0^v) \boxtimes_{tA:(i \rightarrow j), tB:(i \rightarrow j)} \\
 &(((A_0^s \boxtimes_{r5:s, r6:s} B_0^s) \triangleleft_{p:s, q:s} P_0^s) \triangleleft_{x:s, y:s} T_0^s)
 \end{aligned}$$

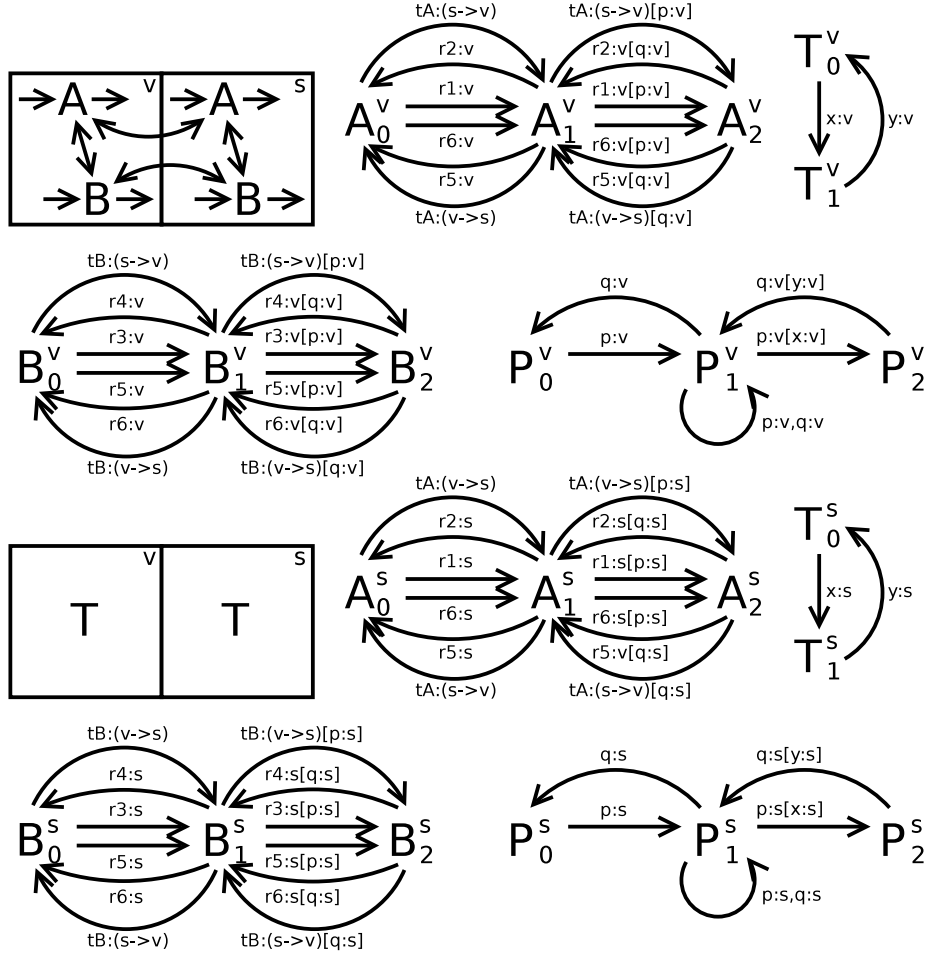


Fig. 3. Graphical representation of the processes.

A graphical representation of these processes is depicted in Figure 3. In this example one can see how hooks are placed at concentration thresholds, linking the biochemical layer formed by molecules A and B with higher layers. Higher layers can have biological meaning, such as processes T_i^j , representing tissue phenotypes. Alternatively, they can be intermediate layers, that help glue other layers together, such as processes P_i^j .

6 Related Work

As we have already mentioned, this work is related to other process algebras, PEPA [10] and Bio-PEPA [6]. An alternative way to implement hook synchronisation might be using priority of actions in PEPA. Biochemical actions would have the lowest priority, while actions with higher priority could be used to keep higher layers consistent with the biochemistry. There are two disadvantages with this approach. First, actions with high priority would interleave

with biochemical actions or with actions with even higher priority generating extra intermediate states that could be avoided *a priori* using hook synchronisation. Second, removing these extra states would result in removing all actions with the exception of the biochemical ones. Although the processes representing higher layers of abstraction would be consistent, we would lose the capability of performing action based equality checking between models, with respect to selected layers of abstraction.

The concept of using processes to “listen” to actions in a process algebra model was first introduced with *Probes* [1,7]. In this setting, processes (probes) are constructed using regular expressions and are used to query a model. Special *start* and *stop* labels are added to certain actions to indicate entering and leaving states that satisfy the query. Although there are analogies, our approach does not aim to query the system, but to formalise and characterise the way we can observe its behaviour from different layers of abstraction. Moreover, regular expressions might in some cases not be powerful enough to construct the processes that we need to listen to biochemical actions.

7 Conclusions and Future Work

A novel process algebra, PAH, that aims to formalise models of pattern formation has been presented. Its main feature is the ability to model different layers of abstractions, by an action synchronisation that works bottom-up. It also includes an explicit representation of geometrical space and transport between locations.

In PAH, the lowest layer of abstraction is the biochemistry, where processes denote levels of concentration of species. Processes at higher layers denote tissue or any other layer of abstraction. At all levels there is an explicit notion of location in geometrical space. The semantics is given by a labelled transition system, which is then filtered to provide a more concise form, without hooks, tailored to a given layer of abstraction.

We have demonstrated, through examples, how biochemical reactions at a lower layer can trigger behaviour at a higher layer when a concentration threshold is crossed, or when the difference between two concentrations reaches a threshold, and when sets of hooks can trigger behaviour in sequence or in parallel.

In this paper, the explicit notion of space in the syntax has a limited function, such as improving comprehensiveness of model descriptions. In further development of PAH we plan to use this notation in the context of spatial modifications, such as tissue growth. Future work also includes defining equivalences or other relations between models so we can determine, for example, when two different biochemistries lead to the same patterns.

Acknowledgements. Andrea Degasperi is supported by a Lord Kelvin/Adam Smith Scholarship of the University of Glasgow and by the EPSRC funded [SIGNAL project](#).

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A Stochastic Semantics

To define a stochastic version of PAH, we need to associate a rate with each transition of the temporary LTS. The rate is a positive real number that is the parameter of the exponential distribution of the time necessary for a transition, i.e. an action, to happen.

Since the rates of biochemical reactions are usually functions of the concentration of species, we employ *functional rates*. Every biochemical action $a:m \in \text{BioAct}$ is associated with a functional rate $f_{a:m}$. We define as \mathbb{F} the set of functional rates such that $f_{a:m} \in \mathbb{F}$.

The details of how a functional rate is evaluated are in Appendix C. Here, it is sufficient to say that a rate $r_{a:m}$ is evaluated from a functional rate $f_{a:m} \in \mathbb{F}$ and an environment Γ , which is a function that associates variable names with values. We define it as “ $\Gamma: \text{Names} \rightarrow \mathbb{R}$ ”, with $\text{Names} = \mathbb{C} \cup \text{Species}$, $\mathbb{C} \subseteq \text{Names}$ the set of constant names, $\text{Species} \subseteq \text{Names}$ the set of biochemical species and $\mathbb{C} \cap \text{Species} = \emptyset$.

We now introduce the stochastic semantics of PAH. With respect to the original semantics, derivation rules *Prefix*, *Choice Left* and *Choice Right* are unaltered. These are the modified rules:

Constant

$$\frac{S_1 \xrightarrow{A[\mathcal{H}]} C_2^v}{C_1^v \xrightarrow{A[\mathcal{H},\Gamma]} C_2^v}, \quad \begin{array}{l} C_1^v \triangleq S_1 \wedge \text{if species}(C_1^v) \in \text{Species} \text{ then} \\ \Gamma = \{(\text{species}(C_1^v), \text{levels}(C_1^v) \cdot h)\} \text{ else } \Gamma = \emptyset \end{array}$$

Cooperation Left

$$\frac{P_1 \xrightarrow{A[\mathcal{H},\Gamma]} P_3}{P_1 \boxtimes_{\mathcal{L}} P_2 \xrightarrow{A[\mathcal{H},\Gamma]} P_3 \boxtimes_{\mathcal{L}} P_2}, \quad \mathcal{A} \cap \mathcal{L} = \emptyset$$

Cooperation Right

$$\frac{P_2 \xrightarrow{A[\mathcal{H},\Gamma]} P_4}{P_1 \boxtimes_{\mathcal{L}} P_2 \xrightarrow{A[\mathcal{H},\Gamma]} P_1 \boxtimes_{\mathcal{L}} P_4}, \quad \mathcal{A} \cap \mathcal{L} = \emptyset$$

Regular Cooperation

$$\frac{P_1 \xrightarrow{A[\mathcal{E},\Gamma_1]} P_3 \quad P_2 \xrightarrow{B[\mathcal{F},\Gamma_2]} P_4}{P_1 \boxtimes_{\mathcal{L}} P_2 \xrightarrow{(A \cup B[\mathcal{E} \cup \mathcal{F}], \Gamma_1 \cup \Gamma_2)} P_3 \boxtimes_{\mathcal{L}} P_4}, \quad \mathcal{A} \cap \mathcal{B} \cap \mathcal{L} \neq \emptyset$$

Hook Ignore

$$\frac{P_1 \xrightarrow{A[\mathcal{H},\Gamma]} P_2}{P_1 \triangleleft_{\mathcal{L}} C^v \xrightarrow{A[\mathcal{H},\Gamma]} P_2 \triangleleft_{\mathcal{L}} C^v}, \quad \mathcal{H} \cap \mathcal{L} = \emptyset$$

Hook Synchronisation

$$\frac{P_1 \xrightarrow{(\mathcal{A}[\mathcal{E}], \Gamma_1)} P_2 \quad C_1^v \xrightarrow{(\mathcal{B}[\mathcal{F}], \Gamma_2)} C_2^v}{P_1 \triangleleft_{\mathcal{C}} C_1^v \xrightarrow{(\mathcal{A} \cup \mathcal{B}[\mathcal{E} \cup \mathcal{F}], \Gamma_1 \cup \Gamma_2)} P_2 \triangleleft_{\mathcal{C}} C_2^v}, \quad \mathcal{B}[\mathcal{F}] \text{ cond}$$

The side condition $\mathcal{B}[\mathcal{F}] \text{ cond}$ is unaltered. Notice that C_1^v is on an higher layer of abstraction, so, if the model is well-formed, $\text{species}(C_1^v) = \perp$ and $\Gamma_2 = \emptyset$.

A *stochastic temporary LTS* is defined as $\mathfrak{L}_{s,u} = (\mathbb{P}_m, \text{Act}, \rightarrow_{s,u})$, where the transition relation $\rightarrow_{s,u} \subseteq \mathbb{P}_m \times \text{Ext} \times 2^{\text{Species} \times \mathbb{R}} \times \mathbb{P}_m$ is the minimal relation that satisfies the stochastic semantics of PAH.

The filtering of a stochastic temporary LTS is used both to select the actions on the labels relative to a layer of abstraction of interest, and to compute the rate of the transitions. In analogy with the non stochastic case, we use the following curried function:

$$\text{filter}_s : 2^{\mathbb{C} \times \mathbb{R}} \longrightarrow (2^{\text{Act}} \longrightarrow (2^{\mathbb{P}_m \times \text{Ext} \times 2^{\text{Species} \times \mathbb{R}} \times \mathbb{P}_m} \longrightarrow 2^{\mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{R} \times \mathbb{P}_m}))$$

Given an environment $\Gamma \subseteq \mathbb{C} \times \mathbb{R}$ and a set of actions \mathcal{T} , which contains actions relative to a specific layer of abstraction, the function $\text{filter}_s(\Gamma)(\mathcal{T})$ replaces each transition $(P, \mathcal{A}[\mathcal{H}], \Gamma', Q)$, with a transition (P, \mathcal{B}, r, Q) , where \mathcal{B} is the set intersection of \mathcal{T} and \mathcal{A} and r is the rate of the transition. Assuming a well-formed PAH model, \mathcal{A} contains exactly one biochemical action $a:m$, with associated functional rate $f_{a:m}$. Rate r is computed from $f_{a:m}$ and the union of the environments Γ and Γ' . As in the non stochastic case, if the intersection of \mathcal{T} and \mathcal{A} is empty, \mathcal{B} is equal to $\{\tau\}$. Function filter_s is defined formally in Definition B.4.

Definition A.1 *Stochastic Filtered LTS.* Given a stochastic temporary LTS $\mathfrak{L}_{s,u} = (\mathbb{P}_m, \text{Act}, \rightarrow_{s,u})$, an environment $\Gamma \subseteq \mathbb{C} \times \mathbb{R}$ and a set of actions $\mathcal{T} \subseteq \text{Act}$, the corresponding *stochastic filtered LTS* $\mathfrak{L}_{s,p} = (\mathbb{P}_m, \text{Act}, \rightarrow_{s,p})$, with $\rightarrow_{s,p} \subseteq \mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{R} \times \mathbb{P}_m$, is given by $(\mathbb{P}_m, \text{Act}, \text{filter}_s(\Gamma)(\mathcal{T})(\rightarrow_{s,u}))$.

B Formal definitions

Definition B.1 $\mathcal{B}[\mathcal{F}] \text{ cond}$. In the derivation rule ‘‘Hook synchronisation’’, we define formally $\mathcal{B}[\mathcal{F}] \text{ cond}$ by: $\mathcal{B} \subseteq \mathcal{E} \cap \mathcal{L} \wedge \bigcup_{i > |\mathcal{B}|} \Phi_i(C_1^v)(\mathcal{E} \cap \mathcal{L}) = \emptyset$, where $|\mathcal{B}|$ is the cardinality of \mathcal{B} and Φ_k is defined as:

$$\begin{aligned} \Phi_k(\mathcal{A}[\mathcal{H}].C^v) &= \lambda X. \{\mathcal{A}[\mathcal{H}]\} \quad \text{if } |\mathcal{A}| = k \wedge \mathcal{A} \subseteq X \\ \Phi_k(S_1 + S_2) &= \lambda X. (\Phi_k(S_1)(X) \cup \Phi_k(S_2)(X)) \\ \Phi_k(\text{nil}) &= \lambda X. \emptyset \end{aligned}$$

Definition B.2 *Well formed PAH model.* A PAH model is well formed if the following conditions are met:

- when defining sequential components, sets of regular actions that contain biochemical actions can only be singletons, i.e. given $\mathcal{A}[\mathcal{H}].C^v$, if $\exists a:m \in \text{BioAct}$ s.t. $a:m \in \mathcal{A}$ then $\mathcal{A} = \{a:m\}$;
- species consistency, i.e. if $C^v \neq \text{nil}$, $\Psi(C^v) = \text{species}(C^v)$, with Ψ defined as:
 $\Psi(\mathcal{A}[\mathcal{H}].C_1^v) = \{\text{species}(C_1^v)\}$,
 $\Psi(S_1 + S_2) = \Psi(S_1) \cup \Psi(S_2)$.
- hooks never contain biochemical actions, i.e. given $\mathcal{A}[\mathcal{H}].C^v$ then $\mathcal{H} \cap \text{BioAct} = \emptyset$,
- biochemical processes offer only biochemical actions, i.e. if $\text{species}(C^v) \in \text{Species}$ and $a:m[\mathcal{H}].C^v \xrightarrow{a:m[\mathcal{H}]}$ C^v then $a:m \in \text{BioAct}$. Moreover, if $\text{species}(C^v) = \perp$ and $\mathcal{A}[\mathcal{H}].C^v \xrightarrow{\mathcal{A}[\mathcal{H}]}$ C^v then $\mathcal{A} \cap \text{BioAct} = \emptyset$.
- the lowest layer of abstraction contains biochemical processes and there is only one process for each species in the model, i.e. $\chi(P) = (A, B, C)$ and $A \subseteq \text{Species}$, $B = \emptyset$ and $C \cap \text{Species} = \emptyset$, with χ defined as:
 $\chi(C^v) = (\{\text{species}(C^v)\}, \emptyset, \emptyset)$,
 $\chi(P_1 \boxtimes P_2) = (A \cup X, B \cup Y \cup (A \cap X), C \cup Z)$, where $\chi(P_1) = (A, B, C)$
and $\chi(P_2) = (X, Y, Z)$,
 $\chi(P \triangleleft_c C^v) = (A, B, \{\text{species}(C^v)\} \cup C)$, where $\chi(P) = (A, B, C)$.

Definition B.3 filter function.

$$\begin{aligned} \text{filter} : 2^{\text{Act}} &\longrightarrow (2^{\mathbb{P}_m \times \text{Ext} \times \mathbb{P}_m} \longrightarrow 2^{\mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{P}_m}) = \\ &\lambda Y.(\lambda X.(\{ \text{filter}_{\text{lab}}(Y)(\alpha) \mid \alpha \in X \})) \\ \text{filter}_{\text{lab}} : 2^{\text{Act}} &\longrightarrow (\mathbb{P}_m \times \text{Ext} \times \mathbb{P}_m \longrightarrow \mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{P}_m) = \\ &\lambda Y.(\lambda X.((P, \text{filter}_{\text{set}}(Y)(\mathcal{A}), Q), \text{ where } X = (P, \mathcal{A}[\mathcal{H}], Q))) \\ \text{filter}_{\text{set}} : 2^{\text{Act}} &\longrightarrow (2^{\text{Act}} \longrightarrow 2^{\text{Act}}) = \\ &\lambda Y.(\lambda X.(\text{ if } \mathcal{A} = \emptyset \text{ then } \tau \text{ else } \mathcal{A}, \text{ where } \mathcal{A} = \{a:m \mid a:m \in X \cap Y\})) \end{aligned}$$

Definition B.4 filter_s function. Given $(P, \mathcal{A}[\mathcal{H}], \Gamma, Q) \in \rightarrow_{s,u}$, we know that $\mathcal{A} \cap \text{BioAct} = \{a:m\}$. This is because, if a PAH model is well-formed then there is exactly one biochemical action for each transition. We use this observation in the following curried functions, defined to produce the stochastic filtered LTS.

$$\begin{aligned} \text{filter}_s : 2^{\mathbb{C} \times \mathbb{R}} &\longrightarrow (2^{\text{Act}} \longrightarrow (2^{\mathbb{P}_m \times \text{Ext} \times 2^{\text{Species} \times \mathbb{R}} \times \mathbb{P}_m} \longrightarrow 2^{\mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{R} \times \mathbb{P}_m})) = \\ &\lambda Z.(\lambda Y.(\lambda X.(\{ \text{filter}_{s,\text{lab}}(Z)(Y)(\alpha) \mid \alpha \in X \})) \\ \text{filter}_{s,\text{lab}} : & \\ 2^{\mathbb{C} \times \mathbb{R}} &\longrightarrow (2^{\text{Act}} \longrightarrow (\mathbb{P}_m \times \text{Ext} \times 2^{\text{Species} \times \mathbb{R}} \times \mathbb{P}_m \longrightarrow \mathbb{P}_m \times 2^{\text{Act}} \times \mathbb{R} \times \mathbb{P}_m)) = \end{aligned}$$

$$\lambda Z. \left(\lambda Y. \left(\lambda X. \left((P, \text{filter}_{\text{set}}(Y)(\mathcal{A}), \text{eval}(f_{a:m}, \Gamma \cup Z), Q), \right) \right) \right) \left(\begin{array}{l} \text{where } X = (P, \mathcal{A}[\mathcal{H}], \Gamma, Q) \text{ and} \\ \{a:m\} = \mathcal{A} \cap \text{BioAct} \end{array} \right) \right)$$

Function “eval” is defined in Definition C.1.

C Details about functional rates

Each biochemical reaction is associated with a *velocity*, also called a *kinetic law*, which determines the amount of concentration (e.g. Molars) converted by the reaction per time unit (e.g. seconds). A rate $r_{a:m}$ can be derived using the velocity of the reaction associated to $a:m$. First, the velocity is formalised as a functional rate. Second, when required, the functional rate is evaluated based on the concentration of the species at a particular state.

Derivation of rates in a CTMC with levels model. Given an action $a:m$, a velocity v of the biochemical reaction associated with $a:m$, S_i ($i = 1, \dots, n$) species involved in the reaction, $[S_i]$ to indicate the concentration of S_i , $\langle S_i \rangle$ to indicate the current level of concentration of S_i , $k_i \in \mathbb{Z}$ to indicate their stoichiometry in the reaction and h as the step size, the variation in time of $[S_i]$ is given by:

$$\frac{\delta[S_i]}{\delta t} = k_i \cdot v$$

We introduce $\Delta \langle S_i \rangle = k_i$ as the change in number of levels that has to be applied to S_i when $a:m$ is triggered. Substituting $\delta[S_i]$ with $\Delta \langle S_i \rangle \cdot h$:

$$\frac{\delta[S_i]}{\delta t} \approx \frac{\Delta[S_i] \cdot h}{\Delta t} = k_i \cdot v \implies \frac{1}{\Delta t} = \frac{v}{h}$$

If we consider Δt as the average of the exponential distribution of the time necessary for $a:m$ to happen, then $1/\Delta t$ can be used as a rate for such a distribution. We then formalise v as a functional rate and we divide the evaluation of v by h , to produce the correct rate.

Derivation of mass action velocities from diffusion constants. The models of pattern formation we intend to formalise are defined by partial differential equations that have two components: diffusion and local reactions:

$$\frac{\delta[S]}{\delta t} = D_S \nabla^2[S] \pm \text{React}$$

If we divide the space into a grid as described in Section 4, we can derive approximate mass action rates to move from a slot to the adjacent ones of equal volume, using the *finite difference method*. For example, in the case of one-dimensional Cartesian coordinates, the velocity $v_{i,i+1}$, used to move concentration of S from position i to $i + 1$, is equal to $D_S/\Delta x^2 \cdot [S^i]$.

Formalisation of functional rates. A functional rate can be described as a mathematical expression where the basic elements are real numbers, constants and biochemical species. We use the following syntax:

$$f_rate = \text{real} \mid \text{name} \mid f_rate \text{ op}_1 f_rate \mid \text{op}_2(f_rate) \mid f_rate^{f_rate}$$

$$\text{op}_1 = + \mid - \mid * \mid / \quad \text{op}_2 = \text{exp} \mid \text{log} \mid \text{sin} \mid \text{cos}$$

- $real \in \mathbb{R}$
- $name$ is the name of a variable that can be either a model constant or a species. We assume that model constants are declared before the functional rates in the form of the assignment “name = real”. Each assignment can be regarded as a pair $(name, real) \in \mathbb{C} \times \mathbb{R}$. Consequently we can update the environment to $\Gamma = \Gamma \cup \{(name, real)\}$. Species and their concentration, in the form of pairs $(S, real) \in \text{Species} \times \mathbb{R}$, will be gathered during the application of the stochastic semantics and added to the environment before the evaluation of a rate (see Section A).
- op_1 is a binary operator with associativity always to the left and with $*$ and $/$ having priority over $+$ and $-$. op_2 is a unary operator.

We use the following semantics to evaluate the functional rates:

Constant

$$\frac{}{\Gamma \vdash n \rightarrow n}, \quad n \in \mathbb{R}$$

Variable

$$\frac{}{\Gamma \vdash name \rightarrow n}, \quad \Gamma(name) = n$$

Unary operator

$$\frac{\Gamma \vdash exp \rightarrow n_1}{\Gamma \vdash op_2(exp) \rightarrow n_2}, \quad n_2 = op_2(n_1)$$

Binary operator

$$\frac{\Gamma \vdash exp_1 \rightarrow n_1 \quad \Gamma \vdash exp_2 \rightarrow n_2}{\Gamma \vdash exp_1 op_1 exp_2 \rightarrow n_3}, \quad n_3 = n_1 op_1 n_2$$

Exponential operator

$$\frac{\Gamma \vdash exp_1 \rightarrow n_1 \quad \Gamma \vdash exp_2 \rightarrow n_2}{\Gamma \vdash exp_1^{exp_2} \rightarrow n_3}, \quad n_3 = n_1^{n_2}$$

Definition C.1 *Evaluation of a functional rate.* Given an environment $\Gamma \subseteq \text{Names} \times \mathbb{R}$, a functional rate $f_{a:m} \in \mathbb{F}$ is evaluated to a rate $r_{a:m} = x/h$, with $x \in \mathbb{R}$, written $\text{eval}(f_{a:m}, \Gamma) = r_{a:m}$, iff $\Gamma \vdash f_{a:m} \rightarrow x$.

Example. Let $\Gamma = \{(B, 2)\}$, $f = 5 + 4/B$ and $h = 0.5$. It follows that $\Gamma \vdash f \rightarrow 7$, and so $\text{eval}(f, \Gamma) = 7/0.5 = 14$, with the following derivation:

$$\frac{\frac{}{\{(B, 2)\} \vdash 5 \rightarrow 5} \quad \frac{\frac{}{\{(B, 2)\} \vdash B \rightarrow 2} \quad \frac{}{\{(B, 2)\} \vdash 4 \rightarrow 4}}{\{(B, 2)\} \vdash 4/B \rightarrow 2}}{\{(B, 2)\} \vdash 5 + 4/B \rightarrow 7}}$$