A Deductive Compositional Approach to Petri Nets for Systems Biology

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Abstract. We introduce the language $\mathcal{CP}$, a compositional language for place transition petri nets for the purpose of modelling complex biological systems. The language $\mathcal{CP}$ is especially well suited for modelling signalling pathways, where possibly interdependent events with different durations can co-occur. We give the operational semantics of the language $\mathcal{CP}$ by means of a proof theoretical deductive system which extends multiplicative exponential linear logic with a self-dual non-commutative logical operator. This makes it possible to compose petri nets at the same level and as nested abstractions, while allowing to do deductive reasoning on the biological systems being modelled by these nets. We demonstrate the use of the language on a model of a signalling pathway for Fc receptor-mediated phagocytosis.

1 Introduction

The view of biological systems as complex reactive systems is becoming increasingly wide-spread. As new techniques emerge, their applications shed light to behaviour and interrelations of the components of complex biological systems. By means of abstractions from biological data, these computational methods allow to formally represent interactions and reactions of the components of a biological system. This way, it becomes possible to build computational models for hypothesis generation and analysis. [1]

Symbolic computational methods, with different representation schemes, expressive capabilities, and tools, have been proposed by various authors. Stochastic π-calculus [24, 25, 23, 4] and PEPA [3] are examples to process algebra approaches. Others include the PRISM language [13], petri nets [21, 8, 14], and $\mathcal{K}$-calculus [7, 6]. Pathway logic [32, 34] is another approach based on petri nets.

One of the main advantages of symbolic computational methods in modelling of biological systems is their compositionality: in the context of modelling, from an analytic bottom-up point of view, compositionality is the idea of considering parts of a complex biological system in isolation, and this way building models

[1] Preliminary versions of this paper had been presented at the *Workshop on Rule-Based Modeling of Biochemical Systems at the Santa Fe Institute (June 2007)* and as poster at the *Computational Methods in Systems Biology Conference, 2007.*

and composing parts gradually to build more complex models. From a dual top-down point of view, compositionality allows to add detail to the components of a model so that models can be considered at lower levels of abstraction, while moving from greater parts of building blocks towards smaller components. An example for this would be moving from protein complexes to proteins, then to amino-acids, and then to chemical compounds, etc. The combination of these two perspectives of modelling (top-down and bottom-up) then results in the so called middle-out approach to modelling.

Petri nets was originally conceived as a language for studying complex information systems. Petri nets have been being used also to model biological systems. Petri nets have a graphical representation which resembles conventional representations of biochemical networks. Thus, they can communicate the biological data in a way that is natural for biologists while remaining in formal grounds. Because petri nets are akin to chemical reactions, they can be used to model biological systems that can be expressed in terms of chemical reactions. They can thus be used as a graphical interface to ordinary differential equation models of biological systems (see, e.g., [14]). Petri nets have been used to model signalling pathways and simple genetic networks (see, e.g., [27]). [2]

Petri nets are well suited for analysing causality and independence of components in biological systems such as those involved in a signalling cascade. However, petri nets lack a broadly accepted formal compositional semantics which would allow to model and analyse biological systems compositionally. In this paper, we introduce a compositional language, called $\mathcal{CP}$, for place transition petri nets. The language $\mathcal{CP}$ is equipped with sequential and parallel composition and a proof theoretical operational semantics. This way, concurrent signals in a biological pathway can be represented as in process algebra at the same syntactic level and logical deductive reasoning can be performed on these processes. Because biological signals have durations the synchronisation is not performed by means of a hand-shake operation as in process algebra, but by means of common successors and predecessors of concurrent processes due to the causality relation between processes. The non-deterministic choice is embedded into the operational semantics of the underlying logic.

As an example for an application of the language $\mathcal{CP}$, throughout the paper we consider a signalling cascade which occurs during *phagocytosis* where cells engulf particles of greater size: in Fc receptor mediated phagocytosis (see, e.g., [30]), cells engulf particles by means of membrane protrusion around the internalised particle. This protrusion is due to the growth of the actin meshwork in the cytoskeleton, as a result of the signal originating from the interactions between the Fc receptors and the internalised particle on the cell membrane; the Rho GTP binding proteins Cdc42 and Rac get activated by means of a signalling cascade that results in two concurrent pathways of actin polymerisation [30, 4]. The Rac signal results in a branching structure of actin, whereas Cdc42 results in a linear actin structure. These two processes act in concert and this way extend the cytoskeleton around the engulfed particle. These two processes are initiated

[2] For surveys on petri nets in systems biology, see [19, 22, 12].

by a common signalling pathway, however Cdc42 signal is more dominant at the early stages of actin polymerisation, whereas Rac signal becomes more dominant at the later stages [30]. Thus, although their initiation is synchronised, because they have durations, this synchronisation does not occur in a handshake-manner, but instead by means of their common successors and predecessors.

The language $\mathcal{CP}$ is obtained by encoding the petri nets in a proof theoretical deductive system, called system NEL [10, 11]. System NEL is an extension of multiplicative exponential linear logic with a self-dual non-commutative logical operator. System NEL cannot be designed in a standard sequent calculus, because a notion of deep rewriting is necessary in order to derive all the provable formulae of system NEL [33]. System NEL is designed within the proof theoretical methodology of *deep inference* (see, e.g., [9, 28]) which allows such a deep rewriting. System NEL enjoys the cut elimination property. From a proof theoretical point of view, the cut elimination property can be considered as a certificate of mathematical rigour. Although it is unknown whether multiplicative exponential linear logic is decidable or not, in [29], Straßburger showed that system NEL is Turing-complete.

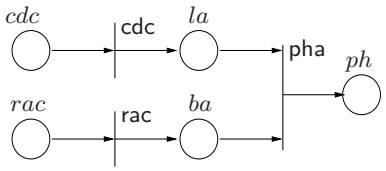
The self-dual non-commutative operator of system NEL, called *seq*, resembles the prefixing of the process algebra. In language $\mathcal{CP}$, while parallel composition of transitions is mapped to the par operator of linear logic, their sequential composition is naturally mapped to the operator seq. Thus, in language $\mathcal{CP}$, parallel and sequential composition of the processes are expressed at the same logical level. However, system NEL is not only an elegant interface for encoding the transitions of petri nets as processes: the underlying deductive system can be used to do logical reasoning in an interesting and useful way without sacrificing from mathematical purity. While parallel and sequential composition of transitions and their firings correspond to derivations of system NEL, the availability of deep inference makes it possible to do reasoning locally on components of the considered petri net. This allows to work on the parts of the biological system in isolation to build models of larger systems or to add more detail to a model at will. Our implementations of deep inference deductive systems provide the reasoning tools for the proposed approach [15]. Space restrictions do not permit us to give the proofs of the results here, we refer to [16].

2 $\mathcal{P}/\mathcal{T}$ Petri Nets

We represent the petri nets as multiset rewriting systems (see, e.g., [5]).

Definition 1. *A* multiset rewriting system $\mathcal{M}$ *over a set* $\mathcal{F}$ *is a set of* multiset rewrite rules *of the form* $\mathsf{a} : \mathsf{a}.pre \rightarrow \mathsf{a}.post$ *where* a *is the name of the rule, and* $\mathsf{a}.pre$ *and* $\mathsf{a}.post$ *are multisets over* $\mathcal{F}$*, called* preset *and* postset *of* a [3]*. Given a multiset* M*, a rule* a *is* enabled *at* M *if* $\mathsf{a}.pre$ *is a submultiset of* M*. If* a *is enabled*

[3] Multisets are denoted by the curly brackets "$\dot{\{}$" and "$\dot{\}}$". The empty multiset is denoted by $\dot{\emptyset}$. $\dot{\cup}$, $\dot{-}$, and $\dot{\subseteq}$ denote the multiset operations corresponding to the usual set operations $\cup$, $-$, and $\subseteq$, respectively.



$$\mathcal{N}_1 = \{\ \mathsf{rac} : \dot{\{}\, rac \,\dot{\}} \to \dot{\{}\, ba \,\dot{\}}\ ,\quad \mathsf{cdc} : \dot{\{}\, cdc \,\dot{\}} \to \dot{\{}\, la \,\dot{\}}\ ,\quad \mathsf{pha} : \dot{\{}\, ba, la \,\dot{\}} \to \dot{\{}\, ph \,\dot{\}}\ \}$$

Fig. 1. A model of branching (ba) and linear (la) actin polymerisation resulting in phagocytosis (pha).

at M, the application of a *on M produces the multiset $M' = M \dot{-} \mathsf{a}.pre \dot{\cup} \mathsf{a}.post$. We write in this case $M \xrightarrow{\mathsf{a}} M'$.*

In the multiset rewriting representation of petri nets, each multiset rewriting rule denotes a petri net transition. The bold lower case names of the multiset rewriting rules are the transition names. Italic lower case names denote the place names. Thus, presets of multiset rewriting rules are the tokens consumed by a transition and the postsets are the tokens that are produced by a transition when that transition is enabled and it fires.

Definition 2. *A* place/transition petri net *($\mathcal{P}/\mathcal{T}$* net*) is a pair $\mathcal{N} = (\mathcal{F}, \mathcal{M})$, where $\mathcal{F}$ is a set of* places *and $\mathcal{M}$ is a multiset rewriting system over $\mathcal{F}$. The elements of $\mathcal{M}$ are called* transitions*. A $\mathcal{P}/\mathcal{T}$* net system *is a pair $(\mathcal{N}, M)$ where M is a multiset over $\mathcal{F}$ called* marking*. The application of an enabled transition to a marking is referred to as the* firing *of that transition.*

Example 1. Consider the petri net depicted in Figure 1 which models phagocytosis (ph) as an outcome of branching (ba) and linear (la) actin polymerisation, represented by the transition pha. The polymerisation of actin along these two pathways causes the extension of cytoskeleton around the engulfed particle. The branching and linear actin polymerisation result from activation of the Rho GTP binding proteins Rac (rac) and Cdc42 (cdc), respectively [31]. In Figure 1, the activation of these proteins are represented by the transitions rac and cdc, respectively. A state of this net where these two transitions are enabled can be given by the marking $M = \dot{\{}\, cdc, rac \,\dot{\}}$ which is depicted as the left-most net in Figure 3. Firing of the enabled transition cdc then results in the marking $M' = \dot{\{}\, la, rac \,\dot{\}}$.

3 System NEL

In the following sections, we define the language $\mathcal{CP}$ and its operational semantics, by means of an encoding in the proof theoretical deductive system NEL (non-commutative exponential linear logic) [10, 11]. [4] In a deductive setting provided by the underlying proof theoretical operational semantics, computations are performed by means of proof constructions.

[4] By resorting to the proof theoretical convention, we use the terms deductive system and logic synonymously.

The language $\mathcal{CP}$ could be defined independently without resorting to system NEL. However, our encoding in system NEL profits from the deductive reasoning provided by this logic. This way, also because system NEL is Turing-complete [29], the language $\mathcal{CP}$ remains prone to extensions, which can address other aspects of biological systems such as the structure of gene strands or representation of compartments, within the formal setting of this logic.

System NEL is a conservative extension of multiplicative exponential linear logic with the rules mix and mix0 (see, e.g., [1]) and a non-commutative self-dual logical operator, resembling prefixing in the process algebra. In our encoding, we use this self-dual non-commutative operator for encoding sequential composition of the transitions of the petri nets. This way, we are able to encode the sequential composition at the same logical level as parallel composition which is encoded as the commutative par operator of linear logic. Furthermore, extending multiplicative linear logic with the rules mix and mix0 makes it possible to map the units 1 and $\bot$ of multiplicative linear logic to a single unit $\circ$ (see, e.g., [9]). Because of this, we are able use the unit $\circ$ to denote both the empty transition and the empty place.

The logical expressions of system NEL are called structures. Structures are entities which share properties of formulae and sequents, and they are written in a notation which highlights their algebraic properties. In particular, we consider the structures equivalent modulo equational theories such as associativity and commutativity. The structure notation becomes useful while exploiting the associativity and commutativity of the logical operators to encode different data structures such as multisets and lists as it is the case in this paper.

Definition 3. *There are infinitely many atoms, denoted with* $a, b, \mathsf{a}, \mathsf{b}, ab, \mathsf{ab}, \ldots$ NEL structures *are generated by*

$$R ::= \circ \mid a \mid [\,R\,,\,R\,] \mid (\,R\,,\,R\,) \mid \langle\,R\,;\,R\,\rangle \mid ?R \mid !R \mid \overline{R}$$

Every atom is a structure. $\bar{\_}$ *denotes the negation of a structure.* $[\_,\_]$ *and* $(\_,\_)$ *are called* par *and* copar *and they denote the operators* $\parr$ *and* $\otimes$ *of linear logic, respectively. Par and copar are De Morgan duals of each other.* $\langle\_,\_\rangle$ *is called* seq*, it is self-dual, i.e.,* $\overline{\langle R,T\rangle} = \langle \bar{R}, \bar{T}\rangle$*. Par and copar are associative and commutative, whereas seq is associative but not commutative.* $\circ$ *is the unit for par and copar, and it is left-unit and right-unit for seq. The exponentials* $!$ *and* $?$ *of linear logic are De Morgan duals of each other. On the* NEL *structures, we also impose the equalities* $??R = ?R$*,* $!!R = !R$*,* $?\circ = \circ$ *and* $!\circ = \circ$*.*

All NEL structures can be equivalently considered in normal form by always pushing the negation inwards to atoms and removing all the units.

Example 2. The structure $\langle \bar{a}; (b, \bar{c})\rangle$ is a normal form of $\overline{\langle a; \circ; [c, \bar{b}, \circ]\rangle}$ modulo associativity and commutativity of the structures. In order to see the relationship between system NEL and multiplicative exponential linear logic consider the structure $![(?a, b), \bar{a}, !\bar{b}]$ which corresponds to $!\,(\,(?a \otimes b) \parr \bar{a} \parr !\bar{b})$. However, the logical operator seq, which we use to model sequential composition, does not have an equivalent in multiplicative exponential linear logic.

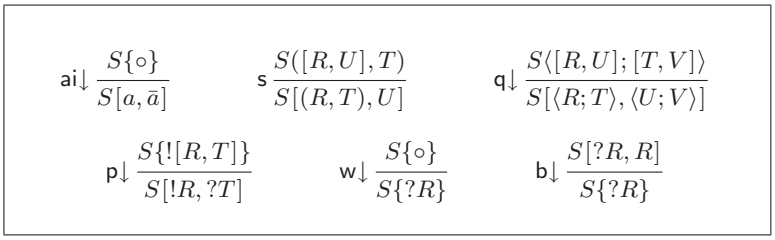


Fig. 2. System NEL

Definition 4. *A* structure context*, denoted as in* $S\{\ \}$*, is a structure with a hole that does not appear in the scope of negation. The structure* R *is a* substructure *of* $S\{R\}$ *and* $S\{\ \}$ *is its* context*. Context braces are omitted if no ambiguity is possible.*

Definition 5. *The system in Figure 2 is called* non-commutative exponential linear logic*, or system* NEL*.*

In our encoding, we use the negation to give a logical meaning to the interaction between a transition which produces a token at a place and another transition which consumes this token. This production/consumption relationship is represented by the annihilation of dual atoms at an instance of the rule ai↓ (atomic interaction) given in Figure 2. This is similar to the notion of interaction in process algebra where an input and an output process synchronise over a name. Also here, this interaction is used to implement a synchronisation mechanism for the signals, however this synchronisation is not a hand-shake synchronisation as in process algebra, but a synchronisation via common predecessor and successor transitions (see Section 7).

Definition 6. *A derivation* Δ *is a finite chain of instances of inference rules. A derivation can consist of just one structure. The top-most structure in a derivation, if present, is called the* premise*, and the bottom-most structure is called its* conclusion*. A derivation* Δ*, whose premise is* T*, conclusion is* R*, and inference rules are in* $\mathscr{S}$*, is written as* $\begin{array}{c} T \\ \Delta \Vert \mathscr{S} \\ R \end{array}$ *.*

System NEL is equipped with the notion of *deep inference*, which is useful to implement a local form of reasoning on the structures: deep inference, realised by means of structure contexts, is the capability of applying the inference rules at arbitrary depths inside the logical expressions in a way that is similar to the application of term rewriting rules. The substructures to which the inference rules are applied are determined by the structure contexts. Because the hole of a structure context can be at an arbitrary depth inside the structure, inference rules can be used to do reasoning locally on the substructures inside a context without considering the whole structure.

Example 3. Consider the structure $[a, (\bar{a}, \langle [b, \bar{b}]; [c, \bar{c}] \rangle)]$. For the following two instances of the rule $\mathsf{ai}{\downarrow}$ where it is applied bottom-up, there are the structure contexts $[a, (\bar{a}, \langle \{\ \}; [c, \bar{c}] \rangle)]$ and $[a, (\bar{a}, \langle [b, \bar{b}]; \{\ \} \rangle)]$. Below, the holes are marked with grey shades.

$$\mathsf{ai}{\downarrow} \frac{[a, (\bar{a}, [c, \bar{c}])]}{[a, (\bar{a}, \langle [b, \bar{b}]; [c, \bar{c}] \rangle)]} \qquad \mathsf{ai}{\downarrow} \frac{[a, (\bar{a}, [b, \bar{b}])]}{[a, (\bar{a}, \langle [b, \bar{b}]; [c, \bar{c}] \rangle)]}$$

For a detailed discussion on proof theory of NEL and the precise relation between NEL and MELL (multiplicative exponential linear logic), the reader is referred to [10, 11, 9, 18].

4 Syntax of the Language $\mathcal{CP}$

In this section, we introduce the syntax of the language $\mathcal{CP}$. We first define process structures, which are expressions denoting the transition histories of a given net. They are similar to process expressions of process algebra, however built from atomic petri net transition names.

Definition 7 (process structure). *A* process structure *is generated by*

$$\mathsf{P} ::= \circ \mid \mathsf{a} \mid [\,\mathsf{P}\,,\,\mathsf{P}\,] \mid \langle\,\mathsf{P}\,;\,\mathsf{P}\,\rangle$$

where $\circ$ *denotes the empty process and* a *denotes atoms representing transition names.* $[\_, \_]$ *and* $\langle \_; \_ \rangle$ *denote parallel and sequential composition, respectively.*

Example 4. Consider the process structure $\mathsf{P} = \langle [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha} \rangle$. In P, following the concurrent firing of the transitions cdc and rac, the transition pha fires.

The meaning of concurrent and sequential composition of transitions is defined in Subsection 5 where we discuss the operational semantics of the language $\mathcal{CP}$. However, the intuition behind the compositions of transitions is that the concurrent firing of two transitions that are composed in parallel produces an effect that is consumed by their successors, composed to them sequentially. The concurrent effect of two transitions is same as their simultaneous firing when there are no resource conflicts between the two transitions. Let us now define our encoding of transitions and nets in the language of system NEL.

Definition 8 (transition structure). *Given a transition* $\mathsf{a} : \dot{\{}\, c_1, \ldots, c_p \,\dot{\}} \rightarrow \dot{\{}\, e_1, \ldots, e_q \,\dot{\}}$*, the* transition structure *(denoted with* Q*) of* a*, is a structure of the following form:*

$$\langle (\bar{c}_1, \ldots, \bar{c}_p); \mathsf{a}; [e_1, \ldots, e_q] \rangle$$

Definition 9 (net structure). *Given a* $\mathcal{P}/\mathcal{T}$ *system* $(\mathcal{N}, M)$ *where* $M = \dot{\{}\, r_1, \ldots, r_n \,\dot{\}}$*, let* $\mathsf{Q}_1, \ldots, \mathsf{Q}_s$ *be the transition structures for all the transitions in* $\mathcal{N}$*. Let* P *be a process structure that we call* history. The net structure *(denoted with* $\mathcal{R}$*) for* $(\mathcal{N}, M)$ *with history* P *is defined as follows:*

$$[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, \langle \mathsf{P}; [r_1, \ldots, r_n] \rangle]$$

In the language $\mathcal{CP}$, the net structures provide a syntactic representation of petri nets together with a history of previous transitions: in the definition of net structures above, process P, which can be the empty process $\circ$, keeps the information on the history of the previous firings of the net.

Example 5. The net structure for the petri net depicted in Figure 1, where the initial marking is $M = \dot{\{}\, cdc, rac \,\dot{\}}$ and the history $\mathsf{P} = \circ$, is as follows:

$$[?\langle c\bar{d}c; \mathsf{cdc}; la\rangle, ?\langle r\bar{a}c; \mathsf{rac}; ba\rangle, ?\langle(\bar{la}, \bar{ba}); \mathsf{pha}; ph\rangle, [cdc, rac]\,]$$

5 Operational Semantics

In this subsection, we define the operational semantics of the language $\mathcal{CP}$ as analytic bottom-up proof constructions in system NEL. In a bottom-up [5] proof construction, derivations and proofs are constructed by starting from the conclusion, and by going up by applications of the inference rules.

Definition 10 (securing). *A* securing*, denoted with* S*, is a structure of the form* $\langle \mathsf{a_1}; \ldots; \mathsf{a_n}\,\rangle$ *where* $n \geq 1$*. For a net* $\mathcal{N}$*, we say that* M' *results from applying* $\mathsf{S} = \langle \mathsf{a_1}; \ldots; \mathsf{a_n}\rangle$ *to marking* M *if there are transitions* $\mathsf{a_1}, \ldots, \mathsf{a_n} \in \mathcal{N}$ *and markings* $M_1, \ldots, M_n$ *such that* $M \xrightarrow{\mathsf{a_1}} M_1 \xrightarrow{\mathsf{a_1}} \ldots \xrightarrow{\mathsf{a_n}} M_n$ *and* $M_n = M'$*. We then write* $\Phi(\mathsf{S}, M) = M'$*.*

Example 6. Consider the net structure in Example 5. $\langle \mathsf{cdc}; \mathsf{rac}; \mathsf{pha}\rangle$ is a securing.

Definition 11 (firing). *The following rule is called* firing*:*

$$\mathsf{firing}\ \frac{S[\,?\langle\,(\bar{c}_1, \ldots, \bar{c}_p); \mathsf{a};\ E\rangle,\ \langle \mathsf{P}; \mathsf{a}; [E, R]\rangle\,]}{S[\,?\langle\,(\bar{c}_1, \ldots, \bar{c}_p); \mathsf{a};\ E\rangle\,, \langle \mathsf{P}; [c_1, \ldots, c_p, R]\rangle\,]}$$

In an instance of the rule firing*,* $\langle\,(\bar{c}_1, \ldots, \bar{c}_p); \mathsf{a};\ E\rangle$ *is called the* active transition structure*.*

For any pair $(\mathcal{N}, M)$ and securing S, we can compute the marking resulting from applying the securing to the marking by applying the rule firing bottom-up.

Example 7. The net structure given in Example 5 is the conclusion of the derivation below. By means of bottom-up proof construction, we compute the marking resulting from applying the securing $\langle \mathsf{cdc}; \mathsf{rac}; \mathsf{pha}\rangle$ to $M = \dot{\{}\, cdc, rac \,\dot{\}}$ as follows:

$$\mathsf{firing}\ \frac{\mathsf{firing}\ \dfrac{\mathsf{firing}\ \dfrac{[?\langle c\bar{d}c; \mathsf{cdc}; la\rangle, ?\langle r\bar{a}c; \mathsf{rac}; ba\rangle, ?\langle(c\bar{d}c, r\bar{a}c); \mathsf{pha}; ph\rangle, \langle \mathsf{cdc}; \mathsf{rac}; \mathsf{pha}; [ph]\rangle\,]}{[?\langle c\bar{d}c; \mathsf{cdc}; la\rangle, ?\langle r\bar{a}c; \mathsf{rac}; ba\rangle, ?\langle(c\bar{d}c, r\bar{a}c); \mathsf{pha}; ph\rangle, \langle \mathsf{cdc}; \mathsf{rac}; [la, ba]\rangle\,]}}{[?\langle c\bar{d}c; \mathsf{cdc}; la\rangle, ?\langle r\bar{a}c; \mathsf{rac}; ba\rangle, ?\langle(c\bar{d}c, r\bar{a}c); \mathsf{pha}; ph\rangle, \langle \mathsf{cdc}; [la, rac]\rangle\,]}}{[?\langle c\bar{d}c; \mathsf{cdc}; la\rangle, ?\langle r\bar{a}c; \mathsf{rac}; ba\rangle, ?\langle(c\bar{d}c, r\bar{a}c); \mathsf{pha}; ph\rangle, [cdc, rac]\,]}$$

The bottom-up reading of this derivation describes the situation depicted in Figure 3, where the left-most net corresponds to conclusion of this derivation and the right-most net corresponds to the premise.

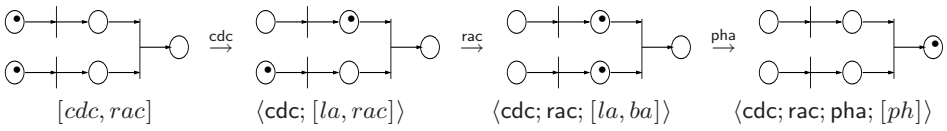


Fig. 3. Firings of the net in Figure 1 that correspond to the derivation in Example 7.

Definition 12. *A rule* $\rho\,\dfrac{T}{R}$ *is derivable for* $\mathscr{S}$ *if there is a derivation* $\Delta\!\left[\!\!\left[\dfrac{T}{R}\right]\!\!\right]_{\mathscr{S}}$.

Lemma 1. *The rule* firing *is derivable for system* NEL.

Proof. Take the following derivation:

$$\mathsf{b}\!\downarrow\dfrac{\mathsf{q}\!\downarrow\dfrac{\mathsf{q}\!\downarrow\dfrac{\mathsf{i}\!\downarrow\dfrac{\mathsf{q}\!\downarrow\dfrac{S[\,?\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle\mathsf{P};\mathsf{a};\,[E,R]\rangle]}{S[\,?\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle\mathsf{P};[\langle\mathsf{a};\,E\rangle,R]\rangle]}}{S[\,?\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle\mathsf{P};[\langle[c_1,\ldots,c_p,(\bar{c}_1,\ldots,\bar{c}_p)];\mathsf{a};\,E\rangle,R]\rangle]}}{S[\,?\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle\mathsf{P};[c_1,\ldots,c_p,\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle,R]\rangle]}}{S[\,?\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle\mathsf{P};[c_1,\ldots,c_p,R]\rangle]}}{S[\,?\langle(\bar{c}_1,\ldots,\bar{c}_p);\mathsf{a};\,E\rangle\,,\langle\mathsf{P};[c_1,\ldots,c_p,R]\rangle]}$$

Composition of Processes By composing the transitions with each other by means of parallel and sequential composition, we can treat processes as atomic transitions. This way, we can treat transitions and processes compositionally.

Definition 13 (sequential)**.** *The following rule is called* sequential composition*:*

$$\mathsf{sequential}\,\frac{S\langle C;\mathsf{P}_1;\mathsf{P}_2;[E_1,E_2]\rangle}{S[\langle C;\mathsf{P}_1;[r_1,\ldots,r_m,E_1]\rangle,\langle(\bar{r}_1,\ldots,\bar{r}_m);\mathsf{P}_2;E_2\rangle]}$$

Definition 14 (parallel)**.** *The following rule is called* parallel composition*:*

$$\mathsf{parallel}\,\frac{S\langle(C_1,C_2);[\mathsf{P}_1,\mathsf{P}_2];[E_1,E_2]\rangle}{S[\langle C_1;\mathsf{P}_1;E_1\rangle,\langle C_2;\mathsf{P}_2;E_2\rangle]}$$

Lemma 2. *The rules* sequential *and* parallel *are derivable for system* NEL.

Proof. Take the following derivations, respectively:

$$\mathsf{q}\!\downarrow\dfrac{\mathsf{i}\!\downarrow\dfrac{\mathsf{q}\!\downarrow\dfrac{\mathsf{q}\!\downarrow\dfrac{S\langle C;\mathsf{P}_1;\mathsf{P}_2;[E_1,E_2]\rangle}{S\langle C;\mathsf{P}_1;[\langle\mathsf{P}_2;E_2\rangle,E_1]\rangle}}{S\langle C;\mathsf{P}_1;[\langle[E,\bar{E}];\mathsf{P}_2;E_2\rangle,E_1]\rangle}}{S\langle C;\mathsf{P}_1;[E,\langle\bar{E};\mathsf{P}_2;E_2\rangle,E_1]\rangle}}{S[\langle C;\mathsf{P}_1;[E,E_1]\rangle,\langle\bar{E};\mathsf{P}_2;E_2\rangle]}$$

$$\mathsf{q}\!\downarrow\dfrac{\mathsf{s}\dfrac{S\langle(C_1,C_2);[\mathsf{P}_1,\mathsf{P}_2];[E_1,E_2]\rangle}{S\langle[C_1,C_2];[\mathsf{P}_1,\mathsf{P}_2];[E_1,E_2]\rangle}}{S\langle[C_1,C_2];[\langle\mathsf{P}_1;E_1\rangle,\langle\mathsf{P}_2;E_2\rangle]\rangle}$$

[5] The use of the word "bottom-up" here is purely mechanical, and should not be confused with the conceptual use of this word in the introduction.

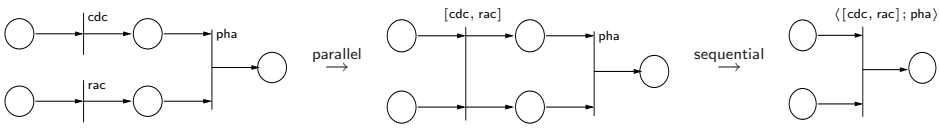


Fig. 4. The transformations of the transitions of the petri net in Figure 1 with respect to the derivation given in Example 8.

The definitions of sequential and parallel composition of processes allow to lift the notion of firing from transitions to processes. By composing the transitions of a petri net by means of bottom-up applications of the rules parallel and sequential we transform a set of transitions of a net a to a single composed transition.

Example 8. Consider the petri net depicted in Figure 1. We can now compose the causally independent transitions cdc and rac in parallel, and obtain the process in the premise of the following derivation. Because the postsets of these two transitions provide the resources required by the preset of the transition pha, we can then compose this transition sequentially. This results in the transformation depicted in Figure 4.

$$\begin{array}{r} \mathsf{sequential} \\ \mathsf{parallel} \end{array} \frac{\langle (c\bar{dc}, r\bar{ac}); \langle [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha} \rangle; ph \rangle}{[\langle (c\bar{dc}, r\bar{ac}); [\mathsf{cdc}, \mathsf{rac}]; [ba, la] \rangle, \langle (\bar{ba}, \bar{la}); \mathsf{pha}; ph \rangle]} \\ [\langle c\bar{dc}; \mathsf{cdc}; ba \rangle, \langle r\bar{ac}; \mathsf{rac}; la \rangle, \langle (\bar{ba}, \bar{la}); \mathsf{pha}; ph \rangle]$$

In the process given in the premise of this derivation, the transitions cdc and rac fire concurrently, because they are synchronised by the transition pha, which requires the resources these two transitions produce in order to fire. In [31], it is reported that the Cdc42 signal is more dominant at the early stages of phagocytosis, whereas Rac signal becomes more dominant in later stages. Because the biological signals that these two transitions model have different durations, such a model of synchronisation by means of common successors and predecessors is well suited for modelling such signalling pathways (see Section 7).

Theorem 1 (soundness). *Let $\mathcal{R}$ be a net structure of a $\mathcal{P}/\mathcal{T}$ system $(\mathcal{N}, M)$. For a marking $M' = \dot{\{}\, r_1, \ldots, r_n \,\dot{\}}$ and transitions $\mathsf{a}_1, \ldots, \mathsf{a}_k \in \mathcal{N}$, if M' results from applying $\langle \mathsf{a}_1; \ldots; \mathsf{a}_k \rangle$ to M then there is a derivation*

$$\begin{array}{c} \langle \mathsf{a}_1; \ldots; \mathsf{a}_k; [r_1, \ldots, r_n] \rangle \\ \vartriangle \!\!\! \| \, \mathsf{NEL} \\ \mathcal{R} \end{array} .$$

Theorem 2 (completeness). *Let $\mathcal{R}$ be a net structure. If there is a process* P *and a derivation* $\begin{array}{c} \langle \mathsf{P}; [r_1, \ldots, r_n] \rangle \\ \vartriangle \!\!\! \| \, \mathsf{NEL} \\ \mathcal{R} \end{array}$ *then for any securing* S *such that there is a derivation* $\begin{array}{c} \mathsf{S} \\ \vartriangle \!\!\! \| \, \{\mathsf{q}\downarrow\} \\ \mathsf{P} \end{array}$, *we have that $\dot{\{}\, r_1, \ldots, r_n \,\dot{\}}$ results from applying* S *to M.*

By resorting to Theorem 2 and Theorem 1, we can search for processes by exploring a search space that is constructed by applications of the rules firing, sequential and parallel. This allows to formulate petri net reachability queries as proof search for a given $\mathcal{P}/\mathcal{T}$ net, i.e., "for two markings M and M', is there a process P such that M' results from applying P to M?".

6 Composition of Petri Nets

Previously, we have seen how process can be composed. However, it is often desirable to study subsystems of a larger system as separate petri nets, and then compose the knowledge on the components at will to obtain systems of desired size and complexity without committing to a particular process of a subsystem. In this section, we define a notion of composition of petri nets which makes it possible to build models of a larger systems by composing the models of subsystems. We then define a notion of *nesting* which allows to replace the model of a subsystem in a petri net with a less abstract more detailed model.

Definition 15 (net composition). *Let $\mathcal{R}_1$ and $\mathcal{R}_2$ be the two net structures $[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, \langle \mathsf{P}; [r_1, \ldots, r_n] \rangle]$ and $[?\mathsf{Q}'_1, \ldots, ?\mathsf{Q}'_k, \langle \mathsf{P}'; [r'_1, \ldots, r'_m] \rangle]$. Their composition is defined as the structure given by the premise of the inference rule below where the two structures to be composed are given in the conclusion in a par structure.*

$$\mathsf{compose}\ \frac{S[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, ?\mathsf{Q}'_1, \ldots, ?\mathsf{Q}'_k, \langle [\mathsf{P}, \mathsf{P}']; [r_1, \ldots, r_n, r'_1, \ldots, r'_m] \rangle]}{S[[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, \langle \mathsf{P}; [r_1, \ldots, r_n] \rangle], [?\mathsf{Q}'_1, \ldots, ?\mathsf{Q}'_k, \langle \mathsf{P}'; [r'_1, \ldots, r'_m] \rangle]]} \quad .$$

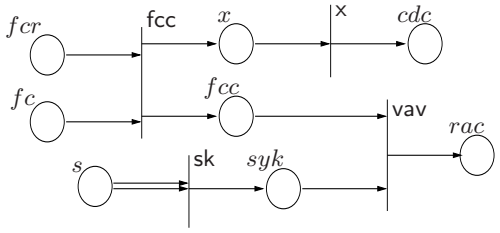
Proposition 1. *The rule* compose *is derivable for system* NEL.

Proof. Take the following derivation.

$$\begin{array}{l} \mathsf{q}{\downarrow}\ \dfrac{S[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, ?\mathsf{Q}'_1, \ldots, ?\mathsf{Q}'_k, \langle [\mathsf{P}, \mathsf{P}']; [r_1, \ldots, r_n, r'_1, \ldots, r'_m] \rangle]}{S[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, ?\mathsf{Q}'_1, \ldots, ?\mathsf{Q}'_k, \langle \mathsf{P}; [r_1, \ldots, r_n] \rangle, \langle \mathsf{P}'; [r'_1, \ldots, r'_m] \rangle]} \\ = \dfrac{}{S[[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, \langle \mathsf{P}; [r_1, \ldots, r_n] \rangle], [?\mathsf{Q}'_1, \ldots, ?\mathsf{Q}'_k, \langle \mathsf{P}'; [r'_1, \ldots, r'_m] \rangle]]} \end{array}$$

From the point of view of the standard graphical representation of petri nets, the notion of net composition above could be seen as merging the places with the same names of two nets in order to obtain a new petri net.

Example 9. Consider the net depicted in Figure 5: in Fc receptor-mediated phagocytosis [31], the binding of the Fc receptor (fcr) with the Fc (fc), while resulting in FcR-Fc complex (fcc), initiates a cascade (fcc) that activates the Rho GTP binding protein Rac. However, the activation of Rac (rac) is also causally dependent on the prior activation of Syk (syk) as a result of phosphorylation of the two tyrosine residues (s) on the *ITAM* (immunoreceptor tyrosine-based activation motif) located on the cytoplasmic tail of the *Fc receptor*. Active Syk then activates a guanosine-nucleotide exchange factor (GEF) (vav) which activates Rac (rac). Furthermore, another Rho GTP binding protein Cdc42 (cdc)



$$\mathcal{N}_2 = \{\, \mathsf{fcc} : \dot{\{}\, fcr, fc \,\dot{\}} \to \dot{\{}\, x, fcc \,\dot{\}}\,,\ \mathsf{sk} : \dot{\{}\, s, s \,\dot{\}} \to \dot{\{}\, syk \,\dot{\}}\,,\ \mathsf{x} : \dot{\{}\, x \,\dot{\}} \to \dot{\{}\, cdc \,\dot{\}}\,,\ \mathsf{vav} : \dot{\{}\, fcc, syk \,\dot{\}} \to \dot{\{}\, rac \,\dot{\}}\, \}$$

Fig. 5. A model of signalling during phagocytosis which is initiated by the binding of the Fc receptor with Fc.

becomes activated by an unknown GEF (x) as a result of Fc receptor and Fc binding [31]. Let $\mathcal{R}_1$ and $\mathcal{R}_2$ be the net structures of the petri nets given in Figure 1 and Figure 5, respectively.

$$\mathcal{R}_1 = [?\langle c\bar{d}c; \mathsf{cdc}; ba\rangle, ?\langle r\bar{a}c; \mathsf{rac}; la\rangle, ?\langle(\bar{ba}, \bar{la}); \mathsf{pha}; ph\rangle]$$

$$\mathcal{R}_2 = [?\langle(\bar{fcr}, \bar{fc}); \mathsf{fcc}; [x, fcc]\rangle, ?\langle(\bar{s}, \bar{s}); \mathsf{sk}; syk\rangle, ?\langle\bar{x}; \mathsf{x}; cdc\rangle, ?\langle(\bar{fcc}, \bar{syk}); \mathsf{vav}; rac\rangle]$$

Both $\mathcal{R}_1$ and $\mathcal{R}_2$ are not instantiated by any markings and they do not have a history of previous firings of transitions. Thus, their composition is given by $[\mathcal{R}_1, \mathcal{R}_2]$ which is the net structure of the petri net given in Figure 6.

Another notion of compositionality emerges when we want to study a subsystem in more detail. The following definition serves this purpose.

Definition 16 (nesting). *Let* $\mathsf{Q} = \langle(\bar{c}_1, \ldots, \bar{c}_p); \mathsf{a}; [e_1, \ldots, e_q]\rangle$ *be a transition structure and let* $\mathcal{R}$ *be the net structure* $[?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s]$*. The nesting of* $\mathcal{R}$ *in* Q *is defined as* $\langle(\bar{c}_1, \ldots, \bar{c}_p); [?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, c_1, \ldots, c_p]\rangle$ *. We say* $\mathcal{R}$ *is well nested in* Q *by* Δ *if there is a process structure* P*, a structure* $[r_1, \ldots, r_n]$ *and a derivation*

$$\begin{array}{c} \langle(\bar{c}_1, \ldots, \bar{c}_p); \mathsf{P}; [e_1, \ldots, e_q, r_1, \ldots, r_n]\rangle \\ \Delta \,\|\!|\, \mathsf{NEL} \\ \langle(\bar{c}_1, \ldots, \bar{c}_p); [?\mathsf{Q}_1, \ldots, ?\mathsf{Q}_s, c_1, \ldots, c_p]\rangle \end{array} .$$

We can replace any transition structure in a net structure with a well nested nesting. This corresponds to adding more detail to a transition in a petri net.

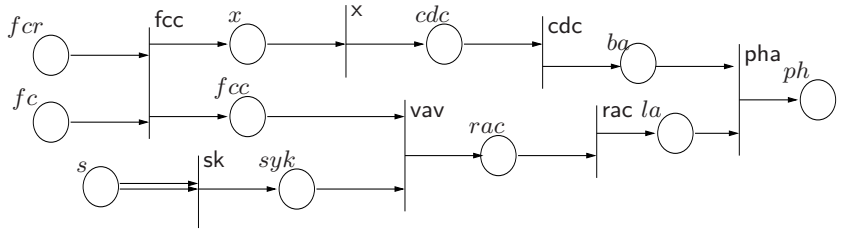
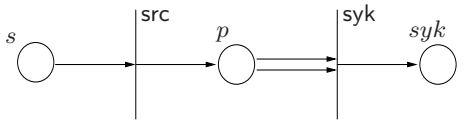


Fig. 6. The petri net resulting from composing the nets given in Figures 1 and 5.



$$\mathcal{N}_3 = \{\ \mathsf{src} : \dot{\{}\, s \,\dot{\}} \to \dot{\{}\, p \,\dot{\}}\ ,\quad \mathsf{syk} : \dot{\{}\, p, p \,\dot{\}} \to \dot{\{}\, syk \,\dot{\}}\ \}$$

Fig. 7. A model of the activation of the protein Syk as a result of the phosphorylation of two tyrosine residues on the immunoreceptor tyrosine-based activation motif.

Example 10. Let us consider the transition sk of Example 9 in Figure 5 given with the transition structure $\langle(\bar{s},\bar{s});\mathsf{sk};syk\rangle$. This transition models the phosphorylation of the two tyrosine residues on the *ITAM* located on the cytoplasmic tail of the *Fc receptor*. When we consider this process in more detail, we learn that protein *Src*, anchored to the cell membrane, performs the phosphorylation, and then the protein *Syk* binds to these two phosphorylated domains and transmits the signal further [31]. We can model this scenario as the petri net depicted in Figure 7 with the net structure $\mathcal{R}_3 = [?\langle\bar{s};\mathsf{src};p\rangle, ?\langle(\bar{p},\bar{p});\mathsf{syk};syk\rangle]$. By nesting the net structure in sk, we obtain $\langle(\bar{s},\bar{s});[?\langle\bar{s};\mathsf{src};p\rangle, ?\langle(\bar{p},\bar{p});\mathsf{syk};syk\rangle, s, s]\rangle$ which is well nested, because we have the following derivation:

$$\dfrac{\mathsf{sequential}\ \dfrac{\mathsf{firing}\ \dfrac{\langle(\bar{s},\bar{s});[\mathsf{src},\mathsf{src}];\mathsf{syk};syk\rangle}{\langle(\bar{s},\bar{s});[\langle(\bar{s},\bar{s});[\mathsf{src},\mathsf{src}];\mathsf{syk};syk\rangle, s, s]\rangle}}{\langle(\bar{s},\bar{s});[\langle(\bar{s},\bar{s});[\mathsf{src},\mathsf{src}];[p,p]\rangle, \langle(\bar{p},\bar{p});\mathsf{syk};syk\rangle, s, s]\rangle}}{\mathsf{parallel}\ \dfrac{}{\langle(\bar{s},\bar{s});[\langle\bar{s};\mathsf{src};p\rangle, \langle\bar{s};\mathsf{src};p\rangle, \langle(\bar{p},\bar{p});\mathsf{syk};syk\rangle, s, s]\rangle}}$$

$$\|_{\{\mathsf{b}\downarrow,\mathsf{w}\downarrow\}}$$

$$\langle(\bar{s},\bar{s});[?\langle\bar{s};\mathsf{src};p\rangle, ?\langle(\bar{p},\bar{p});\mathsf{syk};syk\rangle, s, s]\rangle$$

We can then replace the transition sk with the nesting of $\mathcal{R}_3$ in sk in any context, thus give a more detailed model in comparison with the model of Figure 6 by replacing the transition sk with the net $\mathcal{N}_3$ depicted in Figure 7.

The notions of *petri net composition* and *nesting* introduced above reflect the two complimentary approaches to composition of models. On one hand, *petri net composition* allows to consider the parts of a complex biological system in isolation, and this way build models by composing these parts gradually at the same level to build more and more complex models. On the other hand, *nesting* allows to add more and more detail to components so that models can be considered at lower and lower levels of abstraction, while moving from greater parts of building blocks towards smaller components.

7 Process Structures Revisited

The proof theoretical operational semantics of language $\mathcal{CP}$ provides a platform for using the underlying deductive system to perform logical reasoning on the petri nets being studied. Apart from petri net reachability queries, the underlying deductive system can be used to check if process structures which are same in terms of their input and output are interleavings of the same process structure.

This is because a process structure P gives a canonical representation of securings, determined by all the derivations $\overset{\mathsf{S}}{\underset{\mathsf{P}}{\Delta\!\!\!\!\!\!\parallel_{\{\mathsf{q}\downarrow\}}}}$ where the rule $\mathsf{q}\downarrow$ serves as the expansion law in process algebra. In other words, a process structure provides a syntactical representation of a partial order of transitions. This observation allows to define a notion of equivalence on the process structures.

Definition 17. *Given a process structure* P*, two process structures* P_1 *and* P_2 *are* P-equivalent *if there are the derivations* $\overset{\circ}{\underset{[\mathsf{P},\bar{\mathsf{P}}_1]}{\Delta\!\!\!\!\!\!\parallel_{\{\mathsf{ai}\downarrow,\mathsf{q}\downarrow\}}}}$ *and* $\overset{\circ}{\underset{[\mathsf{P},\bar{\mathsf{P}}_2]}{\Delta\!\!\!\!\!\!\parallel_{\{\mathsf{ai}\downarrow,\mathsf{q}\downarrow\}}}}$.

Proposition 2. *If process structures* P_1 *and* P_2 *are* P*-equivalent then for any marking* M *such that* P *is enabled at* M*,* $\Phi(\mathsf{P}_1, M) = \Phi(\mathsf{P}, M) = \Phi(\mathsf{P}_2, M)$*.*

Example 11. Let $\mathsf{P} = \langle [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha} \rangle$, then the process structures $\langle \mathsf{cdc}; \mathsf{rac}; \mathsf{pha} \rangle$ and $\langle \mathsf{rac}; \mathsf{cdc}; \mathsf{pha} \rangle$ are P-equivalent, because we have the two proofs below.

$$\mathsf{q}\downarrow \dfrac{\mathsf{ai}\downarrow \dfrac{\mathsf{ai}\downarrow \dfrac{\mathsf{ai}\downarrow \dfrac{\overset{\circ}{}}{[\mathsf{rac}, \bar{\mathsf{rac}}]}}{[\mathsf{rac}, \langle [\mathsf{cdc}, \bar{\mathsf{cdc}}]; \bar{\mathsf{rac}} \rangle]}}{[\mathsf{cdc}, \mathsf{rac}, \langle \bar{\mathsf{cdc}}; \bar{\mathsf{rac}} \rangle]}}{\langle [\mathsf{cdc}, \mathsf{rac}, \langle \bar{\mathsf{cdc}}; \bar{\mathsf{rac}} \rangle]; [\mathsf{pha}, \bar{\mathsf{pha}}] \rangle}}{[\langle [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha} \rangle, \langle \bar{\mathsf{cdc}}; \bar{\mathsf{rac}}; \bar{\mathsf{pha}} \rangle]}$$

$$\mathsf{q}\downarrow \dfrac{\mathsf{ai}\downarrow \dfrac{\mathsf{ai}\downarrow \dfrac{\mathsf{ai}\downarrow \dfrac{\overset{\circ}{}}{[\mathsf{cdc}, \bar{\mathsf{cdc}}]}}{[\mathsf{cdc}, \langle [\mathsf{rac}, \bar{\mathsf{rac}}]; \bar{\mathsf{cdc}} \rangle]}}{[\mathsf{cdc}, \mathsf{rac}, \langle \bar{\mathsf{rac}}; \bar{\mathsf{cdc}} \rangle]}}{\langle [\mathsf{cdc}, \mathsf{rac}, \langle \bar{\mathsf{rac}}; \bar{\mathsf{cdc}} \rangle]; [\mathsf{pha}, \bar{\mathsf{pha}}] \rangle}}{[\langle [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha} \rangle, \langle \bar{\mathsf{rac}}; \bar{\mathsf{cdc}}; \bar{\mathsf{pha}} \rangle]}$$

Proposition 3. *For any process structure* $\mathsf{P}, \mathsf{P}_1, \mathsf{P}_2$*;* P_1 *and* P_2 *are* P-equivalent *if there are derivations* $\overset{\mathsf{P}_1}{\underset{\mathsf{P}}{\Delta\!\!\!\!\!\!\parallel_{\{\mathsf{q}\downarrow\}}}}$ *and* $\overset{\mathsf{P}_2}{\underset{\mathsf{P}}{\Delta\!\!\!\!\!\!\parallel_{\{\mathsf{q}\downarrow\}}}}$.

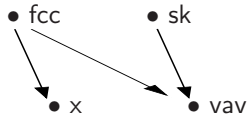
When we examine the graphical structure of the petri nets, we can also observe partial orders of the transitions which demonstrate the possible firings of the petri net. However, the syntactic representation of process structures sets a boundary which is meaningful from the point of view of concurrent messages as, for example, those in the signalling pathways in Fc receptor mediated phagocytosis. A partial order which is represented by a process structure is an N-free partial order, which is defined as follows:

Definition 18. *A partial order* $\leq \subseteq \mathscr{A} \times \mathscr{A}$ *is* N-free (series-parallel) *if and only if, for all* $\mathsf{a}, \mathsf{b}, \mathsf{c}, \mathsf{d} \in \mathscr{A}$*,* $\{(\mathsf{a}, \mathsf{b}), (\mathsf{c}, \mathsf{d}), (\mathsf{c}, \mathsf{b})\} \subseteq \leq$ *implies* $(\mathsf{a}, \mathsf{d}) \in \leq$*.* N-free closure *of a partial order* $\leq$ *is the smallest N-free partial order containing* $\leq$*.*

Example 12. Consider the partial orders denoted by the graphs below, which are given in the notation of event structures (see, e.g., [35]), where nodes denote events and arrows denote dependencies with respect to causality between events: the one on the left is an N-free partial order, whereas the one on the right is not.

From the point of view of concurrent messages as those in signalling pathways, a representation of signalling as N-free partial orders is meaningful: when the common predecessor (meet) and the common successor (join) of two processes are considered as points in time, these N-free partial orders provide a representation of synchronisation of processes while taking their duration into consideration: because the representation of resources provides a model of dependencies, processes with a common meet and join can be executed concurrently. However, such an observation is impossible in a partial order that is not N-free. Although a partial order of transitions of a petri net can provide a canonical representation of a class of securings, N-free closures of such partial orders need to be considered when modelling concurrent transitions. Because the process structures allow the representation of only N-free partial orders, they are well suited for modelling concurrent transitions as those in signalling pathways, also because of their capability of capturing the duration of processes.

Example 13. Let us consider the petri net depicted in Figure 5. The partial order of the transitions of this net in terms of their dependencies is depicted in the following graph where nodes denote transitions and arrows denote causal dependencies in the event structures notation [35].



In this graph, we observe that the transitions fcc and sk are partially ordered because they are independent from each other due to the resources that they require to fire. Similarly the pairs x, vav and sk, x are partially ordered. Because such partially ordered transitions can fire in any order, this graph provides a canonical representation of the following securings:

$\langle \mathsf{fcc}; \mathsf{sk}; \mathsf{x}; \mathsf{vav} \rangle \quad \langle \mathsf{fcc}; \mathsf{sk}; \mathsf{vav}; \mathsf{x} \rangle \quad \langle \mathsf{fcc}; \mathsf{x}; \mathsf{sk}; \mathsf{vav} \rangle \quad \langle \mathsf{sk}; \mathsf{fcc}; \mathsf{x}; \mathsf{vav} \rangle \quad \langle \mathsf{sk}; \mathsf{fcc}; \mathsf{vav}; \mathsf{x} \rangle$

However, if one considers the concurrent firings, we observe that if the transitions fcc and sk fire concurrently, then sk and x cannot fire concurrently because x requires fcc to fire. In this system, the possible concurrent firings are the ones that are given by the process structures $\langle \mathsf{fcc}; [\mathsf{sk}, \mathsf{x}]; \mathsf{vav} \rangle$ and $\langle [\mathsf{fcc}, \mathsf{sk}]; [\mathsf{x}, \mathsf{vav}] \rangle$. It is important to observe that these process structures denote N-free closures of the partial order depicted above. Their graphical representations are depicted as the following Hasse-diagrams, respectively.

These two process structures indicate two equally possible flows of the signal in this model with the same presets and postsets, however the latter process structure is more parallelised, thus less restricted, than the former.

Example 14. Let us consider the net structure $\mathcal{R}_2$ of the petri net depicted in Figure 5 together with the marking $M = \dot{\{}\, s, s, fc, fcr \,\dot{\}}$. We can construct the derivation Δ_1 below with the process structure $\langle[\mathsf{fcc}, \mathsf{sk}]; [\mathsf{x}, \mathsf{vav}]\rangle$ of Example 13 at the premise. By composing $\mathcal{R}_1$ and $\mathcal{R}_2$ as in Example 9, we can then construct the derivation Δ_2 below on the right.

$$\begin{array}{c} [\mathcal{R}_2, \langle[\mathsf{fcc}, \mathsf{sk}]; [\mathsf{x}, \mathsf{vav}]; [cdc, rac]\rangle] \\ \Delta_1 \,\big[\!\big|\, \mathsf{NEL} \\ [\mathcal{R}_2, s, s, fc, fcr] \end{array} \qquad \begin{array}{c} [\mathcal{R}_1, \mathcal{R}_2, \langle[\mathsf{fcc}, \mathsf{sk}]; [\mathsf{x}, \mathsf{vav}]; [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha}; ph\rangle] \\ \Delta_2 \,\big[\!\big|\, \mathsf{NEL} \\ [\mathcal{R}_1, \mathcal{R}_2, \langle[\mathsf{fcc}, \mathsf{sk}]; [\mathsf{x}, \mathsf{vav}]; [cdc, rac]\rangle] \end{array}$$

Let us then consider the net structure $\mathcal{R}_3$ of the petri net depicted in Figure 7. We nest $\mathcal{R}_3$ in the transition structure $\langle(\bar{s}, \bar{s}); \mathsf{sk}; syk\rangle$ of the transition sk as in Example 10. Thus, by nesting we replace the well nested structure

$$\langle(\bar{s}, \bar{s}); [?\langle\bar{s}; \mathsf{src}; p\rangle, ?\langle(\bar{p}, \bar{p}); \mathsf{syk}; syk\rangle, s, s]\rangle$$

with the shaded region in the structure

$$\mathcal{R}_2 = [?\langle(\bar{fcr}, \bar{fc}); \mathsf{fcc}; [x, fcc]\rangle, ?\langle(\bar{s}, \bar{s}); \mathsf{sk}; syk\rangle, ?\langle\bar{x}; \mathsf{x}; cdc\rangle, ?\langle(\bar{fcc}, \bar{syk}); \mathsf{vav}; rac\rangle]$$

and obtain a structure that we call $\mathcal{R}_2'$. Then, by using the derivation in Example 10, we obtain the following net structure.

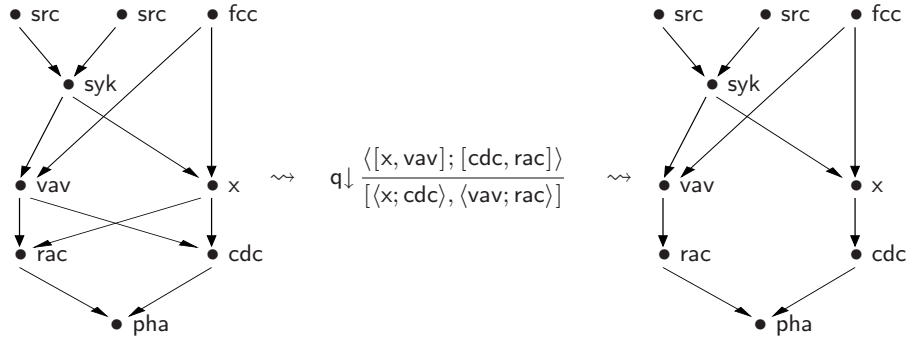
$$[?\langle(\bar{fcr}, \bar{fc}); \mathsf{fcc}; [x, fcc]\rangle, ?\langle(\bar{s}, \bar{s}); [\mathsf{src}, \mathsf{src}]; \mathsf{syk}; syk\rangle, ?\langle\bar{x}; \mathsf{x}; cdc\rangle, ?\langle(\bar{fcc}, \bar{syk}); \mathsf{vav}; rac\rangle]$$

We call this net structure $\mathcal{R}_2''$, and we use Δ_3 to denote the net structure of Example 10. We can then construct the following derivation which delivers at its premise a model of the signalling cascade in Fc receptor mediated phagocytosis.

$$\begin{array}{c} [\mathcal{R}_2'', \mathcal{R}_1, \langle[\mathsf{fcc}, \langle[\mathsf{src}, \mathsf{src}]; \mathsf{syk}\rangle]; [\mathsf{x}, \mathsf{vav}]; [\mathsf{cdc}, \mathsf{rac}]; \mathsf{pha}\rangle; ph] \\ \Delta_2 \,\big[\!\big|\, \mathsf{NEL} \\ [\mathcal{R}_2'', \mathcal{R}_1, \langle[\mathsf{fcc}, \langle[\mathsf{src}, \mathsf{src}]; \mathsf{syk}\rangle]; [\mathsf{x}, \mathsf{vav}]; [cdc, rac]\rangle] \\ \Delta_1 \,\big[\!\big|\, \mathsf{NEL} \\ [\mathcal{R}_2'', \mathcal{R}_1, s, s, fc, fcr] \\ \Delta_3 \,\big[\!\big|\, \mathsf{NEL} \\ [\mathcal{R}_2', \mathcal{R}_1, s, s, fc, fcr] \end{array}$$

When we consider the process structure in the premise of this derivation graphically, we obtain the Hasse-diagram depicted on the left below. In this diagram, we see that the transition cdc appears causally dependent on vav as well as x. Similarly, the transition rac appears causally dependent on both vav and x. However, although it is known that Vav (vav) is a GEF for Rac

(rac) [31], there is no biological evidence for causal dependency between Vav (vav) and Cdc42 (cdc) and the unknown GEF (x) of Cdc42 and Rac. Based on this data, we check in our model if we can relax this causality by logical reasoning. We observe that the process structures $\mathsf{P}_1 = [\langle \mathsf{x}; \mathsf{cdc}\rangle, \langle \mathsf{vav}; \mathsf{rac}\rangle]$ and $\mathsf{P}_2 = \langle [\mathsf{x}, \mathsf{vav}]; [\mathsf{cdc}, \mathsf{rac}]\rangle$ are P_1-equivalent. Because P_1 is enabled at $M = \Phi([\mathsf{fcc}, \langle [\mathsf{src}, \mathsf{src}]; \mathsf{syk}\rangle], \{\!\!\{ s, s, fc, fcr \}\!\!\})$, by Proposition 2, we can replace P_1 with P_2 in the process structure without changing the final marking.



This way, we obtain the process structure corresponding to Hasse-diagram on the right, which delivers a model of the signalling pathway in Fc receptor-mediated phagocytosis.

8 Discussion

We introduced a compositional language, called $\mathcal{CP}$, for place transition petri nets for modelling biological signalling pathways. The language $\mathcal{CP}$ is equipped with parallel and sequential composition and a proof theoretical deductive operational semantics that allows to perform logical reasoning on the processes which are being analysed. The operational semantics is obtained by encoding the multiset rewriting representation of the place transition petri nets in an extension of multiplicative exponential linear logic with a self-dual non-commutative operator called seq. While parallel composition of processes is naturally mapped to the par operator of linear logic, the seq operator serves as a data structure to represent sequential composition at the same logical level with parallel composition. This allows the models to be built by starting from any level of abstraction and extending the model compositionally, also by adding more data at lower levels of abstraction at will. Our implementations of deep inference deductive systems provide the reasoning tools for the proposed approach [15]. [6]

The notion of parallel and sequential composition that we define on petri nets originally emerged in [16]. Similar to our notion of parallel and sequential composition of transitions, in [2], Breitling et al. give a notion of composition on petri net models which they call horizontal and vertical composition. In[14], Heiner et al. study the petri nets as a unifying framework for the qualitative,

[6] Implementations of tools, mainly in Maude language, are available for download at `http://www.doc.ic.ac.uk/~ozank/maude_cos.html`.

stochastic and continuous paradigms for modelling and analysing biological systems. The authors also adapt the multiset rewriting approach in their qualitative analysis while emphasising the partial order semantics. They address behavioural properties of the qualitative models and relate the quantitative and qualitative aspects of petri net models. We believe that a stochastic semantics of our approach can be obtained analogously by considering tokens as discrete quantities, and by resorting to the isomorphism between continuous time Markov chains and securings which are interleavings of process structures.

In language $\mathcal{CP}$, the process structures which are obtained by composing processes are N-free partial orders. These N-free partial orders provide an explicit representation of possible signalling pathways, and a platform for analysis, where the transitions can be composed in different ways. Because of the causal dependencies captured by the petri nets due to the resources which enable transitions, the common predecessors and successors of processes provide a synchronisation mechanism. Such a view of language $\mathcal{CP}$ is also in agreement with the event structure [35] view of the processes, which is a topic of ongoing work [17].

When the synchronisation mechanism of language $\mathcal{CP}$ is compared with the synchronisation in process algebra, e.g., π-calculus [20], in language $\mathcal{CP}$ we are not restricted to binary interactions, because more than two processes can share predecessors and successors. Furthermore, such a synchronisation mechanism also captures the modelling of possibly different durations of concurrent signals. However, binary reactions as hand-shake synchronisation can be simulated by extending the definition of transition structures with a synchronisation token as in the following example.

Example 15. Consider the two transitions $\mathsf{p} : \{\!\!\{ a \}\!\!\} \to \{\!\!\{ c \}\!\!\}$ and $\mathsf{q} : \{\!\!\{ b \}\!\!\} \to \{\!\!\{ d \}\!\!\}$. We synchronise these two transitions over the name x as follows:

$$\mathsf{parallel}\ \dfrac{\mathsf{q}\downarrow\ \dfrac{\mathsf{ai}\downarrow\ \dfrac{\langle (\bar{a}, \bar{b}); [\mathsf{p}, \mathsf{q}]; [c, d] \rangle}{\langle (\bar{a}, \bar{b}); [\mathsf{p}, \mathsf{q}]; [x, \bar{x}]; [c, d] \rangle}}{\langle (\bar{a}, \bar{b}); [\langle \mathsf{p}; x \rangle, \langle \mathsf{q}; \bar{x} \rangle]; [c, d] \rangle}}{[\langle \bar{a}; \mathsf{p}; x; c \rangle, \langle \bar{b}; \mathsf{q}; \bar{x}; d \rangle]}$$

The petri net formalism is well developed with a variety of languages and tools, including those for quantitative analysis. Directions of future investigation include integrating and adapting these ideas, and also considering more involved data structures without departing from mathematical rigour by exploiting the logical operators and exponentials of system NEL, e.g., for representing compartments as in [26], or to represent the DNA by means of sequential composition.

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