Process Algebra with Hooks for Models of Pattern Formation

Andrea Degasperi[1] and Muffy Calder[2]

Department of Computing Science
University of Glasgow
Glasgow, Scotland

Abstract

We introduce Process Algebra with Hooks (PA[$\mathcal{H}$]). In PA[$\mathcal{H}$] 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]. More recently, attention has turned to spatial aspects of behaviour, and there are several approaches that take space into account, usually in 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* (PA[$\mathcal{H}$]),

[1] Email: andrea@dcs.gla.ac.uk
[2] Email: muffy@dcs.gla.ac.uk

This paper is electronically published in
Electronic Notes in Theoretical Computer Science
URL: www.elsevier.nl/locate/entcs

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].

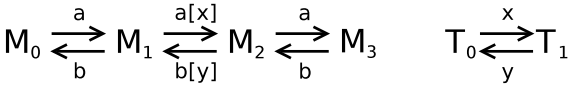
Following these concepts, in PA[$\mathcal{H}$] we use processes to represent different layers of abstraction, e.g. from biochemistry to tissue. A bottom-up synchronisation of these layers via actions called *hooks* ensures the consistency of the abstractions. Moreover, an explicit notion of geometrical 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.

Finally, using PA[$\mathcal{H}$] we produce an *un-processed labelled transition system* (un-processed LTS), where the labels on the transitions require to be processed, 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.

The paper is organised as follows. In Section 2 we introduce PA[$\mathcal{H}$] by examples, before presenting the formal syntax and semantics in Section 3. In Section 4 we show how to model the biochemical layer in PA[$\mathcal{H}$], while the stochastic semantics is in Section 5. We conclude with related work in Section 6 and conclusions and future work in Section 7. The interested reader will find additional formal definitions in Appendix A, an example of the use of PA[$\mathcal{H}$] in Appendix B and the details of our formalisation of functional rates in Appendix C.

2 Process Algebra with Hooks by Examples

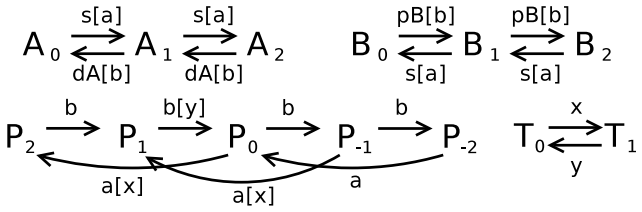
Example 1. Consider the following graphical representation of concurrent processes M_0, M_1, M_2, M_3, T_0, T_1:



Using the *process as level of concentration* abstraction, let M_i be the process representing the morphogen M at a certain position in space, with concen-

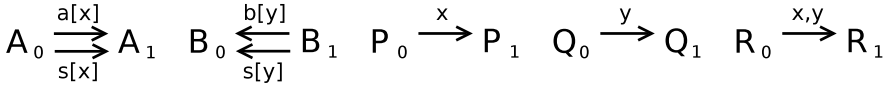
tration level i. Actions a and b represent biochemical reactions that increase or decrease, respectively, the concentration of M. Processes T_0 and T_1 are a higher layer, representing the possible states (the phenotypes) of the tissue T at the current location. The state of T changes when the absolute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



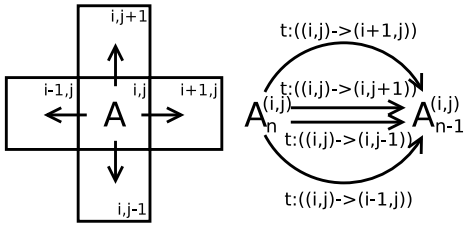
A can degrade (dA), B can be produced (pB), while both A and B can synchronise (s) so that a level of B is converted into a level of A. P_i represents the difference A−B, while a and b actions represent events that make this difference increase by two and decrease by one respectively. An example of a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

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 $((A_0 \underset{s}{\bowtie} B_1) \underset{x}{\lhd} P_0) \underset{y}{\lhd} Q_0 \xrightarrow{s,x,y[x,y]} ((A_1 \underset{s}{\bowtie} B_0) \underset{x}{\lhd} P_1) \underset{y}{\lhd} Q_1$ and $(A_0 \underset{s}{\bowtie} B_1) \underset{x,y}{\lhd} R_0 \xrightarrow{s,x,y[x,y]} (A_1 \underset{s}{\bowtie} B_0) \underset{x,y}{\lhd} R_1$, 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 $A_n^{(i,j)}$ denote the process representing a concentration level n of species A at location (i, j). Concentration can migrate to and from the current position 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 above. For example, A can decrease a level of concentration, from A_n^v to A_{n-1}^v at a position $v = (i, j)$, through a transport reaction of the form $t{:}(v \to s)$. t is the action name, and v and s are locations. $(v \to s)$ denotes transport from location v to location s. At position s, a process A_m^s will synchronise and become A_{m+1}^s. Simply substituting $t{:}(v \to s)$ with $t{:}(v \to s)[b]$ we can add these actions to Example 2 and P_i, without modifications, will synchronise with them.



3 Syntax and Semantics

We now define PA[$\mathcal{H}$] formally.

Syntax of PA[$\mathcal{H}$]. The syntax of PA[$\mathcal{H}$] is defined as:

$$S^v ::= nil \mid \mathcal{L}'[\mathcal{L}''].C^v \mid S^v + S^v \qquad P ::= P \underset{\mathcal{L}}{\bowtie} P \mid P \underset{\mathcal{L}}{\lhd} C^v \mid C^v$$

$$\mathcal{L} ::= \emptyset \mid \mathcal{L}' \qquad \mathcal{L}' ::= a{:}m \mid a{:}m, \mathcal{L}' \qquad \mathcal{L}'' ::= \emptyset \mid a{:}m$$

$$m ::= v \mid (v \to v) \qquad v ::= (z, z, z) \qquad C^v \triangleq S^v$$

where:

- S^v and P are respectively the *sequential component*, used to represent the concentration of biochemical species or the behaviour at higher layers of abstraction, and the *model component*, that combines the sequential components into the final process algebra model. Sequential and model components are in general referred to as components or *processes* and form the

set of processes $\mathbb{P}$;

- $a \in \mathbb{A}$, $\mathbb{A} = \{a, b, c, ...\}$, is an action name belonging to $\mathbb{A}$;
- $a{:}m \in Act$, $Act = \{a{:}m_1, b{:}m_2, c{:}m_3, ...\}$, 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 process or an action, or the sequence 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 sequential component;
- $S^v + S^v$ is the choice between sequential components;
- $P \underset{\mathcal{L}}{\bowtie} P$ is the cooperation of model components, synchronising on the actions in $\mathcal{L}$;
- $P \underset{\mathcal{L}}{\lhd} C^v$ 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 is a constant defined as $C^v \triangleq S^v$: every time S^v is found in a derivation, it can be substituted by the constant C^v.

Given $\mathcal{A}[\mathcal{H}] \in Ext$, two short hand notations are: if $\mathcal{H} = \emptyset$, $\mathcal{A}[\mathcal{H}]$ can be written $\mathcal{A}$ and if $\mathcal{A} = \{a{:}m\}$ it can be written simply $a{:}m$.

Semantics of PA$[\mathcal{H}]$. The semantics of PA$[\mathcal{H}]$ is given by an *unprocessed* LTS $\mathfrak{L}_\mathfrak{u} = (\mathbb{P}, Act, \rightarrow_u)$, where $\mathbb{P}$ is the set of Processes, Act is the set of actions and $\rightarrow_u$ is a transition relation such that $\rightarrow_u \subseteq \mathbb{P} \times Ext \times \mathbb{P}$. $\mathfrak{L}_\mathfrak{u}$ is defined by the following derivation rules:

Prefix

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

Constant

$$\frac{S_1^v \xrightarrow{\mathcal{A}[\mathcal{H}]} C_2^v}{C_1^v \xrightarrow{\mathcal{A}[\mathcal{H}]} C_2^v}, \quad C_1^v \triangleq S_1^v$$

Choice Left

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

Choice Right

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

Cooperation Left

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

Cooperation Right

$$\frac{P_2 \xrightarrow{\mathcal{A}[\mathcal{H}]} P_4}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{\mathcal{A}[\mathcal{H}]} P_1 \underset{\mathcal{L}}{\bowtie} P_4}, \ \mathcal{A} \cap \mathcal{L} = \emptyset$$

Regular Cooperation

$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{E}]} P_3 \quad P_2 \xrightarrow{\mathcal{B}[\mathcal{F}]} P_4}{P_1 \underset{\mathcal{L}}{\bowtie} P_2 \xrightarrow{\mathcal{A} \cup \mathcal{B}[\mathcal{E} \cup \mathcal{F}]} P_3 \underset{\mathcal{L}}{\bowtie} P_4}, \ \begin{matrix} \mathcal{A} \cap \mathcal{B} \subseteq \mathcal{L} \\ \wedge \mathcal{A} \cap \mathcal{B} \neq \emptyset \end{matrix}$$

Hook Ignore

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

Hook Synchronisation

$$\frac{P_1 \xrightarrow{\mathcal{A}[\mathcal{E}]} P_2 \quad C'^v \xrightarrow{\mathcal{B}[\mathcal{F}]} C''^v}{P_1 \underset{\mathcal{L}}{\lhd} C'^v \xrightarrow{\mathcal{A} \cup \mathcal{B}[\mathcal{E} \cup \mathcal{F}]} P_2 \underset{\mathcal{L}}{\lhd} C''^v}, \ \mathcal{B}[\mathcal{F}] \ cond$$

$\mathcal{B}[\mathcal{F}]$ *cond*: given $C'^v \triangleq \mathcal{B}_1[\mathcal{F}_1].C_1^v + \mathcal{B}_2[\mathcal{F}_2].C_2^v + ... + \mathcal{B}_n[\mathcal{F}_n].C_n^v$, let $\mathcal{B}$ be a $\mathcal{B}_i$ in $\mathcal{B}_1, \mathcal{B}_2, ..., \mathcal{B}_n$ 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 B_j in $\mathcal{B}_1, \mathcal{B}_2, ..., \mathcal{B}_n$ with larger cardinality than $\mathcal{B}_i$ such that $\mathcal{B}_j \subseteq \mathcal{E} \cap \mathcal{L}$. We define this formally in Definition A.1.

As an example of hook synchronisation, consider the following sequential components:

$$A \triangleq x[a].A \qquad B \triangleq x[b].B \qquad C \triangleq x[c].C$$
$$Q_0 \triangleq a.Q_1 + a, b.Q_2 + a, b, d.Q_3$$

The transition $(A \underset{x}{\bowtie} B \underset{x}{\bowtie} C) \underset{a,b,c}{\lhd} Q_0 \xrightarrow{x,a,b[a,b,c]} (A \underset{x}{\bowtie} B \underset{x}{\bowtie} C) \underset{a,b,c}{\lhd} Q_2$, 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 $\{a,b,d\} \nsubseteq \{a,b,c\} \cap \{a,b,c\}$.

Well-formed PA[$\mathcal{H}$] model. We now introduce additional definitions, necessary to define a well-formed PA[$\mathcal{H}$] model.

Definition 3.1 *Biochemical Species.* The set *Species* is the set of biochemical species. Every biochemical species S $\in$ *Species* is associated with one or more processes, the *biochemical processes*, which represent different levels of concentration for S.

Definition 3.2 *Functions* species *and* level. "species: $\mathbb{P} \rightarrow$ *Species*" is the function that given a process P returns the species S it is associated with. If P is not associated with a biochemical species, species(P) returns $\perp$. Similarly, "level: $\mathbb{P} \rightarrow \mathbb{N}$", is the function that converts processes in their corresponding

level of concentration. In analogy with the species function, level(P) returns $\perp$ if P is not associated with a biochemical species.

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

Definition 3.4 *Well formed* PA[$\mathcal{H}$] *model.* A PA[$\mathcal{H}$] 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;
- 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 species(C_1^v)=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 A.2.

Processed LTS. The LTS $\mathfrak{L}_u$ is called un-processed 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 processed, 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 *processed* 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 process the un-processed LTS:

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

Given a set of actions $\mathcal{T}$, which contains actions relative to a specific layer of abstraction, the function proc($\mathcal{T}$) 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 proc is defined formally in Definition A.3.

Definition 3.5 *Processed LTS.* Given an un-processed LTS $\mathfrak{L}_u = (\mathbb{P}, Act, \rightarrow_u)$ and a set of actions $\mathcal{T}$, the *processed* LTS $\mathfrak{L}_p = (\mathbb{P}, Act, \rightarrow_p)$, with $\rightarrow_p \subseteq \mathbb{P} \times 2^{Act} \times \mathbb{P}$, is given by $(\mathbb{P}, Act, \text{proc}(\mathcal{T})(\rightarrow_u))$.

An example of LTS processing is shown in Figure 1.

4 Abstraction of Biochemistry

PA[$\mathcal{H}$] has been designed to model biochemical interactions localised in space, using the *processes as levels of concentration* abstraction. The concentration of

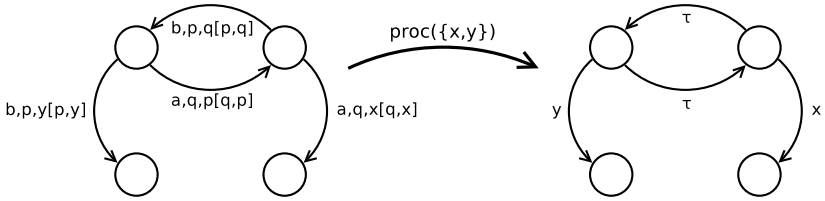


Fig. 1. An un-processed labelled transition system (left) is processed, removing hooks and labels that are not in the set $\{x, y\}$ (right).

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 $h = M_{\mathrm{S}}/N_{\mathrm{S}}$. 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 size 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 $N_{\mathrm{S}} + 1$ processes (sequential components) $S_0^v, S_1^v, ..., S_{N_{\mathrm{S}}}^v$, which represent different levels of concentration of S^v and from which the concentration can be computed simply by level$(S_n^v){\cdot}h$.

Example. Consider the following reaction:

$$\mathrm{A}^v + \mathrm{B}^v \rightarrow_{prodC:v} \mathrm{C}^v$$

A and B combine to produce C at location v. Initially there is no C and equal amounts of A and B. Let *prod*:v be the indentifier of the reaction. In a PA[$\mathcal{H}$] model there is one process for each species, the level of each species denoting the initial conditions.

Let $N_{\mathrm{A}^v} = N_{\mathrm{B}^v} = N_{\mathrm{C}^v} = 1$ and $\mathbb{A} = \{prodC\}$ and $Act = \{prodC{:}v\}$. The corresponding sequential and model components are:

$$A_0^v \triangleq nil \qquad B_0^v \triangleq nil \qquad C_0^v \triangleq prodC{:}v.C_1^v$$

$$A_1^v \triangleq prodC{:}v.A_0^v \quad B_1^v \triangleq prodC{:}v.B_0^v \quad C_1^v \triangleq nil$$

$$A_1^v \underset{prodC:v}{\bowtie} B_1^v \underset{prodC:v}{\bowtie} C_0^v$$

5 Stochastic Semantics

To define a stochastic version of PA[$\mathcal{H}$], we need to associate a rate with each transition of the un-processed 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 $a{:}m \in BioAct$ 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 "Γ: $Names \to \mathbb{R}$", with $Names = \mathbb{C} \cup Species$, $\mathbb{C} \subseteq Names$ the set of constant names, $Species \subseteq Names$ the set of biochemical species and $\mathbb{C} \cap Species = \emptyset$.

We now introduce the stochastic semantics of PA[$\mathcal{H}$]. With respect to the original semantics, derivation rules $Prefix$, $Choice\ Left$ and $Choice\ Right$ are unaltered. These are the modified rules:

Constant

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

Cooperation Left

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

Cooperation Right

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

Regular Cooperation

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

Hook Ignore

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

Hook Synchronisation

$$\frac{P_1 \xrightarrow{(\mathcal{A}[\mathcal{E}],\Gamma_1)} P_2 \quad C_1^v \xrightarrow{(\mathcal{B}[\mathcal{F}],\Gamma_2)} C_2^v}{P_1 \underset{\mathcal{L}}{\triangleleft} C_1^v \xrightarrow{(\mathcal{A}\cup\mathcal{B}[\mathcal{E}\cup\mathcal{F}],\Gamma_1\cup\Gamma_2)} P_2 \underset{\mathcal{L}}{\triangleleft} C_2^v}, \quad \mathcal{B}[\mathcal{F}] \; cond$$

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

A *stochastic un-processed* LTS is defined as $\mathfrak{L}_{\mathfrak{s},\mathfrak{u}} = (\mathbb{P}, Act, \rightarrow_{s,u})$, where the transition relation $\rightarrow_{s,u} \subseteq \mathbb{P} \times Ext \times 2^{Species\times\mathbb{R}} \times \mathbb{P}$ is the minimal relation that satisfies the stochastic semantics of PA$[\mathcal{H}]$.

Stochastic processed LTS. The processing of a stochastic un-processed 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:

$$\text{proc}_\text{s} : 2^{\mathbb{C}\times\mathbb{R}} \longrightarrow (2^{Act} \longrightarrow (2^{\mathbb{P}\times Ext\times 2^{Species\times\mathbb{R}}\times\mathbb{P}} \longrightarrow 2^{\mathbb{P}\times 2^{Act}\times\mathbb{R}\times\mathbb{P}}))$$

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 $\text{proc}_\text{s}(\Gamma)(\mathcal{T})$ 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 PA$[\mathcal{H}]$ 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 proc_s is defined formally in Definition A.4.

Definition 5.1 *Stochastic Processed LTS.* Given a stochastic un-processed LTS $\mathfrak{L}_{s,u} = (\mathbb{P}, Act, \rightarrow_{s,u})$, an environment $\Gamma \subseteq \mathbb{C} \times \mathbb{R}$ and a set of actions $\mathcal{T} \subseteq Act$, the corresponding *stochastic processed* LTS $\mathfrak{L}_{s,p} = (\mathbb{P}, Act, \rightarrow_{s,p})$, with $\rightarrow_{s,p} \subseteq \mathbb{P} \times 2^{Act} \times \mathbb{R} \times \mathbb{P}$, is given by $(\mathbb{P}, Act, \text{proc}_\text{s}(\Gamma)(\mathcal{T})(\rightarrow_{s,u}))$.

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 synchro-

nisation. 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, PA[$\mathcal{H}$], that aims to formalise models of pattern formation has been presented, along with its stochastic semantics. 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 PA[$\mathcal{H}$], 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 the then processed to provide a more concise form, without hooks, tailored to a given layer of abstraction. A stochastic semantics is also defined, based on functional rates associated with biochemical reactions.

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.

Future work includes defining equivalences between models so we can determine, for example, when two different biochemistries lead to the same patterns.

8 Acknowledgements

Andrea Degasperi is supported by a Lord Kelvin / Adam Smith Scholarship of the University of Glasgow and by the EPSRC funded SIGNAL project.

References

[1] Argent-Katwala, A., J. T. Bradley and N. J. Dingle, *Expressing performance requirements using regular expressions to specify stochastic probes over process algebra models*, Fourth International Workshop on Software and Performance (2004), pp. 49–58.

[2] Calder, M., S. Gilmore and J. Hillston, *Modelling the influence of RKIP on the ERK signalling pathway using the stochastic process algebra PEPA*, Lecture Notes in Computer Science **4230** (2006), pp. 1–23.

[3] Calder, M. and J. Hillston, *Process algebra modelling styles for biomolecular processes*, LNCS **5750** (2009), pp. 1–25.

[4] Calzone, L., F. Fages and S. Soliman, *Biocham: An environment for modelling biological systems and formalizing experimental knowledge*, Bioinformatics **22** (2006), pp. 1805–1807.

[5] Cardelli, L., *Brane calculi*, Lecture Notes in Bioinformatics **3082** (2005), pp. 257–278.

[6] Ciocchetta, F. and J. Hillston, *Bio-PEPA: A framework for the modelling and analysis of biological systems*, Theoretical Computer Science **410** (2009), pp. 3065–3084.

[7] Clark, A. and S. Gilmore, *State-aware performance analysis with eXtended stochastic probes*, LNCS **5261** (2008), pp. 125–140.

[8] Danos, V., J. Feret, W. Fontana, R. Harmer and J. Krivine, *Rule-based modelling of cellular signalling*, Lecture Notes in Computer Science (2007), pp. 17–41.

[9] Degasperi, A. and M. Calder, *On the formalisation of gradient diffusion models of biological systems*, PASTA Workshop 2009 (2009).
URL http://www.dcs.gla.ac.uk/~andrea/files/DegasperiCalder_Bio-PASTA2009.pdf

[10] Hillston, J., "A Compositional Approach to Performance Modelling," Cambridge University Press, 1996.

[11] Meinhardt, H., *Tailoring and coupling of reaction-diffusion systems to obtain reproducible complex pattern formation during development of the higher organisms*, Applied Mathematics and Computation **32** (1989), pp. 103–135.

[12] Meinhardt, H., *Models of biological pattern formation: from elementary steps to the organization of embryonic axes*, Curr. Top. Dev. Biol. **81** (2008), pp. 1–63.

[13] Meinhardt, H., *Models for generation and interpretation of gradients*, Cold Spring Harbor Perspectives in Biology (2009), pp. 1–14.

[14] Priami, C. and P. Quaglia, *Beta-binders for biological interactions*, LNCS **3082** (2005), pp. 20–33.

[15] Priami, C., A. Regev, E. Shapiro and W. Silverman, *Application of a stochastic name-passing calculus to representation and simulation of molecular processes*, Inf. Process. Lett. **80** (2001), pp. 25–31.

[16] Regev, A., E. Panina, W. Silverman, L. Cardelli and E. Shapiro, *Bioambients: An abstraction for biological compartments*, Theoretical Computer Science **325** (2004), pp. 141–167.

[17] Regev, A., W. Silverman and E. Shapiro, *Representation and simulation of biochemical processes using the pi-calculus process algebra*, Pacific Symposium on Biocomputing (2001), pp. 459–470.

[18] Turing, A., *The chemical basis of morphogenesis*, Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences **237** (1952), pp. 37–72.

A Formal definitions

Definition A.1 $\mathcal{B}[\mathcal{F}]$ *cond.* In the derivation rule "Hook synchronisation", we define formally $\mathcal{B}[\mathcal{F}]$ *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:

$\Phi_k(\mathcal{A}[\mathcal{H}].C^v) = \lambda X.\{\mathcal{A}[\mathcal{H}]\} \quad$ if $|\mathcal{A}| = k \wedge \mathcal{A} \subseteq X$

$\Phi_k(S_1^v + S_2^v) = \lambda X.(\Phi_k(S_1^v)(X) \cup \Phi_k(S_2^v)(X))$

$\Phi_k(nil) = \lambda X.\emptyset$

Definition A.2 *Well formed* PA$[\mathcal{H}]$ *model.* A PA$[\mathcal{H}]$ 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 $\exists a{:}m \in BioAct$ *s.t.* $a{:}m \in \mathcal{A}$ then $\mathcal{A} = \{a{:}m\}$;
- species consistency, i.e. if $C^v \neq nil$, $\Psi(C^v)$=species(C^v), with Ψ defined as:
  $\Psi(\mathcal{A}[\mathcal{H}].C_1^v) = \{\text{species}(C_1^v)\}$,
  $\Psi(S_1^v + S_2^v) = \Psi(S_1^v) \cup \Psi(S_2^v)$.
- hooks never contain biochemical actions, i.e. given $\mathcal{A}[\mathcal{H}].C^v$ then $\mathcal{H} \cap BioAct = \emptyset$,
- biochemical processes offer only biochemical actions, i.e. if species$(C^v) \in Species$ and $a{:}m[\mathcal{H}].C^v \xrightarrow{a:m[\mathcal{H}]} C^v$ then $a{:}m \in BioAct$. Moreover, if species$(C^v) = \perp$ and $\mathcal{A}[\mathcal{H}].C^v \xrightarrow{\mathcal{A}[\mathcal{H}]} C^v$ then $\mathcal{A} \cap BioAct = \emptyset$.
- 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 $A \subseteq Species$, $B = \emptyset$ and $C \cap Species = \emptyset$, with χ defined as:
  $\chi(C^v) = (\{\text{species}(C^v)\}, \emptyset, \emptyset)$,
  $\chi(P_1 \underset{\mathcal{L}}{\bowtie} P_2) = (A \cup X, B \cup Y \cup (A \cap X), C \cup Z)$, where $\chi(P_1) = (A, B, C)$ and $\chi(P_2) = (X, Y, Z)$,
  $\chi(P \underset{\mathcal{L}}{\triangleleft} C^v) = (A, B, \{\text{species}(C^v)\} \cup C)$, where $\chi(P) = (A, B, C)$.

Definition A.3 proc *function.*

$$\text{proc} : 2^{Act} \longrightarrow (2^{\mathbb{P} \times Ext \times \mathbb{P}} \longrightarrow 2^{\mathbb{P} \times 2^{Act} \times \mathbb{P}}) =$$
$$\lambda Y.(\lambda X.(\ \{\ \text{proc}_{\text{lab}}(Y)(\alpha) \mid \alpha \in X\}\ ))$$

$$\text{proc}_{\text{lab}} : 2^{Act} \longrightarrow (\mathbb{P} \times Ext \times \mathbb{P} \longrightarrow \mathbb{P} \times 2^{Act} \times \mathbb{P}) =$$
$$\lambda Y.(\lambda X.(\ (P, \text{proc}_{\text{set}}(Y)(\mathcal{A}), Q), \text{where } X = (P, \mathcal{A}[\mathcal{H}], Q)\ ))$$

$$\text{proc}_{\text{set}} : 2^{Act} \longrightarrow (2^{Act} \longrightarrow 2^{Act}) =$$
$$\lambda Y.(\lambda X.(\ \text{if } S = \emptyset \text{ then } \tau \text{ else } S, \text{where } S = \{a{:}m \mid a{:}m \in X \cap Y\}\ ))$$

Definition A.4 proc_{s} *function.* Given $(P, \mathcal{A}[\mathcal{H}], \Gamma, Q) \in \rightarrow_{s,u}$, we know that $\mathcal{A} \cap BioAct = \{a{:}m\}$. This is because, if a PA$[\mathcal{H}]$ 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 processed LTS.

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

$$\text{proc}_{\text{s,lab}} :$$
$$2^{\mathbb{C}\times\mathbb{R}} \longrightarrow (2^{Act} \longrightarrow (\mathbb{P}\times Ext\times 2^{Species\times\mathbb{R}}\times\mathbb{P} \longrightarrow \mathbb{P}\times 2^{Act}\times\mathbb{R}\times\mathbb{P})) =$$
$$\lambda Z.\left(\lambda Y.\left(\lambda X.\left(\begin{array}{c}(P,\ \text{proc}_{\text{set}}(Y)(\mathcal{A}),\text{eval}(f_{a:m},\Gamma\cup Z),Q),\\ \text{where } X=(P,\mathcal{A}[\mathcal{H}],\Gamma,Q) \text{ and}\\ \{a{:}m\}=\mathcal{A}\cap BioAct\end{array}\right)\right)\right)$$

Function "eval" is defined in Definition C.1.

B A more detailed example

In the slot in position $j\in\{v,s\}$, 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. In chemical form, the reactions are, with $i,j\in\{v,s\}$, $i\neq j$:

Reaction	Chemical form	Action	Reaction	Chemical form	Action
R_1:	$\to$ A	r1	R_5:	A $\to$ B	r5
R_2:	A $\to$	r2	R_6:	B $\to$ A	r6
R_3:	$\to$ B	r3	R_7:	$\text{A}^i \to \text{A}^j$	tA
R_4:	B $\to$	r4	R_8:	$\text{B}^i \to \text{B}^j$	tB

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 2. 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 2 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 PA$[\mathcal{H}]$ model is defined by:

$A_0^i \triangleq r1{:}i.A_1^i + r6{:}i.A_1^i + tA{:}(j\to i).A_1^i$

$A_1^i \triangleq r1{:}i[p{:}i].A_2^i + r6{:}i[p{:}i].A_2^i + r2{:}i.A_0^i + r5{:}i.A_0^i + tA{:}(j\to i).A_2^i + tA{:}(i\to j).A_0^i$

$A_2^i \triangleq r2{:}i[q{:}i].A_1^i + r5{:}i[q{:}i].A_1^i + tA{:}(i\to j).A_1^i$

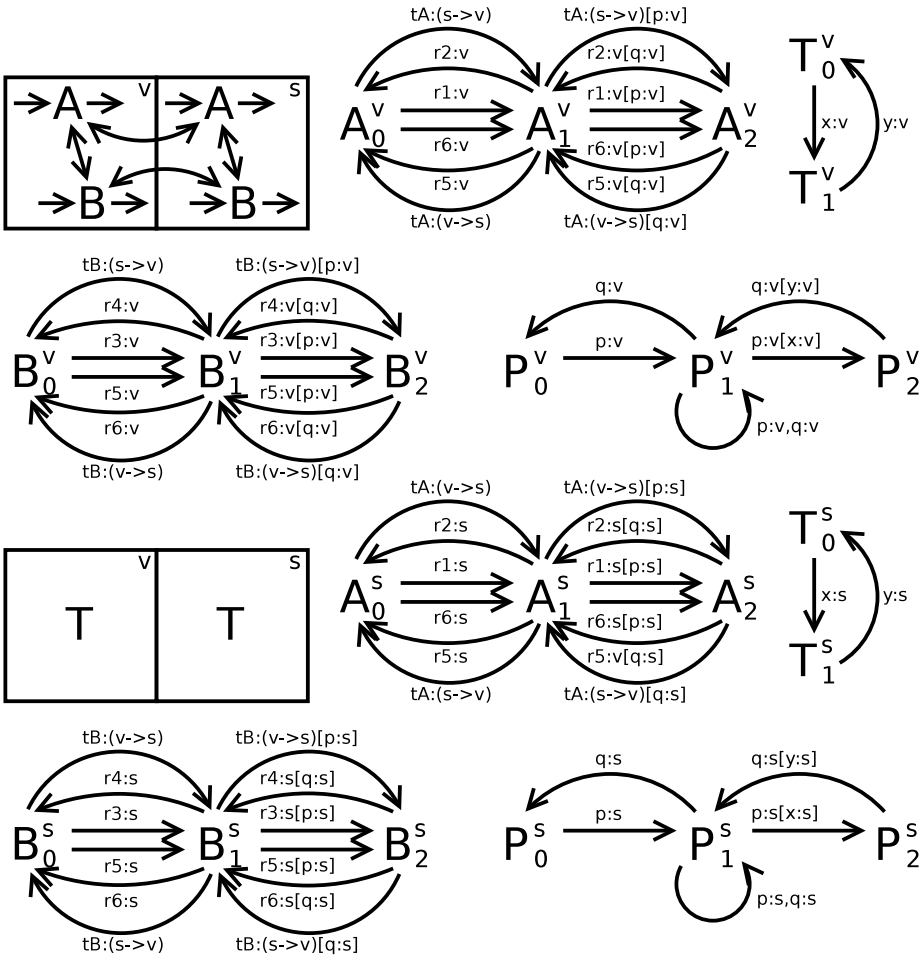


Fig. B.1. Graphical representation of the processes.

$B_0^i \triangleq r3{:}i.B_1^i + r5{:}i.B_1^i + tB{:}(j \to i).B_1^i$

$B_1^i \triangleq r3{:}i[p{:}i].B_2^i + r5{:}i[p{:}i].B_2^i + r4{:}i.B_0^i + r6{:}i.B_0^i + tB{:}(j \to i).B_2^i + tB{:}(i \to j).B_0^i$

$B_2^i \triangleq r4{:}i[q{:}i].B_1^i + r6{:}i[q{:}i].B_1^i + tB{:}(i \to j).B_1^i$

$P_0^i \triangleq p{:}i.P_1^i \qquad P_2^i \triangleq q{:}i[y{:}i].P_0^i$

$P_1^i \triangleq q{:}i.P_0^i + q{:}i, p{:}i[\emptyset].P_1^i + p{:}i[x{:}i].P_2^v$

$T_0^i \triangleq x{:}i.T_1^i \qquad T_1^i \triangleq y{:}i.T_0^i$

$$(((A_0^v \underset{r5:v,r6:v}{\bowtie} B_0^v) \underset{p:v,q:v}{\lhd} P_0^v) \underset{x:v,y:v}{\lhd} T_0^v) \underset{tA:(i\to j),tB:(i\to j)}{\bowtie} (((A_0^s \underset{r5:s,r6:s}{\bowtie} B_0^s) \underset{p:s,q:s}{\lhd} P_0^s) \underset{x:s,y:s}{\lhd} T_0^s)$$

A graphical representation of these processes is depicted in Figure B.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 $(i = 1, ..., n)$ species involved in the reaction, $[\mathrm{S}_i]$ to indicate the concentration of S_i, $\langle \mathrm{S}_i \rangle$ 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 $[\mathrm{S}_i]$ is given by:

$$\frac{\delta[\mathrm{S}_i]}{\delta t} = k_i \cdot v$$

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

$$\frac{\delta[\mathrm{S}_i]}{\delta t} \approx \frac{\Delta[\mathrm{S}_i] \cdot h}{\Delta t} = k_i \cdot v \Longrightarrow \frac{1}{\Delta t} = \frac{v}{h}$$

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: the diffusion and the local reactions:

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

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 $D_{\mathrm{S}}/\Delta x^2 \cdot [\mathrm{S}^i]$.

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 define functional rates using the following syntax:

$$f\_rate = \mathrm{real} \mid \mathrm{name} \mid f\_rate\ \mathrm{op}_1\ f\_rate \mid \mathrm{op}_2(f\_rate) \mid f\_rate^{f\_rate}$$

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

- $real \in \mathbb{R}$
- $name$ is the name of a variable that can be either a constant or a species. In order to evaluate the function we define an environment Γ, that is a function that associates variable names with real values. We define it as "Γ: $Names \to \mathbb{R}$", with $Names = \mathbb{C} \cup Species$, $\mathbb{C} \subseteq Names$ the set of constant names, $Species \subseteq Names$ the set of biochemical species and $\mathbb{C} \cap Species = \emptyset$. We assume that 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)$\in Species \times \mathbb{R}$, will be gathered during the application of the stochastic semantics and added to the environment before the evaluation of a rate (see Section 5).
- 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

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

Variable

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

Unary operator

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

Binary operator

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

Exponential operator

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

Definition C.1 *Evaluation of a functional rate.* Given an environment $\Gamma \subseteq Names \times \mathbb{R}$, 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 $\Gamma \vdash f_{a:m} \to x$.

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

$$\dfrac{\dfrac{}{\{(\text{B},2)\} \vdash 5 \to 5} \qquad \dfrac{\dfrac{}{\{(\text{B},2)\} \vdash \text{B} \to 2} \qquad \dfrac{}{\{(\text{B},2)\} \vdash 4 \to 4}}{\{(\text{B},2)\} \vdash 4/\text{B} \to 2}}{\{(\text{B},2)\} \vdash 5 + 4/\text{B} \to 7}$$